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Chemistry of 1,2,3-triazoles

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Wim Dehaen • Vasiliy A. Bakulev
Editors

Chemistry of 1,2,3-triazoles

With contributions by

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Preface

The chemistry of 1,2,3-triazoles has been an important topic in heterocyclic chemistry since the first such heterocycles were prepared in the nineteenth century by von Pechmann (1888). Publications on triazoles have increased steadily ever since but there has recently been a remarkable additional interest due to the CuAAC (copper-catalyzed acetylene/azide cycloaddition) discovered by Meldal and Sharpless and related azide cycloaddition reactions, leading to a surge of publications and new applications for triazoles. A volume in this series of "Topics in Heterocyclic Chemistry" was already devoted to "Click Triazoles" (2012), edited by Janez Kosmrlj, but certainly not all parts of the versatile 1,2,3-triazole chemistry were covered at that time and this new volume can be seen as complementary.

In the first chapter, we reviewed the rearrangements and ring transformations of 1,2,3-triazoles. Especially the denitrogenative ring transformations enjoy great current interest. Natalya Belskaya et al. cover the progress in the area of the chemistry of the isomeric 2*H*-1,2,3-triazoles (see chapter "Synthesis of 2*H*-1,2,3-Triazoles"). Besides the synthetic procedures towards triazoles related to CuAAC, many others exist and Nazary Pokhodylo gives an overview of the multicomponent and domino processes leading to 1,2,3-triazoles (see chapter "Biological Properties of 1*H*-1,2,3- and 2*H*-1,2,3-Triazoles"). Quaternization of the triazole nucleus leads to interesting materials and this is reflected in two chapters by Jurgen Liebscher and Zekarias Jakob on one hand and Jezus Aizpura et al. on the other hand, who deal , respectively, with triazolium ionic liquids (see chapter "Chemistry of 1,2,3-Triazolium Salts") and mesoionic and carbene derivatives of triazole (see chapter "Mesoionic 1,2,3-Triazoles and 1,2,3-Triazole Carbenes"). Vitor Ferreira et al. are giving an overview of the many biological properties of 1,2,3-triazole derivatives (see chapter "Multicomponent and Domino Reactions Leading to 1,2,3-Triazoles"), and finally there is a survey by Belen Abarca et al. about 1,2,3-triazoles fused to aromatic rings (see chapter "1,2,3-Triazoles Fused to Aromatic Rings").

Our aim in editing this book was to show the versatility of the chemistry of the 1,2,3-triazole ring, and the many applications of this heterocycle in different fields ranging from medicinal chemistry, organocatalysis, development of new reaction

media, structural chemistry or in organic synthesis as starting materials. We thank all authors and the people at Springer for their essential efforts to realize this volume.

Leuven, Belgium — Wim Dehaen
Yekaterinburg, Russia — Vasiliy A. Bakulev
May 2014

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Thermal Rearrangements and Transformations of 1,2,3-Triazoles

Vasiliy Bakulev, Wim Dehaen, and Tetyana Beryozkina

Abstract This chapter concentrates on the thermal rearrangements and transformations of 1,2,3-triazoles. It also contains data on the ring-chain tautomerism of 1,2,3-triazoles and the substituent effect on the position of the equilibrium between diazoimines and 1,2,3-triazoles. The main part of this review has been devoted to transition-metal-catalyzed denitrogenative transformation of 1,2,3-triazoles.

Keywords 1-Tosyl-1,2,3-triazoles · Diazoimines · Flash vacuum pyrolysis · Rearrangements · Rhodium catalysts · Transformations

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Abbreviations

(*R*)-{NTV}$_4$	α*R*-α-(isopropyl)-1,3-dioxo-2H-benz[de]isoquinoline-2-acetato
(*S*)-{NTTL}$_4$	α*S*-α-(tert-butyl)-1,3-dioxo-2H-benz[de]isoquinoline-2-acetato
1,2-DCE	1,2-Dichloroethane
Alk	Alkyl
BDPP	(2R 4R) or (2S, 4S)bis(diphenylphosphino)pentane
Boc	Benzyloxycarbonyl
CuAAC	Copper(I)-catalyzed azide–alkyne cycloaddition
DBU	1,8-Diazabicycloundec-7-ene
DFT	Density Functional Theory
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomer ratio
E	Ester group
ee	Enantiomer excess
FVP	Flash Vacuum Pyrolysis
h	Hour(s)
IR	Infra-Red
Me	Methyl
Ms	Mesyl
MW	Microwave
n-Bu	Normal butyl
Ni(cod)$_2$	Bis(cyclooctadiene)nickel(0)
NMR	Nuclear Magnetic Resonance
P(*n*-Bu)Ad$_2$	Di(1-adamantyl)-*n*-butylphosphine
Ph	Phenyl
Rh$_2$(esp)$_2$	Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]
Rh$_2$(oct)$_4$	Rhodium tetra octanoate
Rh$_2$(piv)$_4$	Rhodium pivalate
Rh$_2$(*S*-DOSP)$_4$	Tetrakis[(*S*)-(-)-*N*-(p-dodecylphenylsulfonyl)prolinato] dirhodium (II)
Rh$_2$(S-PTAD)$_4$	Tetrakis[(*S*)-(+)-(1-adamantyl)-(*N*-phthalimido)acetato] dirhodium(II)
rt	Room temperature
TBDMSO	*tert*-Butyldimethylsilyloxy
Tf	Trifluoromethanesulfonyl (triflyl)
Tf$_2$O	Triflic anhydride
Tpm^{*,Br}	Tris(3,5-dimethyl-4-bromopyrazolyl)methane]
Ts	Tosyl 4-toluenesulfonyl

1 Introduction

Rearrangements and transformations of heterocyclic rings constitute a special and interesting approach to other heterocyclic compounds [1–14]. These processes are often occurring via interesting but little known reaction mechanisms. The ring-chain tautomerism of 1,2,3-triazoles was discovered more than 50 years ago [7]. Following this, it has been shown that reversible ring opening of the 1,2,3-triazole ring followed by re-cyclization to form other rings are the key steps for the Dimroth, Conforth and L'abbé rearrangements [1–32].

Thermal transformation of 1,2,3-triazoles was also discovered and studied in the second part of the twentieth century. Owing mainly to work of MacNab, Wentrup, Rees, Gilchrist and L'abbé (Sect. 4) [33–44] it has been shown that 1,2,3-triazoles are good substrates for their thermal transformation to various heterocyclic compounds such as isoquinolines, indoles, pyrazines, and oxazoles. However, as the rule the yields of the products are rather moderate and in some cases even poor.

In the beginning of the twenty-first century 1,2,3-triazoles became very fashionable and rather available compounds due to the discovery of the CuAAC reaction by the Sharpless/Fokin and Meldal groups [45, 46]. Apart from the applications in medicine, biology, and analytical chemistry they were investigated as unique substrates for the generation of azavinyl carbenoid compounds that are rather reactive but stable enough to be involved in cycloadditions to double and triple bonds and for insertion to C–H, N–H, O–H and C–C bonds. Mainly by the efforts of Gevorgyan, Fokin and Murakami the new paradigm "transition-metal-catalyzed denitrogenative transformation of 1,2,3-triazoles" was developed since 2008 (Sect. 5) [47–79]. The denitrogenative approach has many advantages in comparison with traditional methods and constitutes an efficient, single step interconversion of 1,2,3-triazoles into a huge variety of other heterocyclic compounds and other valuable organic compounds such as cyclopropanes, cyclopropenes, enamines and diazadienes. Interestingly, 4-*N*-phthalimido-1,2,3-triazoles, as shown by the Davies group in 2012 [44], are suitable precursors of azavinyl carbenes on smooth heating even without catalyst.

Herein, we examine the rearrangements of 1,2,3-triazoles and their ring transformation into other heterocyclic compounds accompanied by elimination of dinitrogen, involving subsequent reactions with double and single bonds. Data on the ring-chain tautomerism of 1,2,3-triazoles are also included because of their importance for both the rearrangements and the dinitrogenative ring transformations of 1,2,3-triazoles. The latter part has been recently reviewed by Chattopadhyay and Gevorgyan [45]; however, even in the short time since then more articles on the transformations of 1,2,3-triazoles have been published than those included in the review [45].

2 Ring Chain Tautomerism (Diazoimine – 1,2,3-Triazole Equilibrium)

The ring-chain tautomerism is a phenomenon that is very important in 1,2,3-triazole chemistry, being an essential part of numerous rearrangements and ring transformations. The open chain isomers, diazoimines (chain isomer) **1** are, with a few exceptions, very unstable and undergo spontaneous ring closure to form 1,2,3-triazoles (ring isomer) **2** when they are generated [1] (Scheme 1).

As an example, the diazo group transfer reaction with benzenesulfonyl azide to amidine **3** furnishes a mixture of isomeric triazoles **4** and **5**, most probably via unstable intermediate diazoamidines **6** (Scheme 2). Many other examples are published confirming the higher stability of the triazole ring in comparison with the isomeric diazoimines [2].

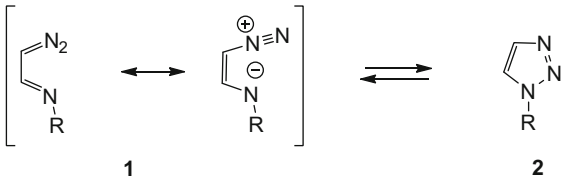
Interestingly, 1-sulfonyl-5-dialkylamino-1,2,3-triazoles **7** prepared by cycloaddition reaction of benzenesulfonyl azide to *N*,*N*-dialkylamino propynes **8** partially undergo ring opening reaction to give, according to IR and NMR spectroscopic data, an equilibrium mixture of triazoles **7** and diazo-amidines **9** [3] (Scheme 3). The existence of this type of equilibrium was the background for the discovery of rearrangements and metal catalyzed denitrogenative transformations of 1,2,3-triazoles (see Sects. 3 and 5).

Another well-known example of the synthesis of relatively stable diazoimines **12** is formed by the reaction of cyanogen azide **10** with acetylene to form a cycloadduct which, according to IR and NMR spectra, exists in solution as a ring-chain tautomeric mixture of 1-cyano-1,2,3-triazoles **11** and α-diazo-*N*-cyanoethylideneimine **12** (Scheme 4). An increase of the temperature and decrease of the polarity of the solvent were shown to shift the equilibrium in favor of the diazoimine form [4].

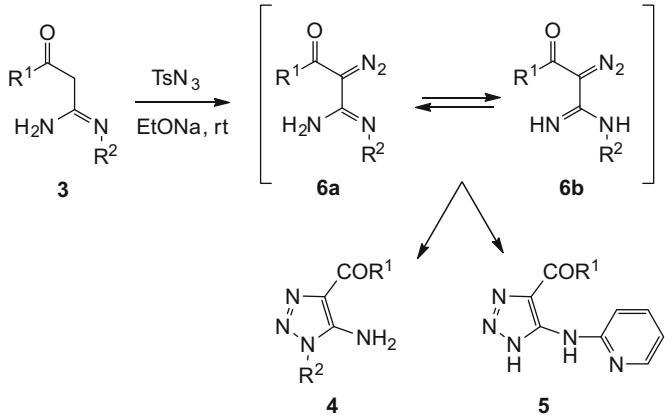
An ab initio and Density Functional Theory (DFT) study was carried out and 1H-1,2,3-triazole **2** was found to be 15–20 kcal/mol stable than diazoethaneimine **1** (Scheme 5). The very low activation energy (9–12 kcal) for the cyclization was explained in terms of a heteroelectrocyclic (pseudopericyclic [5]) mechanism where an input of energy to rotate the terminal groups was not required since the formation of the new N–N bond occurs by the in-plane interaction of the lone pair of electrons on the nitrogen atom of the imino group with the vacant orbital located at the terminal nitrogen atom of the diazo group [6].

The equilibrium between 2-diazomalondiamides **13** and 5-hydroxy-1,2,3-triazoles **14** in ethanol solution is shifted to the chain form [7] (Scheme 6).

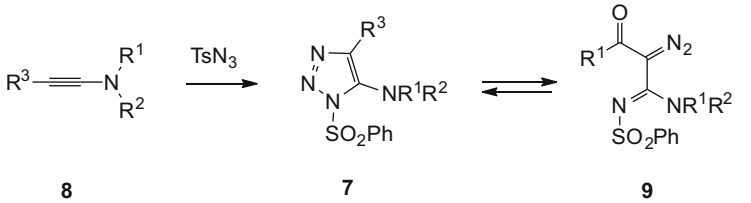
Conversely, the equilibrium between α-diazo-α-cyanoacetamides **15** and its cyclic isomers **16** in the same conditions is shifted to the ring form [8]. The position of the equilibrium was shown to depend strongly on the nature of the solvent. It is shifted towards the cyclic form in polar solvents like water, acetonitrile, and DMSO. On the other hand, the diazo form is predominant in nonpolar benzene solution (see Table 1).



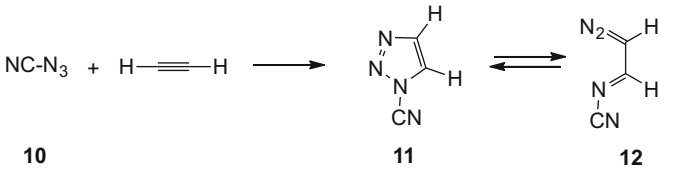
Scheme 1 Diazoimine – 1,2,3-triazole equilibrium



Scheme 2 Reaction of acetamidines **3** with tosyl azide

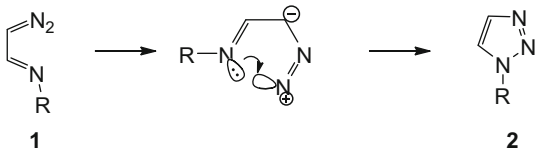


Scheme 3 Reaction of ynamines with tosyl azide



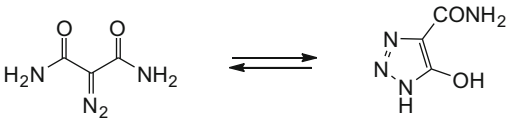
Scheme 4 Cycloadition of cyanogen to acetylene

Scheme 5 The heteroelectrocyclic (pseudopericyclic) mechanism for cyclization of diazoimine **1** to triazole **2**



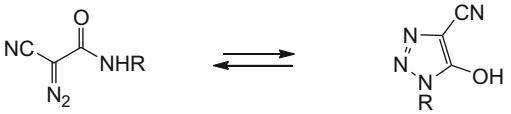
1 **2**

Scheme 6 Tautomerism in the diazomaloamide **13** – 5-hydroxy-1,2,3-triazole **14** system



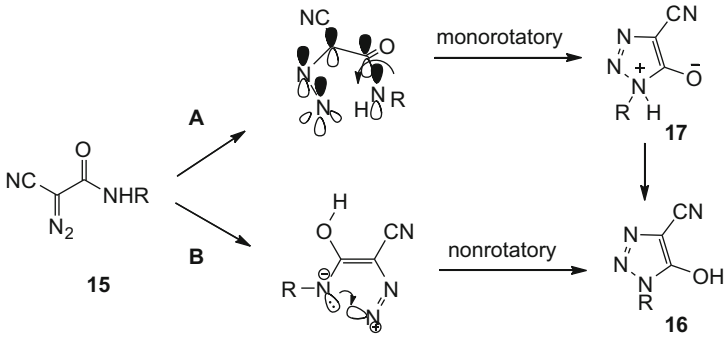
13 **14**

Table 1 The constants of equilibrium between diazo compounds **15** and triazoles **16**



15 a-c **16 a-c**

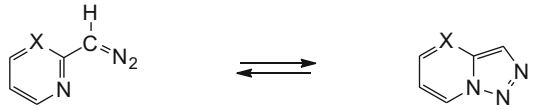
	K = [**16**]/[**15**] at 35°C in various solvents					
R	D_2O	CD_3CN	DMSO-D_6	Acetone-D_6	C_6D_6	C_2D_5OD
4-MeO-C_6H_4	>100		21 ± 3	16 ± 1	0.7 ± 0.1	16 ± 2
Me	45.4 ± 2.1	27 ± 2	3.2 ± 0.8	1.2 ± 0.2	0.3 ± 0.02	11 ± 1
Bn	60 ± 9		6.2 ± 0.2	1.5 ± 0.2	0.24 ± 0.03	19.0 ± 0.8



15 **17** **16**

Scheme 7 Cyclization mechanisms of 2-cyano-acetamides **15**

Based on quantum chemical calculations, kinetic studies, and differences in values of the kinetic isotope effect, a conclusion was made on a difference in mechanisms for the cyclization of *N*-alkyl- and *N*-aryldiazoacetamides **15** (Scheme 7). Cyclization of *N*-alkyl derivatives takes place via a monorotatory



18 **19**

X = CH (ΔΔ G = - 2-6 kcal/mol) X = N (ΔΔ G = -{16-18} kcal/mol)
$\Delta\Delta G = \Delta G_{18} - \Delta G_{19}$

Scheme 8 Relative stabilities of diazoimine and triazole forms in heterocyclic systems

mechanism, while cyclization of the *N*-aryl derivatives takes place by a mechanism where one of the steps is heteroelectrocyclization of 2-diazoacetimidates **17**. [8]. The same mechanisms for the cyclizations of *N*-alkyl- and *N*-arylmalonamides were confirmed by kinetic and theoretical studies of non-symmetrically substituted malondiamides [9].

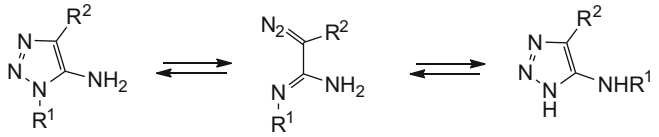
If the imino group is part of an aromatic heterocycle, then it has been shown by careful theoretical study that the relative stability of the diazoimine form increases in comparison with the ring form [10]. In the case of a pyridine ring, the cyclic form **19** is still (2–6 kcal/mol) more stable but the difference in free energies between the cyclic and ring forms is less than for the parent compounds **1** and **2** (15–20 kcal/mol) (Scheme 8). The relative free energy of diazo-pyrimidine **18** (X=N) is even 16–18 kcal/mol less in comparison with the cyclic form **19**. Depending on the nature of the heterocycle, either form can be more stable.

3 Rearrangements of 1,2,3-Triazoles

1,2,3-Triazoles are prone to undergo various ring transformations and rearrangements. This is the base for unique synthetic methods and makes room for the fundamental study of unusual reactions. Rearrangements of 1,2,3-triazoles are governed by the following factors: (1) the facile cleavage of the weak N1–N2 bond, (2) the existence of an equilibrium between 1,2,3-triazoles and α-diazo-imines (see Sect. 2), and (3) the capacity of both imino- and diazo groups to cyclize onto electrophilic and nucleophilic functionalities. L'abbé proposed a classification for rearrangements of five-membered heterocyclic compounds depending on the number of participating side-chain atoms [11].

3.1 Dimroth Type Rearrangements

The term "Dimroth rearrangement" was introduced in 1963 [11] as a process of isomerization for 1-substituted 1,2,3-triazoles of type **20** to 5-amino substituted



20 **21** **22**

Scheme 9 Dimroth rearrangement of 1,2,3-triazoles

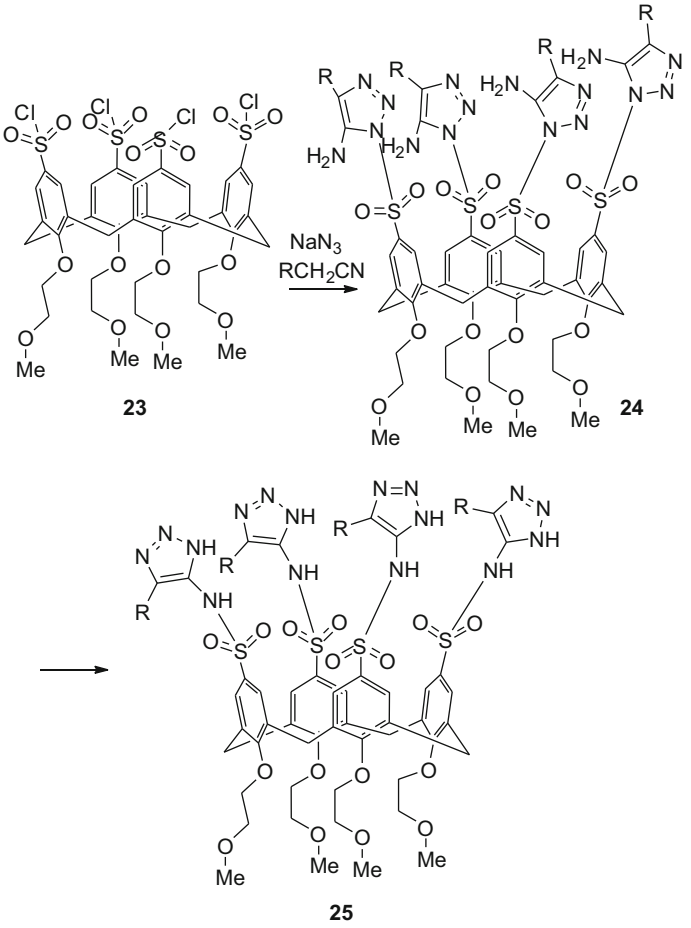
1,2,3-triazoles **22** taking place by ring opening to generate diazo acetamidines **21** and subsequent recyclization of the latter, after amidine tautomerization, onto the nitrogen atom of the former amino group attached to the ring to furnish the final product (Scheme 8). The cyclization of the diazo group onto the nitrogen atoms of a pivotal amidine fragment is a common feature of this type of rearrangement. This rearrangement was first described by O. Dimroth for the isomerization of 1-aryl-5-amino-1,2,3-triazole **20** to 5-anilino-1,2,3-triazoles **21** [7] and afterwards has received much attention in many publications including a couple of reviews [11–14].

The position of the equilibrium depicted in Scheme 9 is shifted towards the acidic form **22** in basic solvents. The more basic the solvent the higher is the ratio **22/20** in the equilibrium mixture. Another tendency is that electron-withdrawing and bulky substituents stabilize the form where they are attached to the exocyclic nitrogen atom. On the other hand, alkyl groups, amino and aryl groups tend to favor the cyclic atom [11]. When R is an arylsulfonyl group, the rearrangement of **24** is so fast that only the rearrangement product, triazole **25** was isolated in the reaction of tetrakis-(azidosulfonyl)calix[4]arenes **23** with 2-cyanoacetamides [15] (Scheme 10).

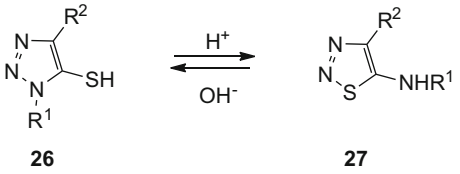
5-Mercapto-1,2,3-triazoles **26** are capable of rearranging in acidic solution to isomeric 5-amino-1,2,3-thiadiazoles **27** (Scheme 11). However, the reverse reaction is more favorable in the presence of bases and in fact represents a general method for the synthesis of 5-mercapto-1,2,3-triazoles **26** [11, 15, 16].

3.2 Cornforth-Type Rearrangements

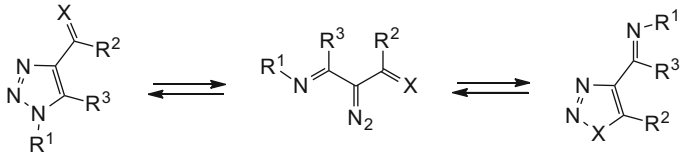
Rearrangements of 1,2,3-triazoles of type **28** bearing a C=N, N=N, and C=S functions at the position 4, to isomeric triazoles **30** were mainly found, carefully studied, and reviewed in the L'abbé laboratory [17–20] (Scheme 12). These involve two atoms of the 4-substituents and are somewhat similar to the interconversion reactions of isomeric 4-acyl-substituted oxazoles via dicarbonyl nitrile ylides discovered by Cornforth in 1949 [1]. The competitive cyclizations of the intermediate diazo function of compound **29** onto the nitrogen atoms of both imino groups are a key feature of this type of rearrangement.



Scheme 10 Dimroth rearrangement of tetrakis-(1,2,3-triazole-5-aminosulfonyl)-calix[4]arenes

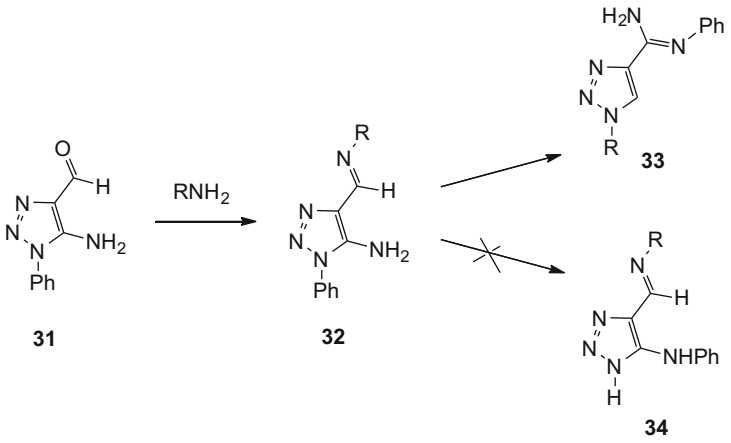


Scheme 11 Rearrangement of 5-mercapto-1,2,3-triazoles **26** to 5-amino-1,2,3-thiadiazoles **27**



28 **29** **30**

Scheme 12 Rearrangement with participation of two atoms of the side chain

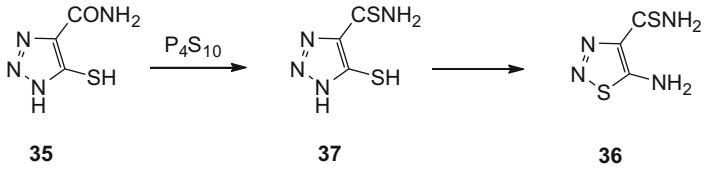


31 **32** **33** **34**

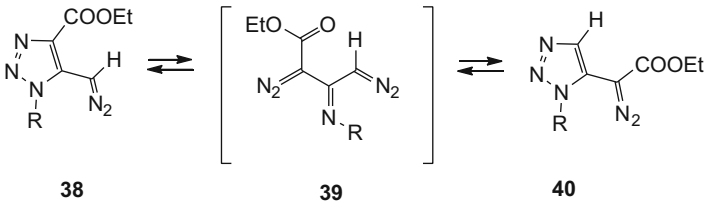
Scheme 13 Competition of Dimroth and Cornforth rearrangements

L'abbé and Vandendriessche made the design and synthesis of 1,2,3-triazoles **32** bearing amino and iminocarbonyl functions in positions 5 and 4 of the ring. Triazoles **32** are in principle capable of transferring via either Dimroth or Cornforth rearrangements to isomeric triazoles **33** or **34** [19]. It has been shown that triazoles **32** rearrange thermally to 4-amidino-substituted triazoles **33** instead of undergoing the Dimroth rearrangement to 5-anilinotriazoles **34** (Scheme 13). The rearrangement takes place for different R groups including alkyl, aryl, hydroxyl, and amino group, showing the generality of the process [18]. As in the case of Dimroth rearrangement, the equilibrium is shifted towards the triazole form possessing the strongest electron-withdrawing substituent at the imine nitrogen.

If $C(X)R^2$ in **28** is substituted by an azo group, a rearrangement can occur to form a tetrazole ring. Thus an attempted crystallization of 5-hydroxy-4-phenylazo-1,2,3-triazole in acetic acid led to its complete isomerization to 2-phenyl-tetrazole 4-carboxamide [21]. When 5-mercapto-1,2,3-triazole-4-carboxamide **35** was reacted with P_4S_{10} in dioxane the formation of 5-amino-4-carbothioamide **37** occurred most probably via Cornforth-type rearrangement of intermediate 5-mercapto-1,2,3-triazole-4-carbothioamide **36** (Scheme 14) [22].



Scheme 14 Cornforth type of rearrangement of 1,2,3-triazole **37** to 1,2,3-thiadiazole **36**



Scheme 15 L'abbé rearrangement of 5-diazomethyl-1,2,3-triazoles

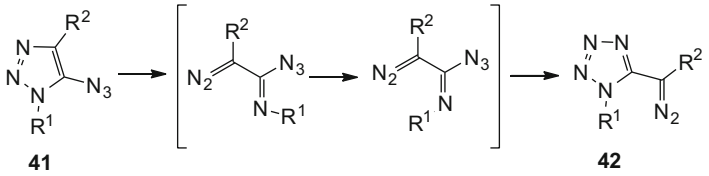
Cornforth type rearrangements are also known for fused 1,2,3-triazoles, for instance:

- 4-amino-1-(arylsulfonyl)benzo[*d*]1,2,3-triazoles to 4-(arylsulfonyl aminobenzo [*d*]1,2,3-triazoles [23]
- 3H-[1,2,3]triazolo[4,5-b]pyridine-7-amine to 1H-[1,2,3]triazolo[4,5-c]pyridine-4-amine [24]
- 3H-[1,2,3]triazolo[4,5-b]pyridine-7-(4H)thione to [1,2,3]thiadiazolo[4,5-c] pyridine-4-amine [24]

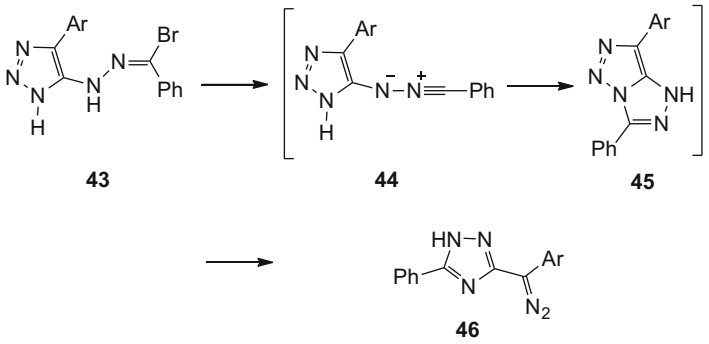
3.3 L'abbé Type Rearrangements

Competitive 1,5-cyclizations of a single imino group onto two 1,3-dipole moieties are another type of rearrangements for 1,2,3-triazoles. An example for this kind of reaction, found by L'abbé and Dehaen, was the rearrangements of 5-diazomethyl-4-ethoxycarbonyl-1,2,3-triazoles **38** to diazoacetates **40** (Scheme 15). The reaction is limited to triazoles bearing electron-withdrawing substituents at positions 1 and 4 of the ring [25, 26].

5-Azido-1,2,3-triazoles **41** bearing strong electron-withdrawing substituents at position 4 such as ester, cyano, aldehyde groups were found to undergo very similar rearrangement to form 5-diazomethyl-tetrazoles **42** [27–31] (Scheme 16). The introduction of an electron-withdrawing substituent at the position 1 of the ring increases the rate of the process. The rearrangement is faster in non-polar solvents, but the effect is small. The rate-limiting step of the reaction was shown to be the ring opening of the 1,2,3-triazole ring [27].



Scheme 16 L'abbé rearrangement of 5-azido-1,2,3-triazoles to 5-diazomethyl-tetrazoles

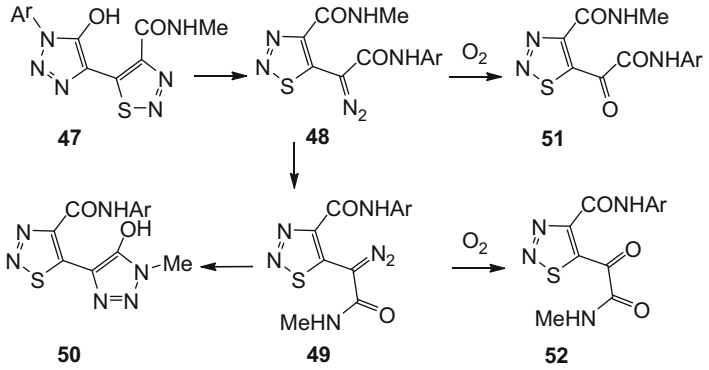


Scheme 17 L'abbé type of rearrangement of 1,2,3-triazol-5-yl nitrilimines to diazomethyl-1,2,4-triazoles

N-Unsubstituted 4-aryl-1,2,3-triazoles **43** bearing a hydrazonoyl bromide group at position 4 in water/acetone 1:1 solution undergo rearrangement to aryl (diazomethyl)-1,2,4-triazole **46** under elimination of HBr. One of the proposed mechanism includes the formation of intermediate nitrilimine **44** with subsequent 1,5-electrocyclic ring closure and ring opening to form final product **46** (Scheme 17).

3.4 Tandem Rearrangements

A single example of the rearrangement for heterocyclic ring conjugates, containing both a 1,2,3-triazole and 1,2,3-thiadiazole ring, was found as a collaboration of our laboratories. We have found that bis heterocycles **47** are capable of undergoing domino-type rearrangements involving both rings to form isomeric 5-(1,2,3-triazol-4-yl)-[1,2,3]-thiadiazoles **50** (Scheme 18). The net result of the process is the interchange of the aryl and methyl groups. The rearrangement proceeds as a three-step process and involves, first, ring opening of the hydroxytriazoles **47** to form diazoamides **48**. The latter undergo the L'abbé rearrangement to form isomeric diazo compounds **49**. Finally, a ring closure occurs to afford hydroxyl triazoles **50**. The formation of the intermediate diazo compounds **48** and **49** was



Scheme 18 Tandem rearrangement of thiadiazolyl triazoles **47** to thiadiazolyl triazoles **50**

confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy of the products in the reaction mixture and of the chemical transformation of intermediate diazo compounds to ketones **51** and **52** [17].

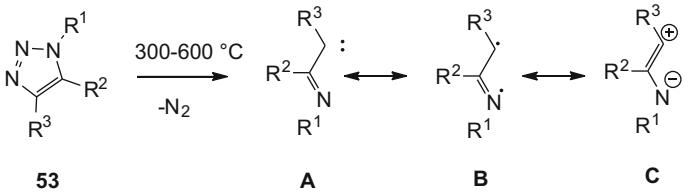
4 Thermolysis of 1,2,3-Triazoles

1,2,3-Triazoles are in general stable compounds due to their aromaticity. Therefore, normally a high temperature is required for the elimination of dinitrogen. To explain the variety of the products formed in the reactions, the generated species are represented as a carbene **A**, diradical **B**, or zwitterion **C** resonance form (Scheme 19).

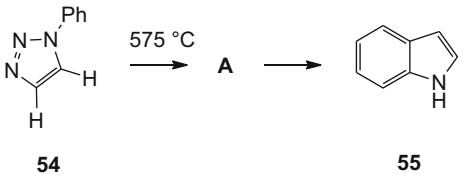
The presence of aromatic substituents stabilizing these forms **A**–**C**, or the introduction of strongly electron withdrawing substituents lowering the activation energy for the elimination of dinitrogen, are required to isolate the reaction products. If the substituents at N1 of the triazole ring or more commonly of benzotriazoles are capable of reacting intramolecularly with radicals, then cyclization occurs leading to a variety of different compounds including heterocyclic systems.

The formation of indoles **55** by thermolysis of 1-aryl-1,2,3-triazoles **54** was interpreted as a process proceeding from singlet form **A** followed by Wolff rearrangement and ring closure to final products [33, 34] (Scheme 20).

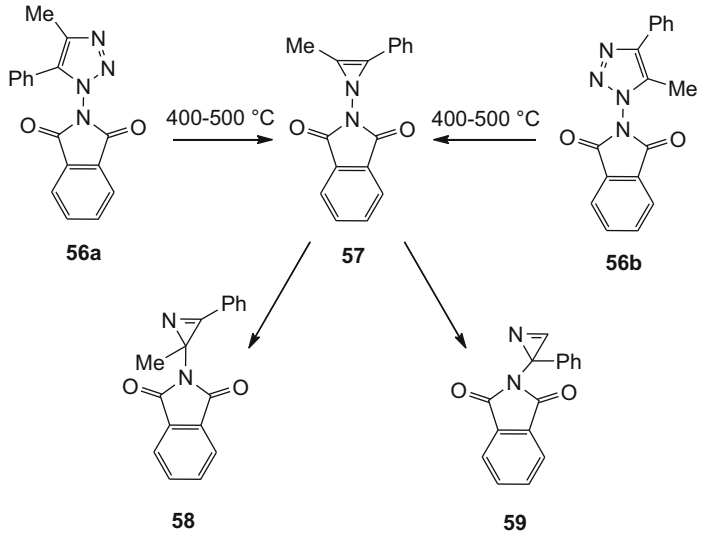
Vacuum pyrolysis of isomeric 1-*N*-phthalimido-1,2,3-triazoles **56a** and **56b** at 400–500°C was shown to yield the compounds **58**–**59** and the products of further transformation of the latter in the same ratio. Based on these results Gilchrist et al. [35, 36] postulated the formation of an identical intermediate 1H-azirine **57** for the reactions of both triazoles. The 1H-azirine **57** underwent isomerization to more stable isomeric 2H-azirines **58**–**59** (Scheme 21).



Scheme 19 Presentation of resonance forms A, B, C of the species formed in pyrolysis of 1,2,3-triazoles **53** at 300–600°C

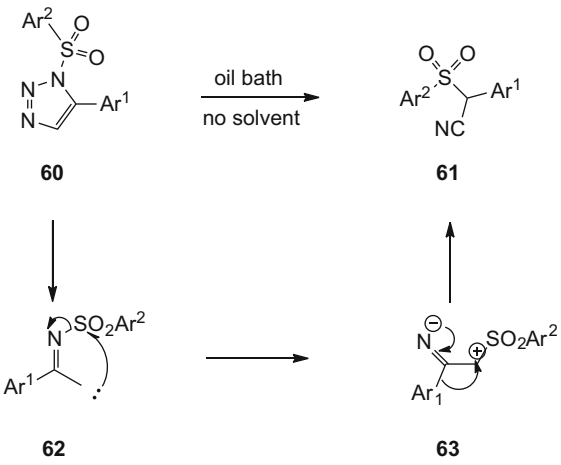


Scheme 20 Transformation of 1-phenyl-1,2,3-triazole to indole

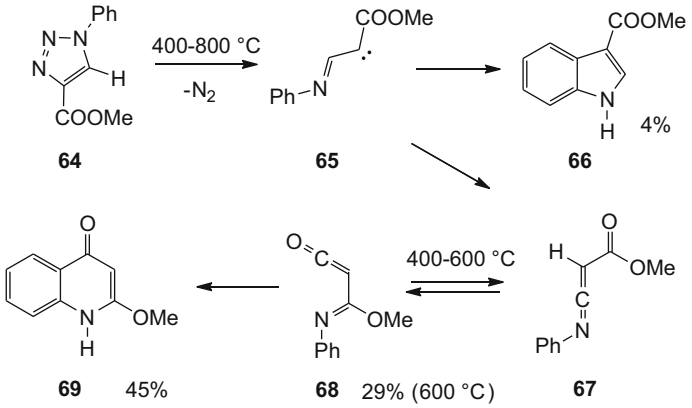


Scheme 21 Vacuum pyrolysis of trisubstituted triazoles

1-Sulfonyl-5-aryl-1,2,3-triazoles **60** were shown recently by the Croatt group to undergo very smooth and fast dinitrogen elimination at 140–190°C to afford α-sulfonyl nitriles **61** in 2–57% yield (Scheme 22). In the same study it was shown that if the temperature is not high enough for fast dinitrogen elimination, then isomerization of 1,5-disubstituted-1,2,3-triazole **60** to the 1,4-isomer took place. The proposed mechanism includes the formation of carbene species **62** in



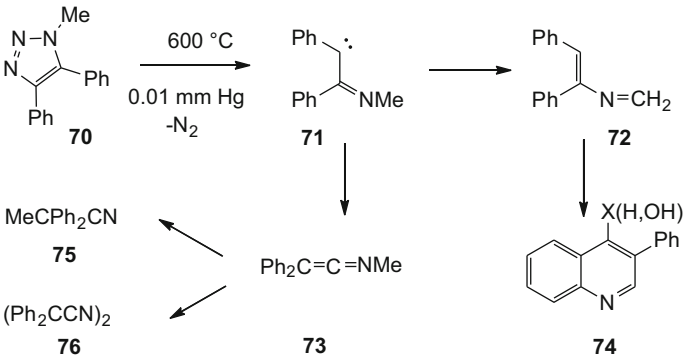
Scheme 22 Synthesis and mechanism for formation of sulfonyl nitriles



Scheme 23 Flash vacuum pyrolysis of methyl 1-phenyl-1,2,3-carboxylate

the first step. The second step involves a 1,3-sulfonyl shift either directly to zwitterion **63** of via a cyclic four-membered ring. Zwitterion **63** in turn underwent an aryl shift to form final product **61** [37].

Wentrup and Fulloon have carefully studied the transformation of methyl 1-phenyl-1,2,3-triazole-4-carboxylate **64** with preparative FVP and managed to isolate indole **66**, keteneimine **67**, and quinolone **69** [38]. They have also shown that elimination of dinitrogen from **64** occurs at 380°C and both ketenimine **67** and ketene **68** are observable by IR spectroscopy. Based on these experiments Wentrup and Fulloon proposed a mechanism (Scheme 23) explaining the skeletal rearrangement by interconversion of imidoylketene **67** to oxoketeneimine **68**, observed also by McNab et al. for ethyl 1-phenyl-1,2,3-triazole-4-carboxylate



Scheme 24 Flash vacuum pyrolysis of *N*-alkyl-4,5-diphenyl-1,2,3-triazoles

[39]. In the case of *N*,*N*-dimethyl-1-aryl-1,2,3-triazole-4-carboxamide, 2-*N*,*N*-dimethylquinolone was obtained [40].

The dinitrogen evolution in *N*-methyl-1,2,3-triazoles **70** required a very high temperature and was accompanied by formation of nitriles **75** and **76** via Wolff rearrangement together with formation of isoquinolines 7**4** [33]. It seems that the formation of compound **74** involves electrocyclization of **72** followed by oxidation to final product (Scheme 24).

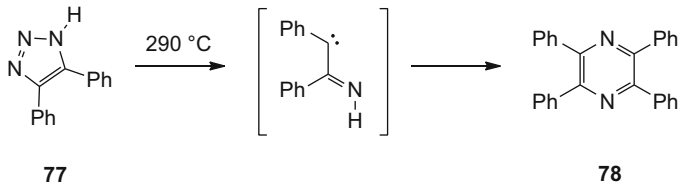
Interestingly, the formation of 2,3,5,6-tetraphenyl pyrazine **78** from 1-NH-triazole **77** occurred at lower temperature [13] (Scheme 25).

McNab et al. have shown that 1,2,3-triazole **79**, bearing both an ester group at position 3 and a pyrazol-3-yl moiety at N_1 is capable of transferring to pyrazolo-pyrimidine **82** after FVP at 600°C (10^{-2} to 10^{-3} Torr) [39]. From ^{13}C labeling experiments they concluded that the mechanism of the reaction involved a ketenimine–imidoylketene rearrangement (Scheme 26).

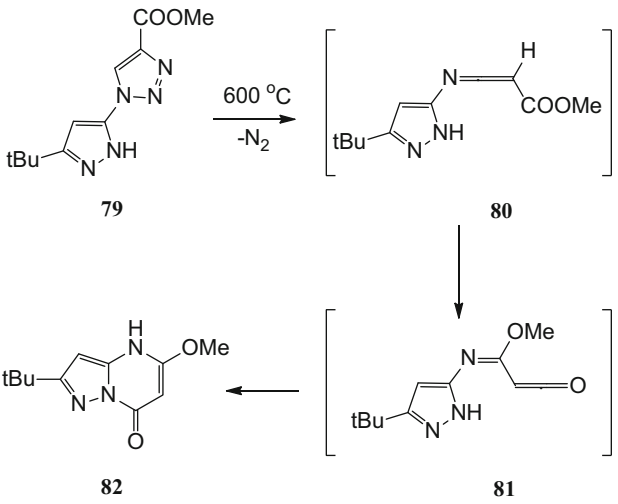
Transformation of a 1,2,3-triazole to an oxazole ring took place when 1-acyl-1,2,3-triazoles **83** were subjected to thermolysis at 150°C in sulfolane solution (Scheme 27). 2-Aryl- and 2-alkyloxazoles **84** were prepared in very good yields, allowing to recommend this transformation of 1-acyl-1,2,3-triazoles as a method of choice for the synthesis of 2-substituted oxazoles of type **84** [13].

2-Substituted benzoxazoles can be prepared similarly to **84** by transformation of 1-acyl-benzo-1,2,3-triazoles. Because thermolytic reactions of benzotriazoles were reviewed a couple years ago [41] they are not included here.

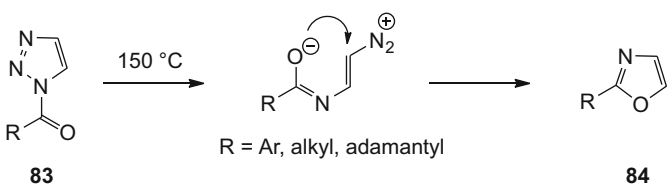
The formation of furans **89** (48%) as main products together with a mixture of isomeric indoles **90** and **91** (46%) occurred when 4-acroleinyl-1-aryl-1,2,3-triazoles **85** were subjected to FVP at 400°C (Scheme 28). Because of the preponderance of 3-substituted indole **90** in the mixture of 2- and 3-acroleinylindoles the authors [42] made the conclusion that iminocarbene **86** formed first and insertion of this carbene into the aromatic C–H bond yielded directly indole **90**. The formation of indole **91** could take place either via rearrangement of carbene **86** to **87** via antiaromatic azirine **87** (pathway **b**) or by rearrangement from indole **90**. The



Scheme 25 Thermolysis of 4,5-diphenyl-1,2,3-triazoles



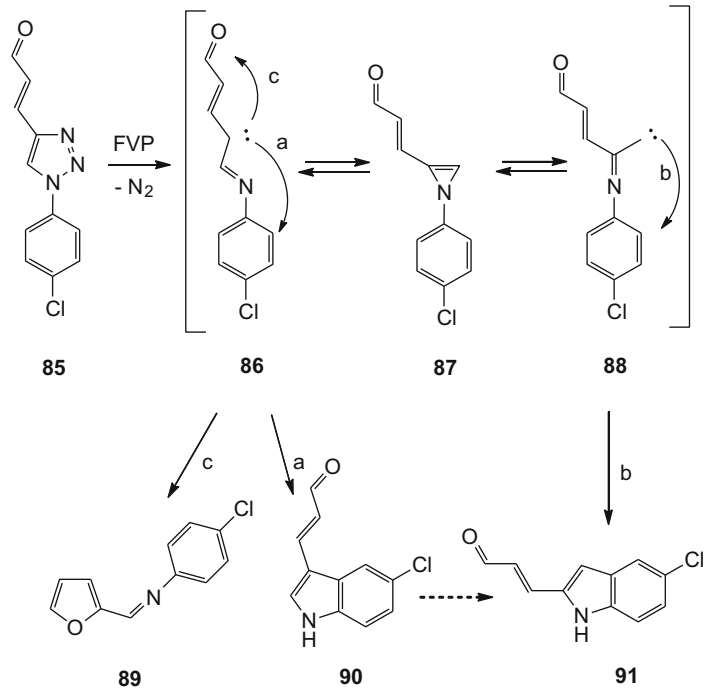
Scheme 26 Flash vacuum pyrolysis of pyrazolyl-1,2,3-triazoles **79**



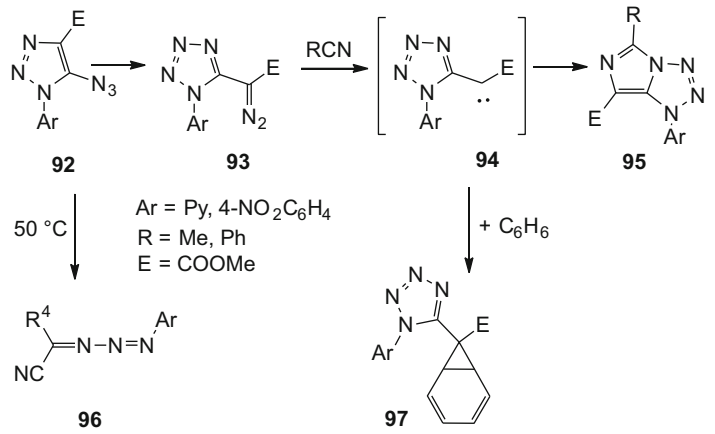
Scheme 27 Thermolysis of 1-acyl-1,2,3-triazoles

presence of oxazole **89** in the reaction mixture was explained by 1,5-heteroelectrocyclization in which the carbene carbon atom attacks the oxygen atom lone pair of electrons to form a furan ring.

Heating of a solution of **92** in either acetonitrile or benzonitrile leads to evolution of dinitrogen to form 5-methylimidazo tetrazole **95** (R=Me) or 6-phenyl imidazotetrazoles **95** (R=Ph) in 65 and 59% yield, respectively (Scheme 29). The mechanism of this transformation included the rearrangement of 5-azidotriazoles to 5-(α-methoxycarbonyl)diazomethyl tetrazoles followed by elimination of dinitrogen

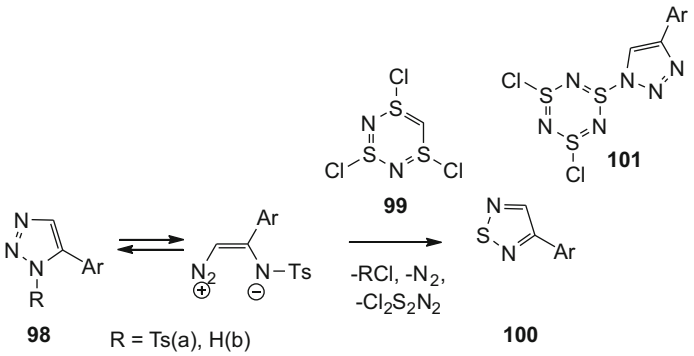


Scheme 28 Flash vacuum pyrolysis of 4-acroleinyl-1-aryl-1,2,3-triazoles **85**



Scheme 29 Thermolysis of 5-azido-1,2,3-triazoles **92**

to form intermediate carbenes **94**. The latter were subjected to cycloaddition reaction with nitriles to form final products **95**. Intermediate diazo compounds **93** were identified by IR and NMR spectroscopy and intermediate carbenes were trapped by



Scheme 30 Conversion of 1,2,3-triazoles **98** to 1,2,5-thiadiazoles **100**

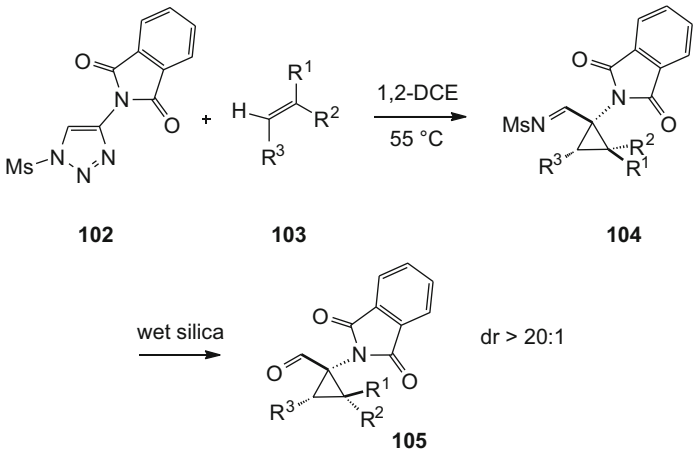
benzene to form norcaradienes **97**. Interestingly, heating of 5-azido-1,2,3-triazoles **92** in petroleum ether at 50°C afforded benzylidene triazenes **96** [27].

Rees and Yue have discovered that a 1,2,3-triazole ring **98**, bearing electron-withdrawing substituents, can be transferred by treatment with trithiazyl trichloride **99** in boiling tetrachloromethane to 1,2,5-thiadiazole **100** [43] (Scheme 30).

Interestingly, the presence of an *N*-tosyl group is not crucial to the reaction although the yield is higher (90%) in the reaction of 1-tosyl-5-nitrophenyl-1,2,3-triazole **98a** in comparison with the reaction of 5-nitrophenyl-1,2,3-triazole **98b** (67%). Because 4-phenyl-1,2,3-triazole did not give 3-phenyl-1,2,5-thiadiazole on treatment with trimer **99** under the same conditions the authors made the conclusion that the presence of a *p*-nitro group is crucial to the reaction. This could indicate that trithiazyl trichloride **99** does not react with the intact triazole but requires at least a small amount of diazoimine tautomer. Rees and Yue proposed that the reaction could go via intermediate **101** in which the triazole is activated to ring opening just as it is in the *N*-tosyl derivative.

Cyclopropanes bearing both carboxaldehyde and disubstituted amino groups of type **105** were successfully synthesized by cyclopropanation of donor/acceptor carbenes in which the donor group is a protected amine functionality [44] (Scheme 31).

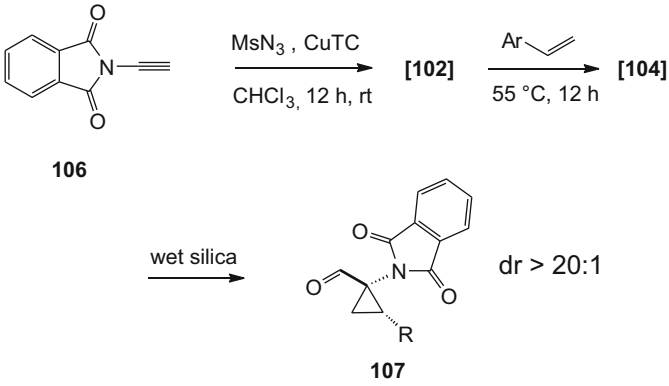
Alford and Davies demonstrated that 4-*N*-phthalimido-*N*-sulfonyl-1,2,3-triazoles **102** are suitable precursor of such kind of carbenes [44]. Thus triazole **102** is shown to react smoothly at 55°C with styrene without catalyst to form cyclopropane imine **104** (Scheme 31). The latter is susceptible to hydrolysis and was easily transformed to aldehyde by treatment with wet silica in excellent yield and high diastereoselectivity. The scope of the reaction with respect to the alkene was examined. A broad range of terminal and internal alkenes, or styrenes bearing either electron-rich or electron-deficient aryl groups, reacted smoothly in good to excellent yields with high diastereoselectivity. Dienes are also capable of reacting with one of the two double bonds with triazole **104** to form cyclopropane alkenes.



102 **103** **104** **105**

R^1 = H; R^2 = CH_2=CH-, $PhCH_2$=CH-, Ph, 4-CF_3-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 2-Me-C_6H_4; R^3 = H, Me

Scheme 31 Syntheses of cyclopropanes **104**, **105**

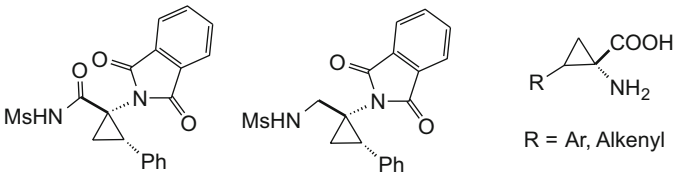


106 **107**

Scheme 32 Synthesis of cyclopropane **107**

The synthesis of α-amino cyclopropane aldehydes is shown to be conducted in a one-pot protocol starting from *N*-ethynylphthalimide **106**. The latter being treated with mesyl azide in the presence of CuCN in chloroform generates 4-phthalimido-*N*-mesyl-1,2,3-triazole **102** [44].

Reaction of intermediate product **102** with styrene at 55°C proceeds within 12 h (Scheme 32). The subsequent treatment of the reaction mixture with wet silica finalizes the process to furnish aldehydes **107** in good yields (74–85%) and with high diastereoselectivity (>20:1). The initial products of the thermal cyclopropanation, sulfonyl imines of type **104** are shown to be valuable reagents in the synthesis of α-amino cyclopropane derivatives [44] (Scheme 33).



108 (88%) **109** (72%) **110** (73-88%)

Scheme 33 Structures of cyclopropanes **108–110**

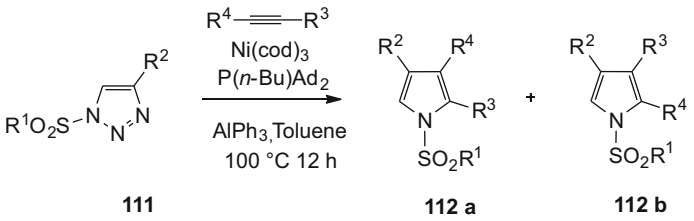
Thus, reduction of **104** with sodium borohydride provided an access to amino substituted cyclopropane **109**. On the other hand, the oxidation of **104** with sodium chlorite according to a Pinnick reaction affords sulfonyl amides **108**. It is worth noting that α-amino cyclopropane aldehydes can be easily converted to cyclopropane α-amino acids **110** by mild Pinnick oxidation of the aldehyde group to the acid, followed by the deprotection of the *N*-phthaloyl moiety by either direct hydrolysis or sodium borohydride reduction [44].

5 Metal Catalyzed Transformations of 1,2,3-Triazoles

Though ring transformations and rearrangements of 1,2,3-triazoles are known from the mid of last century, the use of metal catalysis is a recent trend in the development of 1,2,3-triazole chemistry. Starting from 2007 with reports from the Gevorgyan group and just afterwards by Fokin and Murakami, this new chemistry underwent a very fast evolution comparable to the exponential growth of the chemistry of 1,2,3-triazoles after introduction of the click-reaction concept by Sharpless in 2001. The short review and highlights were published in 2012 and 2013, respectively [47, 48]. Because many publications appeared in 2012 and especially in 2013, that were not included there, these do not cover all aspects of metal catalyzed denitrogenative transformation of 1,2,3-triazoles. This section includes a review of metal catalyzed transformation of 1,2,3-triazoles with focus on the new reports that were not covered in the previous reviews [47, 48]. The data are classified on the reaction type products.

5.1 Synthesis of Pyrroles

Pyrroles are known structural motifs in pharmaceutical agents including a number of natural products. Thus the development of new, efficient methods for their synthesis from readily accessible compounds remains an active field. The protocol of denitrogenative transannulation was recently used for the synthesis of monocyclic, functionalized, and fused pyrroles from easily available



111 **112 a** **112 b**

R^1 = Ar; R^2 = Ar, *n*-Hexyl; R^3, R^4 = *n*-Pr, Ph, Me, *i*-Pr, $SiMe_3$, Bpin, *n*-Bu

Scheme 34 Reaction of *N*-sulfonyl 1,2,3-triazoles **111** with alkynes

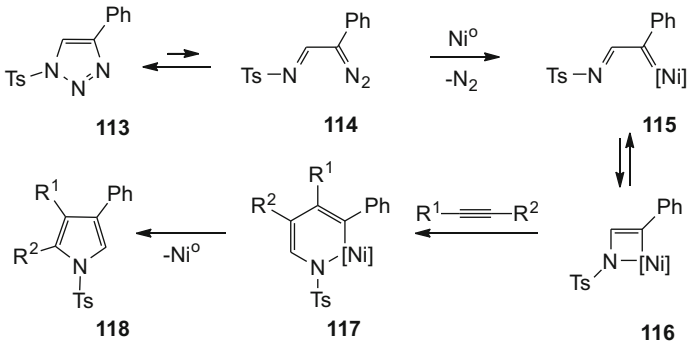
1-sulfonyl-1,2,3-triazoles, 1-(1,2,4-triazol-5-yl)-1,2,3-triazoles, and [1,2,3]-triazolo[1,5-a]pyridines [47–59].

The syntheses of monocyclic tetra-substituted and 1,2,4-trisubstituted-*N*-tosyl pyrroles by denitrogenative reaction of *N*-tosyl-1,2,3-triazoles **111** with nickel and rhodium catalysts were reported by the Murakami [49] and Gevorgyan [52] groups, respectively (Scheme 34). Murakami and co-workers have discovered that the reaction of *N*-sulfonyl-1,2,3-triazoles with [$Ni(cod)_2$] catalyst in the presence of bulky phosphine ligands and $AlPh_3$ is efficient for the transformation of 4-aryl-1,2,3-triazoles to tetra-substituted pyrroles after treatment with internal alkynes [49]. Symmetrical alkynes reacted with *N*-sulfonyl triazoles **111** to afford pyrroles **112** in good yields, except for the 3-*n*-hexyl derivative. Interestingly, the reaction with nonsymmetrically substituted 1,2-dialkynes generates nearly equal amounts of isomeric pyrroles **112a** and **112b**. Terminal alkynes were found not to enter to the reaction probably due to the facile self-oligomerization side reaction.

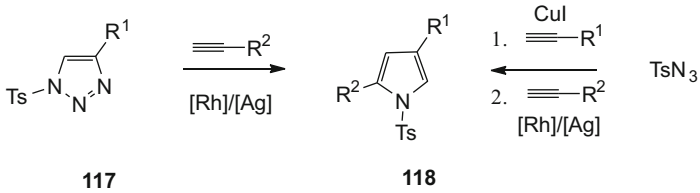
The mechanism of the reaction proposed by Murakami and co-workers [49] is outlined in Scheme 35. According to this report, the process starts from the ring opening of triazole ring **113** to form the isomeric diazo-imine form **114**. An equilibrium exists between ring and chain isomers which is shifted far in favor of the cyclic form. Nickel adds onto the diazo function which releases nitrogen to form a nickel carbenoid **115** that can be in an equilibrium in cyclic form **116**. The insertion of an alkyne into the Ni–C bond of the latter leads to a six-membered nickelacycle **117**. Reductive elimination of Ni^0 furnishes the final product **118**.

Gevorgyan et al. have discovered that involvement of terminal alkynes required the use of a $Rh_2(oct)_4/AgOCOCF_3$ binary system containing both a rhodium catalyst and a Lewis acid, and the usage of nonpolar solvents such as toluene or hexane, under 70°C [50] (Scheme 36).

These conditions have shown to be efficient for ring transformation reactions of a wide range of *N*-tosyl-1,2,3-triazoles with various electron-rich aryl alkenes (Scheme 36). The authors managed to combine the synthesis of triazole **117** from alkyne and copper iodide and denitrogenative reaction of *N*-tosyl-1,2,3-triazole **117** to a three component semi-one-pot protocol for pyrrole **118**.

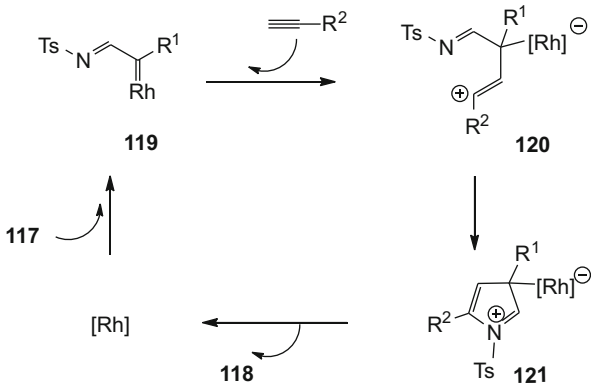


Scheme 35 Proposed mechanism of the nickel-catalyzed denitrogenative transannulation of triazole **113** with internal alkynes



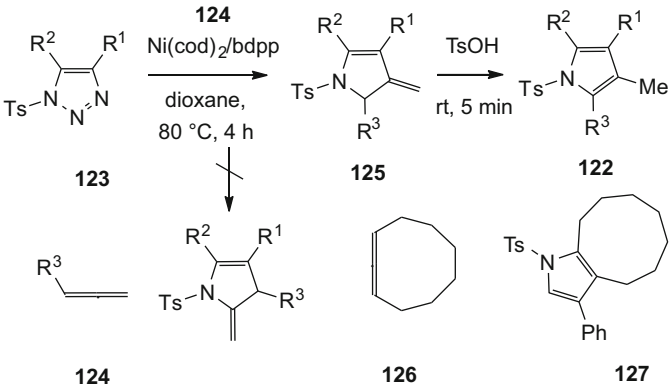
R^1 = Ar, Alk, CO_2Et, H; R^2 = electron rich Ar and cyclohexen-1-yl

Scheme 36 Reactions of tosyl azide and *N*-sulfonyl-1,2,3-triazoles with terminal alkynes



Scheme 37 Proposed mechanism of transformation **117** to **118**

Three pathways were proposed [50] to explain the results of the denitrogenative transformation of triazole **117** to pyrrole **118** (Scheme 37). Based on an experiment with deuterated *o*-tolyl acetylene the authors [50] concluded that the most plausible

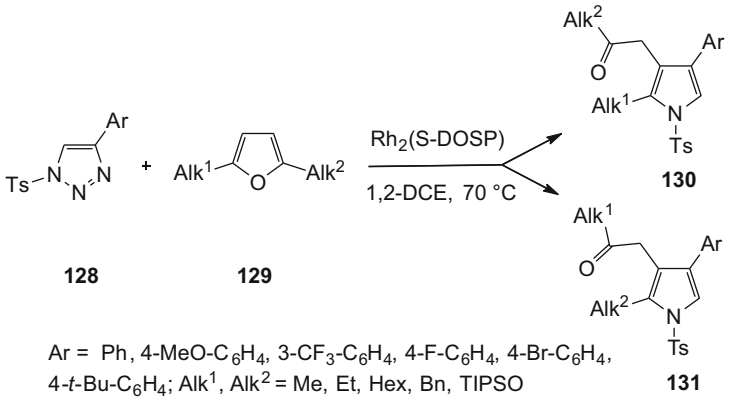


Scheme 38 Synthesis of poly-substituted pyrroles

mechanism includes the primary formation of Rh-iminocarbene **119** upon treatment of triazole **117** with $Rh_2(oct)_4$ followed by direct nucleophilic attack of the terminal alkyne to the latter to produce ylide **120**. In its turn the ylide **120** forms upon cyclization the zwitterionic species **121**. Elimination of rhodium catalyst from the latter affords the final product **118** (Scheme 37).

Murakami and co-workers have been found that monocyclic polysubstituted pyrroles **122** can be efficiently prepared by regiocontrolled reaction of 1-sulfonyl-1,2,3-triazoles **123** and allenes **124** [51] (Scheme 38).

The same authors have also shown that the reaction takes place via initially formed isopyrroles **125**. The latter generally are less stable and rearrange to pyrroles **122**. Normally a mixture of isomeric pyrroles **122** and **125** is formed in this reaction. Interestingly, the reaction of 5-phenyl-1-tosyl-1,2,3-triazole **123** (R^1=Ph, R^2=H) with cyclonona-1,2-diene **126** produces only pyrrole **127**. The addition of *p*-toluenesulfonic acid is shown to be an efficient tool to accelerate the double bond isomerization [49]. This operation together with a nickel(0) catalyst was included to form a general protocol to prepare polysubstituted pyrroles by reaction of *N*-sulfonyl-1,2,3-triazoles **123** with allenes **124**. The authors have examined the generality of this reaction and have shown that various 5- and 4-substituted 1,2,3-triazoles **123** react well with undeca-1,2-diene to form the corresponding pyrroles **122** bearing both electron-withdrawing and -donating substituents at position 4 and 5 of the ring, respectively. Furthermore, 1,4,5-trisubstituted -1,2,3-triazoles **123** are shown to react with undeca-1,2-diene **124** to furnish tetrasubstituted pyrroles **122**. They have also shown that monosubstituted allenes give corresponding pyrroles in good yields. Apart from 1,3-disubstituted cyclic allene **126** that furnishes fused pyrrole **127**, other 1,3-disubstituted allenes are found to be unreactive.



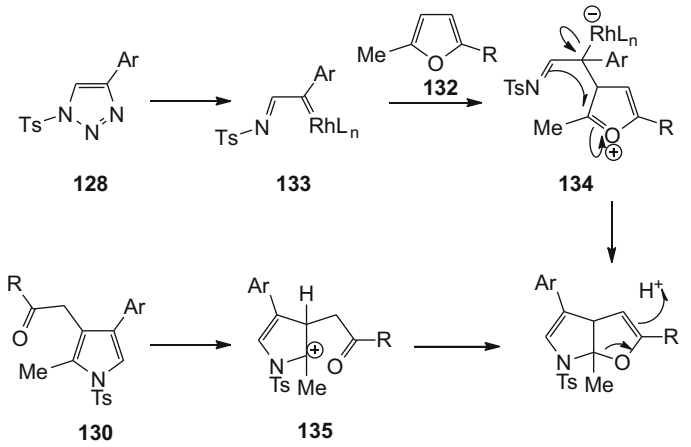
Scheme 39 Reaction of *N*-tosyl-1,2,3-triazoles with furans

An interesting example for the reaction of 1-tosyltriazoles **128** with the double bond of a α-excessive furan ring, leading to formation of pyrroles, was found by Davies with co-workers [52] (Scheme 39). In fact, the discovered reaction represents a novel convergent transformation. It has been shown that various 4-aryl-*N*-tosyl-triazoles **128** readily react with 2,5-dimethylfurans **129** in the presence of a rhodium catalyst to give pyrroles **130** in good yields. 2,5-Dialkylsubstituted furans **129** are shown to be excellent substrates for the pyrrole synthesis [52]. However, in many instances for asymmetrically 2,5-disubstituted furans mixtures of regioisomers **130** and **131** are formed, lowering the synthetic potential of the discovered reaction.

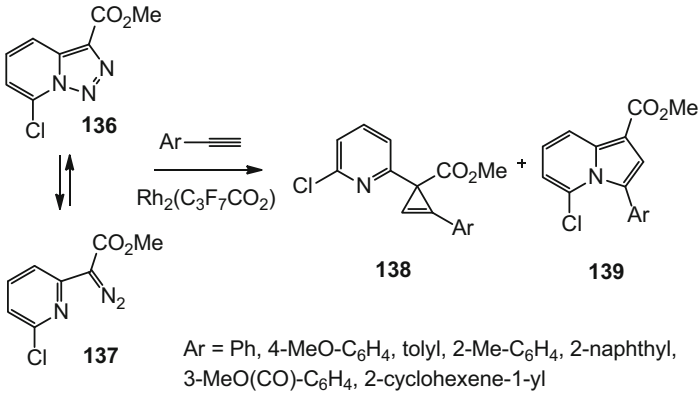
A plausible mechanism for the formation of pyrroles **130** is provided in Scheme 40.

The rhodium carbene complex **133**, formed from triazoles **128** after treatment with rhodium catalyst, attacks the C-3 carbon of furan to generate a cationic intermediate **134**. The latter undergoes cyclization, alternative ring opening, and aromatization of **135** due to deprotonation to afford final product **130**.

Based on the data for the equilibrium in solution between 7-chloro-pyrido [1,2-c]-1,2,3-triazoles **136** and 2-pyridyl diazoalkanes **137** and for experiments with triethylsilane, Gevorgyan and co-workers indicated that 7-halo-substituted pyridotriazoles **136** can serve as convenient precursors of Rh carbenoids [51] (Scheme 41). The reaction of 7-chloro-1,2,3-triazolo[1,5-a]pyridines **136** with arylacetylenes is shown to afford a mixture of 3-pyridyl cyclopropene **138** and indolizine **139**. The ratio of products formed is strongly dependent on the kind of rhodium catalyst. The use of rhodium acetate gives 68% of cyclopropene **138** and 28% of indolizine **139**. Remarkably, the use of rhodium(II) heptafluorobutyrate in the reaction of pyridotriazole **136** with a series of aryl and alkenyl alkynes proceeds chemoselectively to produce cyclopropenes **138** in good yields. Cyclopropenes **138** are still accompanied by 5–10% of indolizines **139**, which are easily separable by column chromatography [53].



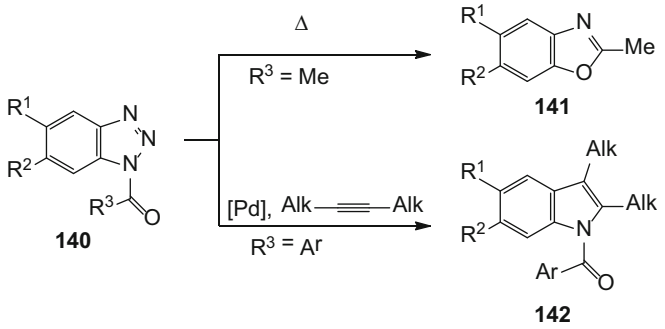
Scheme 40 Plausible mechanism for pyrrole formation from reaction of *N*-tosyltriazoles **128** with furans



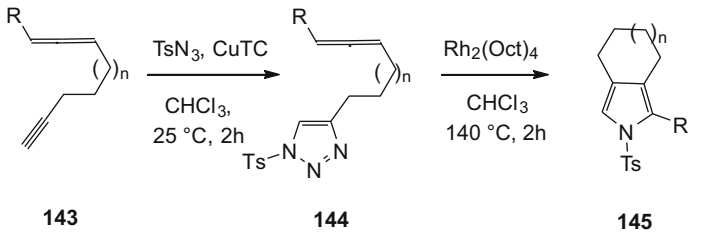
Scheme 41 Reaction of pyridotriazoles with terminal alkynes

In contrast to the thermal reaction of 1-acyl-1,2,3-triazoles (R^3=Me) where the formation of an oxazole ring takes place [41] to furnish compound **141**, the indolization of *N*-aroylbenzotriazoles occurs in the presence of palladium catalyst to form *N*-acylindoles **142** [54] (Scheme 42).

Denitrogenative reaction of *N*-tosyl-1,2,3-triazoles of type **144**, that were prepared by the copper(I) thiophene-2-carboxylate catalyzed Huisgen cycloaddition of acetylene **143** with TsN_3, was applied by Schultz and Sarprong [55] for the synthesis of a series of 3,4-fused pyrroles **145** (Scheme 43). Pyrroles related to **145** have found practical application in the synthesis of dipyrromethene ligands and of the related natural product cycloprodigiosin [55]. Reaction of *N*-tosyl triazole **144** bearing the allene moiety as part of the molecule with $Rh_2(oct)_4$ in chloroform at



Scheme 42 Transformation of *N*-acylbenzo[*d*]triazoles to indoles



R = 2-naphthyl, Ph, 4-F-C_6H_4, 3,4-diF-C_6H_3, 2-MeO-C_6H_4, Alk, n = 0, 1

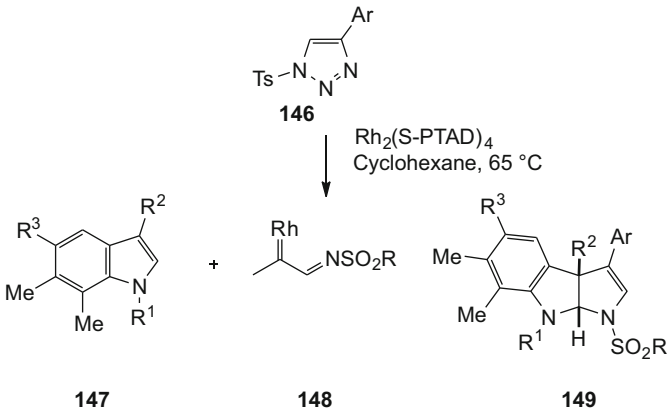
Scheme 43 Synthesis of fused pyrroles **145**

140°C, using microwave enhancement, furnishes 2,3,4-substituted pyrrole **145** (R=Ph) in 80% yield. Since both reactions outlined in the Scheme 43 were conducted in chloroform, the authors [50] devised a one-pot protocol to convert **143** to **145** in 77% overall yield. This one-pot method was applied to prepare a series of fused pyrroles **145**, with various groups from aryl to alkyl in position 2 of the pyrrole ring, in rather good yields.

Shi and Gevorgyan have found that a similar type of compounds can be prepared by intramolecular Rh-catalyzed reaction of alkynyltriazoles. Most likely, the key step of the process involves a Rh-carbene-alkyne metathesis step [56].

The double bond of indoles **147** is shown to react with 1-mesyl-1,2,3-triazoles **146** via formal [3+2] cycloaddition reaction with iminocarbenoid **148** formed from **146** to provide an access to pyrroloindolines **149** [57] (Scheme 44). It is worth noting that this class of compounds is related to the pyrroloindoline alkaloids, that are an important subclass of alkaloid natural products.

Sprangler and Davies extended their research to a catalytic asymmetric synthetic method towards pyrroloindolines [57]. They have found that the use of cyclohexane as a solvent and Rh_2(S-PTAD)$_4$ as a catalyst is optimal for the transformation to form pyrroloindolizines **149** in good yields and high levels of enantioselectivity. The scope of the reaction was explored with respect to the triazole **146** and indole



Ar = Ph, 4-MeO-C_6H_4, 4-Et-C_6H_4, 4-CF_3-C_6H_4, 4-Br-C_6H_4,Tolyl, 3-F-C_6H_4, 3-MeO-C_6H_4, 4-MeO(CO)-C_6H_4, 2-Cyclohexene-1-yl; R^1 = H, Me, Allyl; R^2 = Alk, Ph; R^3 = Br, F, Me, MeO

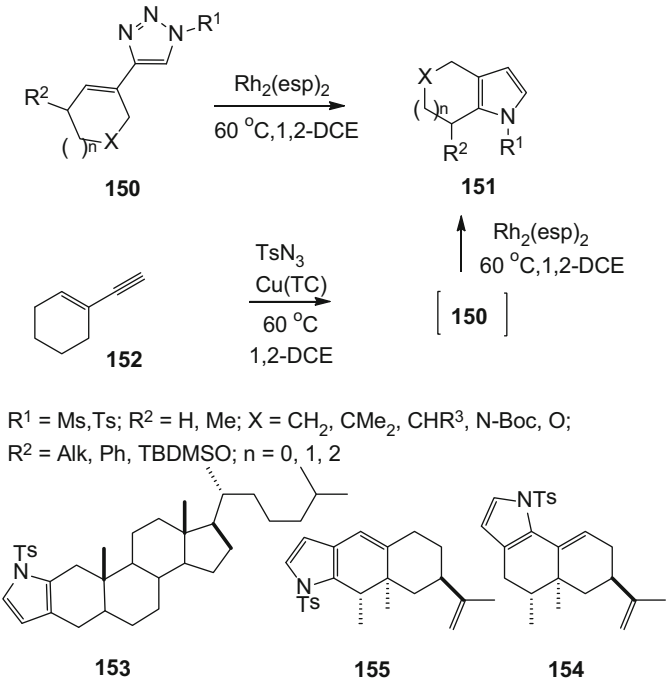
Scheme 44 Cycloaddition of azavinyl carbenoids **148** with indoles **147**

147 coupling partners (Scheme 44). Various 4-aryl substituted triazoles **146** and 3,5,6,7-monosubstituted indoles **147** are compatible with the reaction. However, the reaction was found to be sensitive to the nature of the 1-substituents in both the triazole and the benzimidazole rings: while the 1-mesyl-, ethanesulfonyl-1,2,3-triazoles **146** and 1-H, Me and allylindoles **147** provide the corresponding pyrroloindolines **149** in rather good yields and enantioselectivity, it fails for tosyl triazoles and indoles, bearing bulky and electron-withdrawing substituents at position 1 [57].

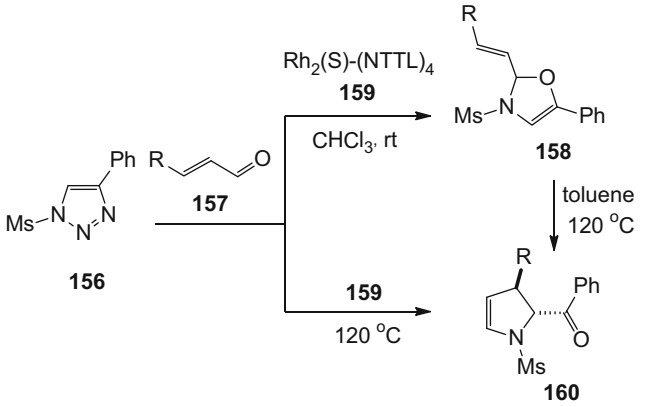
During the course of these studies, Davies and co-workers discovered that 4-cyclohexenyl-1-(sulfonyl)-1,2,3-triazoles **150** undergo a novel rhodium catalyzed intramolecular transannulation reaction to 1,2-annelated pyrroles **151** [58] (Scheme 45).

After screening several rhodium catalysts, it was found that $Rh_2(esp)_2$ is optimal for this transformation. The data in this report [56] allow one to conclude that the reaction is quite general. Changing the size of the cyclohexene ring, and introducing substituents to both the cyclohexene and triazole rings does not change the direction of the reaction and furnishes 1,2-fused pyrroles in good to excellent yields. Because both the synthesis of triazoles **150** and the annulation reaction can readily take place in the same solvents, the Davies group managed to realize an efficient one-pot protocol for the synthesis of bicyclic triazoles **151** in good yields (Scheme 45). The utility of the method was demonstrated by the synthesis of pyrroles **153–155** fused to the steroid derivatives of 5-cholestan-3-one and nootkatone.

The rhodium catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles **156** with alkenes is a method for the synthesis of *N*-mesyl 2,3-dihydropyrroles **160** that are valuable structural fragments of various biologically active compounds. Thus, Murakami

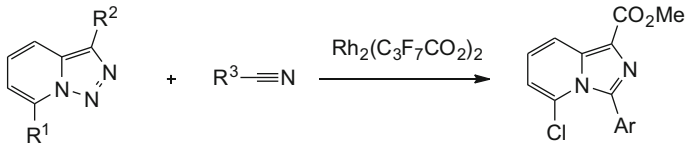


Scheme 45 Synthesis of fused pyrroles



Scheme 46 Transformation of *N*-mesyl-1,2,3-triazoles **156**

and colleagues have found that the reaction of *N*-mesyl-4-phenyl-1,2,3-triazole **156** with α,β-unsaturated aldehydes **157** produces trans-2,3-disubstituted dihydropyrroles **160** in good yields. Interestingly, the reaction has been carried out at room temperature, affording *N*-Ms dihydrooxazoles **158**, which in turn rearrange to dihydropyrroles **160** in toluene at 120°C (Scheme 46) [59].



161 **162**

R^1 = Cl, Br, OMe; R^2 = CO_2Me, 4-CF_3-C_6H_4; R^3 = Ar, Alk, Alken-1-yl

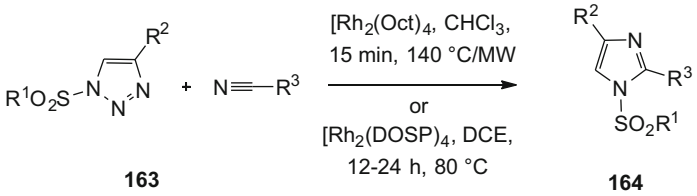
Scheme 47 Reaction of triazolopyridines **161** with nitriles

5.2 Syntheses of Imidazoles

Imidazoles are an important class of five-membered heterocycles found in a number of natural products and pharmaceutical compounds. Denitrogenative annulation reactions of pyrido-triazoles, 1-sulfonyl and 1,2,4-triazolyl-1,2,3-triazoles have recently been used for the synthesis of substituted monocyclic and fused imidazoles, as well as conjugates with other heterocyclic compounds [53, 60–63]. Together with the synthesis of pyrroles **139** described above, the Gevorgyan group developed the ring transformation reaction of triazolopyridines **161** to imidazo-pyridines **162** [53] (Scheme 47). Firstly, triazolopyridines **161** react smoothly with aryl, alkyl, and alkenyl nitriles in the presence of rhodium tetraacetate in a regioselective manner to furnish imidazo[1,5-a]pyridines **162** in good to excellent yields. The presence of electron-withdrawing groups at position 3 of triazole **161** and a halo- or methoxy group at position 7 is required for the reaction to take place.

1-Sulfonyl-1,2,3-triazoles **163** are also capable of reacting with various nitriles under treatment with rhodium catalyst to form 1,2,4-subsituted imidazoles **164** in high to excellent yields [60] (Scheme 48). Both conventional and microwave heating give the same yield of the final products. A series of rhodium catalysts was examined and both rhodium(II) octanoate and Rh_2(S-DOSP)$_4$ were found to be the best. The reaction is found to be general with respect to triazole and nitrile components. Similarly to the reaction of triazolopyridine **161**, the transformation of triazoles **163** is regioselective, forming only imidazole type products **164**.

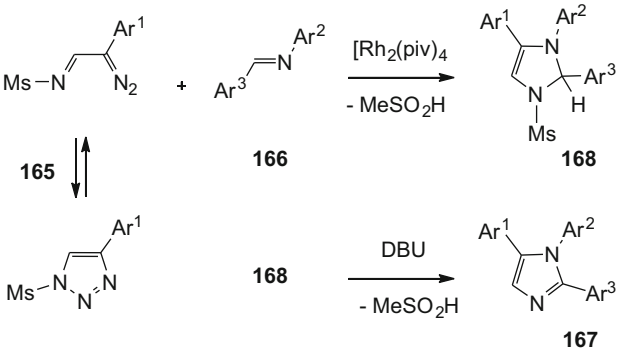
Fokin and co-workers have shown that the double bond of aldimines **166** can react with rhodium (II) azavinyl carbenes derived from *N*-mesyl triazoles **165** under heating at 120°C for 5–10 min with Rh_2(piv)$_4$ to form imidazole derivatives **167** in good yields (Scheme 49). Lowering the temperature to 40°C allowed them to isolate the intermediate imidazoline **168** that was thermally unstable and underwent elimination of sulfinic acid, restoring the aromaticity of the imidazole ring [61]. After the triazole was consumed, 1,8-diazabicycloundec-7-ene (DBU) was added and heating continued for an extra minute to enhance the final aromatization of the product formed. The reaction proceeds smoothly with different 4-aryl-1,2,3-triazoles and aldimines of aromatic aldehydes and anilines.



163 **164**

R^1 = Ph, Tol, 4-Br-FC_6H_4, 4-Me-OC_6H_4, 2,3,4-tri-*i-Pr*; R^2 = Ar, Bn, R^3 = Ar, Alk, 2-cyclohexenyl-1, phenanthrene-1-yl, cyclohepta-1,3,5-triene-7-yl

Scheme 48 Synthesis of *N*-sulfonyl imidazoles



165 **166** **168** **168** **167**

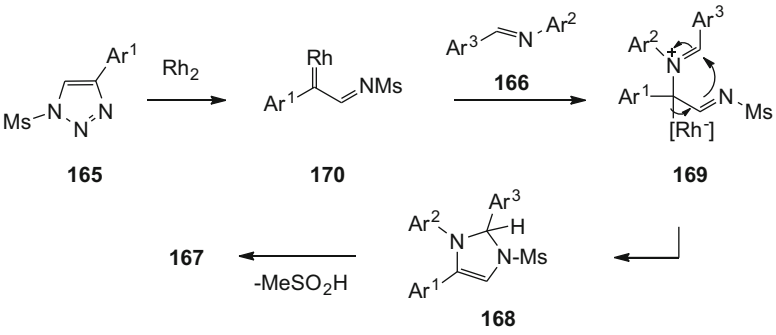
R^1, R^2, R^3 = Ph, Tol, 4-Br-C_6H_4, 4-MeO-C_6H_4, 4-CF_3-C_6H_4, 4-F-C_6H_4, 4-CN-C_6H_4, 2-Naphthyl

Scheme 49 Reactions of *N*-mesyl-1,2,3-triazoles **165** with aldimines **166**

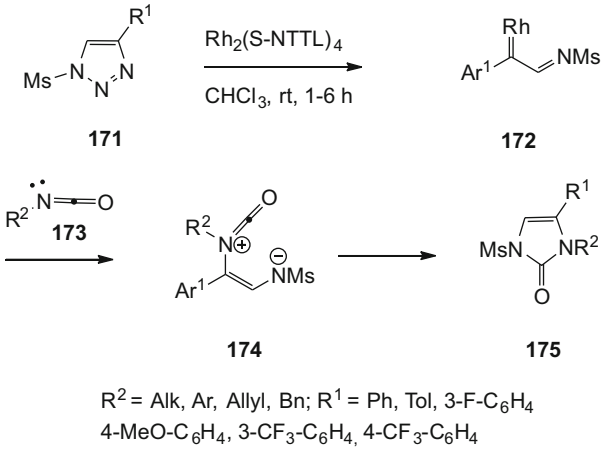
The mechanism of the reaction is presented in Scheme 50. Because imidazoline **168** has been identified, evidence is indicating that the mechanism involves an interaction of the aldimine group with the carbene center of **170** to form a zwitterion **169** which undergoes cyclization to intermediate **168**. The latter, after elimination of sulfinic acid affords the final product **167**.

The imine double bond of isocyanates **173** is shown to react with 1-sulfonyl-1,2,3-triazoles **171** via formal [3+2] cycloaddition reaction to azavinyl carbene **172**, formed from **171**, to provide an access to *N*-sulfonyl imidazolones **175** [62].

Fokin and co-workers have found that the use of *N*-mesyl-1,2,3-triazoles **171** and Rh_2(S-NTTL)$_4$ gives an optimal tool to generate rhodium carbenes suitable to react smoothly and selectively with the C=N bond of various isocyanates **173** to form a variety of 1,3,4-substituted imidazolones **175** in very good yields (Scheme 51). Remarkably, allyl isocyanate **173** (R=allyl) reacts with complete chemoselectivity, favoring ring transformation reaction over cyclopropanation of the C=C double bond of the allyl group. The reaction was found as general with



Scheme 50 The plausible mechanism of transformation of **165**–**167**

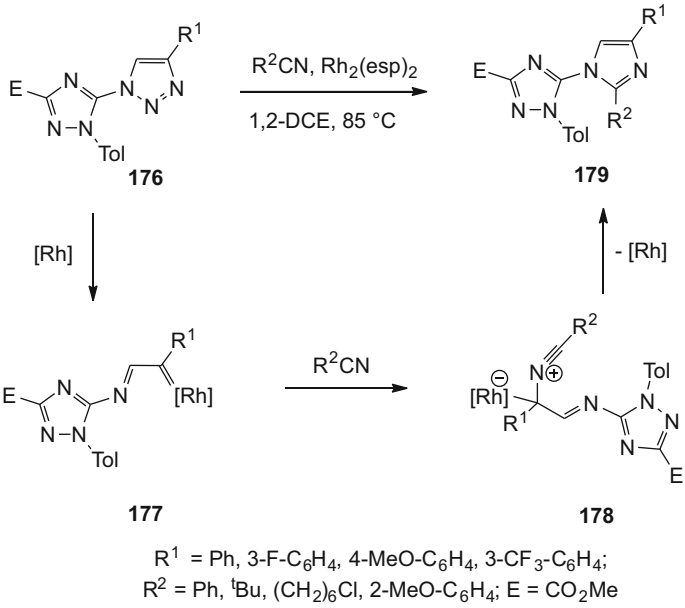


Scheme 51 Reactions of *N*-mesyl-1,2,3-triazoles with isocyanates

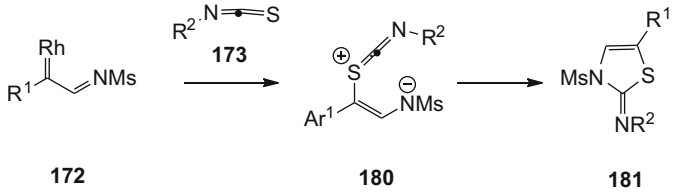
respect to substituents R^1 and R^2 in the 1,2,3-triazole and isocyanate molecules, respectively. A plausible mechanism includes the attack of the lone pair of isocyanate on the azavinyl carbene to generate a zwitterionic intermediate **174**. The latter cyclizes to an imidazole ring via heteroelectrocyclization [2] to form the final product.

Zibinsky and Fokin discovered that an electron-deficient heterocycle at the position 1 of the 1,2,3-triazole ring, similarly to sulfonyl groups, can facilitate its conversion to carbenes [63]. Thus, reaction of 1,2,4-triazolyl-1,2,3-triazoles **176** with aromatic and aliphatic nitriles in the presence of $Rh_2(esp)_2$ in 1,2-DCE at 85°C provided conjugates of 1,2,4-triazole and imidazole rings **179** in 68–85% yields (Scheme 52).

This reaction is similar to the reaction of *N*-sulfonyl-1,2,3-triazoles (see above) and most likely starts with the initial attack of the nitrile nitrogen onto the electrophilic carbene center of **177** to form a zwitterionic product **178**. Subsequent cyclization of the latter to an imidazole **179** finalizes the process.



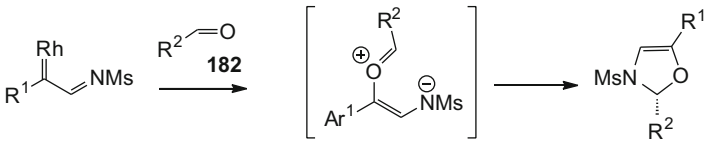
Scheme 52 Plausible mechanism of transformation of *N*-triazolyl-1,2,3-triazoles **176** to imidazoles **179**



Scheme 53 Synthesis of thiazole-2-imines **181**

5.3 Thiazoles and Oxazoles

In contrast to isocyanates, reaction of rhodium azavinylcarbenes **172** with isothiocyanates **173** is directed to the sulfur rather than the nitrogen atom of isocyanate. The generated thiocarbonyl ylide intermediate **180** undergoes cyclization to afford 2-iminothiazoles **181** (Scheme 53). Fokin and co-workers have found that the optimal conditions for the reaction of 1-sulfonyl-1,2,3-triazoles with isocyanates (vide supra) are perfectly applicable to the reaction with isothiocyanates to furnish a variety of 1-mesyl-4- and 2-iminosubstituted-thiazoles **181** in good yields



172 183 184

R^1 = Ph, Tol, 4-CF_3-C_6H_4, 4-MeO-C_6H_4, 3-thienyl, 2-$MeOC_6H_4$, alkenyl, naphtyl, R^2 = Ph, 4-MeO-C_6H_4, 4-CN-C_6H_4, 2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-MeOC(O)-C_6H_4, 4-MeC(O)-C_6H_4, Alk, alkenyl, cycloalkyl, cycloalkenyl

Scheme 54 Synthesis of homochiral oxazolines **184**

[62]. Exceptionally good results were achieved for the reaction of isothiocyanates bearing electron-withdrawing substituents.

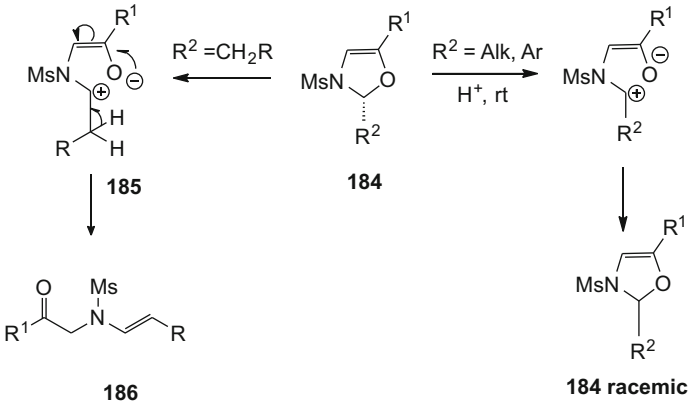
Conversely, reaction of **171** having electron-donating substituents, including both aryls and alkyls, proceeds only reluctantly; the conversion of the process is low and the yields of the thiazoles are poor. Remarkably, the reaction tolerates a large variety of 4-substituted 1,2,3-triazoles **171** as shown in Scheme 54 [62].

Carbonyl ylides **183**, generated from rhodium catalyzed decomposition of diazocarbonyl compounds with ketones are prone to react with ketones via intermolecular 1,3-dipolar cycloaddition. However, azavinylcarbenes **172** react with aldehydes **182** to generate rhodium-zwitterionic adducts that undergo an intramolecular cyclization to form homochiral 3-sulfonyl-4-oxazolines **184** in excellent yields and with high enantioselectivity [61]. Attempts of the authors [61] to trap the zwitterion **183** with reactive dipolarophiles were unsuccessful.

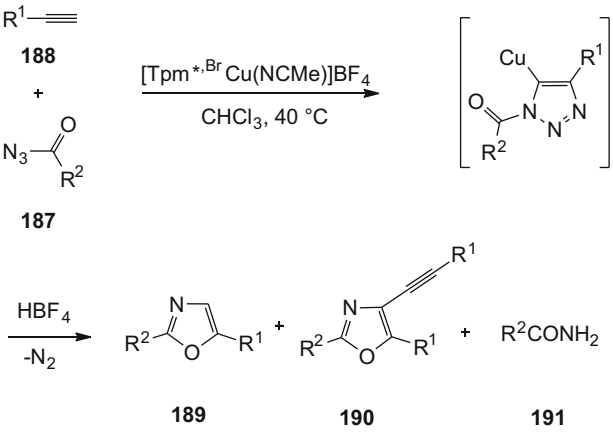
A variety of aromatic and aliphatic aldehydes readily react with 1-mesyl-4-aryl-1,2,3-triazoles **171**. An optimal enantioselectivity is obtained in the reaction of 1-mesyl-1,2,3-triazoles with aldehydes performed at ambient temperature in chloroform with use of $[Rh_2\{(S)\text{-NTTL}\}_4]$ catalyst. A prolonged reaction time is shown to lower the enantiomeric purity of most products. This was explained by the reversible ring opening of products **184** due to the lability of the C–O bond (Scheme 55, right part).

Although various 4-aryl substituted compounds **171** (Scheme 55) react with aldehydes to provide oxazolines **184** in excellent yields and enantioselectivity, the alkyl-substituted triazoles **171** failed to provide oxazoline products. It was explained by the facile 1,2-hydride shift of the carbene **185** to form enamines **186**.

The formation of an aromatic oxazole ring occurs in the reaction of terminal alkynes with carbonyl azides in the presence of a copper catalyst. Thus Cano et al. have shown that carbonyl azides **187** react with acetylenes **188** to form a mixture of mainly oxazoles **189**, and smaller amounts of oxazol-5-yl acetylenes **190** and amides **191** (Scheme 56). The formation of these products was explained by the primary formation of a copper-triazole that undergoes evolution of dinitrogen to form the final products via a multistep process [64].



Scheme 55 Isomerization of 4-oxazolines

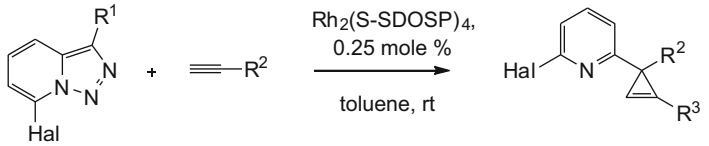


Scheme 56 Synthesis and transformation of *N*-carbonyltriazoles

5.4 Cyclopropenes and Cyclopropanes

In contrast to the reaction of *N*-sulfonyl-1,2,3-triazoles with acetylenes, where the formation of pyrroles was observed (see above) ring transformation of 1,2,3-triazolo[1,2-a]pyridines **192** leads in general to a mixture of pyridyl-cyclopropenes and indoles [53, 65]. V. Gevorgyan and colleagues have found that the use of Rh_2(S-DOSP)$_2$ in the reaction of triazolo-pyridines **192** with acetylenes allowed to selectively prepare a variety of pyridyl-cyclopropenes **193** in good yields (Scheme 57).

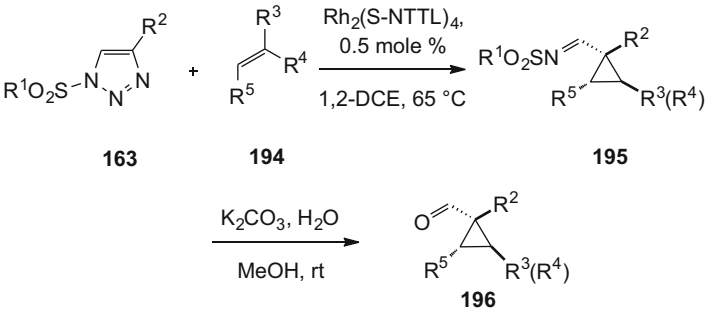
Triazoles **192**, bearing both electron-withdrawing and electron-donating aryl substituents at C-3, are shown to react regioselectively with various alkyl-, aryl-, and alkenyl-containing acetylenes [65].



192 **193**

Hal = Cl, Br; R^1 = Ph, 4-MeO-C_6H_4 , 4-E-C_6H_4, 3-E-C_6H_4, 4-CF_3-C_6H_4; R^2 = Ph, 4-MeO-C_6H_4, 4-E-C_6H_4 ,4-Me-C_6H_4 , *n*-butyl, $(CH_2)_3Cl$; E = COOMe

Scheme 57 Synthesis of cyclopropenes **193**

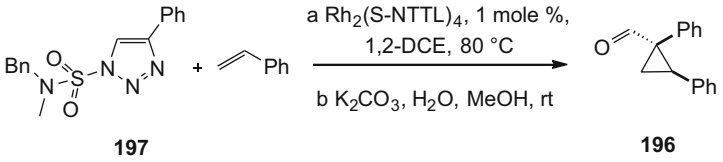


163 **194** **195**

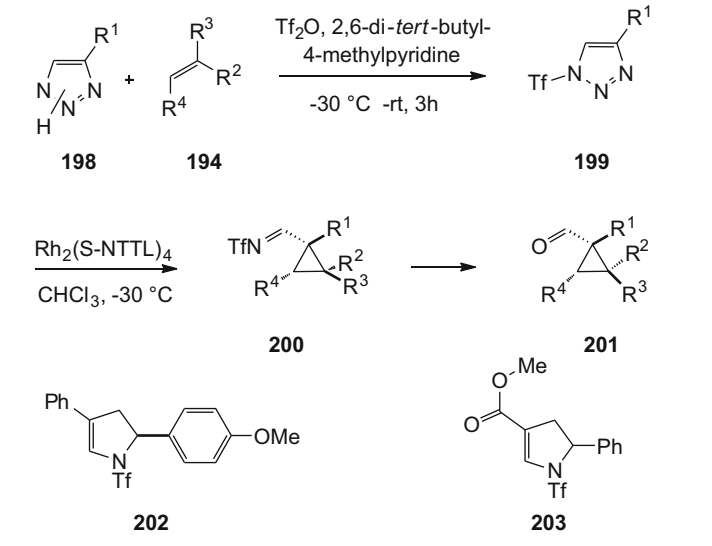
196

Scheme 58 Reactions of *N*-sulfonyl-1,2,3-triazoles with alkenes

The Gevorgyan and Fokin groups reported the formation of 1,2-diphenyl-cyclopropane-1-carbaldehyde **196** when *N*-tosyl-4-phenyl-1,2,3-triazole **163** was reacted with styrene in the presence of rhodium tetra-octanoate [60] (Scheme 58). A careful study for the reaction of 1-sulfonyl-1,2,3-triazoles **163** with a variety of alkenes **194** in the presence of various chiral Rh_2 complexes was made by the Fokin group [66]. The resulting sulfonyl imines **195** are not stable and were smoothly transformed into the corresponding aldehydes **196** by treatment with potassium carbonate in wet methanol. All catalysts used, namely Rh_2(S-DOSP)$_4$, Rh_2(S-PPTL)$_4$, Rh_2(S-PTAD)$_4$, and Rh_2(S-NTTL)$_4$ allowed to prepare target aldehydes **196** in very good yields, mainly with good trans diastereoselectivity. The enantioselectivity is found to depend on the nature of both the catalyst and sulfonyl group. The highest values of enantioselectivity (91-99%) were found in the reaction of 1-alkylsulfonyl-1,2,3-triazoles **163** (R^1=Me-, *n*-C_8H_{17}, *i*-Pr). Interestingly, the reaction of **163** (R^1=*i*-Pr, R^2=Ph) with Rh_2(S-DOSP)$_4$ provides the opposite enantiomer, though with very low (*ee* = <16%) enantioselectivity. The study of the scope of the reaction with respect to the alkene has shown that a broad range of substituted styrenes took part in the reaction to afford aldehydes **196** in good yield and high enantioselectivity. 1-Mesyl-1,2,3-triazoles **171** with both electron-rich and electron-deficient substituents at position 4 smoothly produced 1-mesylimino-1-phenylcyclopropane **196** with excellent regioselectivity.



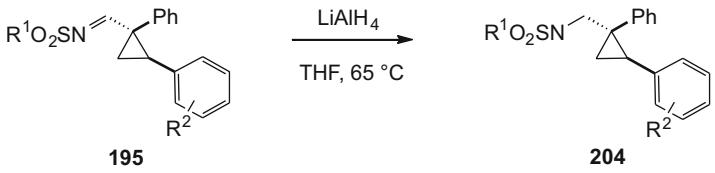
Scheme 59 Reaction of sulfamoyl triazole **197** with alkenes



Scheme 60 Reaction of *N*-triflyl 1,2,3-triazoles with alkenes

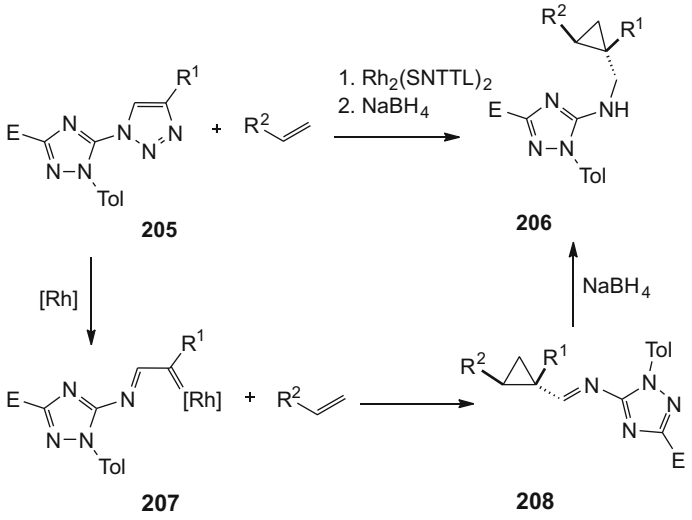
Fokin and co-workers have shown that aldehyde **196** (R^5=H, R^2=R^3=Ph) can be also prepared by an alternative way by reaction of 4-Ph-1-(1,2,4-triazol-5-yl)-1,2,3-triazole **176** (its reactions with nitriles were described above) with styrene, providing a new approach to cyclopropane-4-carboxaldehydes [60]. Furthermore, this compound **196** can also be prepared from sulfamoyl triazole **197** by reaction with styrene in the presence of Rh_2(S-NTTL)$_4$ followed by hydrolysis with potassium carbonate in wet methanol [67] (Scheme 59).

Very reactive 1-triflyl-1,2,3-triazoles **199** that were prepared by reaction of non-substituted 1,2,3-triazoles **198** with triflic anhydride in the presence of 2,6-ditert-butyl-4-methylpyridine were used in situ in reaction with olefins in highly enantio- and diastereoselective transformations. This protocol provided a convenient access to a series of homochiral cyclopropane carboxaldehydes **201** without use of sulfonyl azides (Scheme 60). Interestingly, reactions of electron-rich 4-methoxystyrene with 5-phenyl-1,2,3-triazole and 5-ethoxycarbonyl-1,2,3-triazole



R^1 = Me, R^2 = H (89%, 96% ee); R^1 = *i*-Pr, R^2 = 4-CF_3 (82%, 98% ee);
R^1 = *i*-Pr, R^2 = Cl (77%, 96% ee)

Scheme 61 Synthesis of chiral sulfonylamino homoaminocyclopropanes **204**



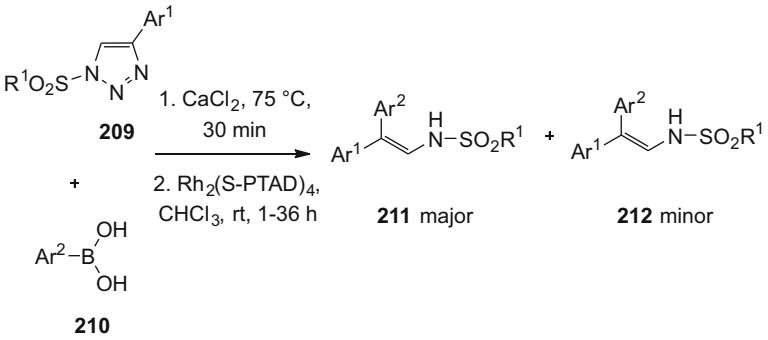
Scheme 62 Synthesis of chiral triazolylamino homoaminocyclopropanes **204**

with styrene proceeds by another path to give 2,3-dihydropyrroles **202** and **203** in 92% and 75% yields, respectively [68].

Because of the susceptibility of imines **195** towards hydrolysis, they were not isolated in pure form. However, fast treatment of the latter with $LiAlH_4$ allowed the Fokin group to provide an easy access to chiral homoaminocyclopropanes **204** (Scheme 61) [66].

Homoaminocyclopropanes **206**, bearing a 1,2,4-triazole substituent, were prepared by a one-pot synthesis from 1,2,4-triazolyl-1,2,3-triazoles after treatment with alkenes in the presence of Rh_2(S-NTTL)$_4$ followed by reduction of the intermediate imine **208** to give final products in good yields with high enantioselectivity. Interestingly, the use of Rh_2(S-DOSP)$_4$ and Rh_2(R-NTV)$_4$ in the reaction of **205** (R^1=R^2=Ph) furnishes the opposite enantiomer **206** in 38% and 66% *ee*, respectively [62] (Scheme 62).

Cyclopropanes bearing both carboxaldehyde and disubstituted amino groups **107** were successfully synthesized thermally, without a catalyst by cyclopropanation of



Scheme 63 Synthesis of *N*-sulfonyl enamines **211** and **212**

donor/acceptor carbenes in which the donor group is a protected amine functionality (see Sect. 2) [44].

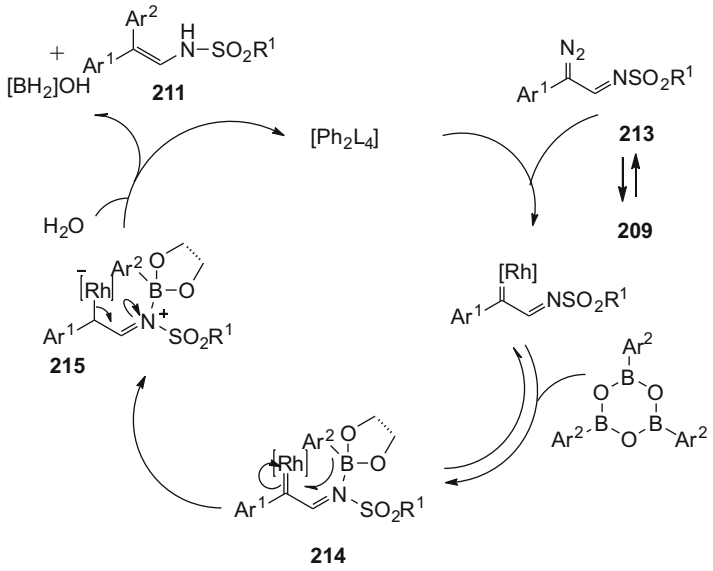
5.5 *Enamines, Enaminones, and Azadienes*

Enamines and enaminones are convenient chemical reagents and used in the syntheses of various classes of organic compounds. Therefore, development of new, efficient methods for their synthesis is always desirable. Fokin and co-workers demonstrated the mild, efficient rhodium and boronic acid catalyzed arylation of 1-sulfonyl-1,2,3-triazoles **209** providing a convenient access to *N*-sulfonyl enamines **211** [69]. They have found that triazoles **209** can react with boronic acids in the presence of various rhodium catalysts, optimally with $Rh_2(SPTAD)_4$, and $CaCl_2$ as an additive to form arylated enamines **211** with high selectivity as shown in Scheme 63.

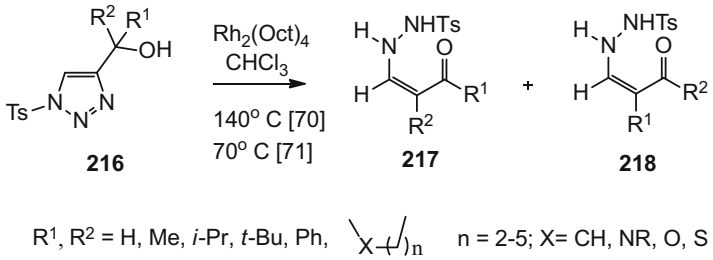
Although the arylation reaction takes place with high stereoselectivity, compounds **211** (R^1=Me, R^2=4-Me-, 4-CF_3, 3-CF_3; R^3=Ph, 3-NO_2, 3-CF_3, 4-Br-C_6H_4) were obtained contaminated with isomer **212** in 10 to 20% amount.

The formation of enamines **211** is proposed to start with the reaction of diazoimine **213**, existing in equilibrium with *N*-sulfonyl-1,2,3-triazole **209**, with a rhodium carboxylate catalyst as shown in the Scheme 64. It was proposed [69] that the lone pair of the sulfonyl imine nitrogen reversibly coordinates onto the empty orbital of the boron atom to generate complex **214**. Then, an irreversible facial-selective shift of the aryl group from boron to carbon occurs to furnish species **215**. The elimination of the rhodium catalyst and boronic acid most likely involves hydrolysis to finalize the process to form enamines **211**.

Remarkably, the Murakami and Fokin groups have published independently about the synthesis of a series of enaminones **217** accompanied by the minor isomer **218** by rhodium(II) catalyzed denitrogenative rearrangement starting from



Scheme 64 Plausible mechanism for arylation of **209**

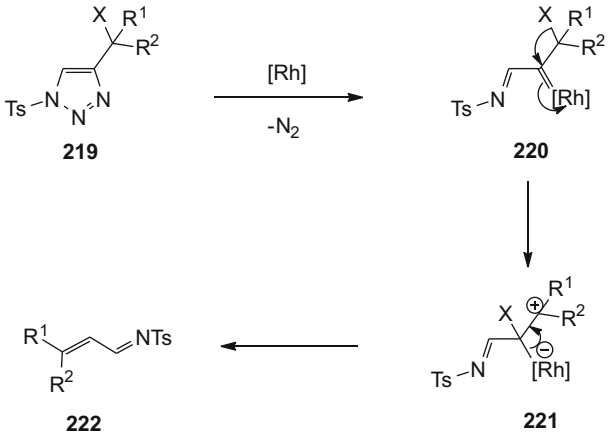


Scheme 65 Synthesis of enaminones **217** and **218**

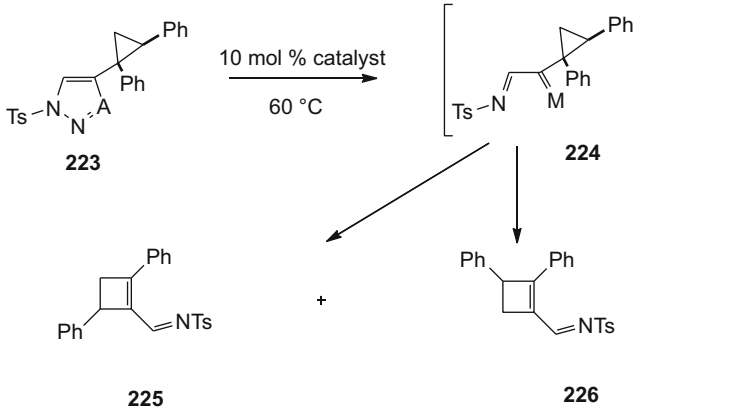
N-sulfonyl-4-hydroxymethyl-1,2,3-triazoles of type **216** [70, 71] (Scheme 65). Moreover, a discussion on the mechanistic details together with a careful analysis of the reaction details was highlighted by Gulevich and Gevorgyan [48]. Generally, the formation of two isomeric products **217** and **218** takes place depending on which substituent migrates to the carbenium center. The migrating ability of various groups was determined and based on these data it is possible to design the selective synthesis of required compounds.

If R^1 and R^2 groups are part of a ring system, intramolecular alkyl migration occurs to form cyclic enaminones **217** with an expansion of the former cycle. Carbocyclic structures were expanded by one carbon atom to form five- to eight-membered rings in 70–99% yields [70, 71].

The formation of 1-azadienes **222** took place in similar conditions with 4-alkyl-1-sulfonyl-1,2,3-triazoles **219** (Scheme 66). Remarkably, the migration of alkyl,



Scheme 66 Synthesis of 1-azadienes **222**

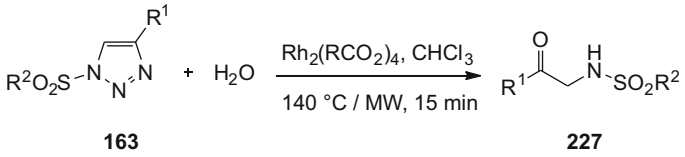


catalyst	$Rh(Oct)_4$	AgOTf	$Cu(MeCN)_4$
reaction time	1 h	4 h	8 h
ratio **225**/**226**	1.2 : 1	> 20 : 1	> 20 : 1
yield, %	82	76	50

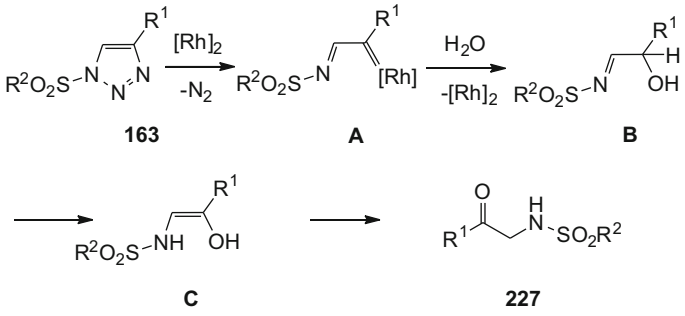
Scheme 67 Synthesis of cyclobutens **225** and **226**

acetoxy, and piperazine groups occurs to furnish azadienes **222** in very good yields [71].

The possibility to expand a cyclopropyl to a four-membered ring was demonstrated by Tang et al. by carrying out the reaction of 4-cyclopropyl-1-tosyl-1,2,3-triazoles **223** with metal catalysts at 60°C [72] (Scheme 67). Although $Rh_2(Oct)_4$ is the most reactive, AgOTf and $Cb(MeCN)_4PF_6$ catalysts provide higher selectivity for the formation of cyclobutene **225** over cyclobutene **226**.



Scheme 68 Synthesis of aminoketones **227**



Scheme 69 Plausible mechanism for the formation of aminoketones **227** from *N*-sulfonyl-1,2,3-triazoles and water

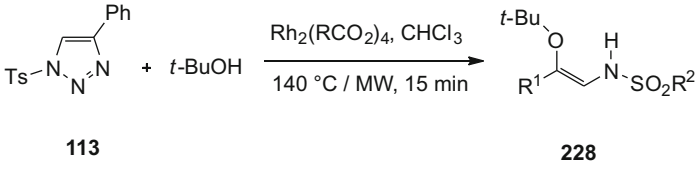
5.6 α-Aminoketones

The Murakami group examined various catalysts for the reaction of 4-aryl-1-(*N*-tosyl)-1,2,3-triazoles **163** and found that the insertion of the α-iminometal carbenoid into the O–H bond of water took place after use of rhodium catalyst to form α-aminoketones of type **227** (Scheme 68). In general, the reaction tolerates both a 4-substituent and substituents on the sulfonyl group. Various 4- and 1-sulfonyl triazoles **163** react with rhodium tetraacetate in chloroform under microwave conditions at 140°C to furnish aminoketones **227** in high yields [73].

A plausible mechanism is depicted in Scheme 69. Initially, a denitrogenative process occurs to generate α-imino rhodium carbenoid **A**. Insertion of **A** into the O–H bond of water leads to the formation of α-iminoalcohol **B** and release of rhodium catalyst. Finally, imine-enamine tautomerism followed by keto-enol tautomerism of enol **C** affords α-aminoketones **227**.

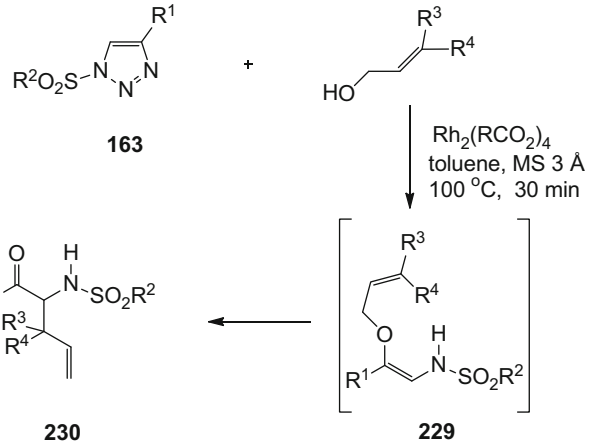
Interestingly, 4-phenyl-*N*-tosyl triazole **113** can also react with *tert*-butyl alcohol to form α-amino enol ether **228**, most probably via carbenoid insertion followed by imine-enamine tautomerization [73] (Scheme 70).

Conversely, reaction of compound **163** with allylic alcohol led to the formation of another type of products, α-allyl-α-aminoketones **230**. The process for formation of the latter most probably involves the Claisen rearrangement of initially formed allyl enol ether **229** (Scheme 71) [74].



113 228

Scheme 70 Synthesis of α-amino enol ether **228**



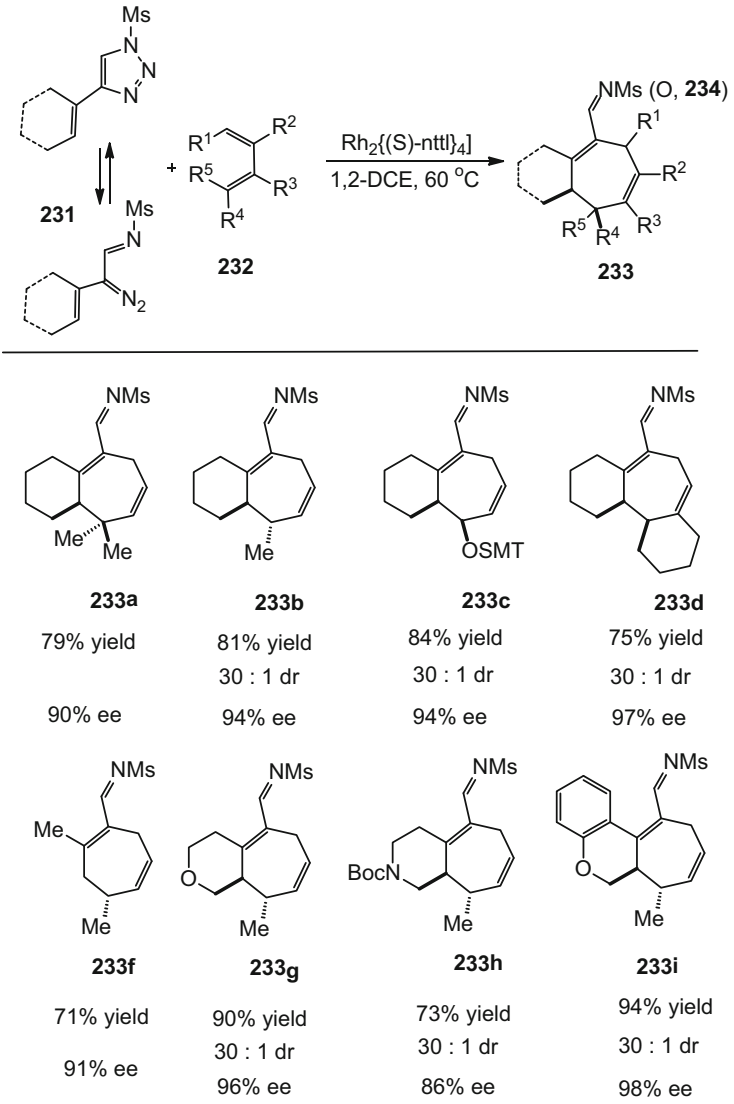
R^1 = Ph, 4-Me-C_6H_4 , 4-CF_3-C_6H_4, 4-MeO-C_6H_4, 4-$EtO_2C_6H_4$, 4-Ph-C_6H_4, 3-thienyl, 1-cyclohexenyl, Alkyl, H; R^2 = Me, Alkyl, 4-Br-C_6H_4, 4-MeO-C_6H_4, 4-Me-C_6H_4; R^3, R^4 = H, Me

Scheme 71 Synthesis of sulfonamide **230**

The Murakami group managed to combine the synthesis of α-allyl-α-amino ketones **230** with a process for the preparation of triazole **163** from terminal acetylenes and azides. Thus they introduced an extremely facile one-pot method to convert terminal alkynes into α-allyl-α-amino ketones through triazoles and vinyl ether intermediates.

5.7 Cycloheptadienes

There is a single paper recently published by the Davies group where formal [4+3] cycloaddition of dienes **231** to rhodium butadienyl aza carbenoid, generated from 4-alkenyl-1-*N*-sulfonyl-1,2,3-triazoles **231**, occurred to afford a series of 1,4-cycloheptadienes **233** in good yields and high enantio- and diastereoselectivity.



Scheme 72 The scope for the reaction of 4-alkenyl-1,2,3-triazoles **231** with dienes **232**

The reaction discovered is general for a broad range of both participants, 4-alkenyl-1-mesyl-1,2,3-triazoles **231** and 1,3-dienes **232**, enabling a stereoselective synthesis of polycyclic imines (Scheme 72) [75]. Furthermore, reaction of 4-alkenyl-1,2,3-triazoles **231** with dienes **230** followed by basic hydrolysis was shown to afford α,β-unsaturated aldehyde **233** in high yield with no observable epimerization.

5.8 Addendum

Syntheses of fused dihydropyrroles [76], sulfonamides [77], *N*-sulfonylamidines [78], and fused indoles [79] were published in the early beginning of 2014 based on the denitrogenative transformation of 1-*N*-sulfonyl-1,2,3-triazoles.

6 Conclusions

Both rearrangements and metal catalyzed transformations of 1,2,3-triazoles are possible because an equilibrium exists between diazoimine and 1,2,3-triazole isomeric forms. The intermediate diazoimine can be intramolecularly trapped by an electrophilic center to give other heterocyclic compounds. On the other hand, an attack of metal catalysts (Rh, Ru, Ni et al.) onto the diazo group of these diazoimines is accompanied by dinitrogen elimination to form an azavinyl carbenoid. The latter can be involved either in cycloaddition to a multiple bond or in an insertion into C–H, C–C, N–H, or O–H bonds to form a variety of heterocycles and other valuable organic compounds such as cyclopropanes, cyclopropenes, enamines, and diazadienes.

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Synthesis of 2*H*-1,2,3-Triazoles

Nataliya Belskaya, Julia Subbotina, and Svetlana Lesogorova

Abstract This chapter gives an overview of methods for the synthesis of NH- and N(2)-substituted 1,2,3-triazoles, their advantages, lacks, scope, and limitations. Moreover, it will give some insights on the reaction mechanisms and will explain how different conditions and structure substrates can influence the direction for reactions. An extensive analysis for the last 20 years (starting at 1990) of NH-1,2,3-triazoles chemistry is presented. Some older data with high importance are also included.

Keywords Alkylation · Arylation · Azide · Cycloaddition · Oxidative cyclization · Rearrangement · Regioselectivity

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Abbreviation

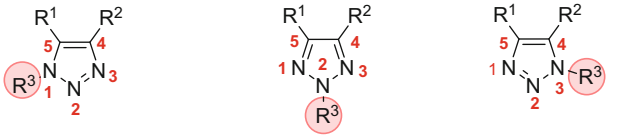
Ac	Acetyl
anhyd	Anhydrous
Ar	Aryl
B3LYP	Becke three-parameter, Lee-Yang-Parr
Bn	Benzyl
Bu	Butyl
cat	Catalyst
COSMO	Conductor-like Screening MOdel
Cy	Cyclohexyl
d	Day(s)
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DFT	Density Functional Theory
DIPA	Diisopropyl amine
DMA	Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppp	1,3-Bis(diphenylphosphino)propane
EDG	Electron-donating group
equiv	Equivalent(s)
EWG	Electron-withdrawing group
Fc	Ferrocenyl
GIAO	Gauge Independent Atomic Orbital
h	Hour(s)

Hex	Hexyl
HMBC	Heteronuclear Multiple Bond Coherence
i-Pr	*Iso*-propyl
KHMDS	Potassium hexamethyldisilazide potassium bis(trimethylsilyl)amide
LHMDS	Lithium hexamethyldisilazide lithium bis(trimethylsilyl)amide
min	Minute(s)
mol	Mole(s)
MW	Microwave irradiation
NICS	Nucleus Independent Chemical Shifts
NMP	*N*-methylpyridine
NOE	Nuclear Overhauser effect
Ph	Phenyl
Pr	Propyl
Pv	Pivaloyl
py	Pyridine
rt	Room temperature
SFC	Solvent free condition
SPS	Solid-phase synthesis
TBAF	Tetrabutylammonium fluoride
t-Bu	*Tert*-butyl
Tf	Trifluoromethanesulfonyl (triflyl)
THF	Tetrahydrofuran
THP	Tetrahydropyran-2-yl
TMS	Trimethylsilyl
Tp	Tetrazole
Ts	Tosyl 4-toluenesulfonyl
XRD	X-ray diffraction

1 Introduction

1,2,3-Triazoles can be divided into three groups depending on the position of substituent at nitrogen atom [1–6]:

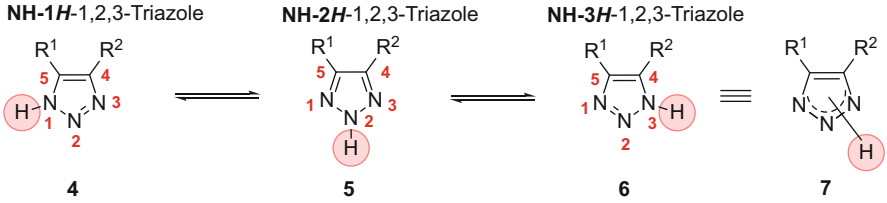
1*H*-1,2,3-Triazole **2*H*-1,2,3-Triazole** **3(1)*H*-1,2,3-Triazole**



1 **2** **3**

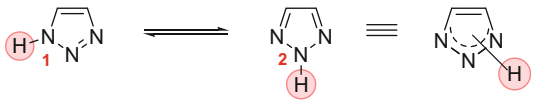
The third isomer **3**, which formally may be named as 3(1)*H*-1,2,3-triazole, was obtained in rare cases (see paragraph 4).

Triazoles **4–6** with unsubstituted ring nitrogen atom have special interest due to their importance for the synthesis of new derivatives. NH-triazoles **4–6** are thermodynamically stable tautomers. They exist in equilibrium in solutions and have very close values of Gibbs energy [1, 2, 6–12]. The ratio of tautomeric forms **4–6** can be determined by spectral methods, although it is impossible to separate them. In modern books it is a common practice not to put a certain form of tautomer to represent NH-1,2,3-triazoles, but rather to use generalized formulas, for example **7** or **10**.



Theoretical calculations of magnetic properties of NH-1,2,3-triazoles performed at B3LYP/6-311++G(d,p) level within GIAO approach confirmed the aromatic character of these *6e*-heterocycles. Nucleus independent chemical shifts (NICS) (1) calculated above the ring centers were −13.51 ppm for tautomers **8** and −13.61 ppm for **9** [7].

Experimental and theoretical studies indicated that the tautomer **8** is more stable in solution, while 2*H*-isomer **9** is more stable in gas phase (~4.0 kcal mol^{-1}) [7–12].

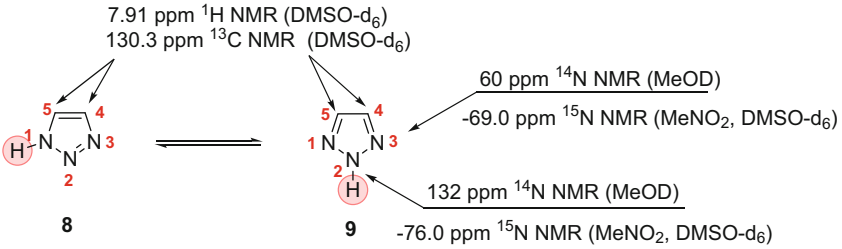


Spectroscopic ^{14}N and ^{15}N NMR data revealed that unsymmetrical 1,2,3-triazoles **4–5** exist in the 2*H*-tautomer form (70–100%) [13, 14]. ^{1}H, ^{13}C, ^{15}N and ^{14}N NMR shifts were identical for the two hydrogen and carbon atoms in positions *4* and *5* and nitrogen atoms at positions *1*, *2* and *3* of 1,2,3-triazoles for both tautomers (Scheme 1) [1, 2, 6, 9].

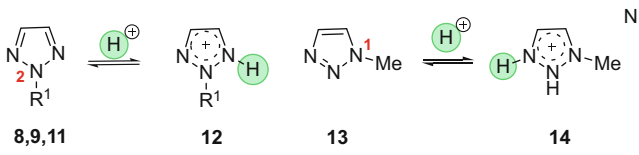
N-Substituted isomers of 1*H* and 2*H*-1,2,3-triazoles can be differentiated based on their polarity. Indeed, the dipole moment of the 1*H*-isomer is substantially higher than for 2*H*-1,2,3-triazoles (Scheme 2) [1, 2, 6].

1,2,3-Triazoles demonstrate amphoteric properties and can behave as a weak base or a weak acid similar to phenol. 2-Methyltriazole **11** shows a much weaker basicity in comparison with 1-methyl-1,2,3-triazole **13** (Scheme 2) [1, 3, 6, 9–14].

1,3-Dipolar cycloaddition of substituted azides to alkynes is a common approach to obtain various N(1)-derivatives of 1,2,3-triazoles. Huisgen was the first one to establish mechanistic details underlying this reaction [15]. The groups of Sharpless et al. [16] and Meldal et al. [17] modified this method. They performed it as a highly

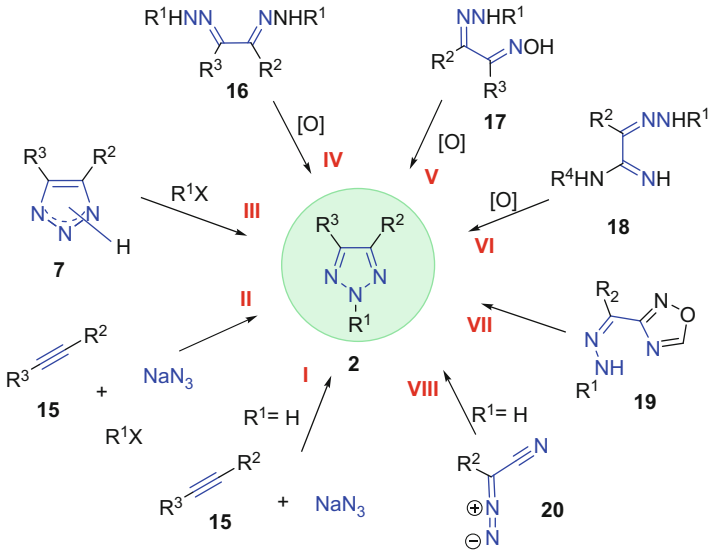


Scheme 1 NMR spectra data for NH-1,2,3-triazoles



N compd	R^1	pK_a	μ (D)
8	H		5.97
9	H	1.17	1.85
11	Me	< 1	0.37
13	Me	1.25	4.46

Scheme 2 Polarity and acidity of 1*H*- and 2*H*-1,2,3-triazoles



Scheme 3 General methods for the synthesis of 2*H*-1,2,3-triazoles

regioselective process catalyzed by Cu(I) and Ru(II) salts taking place under mild conditions and giving desired products with exceptionally high yields [3].

It should be stressed that in opposite to 1*H*-1,2,3-triazoles, there is no universal approach to obtain 2*H*-1,2,3-triazoles, although numerous synthetic methods have been developed (Scheme 3) [1–6]. The most known one among them are: the cycloaddition of azides to acetylenes **15** (I), one-pot three-component cyclization

(II), reaction of 2*H*-1,2,3-triazoles **7** with electrophilic agents (III), the various cyclizations of hydrazones **16–18** (IV-VI), Boulton–Katritzky rearrangement of (*Z*)-3-arylhydrazones of 3-acyl-1,2,4-oxadiazoles **19** (VII), and intra- and intermolecular cyclization of diazocompounds **20** (VIII).

Currently, 2*H*-1,2,3-triazoles are being applied into various fields [18, 19] including their diverse biological activity and unique photonic properties. In that respect, the development of versatile methods for their synthesis became an important direction of triazole chemistry. In the following part of this critical review, we will describe the current state of the art of synthetic approaches listed above in Scheme 3.

2 Thermal 1,3-Dipolar Cycloaddition of Azides to Alkynes

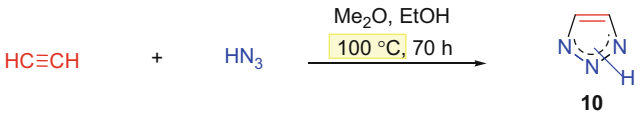
2.1 Cycloaddition of Alkynes to Hydrazoic Acid and Sodium Azide

Dimroth and Fester were first to propose the direct construction of unsubstituted NH-1,2,3-triazole ring by the interaction of hydrogen azide with acetylene [20]. The reaction was carried out by prolonged heating in a sealed tube (Scheme 4). The analogous transformation of phenyl azide with acetylene proceeded faster, in 40 h.

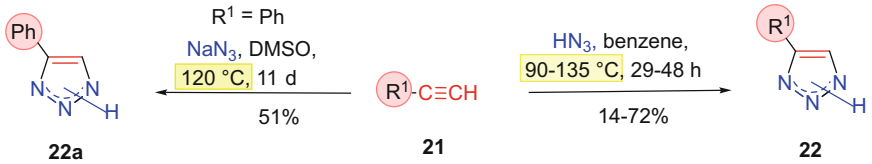
The dipolarophilic substrates used in 1,3-dipolar cycloaddition with azides were acetylenes bearing alkyl [21], aryl [22–27], heterocyclic [28–34], carboxy, formyl, cyano, nitro, phosphonyl, benzoyl [26, 35–44] substituents, and nucleoside residues [45]. Although the cycloaddition of alkynes to azides was characterized by a substantial exothermic effect, its high activation barrier implies that the reaction should be performed at increased temperatures. A general procedure is to heat the reactants at reflux in toluene, benzene, or alcohols, or to heat them in DMF/DMSO. For example, monoalkyl- or monophenylacetylenes **21** can interact with azides in benzene in closed vessels or after heating in DMSO [21, 22, 25] (Scheme 5).

A disadvantage of this protocol is that higher temperatures shift the thermodynamic equilibrium toward the side products and the yield of the desired product can be decreased [38]. The efficiency of the process strongly depends on spatial and electronic factors of the substituents on the alkyne. It was established that introduction of electron-withdrawing groups (EWGs) enhanced the 1,2,3-triazole yields. Conversely increasing the electron-donating properties of the substituent or the presence of several electron-donating groups (EDGs) at the same time on phenylpropiolonitriles **23** led to decreased yields of triazoles **24** down to 54–60% even though a high temperature was employed (Scheme 6) [38].

Ethyne-bisdiphenylphosphine oxide and sulfide **25** reacted exothermally with NaN_3 in methanol to produce the sodium 1,2,3-triazolide salt **26** (X=O, S) (Scheme 7) [40–42]. It should be noted that the reaction with ethyne-bisdiphenylphosphine selenide **25** (X=Se) required longer heating. The reactivity of ethynes in this reaction decreases in the series: $-PPh_2{=}O > -PPh_2{=}S > -PPh_2{=}Se$

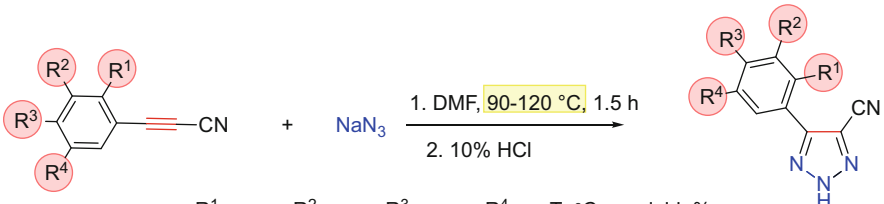


Scheme 4 The first example of the reaction of 1,3-dipolar cycloaddition acetylene to hydrazoic acid



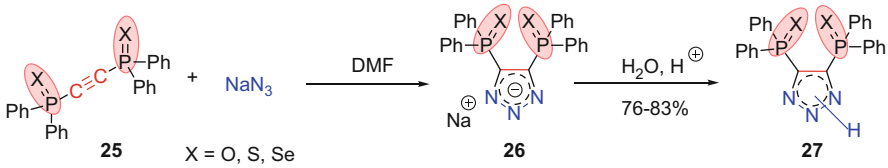
R^1 = H, Me, Et, Pr, Bu, C_5H_{11}, *i*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17}, *n*-C_9H_{19}, *n*-$C_{10}H_{21}$

Scheme 5 Reaction of 4-alkyl(phenyl) acetylenes **21** with hydrazoic acids and sodium azide



R^1	R^2	R^3	R^4	T, °C	yield, %
H	H	H	H	90	80
H	H	MeO	H	90	75
MeO	MeO	H	H	120	60
H	MeO	MeO	MeO	120	54

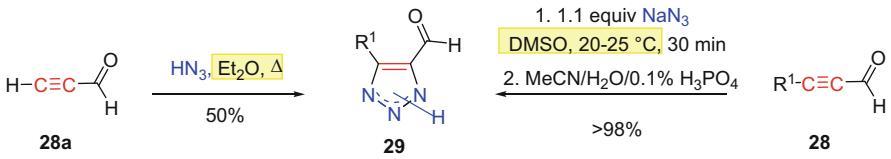
Scheme 6 Electronic substituent effect on the cycloaddition phenylpropiolonitriles **23** to sodium azide



Scheme 7 Reaction of ethyne-bisdiphenylphosphine oxide, sulfide, and selenide **25** with sodium azide

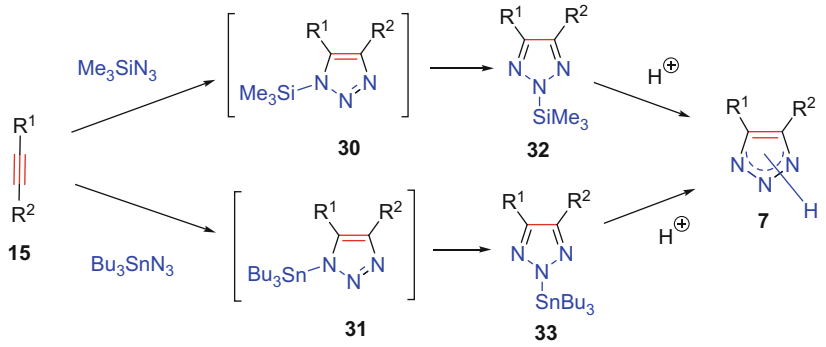
and, consequently, the activity of the triple bond decreased in the same order. Acidification of 1,2,3-triazolides **26** yielded free acid **27** (Scheme 7).

The choice of a solvent is a crucial point for the cycloaddition reaction. Sodium azide reacted with propiolic aldehyde **28a** or its derivatives **28** in DMSO at room temperature and 4-formyl-1,2,3-triazoles **29** were obtained in quantitative yields.



R^1= H, *n*-Bu, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, Ph, $TBSO(CH_2)_n$, $THPO(CH_2)_n$ n = 1,2,3

Scheme 8 Synthetic routines to 2*H*-1,2,3-triazole-4-carbaldehydes



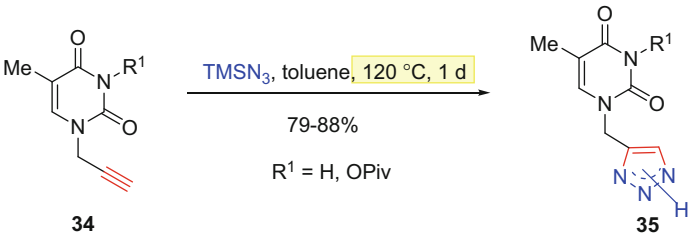
Scheme 9 1,3-Dipolar cycloaddition of acetylenes with trimethylsilyl-/tri-*n*-butylstannylazides

Only moderate yields were obtained by reflux of the same components in ether (Scheme 8) [35–37].

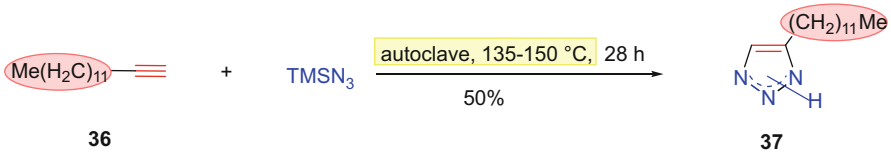
2.2 *Cycloaddition of Alkynes to Azidotrimethylsilane and Azidotributylstannane*

Further methodological development for the synthesis of 2*H*-1,2,3-triazoles via [3+2]-cycloaddition involved the use of trimethylsilyl or tributylstannyl azides as 1,3-dipoles (Scheme 9) [15, 22, 31, 34, 43, 46–58]. Thus, NH-1,2,3-triazoles **7** were obtained via rearrangement followed by hydrolysis of initially formed 1-trimethylsilyl- or 1-tri-*n*-butylstannyl-1,2,3-triazoles **30** and **31** (Scheme 9) in good yields.

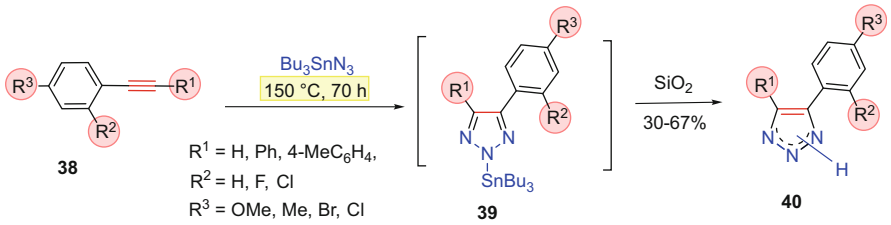
Unlike hydrazoic acid, these azides were thermodynamically stable. Therefore, they are very convenient and relatively safe substitutes for hydrazoic acid in many reactions with various acetylenes. Nevertheless, to obtain triazoles by reaction of these stable azides with acceptable yields, a prolonged heating of substrates in different high boiling solvents (usually DMF, DMA, toluene, xylene) is required. For example, to produce thymine-substituted NH-1,2,3-triazoles **35**, 1-propargyl-thymine **34** and trimethylsilylazide were continuously heated for 1 day in toluene (Scheme 10) [50].



Scheme 10 Synthesis of NH-1,2,3-triazoles **35** with thymine residue



Scheme 11 Reaction of hexacos-13-yne **36** with trimethylsilylazide



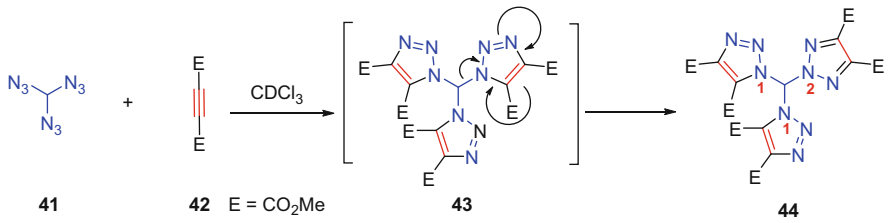
Scheme 12 Synthesis of 4,5-disubstituted NH-1,2,3-triazoles **40** by reaction of acetylenes with tri-*n*-butylstannylazide

In several cases not only a higher temperature but also a higher pressure was involved [34, 56, 57]. 4-Dodecyl-1,2,3-triazole **37** was obtained by heating of tetradec-1-yne **36** in neat trimethylsilylazide in autoclave (Scheme 11) [57]. Thus, this method has an expanded scope of dipolarophiles by including inactivated acetylenes with electron-donating alkyl substituents (Scheme 11).

Further examples of this cycloaddition yielding 4,5-disubstituted NH-1,2,3-triazole **40** in moderate amounts (30–67%) were described [43, 54]. The reaction of tri-*n*-butylstannylazide with mono- and disubstituted alkynes was performed by heating the reaction mixture in a sealed tube (Scheme 12) [43, 54].

2.3 *Cycloaddition of Alkynes to Organic Azide*

2*H*-1,2,3-triazole can be obtained by the reaction of acetylenes with selected organic azides, if they have a leaving group in their structure. Such groups facilitate the hydrolysis or N-N/N-C rearrangements taking place in the next step [54–56,



Scheme 13 Cycloaddition of triazidomethane **41** with DMAD followed by rearrangement

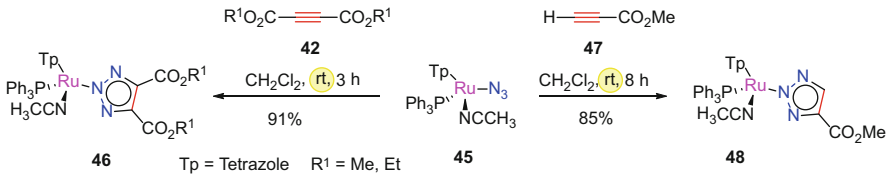
59–72]. It has been shown that 3-nitrobenzoyl, pivaloyloxymethyl, perfluoroalkylvinyl, or trifluoromethansulfonyl azides reacted with acetylenes to form NH-1,2,3-triazole [50, 54, 59–63], while (azidomethanetriyl)tribenzene, 7-azidocyclohepta-1,3,5-triene, ethyl 3-azidoacrylate, 3-azido-1,2,3-tri-*tert*-butylcycloprop-1-ene, diethyl azido(benzamido)methylphosphonate, alkyl 3-azido-2-alkenoates, and azidomethylamines produced a mixture of 2-R-1,2,3-triazole and NH-triazole, or 1- and 2-substituted 1,2,3-triazoles with an excess of the latter isomer [56, 64–71].

An interesting example of tri-(1,2,3-triazole) **44** involved a step of N(1)-N(2) rearrangement occurring during the reaction of triazidomethane **41** with DMAD (Scheme 13) [71].

^{1}H and ^{13}C NMR spectroscopy and single-crystal X-ray diffraction experiments revealed that the 3:1 adduct exists in the structure **44** consisting of one 2-substituted and two 1-substituted triazole units. One of the three initially formed symmetrical triazole rings in **43** underwent a 1,5-sigmatropic alkyl rearrangement to yield **44**. The driving force behind this rearrangement was the demand from the molecular system to relieve the inner steric strain. Elimination of the triazole unit from the symmetrical adduct **43** followed by its re-addition led to the compound **44**.

2.4 *Cycloaddition of Alkynes with Metal-Coordinated Azide Ligands*

Metal-coordinated azido ligands can undergo 1,3-dipolar cycloaddition reactions. Co(III)-, Ru(IV)-, Pd(II)-, Pt(II)-, In(III)-, Ir(III)-, Mo(II)-, Os(IV)-, and Ta(V)-coordinated examples of such complexes were described [73–84]. Usually, metal-azido complexes react with alkynes to produce Stable 2*H*-1,2,3-triazolates at lower temperatures and in shorter reaction time when compared to reactions of NaN_3 and HN_3 with alkynes. It should also be mentioned that the mechanism for the reaction of metal-azide complexes with dipolarophiles is similar to the one for the reaction of $TMSN_3$ and $BuSnN_3$ described above (Scheme 9). However, the complex containing the N(1)-bound triazolate ligand immediately converts into the thermodynamically more Stable N(2)-bound isomer.



Scheme 14 Synthesis of complexes $(CH_3CN)[Ru]\text{-}N_3C_2(CO_2R)_2$ **48** and $(CH_3CN)[Ru]\text{-}N_3C_2(CO_2CH_3)$ **49**

Treatment of ruthenium-coordinated azide **45** with an excess of DMAD, DEAD **42**, or methylpropiolate **47** at room temperature afforded N(2)-bound 4,5-bis(methoxycarbonyl)-1,2,3-triazolate $(CH_3CN)[Ru]\text{-}N_3C_2(CO_2Me)_2$ **46** and 4-(methoxycarbonyl)-1,2,3-triazolate $(CH_3CN)[Ru]\text{-}N_3C_2HCO_2Me$ **48** in high isolated yields. The formation of these complexes was undoubtedly confirmed by the disappearance of the characteristic absorption band of the azide group in the IR spectra. The ^1H NMR-assigned structure for **46** was the N(2)-isomeric form, since its spectrum exhibited a singlet at δ 3.63 ppm for six protons of the methoxycarbonyl group (Scheme 14) [80].

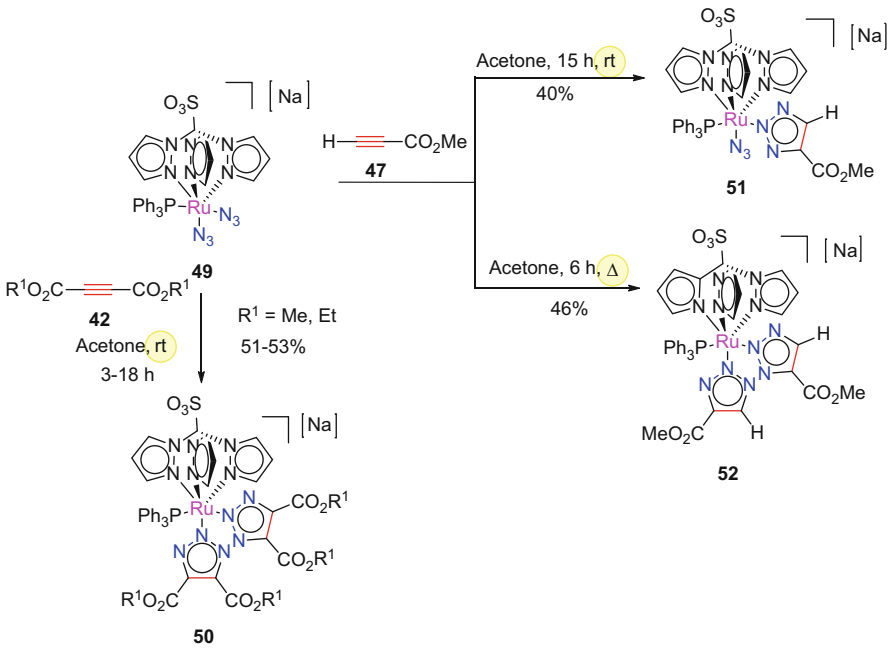
Two singlet resonances were registered at the beginning of the reaction while monitoring the reaction of azide complex **45** with DMAD, DEAD, and methylpropiolate by ^{31}P NMR spectroscopy. Those signals were attributed to the N(1)- and N(2)-isomers observed. The N(1)-isomer completely transformed into the N(2)-isomer at room temperature within ~1–2 h.

Diazido ruthenium complex **49** reacted with alkynes in a 1,3-dipolar cycloaddition fashion. Depending on the alkyne structure and reaction conditions, the cycloaddition occurred through the involvement of one or two azido groups and led to ruthenium coordinated by triazolate ligands through the N(2)-atom as in compounds **50–51** (Scheme 15) [81].

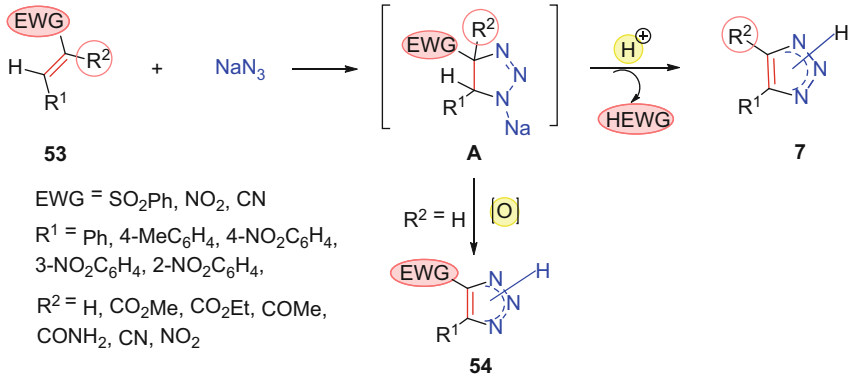
Complexes **50**, **51**, and **52** have been characterized by analytical and spectroscopic methods and X-ray diffraction crystallography.

2.5 Cycloaddition of Activated Alkenes to Azides

Other dipolarophiles that have the ability to react with azides via [3+2]-cycloaddition are activated alkenes. Their [3+2]-cycloaddition proceeds similarly to the cycloaddition of alkyne, but leads to 1,2,3-triazolines initially (**A**, Scheme 16), which was then followed by aromatization. Aromatization was achieved through the elimination of a leaving group (at the same time an EWG) or by oxidation [28, 43, 54, 85–104] (Scheme 16), resulting in two products **7** and **54**. The most convenient approach to perform this transformation was to combine cycloaddition and elimination processes, but not cycloaddition and oxidation.

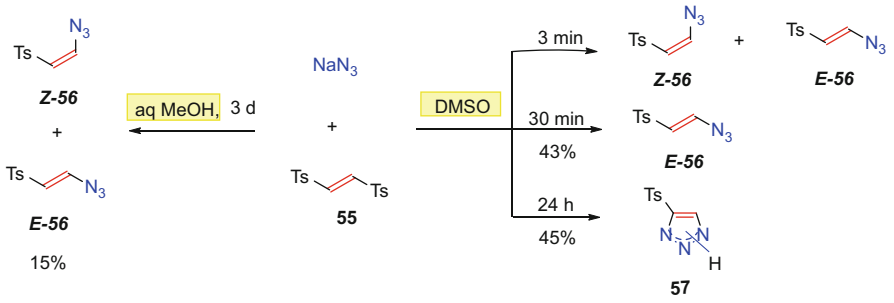


Scheme 15 Synthesis of complexes [Na]{Ru{$k(N^2)$$N_3C_2(CO_2R^1)_2$}$_2${$k^3$(*N*,*N*,*N*)-Tpms}($PPh_3$)] **50**, [Na]{Ru($N_3$){$N_3C_2H(CO_2Me)$}{$k^3$(*N*,*N*,*N*)-Tpms}($PPh_3$) **51**, [Na]{Ru{$N_3C_2H(CO_2Me)$}$_2${$k^3$(*N*,*N*,*N*)-Tpms}($PPh_3$) **52**

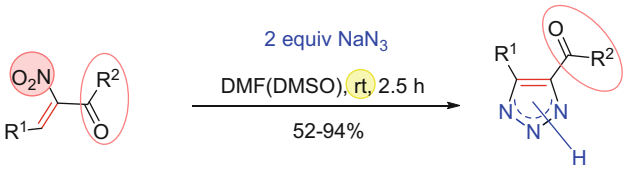


Scheme 16 [3+2]-Cycloaddition of activated alkenes **53** to sodium azide

The yields of cycloadduct were substantially increased if the reaction of alkene with azides was carried out in aprotic solvents [86, 87]. It was observed that the reaction of sodium azide with 1,2-di-*p*-toluenesulfonylethene **55** in aqueous methanol produced azidovinyl *p*-tolyl sulfone **56** as a mixture of *Z*- and *E*-isomers. On the other hand, in DMSO three products, namely *E*-**56**, *Z*-**56**, and NH-1,2,3-triazole **57**,



Scheme 17 Reaction of 1,2-di-*p*-toluenesulfonylethene **55** with NaN_3 in different solvents



R^1 = Ph, 4-$MeOC_6H_4$, 3-furyl, 1-methylindol-3-yl, 1-acetylindol-3-yl

Scheme 18 Reaction of β-acetyl(benzoyl)-β-nitroethenes **58** with sodium azide

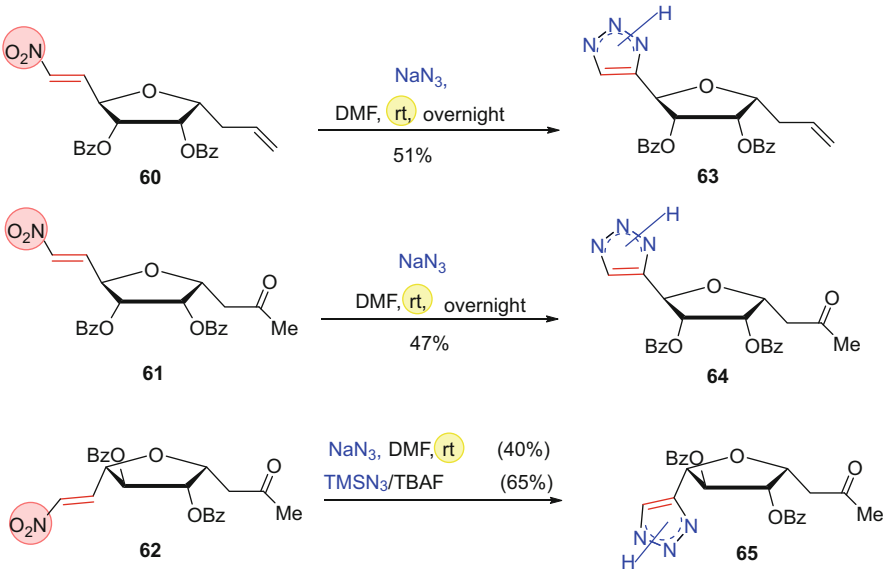
were obtained and their amounts depended on the reaction time. This observation questions the mechanism of reaction as to be simultaneous synchronic [3+2]-cycloaddition and suggests that a two-step formation for azole **57** takes place (Scheme 17).

Due to weaker reactivity of alkenes, their reactions with azides required stronger conditions. Usually, electron-deficient alkenes are utilized in order to improve the reactivity. Experimentally established elimination abilities of electron-deficient substituents on alkenes decreased in the row: benzenesulfonyl > nitro > cyano. Rare examples of halogen or thiol elimination were described as a supportive process for the transformation of 1,2,3-triazolines to 1,2,3-triazoles [99–102].

Alkenes with two geminal electron-withdrawing groups were better substrates for the [3+2]-cycloaddition with azide. The reaction of β-acetyl(benzoyl)-β-nitroethenes **58** with sodium azide proceeded in comparatively mild conditions and gave 4,5-disubstituted-NH-1,2,3-triazoles in moderate to high yields (Scheme 18) [88–92].

Activated geminal nitroethenes containing a carbonyl group as an additional electron-withdrawing unit have high synthetic accessibility and attract a lot of interest due to the ability to introduce in triazole ring biologically active fragments and different heterocycles [28, 54, 89, 91, 98, 101].

Interaction of nitroalkene-containing glycosides **60–62** with sodium azide at room temperature led to ribavirin triazole-base analogous **63–65**, obtained in



Scheme 19 Reactions of nitroalkenyl-containing glycosides **60–62** with sodium azide and trimethylsilyl azide

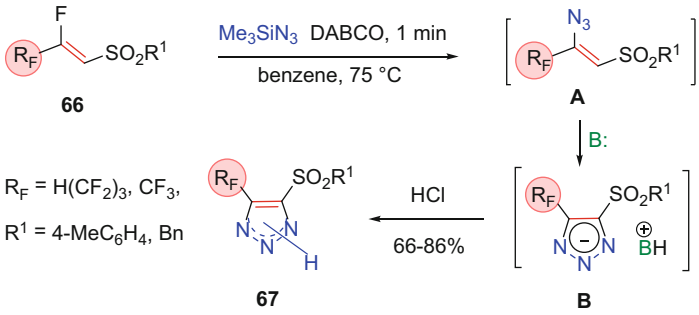
moderate yield (Scheme 19). Higher yields were achieved if the same alkene **62** reacted with $TMSN_3$ activated by *tert*-butyl ammonium fluoride (TBAF) added to the mixture (Scheme 19) [98].

This method was also convenient to synthesize fluorocontaining NH-1,2,3-triazoles [103–105]. The reaction of fluorinated sulfones **66** with trimethylsilyl azide in the presence of base reagent allowed to obtain 5-polyfluoroalkyl-4-arylsulfonyl-1,2,3-triazole **67** in good yields (Scheme 20) [103, 104].

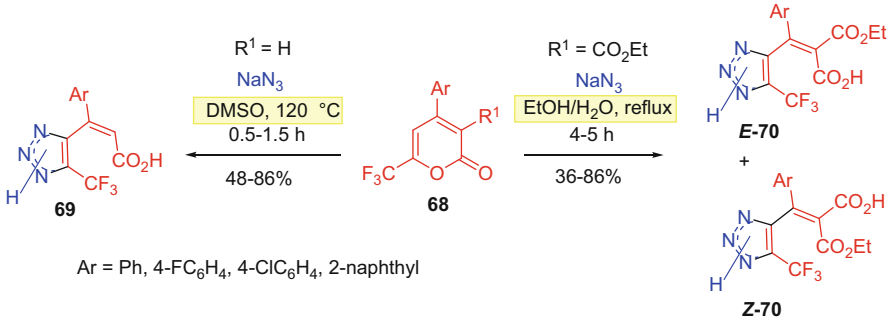
Cyclic alkenes – ethyl 4-aryl-6-(trifluoromethyl)2-oxo-2*H*-pyran-3-carboxylates **68**, reacted with NaN_3 under mild condition, likely because an additional activating EWG substituent was introduced at the pyrone ring. As a result, highly functionalized trifluoromethyl-triazoles: 3-[5-(trifluoromethyl)-1,2,3-triazol-4-yl) cinnamic acids **69** and ethyl esters 3-[5-(trifluoromethyl)-1,2,3-triazol-4-yl) arylmethylidene malonic acids **70** were isolated (Scheme 21) [105].

2.6 *Cycloaddition of Enamines to Azides*

Several published examples of reaction of azides with electron-rich dipolarophiles, such as enamines, have been described [106–110]. Depending on the structure of the substrates different transformations may occur with initially formed 1,2,3-triazolines. Sodium azide reacted with β-monosubstituted-α-chloroenamines **72** (generated from tertiary amides **71**) in mild conditions and, as a result, 5-methyl



Scheme 20 Reaction of 1,1-polyfluoroalkyl alkenylsulfones **66** with trimethylsilyl azide



Scheme 21 Synthesis of CF_3-triazoles **69** and **70** from pyrones **68** and NaN_3

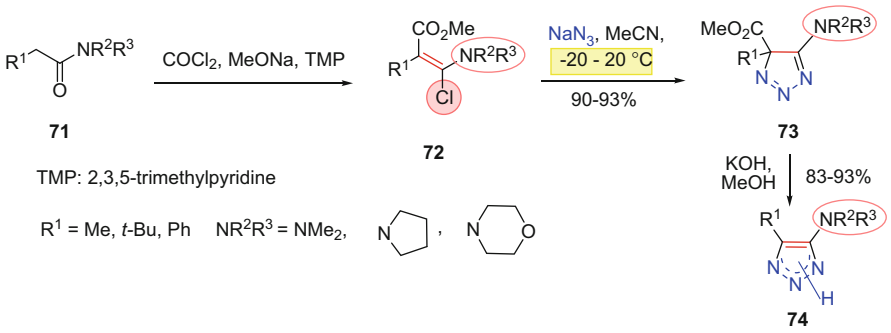
(phenyl)-2*H*-1,2,3-triazol-4-amines **74** were synthesized via 5-amino-4*H*-1,2,3-triazole-4-carboxylate intermediate **73** after saponification and decarboxylation with an excellent yield (Scheme 22) [106, 107].

1,3-Dipolar cycloaddition of heteroaroyl azides **75** to methyl 3-pyrrolidinoacrylate **76** occurred smoothly to produce 1,2,3-triazole **79** by the displacement of the pyrrolidine moiety from the 1,2,3-triazoline ring (Scheme 23) [110].

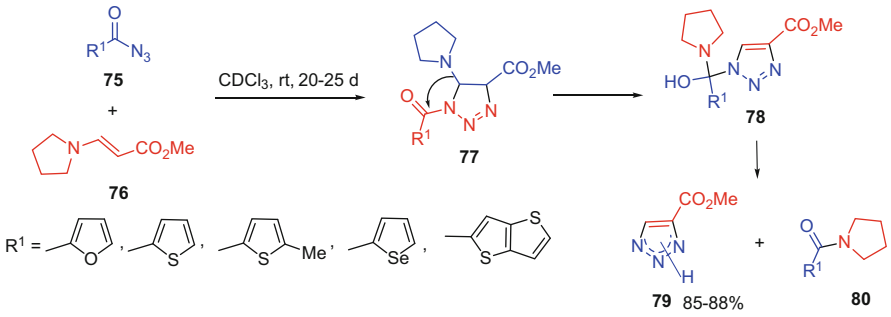
An analogous rearrangement-elimination sequence was observed in the reaction of tosyl azide with nitro- and sulfonyl enamines [108, 109].

2.7 *Cycloaddition of Alkenes to Metal Azides*

As it was mentioned above, the reaction of hydrazoic acid and azide ions with alkenes yields a linear product in the first place existing in dynamic equilibrium with 1,2,3-triazoline cyclic intermediates that may be transformed in several ways affording various by-products. However, when α,β-unsaturated aminoketone **81** reacted with diethylaluminium azide, obtained from diethylaluminium chloride and sodium azide in situ, no linear adduct was detected [111]. Triazole yields strongly depended on the nature of substituents R^1 and R^2 in aminoketone **81**.



Scheme 22 Reaction of sodium azide with β-monosubstituted-α-chloroenamines **72**



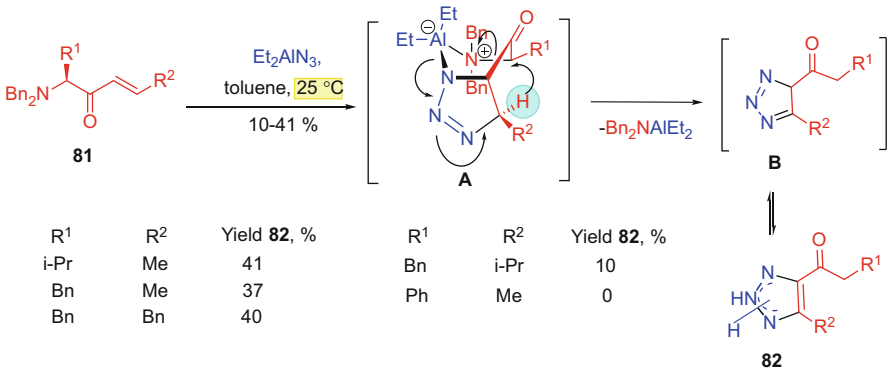
Scheme 23 Reaction of azido(2-heteroaryl)methanones **75** with methyl 3-pyrrolidinoacrylate **76**

Cycloaddition of alkenes **81**, containing electron-withdrawing groups proceeded via the intermediate **A** where two rings were optimally aligned for intramolecular migration of a hydride from the triazoline C(4) atom to the α-carbon atom with a displacement of *N*,*N*-dibenzylamino group, activated by complexation with aluminium (Scheme 24).

The mechanism shown in Scheme 24 was confirmed by isolation of dibenzylamine. Involvement of alkenes bearing electron-donating substituents allowed to expand the scope of the described method of synthesis of 1,2,3-triazoles via [3+2]-cycloaddition with azides.

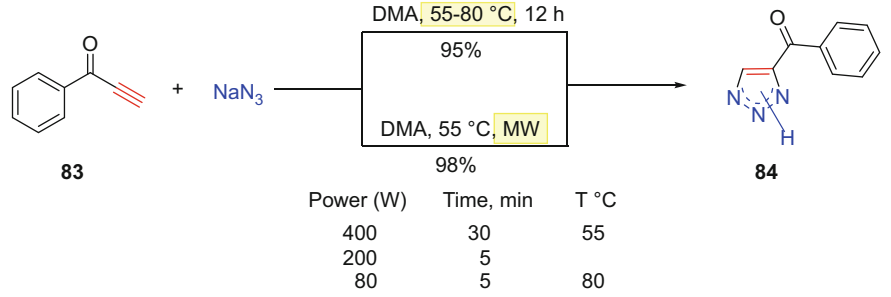
2.8 *Microwave-Assisted and One-Pot Reactions*

In addition to being energy saving, the microwave irradiation also causes a striking reduction of reaction times. To surpass the efficiency of conventional protocols for cycloadditions, microwave-assisted processes were introduced in some cases [23, 51, 112, 113].



R^1	R^2	Yield **82**, %	R^1	R^2	Yield **82**, %
i-Pr	Me	41	Bn	i-Pr	10
Bn	Me	37	Ph	Me	0
Bn	Bn	40			

Scheme 24 Diethylaluminium azide addition to α,β-unsaturated aminoketones **81**

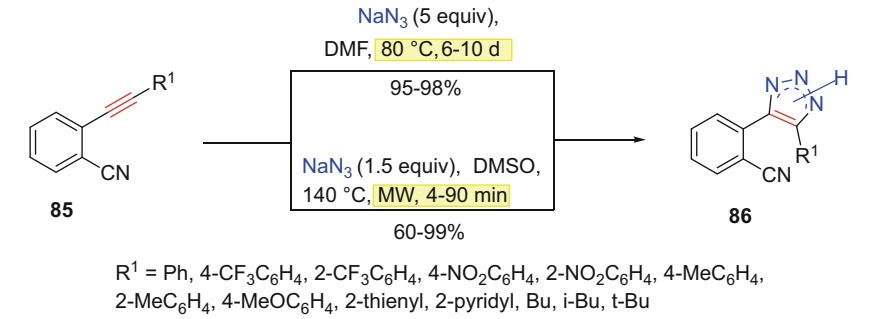


Power (W)	Time, min	T °C
400	30	55
200	5	
80	5	80

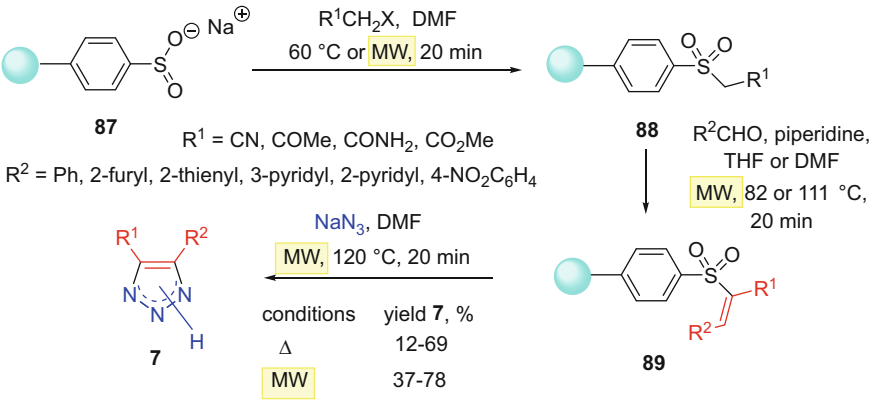
Scheme 25 Reaction of phenyl ethynyl ketone **83** with NaN_3 under conventional condition and microwave assistance

Conventional and microwave heating of the reaction of phenyl ethynyl ketone **83** with NaN_3 in anhydrous dimethylacetamide (DMA) were performed. It was shown that the procedure including microwave heating allowed the authors to achieve the desired compound **84** faster and in better yields compared to the conventional method (Scheme 25) [51].

Cycloaddition of internal alkynes **85** to an excess of sodium azide in DMF required 6 days to be completed and, even increase of sodium azide amounts (up to 10 eq) did not accelerate it (Scheme 26). Indeed, microwave irradiation noticeably improved reaction rates. The process was finished within 10 min, and triazole adduct **86** was obtained in high yield. The reaction was completed in 4–90 min for phenyl alkynes with electron-donating groups on the aromatic ring (Scheme 26) [112].



Scheme 26 Comparative study of conventional and microwave-assisted procedures on the reaction of internal alkynes with NaN_3

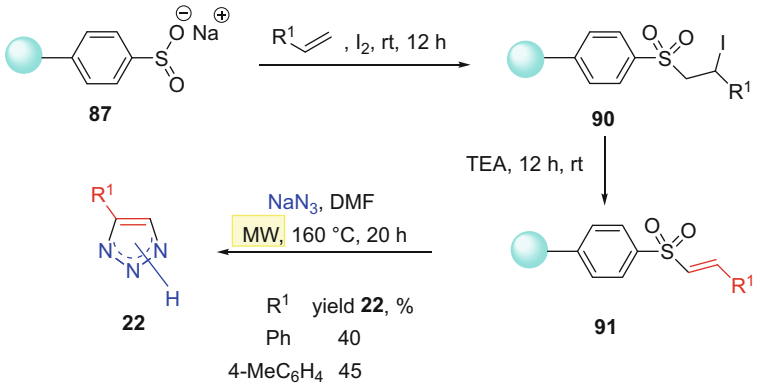


Scheme 27 Sulfinate solid-phase synthesis of 4,5-disubstituted 1,2,3-triazoles **7**

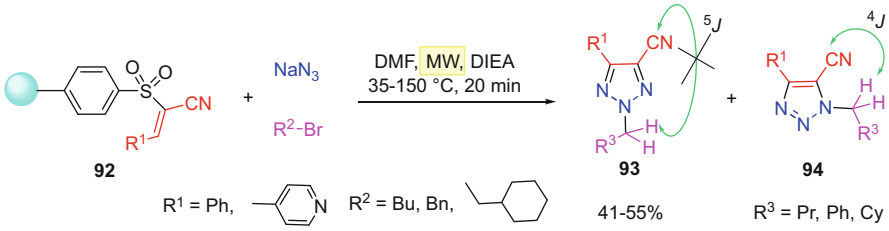
2.9 *Solid-Phase Techniques for [3+2]-Cycloaddition of Azides to Alkenes*

It should be mentioned that [3+2]-cycloaddition of azides to electron-deficient alkenes has received only a little attention because a poor reactivity of substrates requires applying harsh conditions. To overcome this issue solid-phase synthesis (SPS) was introduced.

A convenient solid-phase procedure for regioselective and traceless synthesis of di- and trisubstituted 1,2,3-triazoles **7** was found based on [3+2]-cycloaddition of polymer-bound vinyl sulfone to sodium azide, giving different yields (Scheme 27). Disubstituted vinyl sulfone dipolarophiles **89** were generated via Knoevenagel condensation of **88** with aldehydes. Microwave-assisted procedure in combination with solid-phase technique led to higher conversion rates and higher purity of the product **7** [113].



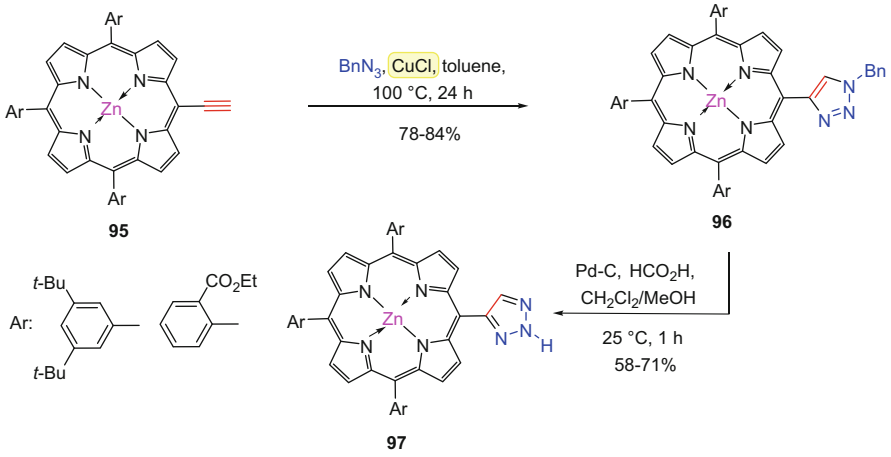
Scheme 28 Sulfinate solid-phase synthesis of monosubstituted 1,2,3-triazoles **22**



Scheme 29 Reaction of resin **92**, sodium azide, and alkyl bromide led to 2-alkyl-1,2,3-triazole **93**

Monosubstituted vinylsulfones **91** were obtained via ionic addition of **87** to alkenes (Scheme 28). Microwave-assisted cycloaddition of vinylsulfones **91** to sodium azide was carried out at high temperature in DMF and resulted in moderate yields of 4-aryl-1,2,3-triazoles **22** [113].

Convenient regioselective one-pot coupling procedure of resin **92** with sodium azide and alkyl halides yielding 2-alkyl-1,2,3-triazoles **93** as major isomer was described (Scheme 29) [113]. The ratio of isomers **93** and **94** in crude mixture was approximately 10:1. Their structures were confirmed by proton–carbon correlation between methylene proton and nitrile carbon in ^{13}C HMBC spectra (Scheme 29). X-ray crystallography also confirmed that the major isomers were 2-substituted 1,2,3-triazoles **93**.



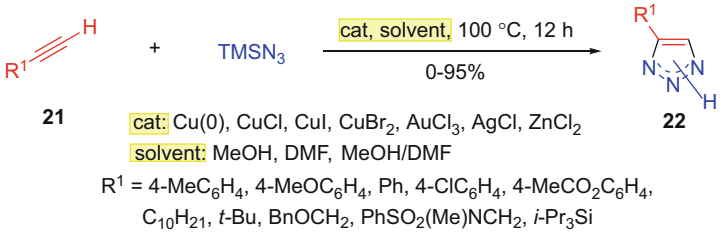
Scheme 30 Synthesis of NH-1,2,3-triazolylporphyrins **97**

3 Catalysis in Synthesis of 2*H*-1,2,3-Triazoles by 1,3-Dipolar Cycloaddition Reactions

Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) offers an efficient method for synthesis of 1,4-disubstituted-1,2,3-triazoles [2–4, 6, 16, 17]. On the other hand, Ru-catalyzed reaction of terminal alkynes with alkyl azides can serve a unique routine towards 1,5-disubstituted-1,2,3-triazoles [2, 6]. In these methods the activity of inorganic azides is suppressed in mild conditions and preparation of 4,5-disubstitued NH-1,2,3-triazoles by 1,3-dipolar cycloaddition reaction is considered being useless. Conversely, there are examples of metal-catalyzed synthesis of NH-1,2,3-triazole based on sodium or lithium azide [23, 27, 114–116]. Other described examples of 1,3-dipoles for this reaction were trimethylsilyl azide [117–119] and organic azides [39, 50, 120–126]. In this case, the reaction with organic azides was followed by a rearrangement or an elimination of organic residue and lead to NH- or 2-R-1,2,3-triazoles.

Using metal salts to catalyze the reaction of organic azides with alkynes resulted in linking the NH-1,2,3-triazole moiety to porphyrinic supramolecular assembles. *meso*-1,2,3-Triazolyl Zn(II) porphyrins **97** were synthesized via Cu(I)-catalyzed 1,3-dipolar cycloaddition of *meso*-ethynyl Zn(II) porphyrins **95** to benzyl azide [122]. The benzyl group was removed by treatment with Pd/C and formic acid (as hydrogen source) in the final step (Scheme 30).

The main problem of regioselectivity for unsymmetrical 4- or 5-monosubstituted and 4,5-disubstituted 1*H*-triazoles is managed by utilization of well-known ‘click chemistry’ approaches. This problem becomes insignificant in case of NH-1,2,3-triazoles and their 2-substituted derivatives due to their tautomerism or symmetry caused by the 2-substituents position. Introduction of the catalyst facilitates the cycloaddition and gives the opportunity to expand the scope of this



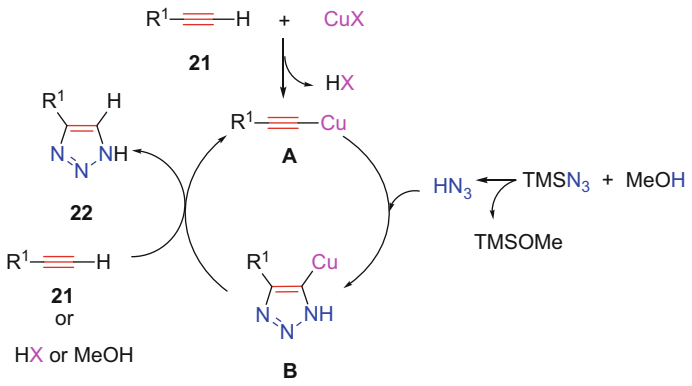
Scheme 31 Synthesis of *N*-unsubstituted 1,2,3-triazoles **22** by catalyzed [3+2]-cycloaddition reaction of nonactivated terminal alkynes **21** and $TMSiN_3$

reaction. This explains why metal-catalyzed syntheses currently are being very popular in triazole chemistry.

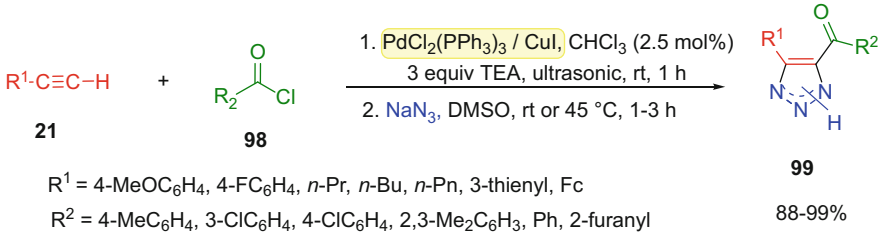
For example, the [3+2]-cycloaddition of nonactivated terminal alkynes **21** and trimethylsilyl azide proceeded smoothly in the presence of Cu(I) catalyst (CuI, CuCl, etc.) to give the corresponding NH-1,2,3-triazoles **22** in good to excellent yields (Scheme 31) [119]. Among all tested solvents, the protic ones had a larger effect on this reaction. A mixture of DMF and MeOH improved the yield of 1,2,3-triazoles **22** up to 59–69% as compared to 14–55% obtained in other cases. Other copper catalysts, such as $Cu(II)Br_2$ and Cu(0) powder, were also effective [119]. The reaction without a copper catalyst was characterized by a lower yield (13%). Non-copper metal catalysts ($AuCl_3$, AgCl and $ZnCl_2$) were not effective at all.

A mechanism for catalyst-activated cycloaddition, performed via multi-component one-pot synthesis technique, was proposed [115, 119, 127–131]. At the very beginning of this reaction CuX interacts with terminal alkynes **21** which result in the copper acetylide **A** [119]. Simultaneously, the formation of HN_3 occurs in situ by the reaction of $TMSN_3$ with MeOH. Since a C–C triple bond in a copper acetylide **A** is already activated the [3+2]-cycloaddition process immediately takes place. Protolysis of the C–Cu bond, initiated by terminal alkynes **21**, HX or MeOH occurred with intermediate **B**, affording NH-1,2,3-triazoles **22** in the final step (Scheme 32) [119].

Metal-catalyzed one-pot synthetic approaches to 1,2,3-triazoles can be classified into two types. The first one takes place as two consequent reactions of coupling and cycloaddition and leads to 4,5-disubstituted NH-1,2,3-triazoles. Sonogashira coupling reaction allows to construct acetylene dipolarophiles participating in the following step in the 1,3-dipolar cycloaddition [113, 114, 132–134]. The sequence of palladium-catalyzed Sonogashira coupling and the 1,3-dipolar cycloaddition of acyl chlorides, terminal acetylenes, and sodium azide was performed in a one-pot ultrasonic-promoted mode and led to 4,5-disubstituted-2*H*-1,2,3-triazoles **99** (Scheme 33) [132]. Reaction parameters (reaction time, yield, etc.) did not depend on the electronic properties of the substituents in the aryl terminal acetylenes and acyl chlorides. Reaction of aliphatic terminal acetylenes proceeded much slower



Scheme 32 Proposed mechanism for the formation of *N*-unsubstituted triazoles **22**



Scheme 33 One-pot synthesis of 4,5-disubstituted 1,2,3-triazoles **98** through Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides, terminal acetylenes, and sodium azide

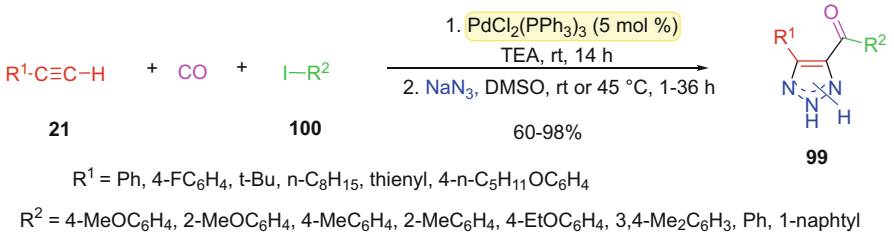
comparing to aryl acetylenes. The length of aliphatic chain was not a crucial factor affecting the yields of this process.

One-pot four-component synthesis of 4,5-disubstituted triazole **99** by Pd-catalyzed reaction of terminal acetylenes **21** with carbon monoxide, aryl iodide **100**, and sodium azide took place in mild conditions (Scheme 34) [133].

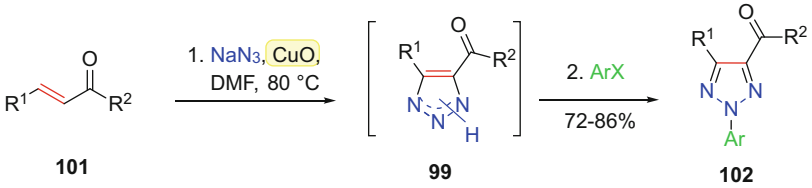
This class of one-pot reactions represents an atom economic approach, which can be easily propagated to industrial scale and is not strictly limited by the chemical diversity of substrates (Schemes 33, 34).

One-pot catalytic reactions of a second type occur when the cycloaddition is followed by nucleophilic substitution (arylation, alkylation, etc.) of the initially formed NH-triazoles, leading to 2-aryl- or 2-alkyl-1,2,3-triazoles [99, 114, 127–131]. A series of 2-aryl-1,2,3-triazoles **102** were obtained in mild conditions and with a high yield by three-component reaction proceeding via an azide-chalcone oxidative cycloaddition and post-arylation of triazoles (Scheme 35) [114]. Opting for chalcones with stronger electron-withdrawing R^1 and R^2 substituents leads to improved reaction yields.

The reaction described above was susceptible to the type of catalyst. The catalytic activity of different copper species, such as $Cu(OAc)_2$, $Cu(acac)_2$, CuI,



Scheme 34 One-pot synthesis of 4,5-disubstituted 1,2,3-triazoles **99** using terminal acetylenes **21**, carbon monoxide, aryl iodides **100**, and sodium azide

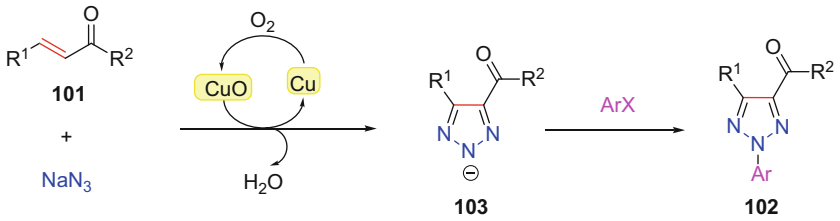


Scheme 35 Three-component reaction azide-chalcone oxidative cycloaddition and post-arylation triazole

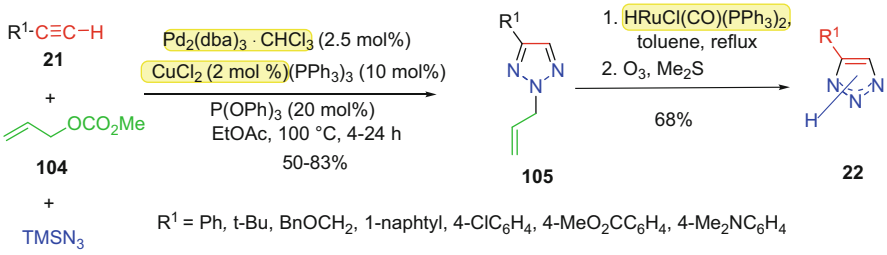
and CuO, was tested. It was found that CuO was superior and its utilization resulted in higher yields. Experimentally observed trends were in line with the proposed mechanism, involving the assumption that CuO acted not only as an oxidant for "triazoline–triazole" transformation (Scheme 16) but also as a trigger of the total catalytic process. The catalytical cycle is closed when Cu(0) is oxidized to Cu(II)O by air oxygen (Scheme 36) [114].

Regioselective formation of 2-allyltriazole **105** via three-component coupling reaction between allylmethylcarbonate **104**, $TMSN_3$ and alkynes in the presence of a catalytic amount of $Pd_2(dba)_3 \cdot CHCl_3$ and 1,3-bis(diphenylphosphino)propane (dppp) (Scheme 37) was reported in several publications [127–130].

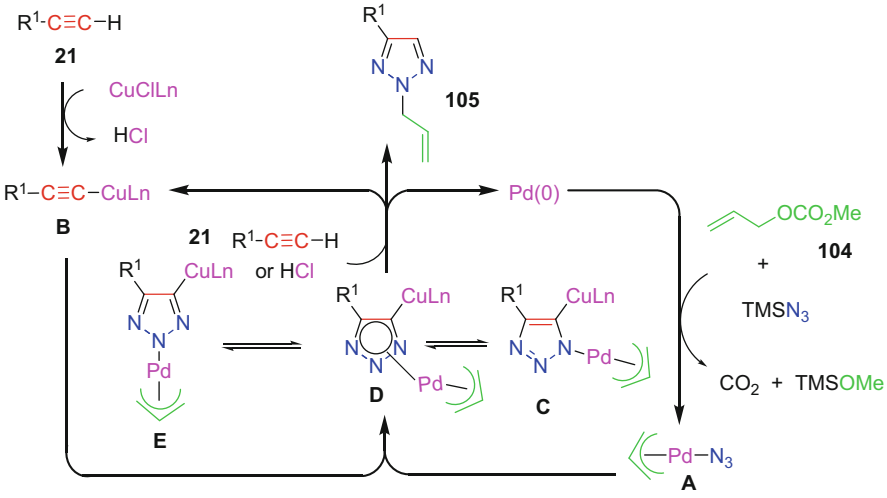
The structures of allyltriazoles **105** were determined by detailed analyses of spectroscopic data: according to ^1H and ^{13}C NMR allyltriazole **105** had a symmetrical structure. The location of allyl group on the triazole ring was confirmed by NOE experiments. The mechanism for this bimetallic catalysis is shown in Scheme 38 [128]. Firstly, allylmethyl carbonate, trimethylsilyl azide, and Pd(0) reacted to yield π-allylpalladium azide complex **A**. This step of the catalytic cycle was accompanied with concomitant evolution of CO_2 and trimethylsilyl methoxide. At the same time, the copper-acetylide **B** would be formed along with the generation of HCl via the reaction of alkynes **21** and CuClLn. Then, 1,3-dipolar cycloaddition between the azide moiety of the complex **A** with copper-acetylide **B** takes place and leads to 1-(η^3-allyl)(η^5-triazoyl)palladium complex **C**. The intermediate complex **C** was suggested to exist in an equilibrium with 2-(η^3-allyl)(η^5-triazoyl)palladium complex



Scheme 36 Proposed mechanism of the catalysis of the azide-chalcone oxidative cycloaddition by the CuO

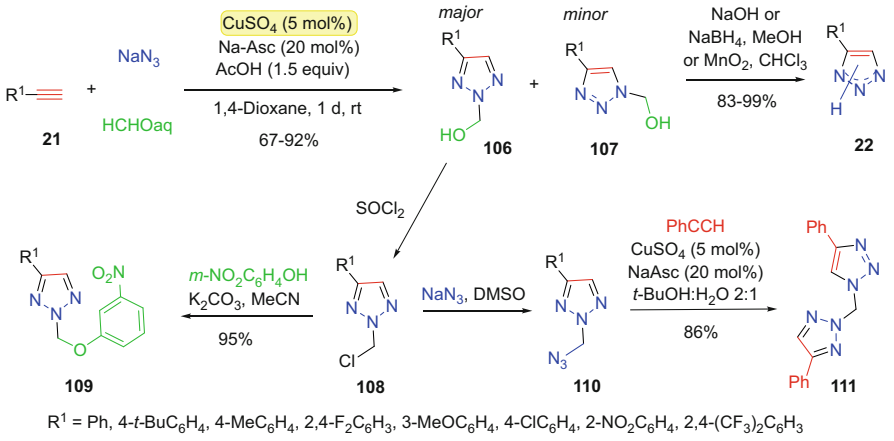


Scheme 37 Catalytic three-component coupling reaction between activated alkynes, allylmethyl-carbonate, and $TMSN_3$



Scheme 38 Proposed mechanism for the formation of 2-allyl-1,2,3-triazoles **105** under the Pd(0)-Cu(I) bimetallic catalyst

E through intervention of the palladium complex **D**. Regeneration of Pd(0) catalyst by reductive elimination of complex **E** results in 2-allyltriazole **105**. Cu would activate the C–C triple bond by forming a copper-acetilyde species. One of the



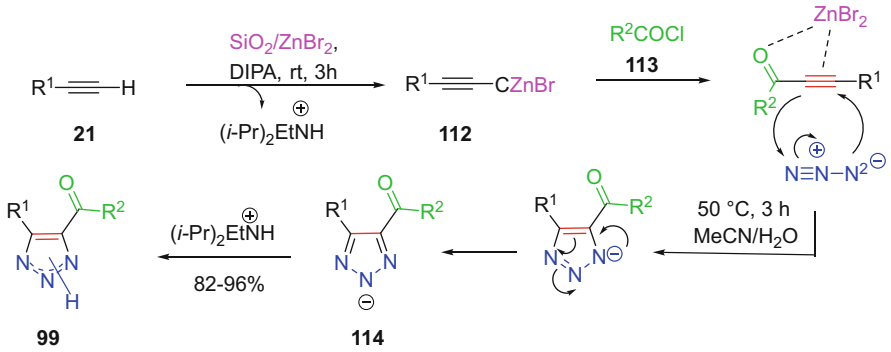
Scheme 39 One-pot two-step synthesis of *N*-hydroxymethyl-1,2,3-triazoles **106**

main particularities of this reaction was the extremely high regioselectivity since no other isomer was registered. The structure of the final product was controlled by the composition of complex catalyst.

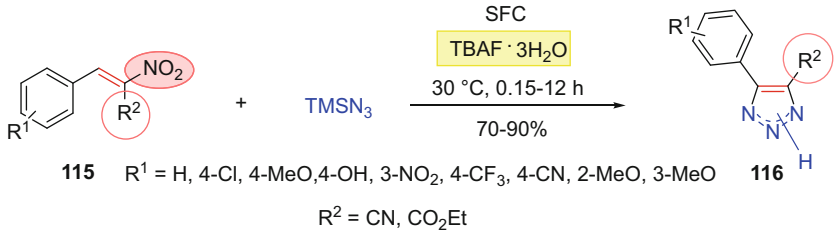
Several examples of the synthesis of 2-hydroxymethyl-2*H*-1,2,3-triazoles **106** were presented in literature [39, 131]. A one-pot stepwise reaction of formaldehyde, sodium azide, and a terminal alkyne **21** took place under slightly acidic (pH 6.5) conditions, representing another example of the synthesis of 2-substituted triazoles by catalytic cycloaddition [131] (Scheme 39).

For all tested alkynes, a mixture of 1- and 2-hydroxymethyl triazoles **106** and **107** was obtained. 2-Substituted triazoles were the major products and this fact was confirmed by the appearance of a characteristic chemical shift of the hydroxymethylene carbon atom in the ^{13}C NMR spectra and by X-ray crystallographic analysis. The identity of the minor product **107** was revealed by the heteronuclear correlation experiments. *N*-Hydroxymethyltriazoles **106** are attractive precursors due to their versatility. The described approach can be very convenient to obtain a broad variety of 2*H*-substituted 1,2,3-triazoles **109–111**, as well as NH-triazoles **22**. The authors also have evaluated the applicability of this method for gram-scale synthesis [131].

4,5-Disubstituted 1,2,3-triazoles **99** were obtained via an efficient one-pot procedure performed as a cross coupling/1,3-dipolar cycloaddition between acyl chlorides **113**, terminal alkynes **21**, and sodium azide [133, 134]. The reaction was performed in the presence of silica-supported zinc bromide (Scheme 40) [134]. When all substrates, $ZnBr_2$ as a catalyst and a base (DIPA or TEA) were dissolved in various solvents (MeCN, dioxane, THF, DMF) a poor yield of the desired 1,2,3-triazole **99** was obtained. However, if the reaction was performed in a sequential mode (the reaction between acyl chloride **113** and acetylene in first place and reaction with added azide afterwards) 62–96% of product was achieved. The reaction was carried out in different solvents or in solvent-free conditions (SFC),



Scheme 40 Synthesis of 4,5-disubstituted 1,2,3-triazoles **99** in the presence of silica supported-zinc bromide

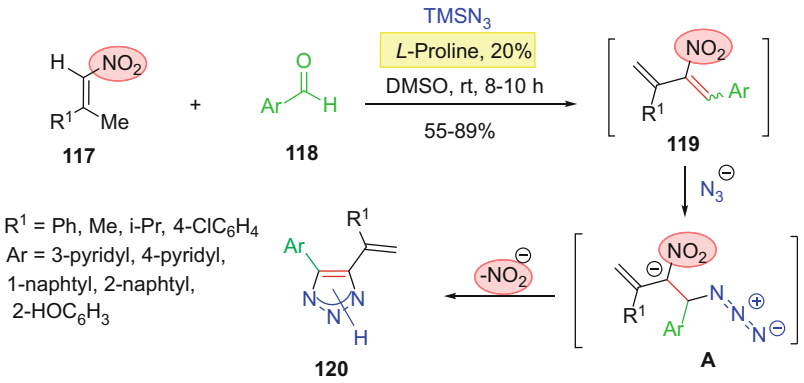


Scheme 41 Synthesis of 4-aryl-1,2,3-triazoles **116** through TBAF-catalyzed [3+2]-cycloaddition of 2-aryl-1-nitroethenes with $TMSN_3$ in SFC

adding $ZnBr_2$ or $ZnBr_2/SiO_2$ (10%) to the acyl chloride/acetylene mixture at initial step. The addition of sodium azide was postponed and 1,3-dipolar cycloaddition via ynone intermediate **112** was then yielding 2*H*-1,2,3-triazole **99** (Scheme 40).

A new chemically efficient, solvent-free, preparative procedure for 4,5-disubstituted NH-1,2,3-triazoles was described and proceeded as TBAF- or TBAB-catalyzed [3+2]-cycloaddition [98, 134, 135]. 2-Aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes **115** did not interact with $TMSN_3$ [98] in SFC and in an absence of any additives, even after 24 h. Addition of tetrabutylammonium bromide (TBABr) acting as catalyst allowed to obtain a triazole **116** (SFC, 30 °˜C). Best results were achieved if 0.1 equiv TBAF was applied. The proposed protocol was simple to perform: no dried glassware or inert atmosphere was required (Scheme 41).

Along with the metals and TBAF, TBAB, proline can catalyze the cycloaddition reaction. A convenient atom-efficient protocol for the preparation of 4,5-substituted NH-triazole **120** was developed as a one-step cascade reaction between nitroalkene,



Scheme 42 One-pot cascade synthesis of 4,5-disubstituted-(NH)-1,2,3-triazole **120**

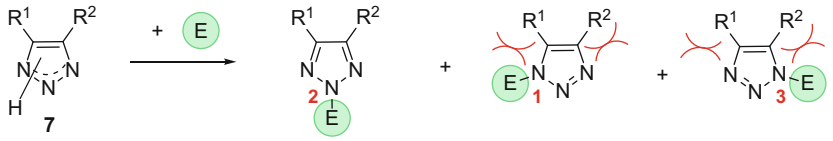
aldehyde, and NaN_3 catalyzed by proline [136, 137]. A variety of aryl aldehydes **118** and β-alkyl nitroalkenes **117** were suitable for this transformation. The reaction performance was controlled by the character of the aromatic substituent on the aldehyde and by the reaction temperature. Non-substituted and electron-deficient aromatic aldehydes worked well in this cascade transformation. The reaction with aryl aldehydes, bearing electron-donating groups, had poorer yields at room temperatures. Improved yields of 1,2,3-triazoles were achieved by increasing the temperature up to 80°C (Scheme 42) [137].

The mechanism for this reaction is shown in Scheme 42. It involves a step of in situ formation of highly reactive intermediate, 2-nitrobuta-1,3-diene **119**. Comparing to conventional procedure for 1,3-dipolar cycloaddition, the cascade approach avoids the difficulties of synthesis of α-nitroalkene dipolarophiles, and, therefore, significantly extends the scope of substrates suitable for this reaction.

The analysis of the literature on this topic has shown that a variety of diverse approaches to synthesize 2*H*-1,2,3-triazoles via a 1,3-dipolar cycloaddition of azides with alkynes/alkenes exist and includes conventional, catalytic, one-pot multi-step, and solid-phase synthetic procedures. There are obvious advantages of using them at larger scales. However, a main challenge to propagate them to industrial scales is the availability and the cost for alkynes/alkenes. In addition, the explosive character of organic/inorganic azides substantially limits their use for industrial synthesis.

4 Synthesis of 2-Substituted 1,2,3-Triazoles by Reactions of NH-1,2,3-Triazoles with Electrophiles

The vast majority of N(1) substituted 1,2,3-triazoles were obtained by the cycloaddition reaction of organic azides to alkynes and alkenes. Nonetheless, these reactions do not allow to obtain 2-substituted triazoles directly. To overcome



Scheme 43 Proposal products of the reaction of NH-triazoles with electrophilic agents

this restriction several approaches have been developed. N(2)-Substituted triazoles were synthesized by rearrangement of 1-substituted triazoles initially formed in cycloaddition of unsaturated C–C bonds to organic azides (paragraph 2.3 and 3), metal-catalyzed three-component cycloaddition (paragraph 3) metal-free solid phase synthesis (paragraph 2.9). These examples were limited to N(2)-hydroxymethyl-, N(2)-allyl, N(2)-aryl-1,2,3-triazoles (Schemes 29, 35, 36, 37, and 39).

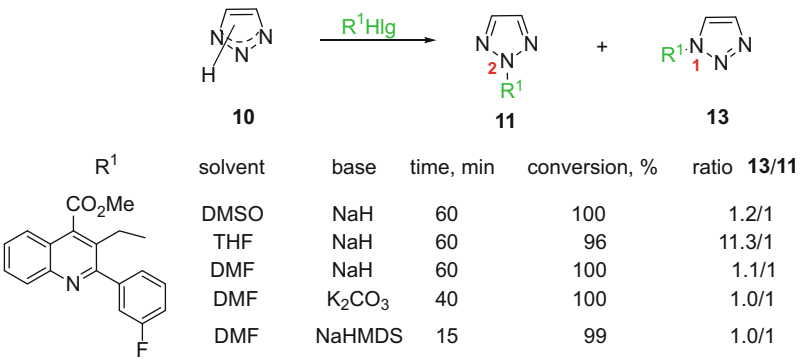
The main route to synthesize N(2)-substituted 1,2,3-triazoles is the reaction of NH-triazoles with electrophiles: alkylation, arylation, acylation, carbamoylation. Synthetic procedures for this type of reactions are well documented [1, 2, 6, 13, 18, 25, 27, 29, 31–34, 47, 49–53, 57, 59, 61, 62, 72, 83, 96, 104, 117, 118, 128, 131, 132, 136–234].

In general, all three nitrogen atoms in triazole cycle can participate in electrophilic substitution [1–6]. Most of the publications describing the transformations occurring in NH-1,2,3-triazoles pointed out that in first place a substitution at the N (1)- or N(3)-nitrogen atoms proceeds, resulting from a higher electronic density on the N(1) or N(3) atoms compared to the one at the N(2) atom (Scheme 43).

However, the thermodynamic stability of N(2)-substituted triazoles is much higher. Furthermore, the steric hindrance, caused by the presence of substituents at C(4)- and C(5)- atoms at the heterocycle, increases the predisposition for the central nitrogen atom to react with electrophiles. All listed factors can easily explain the formation of a mixture of products in the reaction of NH-1,2,3-triazoles with electrophilic agents. As a result, research for routes to increase the selectivity of the synthesis or the development of separation processes (liquid column chromatography, flash chromatography) becomes an integral part for the synthetic approach described above. Due to these reasons a selective N(2)-substitution remains a big challenge for the chemistry of triazole functionalization.

4.1 N-*Alkylation of NH-1,2,3-Triazoles with Alkylhalides*

N-Alkylation of NH-1,2,3-triazoles can be implemented as a nucleophilic substitution onto alkylhalides [25, 33, 50–53, 57, 61, 62, 72, 96, 118, 136, 138–171], diazoalkanes [32, 171], alkyl sulfonates or carboxylates [59, 62, 172–181], alcohols (Mitsunobu reaction) [131, 137, 182–186] or as a nucleophilic addition of alkenes and alkynes activated by EWG-groups (Michael addition) [50, 104, 187–197].



R^1	solvent	base	time, min	conversion, %	ratio **13/11**
CO_2Me	DMSO	NaH	60	100	1.2/1
	THF	NaH	60	96	11.3/1
	DMF	NaH	60	100	1.1/1
	DMF	K_2CO_3	40	100	1.0/1
	DMF	NaHMDS	15	99	1.0/1

Scheme 44 N(1)/N(2)-Selectivity in the alkylation of unsubstituted NH-1,2,3 triazole **10** by alkyl halides

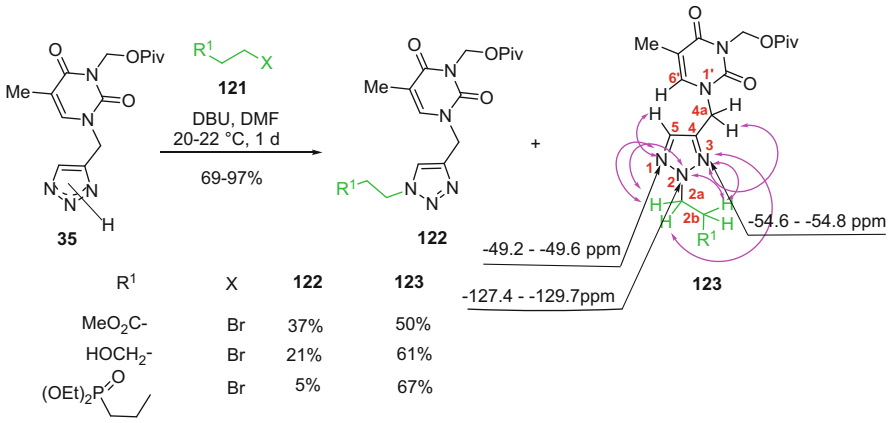
A significant drawback of this method is the formation of a mixture of regio-isomeric *N*-alkyl-1,2,3-triazoles. Quite often the product ratio in this reaction is unfavorable for the N(2)-isomer, especially in the case of simple alkylating agents and unsubstituted, or monosubstituted NH-1,2,3-triazoles [149–153].

The *N*-alkylation of NH-triazoles was carried out in the usual manner in acetone, DMF, DMSO, acetonitrile, EtOH, EtOAc and in the presence of different bases (K_2CO_3, NaH, Na_2CO_3, Cs_2CO_3, EtONa, NaHMDS, LiHMDS, KHMDS, TEA, DBU) [25, 33, 50–53, 57, 61, 62, 72, 96, 117, 136, 138–171]. The application of base is necessary: the reaction was unsuccessful if the base was not added. Screening for optimal reaction conditions revealed that the choice of a solvent and a base was crucial for the kinetics and resulted in different reaction rates. However, the influence of these factors on the reaction regioselectivity is subtle. Stronger bases, such as NaH, caused the deprotonation of NH-proton and favored N(1)-substitution. On the other hand, the nature of electrophile mainly influenced the regioselectivity of the reaction [136].

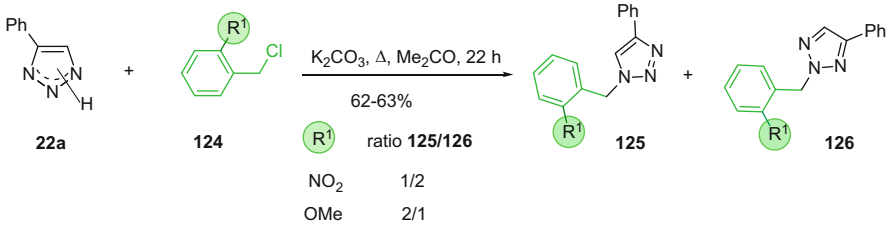
As a result, alkylation of NH-1,2,3-triazole **10** led to two isomers **11** and **13**, and their ratio depended on the electron-withdrawing nature of the substituents on the alkylation agent. The reaction was also sensitive to the type of solvent (Scheme 44) [33, 51, 118, 139–148, 157].

Variation by combination of different conditions (solvent, base and temperature) did not further improve the yield of N(2)-isomer. Despite considerable efforts being made to get a better ratio, a 1:1 mixture of 1*H*- (**13**) and 2*H*-isomers (**11**) was obtained in all circumstances.

The alkylation of C(4)-substituted triazoles may lead to different ratios of three regio-isomers, namely 1-, 2-, and 3-alkylated products, as described in several reports [25, 50, 53, 149–153]. Because of the spatial hindrance between the two neighboring groups, the thermodynamic stability of the latter isomer was decreased and some authors were able to detect this only in trace amounts and in selected cases. For example, 1-(2*H*-1,2,3-triazol-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione **35**



Scheme 45 *N*-Alkylation of 3-(pivaloyloxymethyl)-1-[(NH-1,2,3-triazol-4-yl)methylthymine **35**

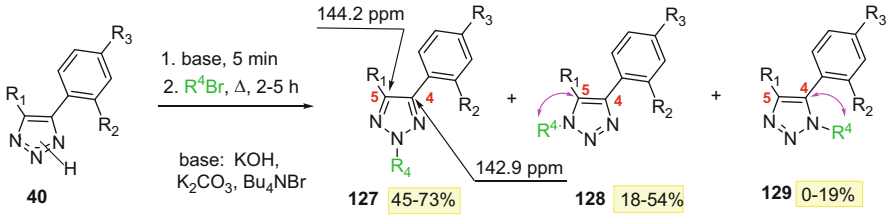


Scheme 46 Reaction of 4-phenyl-1,2,3-triazole **22a** with 2-nitro- and 2-methoxybenzyl chlorides **123**

reacted with methyl bromoacetate, 2-bromoethanol or diethyl 3-bromopropylphosphonate yielding 69–87% (combined) of **122/123** (Scheme 45) [50]. The N(2)/N(1) regioselectivity of the alkylation varied from 37:50 (methylbromoacetate) to 67:5 (diethyl 3-bromopropylphosphonate). Steric effects and the specific nature of the R-substituent on the electrophilic carbon in **121** were considered as factors to impact the course for the alkylation. The structure of 2-alkyl-2*H*-1,2,3-triazolonucleosides **123** was confirmed by ^{1}H-^{15}N HMBC NMR spectra. The triazole nitrogen atoms were identified through their correlation with *exo*-cyclic protons of the side chain.

Alkylation of NH-1,2,3-triazole **22a** with benzyl chlorides **124** confirmed the previously established importance of electronic effects of the alkyl halide substituents R^{1} for the direction of the reaction (Scheme 46) [25]: the ratio of obtained isomers **125** and **126** convincingly reflected this trend.

The problem of regioselectivity is present to the full extent for the alkylation of 4,5-disubstituted 1,2,3-triazoles [52, 53, 62, 72, 137, 154–171]. *N*-Alkylation of unsymmetrical 4,5-disubstituted-1,2,3-triazoles produced a mixture of three regioisomers: **127** N(2)-, **128** N(1)-, and **129** N(3) (Scheme 47) [52]. For this



R^1 = H, Ph, 4-MeC$_6$H$_4$ R^2 = H, Cl, F R^3 = OMe, Me, Cl, Br R^4 = C$_5$H$_{11}$, Bn, CH$_2$C$_6$H$_3$Br-4, CH$_2$CO$_2$Et

Scheme 47 Alkylation of 4,5-disubstituted-1,2,3-triazoles **40**

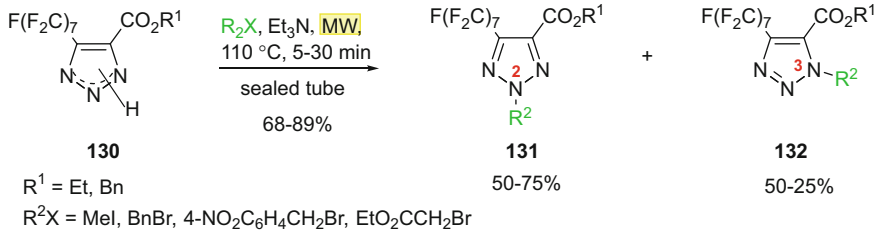
type of substrates, N(2)-isomers were the major products. N(3)-Substituted 1,2,3-triazole **129** was obtained in small proportion or could not be detected, possibly, as a consequence of steric effects.

The question of relative stability of isomers **127–129** was assessed by quantum chemical calculations. The stability of the N(1)-, N(2)-, and N(3)-isomers was evaluated at B3LYP/6-311++ G (d,p) level of theory was in line with experimentally observed ratios.

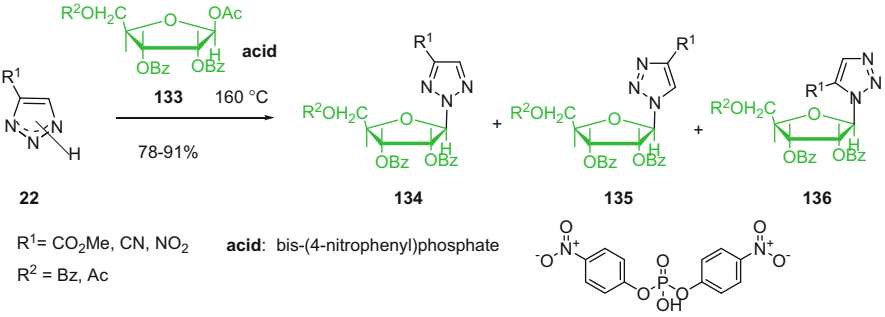
The structural assignment of compounds **127–128** was based on 2D ^{1}H-^{13}C NMR experiments. While no correlation was observed for **127**, the spectra of **128** and **129** exhibited different types of correlations between the H-signal of the CH$_2$-group in the alkyl chain (R^4) and the C(5)- or C(4)-signals for 1,2,3-triazole ring (Scheme 47).

Alkylation of NH-triazole can be performed by a microwave procedure [62, 136, 169, 170]. A series of fluoroalkylated 1,2,3-triazoles **131** and **132** were synthesized in significant yields. Nevertheless, it should be noted that two regioisomeric triazoles were formed. As it was expected, N(2)-isomer of the 4,5-substituted triazole was the major product and the ratio between the N(2)- and N(1)-isomers depended on the spatial effects of the substituents. The structure of the isomers was carefully analyzed by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy and X-ray diffraction [62].

It was shown that the selectivity of N(1)-alkylation of 1,2,3-triazole could be enhanced by introducing metal salts (Ag(I), Tl(III) or Hg(II)) [1]. Glycosylation of ethyl 1,2,3-triazole-4-carboxylate with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in the presence of mercuric cyanide gave N(1)-glycosylated product only [179], while acid-catalyzed fusion led to a mixture of N(1) and N(2)-triazoles [179]. The reaction of NH-1,2,3-triazole with β-bromostyrene resulted in the 2-isomer exclusively if CuI was added, in opposite to an analogous transformation described above (Scheme 48) [146].



Scheme 48 Microwave-assisted alkylation of NH-triazole **129**



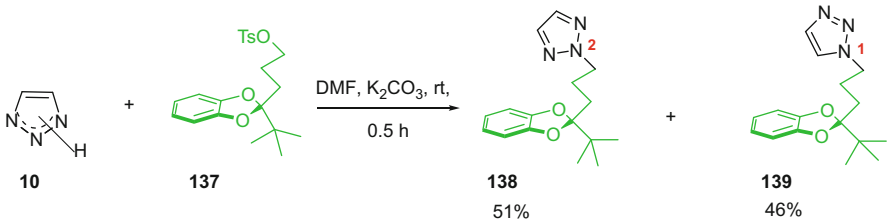
Scheme 49 Synthesis of 1,2,3-triazole nucleosides via procedure of acid-catalyzed fusion

4.2 Alkylation of NH-1,2,3-Triazoles with Alkyl Carboxylates and Sulf(on)ates

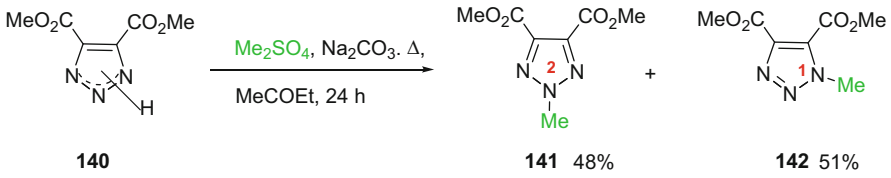
The regioselectivity factor was also very important for the alkylation of NH-1,2,3-triazoles by alkyl carboxylates and sulf(on)ates [59, 62, 172–181]. The fusion of methyl 1,2,3-triazole-4-carboxylate (**22**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofurinose (**133**) in the presence of an acidic catalyst provided a mixture of nucleosides **134** and **135**, and a third isomer **136**, in approximate ratio 60:30:10 ratio (Scheme 49). 1- and 3-glycosyl-4-substituted-l,2,3-triazoles **134** and **136** were identified by comparing them with the same compounds synthesized by alternative reaction via cycloaddition of methyl propiolate with 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl azide (Scheme 49) [177–181].

Reaction of unsubstituted NH-1,2,3-triazole **10** with tosylate catechol ketal **137** at room temperature with a base led to 1,2,3-triazole isomers **138** and **139** with good yields and in equal ratio (Scheme 50) [173].

Methyl 1,2,3-triazole 4,5-dicarboxylate **140** underwent a methylation with dimethyl sulfate in methyl ethyl ketone and anhydrous sodium carbonate (Scheme 51). A mixture of the *N*-methylsubstituted isomers **141** and **142** was isolated in quantitative yield. Isomers were separated by flash-chromatography through a silica-gel column [181] and were characterized by analytical and spectroscopic analyses. The results were in accordance with known data for the isomer **142**



Scheme 50 Reaction of NH-1,2,3-triazole **10** with tosylate catechol ketal **137**



Scheme 51 Reaction of NH-1,2,3-triazole 4,5-dicarboxylate **139** with dimethyl sulfate

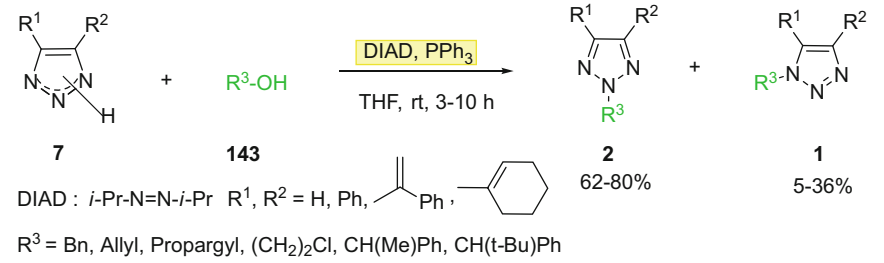
obtained from methyl azide (Scheme 51) [181]. The ratio of isomers **141**/**142** was 51:48, respectively, as determined by gas chromatography.

4.3 Mitsunobu Reaction of NH-1,2,3-Triazoles

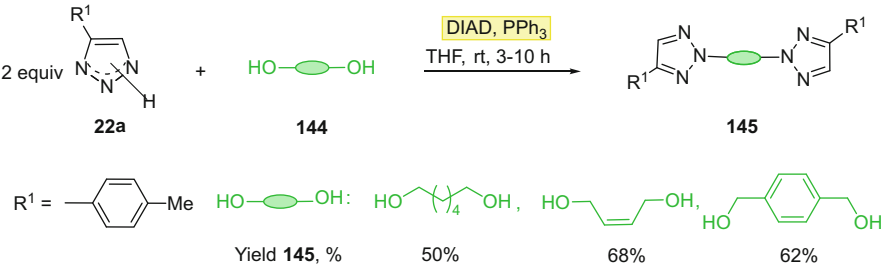
The relatively high acidity (pKa 8–10) and strong nucleophilicity make NH-1,2,3-triazoles suitable partners of alcohols reacting in Mitsunobu reaction (DIAD, PPh_3 in THF) (Scheme 52) [131, 137, 182–186].

Compared to the above described examples of alkylation, significantly higher yields of N(2) products were observed for all cases of the Mitsunobu reaction. The reaction with secondary alcohols required longer times (8–12 h) and provided N(2)-isomers as the major products [184]. The significance of the choice of the alcohol for influencing the N(1)/N(2) selectivity was highlighted for the synthesis of bis-N(2)-triazole derivatives **145** (Scheme 53).

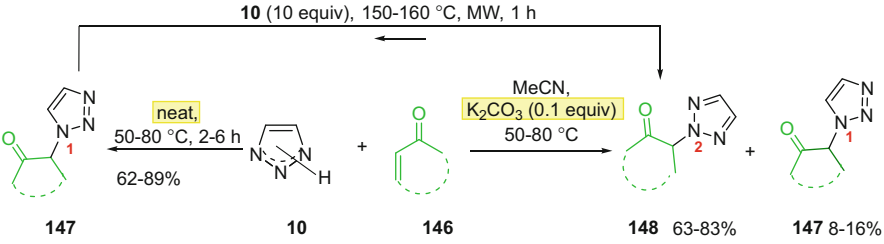
The conditions of the Mitsunobu reaction were suitable for a wide variety of alcohols and in general provided excellent yields of coupling products. Combined yields of N(1) and N(2)-isomers were more than 85%. This method can serve as a good alternative for N(2)-substitution involving no catalysts or sophisticated manipulation while altering the reactivity of the triazoles. Moreover, with the excellent stereochemical control, this method establishes the background for an asymmetric synthesis of pure 2*H*-1,2,3-triazole derivatives [184].



Scheme 52 Mitsunobu reaction of 4,5-disubstituted NH-1,2,3-triazoles **7**



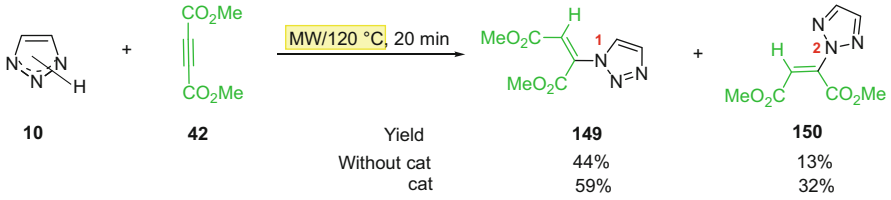
Scheme 53 Synthesis of bis(1,2,3-triazoles) **145** under Mitsunobu conditions



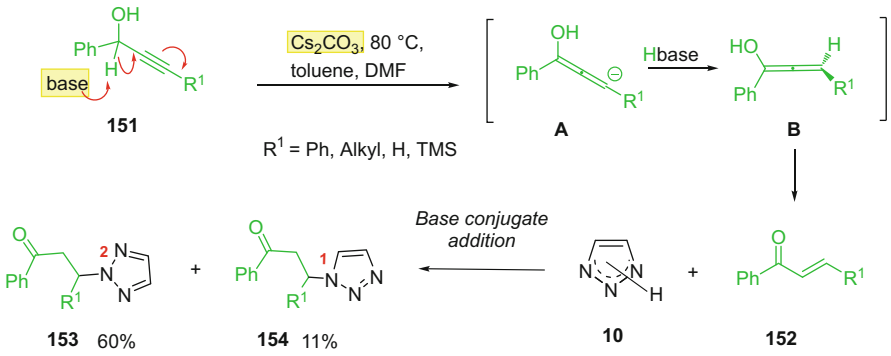
Scheme 54 Michael addition of NH-triazole **10** to α,β-unsaturated ketones **145**

4.4 Michael Addition

Ethyl propiolate, dimethyl acetylenedicarboxylate, phenyl propiolic aldehyde, and ethylphenylpropiolate reacted with triazole salts (triazolides) giving Michael adducts, with preference for the N(2)-isomers [50, 104, 187–197]. The selectivity depended on reaction conditions. Michael addition of neat triazoles with alkynones taking place upon heating led to N(1)-triazoles **147**. However, heating of reagents in aprotic solvents (acetonitrile was the best) and under basic conditions (K_2CO_3) yielded predominantly N(2)-substituted triazoles **148** (Scheme 54) [189].



Scheme 55 Reaction between NH-1,2,3-triazole **10** and DMAD



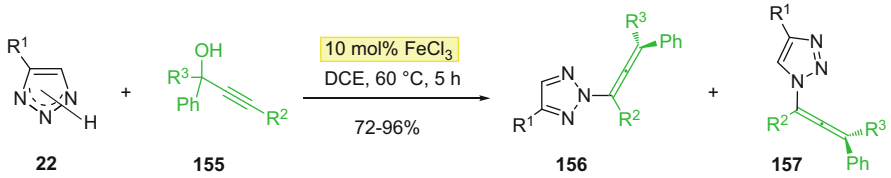
Scheme 56 Reaction of NH-1,2,3-triazole **10** and propargyl alcohols **150** in base condition

Michael addition of NH-1,2,3-triazole **10** and DMAD under microwave irradiation in the absence of catalyst led to a mixture of products **149** (as the *E*-stereoisomer) and **150** (as a of *Z*/*E* mixture in 7:3 ratio) (Scheme 55) [191]. The overall yields of **149** and **150** increased from 57 to 91% with little change in the isomers ratio when silica-bound $AlCl_3$ was used as the catalyst.

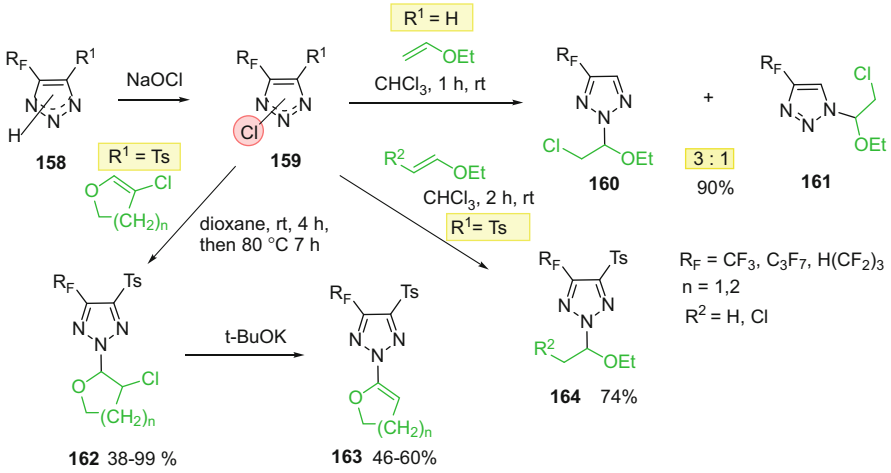
Conjugated addition of triazole to propargyl alcohols **151** in the presence of DBU was unsuccessful [191]. Heating of triazole **10** with propargyl alcohols **151** in toluene with DMF and DBU was sluggish. The corresponding triazoles **153** and **154** (6:1) were isolated in satisfying total yield. Redox-isomerization of accessible propargyl alcohols occurred via conjugated one-step addition of NH-azole **10** proceeded by nucleophilic attack of basic reagent. This reaction displayed a broad scope and tolerated a variety of reactive functional groups (Scheme 56) [187].

Triazole addition to tertiary propargyl alcohols occurred in a regioselective manner in the presence of iron catalyst and led to allene triazoles **156** and **157**. The reaction proceeded under mild conditions, giving a mixture of regioisomers **156** and **157** in good or excellent yields (Scheme 57) [188].

To improve further the regioselectivity of this reaction the screening of different metals ($Cu(OAc)_2$, CuI, $PdCl_2$, $RuCl_3$, $IrCl_3$, $Fe(acac)_3$, $LaCl_3$, $CeCl_3$, $Bi(OTf)_3$, $AlCl_3$, $SnCl_2$, LiCl) as catalyst and different solvents (MeCN, Me_2O, THF, Toluene, MeOH, $MeNO_2$, DMSO, DMF, $CHCl_3$, EtOAc, DCE) was performed. It was found that $FeCl_3$/DCE conditions were the best option [183, 188].



Scheme 57 Reaction of 1,2,3-triazole **22** addition to tertiary propargyl alcohols **155**



Scheme 58 Nucleophilic addition NH-1,2,3-triazole to electron-rich alkenes via *N*-halogenated derivative **158**

Regioselective addition at the N(2)-position of 1,2,3-triazoles should be achieved via their transformation into N(2)-halogen derivatives. N(2)-Chlorotriazoles **159** reacted with double bonds of vinyl ethers [104], 2,3-dihydro-2*H*-furan (DHF), and 3,4-dihydro-2*H*-pyran (DHP) [197] at room temperature (Scheme 58).

Monosubstituted 1,2,3-chlorotriazole **158** (R^1=H) reacted with alkenes giving a mixture of 1- and 2-alkyl derivatives **160** and **161**. At the same time, 4,5-disubstituted triazole **159** led to 2-substituted derivatives **162–164** only. Compound **163** was obtained after elimination of HCl from adduct **162**.

Obviously, due to the formation of the product mixture observed for the most cases of described alkylation examples, the separation of products becomes an important task to be performed at the final step. Luckily, the lower polarity of the desired N(2)-isomers comparing to the N(1)/N(3) ones can substantially facilitate this process.

4.5 N-*Arylation (*N-*Heteroarylation) of NH-1,2,3-Triazoles*

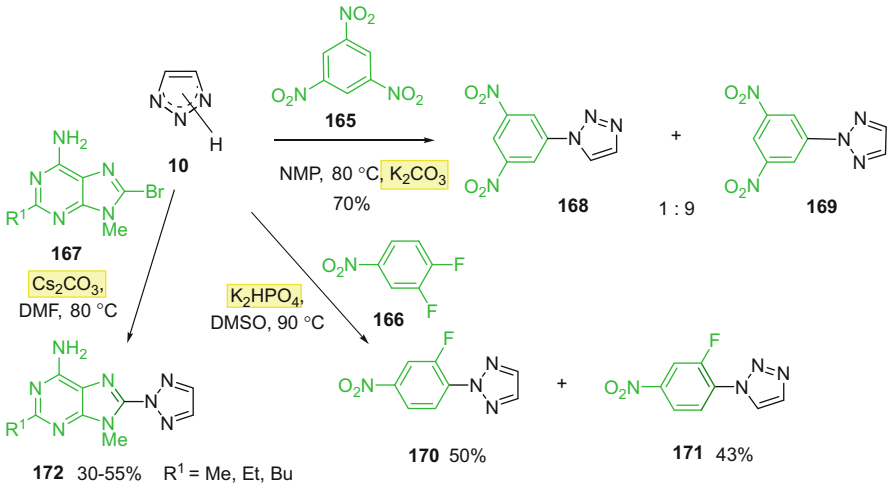
Theoretically, an ideal route to obtain *N*(2)-aryl(heteroaryl)-1,2,3-triazoles would be a direct *N*-arylation(heteroarylation) of NH-1,2,3-triazoles [18, 27, 29, 31, 34, 49, 117, 128, 132, 146, 149, 163, 198–223]. This reaction, occurring at higher temperatures (50–120 °C) in DMF, DMSO, MeCN, acetone, THF and catalyzed by bases (K_2CO_3, Cs_2CO_3, NaH, KOH, K_2HPO_4), could not provide an acceptable yield of desired product. It was because the reaction resulted in in a mixture of two isomers in various ratios and with lower (20–50%) total yields [34, 49, 215, 217, 219]. An increase of the total yields, up to 60–70%, was observed only for *N*-arylation (heteroarylation) of NH-1,2,3-triazoles with activated electrophiles (1,3,5-trinitrobenzene or pentafluoropyridine) (Scheme 59) [18, 31, 132, 163, 200, 202, 210, 217, 219, 223].

To evaluate the regioselectivity for *N*-arylation/heteroarylation, the S_NAr substitution of various NH-1,2,3-triazoles was studied [18]. The product of arylation was stable and no C–N bond exchange occurred under the reaction conditions. This allows to evaluate directly the impact of C(4) and C(5) groups on the regioselectivity of this reaction. The introduction of phenyl group to the C(4)-atom of the 1,2,3-triazole **7** (R^1=Ph, R^2=H) increased the selectivity and resulted in the major N(2)-arylation product, although with small ratio differences for all possible products. As reported previously, the selectivity of the reaction is controlled by both electronic and steric factors. A rise in the temperature leads to the strengthening of conformational factors and increases the steric effects of the C(4)- and C(5)-substituents. Indeed, N(2)-selectivity was noticeably improved with an increase of the reaction temperature (Scheme 60).

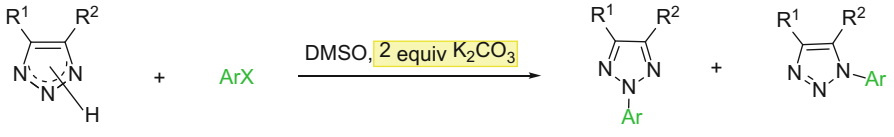
Arylation of NH-1,2,3-triazoles by different agents, including moderately active aryl halides was observed under Ullman conditions, e.g. in the presence of Cu(I,II) salts, and yielded N(2)-aryl-1,2,3-triazoles **176–178** (Scheme 61) [18, 198, 206, 221, 224–229].

The mechanism of this reaction was unresolved until now. Most likely, it involves the formation of Cu(III) intermediate followed by reductive elimination. It was established that the Cu(I) or Cu(II) oxidative addition to the carbon–halogen bond occurs via a catalytic cycle which is strongly dependable on the ligand type. Furthermore, a study of the reaction conditions established that *N*(2)-aryl-1,2,3-triazoles are formed exclusively if ligands were applied as co-catalysts. The best ligand among all co-catalysts tested (proline, glycine, Me-Gly, EDA, DMEDA, TMEDA, DACH) was proline [18].

Biarylphosphine palladium was found to be the most selective metal catalyst for the synthesis of 4,5-unsubstituted and 4-substituted N(2)-arylated 1,2,3-triazoles [207]. A variety of aryl bromides, chlorides, and triflates with ester, ketone, aldehyde, acetal, nitro, and cyano groups could be employed in this reaction. Slightly decreased N(2)-selectivity was observed for the reaction of aryl chlorides bearing an EWG at the *para*-position. For all other substrates an excellent N(2)-selectivity (>95%) was observed (Scheme 62).



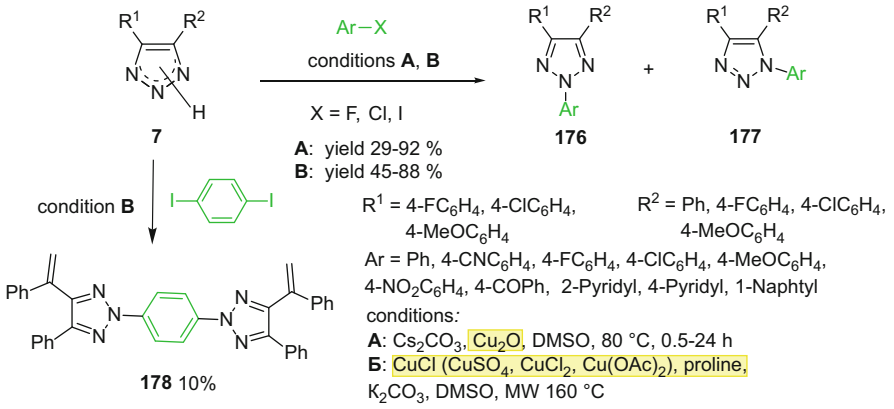
Scheme 59 Reactions of NH-1,2,3-triazole **10** with activated aryls **165**, **166** and 8-Br-purine **167**



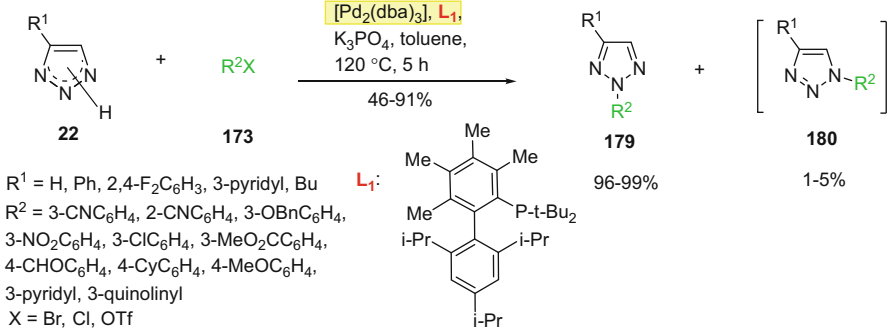
R^1	R^2	ArX	T, °C	time, h	Yield, %	ratio **174**/**175**
H	Ph	2,4-$NO_2C_6H_3F$	rt	2	90	1/7
Ph		2,4-$NO_2C_6H_3F$	rt	2	95	6/1
Ph	PhCO	2,4-$NO_2C_6H_3F$	rt	2	95	Only N(2)
Ph		4-$NO_2C_6H_4F$	80	1	92	10/1
Ph		4-$NO_2C_6H_4Cl$	80	30	90	10/1
Ph		4-CNC_6H_4F	80	30	60	10/1
Ph		4-CNC_6H_4Cl	80	30	-	-

Scheme 60 4,5-Disubstituted triazole **7** arylation via S_NAr reaction

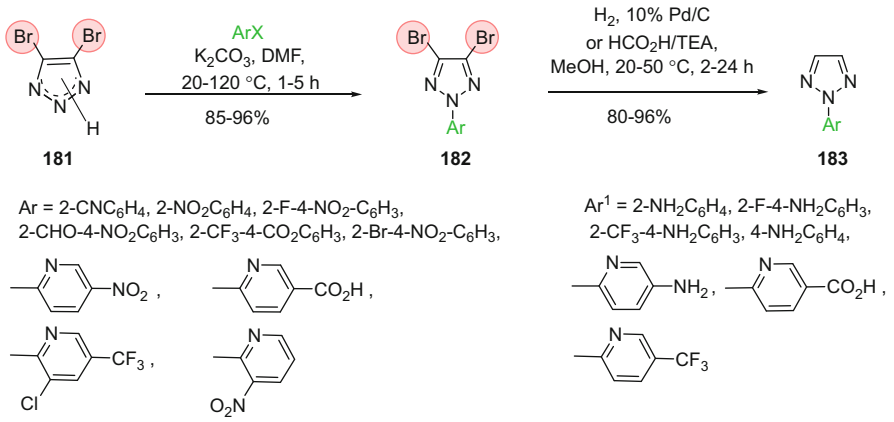
Another protocol for an efficient synthesis of N(2)-aryl-1,2,3-triazoles via highly regioselective N(2)-arylation of 4,5-dibromotriazole was executed (Scheme 63) [210]. Subsequent debromination of these triazoles via a hydrogenation efficiently furnishes 4,5-unsubstituted -2-aryltriazoles in excellent yields. Combination of steric hindrance and an electronic effects induced by 4,5-dibromo substituents



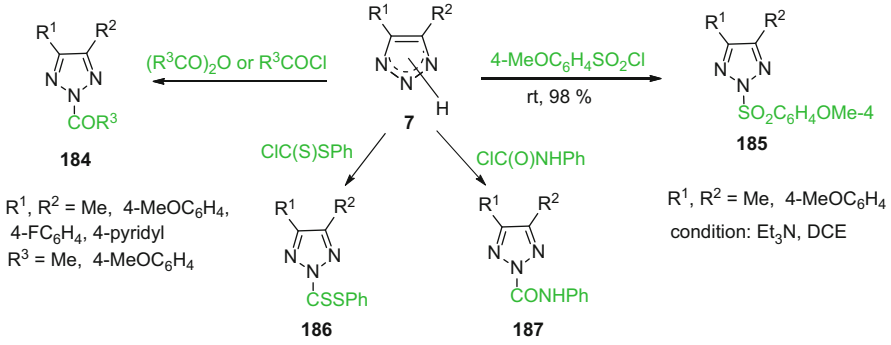
Scheme 61 *N*-Arylation NH-1,2,3-triazole under the Ullman reaction condition



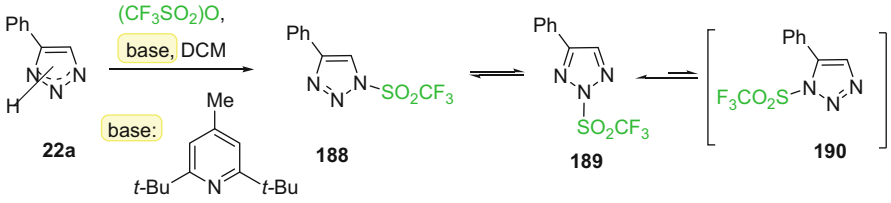
Scheme 62 N(2)-Selective arylation of 4,5-substituted and 4-substituted NH-1,2,3-triazole



Scheme 63 Selective aromatic substitution of 4,5-dibromo-2*H*-1,2,3-triazole



Scheme 64 Reaction of NH-1,2,3-triazole with acyl-, sulfonyl-, and carbamoyl chlorides



Scheme 65 Sulfonation of 4-phenyl-NH-1,2,3-triazole **22a**

contributed to the high regioselectivity observed for this reaction. Thus, the use of 4,5-dibromotriazole **181** as a nucleophile has a substantial practical value for the direct and specific N(2)-arylation of 1,2,3-triazoles.

4.6 N-*Acylation,* N-*Sulfonation, and* N-*Carbamoylation of NH-1,2,3-Triazoles*

In contrast to *N*-alkylation and *N*-arylation, *N*-acylation, *N*-sulfonation, and *N*-carbamoylation of NH-1,2,3-triazoles predominantly yielded 2-acyl-, 2-sulfonyl-, and 2-carbamoyl derivatives **184–187** (Scheme 64) [27, 29, 47, 97, 136, 185, 230–234] due to the lesser stability of N(1)-regioisomers.

2-Acyl-1,2,3-triazoles derivatives itself are relatively stable only under anhydrous and neutral conditions. The treatment of them with an acid or a base causes the hydrolysis and results in NH-1,2,3-triazoles in high yield [136, 233].

Monitoring of the sulfonation of NH-1,2,3-triazole **22a** by ^{1}H NMR spectroscopy allowed to register previously undetected isomer **190**, formed in negligible amounts [233]. Isomers **188** and **189** were formed in approximately 1:1 ratios (Scheme 65).

Nevertheless, all attempts to isolate the corresponding *N*-triflyl triazoles were unsuccessful due to their susceptibility to hydrolysis.

The lower stability of *N*-acyl/sulfonyl derivatives of 1,2,3-triazoles limits their synthetic potential.

5 Synthesis of 2*H*-1,2,3-Triazoles by Transformations of Functionalized Hydrazones

The next major group of methods for the synthesis of 2-substituted 1,2,3-triazoles is based on transformations of hydrazones (oxidative cyclizations, Boulton–Katritzky rearrangement and various types of condensations).

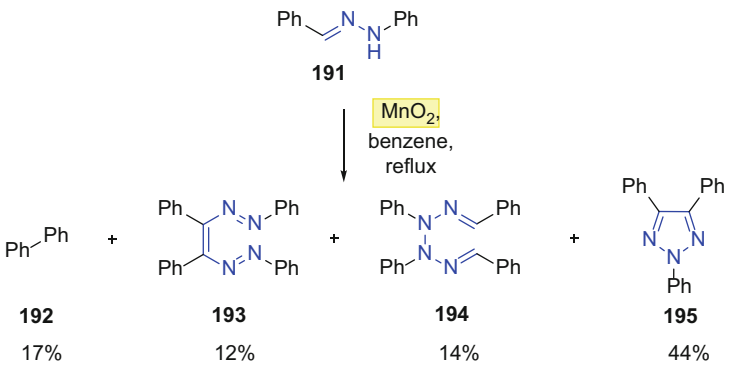
5.1 Oxidation of Mono- and Bis(arylhydrazones)

The first synthesis of a 1,2,3-triazole by the oxidation of bis(hydrazone) of 1,2-aldehydes was carried out by Pechmann [1]. Later this approach was thoroughly studied by other authors [1–6, 235–255]. Heating of ketone phenylhydrazones, bis(hydrazones), bis(aroylhydrazones), or bis(semicarbazones) of 1,2-dicarbonyl compounds in the presence of MnO_2, HgO, $Hg(OAc)_2$, $FeCl_3$, NiO_2, $Pb(OAc)_4$ led to the formation of a mixture of products, including 1,2,3-triazole. Nevertheless, the yield of 1,2,3-triazole was quite low, 15–40%. It was shown that oxidation of arylaldehyde phenylhydrazone **191** with MnO_2 led to 1,4,5-triphenyl-1,2,3-triazole **195** mixed with by-products **192**–**193** (Scheme 66) [235–242].

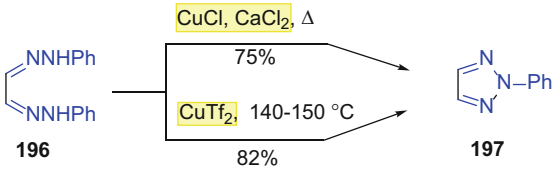
It was also found that oxidative cyclization of bis(hydrazone) **196** of glyoxal proceeded effectively in the presence of copper(I,II) salts (CuOAc, $CuSO_4$, $CuTf_2$, CuCl) (Scheme 67) [243–255].

Oxidative cyclization of bis(hydrazones) is a useful method for the two-step synthesis of triazolyl sugars. For example, D-xylose, D-ribose, D-glucose, and D-galactose were converted into phenylosazones in the first step. The latter underwent an oxidative cyclization with 1% $CuSO_4$, yielding 43–54% of **200** (Scheme 68) [249–255].

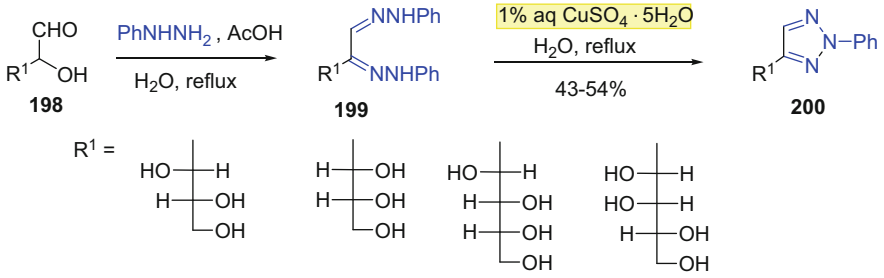
Detailed investigation on the oxidation of arylhydrazones led to the discovery of optimal conditions for the synthesis of 2,4,5-triaryl-1,2,3-triazoles and determined the mechanism of cyclization [244]. The reaction was successfully performed by heating in toluene under air with 20 mol% $Cu(OAc)_2 \cdot 2H_2O$. In polar solvents, such as dioxane, DMSO, and THF, the yield of 2-aryl-1,2,3-triazoles **203** fluctuated from trace amounts to moderate values. The yields increased substantially when molecular oxygen was used. In contrast, the yields of target compounds **203** were reduced in a nitrogen atmosphere. The catalytic activity of different copper sources, such as $Cu(OAc)_2$, $CuCl_2$, $Cu(OTf)_2$, CuCl, and CuI was examined. The catalytic activity of Cu(II) salts was found to be superior to the activity of Cu(I) salts. Control experiments confirmed that no cyclization yielding compounds **203** was observed without a copper source (Scheme 69).



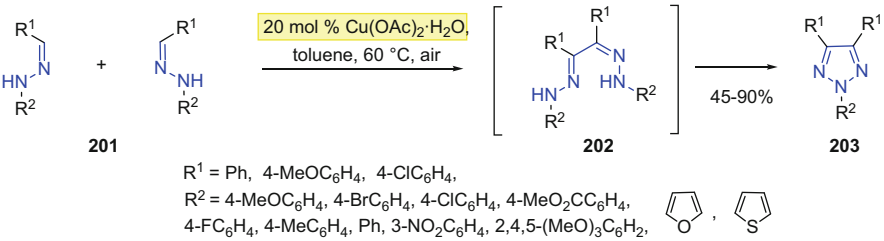
Scheme 66 Phenylhydrazone **191** oxidation in the presence of manganese(IV) oxide



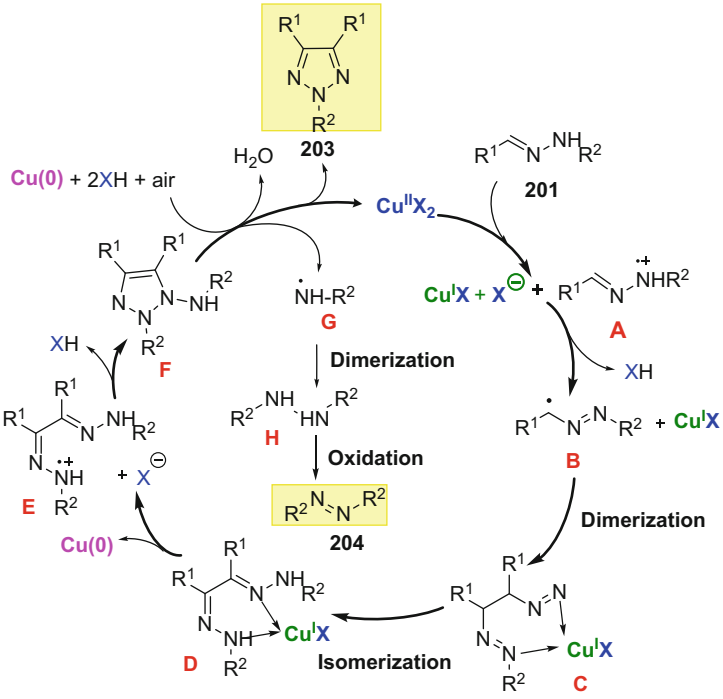
Scheme 67 Cu(I,II) salt catalyzed oxidative cyclization 1,2-bis(2-phenylhydrazono)ethane **196** to 2-phenyltriazole **197**



Scheme 68 Two-step synthesis of triazolyl sugars **200**



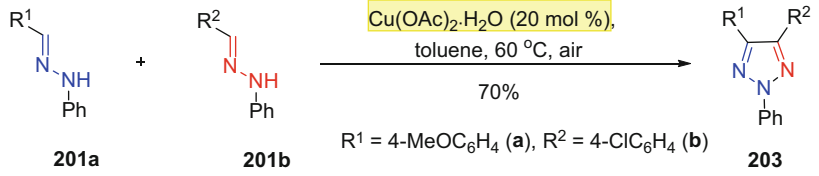
Scheme 69 Copper (II)-catalyzed synthesis of 2,4,5-triaryl-1,2,3-triazoles **201**



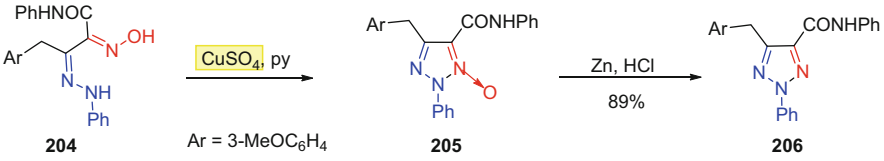
Scheme 70 Proposed catalytic cycle for the synthesis of substituted 2-aryl-1,2,3-triazoles **203** by oxidative cyclization of hydrazone **201**

It should be noted that during the oxidative cyclization of hydrazones **201** into 1,2,3-triazole **203**, intermediates **202** were isolated and their structure was confirmed by X-ray analysis. The result of the addition of TEMPO as an effective radical scavenger to the reaction mixture suggested that this transformation involved a radical intermediate. Analysis of experimental observations helped Guru and Punniyamurthy [244] to propose a plausible scheme for the synthesis of substituted 1,2,3-triazoles (Scheme 70). The generation of copper(0) was confirmed by the powder XRD analysis. Azo compounds **204** were also separated and identified by single-crystal X-ray analysis. The reaction was general, and a series of substrates underwent this cyclization to give target compounds in moderate to high yields.

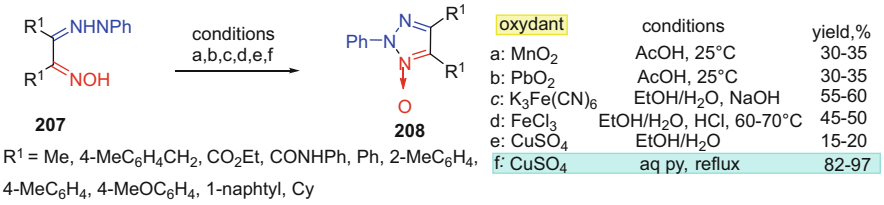
Moreover the reaction conditions were appropriate to obtain unsymmetrical 2,4,5-triaryl-1,2,3-triazoles **203** (Scheme 71) [244]. Finally, an optimal scale-up of the conditions for this reaction was developed to afford desired triazoles in 75–77% yields, but these updated conditions led to slightly extended reaction times.



Scheme 71 Copper(II)-catalyzed synthesis of unsymmetrically substituted 1,2,3-triazole **203**



Scheme 72 Synthesis of 2-phenyl-1,2,3-triazole **206** via the 2-phenyl-2*H*-1,2,3-triazolium 1-oxide **205**



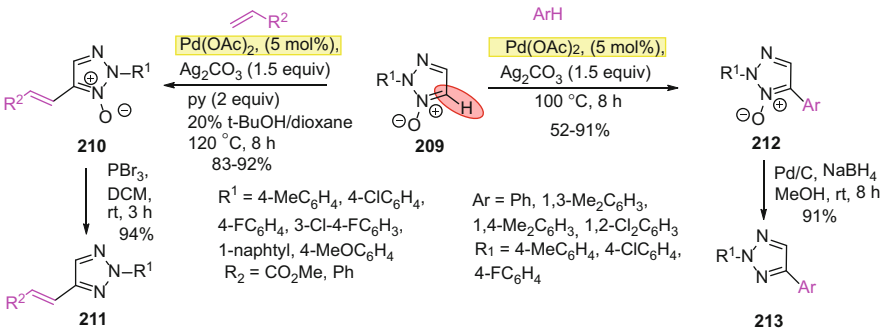
Scheme 73 The influence of various oxidative agent and solvents on the yield of 2-aryl-1,2,3-triazolium 1-oxide **208**

5.2 *Oxidative Cyclization of Arylhydrazonoacetamidoximes and α-Hydrazono-Oximes*

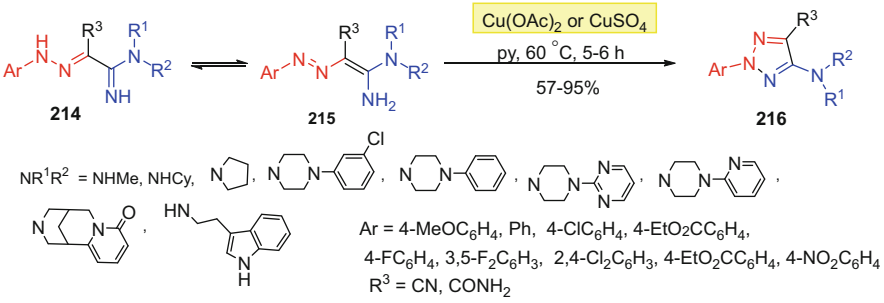
Oxidative cyclization of 2-(2-arylhydrazono)acetaldehyde led to 2-aryl-1,2,3-triazolium 1-oxides [256–268]. 1,2,3-Triazole derivatives **205** were easily transformed into 2-aryl-1,2,3-triazoles **206** by zinc reduction (Scheme 72) [259].

Various oxidative agents were applied for this reaction: $K_3Fe(CN)_6$, PbO_2, MnO_2, $FeCl_3$ $CuSO_4$, and *N*-iodosuccinimide. The heating of substrates in pyridine with copper(II) sulfate was the most effective method to reach an excellent yield (82–97%) (Scheme 73) [263].

This method used to construct the 1,2,3-triazole ring has an important synthetic application. The highly selective character of C–H bond activation occurring in triazolium 1-oxides **209** allowed them to interact with alkenes (site-selective alkenylation) and inactivated arenes (cross-coupling) in a regioselective manner in the presence of a Pd-catalyst (Scheme 74) [257].



Scheme 74 Reactions of 2-aryl-1,2,3-triazolium N-oxides **209** with alkenes and arenes

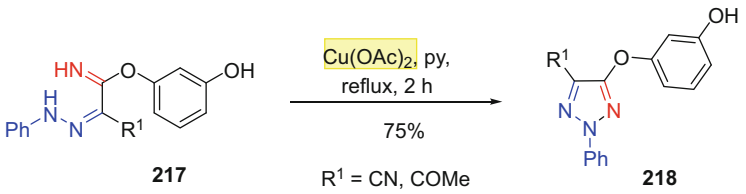


Scheme 75 Oxidative cyclization of hydrazonoacetamidines **214** to 5-amino-2-aryl-2*H*-1,2,3-triazoles **216**

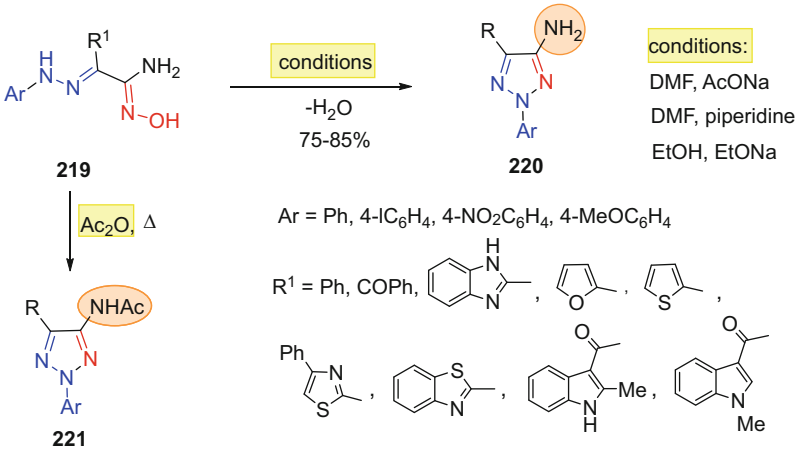
5.3 Oxidative Cyclization of Arylhydrazonoacetamidines

A series of 5-amino-2-aryl-2*H*-1,2,3-triazoles were successfully prepared by oxidation of arylhydrazonoacetamidines with copper(II) salt in pyridine [269–274]. The oxidative cyclization of 2-arylhydrazonoacetamidines **214** was carried out with copper(II) acetate or sulfate in pyridine at 60°C under vigorous stirring and afforded aminotriazoles **216** in good yield (Scheme 75) [270–272, 274]. This synthetic approach allows to introduce amino, amide, and cyano groups in 1,2,3-triazoles, as well as various pharmacophores and fragments of natural products (e.g., tryptamine) and alkaloids (cytosine, piperazine) (Scheme 75).

3-Hydroxyphenyl 2-(2-phenylhydrazono)acetimidate **217** was transformed to 2-aryl-2*H*-1,2,3-triazoles **218** bearing an oxyphenolic group at the C(4) position by an oxidative cyclization occurring in the presence of copper(II) acetate (Scheme 76) [273].



Scheme 76 Oxidative cyclization of 3-hydroxyphenyl 2-(2-phenylhydrazono)acetimidate **217**



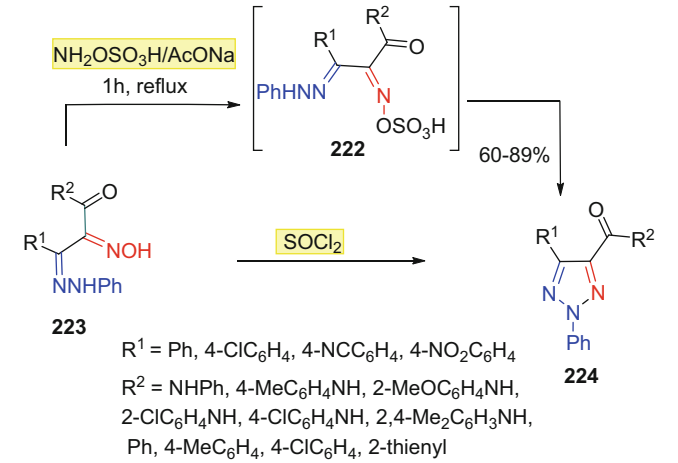
Scheme 77 Cyclization of arylhydrazonoamidoximes **219** to 5-amino- and 5-acylamino-2-aryl-2*H*-1,2,3-triazoles **220** and **221**

5.4 *Intramolecular Cyclization of Bis(hydrazones) and Hydrazonoamidoximes*

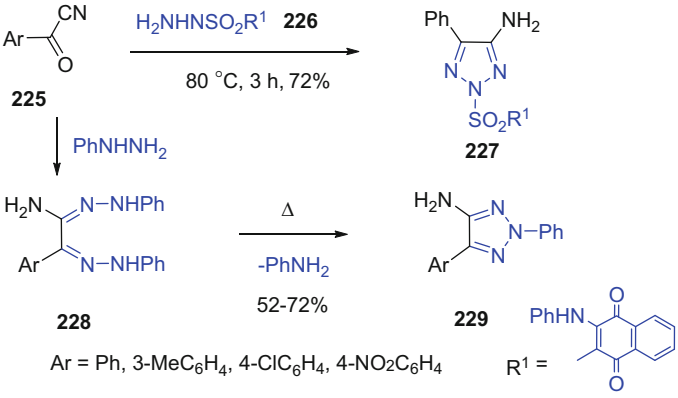
Another transformation of bis(hydrazones), hydrazonoamidoximes, and hydrazonohydrazides yielding 2-aryl-1,2,3-triazoles usually occurs under condensation conditions and is accomplished by the elimination of a leaving group [240, 275–294].

Arylhydrazonoacetamidoximes are widely accessible and can be easily transformed into 5-amino-1,2,3-triazoles by heating in DMF, EtOH with sodium acetate, EtONa, or piperidine, followed by treatment with $POCl_3$, or by reflux in acetic anhydride, under microwave activation [275–281]. Refluxing hydrazones **219** with acetic anhydride causes the cyclization, which usually leads to mono- or diacetylated dehydration products (Scheme 77) [277–279].

It was shown that 1,2,3-triazole can be obtained directly from arylhydrazononitriles by heating them in DMF with hydroxylamine hydrochloride in the presence of sodium acetate [270].



Scheme 78 Cyclization of arylhydrazone α-oximes **222** to 2-aryl-2*H*-1,2,3-triazole-4-carboxamides **224**

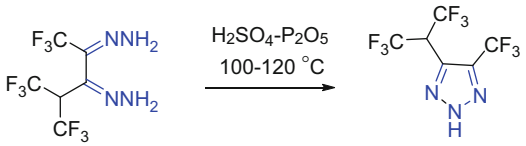


Scheme 79 Reaction of aroylnitriles **225** with the phenylhydrazine and sulfonylhydrazide **226**

Cyclization of arylhydrazone oximes **223** by dehydration agents (Ac_2O, $SOCl_2$, hydroxylamine-*O*-sulfonic acid) led to 2-aryl-1,2,3-triazoles in the same manner (Scheme 78) [282–290].

Reaction of hydrazononitriles **225** with phenylhydrazine or sulfonylhydrazide **226** afforded 4-amino-1,2,3-triazoles **227** via intermediate bis(hydrazone) whose cyclization was accompanied with an elimination of aniline or sulfonamide. Bis (hydrazone) α-dicarbonyl compounds **228** were separated and identified (Scheme 79) [292–294].

Using arylhydrazone substrates with an ethoxycarbonyl group at the α-position provided a synthetic route to 5-hydroxy-2*H*-triazoles [294].



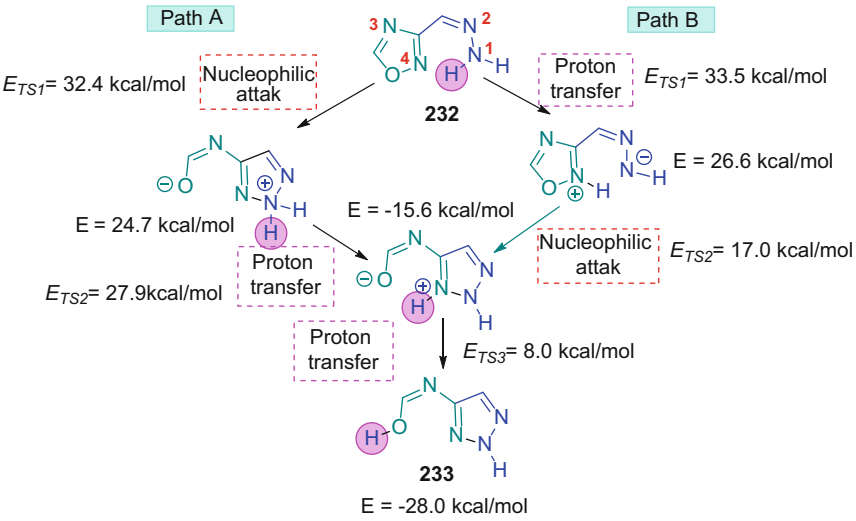
Scheme 80 Synthesis of fluorinated NH-1,2,3-triazole **231** by the cyclization of bis(hydrazone) **230**

The unsubstituted dihydrazone of α-diketone **230**, bearing two fluorinated alkyl substituents at C-hydrazone atom, underwent cyclization into (hexafluoropropan-2-yl)-5-(trifluoromethyl)-2*H*-1,2,3-triazole **231** by treatment with an H_2SO_4-P_2O_5 (3 : 1) mixture [240, 291]. It should be mentioned that α-hydrazone **230**, similarly to their nonfluorinated analogues, can be hydrolyzed exclusively into the α-ketohydrazone in the presence of concentrated H_2SO_4 (Scheme 80).

Intramolecular cyclization of bis(hydrazones) and hydrazones with the oxime groups proceeded selectively and provided novel 1,2,3-triazoles in good yield. Poor variability and availability of starting compounds (α-dicarbonyl substrates and hydrazines) limited greatly the applicability of this approach for the synthesis of new triazoles. Synthesis of 1,2,3-triazoles from bis(hydrazones) cannot be considered as an atom-economic process because aniline elimination is involved although theoretically aniline could be reconverted into phenylhydrazine. Using hydroxylamine derivatives is more useful in this case.

5.5 *Boulton–Katritzky Rearrangement of 3-Hydrazono Oxadiazoles, -Furoxans and -Isoxazoles*

It is well known that 1,2,4-oxadiazoles, 1,2,5-oxadiazoles (furoxans), and isoxazoles bearing a hydrazone group in the α-position of the side chain can be easily transformed into 2-aryl-1,2,3-triazoles via the Boulton–Katritzky monocyclic rearrangement [295–326]. This type of reaction represents an example of azole–azole interconversion. This peculiar case was also described as "monocyclic rearrangement of heterocycles"(MHR) recognized by Boulton and Katritzky as a general class of ring–ring rearrangements [327]. Besides its synthetic applications, this rearrangement gets a lot of attention due to the interesting aspects of its mechanism [295–304]. The process can be depicted as an internal (intramolecular) nucleophilic substitution (S_{Ni}), and therefore the reactivity of substrates can be related to the main factors affecting the reactivity towards S_N reactions, i.e.: (1) the nucleophilicity of the arylhydrazone α-nitrogen, (2) the electrophilic character of the N(2)-atom in the heterocycle, and (3) the strength of the N(2)/O(1) bond for the cleavage in the starting ring (1,2,4-oxadiazole, isoxazole, 1,2,5-oxadiazole) and, hence, the mobility of the O(1)-leaving group [295–304]. The last factor can be

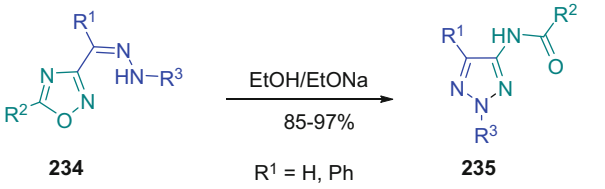


Scheme 81 Schematic representation of two pathways for intramolecular rearrangement of *Z*-hydrazone of 3-formyl-1,2,4-oxadiazole **232** to 1,2,3-triazole **233**

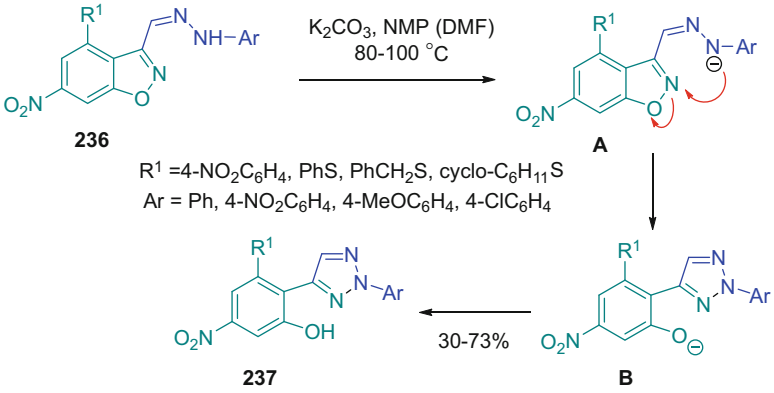
modulated by changing the type of azoles since in general the strength of N(2)–O (1) bond in general depends on the ability of the leaving group to accommodate the negative charge. It should be mentioned that the concentration of base is another crucial factor for the rearrangement process. Different pathways were confirmed to exist: a proton-concentration-independent or *uncatalyzed* pathway, and proton-concentration-dependent or *base-catalyzed* one, requiring either a general or a specific base catalyst [295–301].

Several investigations indicated the effect of the substituents on the arylhydrazone moiety on the electronic properties of the key atoms involved in the MHR, namely the hydrogen atom bound to the N(α)-atom, and the N(2) and C (5) atoms. Electron-withdrawing substituents were responsible for a decrease of reactivity of these atoms [298, 300, 304]. This S_N reaction was described in terms of push–pull shifts of electron density around the framework of broken/formed bonds. This phenomenon was accepted as an evidence for a concerted mechanism [300].

The mechanism for the uncatalyzed rearrangement of the *Z*-hydrazone of 3-formyl-1,2,4-oxadiazole was studied with DFT calculations. The study has shown that in vacuo the rearrangement occurs in a non-concerted mode along a stepwise pathway A with an activation barrier of 26.1 kcal/mol for the rate-determining step. Solvent effects (H_2O, DMSO), calculated via the COSMO continuum model, have a drastic influence on the activation barrier for the second step (this disappeared) while they slightly suppress the barrier for the first step. This suggests that under experimental conditions the reaction should proceed via an asynchronous concerted transition state where the nucleophilic attack and proton transfer occur in one kinetic step but not simultaneously (Scheme 81) [303].



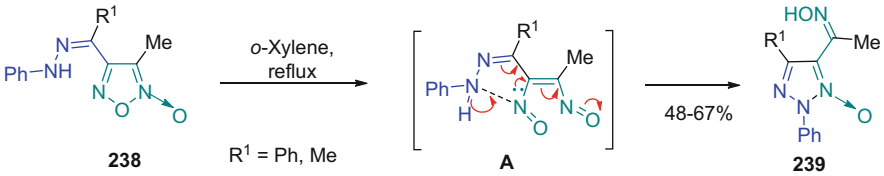
Scheme 82 Intramolecular rearrengement of the *Z*-arylhydrazones of 1,2,4-oxadiazole **234** to 5-acylamino-2-aryl-1,2,3-triazoles **235**



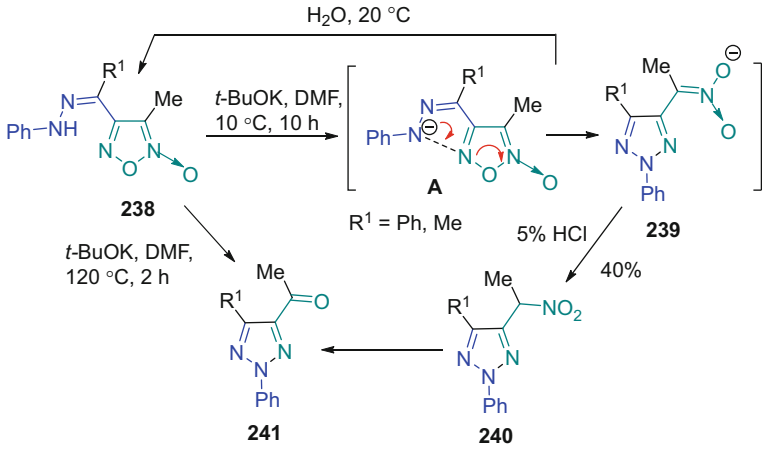
Scheme 83 Rearrangement of the hydrazone of benzo[*d*]isoxazole **236** to 2-aryl-2*H*-1,2,3-triazole **237**

Well-documented examples of this rearrangement include transformations of 1,2,4-oxadiazoles, bearing an arylhydrazone group [295–318]. They were observed at room and higher temperatures and in different solvents: dioxane/water system with buffers, in benzene and other organic solvents with various amines or activated by pyrrolysis, copper catalysis, or photo- and microwave irradiation. The processes occurred faster in aprotic dipolar solvents, such as DMSO. Heating of substrates above their melting points could also trigger the rearrangement [300]. The availability of the substrates and the considerably convenient reaction conditions allowed to obtain a large series of 1,2,3-triazoles by this method (Scheme 82) [295–318].

Hydrazones of isoxazoles, benzoisoxazoles, and pyrazoloisoxazoles underwent ring-opening/recyclization when treated with K_2CO_3 in *N*-methylpyridine (NMP) or EtOH and gave 1,2,3-triazoles **237** with moderate yield (Scheme 83) [319–322].



Scheme 84 Thermally induced rearrangement of furoxanoketones phenylhydrazones **238**



Scheme 85 Base-induced rearrangement of furoxanylketone phenylhydrazones **238**

The study of rearrangements of noncondensed furoxan hydrazone derivatives **238** helped to identify two kinds of processes: rearrangement through dinitrosoethylene intermediate (1) (Scheme 84) and rearrangement resulting in 1-nitroalkylazoles (2) (Scheme 85). Reactions were initiated either thermally or by adding various bases. The thermally induced rearrangement leading to **239** was executed by refluxing a solution of furoxan phenylhydrazones in *o*-xylene [323–326].

The second variant of rearrangement for *Z*-phenylhydrazones was observed in basic conditions and at different temperatures. The best yield was achieved with a *t*-BuOK solution in DMF at 10 °C.

Rearrangement of *Z*-phenylhydrazones **238** occurred in the presence of base at different temperatures. In order to isolate the target compounds the reaction mixture was acidified in the final step. An attempt to isolate the product by slow dropwise addition of water to the reaction mixture resulted in the starting phenylhydrazones **238**. The reversible monocyclic rearrangement of the intermediate 1,2,3-triazole **239** into the corresponding furoxan was observed in aqueous alkaline media. The rearrangement of compounds **238** in the presence of *t*-BuOK at high temperature resulted in 3-acetyl-2,4-diphenyl-2*H*-1,2,3-triazoles **241** (Scheme 85). The formation

of compounds **241** may be explained by the participation of 5-(nitroethyl)-1,2,3-triazole **240** formed at the first stage in a Nef-type reaction. An insignificant amount of ketone **241** was also detected when the reaction was performed at 10°C (TLC monitoring) [323–326].

These examples of rearrangement of hydrazone derivatives were actively studied during the last decade. The attention was caused by the interest in the mechanistic details for this transformation. The main advantage for this method towards 1,2,3-triazoles consists of the possibility to introduce desired functional groups (cyano, amine, amide, ketone, etc.), while condensation of bis(hydrazones) and α-oxime hydrazones lacks this opportunity.

6 Intra- and Intermolecular Reactions of Diazocompounds

Dipolar cycloaddition of diazoalkanes **242** to nitriles **243** in the presence of base (*t*-BuOK) led to 4,5-disubstituted 2*H*-1,2,3-triazoles **7** (Scheme 86) [328–333]. In the reaction with diazomethane were obtained three regioisomers, namely **245**–**247**, as a result of alkylation of NH-triazoles **7**.

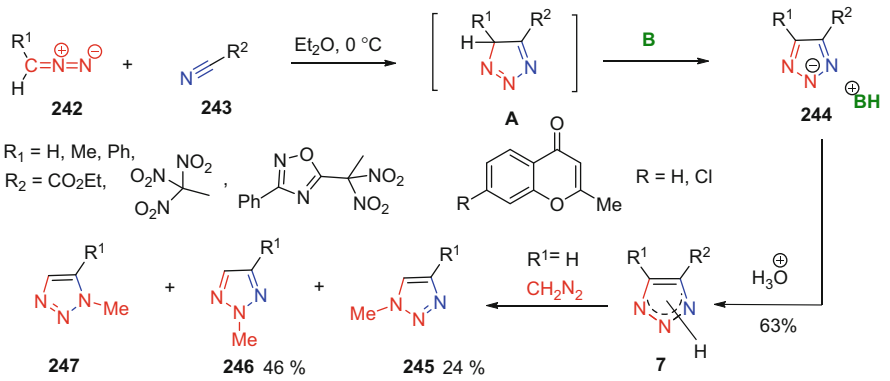
The high reactivity of exocyclic carbonitrile substituent at position *6* in uracil **248** caused it to interact with trimethylsilyldiazomethane (two equiv). Formed NH-1,2,3-triazole underwent in situ the methylation of N2 atom at the next step and derivative **249** was obtained (Scheme 87) [331].

Other groups than nitriles can be involved in this type of reaction. Examples of azomethine double bonds reacting in 1,3-dipolar cycloaddition with diazomethane, yielding two or three isomers of *N*-alkylated triazoles, are also known [332, 333]. The reaction of 1,2-bis(arylmethylene)hydrazines **250** with (diazomethyl) benzene **251** led to symmetrical 4,5-diaryltriazoles **252** (Scheme 88). However, yields were significantly lower than the ones for the reaction shown in Scheme 87 [332].

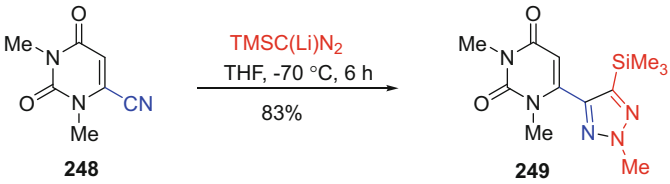
The cyclization of diazo compounds containing cyano, amide, amidine, imidate groups at the α-position served as a convenient tool to obtain various derivatives of 1,2,3-triazole (Scheme 89) [334–337].

Intramolecular cyclization of diazo compounds, obtained by diazotization of *N*-(2-amino-1,2-dicyanovinyl)amides **255** in aqueous HCl, proceeded very fast and led to 5-cyano-2*H*-1,2,3-triazole-4-carboxylic acid amide **257** (Scheme 90) [334].

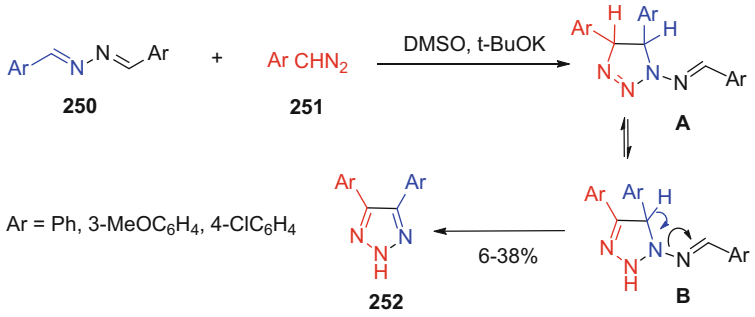
Besides the synthetic importance, diazo compounds are considered as attractive models to investigate the theoretical aspects of pericyclic/heteroelectrocyclic reactions frequently observed in heteroatomic π-conjugated compounds [337]. A spatial arrangement of frontier orbitals in the substrates induced them to react via symmetry-controlled pericyclic or symmetry-control-independent pseudopericyclic reactions (Scheme 91) [338]. The absence of electron–electron repulsion for the latter type of reaction substantially decreases the activation barriers and explains why this type of reaction can occur relatively easily.



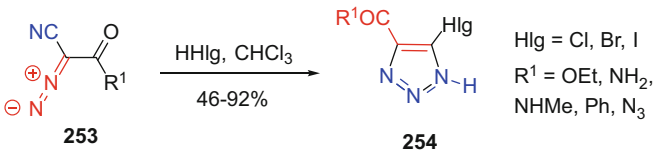
Scheme 86 Reaction of diazomethanes **242** with nitriles **243**



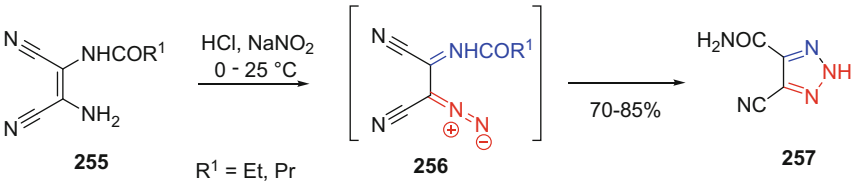
Scheme 87 Reaction of 1,3,6-trimethyluracil **248** with TMSC(Li)N_2



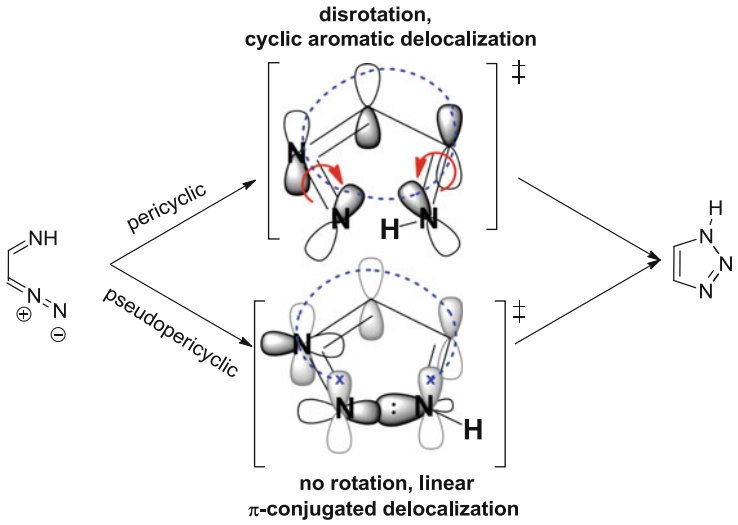
Scheme 88 Reaction of 1,2-bis(arylmethylene)hydrazines **250** with (diazomethyl)benzene **251**



Scheme 89 Intramolecular cyclization of α-diazonitriles **254**



Scheme 90 Intramolecular cyclization of *N*-(2-amino-1,2-dicyanovinyl)propionamide **255**



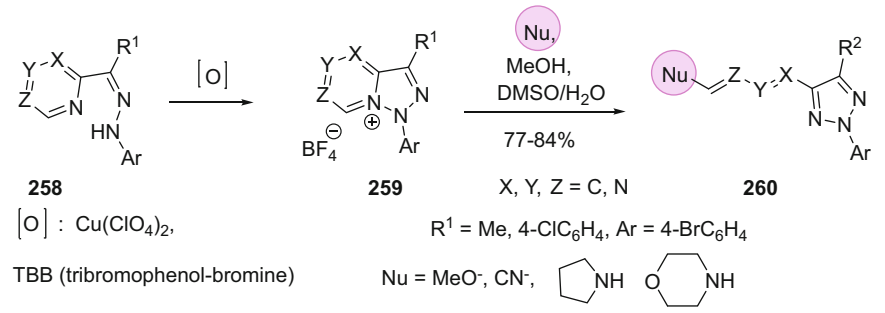
Scheme 91 Mechanism of intramolecular cyclization of 2-diazo-2-ethane imine

7 Heterocycle Transformations in the Synthesis of 2*H*-1,2,3-Triazoles

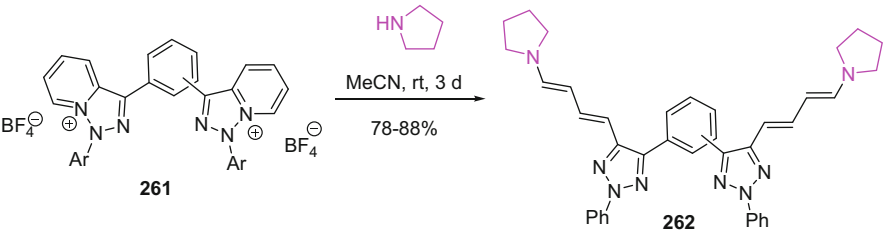
An interesting way to construct 2-aryl-1,2,3-triazoles was to use the ring-opening of bridgehead nitrogen-containing azoles yielding conjugated triazoles **260**. The starting heterocyclic salts were obtained by an oxidative cyclization of hydrazone precursor **258** (Scheme 92) [340–349].

The *m*- and *p*-phenylene-bridged bis(azolopyridinium)salts **261** were converted into the corresponding bis(dienamines) **262** by reaction with pyrrolidine (Scheme 93) [342].

A number of examples for rearrangement of 5-amino-1,2,3-thiadiazoles into 1,2,3-triazoles, also known as Dimroth rearrangement [350], have been described in detail in *Chapter 1*. In spite of the relative simplicity and the one-pot fashion of this rearrangements their preparative power to obtain various 1,2,3-triazoles is limited by the scope of the involved substrates (Schemes 92 and 93).



Scheme 92 Ring-opening reaction of bridgehead nitrogen-containing azoles



Scheme 93 Ring-opening transformation of bis(triazolopyrimidinium) salts with pyrrolidine

8 Conclusion

This extensive review of synthetic approaches to obtain 2*H*-1,2,3-triazoles has shown that they can be classified into several distinct types.

NH-1,2,3-Triazoles and their 2-alkyl- and, rarer, 2-aryl substituted analogues can be synthesized by Huisgen azide-alkyne dipolar cycloaddition combined with postalkyl(aryl)ation or performed in a multicomponent and solid-phase fashion.

The nucleophilic substitution cannot be effectively used to obtain 2-substituted 1,2,3-triazoles since the regioselectivity of *N*-substitution is difficult to control kinetically and the N(1) atom becomes a preferred nucleophilic site under the reaction circumstances, especially for triazoles of a greater practical interest (e.g., 2-aryl and non-exchangeable N(2)-alkyl ones). It is also important to stress that acyl, sulfonyl, carbamoyl, and similar 2-substituted 1,2,3-triazoles are easily obtainable by nucleophilic substitution, but unfortunately unstable and thus did not find broad application.

Different types of cyclizations, such as oxidation, condensation, and rearrangement, occurring for arylhydrazones with an additional nitrogen-containing functional group (amidines, oximes, amidoximes) or heterocycles (1,2,4-oxadiazoles, 1,2,5-oxadiazoles, oxazoles), can also provide a convenient approach to 2-arylsubstituted 1,2,3-triazoles. Availability of substrates, convenient conditions, high yields, and regioselectivity are not the only features for this method

to be highlighted. This routine is also very useful because it provides the possibility to introduce various substituents and functional groups in order to design new materials with desired physical and biological properties.

The cumulative interest into methods of synthesis for 2*H*-1,2,3-triazoles is based on the need to develop a simple and effective synthetic approach to obtain them, as well as on the fundamental interest to the mechanistic aspects of these reactions.

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Biological Properties of 1*H*-1,2,3- and 2*H*-1,2,3-Triazoles

Fernando de Carvalho da Silva, Mariana Filomena do Carmo Cardoso, Patricia Garcia Ferreira, and Vitor F. Ferreira

Abstract Triazoles, which are an important class of heterocyclic compounds, have been studied for over a century and continue to attract considerable attention because of their broad range of biological activities. More recently, there has been significant interest in the development of novel triazoles with anti-inflammatory, antiplatelet, antimicrobial, antimycobacterial, antitumoral, and antiviral properties and activity against several neglected diseases. In this chapter, we covered some important biological properties of the 1*H*-1,2,3- and 2*H*-1,2,3-triazoles.

Keywords Biological activity · Cancer · Chagas' disease · Diabetes · Diseases · Triazoles · Tuberculosis

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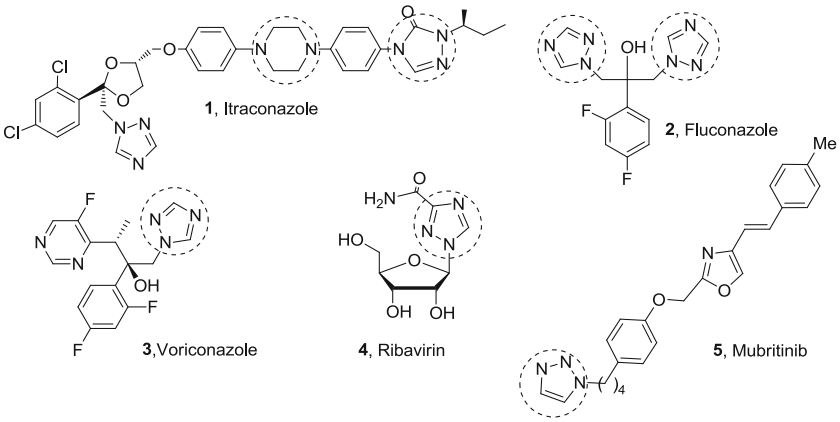


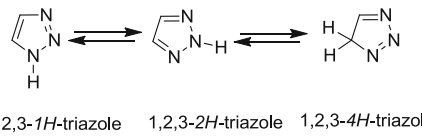
Fig. 1 Drugs having triazole rings available in their therapeutic arsenal

1 Introduction

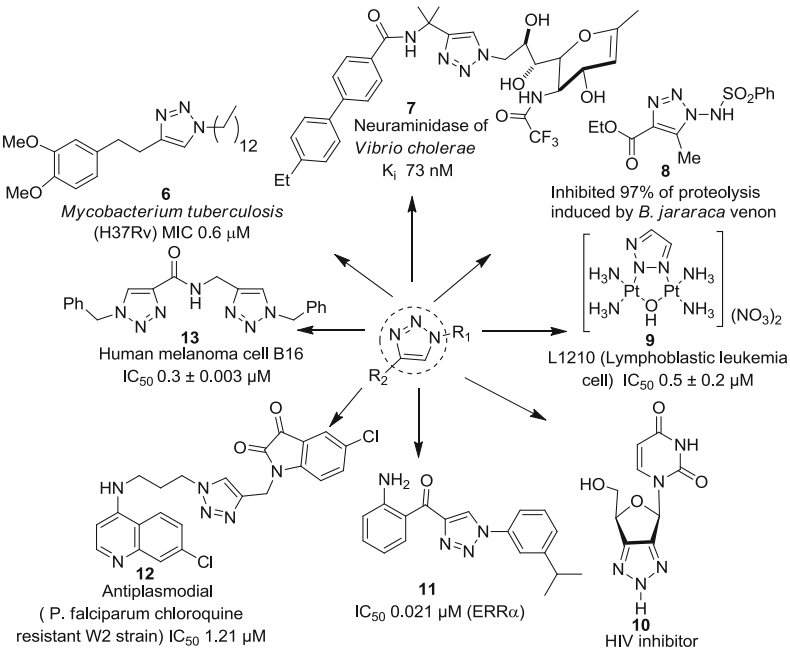
The 1*H*-1,2,3- and 2*H*-1,2,3-triazoles have been studied for many years as an important class of heterocyclic compounds, and they continue to attract considerable attention due to their use in several applications, such as organocatalysis [1–5], in ionic liquids [6], in a broad range of biological activities, including anti-inflammatory, antiplatelet, antimicrobial [7], antitubercular, antitumoral, and antiviral as well as activities against several neglected diseases. Because of the success of several members of the triazole family that have entered the pharmaceutical market [8], many companies and research groups have shown interest in developing new methods of synthesis and screening of their biological activities [9]. Figure 1 shows that 1,2,3-1,2,4-triazoles are commonly used as drugs for the treatment of various diseases. For example, antifungal drugs containing the triazole ring include the following: (**1**) itraconazole, (**2**) fluconazole, (**3**) voriconazole, (**4**) [10] the anti-viral drug ribavirin, and (**5**) mubritinib (used for breast, bladder, kidney, and prostate cancers) (Fig. 1). Note that ribavirin (**4**) [11, 12] became a reference [13] drug for the treatment of viral infections, such as respiratory, herpes, and hepatitis [14].

The 1,2,3-triazoles are five-membered rings with three nitrogens in the ring. The triazoles that are unsubstituted at the nitrogen may exist in a tautomeric equilibrium in three structures, as shown in Scheme 1 [15].

This chapter emphasizes the recent advances in the biological activities of novel 1*H*-1,2,3- and 2*H*-1,2,3-triazole derivatives and their potential in the development of new chemical entities and new pharmaceuticals. Due to the broad biological activities of the triazoles, this chapter will emphasize their bioactive potential on tuberculosis, *Trypanosoma cruzi*, cancer cells, and glucosidase enzymes. However, 1,2,3-triazoles have shown many important biological properties, such as antibacterial [16, 17], antifungal [18–20], antiviral [21–23], β-lactamase [24], antiepileptic [25], antiplatelet [26, 27], schizophrenia [28], anti-inflammatory [29–32], anti-allergic [33–36],



Scheme 1 Tautomeric equilibrium in the 1,2,3-triazole series



Scheme 2 Selected examples of bioactive 1,2,3-triazole derivatives

antimicrobial [37–42], anti-viral [43], anticonvulsants [44], tripanocidal [45, 46], antileishmanial [47, 48], anhydrase and protease inhibitors [49–51], anti-Alzheimer [52], cyclooxygenase [53], NO production inhibitors [54], anticaspase-3 [55] fatty acid synthase [56], antimycobacterial (**6**) [57], Vibrio cholerae (**7**) [58, 59], hemolysis (**8**) [60], leukemia L1210 (**9**), anti-HIV (**10**) [61], snake venom [62], breast cancer, phytotoxicity [63], and antiplasmodial (**12**) [64] (Scheme 2).

2 General Remarks

Currently, there are four 1*H*-1,2,3-triazoles in clinical trials that may become new drugs in the next few years (Fig. 2). These triazoles are the following: tazobactam (**14**, antibiotic) [65, 66], cefatrizine (**15**, anticancer) [67], carboxyamidotriazole or

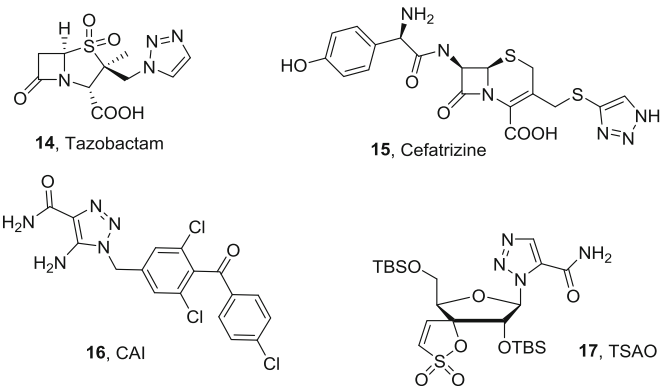


Fig. 2 1*H*-1,2,3-triazoles currently under clinical trials

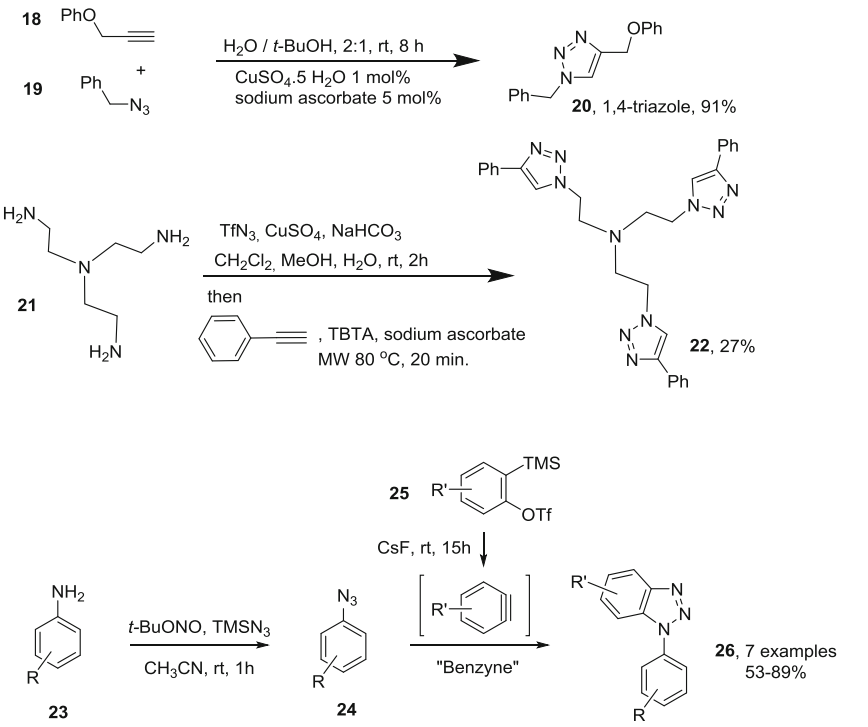
CAI (**16**, anticancer) [68], and *tert*-butyldimethylsilylspiroaminooxathioledioxide or TSAO (**17**, HIV reverse transcriptase inhibitor) [69, 70].

There are several procedures available for the preparation of 1*H*-1,2,3-triazoles [71–75], particularly those in which a 1*H*-1,2,3-triazole is incorporated into compounds containing other heterocyclic rings [76–79]. However, the interest in this class of compounds in medicinal chemistry began to increase after the publication by Sharpless and coworkers that adapted the Huisgen 1,3-dipolar cycloaddition reaction [80–83] to obtain a selective preparation of the 1,4-disubstituted triazole adduct using copper (I) as the catalyst [84] or the 1,5-disubstituted triazole using a ruthenium catalyst [85].

The Huisgen 1,3-dipolar cycloaddition reaction is a highly atom-economic and efficient coupling reaction that is especially useful for the construction of complex macrocycles [86]. Several original papers and reviews have been published recently describing Sharpless' catalytic methodology under several reaction conditions, [87] in several solvents [88–91], using different combinatorial processes [92], and describing the mechanism of the reaction [93] and biological activities (e.g., **20** and **22**) [94]. Another important procedure is the preparation of 1,2,3-1*H*-triazole derivatives described by Zhang and Moses [95] that showed an efficient synthesis of substituted benzotriazoles (**26**) using an azide-alkyne 1,3-dipolar cycloaddition via benzyne intermediates. Additionally, the method using a diazo transfer reaction to an amine cycloaddition reaction under copper (I) catalysis in a two-step, one-pot reaction has also proven to be effective (Scheme 3) [96].

1-Aryl-1,4,5-trisubstituted 1,2,3-1*H*-triazole derivatives can also be easily obtained via a one-pot three-component reaction involving boronic acids, sodium azide, and active methylene ketones [97].

Certain authors have speculated that 1,2,3-triazoles offer an appealing structural motif for peptidomimetic research because their structural and electronic characteristics are similar to those of a peptide bond [69, 98, 99]. The triazole ring can be considered a bioisostere of the amide group because these moieties have a similar H–bond acceptor capacity, a similar distance between substituents (3.8–3.9 Å in



Scheme 3 Preparation of 1,2,3-1*H*-triazole derivatives by Sharpless' methodology and a diazo transfer reaction

amides and 5.0–5.1 Å in triazoles), and a similar dipolar character (amide 4.0 Debye; triazole 5.0 Debye) [83, 100]. In addition, the ability of the 1,2,3-triazoles to participate in hydrogen bonding and dipole interactions [101] may favor binding to biomolecular targets and improve their solubility [102, 103]. The 1,2,3-triazoles are very stable under basic and acidic hydrolysis and reductive and oxidative conditions, indicative of a high aromatic stabilization [104, 105]. All of these studies demonstrate that the 1*H*-1,2,3-triazoles can display different bioactive profiles when properly functionalized [83, 106, 107].

The 2*H*-1,2,3-triazoles represent an another important class of 1,2,3-triazoles that can also be prepared by several synthetic routes [108–113], but most of the routes are complex and present few opportunities to explore their biological diversity. The 2*H*-1,2,3-triazoles have diverse applications, such as anesthetic (**27**) [114], antiarrhythmic (**28**) [115], and antitubercular (**29**) activities [116], among others. Recently, several patents were filed regarding a family of compounds containing the 2*H*-1,2,3-triazole nucleus (**30**) that are involved in pharmaceutical formulations to treat Duchenne muscular dystrophy, Becker muscular dystrophy or cachexia, and (**31**) asthma [117] or rhinitis (Fig. 3) [118]. Preparation of 4,5-disubstituted 1,2,3-(NH)-triazoles can be achieved by an efficient one-pot

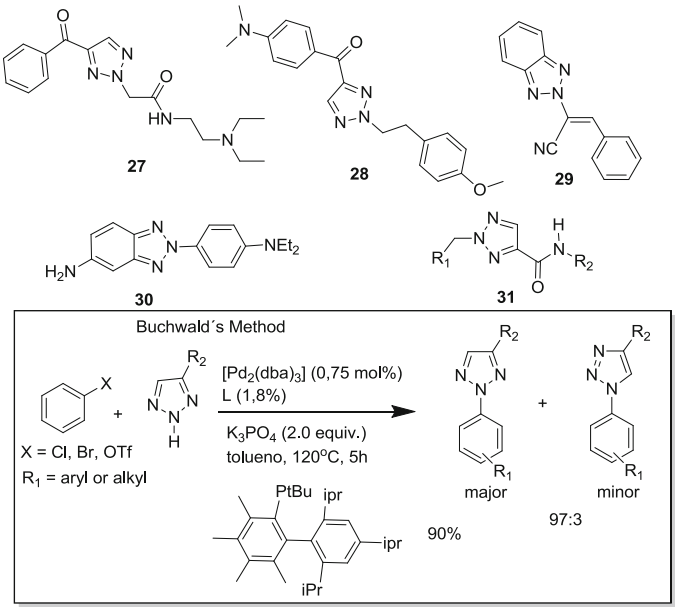


Fig. 3 Synthesis of 2*H*-1,2,3-triazole by Buchwald's method

cross-coupling/1,3-dipolar cycloaddition sequence starting from various acid chlorides, terminal alkynes, and sodium azide in the presence of silica supported-zinc bromide under aerobic conditions [119]. Buchwald and coworkers have developed a regioselective methodology (see box in Fig. 3) to add an aryl group to unsubstituted and substituted 2*H*-N triazoles in high yields. This method of preparation of 2*H*-1,2,3-triazoles is versatile and uses the coupling between aryl halides and the NH bond catalyzed by palladium complexes (Fig. 3) [120].

3 Tuberculosis

Many reports in the literature have shown that 1,2,3-triazoles display antimicrobial activity against several bacteria [121], especially against the *Mycobacterium tuberculosis*.

Tuberculosis (TB) is a highly infectious disease that has been affecting humans and animals for millennia. TB is highly contagious and begins with a bacterial infection in the lungs that spreads through the air causing a high level of mortality and morbidity. The challenge to discover new active compounds with low toxicity for use primarily on multi-drug resistant strains continues globally [122].

TB in humans is caused by several *Mycobacteria*, with *M. tuberculosis* being the primary bacillus causing the disease. TB can be asymptomatic in healthy individuals whose immune systems are able to block the action of the bacteria; however, in

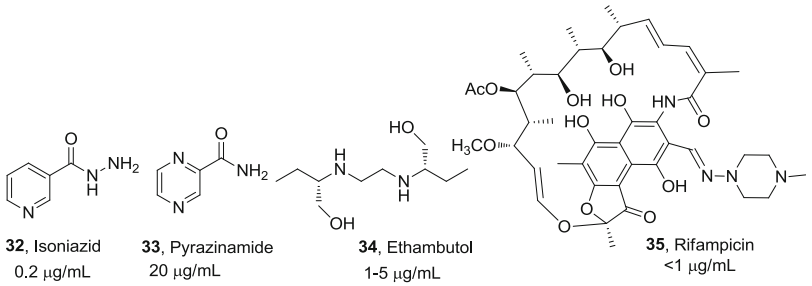


Fig. 4 Drugs primarily used against tuberculosis

most people, its symptoms include cough, fever, chest pains, weakness, weight loss, and night sweats. An estimated 70% of the population in poor countries are infected with *M. tuberculosis,* and approximately 8.8 million new cases occur annually, leading to the death of 1.4 million people [123–125]. Although the incidence of TB has been decreasing, recent statistics have shown alarming numbers of new infections. In 2011, there were an estimated 8.7 million new cases of TB (13% co-infected with HIV), and 1.4 million people died from TB, including almost one million deaths among HIV-negative individuals and 430,000 deaths among people who were HIV-positive [126]. The high rate of occurrence of this disease in poor countries is closely related to poor living conditions and the spread of the HIV-virus.

Strains of *M. tuberculosis* that are resistant to the old and new drugs on the market present a serious problem. These strains have been systematically detected in countries that do not emphasize public health and fail to heed recommendations regarding the importance of treatment adherence. Therefore, the cost for the treatment of drug resistant TB is growing, and there is an alarming weakness in the medical armamentarium.

The primary treatment for TB uses a combination of the following four drugs: isoniazid (**32**), pyrazinamide (**33**), ethambutol (**34**), and rifampicin (**35**) (Fig. 4). The intention of using this combination of existing drugs is to increase patient adherence to the treatment and, thus, to avoid the emergence of new resistant strains of bacteria that utilize different mechanisms of action. Rifampicin (**35**) inhibits the biosynthesis of RNA polymerase, isoniazid (**32**) inhibits mycolic acid synthesis, pyrazinamide (**33**) inhibits cell membrane synthesis, and ethambutol (**34**) inhibits cell-wall biosynthesis. However, these older drugs have severe side effects, and various strains of bacteria have developed resistance to them. Therefore, the development of new and more efficient drugs that act on other targets of *M. tuberculosis* is imperative [127–130].

Some of the new compounds have completed phase I clinical trials and are being evaluated in phase II trials in humans with TB to determine their safety, tolerability, efficacy, pharmacokinetics, and dosing regimen. If these candidates pass to phase II, they will proceed to phase III trials (Fig. 5).

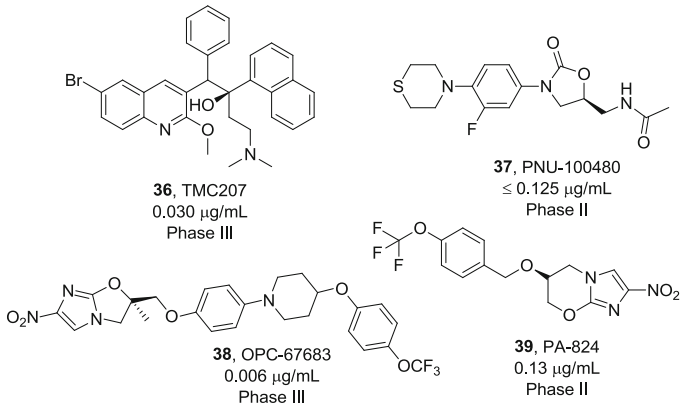


Fig. 5 New candidates for anti-TB drugs that are in phases II and III [131–134]

Because the population of the resistant new strains of *M. tuberculosis* continues to grow, the search for new lead compounds, preferably ones that can act on innovative targets, is urgent. Several research programs have focused on the search for new inhibitors of *M. tuberculosis*. These new *M. tuberculosis* growth inhibitors include compounds with unknown mechanisms of action and others whose mechanisms of action are known, such as the glycophospholids, which affect the biosynthesis of cell walls to weaken interactions with host cells [135, 136]. Several reviews have been published describing the development of novel synthetic and natural product candidates as prototypes against *M. tuberculosis* and the possible biological targets of these candidates [137–139].

Drug candidates containing 1*H*-1,2,3-triazoles are relatively new, and there are no drugs or products in advanced clinical trials containing this moiety. The primary reason that these compounds have not been submitted to clinical trials is that the preparation of these heterocycles has been limited to a few synthetic methodologies, and these methods are unable to produce compounds with molecular diversity.

Interest in the 1*H*-1,2,3-triazoles in medicinal chemistry began to increase after the publication of the seminal work of Sharpless, who improved the Huisgen 1,3-cycloaddition reaction to selectively obtain the 1,4-disubstituted adduct of the 1*H*-1,2,3-triazoles using copper (I) as a catalyst [80–82, 107]. This cycloaddition reaction between an azide and an alkyne occurs under mild conditions with high yields and is an example of "click chemistry" [84]. A large number of original papers and reviews have been published describing Sharpless' robust methodology in several solvents [88], as well as detailing combinatorial methods [92] and the mechanism of the reaction [93]. Subsequently, many new 1*H*-1,2,3-triazoles have been synthesized and widely exploited for their biological activities [94, 140, 141]. These triazoles are also able to display several bioactivity properties against several targets when the triazole is properly functionalized [84, 106, 107]. The 1*H*-1,2,3-triazoles have an appealing structural motif and electronic characteristics similar to those of a peptide bond (for peptidomimetic research) [98, 99]. In

Fig. 6 General structures of 1,4- and 1,5-isomers of 1*H*-1,2,3-triazoles

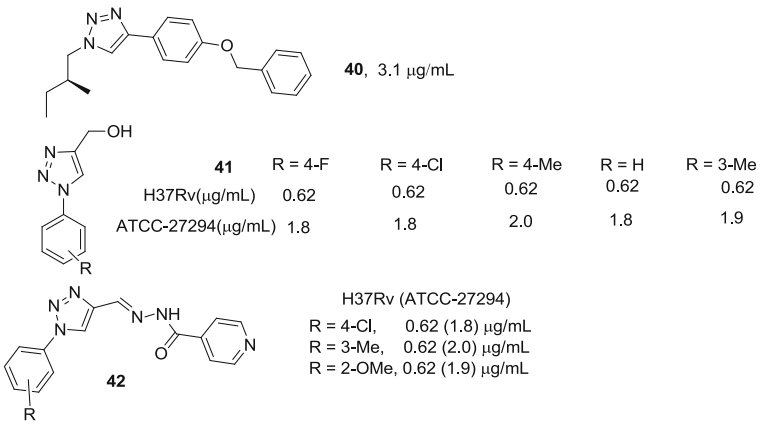


Fig. 7 *N*-Alkyl- and *N*-aryl-1,4- disubstituted of the 1*H*-1,2,3-triazoles with anti-TB activity

addition, their ability to participate in hydrogen bonding and dipole interactions may favor binding to biomolecular targets and improve their solubility [102, 103].

The 1*H*-1,2,3-triazoles have been screened against several strains of *M. tuberculosis*, and some of them are candidates for antitubercular treatment [37]. In the disubstituted 1*H*-1,2,3-triazole series, it is possible to have two isomers, the 1,4- and 1,5-disubstituted isomers. Preparation of 1,4-disubstituted 1*H*-1,2,3-triazoles is easier than that of 1,5-disubstituted 1*H*-1,2,3-triazoles. Therefore, there are many more studies involving the synthesis and antitubercular activity of the 1,4-isomers than the 1,5-isomers (Fig. 6).

N-Alkyl- and *N*-aryl-1,4-isomers of the 1*H*-1,2,3-triazoles have been reported to have antimycobacterial activity. Gallardo et al. [142] found that compound **40** has a minimal inhibitory concentration (MIC) against *M. tuberculosis* H37Rv and ATCC 27294 of 3.1 μg/mL, indicating that a large series of this compound could be expanded, and its activity can be improved (Fig. 7). Following this lead, Boechat and coworkers prepared a large series (**41**) of 4-substituted *N*-phenyl-1*H*-1,2,3-triazole derivatives (Fig. 7) [37]. The basic structure of the triazoles was modified at positions 1 and 4 on the ring with various functional groups. In addition, from the aldehyde series, Boechat and coworkers prepared several new compounds containing the isoniazid (**42**) structural unit, which is a drug that is active against *M. tuberculosis* (MIC 0.002–0.006 μg/mL) and inhibits the synthesis of mycolic acids, which are

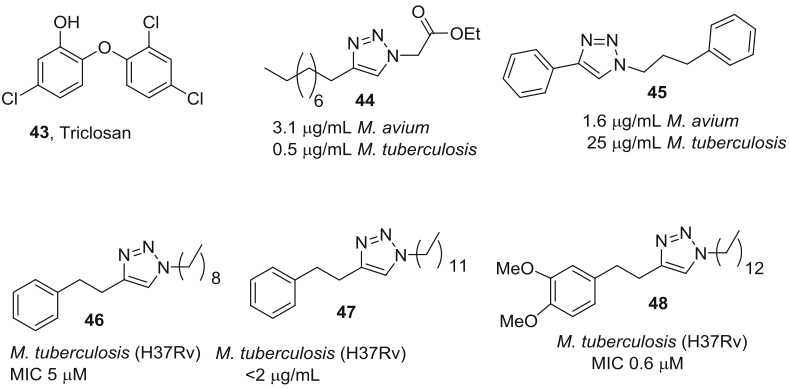


Fig. 8 Triazoles used for anti-TB targeting of 2-*trans*-enoyl-ACP reductase

components of the cell wall. This synthetic strategy has also been used by other research groups [143–145]. The substituents at the 4-position showed a more significant inhibitory activity than substituents at other positions. The reactivity order of the compounds having substituents at the 4-position on the triazole was the following: vinyl > CHO > CHF_2 > CF_3 > CH_2F > $COOCH_3$ > CH_2OH. Derivatives of isoniazid (**1**), (*E*)-*N*′-[(1-aryl)-1H-1,2,3-triazole-4-yl)methylene] isonicotinoyl hydrazides exhibited significant activity, with MIC values ranging from 2.5 to 0.62 μM. In addition, these derivatives displayed low cytotoxicity against liver cells (hepatoma HepG2) and kidney cells (BGM), thereby exhibiting a high therapeutic index.

The acyl carrier protein 2-*trans*-Enoyl-ACP reductase is an important enzyme for the growth of *M. tuberculosis* sp. [146] because it is involved in mycolic acid biosynthesis. Thus, this enzyme is an important target for drugs to inhibit these bacteria. The drug triclosan (**43**) has been shown to significantly inhibit InhA· [147] which is also the primary target of isoniazid (**32**), a leading drug used to treat tuberculosis. Menendez et al. synthesized and tested several 1*H*-1,2,3-N-alkyl-triazoles for the inhibition of InhA in *M. tuberculosis* H37Rv and found good inhibitors of *M. tuberculosis* but weak inhibitors of InhA [148]. Certain compounds showed good activity toward *M. tuberculosis* with minimum inhibitory concentrations ranging from 2.0 to 5.0 μg/mL. In the same year, Labadie and coworkers [149] prepared a small library of 1*H*-1,2,3-N-alkyl-triazoles, which could mimic the phenol central core of triclosan, and tested them against two strains of mycobacteria, *M. avium* and *M. tuberculosis*. More recently, Menendez et al. [150] continued their previous work and synthesized novel triazoles. Compounds possessing a methylene group (**41–48**) between the aromatic group and the triazole core inhibited *M. tuberculosis* H37Rv at 5 μg/mL or higher. Note that the length of the alkyl chain attached to the triazole core does not significantly influence the activities, but in general, the length of the alkyl chain is important (Fig. 8). The best results were obtained for the 12-carbon chain derivatives (e.g., **48**, which shows an MIC value of 0.6 μM).

Modification of antimicrobial agents sold in the pharmaceutical market is a strategy that has been used by several research groups. For example, the success

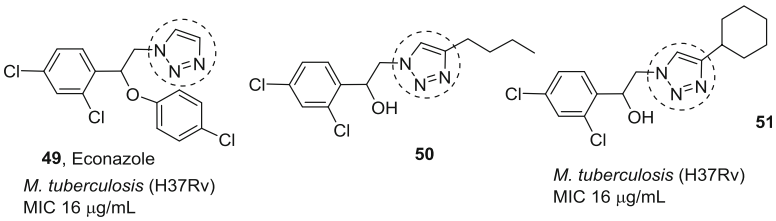
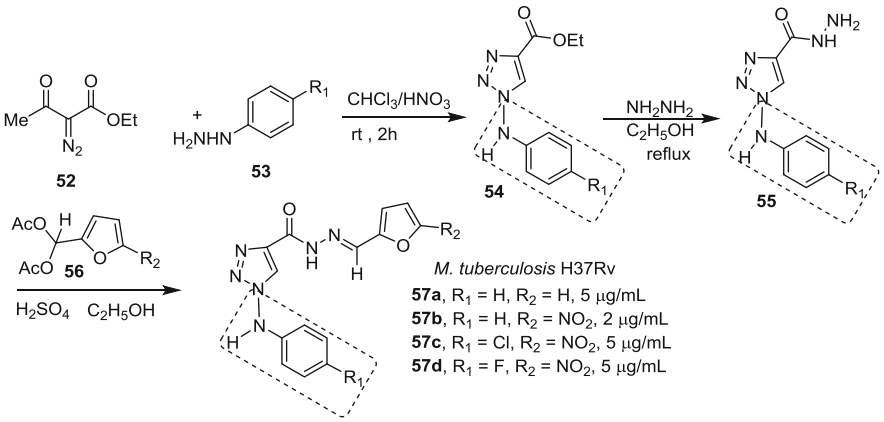


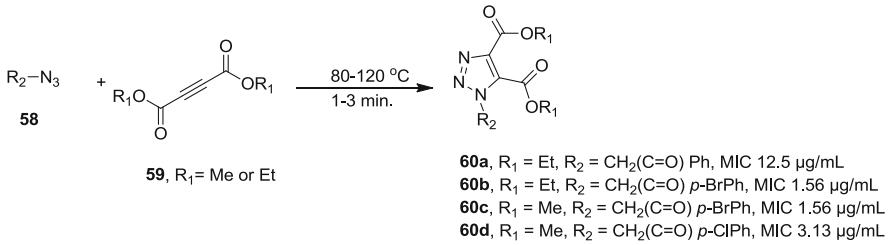
Fig. 9 1*H*-1,2,3-triazoles linked to the econazole framework



Scheme 4 NH linker with 1*H*-1,2,3-triazoles

of econazole (**49**) has encouraged the search for new analogs with antitubercular activity. Kim and coworkers explored the antitubercular activity of the 1*H*-1,2,3-triazoles linked to econazole and miconazole that have previously been successful in the treatment of multiple resistant TB (MDR-TB) and are active against *M. tuberculosis* CYP130 [151]. Two compounds, **50** and **51**, were promising because they were more active than econazole (**49**) and another compound that was equally active, indicating that the imidazole moiety of econazole can be replaced by the 1*H*-1,2,3-triazole core with the retention of the antitubercular activity (Fig. 9) [151, 152].

Cunha and coworkers studied substitution of the radical N-alkyl by an amino-sulfonic group. Their group synthesized several 1*H*-1,2,3-triazoles with a nitrogen atom as the linker between the heterocyclic ring and the aryl group [38]. Triazoles **54** were obtained in good yields by reacting α,α-dicarbonyl compounds, such as ethyl diazoacetoacetate (**52**), with suitably substituted hydrazines (**53**). The triazoles obtained in this reaction were transformed into hydrazides (**55**), which were then coupled with various aldehydes or acetals. The triazoles **57a–d** showed activity against *M. tuberculosis* H37Rv, with MIC values ranging from 2.0 to 5.0 μg/mL. The best compound of this series was the triazole **57b**, which presented a MIC of 2.0 μg/mL (Scheme 4).

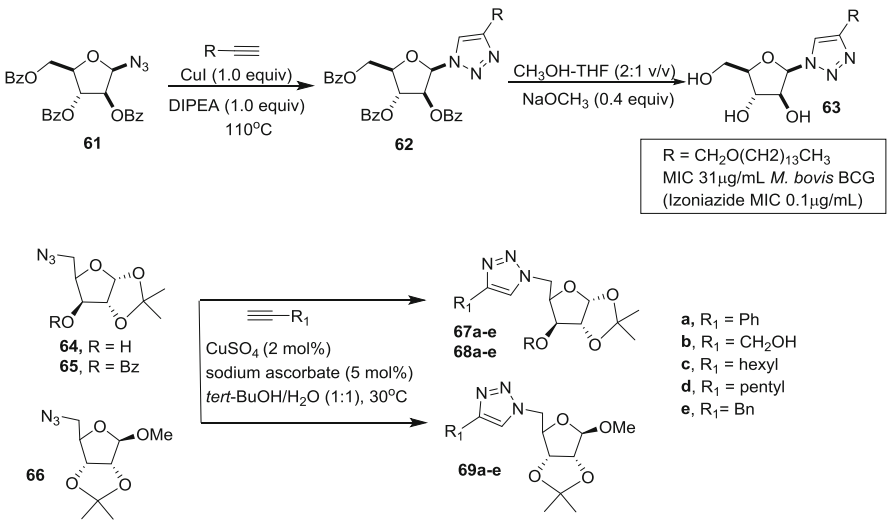


Scheme 5 Preparation of antitubercular 1,4,5-trisubstituted 1*H*-1,2,3-triazoles

Only a few examples of 1,4,5-trisubstituted 1*H*-1,2,3-triazoles have been synthesized and evaluated as antitubercular agents. Shanmugavelan et al. prepared several 1,4,5-trisubstituted 1*H*-1,2,3-triazoles (**60a–d**) in good yields using the classical Huisgen cycloaddition between alkyl or aryl azides (**58**) and diethyl or dimethyl acetylenedicarboxylate (**59**). The novelty of this methodology is the use of solvent-free reaction conditions, which is consistent with the principles of green chemistry. The compounds were tested against *M. tuberculosis* (H37Rv), and they presented moderate MIC values in the range of 1.56–3.13 µg/mL. The compounds **60b** and **60c** showed MIC values of 1.56 µg/mL, which is 2.08 times more active than the standard drug ethambutol (MIC 3.25 µg/mL) but less potent than the standard drug isoniazid (MIC 0.75 µg/mL) (Scheme 5) [153].

Lipids and polysaccharides containing mycolic acids, arabinogalactan, and peptidoglycan are abundant in the cell wall of mycobacteria. Because the mycolyl-arabinogalactan-peptidoglycan complexes are important for the bacteria, inhibition of their biosynthesis will affect the growth of these microorganisms [154]. Indeed, there are several drugs on the market used for the treatment of TB that target the mycobacterial cell-wall biosynthesis (e.g., thiacetazone, isoniazid, ethambutol, pyrazinamide, and ethionamide). Biomass-based carbohydrates are the most abundant natural products and have been used to develop technologies for the generation of chain products, such as fuels, chemical intermediates, and derivatives for the fine chemical industry. Glycoconjugates have a carbohydrate moiety and are involved in important biological functions, including those on the cell surface, such as the recognition of host compounds, immunological responses, inflammation, cell-cell recognition, bacterial and viral infection, cell communication, metastasis, and many important functions inside cells. Synthesis of triazole-tethered carbohydrates [155] or nucleosides represents a significant therapeutic opportunity for the development of new anti-tubercular agents.

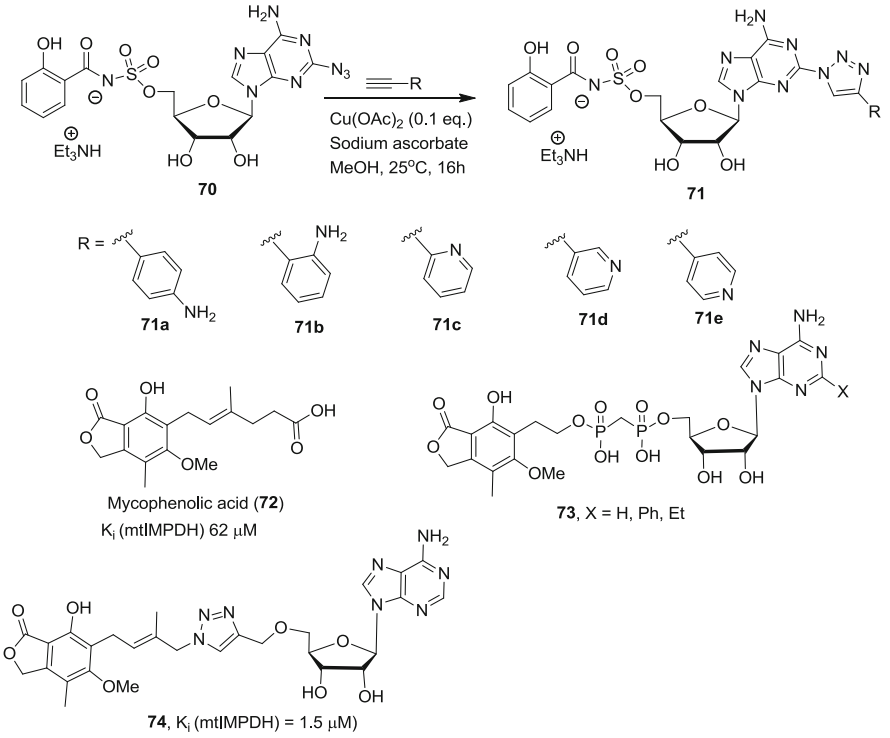
Fairbanks and his research group have focused on the discovery of arabinosyl transferase inhibitors [156], and using **61,** they synthesized a series of arabino glycosyl triazoles with hydrophobic ligands as potential inhibitors of decaprenol-phosphoarabinose, thus targeting the biosynthesis of the mycobacterial cell wall. The compounds were tested against *Mycobacterium bovis* BCG (bovine tuberculosis), and the best result was obtained for **63**, which presented moderate



Scheme 6 Synthesis of carbohydrate-based 1*H*-1,2,3-triazoles

antitubercular activity at a concentration of 31 μg/mL, indicating that activity is strongly dependent on the hydrophobic side chain [156]. Similarly, Singh and coworkers have synthesized 1,2,3-triazoles linked to xylose acetonide by reacting 5-azido-5-deoxy-1,2-*O*-isopropylidne-α-D-xylofuranose (**64** or **65**) with several alkynes (Scheme 6) [157]. Likewise, 5-azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (**66**) was reacted with different alkynes. All of the obtained compounds (**67**, **68** and **69**) showed moderate MIC values against *M. tuberculosis* (H37Rv) of only 12.5 μg/mL (R=OH and R_1=H), whereas the MIC values for isoniazid (**28**, 0.65 μg/mL), rifampicin (**31**, 0.75 μg/mL), and ethambutol (**30**, 3.25 μg/mL) were much lower.

Nucleosides tethered to the triazole nucleus have been explored as potential drugs, and some of them have become pharmaceuticals (e.g., Ribavirin). Gupte and coworkers [158] synthesized several nucleosides with the core triazole moiety linked to an adenosine, resulting in new compounds with excellent activity against *M. tuberculosis* H37Rv. The 5′-*O*-[*N*-(salicyl) sulfamoyl] adenosine series is shown in Scheme 7. Compounds **71a–71e** showed very low MIC values (0.78 μg/mL). Another approach was used by Pankiewicz and co-workers [159] in which new compounds were designed to act on inosine monophosphate dehydrogenase (IMPDH), which is a key NAD-dependent enzyme that converts inosine monophosphate to xanthosine monophosphate. Inhibition of IMPDH depletes the supply of guanine nucleotides that are required for the growth and proliferation of cells, viruses, and bacteria [159]. In the strategy used by Pankiewicz, the structure of mycophenolic acid (**72**, Scheme 7), a known immunosuppressant drug used to prevent rejection in organ transplantation (CellCept or Myfortic), which inhibits

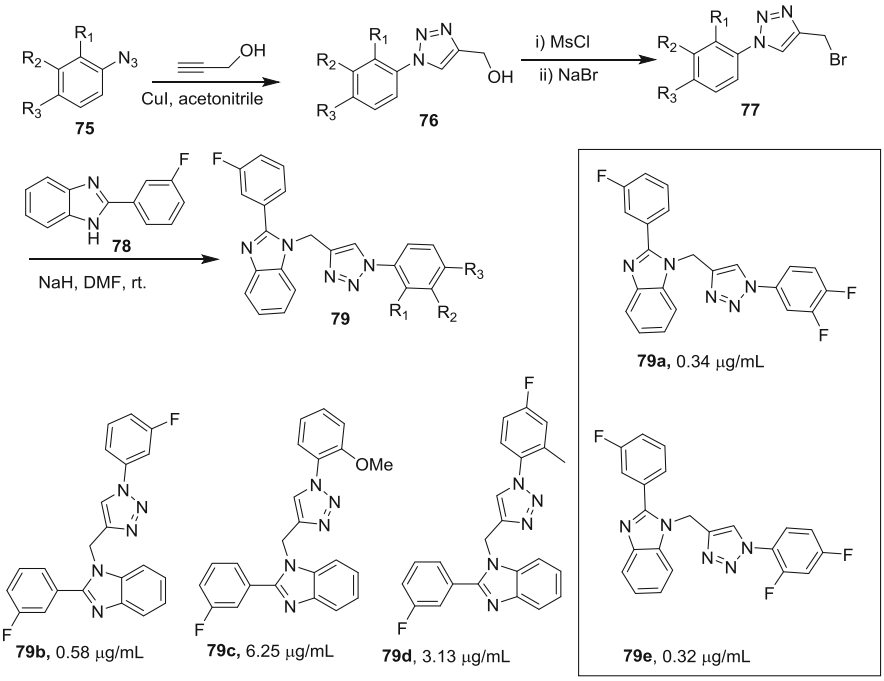


Scheme 7 Synthesis and antitubercular evaluation of triazoles linked with nucleosides

IMPDH by binding at its *N*-subsite, is joined with dinucleotide analogues of NAD. The NAD analogues interact with the subsites of the NAD cofactor-binding domain [160], which is present in the methylenebis(phosphonate) analogues of mycophenolic adenine (**74**), for which potential differentiation agents against human leukemia was found [161]. The NAD-mimicking inhibitors of IMPDH in which 1,2,3-triazole linkers replaced the pyrophosphate linker maintained the overall geometry and position of the mycophenolic moiety within the binding site of *M. tuberculosis* IMPDH (mtIMPDH). Evaluation of these inhibitors led to the identification of a low micromolar inhibitor (**74**, $K_i = 1.5$ μM) of human IMPDH and, more importantly, the first potent inhibitor of mtIMPDH [162]. It is possible that other analogues with different linkers would also enhance the selectivity against mtIMPDH.

Nitrogenated heterocycles typically present some type of biological activity. In view of this observation, the combination of different heterocycles has been a good strategy to discover new lead compounds in medicinal chemistry.

Gill and coworkers [163] prepared a group of imidazoles linked to triazole rings using 4-bromomethyl-1-phenyl-1*H*-1,2,3-triazole (**77**) as the coupling reagent with the imidazole (**78**). Several compounds (**79a–e**) were synthesized and two of those

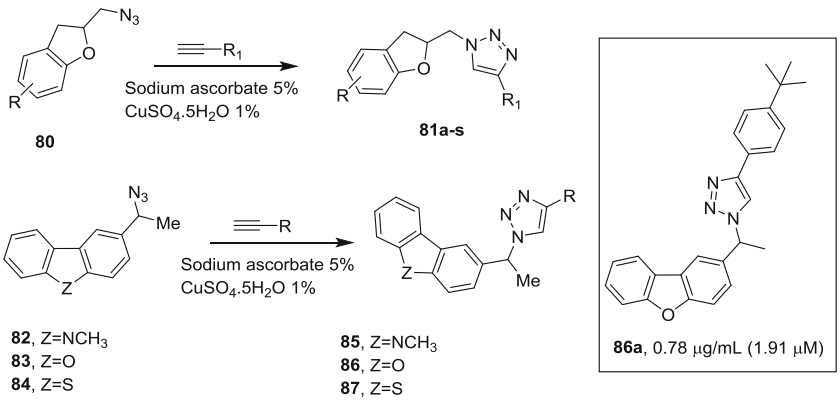


Scheme 8 Antitubercular triazole compounds tethered to an imidazole nucleus

compounds displayed excellent biological activities (**79a** and **79e**) against *M. tuberculosis* with MIC values ranging between 0.32 μg/mL and 0.58 μg/mL (Scheme 8). Botta and coworkers have also synthesized 1*H*-1,2,3-triazoles tethered to imidazole rings, but their compound showed a modest MIC value against *M. tuberculosis* H37Rv (ATCC 27294) [164].

A series of 1*H*-1,2,3-triazoles linked to dihydro-benzofuran were synthesized in good yields (59–94%) via a click reaction with 2-(azidomethyl)-benzofurans (**80**) (Scheme 9) [165]. These compounds were tested against *M. tuberculosis* H37Rv and were found to have MIC values between 3.12 and 5.12 mg/mL. Similarly, Patpi and coworkers have synthesized three series of 1*H*-1,2,3-triazoles linked to benzofuran and benzothiophene 9*H*-carbazole in excellent yields (82–96%). Evaluations against *M. tuberculosis* H37Rv (ATCC 27294 Strain) indicated that the MIC values were superior to those for ethambutol (**34**) and pyrazinamide (**33**) (Scheme 9) [166].

The quinoline or 1-azanaphthalene moiety is a structural feature present in many natural products and synthetic compounds that have become drugs in the therapeutic arsenal, especially as anticancer, antimalarial, and antimicrobial compounds [167–169]. Quinoline tethered to a triazole nucleus has also demonstrated potential bioactivity [170]. Promising activities have been shown by 4-(adamant-1-yl)-2-quinolinecarbohydrazide (**88**) and its analogues [171] against drug-sensitive and



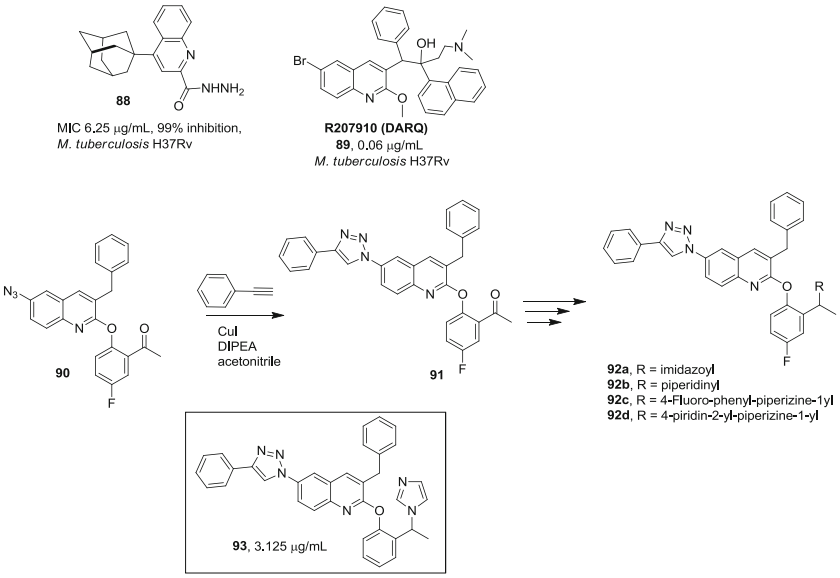
Scheme 9 Triazoles linked to dihydro-benzofurans, dibenzothiophenes and 9*H*-carbazoles

resistant *M. tuberculosis* H37Rv strains [172]. In addition, diarylquinolines (DARQs, e.g., **89**) have demonstrated potent anti-mycobacterial activity against replicating bacilli both in vitro and in vivo, which has resulted in compound R207910 [173–175] that selectively inhibits the ATP synthase proton pump of both drug-sensitive and drug-resistant *Mycobacterium tuberculosis* with an MIC value of 0.06 μg/mL [131]. Therefore, Upadhayaya and coworkers [175] have synthesized a series of 20 quinoline derivatives possessing triazolo, ureido, and thioureido substituents. All of the compounds were evaluated against *M. tuberculosis*, but only one compound (**93**, R=imidazoyl) showed good results, with a 96% growth inhibition of *M. tuberculosis* H37Rv and a minimum inhibitory concentration of 3.125 μg/mL (Scheme 10).

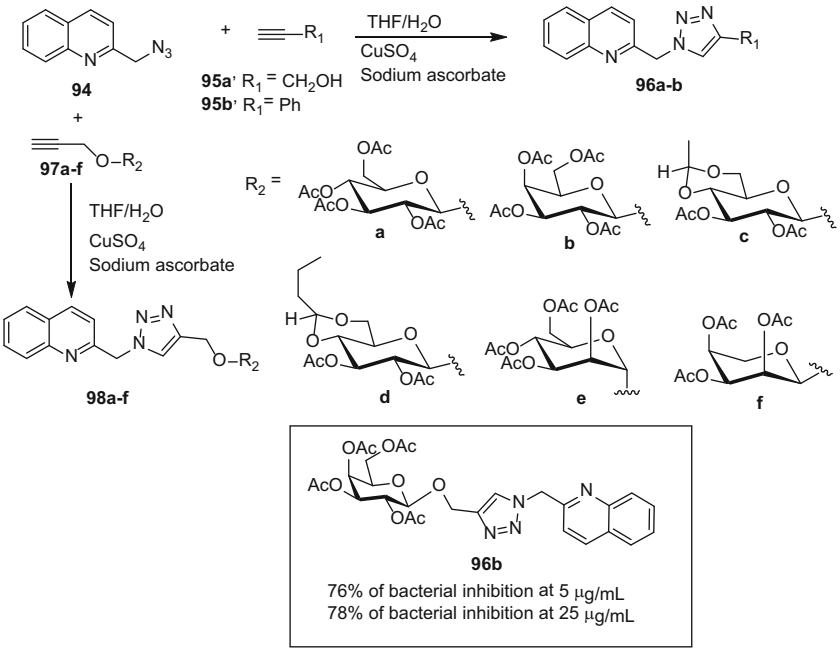
Kumar et al. used the same strategy and coupled the triazole nucleus at position 2 of the quinolinic ring (**96a–s** in Scheme 12) [176]. The triazole-quinoline derivative **96b** showed the best result, inhibiting bacterial growth by 76% and 78% at concentrations of 5 μg/mL and 25 μg/mL, respectively (Scheme 11).

Thomas et al. synthesized a series of 1*H*-1,2,3-triazoles attached to position 4 of the quinoline nucleus (**99–101**) [177]. These substances were tested against *M. tuberculosis* H37Rv and displayed excellent results with a minimum inhibitory concentration of 0.625 μg/mL; the MIC values obtained for **35** (rifampicin) and **32** (isoniazid) were 0.5 and 0.7 μg/mL, respectively (Scheme 12). β-lactam-ferrocene-triazole conjugate triazoles were prepared and tested against *M. tuberculosis* $mc^2$7000 using cephalexin, a β-lactam antimicrobial, as a positive control (MIC value of 10–25 μg/mL), but even at high doses, they failed to inhibit growth [178].

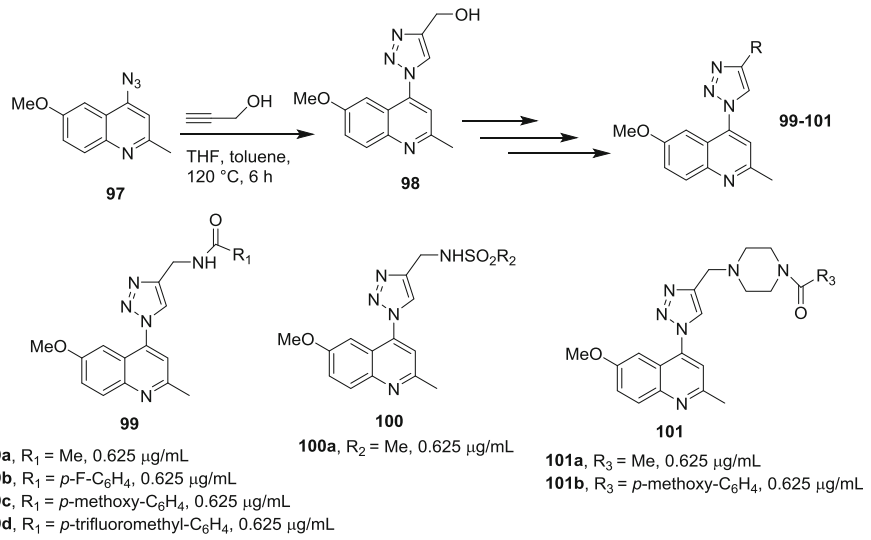
Several triazole compounds linked to a spirochromone were synthesized by Muthukrishnan and coworkers [179], and their MIC values ranged from 0.78 to 25 μg/mL. The compound **103a** was the most active of the series against *M. tuberculosis* H37Rv (ATCC27294) (Scheme 13).



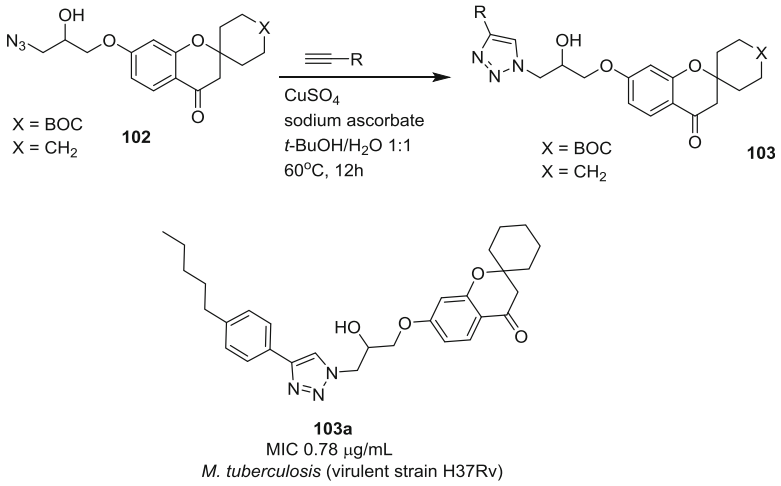
Scheme 10 Synthesis of antitubercular triazoles tethered to quinoline rings



Scheme 11 Antitubercular triazoles linked at the 2-position of quinoline



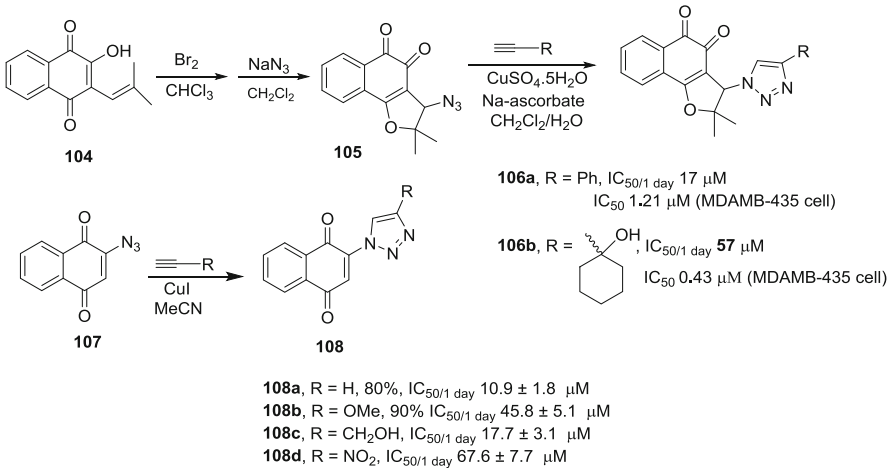
Scheme 12 1*H*-1,2,3-triazoles linked at position 4 of the quinoline



Scheme 13 Triazole-spirochromone conjugates as antitubercular agents

4 *Trypanosoma cruzi*

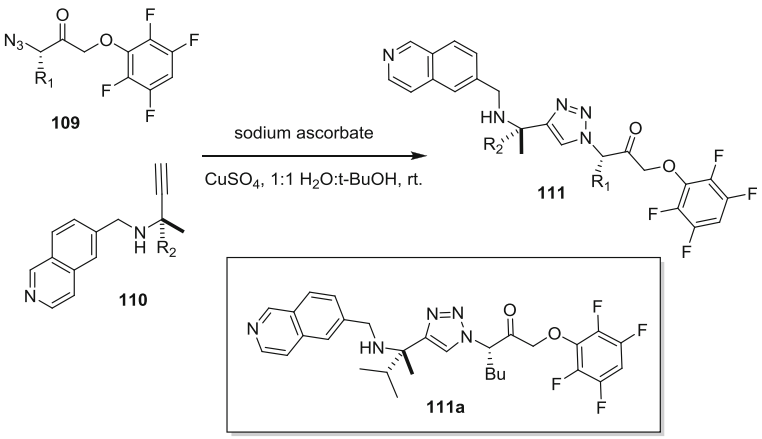
Quinones are natural products present in various families of plants, fungi bacteria, and insects linking the electron transport chains in the metabolic pathway with the oxidative processes. Because of these properties, over the past few years, several series of synthetic substances have been investigated as prototype bioactive



Scheme 14 Trypanocidal compounds obtained by molecular hybridization of naphthoquinone and 1,2,3-1*H*-triazole moieties

compounds to be used to treat several diseases. Certain compounds of this class have become pharmaceuticals and others have remained prototypes. This fact can be demonstrated by the large number of publications exploring the actions of these substances in various biological functions [180–182]. Briefly, quinones have been studied for antitumor [183, 184], molluscicidal [185–187], leischmanicidal [188], anti-inflammatory [189], antifungal [190], and trypanocidal [191, 192] activities. Regarding the trypanocidal agents, Chagas' disease is an enormous public health problem caused by the parasite *T. cruzi* that is endemic in Latin America and transmitted by triatomine insects while blood feeding on a human host.

Ferreira and coworkers, for the first time, incorporated a triazole ring to a naphthoquinone framework and assayed them against the infective bloodstream trypomastigote form of *T. cruzi* [193]. All of the derivatives were more active than the original quinones, with IC_{50}/1 day values in the range of 17–57 μM. The two most active compounds were substituted triazoles **106a** and **106b** (Scheme 14). This series of triazole-naphthoquinones emerged as interesting new lead compounds in drug development for Chagas' disease. Note that these furonaphthoquinone-1,2,3-triazoles also have potential clinical utility in the treatment of human cancer. These compounds have had their cytotoxic activities evaluated against the following six neoplasic cancer cell lines: SF-295 (central nervous system), HCT-8 (colon), MDAMB-435 (melanoma), HL-60 (leukemia), PC-3 (prostate), and B-16 (murine melanoma) and against one normal cell, the murine fibroblast L-929. The same triazoles **106a** and **106b** showed high and selective activity against melanoma cell line MDAMB-435 (Scheme 14) [45]. Similar molecular hybridization of furonaphthoquinone linked to 1,2,3-triazole was extended for the synthesis of a 1,4-naphthoquinone linker to 1,2,3-triazole (**108a–d**) and tested against *T. cruzi* trypomastigote forms. The authors [194] also observed

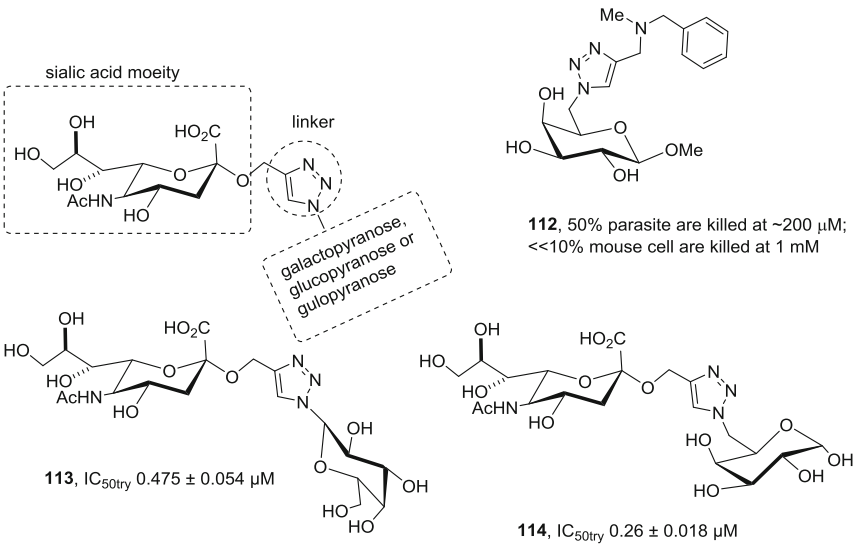


Scheme 15 Triazoles as nonpeptidic inhibitors of cruzain

that insertion of a 1,2,3-1H-triazole moiety into 1,4-naphthoquinone enhanced its trypanocidal activity (Scheme 14).

Ellman and co-workers prepared by regioselective Cu(I)-catalyzed 1,3-dipolar cycloaddition a series of 1,2,3-1*H*-triazole tetrafluorophenoxy (**111**) compounds to be tested as nonpeptidic inhibitors against the key enzyme cruzain from *T. cruzi* (Scheme 15) [195, 196]. The triazole **111a** was found to be an irreversible inhibitor that completely eradicated the *T. cruzi* parasite in cell culture (Scheme 15). The mode of inhibition and the binding interactions of **111a** were revealed by the high-resolution X-ray structure of the co-crystal with cruzain. Treatment of mice infected with *T. cruzi* parasites (trypomastigotes) for 27 days with **111a** substantially improved the symptoms of acute Chagas´ disease with no apparent toxicity.

The trans-sialidase from *T. cruzi* (TcTS) is a unique glycosyltransferase enzyme involved in mammalian host-cell invasion by transferring sialic acids from glycoconjugates of the host to the terminal β-galactopyranosyl units present on the surface of the parasite [197, 198]. Thus, this enzyme is an important target for preparing new compounds that can inhibit its action and, consequently, the growth of *T. cruzi* [199]. To date, there are several synthetic and natural compounds that have been classified as inhibitors of TcTS [199–201]. Carvalho and coworkers, in an effort to find new inhibitors of this enzyme, prepared a series of 1,2,3-triazole galactosyl derivatives and sialylmimetic neoglycoconjugates for the evaluation against trypomastigote forms of the *T. cruzi* Y strain [202] and the *T. cruzi* Tulahuen strain [141], respectively. The *N*-methyl benzylamine derivative (**112**) was the best candidate of the galactosyl series, and the compounds **113** and **114** presented good inhibitory effects against the parasite in a nanomolar range, indicating that the 1,2,3-triazole ring is a good moiety for the design of trypanocidal compounds (Scheme 16).

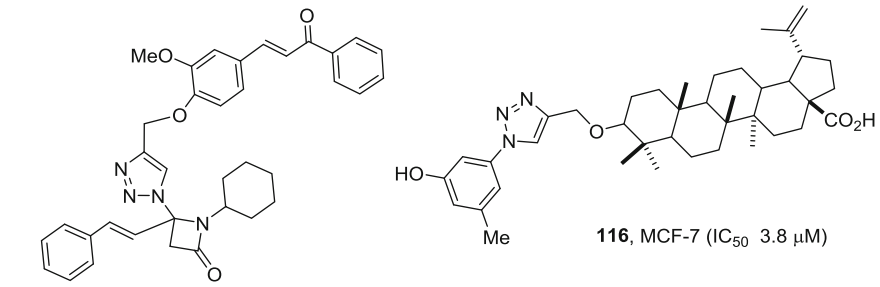


Scheme 16 1,2,3-triazole galactosyl sialylmimetic derivatives against *T. cruzi*

5 Anticancer Activity

The discovery of new drugs for cancer therapy is one of the medicinal chemistry's most investigated areas because the global prevalence of this disease continues to grow. The greatest challenge for scientists in this area is to develop new drugs that are more effective and have lower toxicity. Selectivity is the dilemma in cancer therapy for the achievement of drug delivery to a localized tumor and for an even distribution throughout the body, including the tumor tissues. Other challenges in the treatment of cancer using chemotherapy include drugs with short half-lives in blood circulation, fewer side effects, and effectiveness. The development of research in this area aims to attack the problem from different angles, such as chemotherapy conjugated with drug carriers to act as magic bullets or to enhance distribution of the drug molecule in the body [203].

Recently, several triazoles have been found to have activities against several cancer cell lines [83, 204, 205]. The researchers are focusing their efforts on the anticancer activity [206–208] in compound hybrids of 1,2,3-1*H*-triazole tethered with the β-lactam (**115**), triterpenoid (**116**), and chalcone (**117**, **118**) moieties that were evaluated against several cancer cell lines and were selective to A-549(lung) [209], chalcone-pyrrolo[2,1-c] [1,4]benzodiazepine conjugates containing alkane spacers with promising in vitro anticancer activity in concentrations ranging from <0.1–2.92 μM [210]. These compounds have also been screened on the apoptosis enzymes that regulate cellular programmed cell death of unnecessary cells as shown in Fig. 10 [211, 212].



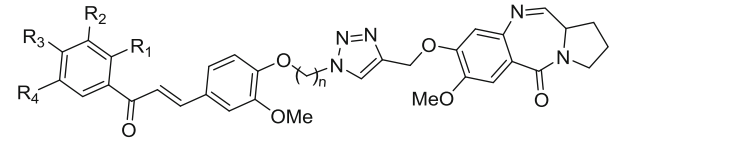
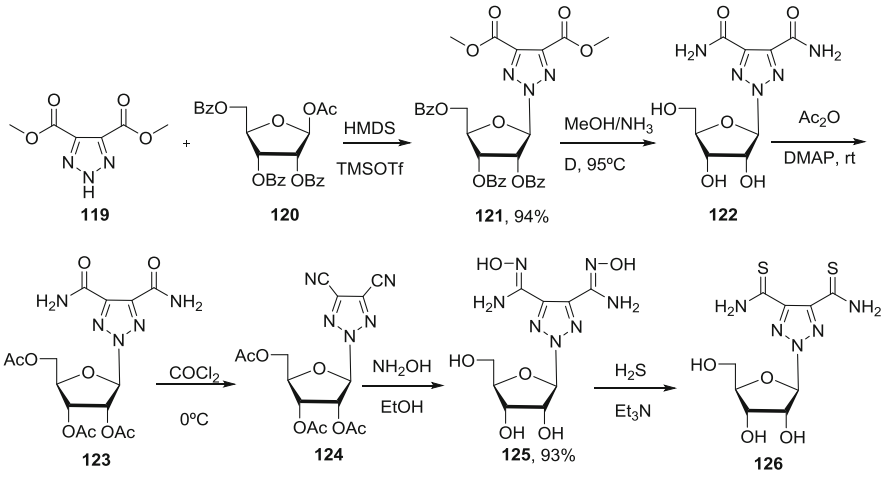


Fig. 10 Examples of triazole linkers active against cancer cell lines



Scheme 17 1,2,3-2H-triazole analogues of ribavirin

Drugs used therapeutically for other diseases can serve as models in the search for new lead compounds. Revankar and coworkers synthesized a series of six analogues of the antiviral drug ribavirin (**121–126**) containing 1,2,3-2H-triazoles and studied them as inhibitors of the tumor cell line HL-60 [213]. The derivatives were obtained by a synthetic sequence (Scheme 17) that begins with a condensation reaction between the triazole compound (**119**) and ribofuranoside (**120**) catalyzed

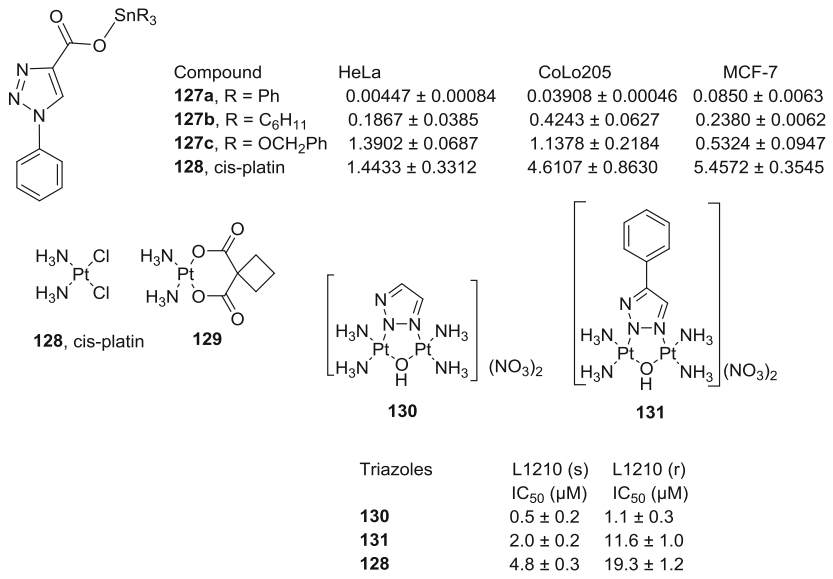
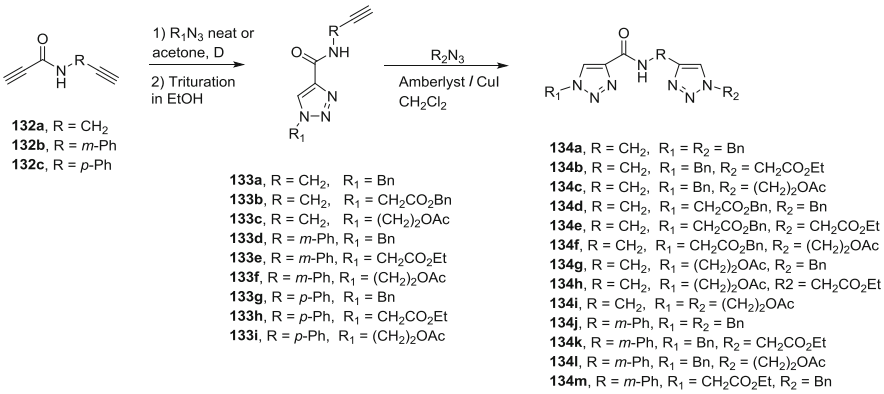


Fig. 11 Platinum complexes with triazoles and their activities in tumor cell lines

by a Lewis acid, trimethylsilyl triflate. The product **121** is then converted by several reactions to the nucleosides **122–126. 126** inhibited HL-60 at a level that was 50% of the inhibitory effect of ribavirin (Scheme 17).

Metal complexes are widely used in chemistry and in many treatments of diseases, including cancer chemotherapy. For example, organotin (IV) carboxylates are used in many applications in chemistry and biology, such as antitumor activity [214]. Tiam and coworkers synthesized three triorganotin 2-phenyl-1,2,3-triazole-4-carboxylates (**127a–c**), and a bioassay showed that these compounds have good antitumor activity against three human tumor cell lines (HeLa, CoLo205, and MCF-7) [215]. In addition, platinum complexes are widely used in cancer chemotherapy. For example, cisplatin, approved by the FDA in 1978, and carboplatin [216], are the most commonly used anticancer platinum complexes in the clinical treatment of testicular and ovarian malignant tumors [217–219], and their mechanism of action is the induction of apoptosis [220, 221]. Considering these findings, Reedijk and coworkers [222] synthesized two binuclear platinum complexes [223] with triazoles as ligands. The compounds **130** and **131** demonstrated to have better anticancer activity (18 times more cytotoxic) than cisplatin against tumor cell lines (acute lymphoblastic leukemia cisplatin-sensitive and cisplatin-resistant) (Fig. 11).

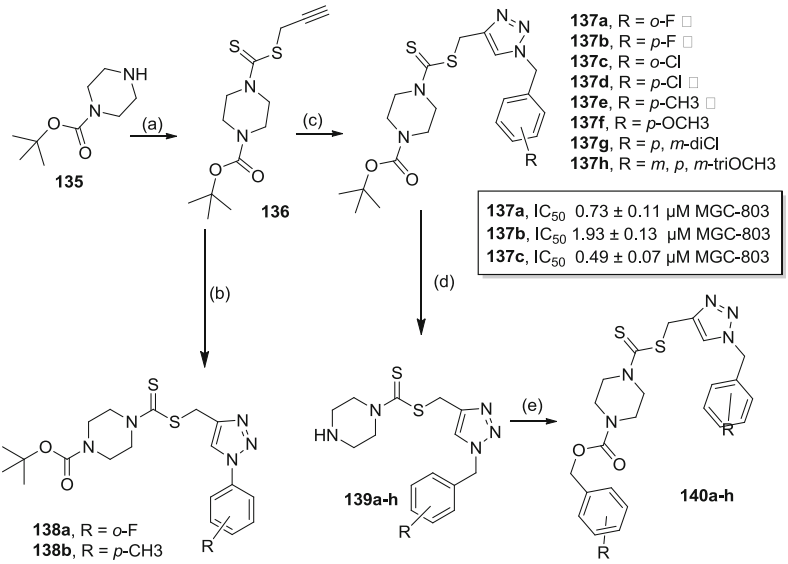
Girard and coworkers [224, 225] synthesized mono- and bis-1,2,3-triazoles from bis-alkynes to be tested against the human tumor strain B16 (murine melanoma cell line) that is highly malignant, metastatic, and chemoresistant [226–228]. The new compounds were obtained based on the previous experiments conducted by the group, which synthesized 1,4-disubstituted-1,2,3-triazole analogs of combretastatin



Scheme 18 Series of 1,4-disubstituted mono- and bis-1,2,3-triazoles with some cytotoxic activity in tumor strain B16

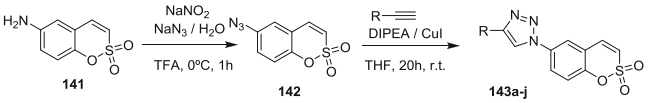
A-4 (a natural stilbenoid isolated from *Combretum caffrum*). All of the compounds, including their precursors, were tested in cultures of human melanoma cells B16. The presence of one triazole ring did not prove to lead to a good inhibitor; on the contrary, the alkyne precursors **133a** (38.0 ± 0.4 μM), **133b** (0.3 ± 0.008 μM), and **133c** (6.3 ± 0.3 μM) were generally more active than the mono-substituted-1,2,3-triazoles **134a–i**. The bis-triazoles showed significant changes in the cytotoxicity. The derivatives **134a** (0.3 ± 0.003 μM) and **134j** (4.5 ± 0.3 μM) showed the most favorable results from this series (Scheme 18).

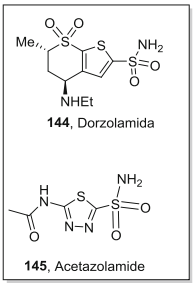
Dithiocarbamate derivatives are well known in the literature as fungicidal [229] and bactericidal [230] compounds, as well as inhibitors of carbonic anhydrase enzymes [231, 232]. Liu and coworkers [233–235] prepared 1,2,3-triazoles containing a dithiocarbamate pharmacophoric group and studied their antitumor activity [236–238]. The desired dithiocarbamate-alkynes were synthesized in a one-pot reaction using the carbamate **135**, CS_2, and propargyl bromide. The appropriate dithiocarbamate-alkynes were reacted with azides via click chemistry to produce several series of dithiocarbamate-triazoles (**136**). The compounds were tested in cell lines of MGC-803 (gastric cancer), MCF-7 (breast cancer), PC-3 (human prostate cancer), and EC-109 (esophageal squamous cell carcinoma) using a 5-fluorouracil standard positive control (IC_{50} MGC-803 7.01 ± 1.34; MCF-7, 7.54 ± 0.7; PC-3 27.07 ± 4.21; EC-109 3.34 ± 0.86). The results of the inhibition of the growth of cells of all of the synthesized derivatives have shown that the compound **137a** is more cytotoxic than the positive control as an injectable or in topical applications [239]. In addition, compound **137c** showed good activity, 14 times more active than the positive control for the strain MGC-803 (gastric cancer), but was less active than the control only for strain EC-109 (esophageal cancer). Removal of the tertiary butyl oxycarbonyl group (series **139a–h**) generates a loss of activity and the introduction of the carbobenzoxy group (series **139a–h**) (Scheme 19).



Scheme 19 Synthesis and anticancer activities of 1,2,3-triazole-dithiocarbamates

Human carbonic anhydrase (hCA) is a metalloenzyme with 15 isoforms [240] that are involved in various physiological processes [241], such as breathing, CO_2/bicarbonate transport between tissues and lungs [242], homeostasis, biosynthetic reactions, bone resorption, calcification, growth, and virulence of several pathogens [243] and tumorigenicity [244, 245]. The hCA isozymes IX and XII are overexpressed in cancer cells where they regulate a pH level that contributes to hypoxic tumor cell survival and proliferation. These enzymes are important for the growth of primary breast cancer tumors and metastasis [246]. Coumarins significantly inhibit carbonic anhydrase [247–250]. Coumarin bioisosteres, sulfocoumarins, also target human carbonic anhydrase-associated tumors, as reported by Supuran and coworkers [251–253]. Dorzolamide **144** (Trusopt) is an approved pharmaceutical drug that targets carboxylic anhydrase and is used in ophthalmic compositions for the treatment of ocular hypertension or glaucoma. The sulfohexyl moiety appears to be important for the activity of this compound. Recently, Zalubovskis and coworkers [254] prepared a facile synthetic protocol to prepare a series bioisosteres in which the carbonyl group is replaced by a sulfonyl group (Scheme 20). The synthesis begins with the diazotization of the sulfocoumarin **141**, which is transformed into an azide and then reacted with various alkynes to form the triazoles **143a–j** by 1,3-dipolar cycloaddition. These triazoles have shown inhibitory activity in both hCA I and II enzymes and for hCA





Compounds	R	hCA I (μM)	hCA II (μM)	hCA IX (μM)	hCA XII (μM)
143a	Ph	6.86	7.76	0.029	0.032
143b	CO_2Me	8.05	6.33	0.095	0.012
143c	CO2Et	8.88	9.21	0.086	0.013
143d	Me_3Si	6.00	7.20	0.060	0.009
143e	CH_2OH	7.20	9.29	0.058	0.016
143f	CH_2NEt_2	8.11	9.37	0.025	0.007
143g	4-$OCF_3C_6H_4$	8.43	9.64	0.074	0.014
143h	4-MeO-C_6H_4	8.93	9.35	0.018	0.039
143i	3-F_3C-C_6H_4	6.71	7.72	0.048	0.013
143j	3-MeO-C_6H_4	7.47	8.61	0.049	0.021
145	-	0.25	0.012	0.025	0.005

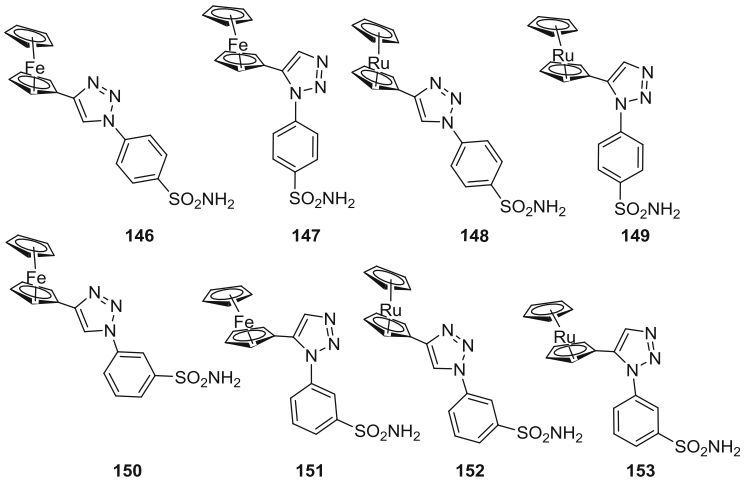
Scheme 20 Synthesis of 1,2,3-triazole-sulfocoumarins

IX and XII enzymes, which are related malignant tumors in nanomolar concentrations. The derivative **143b** showed the best inhibitory activity for hCA IX, and **143c** was 11 times more potent than acetazolamide **145** (a carbonic anhydrase inhibitor for the treatment of glaucoma, epileptic seizures, etc.), which was used as a positive control.

Metal complexes are widely used as pharmaceuticals in several diseases, including cancer treatment. Further attention has been focused on the iron complexes, ferrocenes, because they can be administered orally and have very low toxicity. Therefore, ferrocene-based compounds have been used in several therapies. Poulsen et al. [255] planned the synthesis of 1,2,3-triazoles tethered (**146–153**) with a phenyl sulfonamide ($PhSO_2NH_2$) tail, a recognized pharmacophore that inhibits hCA enzymes, and with a head composed of a ferrocene (iron) or ruthenocene (ruthenium) complexes that also affect the hCA enzyme. Compound **151** from this series was the most potent ferrocene-based inhibitor with a K_i value of 5.9 and 6.8 nM for hCA IX and XII, respectively (Fig. 12).

6 Diabetes Mellitus

A glycosidic bond, consisting of α- or β-linkages at the anomeric center, is a covalent chemical bond that joins two simple sugars using an oxygen atom. Many polysaccharides are formed by joining monosaccharides by α- or β-glycosidic bonds. During the digestion process, these bonds are hydrolyzed by specific glycosidase enzymes, liberating the carbohydrate units as nutrients [256]. For example, the amylase enzymes are produced in the digestive system to break down the α-glysosidic bonds of starch. There are several enzymes that control carbohydrate usage as nutrients. Peroxisome proliferator-activated receptor (PPAR) agonists have the ability to improve glucose tolerance in type 2 diabetic



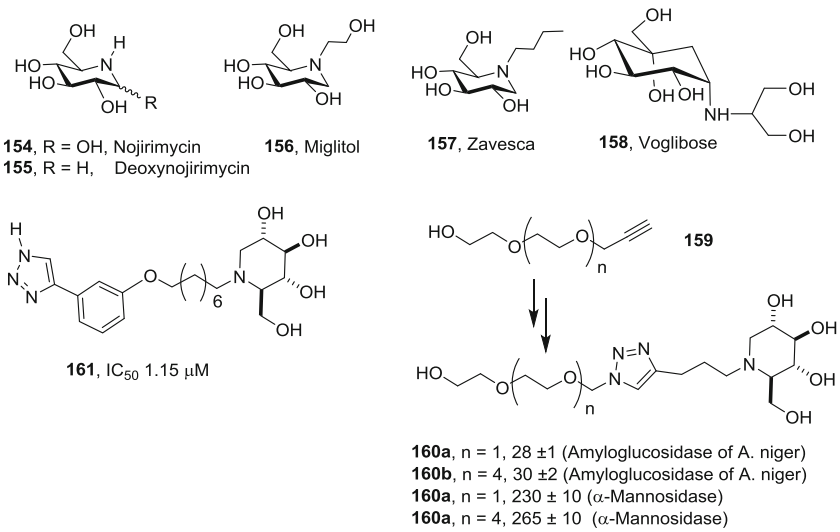
	K_i (nM)		
	hCA I	hCA II	hCA IX
146	3900	80	85
147	1600	36	65
148	44	9.7	10.3
149	9	12.3	64

	K_i (nM)			
	hCA I	hCA II	hCA IX	hCA XII
150	1790	4165	33.1	18.8
151	361	3.2	5.9	6.8
152	70	6.9	8.2	5.5
153	54	5.2	8.8	6.9

Fig. 12 Ferrocene- and ruthenocene-based compounds tethered to 1,2,3-triazoles

patients [257] and improve the regulation of glycosidase enzymes. The latter enzymes are involved in important biological processes, such as intestinal digestion and lysosomal catabolism of glycoconjugates. The inhibitors are designed to act as antagonists of α- and β-glucosidase enzymes, interfering with the digestion of carbohydrates and slowing the rate of absorption of monosaccharides, resulting in decreased levels of blood glucose. In addition, the PPAR agonists are useful as antiviral agents [258, 259], anti-cancer metastasis [260], against obesity, genetic diseases, and as anti-diabetic agents. Therefore, inhibition of digestive α- and β-glucosidases could be used therapeutically for the treatment of metabolic diseases, such as diabetes mellitus, which is a chronic metabolic disorder characterized by hyperglycemia (an abnormal increase in blood glucose from insufficient secretion and insulin action).

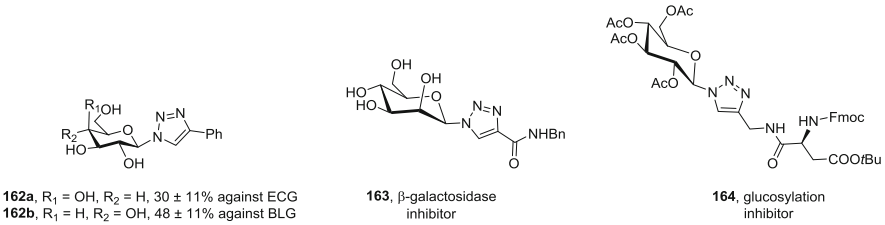
Many organisms have endogenous inhibitors that regulate the activity of their glycosidases and glycosyl transferases. Nojirimycin (**154**) and deoxynojirimycin (**155**, 1-DNJ) are two classical iminosugars [261, 262] glycosidase inhibitors that act in the early stages of glycoprotein processing and are isolated from plants or the cultured broth of the Streptomyces species. Nojirimycin (**154**) was the first natural piperidine heterocycle that mimicked D-glucose with a nitrogen atom in place of the ring oxygen with potent inhibition activity for α- and β-glucosidases from various sources. These natural iminosugar products have served as a model for the design and synthesis of tethered or fused [263] compounds that incorporate their



Scheme 21 Examples of hybrid iminosugars based on 1-DNJ inhibitors of glycosidases

most important structural features [264, 265]. Currently, the following three drugs are used therapeutically in the treatment of non-insulin-dependent diabetes as anti-glucosidases: 1-(2-hydroxyethyl)-2-(hydroxymethyl)-1-deoxynojirimycin (**156**, Miglitol or Glyset) [266], *N*-butyl-1-deoxynojirimycin (**157**, Zavesca) and voglibose (**158**, Vogli, Basen, or Prandial) (Scheme 21). New compounds with inhibitory activity on glycosidases led to the discovery that five-membered azaheterocycles mimic the sugar moieties; thus, various compounds containing the pyrrole, imidazole [267, 268], tetrazolo-glyco-derivatives, and [1,2,3]-1*H*-triazole [269–275] groups were prepared and evaluated. Because the alkyl chain linker of *N*-butyl-1-deoxynojirimycin (**157**) does not have a deleterious effect on the inhibition of α-glucosidases on glycosidase activity, Zhou and coworkers [276] designed and synthesized a series of triazoles linked to nojirimycin (**154**) and evaluated their ability to inhibit α-glucosidase from *Bacillus stearothermophilus*. The compound **161** shown in Scheme 21 was more active than nojirimycin (**154**, IC_{50} 1.67 μM). More recently, Kovensky et al. [277] reported the synthesis of several iminosugars using the click chemistry methodology between oligoethylene and the azide of *N*-substituted deoxynojirimycin. The compounds **160a** ($n = 1$) and **160b** ($n = 4$), which are derivatives of the 1-deoxynojirimycin compound, are moderate inhibitors toward different glycosidases (Scheme 21). The compounds of this series did not show better activity when tested against glycosidases compared with 1- deoxynojirimycin (**155**).

There is also considerable interest in designing molecules that are able to mimic the carbohydrate units and evaluating them against glucosidase enzymes [278]. The combination of both carbohydrate and 1,2,3-triazole structural units has proven to be useful for the production of new compounds with various biological activities



162a, R_1 = OH, R_2 = H, 30 ± 11% against ECG
162b, R_1 = H, R_2 = OH, 48 ± 11% against BLG

163, β-galactosidase inhibitor

164, glucosylation inhibitor

Fig. 13 Examples of glycotriazoles that mimic iminosugar inhibitors

[279–282]. One of the first examples of this approach was the synthesis [283] of glycosyl triazoles (**162a,b**) at the anomeric position followed by inhibitory evaluation against *Escherichia coli* galactosidase (ECG) and bovine liver galactosidase (BLG). These compounds showed the modest anti-glucosidase activity compared with nojirimycin (**154**) and deoxynojirimycin (**155**) [284]. Recently, the 1-glucopyranosyl 1,2,3-1*H*-triazole series was synthesized using improved methodology and with the introduction of halogens at position 5 of the triazole ring [285] (Fig. 13).

Several new glycosidase inhibitors have been isolated from plants and microorganisms [286]. A search for glycosidase inhibitors led to the discovery of acarbose (**165**) (Glucobay®, Precose), isolated from the Actinoplanes strain SE 50. This drug is a complex oligosaccharide for oral administration that is an inhibitor of α-glucosidase, which acts by delaying the digestion of carbohydrates ingested in the diet, thereby reducing the concentration of blood sugar after meals. Because of the reduction of blood glucose levels, there is a decrease in the glycosylated hemoglobin in patients with diabetes mellitus type II (non-insulin dependent). Following the previous pattern of introducing the triazoles ring into the structure's natural product, several compounds were synthesized and tested as glycosidase inhibitors [271]. Surprisingly, the mimetic triazole (**168**) did not improve the inhibitory activity. The compound with more carbohydrate units (**167**) did not show high activity, but the compound with only one glycol-triazole (**166**) with one carbohydrate unit was more active than acarbose against α-glucosidase and certain other glycosidases (Fig. 14).

Ferreira and coworkers [274] have synthesized a series of glycosyl triazoles (**169–172**) that have also demonstrated strong action as α-glucosidase inhibitors, and their bioactivity has been associated with their ability to mimic the charge buildup and/or the conformational distortion of the transition state thought to develop in the glycosidic bond during enzymatic cleavage. All of the compounds were initially screened for α-glucosidase inhibition at 500 μM, and the results revealed that most of them presented an inhibitory profile higher than that of acarbose (IC_{50} 108.8 ± 12.3 μM); notably, the ribosyl derivatives had the following IC_{50} values: **169b** (IC_{50} 3.8 ± 0.5 μM); **169e** (IC_{50} 5.7 ± 0.3 μM), and **169g** (IC_{50} 5.2 ± 0.9 μM). The pharmacological potential of this triazole series was demonstrated by the reduction of post-prandial blood glucose levels in normal rats treated with a 50 mg/kg oral dose of compounds **169a** or **169e.** This result

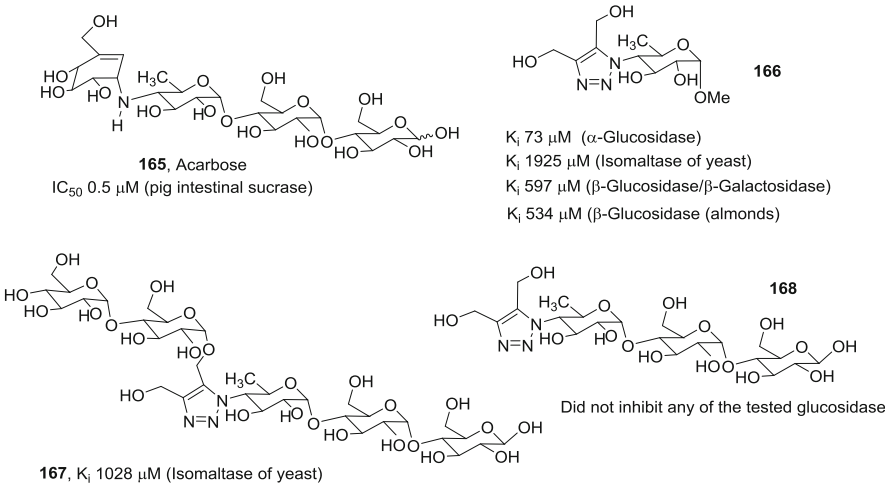


Fig. 14 Glycotriazoles that are structurally related to acarbose (**165**)

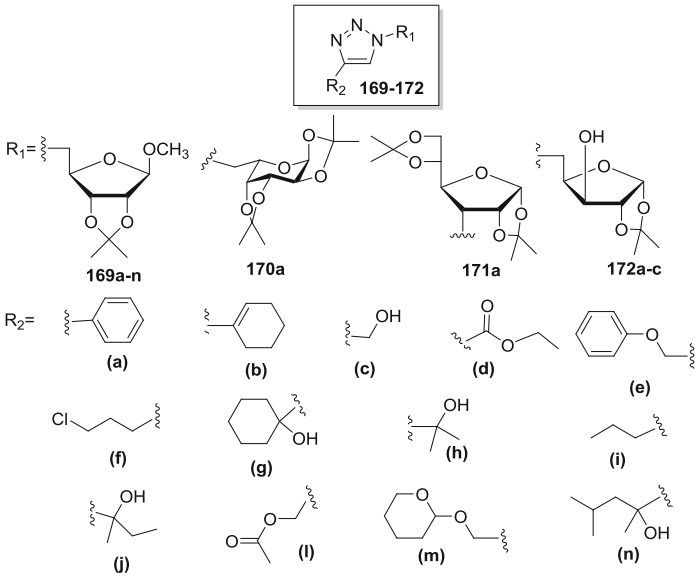


Fig. 15 Glycosyl 1*H*-1,2,3-triazoles (**169–172**) as antidiabetes candidates

indicates that this triazole series could represent new candidates for the development of novel drugs for the treatment of metabolic diseases, such as diabetes (Fig. 15).

Polyhydroxylated alkaloids have been isolated from plants and micro-organisms and are good glycosidase inhibitors that are potential therapeutic agents [260, 287]. For example, castanospermine (**173**), isolated from *Castanospermum*

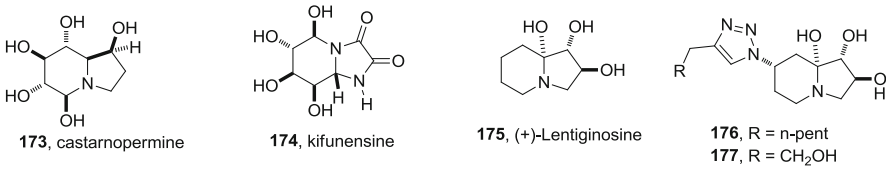


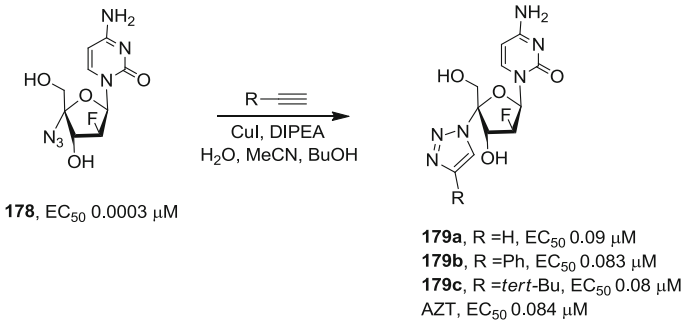
Fig. 16 Polyhydroxylated alkaloids from plants and triazole hybrids

australe, can inhibit both α-glucosidases and β-glucosidases [288], kifunensine (**174**), isolated from *Kitasatosporia kifunense,* showed its ability to act as an anticancer agent and α-mannosidase inhibitors [289], and (+)-lentiginosine (**175**), isolated from the leaves of *Astragalus lentiginosus*, among many others, is a good glycosidase inhibitor. Following the same pattern described above, new hybrid compounds of the piperidine or pyrrolidine alkaloids class tethered to triazole, tetrazole, pyrazole, or a pyrrole ring have been synthesized [263] and studied as inhibitors of various glycosidases. The triazoles **176** and **177** were synthesized based on the structure of (+)-lentiginosine (**175**) and showed better activities on β-glucosidase (EC 3.2.1.21) at 1 mM concentration than (+)-lentiginosine (**175**) (Fig. 16) [290].

The antiviral drug ribavirin (**4**, see Fig. 1) was used as inspiration for the synthesis of 2*H*-1,2,3-triazoles [291, 292], and compounds that mimic nucleosides [293] have been selected and synthesized [294] over the years to target enzymes of many infectious diseases. There are several drugs on the market for the treatment of diseases, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), based on this concept. Recently, Chang and coworkers reported the classical synthesis of several new 1,2,3-1*H*-triazole moieties at the 4′-C substituted-2′-deoxynucleosides, based on their past experience that most of the 4′-C substituted-2′-deoxynucleosides exhibited potent anti-HIV-1 activity without significant cytotoxicity [295, 296]. The evaluation of the triazole-nucleosides indicated that most of these compounds also exhibited potent anti-HIV-1 activity without significant cytotoxicity, and the best results (**179a–c**) are presented in Scheme 22 [297]. None of the compounds displayed better EC_{50} values than the starting material (**178**) or AZT.

Recently, a novel class of deoxyribonucleosides having tropone-fused nitrogen heterocycles as nucleobases was prepared and presented weak antiviral activities for herpes simplex virus type 1 and herpes simplex virus type 2 compared with those of acyclovir (ACV). These nucleosides showed no cytotoxicity on a lung cancer cell line (A549) or on two colon (HT-29 and HCT-116) cancer cell lines.

Certain triazole compounds did not exhibit biological activity, and the linkage of this heterocycle with other moieties that have a recognized activity did not always increase the antimicrobial activity. This result occurred with the following compounds: 1,2,3-1*H*-triazole-tethered β-lactams (**180**) that were inactive against *M. tuberculosis* [298], 1,2,3-2*H*-triazole-tethered indole (**181**) as an antibacterial [299], hybrid compounds having 1,2,3-1*H*-triazole, piperidine, and



Scheme 22 Triazole-nucleosides as anti-HIV-1 prototypes

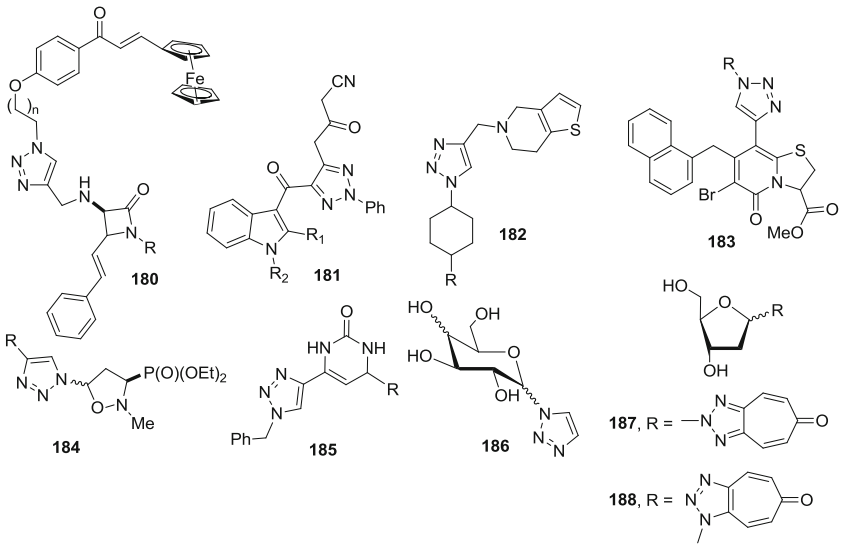


Fig. 17 Triazoles that exhibited no biological activity in their targets

tetrahydrothieno pyridine rings (**182**) showed the very modest antifungal activity (*Candida* spp.) [300], the series of triazole derivatives only exhibited very weak inhibition against α-glucosidase [301], triazoles that were ring-fused with 2-pyridones (**183**) showed low or no antibacterial activity [302], the *trans*- and *cis*-(1,2,3-triazolyl)isoxazolidinephosphonate series (**184**) were evaluated against a broad-spectrum of viruses but found not active at 250 μM [303]; triazolyl dihydropyrimidine-2-thiones (**185**) were prepared by an efficient route, but most of them exhibited poor antibacterial activity compared with tetracycline [304], the glycosyl or galactosyl 1,2,3-triazoles (**186**) did not display inhibitory activity against the tested glycosidases [305], cyclohepta[d]triazol nucleosides (**187–188**) had weak antiviral activities against herpes simplex virus types 1 and 2 compared with acyclovir [306] (Fig. 17).

7 Conclusion

Drug discovery depends on the synthesis of a large group of small molecules that are easy to prepare and that can be active in biomolecule receptors and proteins. The triazole class fulfills these requirements, and they have been studied in recent years. This chapter demonstrated that this important class of heterocyclic compounds has attracted considerable attention because of their wide range of biological activities against various microorganisms, cells, and viruses and their inhibitory activities toward several enzymes. Due to the success of triazoles, some have entered the pharmaceutical market and are still being used as medicines. Many companies and research groups have shown interest in developing new methods for the synthesis and biological evaluation of these compounds. This class of compounds shows great potential as an antibacterial, antiprotozoal, anticancer, and inhibitor of the glucosidase enzymes, especially when incorporated into compounds containing other heterocyclic rings. There are two important aspects about these compounds. Hybrid triazole compounds with long chains that increase lipophilicity show enhanced permeation through the cell membranes and, thus, have enhanced inhibitory activity, and triazoles tethered to carbohydrates and other heterocycles have an increased number of hydrogen bonds and an increased number of interactions with bio-glycoconjugates on the surface of the microorganisms, thus, increasing their activities.

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Chemistry of 1,2,3-Triazolium Salts

Zekarias Yacob and Jürgen Liebscher

Abstract 1,2,3-Triazolium salts have been known for a long time. However, their potential as ionic liquids and catalysts was recognized only quite recently. 1,2,3-Triazolium ionic liquids can serve as solvent, as catalyst, as hosts in anion recognition and as components of molecular machines. The major trends in application involve tethering catalytically active species such as (*S*)-proline with triazolium ionic liquids and the use as anion recognizing organocatalysts. Such catalysts are interesting not only due to their recyclability but also because of their outstanding tuneable properties. They can have wide liquid range, thermal stability, tuneable polarity, low flammability, tuneable solubility and low vapour pressure along with ease of separation. The syntheses of 1,2,3- triazolium salts are mainly based on the copper catalysed azide-alkyne cycloaddition (CuAAC) as the most famous click reaction, and subsequent *N*-alkylation of the resulting 1,2,3-triazoles. This synthetic route has the advantage of having four structural units, i.e. the alkyne, the azide, the alkylating agent and the counter anion that can be manipulated in order to tune the properties of the resulting ionic liquid. Unlike the imidazolium ionic liquids 1,2,3-triazolium salts do not have an acidic proton at position 2, which could make them inappropriate for reactions under basic conditions. The low acidity of 1,2,3-triazolium salts in position 4 is exploited in the formation of 1,2,3-triazol-4-ylidene metal complexes with marked catalytic properties.

Keywords 1,2,3-triazolium salt · Alkylation · Catalysis · Click reaction · CuAAC · Ionic liquid

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Abbreviations

Ar	Aryl
Bn	Benzyl
Boc	*Tert*-butoxycarbonyl
cat	Catalyst
Cbz	Benzyloxycarbonyl
CuAAC	Copper catalysed azide-alkyne cycloaddition
d	Day(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	*N N*-dicyclohexylcarbodiimide
DMAP	4-(*N N*-dimethylamino)pyridine
DMF	*N N*-dimethylformamide
DMSO	Dimethyl sulphoxide
dr	Diastereomer ratio
ee	Enantiomer excess
equiv	Equivalent(s)
Et	Ethyl
Fmoc	9-Fluorenylmethoxycarbonyl
h	Hour(s)
IL(s)	Ionic liquids
*i*Pr	Isopropyl
KHMDS	Potassium hexamethyldisilazide potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
Me	Methyl
min	Minute(s)
mol	Mole(s)
*n*Bu	*n*-butyl
Nu	Nucleophile
Ph	Phenyl
Pr	Propyl
py	Pyridine

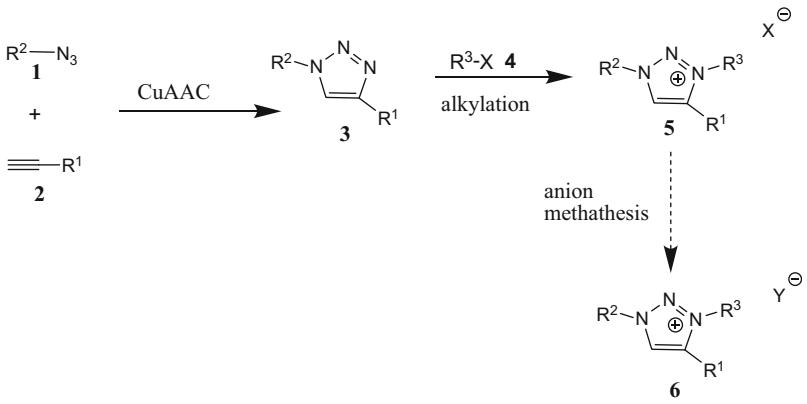
rt	Room temperature
RTILs	Room temperature ionic liquids
s	Second(s)
TBAF	Tetrabutylammonium fluoride
TBDMS	Tert-butyldimethylsilyl
Tf	Trifluoromethanesulphonyl (triflyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-t etramethyl- 1,2-ethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl (Tosyl) 4-toluenesulphonyl

1 Introduction

Ionic liquids (ILs) are in most cases salts of large organic cations and inorganic anions with melting point below 100°C. Salts that are liquid at ambient temperature are referred as room temperature ionic liquids (RTILs). The organic cations of ionic liquids mostly contain a positively charged nitrogen atom or sometimes positively charged phosphorous or sulphur atoms on a heterocyclic or acyclic species. Some common ionic liquid cations are quaternary ammonium [1, 2], 1,3-dialkylimidazolium [3–5], pyridinium [6], phosphonium [7], 1,2,3-triazolium [8, 9], 1,2,4-triazolium [10, 11],1,3-thiazolium [12, 13], sulphonium [14], pyrazolium [15, 16], and oxazolium [17, 18].

ILs have drawn a great deal of attention in the last decade due to their distinctive properties. Among those are exceptionally low vapour pressure, high solvation ability for a variety of compounds, wide liquid range, high polarity, good recyclability, low inflammability, high thermal and electrical stability and good chemical stability (resistance to reduction and oxidation). Additionally, most of the physicochemical properties of ionic liquids can be tuned to improve or to attain a required physical property. Due to these interesting properties, ILs are considered as designer solvents of the future with a great potential of substituting the commonly used classic volatile organic solvents [19–21].

In the past decade, the research in ionic liquids has been dominated by the ionic liquids based on imidazolium salts [22]. However, recently 1,2,3-triazolium ionic liquids are gaining popularity as phase tags, catalysts and solvents [8, 9, 23, 24]. Here, we provide a comprehensive up-to-date review on the synthesis, properties and applications of 1,2,3-triazolium ILs.



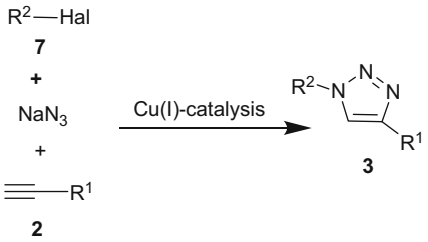
Scheme 1 Major synthetic route towards 1,2,3-triazolium salts

2 Synthesis of 1,2,3-Triazolium Ionic Liquids

The synthesis of 1,3,4-trisubstituted-1,2,3-triazolium ionic liquids involves two basic steps, namely the preparation of the 1,2,3-triazole ring system **3** and its *N*-alkylation. 1,4-Disubstituted 1,2,3-triazoles **3** are easily accessible by the copper(I)-catalysed regioselective [3+2] Huisgen cycloaddition of azides with terminal alkynes (CuAAC) developed by Meldal and Sharpless [25, 26]. This reaction has an extremely wide scope and occurs under mild conditions. The isolation and purification of the products is straightforward [27, 28]. It is important to obtain the 1,2,3-triazole **3** in a pure state before it is transformed into a 1,3,4-trialkyl-1,2,3-triazolium salt (ionic liquid) **5** in the subsequent alkylation step, since purification of the final ionic liquids can be difficult if they are contaminated with other salt-like structures.

The structure of 1,2,3-triazolium-based ionic liquids **5** can be dictated by the CuAAC reaction and by the consecutive alkylation step. Eventually, the anion of the resulting triazolium salt is exchanged by salt metathesis providing salts **6** with a more appropriate anion. The CuAAC is a robust process, which can tolerate a very wide range of functional groups. Thus, functional groups or complete molecular fragments can be introduced into the 1,2,3-triazole ring by choosing appropriate reactants in the CuAAC reaction or by using a functionalized alkylating reagent in the alkylation step (Scheme 1). These possibilities provide a versatile way to assemble a wide scope of molecular structures in the 1,2,3-triazolium ring system to obtain an IL, which is hardly available in the synthesis of other types of ILs.

The copper catalysed [3+2] Huisgen cycloaddition (CuAAC) of a terminal alkyne and an azide produces the 1,4-disubstituted-1,2,3-triazoles **3** with high regioselectivities and yields [28–31]. The copper catalyst can be applied in various forms such as Cu(I) salt or Cu(II) salt together with an in situ reducing agent (sodium ascorbate) [27], Cu(I) salts with triphenylphosphine, with iminopyridine or



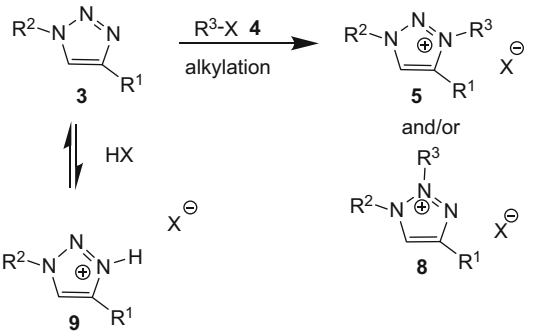
Scheme 2 One-pot synthesis of 1,2,3-triazoles 3 from alkyl halides, sodium azide and terminal alkynes

with mono or multidentate nitrogen ligands, Cu(I) isonitrile complex in water [32], Cu(0) nanoclusters [33, 34] and copper sulphate immobilized on chitosan [35].

There are also alternative methods for obtaining 1,2,3-triazoles from alkynes and azides that have not gained much relevance in the synthesis of 1,2,3-triazolium salts so far. The traditional [3+2] Huisgen cycloaddition reaction of azides with terminal alkynes is performed under thermal conditions in the absence of a copper catalyst. This method, however, results in lower yields and mixtures of regioisomeric 1,4- and 1,5-disubstituted 1,2,3-triazoles, which are difficult to separate. The Cu-free [3+2] dipolar cycloaddition of azides with strained cyclic alkynes such as cyclooctynes runs easier and provides better yields but has structural restrictions and has not gained importance for the synthesis of 1,2,3-triazolium IL [36–39]. Another methodology for copper free [3+2] cycloaddition of terminal alkynes to azide makes use of hydroxide bases and the high acidity of aryl acetylenes. Since this methodology produces 1,5-diaryl substituted 1,2,3-triazoles its scope is restricted [40].

The handling of potentially explosive and dangerous organic azides **1** during the synthesis of 1,4-disubstituted 1,2,3-triazoles **3** can be avoided by means of a one-pot reaction procedure (Scheme 2). The reaction involves an in situ synthesis of the organic azide followed by CuAAC reaction. Various organic azides were in situ synthesized from alkyl halides **7** and used for click reaction. This procedure is efficient for various kinds of alkyl halides **7** and can be applied to iodoarenes, which are nonreactive to nucleophilic substitution by azide under normal conditions. The copper(I) catalyst mediates both the nucleophilic substitution of the halide by an azide and the subsequent [3+2] cycloaddition [41, 42].

The regioselectivity of the [3+2] cycloaddition of azides to alkynes can be altered to the 1,5-disubstituted 1,2,3-triazoles by using other transition metal-based catalysts such as ruthenium [43, 44], palladium [45], or by the use of silyl acetylene or a bromomagnesium acetylide [46, 47]. In a recent approach, the synthesis of 1,5-disubstituted 1,2,3-triazoles was achieved from 1,3,4-trisubstituted 1,2,3-triazolium salts with a 3,4-dimethoxybenzyl protecting group at position 1, which was later removed by means of ammonium nitrate or ceric ammonium nitrate (CAN) [48]. Such 1,2,3-triazoles have, however, not yet been used for triazolium salt formation.

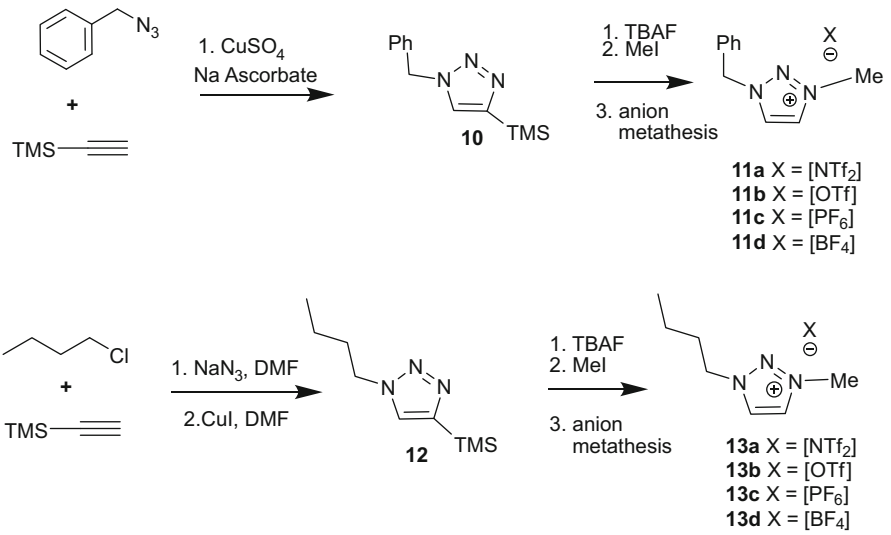


Scheme 3 Regioisomerism in alkylation of 1,2,3-triazoles and protonation of 1,2,3-triazoles

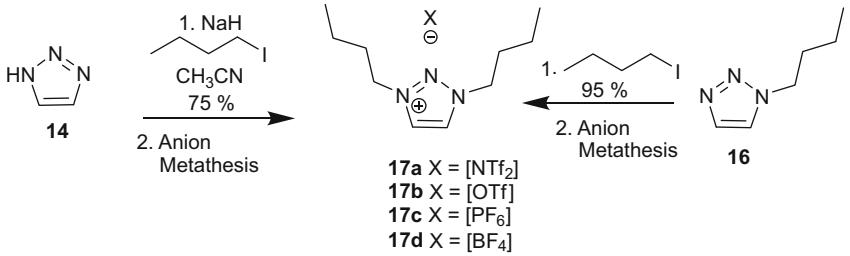
1,4-Disubstituted 1,2,3-triazoles **3** can be transformed into 1,2,3-triazolium salts by alkylation or protonation. The alkylation of 1,2,3-triazoles can furnish 1,3,4- trisubstituted triazolium salt **5** or 1,2,4-trisubstituted triazolium salt **8** depending on the kind of alkylating reagent (Scheme 3). It usually gives high yields. The regioselective 3-alkylation to triazolium salts **5** can be achieved by using soft alkylating agents such as alkyl halides, benzyl halides, allyl halides, sulphates and sulphonates [49]. The treatment of 1,4-disubstituted 1,2,3-triazoles **3** with an inorganic acid can produce a protonated 1,2,3-triazolium salt **9**; however, such salts are unstable in particular under basic conditions and of little use as solvents or catalysts [50].

Among the first triazolium-based ILs, which were utilized as solvent are 1-benzyl-3-methyl-1,2,3-triazolium salts **11**, 1-butyl-3-methyl-1,2,3-triazolium salts **13** and 1,3-dibutyl-1,2,3-triazolium salts **17**. These ILs have substituents only at 1 and 3 positions and are analogues to the 1,3-disubstituted imidazolium ILs. In order to synthesize 1,2,3-triazolium ionic liquids with substituents only at positions 1 and 3 trimethylsilylacetylene can be used as a click reaction substrate and the TMS group is removed from the resulting 1,2,3-triazole by fluoride reagents [51, 52]. Another easy approach towards 1,3-disubstituted-1,2,3-triazolium salts **17** is the alkylation of 1-alkyl-1,2,3-triazole or the alkylation of 1,2,3-triazole with excess of 1-chlorobutane in the presence of a base (Scheme 5) [53].

The 1,3-disubstituted-1,2,3-triazolium salts **11** and **13** were synthesized starting with 1,2,3-triazoles prepared by CuAAC of the corresponding benzyl azide or in situ generated *n*-butyl azide with 1-trimethylsilylacetylene (Scheme 4). The resulting TMS substituted 1,2,3-triazoles **10** and **12** were subjected to TBAF-mediated removal of the TMS group and alkylated with methyl iodide. After anion metathesis with $LiNTf_2$, KOTf, $LiPF_6$, or $AgBF_4$ the respective 1,3-disubstituted 1,2,3-triazolium ILs **11** and **13** were obtained in good yields (Scheme 4). The regiochemistry of the *N*-methylation was confirmed by 1D-NOE analysis [52].



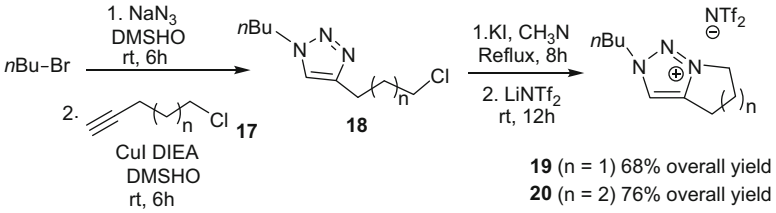
Scheme 4 Synthesis of 1,3-disubstituted 1,2,3-triazolium ionic liquids with unsubstituted positions 4 and 5 using TMS-acetylene



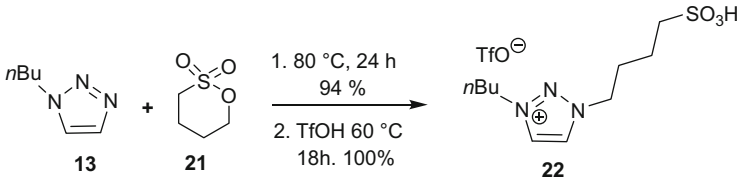
Scheme 5 Synthesis of 1,3,-dibutyl-1,2,3-triazolium ionic liquids with unsubstituted positions 4 and 5 by *N*-alkylation

As an alternative access to triazolium salts with unsubstituted positions 4 and 5, *N*-alkylation of 1H-1,2,3-triazole **14** (excess alkylating reagent, after deprotonation by NaH) or 1-substituted 1,2,3-triazole is possible as shown by the synthesis of the 1,3-dibutyl-1,2,3-triazolium ILs **17**. They were obtained after final salt metathesis with $LiNTf_2$, KOTf, $LiPF_6$, or $AgBF_4$ in good yields (Scheme 5).

The bicyclic triazolium ionic liquids [b-3C-tr][NTf_2] **19** and [b-4C-tr][NTf_2] **20** represent another new class of 1,2,3-triazolium-based RTILs investigated as solvents. These ionic liquids were synthesized by in situ generation of *n*-butyl azide from *n*-butyl bromide and sodium azide, followed by CuAAC with 5-chloropentyne or 6-chlorohexyne resulting in 1,2,3-triazoles **18** (Scheme 6). Intramolecular cyclization by *N*-alkylation under Finkelstein reaction conditions and subsequent metathesis of the iodides with $LiNTf_2$ furnished the desired 1,2,3-triazolium ILs **19** and **20** in good yields.



Scheme 6 Synthesis of bicyclic 1,2,3-triazolium ionic liquids **19** and **20**



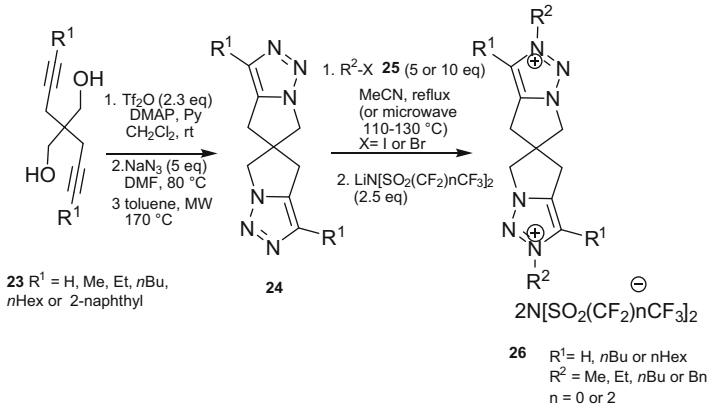
Scheme 7 Synthesis of SO_3H-functionalized 1,2,3-triazoliumIL **22**

By the application of the cyclic sulphonate **21** as alkylating reagent a 1,2,3-triazolium IL was obtained with a terminal sulphonic acid group useful as IL-tagged Brønsted acid [54] (Scheme 7).

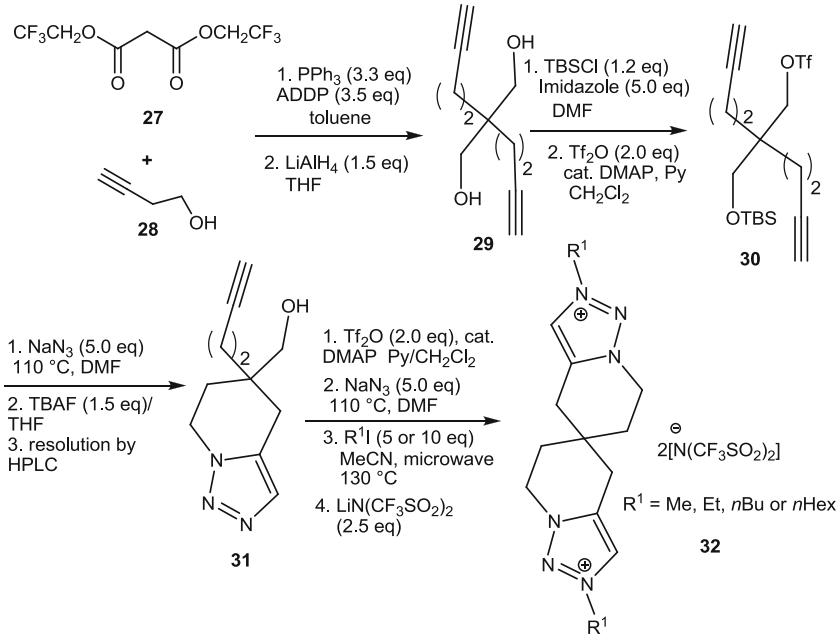
Unlike imidazolium ILs there are only a few 1,2,3-triazolium-based salts known for potential use as chiral reaction medium (for chiral triazole ILs as organocatalysts, see Sect. 4.2). The *spiro*-bis(1,2,3-triazolium) salts **26** were developed as potential chiral reaction medium [55, 56]. Their synthesis starts from the ynediol **23**, which was transformed into a diazide via triflation followed by twofold intramolecular Huisgen [3+2] dipolar cycloaddition under microwave conditions. Chiral HPLC was used to separate the enantiomers of the resulting spirotriazoles **24**. Subsequent alkylation and ion metathesis furnished the chiral spirocyclic 1,2,3-triazolium salts **26** (Scheme 8).

Initial investigations of the *spiro*-bis(1,2,3-triazolium) salts **26** and their iodide precursors demonstrated high melting points except the melting point of those with $R^1 = H$, $R^2 = n$Bu, $n = 0$. The melting point was significantly reduced for *spiro*-bis(1,2,3-triazolium) salts with tetra-alkyl substituents due to their inefficient crystal packing.

Alternatively, enantiopure *spiro*-bis(1,2,3-triazolium) salts with spiro[5.5] undecane skeleton **32** were synthesized in order to obtain chiral 1,2,3-triazolium ILs with lower melting temperature (Scheme 9). The synthesis started with a Mitsunobu reaction of bis(2,2,2-trifluoroethyl) malonate (**27**) with but-3-yn-1-ol **28** followed by reduction with $LiAlH_4$ to the corresponding diol **29** and selective



Scheme 8 Synthesis of chiral *spiro*-bis(1,2,3-triazolium) salts



Scheme 9 Synthesis of enantiomerically pure spiro [5.5]undecane

silylation of one of the hydroxy groups with TBS-Cl. The free hydroxyl group of the monosilylated diol was then triflated to result in compound **30**, which was treated with NaN_3 and heated for intramolecular [3+2] dipolar cycloaddition. Deprotection and resolution by chiral HPLC gave either enantiomer of the triazole **31**. This underwent the same sequence to form the second triazole ring. At the end, both triazole rings were *N*-alkylated by alkyl iodides and the iodide replaced by salt

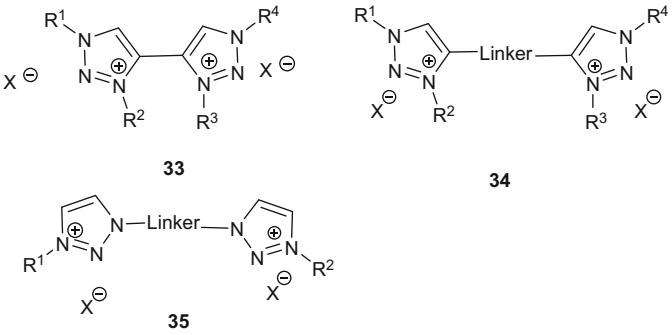


Fig. 1 ILs with two 1,2,3-triazolium units

metathesis providing the bis(1,2,3-triazolium) ILs **32** (Scheme 9). The melting points of **32** were lower than those of triazolium salts **26** while the glass transition temperature (Tg) shows a decrease to less than −11°C. Ionic liquids with Tg as low as −32°C were achieved with the use of long alkyl chains (R^1 = *n*Hex) and fluoroalkyl counter anions $[N(SO_2CF_3)_2]^-$.

The potential of the *spiro*-triazolium salts in molecular recognition was investigated by using an in situ ^{1}H NMR of the diastereomeric interaction between a racemic *spiro*-bis(1,2,3-triazolium) salt cation and (*S*)-Mosher's acid chiral anion. The synthetic sequence of CuAAC, alkylation and salt metathesis can also be applied to obtain ILs **33**–**35** with two 1,2,3-triazolium units (Fig. 1) [57–59].

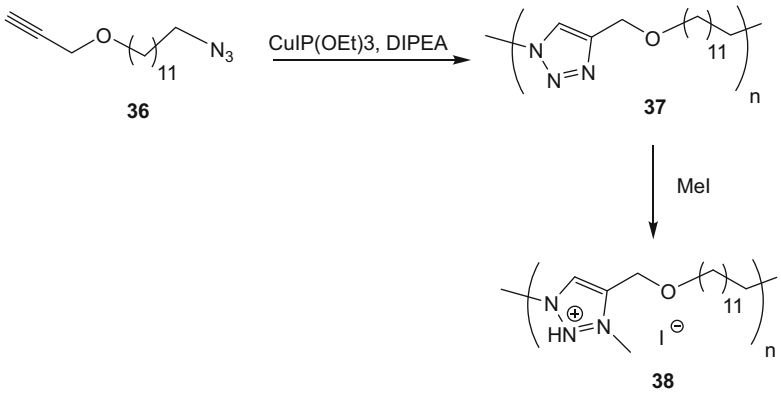
In a similar route also poly(1,2,3-triazolium) ILs can be obtained as demonstrated by the synthesis of the polysalt **38** starting from propargyl 12-azidododecanyl ether **36** (Scheme 10) [60]. Because of their thermodynamic and kinetic stability, they might serve as polymer-electrolytes in fuel cells.

In principle, it is also possible to start with 1,2,3-triazolium salts and to introduce a substituent in position 5 by alkylation as shown with bicyclic 1,2,3-triazolium ionic liquids **19** and **20** (Scheme 11)**.** They were C-alkylated at position-5 after deprotonation with NaH to achieve 1,2,3-triazolium ionic liquids **39** and **40**. This alkylation step was targeted to the prevention of abnormal N-heterocyclic carbene (NHC) formation [61].

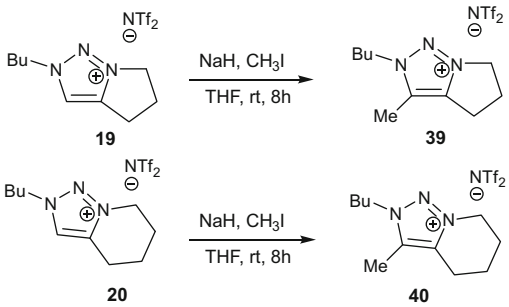
Table 1 gives an overview about triazolium ILs, further examples are mentioned in Sect. 4 where applications of 1,2,3-triazolium ILs are discussed.

3 Properties of 1,2,3-Triazolium Ionic Liquids

One of the most crucial physical characteristics of ionic liquids is their liquid state at temperatures below 100°C, preferably at ambient temperature. Most 1,3,4-trisubstituted-1,2,3-triazolium salts are found to be liquids at ambient temperature and have lower melting points than their parent 1,4-disubstituted 1,2,3-triazoles.



Scheme 10 Synthesis of poly(1,2,3-triazolium) ILs

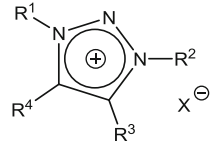


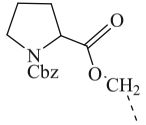
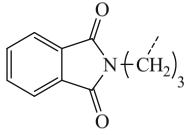
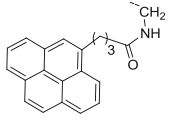
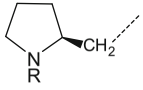
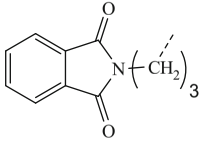
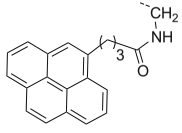
Scheme 11 C-Alkylation of 1,2,3-triazolium ILs **19** and **20**

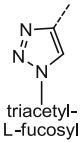
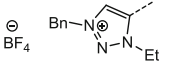
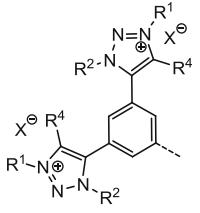
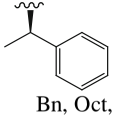
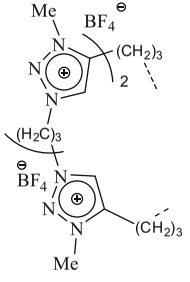
1,2,3-Triazole-based ionic liquids are usually soluble in polar solvents such as water, methanol, DMF, DMSO and acetonitrile while being immiscible with non-polar solvents such as diethyl ether and hexanes. The 1,2,3-triazolium IL-tagged molecules derived from various amino acids such as proline and lysine also exhibit ionic liquid characteristics in most cases and show similar solubility [8, 42, 65, 74].

Most ILs including 1,2,3-triazolium-based ILs are hygroscopic in nature. The moisture content of ionic liquids plays a significant role in their physicochemical properties and their performance as solvent or catalysts. Due attention must be given to the moisture content (or removal of the moisture) in the ionic liquid before determination of any physicochemical parameter. The hygroscopic nature of ionic liquids depends on its constituents. Some ionic liquids such as those with haloaluminate counter anions may absorb moisture very fast while those with bis (trifluoromethanesulphonyl)imide ($[NTf_2]^-$) or perfluoroalkylphosphate have less affinity to water but still are hygroscopic. The NTf_2^-salts and the PF_6^- salts are not miscible with H_2O, but the BF_4^- salts are [8, 42, 65, 74].

Table 1 Compilation of 1,2,3-triazolium salts **5** and **6**

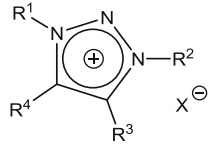


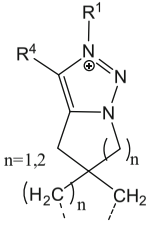
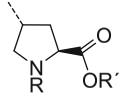
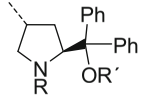
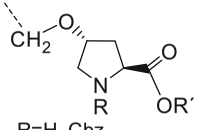
R^1	R^2	R^3	R^4	X or Y	Ref
*n*Bu, Bn, 4-BnOBn	Me	Alkyl, Hydroxyalkyl	H	CF_3SO_3, I, $(MeO)PO_3$, $N(CN)_2$ or BF_4, $MeSO_4$, TsO	[8, 42]
Bn	Me		H	I	[8]
4-MeOBn	Et		H	Br	[8]
4-MeOBn	*n*-Pr		H	I	[8]
	Me	*n*-Pentyl, Ph	H	I	[8, 62]
	Me		H	I	[8]
Bn, *n*Bu	Alkyl	H	H	NTf_2, OTf, PF_6 or BF_4	[52]
Allyl, 3,4-$(MeO)_2$Bn	Me	*n*-Pentyl	H	I	[42]

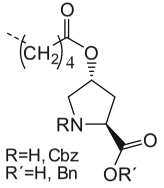
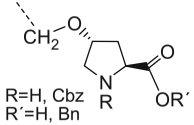
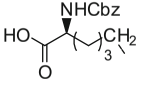
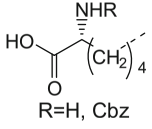
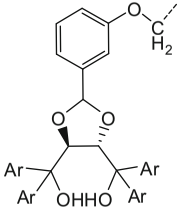
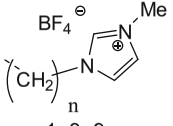
4-NCC_6H_4	 triacetyl-L-fucosyl	Et	H	BF_4	[57]
4-*t*$BuC_6H_4CH_2$	Me		H	BF_4	[57]
	 Bn, Oct,	Me	H or I	OTf or PF_6	[42]
n-Octyl	Me	Ph	H	NTf_2	[63]
R^1/R^3	Me	R^1/R^3 = 	H	BF_4	[64]
*n*Bu, Bn	Alkyl	H	H	NTf_2, OTf, PF_6 or BF_4	[52]
*n*Bu	R^2/R^3	$R^2/R^3 = -(CH_2)_n-$ $n = 3,4$	H, Me	NTf_2	[65]
*n*Bu	---$(CH_2)_4-SO_3H$	H	H	NTf_2, OTf, PF_6 or BF_4	[54]

(continued)

Table 1 (continued)

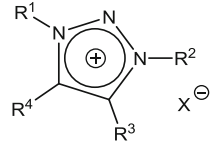


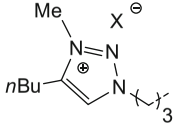
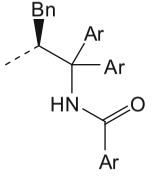
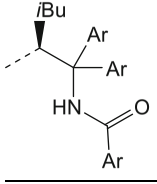
R^1	R^2	R^3	R^4	X or Y	Ref
Alkyl, Bn	R^2/R^3	R^2/R^3= 	H, *n*-Bu or *n*-Hex	$N[SO_2(CF_2)_nCF_3]_2$	[55]
 R=H, Cbz R´=H, Bn	Me	*n*Bu; H	H	BF_4, I CF_3SO_3	[66] [67]
 R=H, Cbz R´=H, TMS	Me	Alkyl	H	PF_6	[68]
 R=H, Cbz R´=H, Bn	Me	*n*-Dodecyl	H	I, BF_4	[66]

 R=H, Cbz R´=H, Bn	*n*-Bu	*n*Bu	H	Br,BF_4	[69]
 R=H, Cbz R´=H, Bn	Me	CH_2CO_2R (R = H, Me) 	H	I, BF_4	[51]
 R=H, Cbz	Me	*n*-Decyl	H	I, BF_4	[51]
*n*Bu, Bn	Me		H	I, BF_4	[70]
*n*Bu, Bn	Me	 n = 1, 3, 9	H	I, BF_4	[58]

(continued)

Table 1 (continued)



R^1	R^2	R^3	R^4	X or Y	Ref
	Me	*n*Bu	H	I, BF_4	[58]
	Bn, 4-CF_3Bn	2-R-C_6H_4 (R = H, Me, Ph), 2-C_6H_5-4-$CF_3C_6H_4$	H, Me	Br	[71, 72]
	Bn 4-CF_3Bn	2-RC_6H_4 (R = Ph, CF_3, *i*Pr), 2-C_6H_5-4-$CF_3C_6H_4$	H	Br	[73]

The 1,3,4-trisubstituted 1,2,3-triazolium ionic liquids are found to be viscous liquids similar to 1,3-disubstituted imidazolium ionic liquids. The decrease in the cation–anion binding has strong influence on the viscosity of 1,2,3-triazolium-based ILs. Lower viscosity is observed in case of large anions, which can delocalize charge.

Analogous to the melting point of any salt the melting point of an IL is dependent on the anion–cation binding strength. Lower binding results in lower melting point [74, 75]. In the case of 1,2,3-triazolium-based ILs, anions such as halides, triflate or tetrafluoroborate give rise to higher melting points when compared to tosylates [8, 76]. It is a known phenomenon that asymmetrically substituted molecules exhibit lower melting points than symmetric molecules. Likewise, asymmetrically substituted 1,2,3-triazolium as well as imidazolium ionic liquids shows relatively lower melting points, mainly due to an ineffective crystal packing when compared to salts with symmetrical cations [3, 77]. There is also some indication that the substituents at position 1 and 3 of the triazolium ring induce more influence on the phase behaviour of the triazolium salts than the substituents at position 4 [74].

Among the most important physical characteristics of ILs, which render them environmentally benign "green" credentials are their low volatility and their recyclability. In order to be a recyclable solvents or catalysts the ionic liquid must sustain extended stability for the duration of the reaction, while the reaction condition can be mild or harsh such as basic, acidic, oxidizing or reducing at higher temperatures. The thermal stability of 1,2,3-triazolium salts is highly dependent on the type of the counter anion [14, 52]. Contrary to the increase in melting points, strongly binding anions usually reduce the thermal decomposition temperature of the 1,2,3-triazolium-based ILs. ILs with loosely bound cation anion pairs have good thermal stability [18]. ILs can decompose by carbene formation, by deprotonation, by dealkylation of the quaternary nitrogen, by Hoffman elimination or thermally. The thermal, chemical and electrochemical stability of 1,2,3-triazolium-based ionic liquids depends on various factors. However, it is possible to tune the stability of 1,2,3-triazolium ionic liquids by the substituents in the cations and the anions. The unsubstituted 1,2,3-triazolium salts with oxygen-rich anions can be very unstable and possess high explosive nature. Hence, they need to be handled with care.

Differential thermogravimetry (TGA) measurements of some 1,3,4-trisubstituted-1,2,3-triazolium ILs indicated good thermal stability in the range between 200 and 355°C [8, 52]. This value is often lower than that of comparable 1,3-dialkylimidazolium-based ILs, which mostly have thermal decomposition temperature of around 300°C. The thermal stability of 1,2,3-triazolium ILs is strongly dependent on several variables such as the kind of counter-ion and the nature of substituents on the triazolium ring. The 1,2,3-triazolium iodides and triflates show lower thermal stability (near or slightly below 200°C) as compared with respective tosylates, tetrafluoroborates, hexafluorophosphates and bis(trifluoromethylsulphonyl)imides. Relative anion stabilities were suggested to decrease in the order PF_6^-, Tf_2N^-, $BF4^-$, TfO^- and I^-. In general, 1,2,3 triazolium ILs show weaker thermal stabilities with the onset of decomposition occurring at about

100 °C when the counter ions are iodide or TfO^-, while salts with bulky anions such as bis(trifluoromethylsulphonyl)amide, hexafluorophospate and tetrafluoroborate show much higher stabilities [8, 52].

Conductivity measurements of 1,3,4-trisubstituted-1,2,3-triazolium tosylates and triflates revealed values being in a similar order of magnitude as imidazolium ILs with comparable cation sizes but the former have higher conductivity than quaternary ammonium and sulphonium salts [74]. In addition, normal Walden type conductivity was found, which is inversely proportional to the viscosity and arises from migration of charge carriers. Among the 1,2,3-triazolium salts the 1,3,4-trisubstituted-1,2,3-triazolium triflates show higher ionic conductivity than the 1,3,4-trisubstituted-1,2,3-triazolium tosylates. This is due to the smaller size of the triflate, its higher mobility and weaker cation–anion binding.

The electrochemical stability of some 1,2,3-triazolium-based ILs was investigated over a range of −3.2 to +3.2 V using a platinum working electrode, silver wire immersed in 0.01 M $AgNO_3$ in acetonitrile as reference electrode and platinum as counter electrode. The 1,2,3-triazolium ILs exhibited a large electrochemical window of more than 4 V [74]. 1,2,3-Triazolium tosylates possess oxidative stability in the range of 2.5–2.6 V, while corresponding triflates show lower chemical stability in the range of 2.15–2.4 V. 1,2,3-Triazolium cations exhibit better cathodic stability than pyridinium cations but are less stable than quaternary ammonium cations and imidazolium cations. The anions of ILs can be considered to be more stable towards reduction and oxidation than the cations. The cathodic and anodic decomposition potentials of 1,2,3-triazolium ILs are influenced by the cations in a similar manner as 1,3-dialkylimidazolium salts unlike in quaternary ammonium salts where the cathodic limit is governed by reduction of the cation and the anodic limit by oxidation of the anions [74].

1,2,3-Triazolium salts are chemically relatively stable. However, nucleophilic displacement of the alkyl group in position 3 of the triazole ring can occur in some cases.

Properties of ionic liquids often overlooked are their acidity and basicity. IL cations can have Brønsted as well as Lewis acidity whereas anions can have Brønsted and Lewis basicity. Acidity or basicity plays an important role on the stability of ionic liquids additional to their reactivity. Unlike imidazolium salts, 1,2,3-triazolium ionic liquids do not possess acidic hydrogen at position 2 of the triazolium ring and hence are more stable under mildly basic conditions. Therefore, they can serve as innocent reaction medium for base catalysed reactions wherein imidazolium ILs would form carbenes [21, 78]. For example, 1,3,4-trisubstituted-1,2,3-triazolium-based ILs were found to be highly stable under mildly basic conditions such as 0.1 N NaOH while imidazolium ionic liquids show very low stability [74]. Deprotonation at position 4 or 5 of 1,2,3-triazoles is more difficult and was observed with strong bases under H-D exchange conditions in NMR investigations [79]. The formation of transition metal complexes was disclosed in a number of cases recently wherein the triazolium unit was transformed into an N-heterocyclic carbene acting as a 1,2,3-triazol-5-ylidene ligand. This property leads to interesting applications in catalysis of a range of reactions (see Sect. 4.2).

Deuterium isotope exchange experiments for triazolium ionic liquids **19**, **20**, **39** and **40** were conducted under neutral and basic conditions in order to establish the stability of these ILs. ILs **39** and **40** lacking protons in positions 4 and 5 demonstrate very low deuterium isotope exchange after being kept in basic solution for a week. However, triazolium ILs **19** and **20**, which have ionisable protons at carbon-5 underwent deuterium exchange within a few minutes when mixed with the basic deuterium solvent (0.1MKOD in 7:3 mixture of CD_3OD and D_2O) [65].

Under slightly acidic conditions (CD_3OD/D_2O = 7:3, v/v) the ionic liquids **19**, **20, 39** and **40** did not undergo deuterium isotope exchanges at ambient temperature and were found to be chemically stable for 24 h. However with the elongation of the time to one week the ionic liquids **19** and **20** suffer deuterium isotope exchange of 75% and 11%, respectively, while the ionic liquids **39** and **40** showed no noticeable exchange [65].

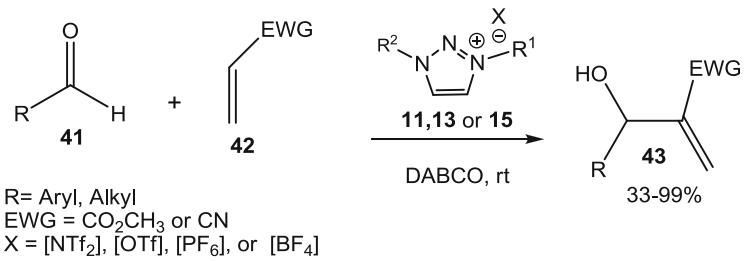
The ionic liquids **19** and **20** have relatively high chemical stability when compared with analogous imidazolium ionic liquids [b-3C-im][NTf_2] and [b-4C-im][NTf_2] under the same basic conditions [80]. This stability makes 1,2,3-triazolium ILs attractive as solvents when bases are applied and for alkaline fuel cell membranes. On the other hand the weak acidity of 1,2,3-triazolium salts allows to form 1,2,3-triazol-5-ylidene complexes with transition metals by deprotonation [81, 82].

4 Application of 1,2,3-Triazolium ILs

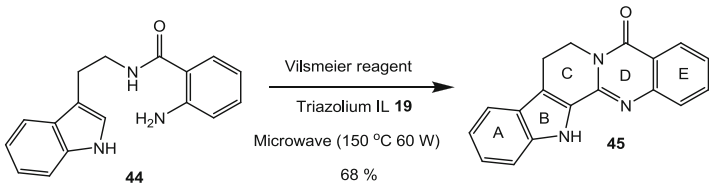
Unlike the imidazolium-based ILs, 1,2,3-triazolium ILs have not yet been commercially produced. This limited availability hampers their utilization as reaction medium. 1,2,3-Triazolium ILs are mainly developed as recyclable designer solvents, catalysts, reagent supports, ionic liquid tags for a specific reaction or as anion recognizing agents or parts of molecular machines.

4.1 Application of 1,2,3-Triazolium Ionic Liquids as Solvents

One of the most interesting properties of 1,2,3-triazolium-based ionic liquids which can be advantageous for application as solvents or catalysts is their tune ability. Various parameters of the triazolium-based ionic liquids such as compatibility with the reaction mixture, polarity, solubility and melting point can be manipulated in order to attain essential characteristics. In addition, various functional groups can also be introduced in the structure of the ILs. For instance, one can introduce a Brønsted acid functional group to the cation of the ionic liquid in order to create an ionic liquid, which can serve as a solvent as well as a catalyst for Brønsted acid catalysed reactions. Similarly, ionic liquids with anions that possess Lewis base characteristics can be synthesized and utilized in a variety of Lewis base catalysed



Scheme 12 Baylis–Hillman reaction in 1,3-disubstituted 1,2,3-triazolium ionic liquids



Scheme 13 Synthesis of rutaecarpine 45 in 1,2,3-triazolium IL **19** as solvent

reactions. These solvent systems are less volatile than conventional solvents and can be recycled by straightforward extraction of the products with non-polar organic solvents, which ultimately increases the efficiency of the solvent and reduces the amount of waste released to the environment and provides economic benefits.

1,3-Dialkyl-1,2,3-triazolium salts were investigated as recyclable solvents for Baylis–Hillman reaction between various aromatic or aliphatic aldehydes and methyl acrylate or acrylonitrile at room temperature in the presence of DABCO (Scheme 12). The 1,2,3-triazolium ILs **11**, **13** and **15** gave the Baylis–Hillman adduct in satisfactory 46% to excellent 96% yields. A comparison made with structurally analogous 1,3-disubstituted imidazolium ILs with identical anions indicated that the 1,3-disubstituted 1,2,3-triazolium ILs provide better yields in shorter reaction times. The weaker performance of the imidazolium ILs results from their low stability in the presence of bases such as DABCO [52, 83]. The 1,2,3-triazolium ionic liquid **13a** was recycled up to four times without a significant loss in yield after extracting the products with diethyl ether.

The bicyclic IL **19** was applied as solvent in the microwave assisted one step production of the C- and D-rings of rutaecarpine. Rutaecarpine, an indolopyridoquinazolinone, is a cytotoxic alkaloid isolated from *Evodiarutaecarpa* and related herbs. The reaction occurred smoothly in the presence of the Vilsmeier reagent to furnish rutaecarpine **45** with 68% isolated yield without any aromatization (Scheme 13) [65].

4.2 Application of 1,2,3-Triazolium Ionic Liquids in Catalysis

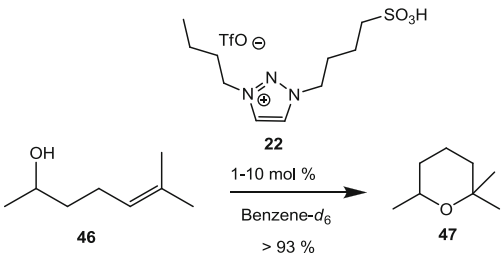
ILs can be applied in catalysis in four different ways. They can serve as solvents, as catalyst, as support for catalytic moieties or as precursors for ligands of catalytic transition metal complexes. Since in the latter case 1,2,3-triazolium salts are transformed into N-heterocyclic carbenes (1,2,3-triazolyl-5-ylidenes) and thus are not any longer ILs; this aspect is only briefly addressed at the end of this chapter. The application of 1,2,3-triazolium ILs as solvents in catalysis or as catalysts has not yet been published. On the other hand, a number of interesting cases were reported, wherein catalytic moieties were linked to 1,2,3-triazolium ILs.

In general, the most common methodology to immobilize catalysts is by means of heterogeneous solid, polymer or gel supports. This methodology offers simplified product isolation by filtration or centrifugation, easy recovery of catalysts, potential for use in continuous processes and enhanced stability when compared to homogenous catalysts. However, such heterogeneous supports often result in low mechanical strength, mass transfer-dependent diffusion, diminished selectivity, reactivity loss, and restricted thermal, chemical and oxidative stability.

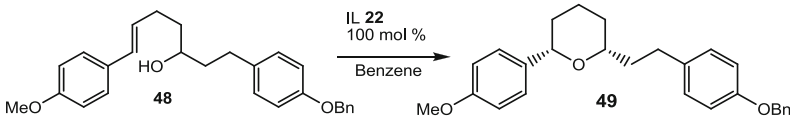
Due to their unique and environmentally benign "green" characteristics, functionalized ionic liquids were implemented as phase tagged organocatalysts. Ionic liquid tagged catalysts combine the advantages of homogeneous catalysis such as higher diffusion, activity and selectivity with the characteristics of heterogeneous catalysts such as ease of separation and reusability. An ionic liquid tag can modify the solubility profile of a catalyst by increasing its partition coefficient in polar solvents and making it insoluble in nonpolar solvents. This makes ionic liquid tagged catalysts pseudohomogeneous and provides a way for recycling by extraction of the reaction products with nonpolar solvents. In addition to an easier recycling, a synergistic improvement of catalytic performance can also result by the tagging of organocatalysts with ionic liquids when compared to non-tagged catalysts [84, 85].

The major pathway of ionic liquid tagging pioneered by Davis and co-workers is covalently linking catalytic functionalities, mainly organocatalysts, to a branch of the ionic liquid cation [86]. There are several examples of imidazolium, ammonium, and 1,2,3-triazolium ionic liquid tagged catalysts [87, 88]. The application of 1,2,3-triazolium ionic liquids as phase tags for catalyst immobilization is a very recent methodology.

The 1,2,3-triazolium IL **22** synthesized by alkylation of the respective 1-butyl-1,2,3-triazole with a cyclic sulphonate contain a strong Brønsted acid at the terminus of one *N*-substituent. It was applied as such in intramolecular hydroalkoxylations of alkenyl alcohols. A 95% yield of the tetrahydropyran **47** was achieved with a catalyst loading as low as 1 mol%. Various kinds of alkenyl alcohols including primary, secondary, aliphatic and aromatic alcohols afford tetrahydropyrans and tetrahydrofurans in this way [54]. The reactions primarily furnished the Markovnikov cyclic ethers regioselectively, which result from the more



Scheme 14 Intramolecular hydroalkoxylation of (±)-6-methyl-5-hepten-2-ol catalysed by IL **22**



Scheme 15 Application of triazolium IL **22** in the synthesis of (±)-centrolobine **49**

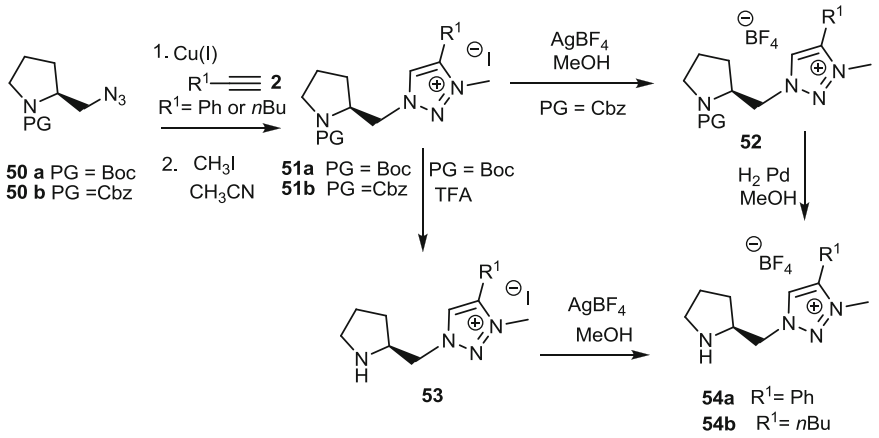
substituted carbocation intermediates. Formation of five membered tetrahydrofuran products is mainly favoured over the six membered tetrahydropyran formation; however, in the presence of an opportunity to form benzylic or tertiary carbocations tetrahydropyrans are favoured products (Scheme 14).

The sulphonic acid functionalized triazolium IL **22** was also investigated in the preparation of (±)-*centrolobine* **49**, an antibacterial agent isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile*. The product **49** was obtained as the *cis* isomer by cyclization of the alcohol **48** in 82% yield (Scheme 15) [54].

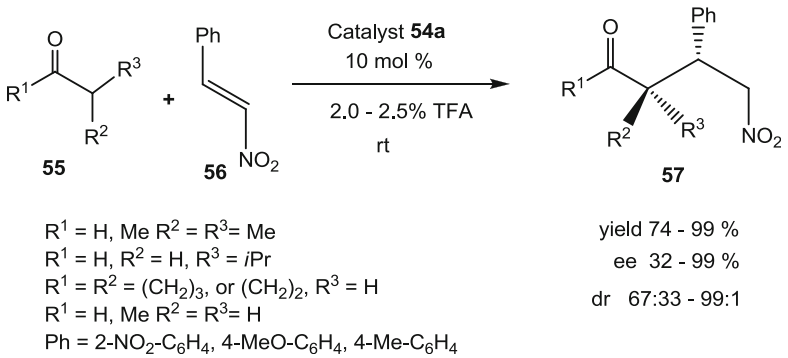
Chiral organocatalysts made from an amino acid derivative tethered to 1,2,3-triazolium ILs have been successfully applied in various organocatalytic reactions [51, 62, 68, 89]. The 1,2,3-triazolium IL tagged pyrrolidines **54** were obtained from (*S*)-prolinol derived azides **50** in a 4-step procedure by first CuAAC with terminal alkynes and then *N*-alkylation providing the triazolium iodides **51**, which were transformed into the triazolium tetrafluoroborates **54** by salt metathesis with Ag-tetrafluoroborate and deprotection (Scheme 16) [62].

It is worth mentioning that hydrogenative removal of the Cbz protecting group from the iodide **51b** failed probably due to poisoning of the Pd catalyst while it occurred smoothly at the tetrafluoroborate **52**.

The 1,2,3-triazolium-tagged pyrrolidines **54** were applied in asymmetric Michael addition of various unmodified aldehydes and ketones **55** to *trans*-β-nitrostyrenes **56**. It turned out that the substituent R (*n*-butyl or phenyl) in the triazolium ring does not seem to have an influence on the outcome of the reaction. The 1,2,3-triazolium IL **54a** was found to be a very efficient recyclable catalyst. It gave excellent enantioselectivities up to 99% and diastereoselectivities up to 99:1 with yields reaching 98%. The reactions were undertaken with 10 mol%



Scheme 16 Synthesis of 1,2,3-triazolium ionic liquid-tagged chiral pyrrolidinemethyl organocatalysts **54a** and **54b**



Scheme 17 Application of the triazolium catalyst **54a** in Michael addition of carbonyl compounds to *trans*-β-nitrostyrene

of the catalyst in the presence of 2.0–2.5% TFA additive and the carbonyl component was used in excess as solvent (Scheme 17). β-Nitrostyrenes comprising electron donating (4-MeO, 4-Me) or electron withdrawing (2-NO_2) groups in the aryl ring gave rise to excellent yields and diastereoselectivities but with somewhat lower enantioselectivities (83–90%).

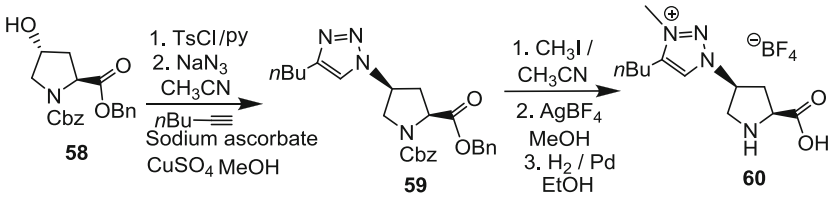
Among the various carbonyl compounds used as substrates for the Michael addition to *trans*-β-nitrostyrene, acetone furnished 85% yield and low (52%) enantioselectivity in a shorter reaction period. This result resembles the one found by Yan et al. using a similar 1,2,3-triazole catalyst [90]. Cyclopentanone was often reported to give low selectivity for non-immobilized catalysts under Michael addition to *trans*-β-nitrostyrenes. This was also observed with the 1,2,3-triazolium IL tagged catalysts **54** in which a low (67:33) diastereoselectivity and

82% enantioselectivity was achieved. Furthermore, catalysts **54** catalysed efficiently the reaction between aldehydes and β-nitrostyrene. This reaction is known to have complications due to the relatively higher reactivity of aldehydes and their tendency to undergo detrimental intermolecular self-aldol reactions [91]. 1,2,3-Triazolium IL-based catalysts **54** furnished high yields, high diastereoselectivities but lower and less convincing enantioselectivities. As checked for the Michael addition of cyclohexanone to *trans*-β-nitrostyrene, 1,2.3-triazolium IL catalysts could easily be recycled by extraction of the reaction products with diethyl ether and combining the remainder with a fresh batch of reactants. The triazolium iodide catalyst **53** (R^1 = Ph) was recyclable up to four times. The products exhibited constantly high diastereoselectivities (higher than 93:7). However, the enantioselectivity dropped from 99% in the first run to 58% in the fourth run. The yield also showed decline from 98% in the first run to 74% in the fourth run. However, the recyclability of the catalysts was improved after anion metathesis. Catalysts **54** with the tetrafluoroborate counter anion showed improved recyclability as compared with their iodide counterparts. Catalyst **54a** was recycled four times without any drop in the yield or enantioselectivity of the product [92]. When the amount of the catalyst **53** (R^1 = Ph) was reduced to 5 mol% the enantioselectivity decreased to 82% and the reaction required slightly longer time to complete. However, the yield (>95%) and the diastereoselectivity (97:3) remained high.

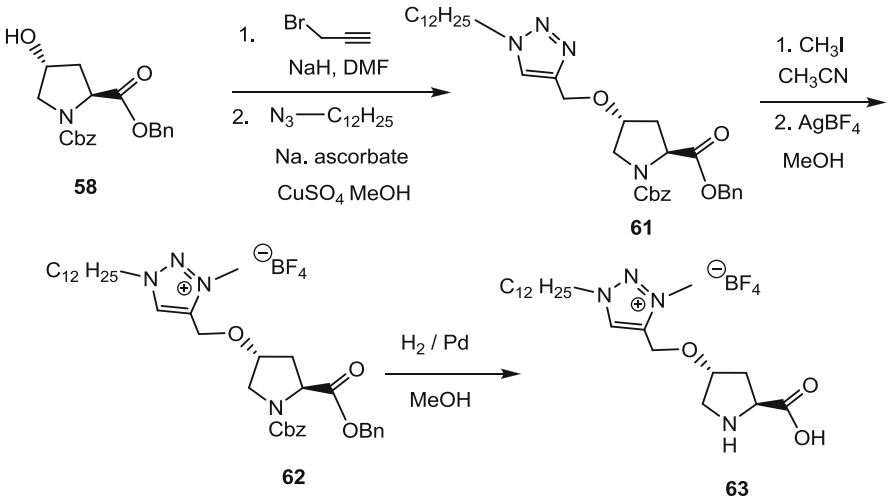
Proline and its derivatives belong to the most versatile and frequently used organocatalyst systems. One of the methods of tagging proline with 1,2,3-triazolium ILs involves the use of a 4-hydroxy substituent on (*S*)-proline while keeping the 2-carboxylic acid functional group intact, eventually via intermediate protection or transforming the latter into a diphenylhydroxymethyl moiety.

One way to tag *trans*-4-hydroxy-(*S*)-proline with 1,2,3-triazolium ionic liquid was found by converting the 4-hydroxy group into an azido or a terminal alkyne derivative for CuAAC reaction. Alternatively, the 4-hydroxy group can be transformed into a leaving group for nucleophilic substitution by a 1,2,3-triazole forming a triazolium salt. In the first strategy, the *N*-Cbz protected-4-hydroxyproline benzyl ester **58** was treated with tosyl chloride to obtain a tosylate substituted precursor, which can easily undergo nucleophilic substitution by sodium azide resulting in the 4-*cis* azido substituted product. Click reaction of this azide derivative with 1-hexyne furnished the 1,2,3-triazole **59** in good yield. The 1,2,3-triazole derivative was alkylated by methyl iodide and subjected to salt metathesis with silver tetrafluoroborate ($AgBF_4$). The resulting 1,2,3-triazolium IL derivative was submitted to palladium catalysed hydrogenation (H_2/Pd) for a simultaneous deprotection of the Cbz and the benzyl ester group to furnish the target catalyst **60** in excellent yield (Scheme 18) [66].

The 4-hydroxy group of *N*-Cbz protected *trans*-4-hydroxy-(*S*)-proline **58** can also be used as a propargyl component in CuAAC click reaction. In this methodology the synthesis of 1,2,3-triazole tagged catalyst begins by a base catalysed introduction of the propargyl group with propargyl bromide. Subsequent CuAAC reaction with 1-azidododecane furnished the triazole **61** in 71% yield. Alkylation with methyl iodide and anion metathesis led to the catalyst precursor **62**. Final



Scheme 18 1.2.3-Triazole tagging of *(S)*-proline via a 4-hydroxy group

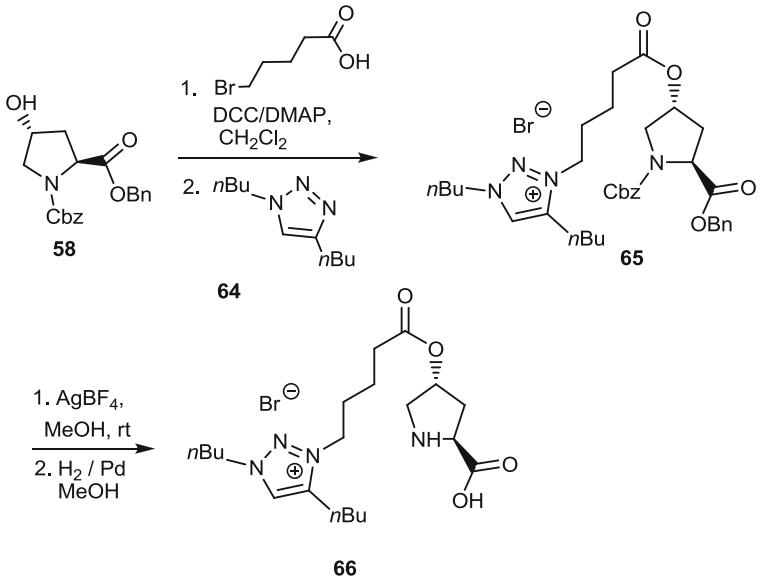


Scheme 19 Synthesis of 1,2,3-triazolium tagged catalyst from propargylated *trans*-4-hydroxy *S*-proline

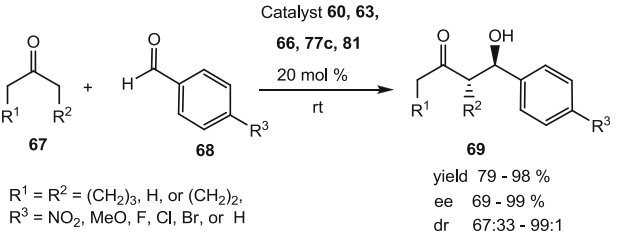
double deprotection of both the benzyl and Cbz group by catalytic hydrogenation gave the desired catalyst **63** (Scheme 19) [66].

Another 1,2,3-triazolium ionic liquid tagged catalyst **66** obtained from diprotected *trans*-4-hydroxy proline **58** utilizes an ester linkage formed by reaction of *trans*-4-hydroxy proline with 5-bromovaleric acid. The resulting bromo substituted product was further used as alkylating reagent for 1,4-di(*n*-butyl)-1,2,3-triazole **64**. Anion metathesis of the resulting triazolium bromide **65** with $AgBF_4$ followed by catalytic hydrogenation furnished the target catalyst **66** (Scheme 20) [66].

Catalysts **60** and **63** were found to be highly efficient in direct aldol reactions. The reaction of various aromatic aldehydes with acetone, cyclohexanone, or cyclopentanone catalysed by catalyst **60** furnished high yields (>84%) and enantioselectivities (>76%). Both aromatic aldehydes substituted with electron withdrawing 4-nitro- and electron donating 4-methoxy group furnished excellent yields (>91%) and enantioselectivities (> 98%) as well as diastereoselectivities (>97:3). Variation of the substituent on the aromatic ring of the aldehyde from the



Scheme 20 Synthesis of 1,2,3-triazolium ionic liquid tagged catalyst **66**. Counter anion of 66 must be BF_4

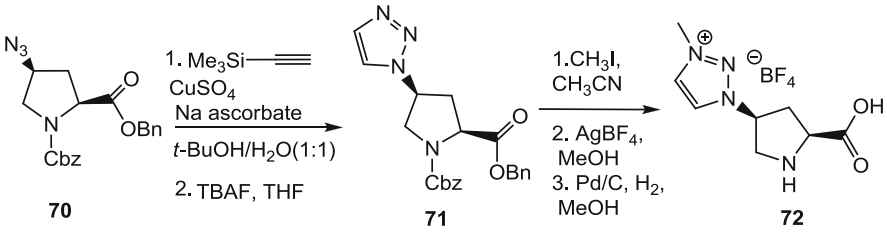


Scheme 21 Aldol reactions catalysed by 1,2,3-triazolium tagged catalysts **60, 63, 66, 77c**, **81**

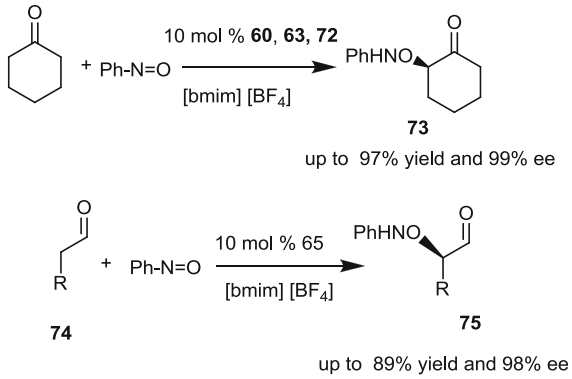
electron withdrawing nitro group to the electron donating methoxy group did not influence the outcome of the reaction. Catalysts **60**, **63** and **66** furnished better enantioselectivities for acetone as enol component as compared to other catalysts [66] (Scheme 21).

Catalyst **60** was recycled by extraction of the reaction products with diethyl ether or cyclohexane. The latter gave better results in recycling providing 88% yield and 68% ee in the fifth cycle. Performing the aldol reaction catalysed by **60** in [bmim] [BF_4] ionic liquid leads to detrimental effects in recycling [66].

In order to obtain proline with a 1,2,3-triazolium tag, which has no substituent at position 4, TMS-ethyne was applied as alkyne component in CuAAC with 4-azidoproline derivative **70** (Scheme 22). The TMS-group was removed by tetrabutyl ammonium fluoride and the resulting 1,2,3-triazole derivative **71** alkylated by methyl iodide and subjected to salt metathesis with silver



Scheme 22 Synthesis of proline tagged with 4-unsubstituted 1,2,3-triazolium **IL**



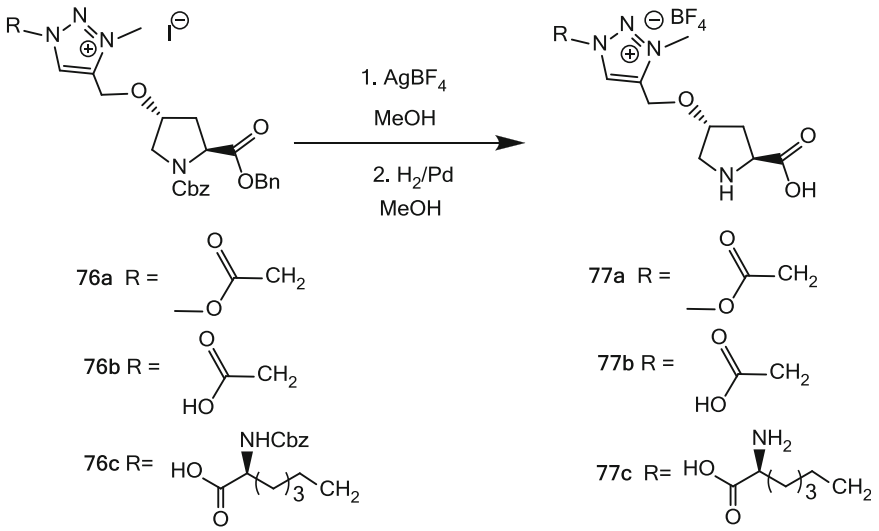
Scheme 23 Application of triazolium tagged catalysts in α-aminoxylation of carbonyl compounds in [bmim] [BF_4] solvent

tetrafluoroborate ($AgBF_4$). Deprotection by palladium catalysed hydrogenation provided the target catalyst **72** (Scheme 22) [66]. This strategy was also used by Jeong and Ryu [52] in order to synthesize 1,3-dialkyl-1,2,3-triazolium ionic liquid solvents independently of our work.

Catalyst **72**, which lacks a substituent at position 4 of the 1,2,3-triazole ring was investigated in asymmetric α-aminoxylation using [bmim] [BF_4] ionic liquid. It showed lower efficiency (82% yield and 78% ee) when compared to catalysts with alkyl substituent at position 4 such as catalyst **60** or **63** providing excellent yields and enantioselectivities (Scheme 23) [67]. In these cases[67] even better results were obtained than with untagged (*S*)-proline and its derivatives.

The potential of catalyst **63** was also investigated in Michael addition of cyclohexanone, cyclopentanone and acetone to various *trans*-β-nitrostyrenes similar to the application of catalyst **60** (Scheme 21). The Michael addition products were obtained with high yield and diastereoselectivities but with somewhat lower enantioselectivities [66].

The flexibility of the 2-step synthesis of 1,2,3-triazolium salts was further explored to attach two potentially catalytically active moieties to the triazole ring (Scheme 24). Following analogous reaction steps as Scheme 19, azidoacetic acid, methyl azidoacetate or a lysine-derived azide were applied as azido component to furnish



Scheme 24 Synthesis of 1,2,3-triazolium IL catalysts with additional functional groups

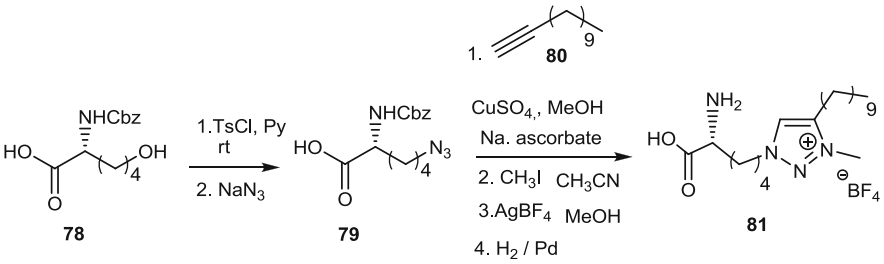
the 1,2,3-triazolium iodides**76**. Anion metathesis with silver tetrafluoroborate and palladium catalysed reductive hydrogenation gave the 1,2,3-triazolium tetrafluoroborates **77** where respective functional groups are found at position 1 in addition to the hydroxyproline moiety at position 4 [67].

However, these additional functionalities found in the 1,2,3-triazolium-tagged catalysts **77a,b** exhibited a detrimental effect in catalysis of the aminoxylation of cyclohexanone with nitrosobenzene in [bmim][BF_4] leading to low enantioselectivities [51, 93].

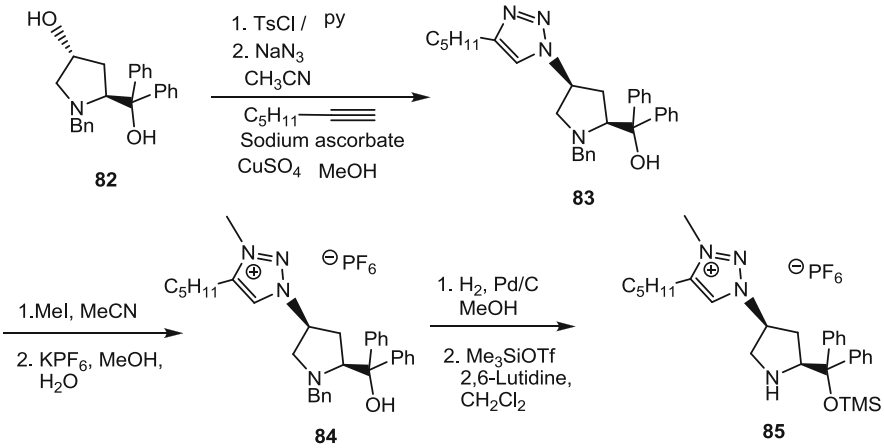
On the other hand, the application of the catalyst **77c** in 20 mol% furnished good yields (87–95%), diastereoselectivities (65:35–99:1) and enantioselectivities (82–98%) in aldol reactions (Scheme 21) [51]. Interestingly, the prolongation of the reaction time from 24 h to 96 h resulted in the decrease of the diastereoselectivities and chemical yields. Reducing the amount of organocatalyst from 20 mol% to 10 and 5 mol% did not affect the diastereoselectivity but resulted in diminished enantioselectivities and yields.

The recyclability of the 1,2,3-triazolium tagged organocatalyst **77c** was investigated by extracting the aldol products with diethyl ether and combining the remainder with a fresh batch of reactants. It was found that the rate of the reaction decreased with each recycling. However, the enantioselectivity remained persistently high (> 90%) for consecutive five cycles. The diastereoselectivities decreased from 98:2 in the first run to 80:20 in the fifth run [51].

A potential lysine derived organocatalyst **81** without an additional proline moiety was obtained from 2-(benzyloxycarbonylamino)-6-hydroxyhexanoic acid **78** by replacing the terminal hydroxyl group with azide followed by the usual protocol: CuAAC with dodecyne, methylation, salt metathesis and deprotection



Scheme 25 Synthesis of a 1,2,3-triazolium tagged *L*-lysine derivative



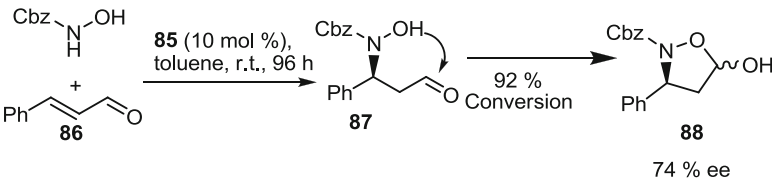
Scheme 26 Synthesis of α, α-diphenylprolinol derived ionic liquid-tagged catalyst

(Scheme 25) [51]. It performed very well as catalyst in aldol reactions (Scheme 21) and gave even better results than the dual 1,2,3-triazolium catalyst **77c**.

As another type of well-known organocatalysts, a Jørgensen type catalyst was tagged with a 1,2,3-triazolium salt. Instead of *trans*-4-hydroxyproline used for prolinyl-1,2,3-triazolium salts the corresponding diphenylcarbinol **82** was transformed into a *cis*-4-azidoderivative and submitted to the general reaction sequence to 1,2,3-triazolium salts by CuAAC, methylation, salt metathesis to give the hexafluorophosphate **85** (Scheme 26) [68].

Catalyst **85** was applied in a domino reaction of cinnamaldehyde with *N*-Cbz protected hydroxyl amine involving an aza-Michael addition followed by an intramolecular acetalization. The product was obtained with 92% conversion and 74% enantioselectivity (Scheme 27) [68].

The methodology of tagging organocatalysts with 1,2,3-triazolium-based ILs was further extended to the area of hydrogen bonding catalysis [70]. α,α, α',α'-Tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL) and substituted analogues showed an outstanding performance in hydrogen bonding catalysis, as bidentate alkoxide ligands and as chiral auxiliaries [94, 95]. 1,2,3-Triazolium tagged TADDOLs

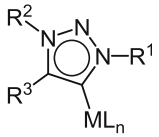


Scheme 27 Domino reaction between *trans*-cinnamaldehyde and *N*-Cbz- hydroxylamine catalysed by ionic liquid catalyst 85

were synthesized starting from 3-propargyloxybenzaldehyde **89** and dimethyl L-(+)-tartrate **90**. After building up the TADDOL skeleton **91** the 1,2,3-triazolium salt unit was established in the usual way (CuAAC, methylation, salt metathesis) providing the 1,2,3-triazolium tetrafluoroborate tagged TADDOLs **93** [70, 92]. These systems were tested in hetero-Diels Alder reactions between activated dienes (Rawal´s and Brassard´s diene) and benzaldehyde but unfortunately showed a weaker performance in terms of yields and enantioselectivity than the untagged parent systems (Scheme 28).

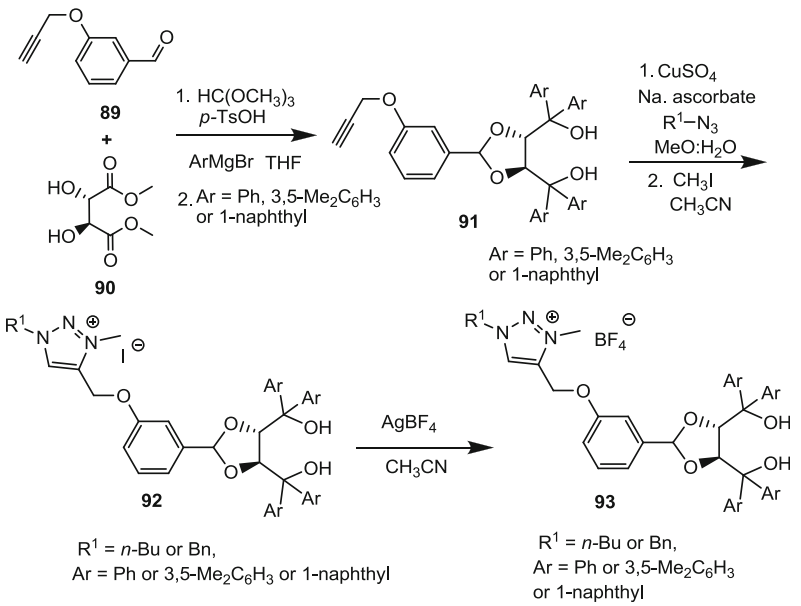
The 1,2,3-triazolium moiety was also used as IL tag for N-heterocyclic carbenes in metal complexes [51]. Thus the 1-imidazolium-ω-1,2,3-triazolium alkanes **96** were synthesized starting from a 1-alkynylimidazole by CuAAC with an azide, double methylation and salt metathesis. It was added to $Pd_2(dba)_3$ in the presence of cesium carbonate forming an imidazolylidene ligand. The resulting complex performed very well in Suzuki-Miyaura coupling (Scheme 29). Its performance was better than when symmetric 1,ω-diimidazolium **95** or 1,ω-ditriazoliumalkanes **94** was used as precursors for NHC-ligands (Fig. 2).

In this context, it has to be mentioned that also 1,2,3-triazolium salts themselves can act as precursors of NHC-ligands for transition metals by deprotonation of position 5 [61, 96–98]. In fact, recent results proved that 1,2,3-triazol-5-ylidene palladium and copper complexes **100** formed from 1,2,3-triazolium salts are efficient catalysts for a number of reactions, such as Suzuki–Miyaura coupling [58, 99–101] Heck-Mizoroki-Heck olefination [102, 103], Sonogashira reaction [102] and CuAAC, respectively [104–106]. The Pd triazol-5-ylidene complexes **100** can even perform better than Pd-imidazolylidene complexes in some cases [99]. Iron and magnesium 1,2,3-triazolylidene complexes **100** served as catalysts in allylation of various nucleophiles [107, 108].

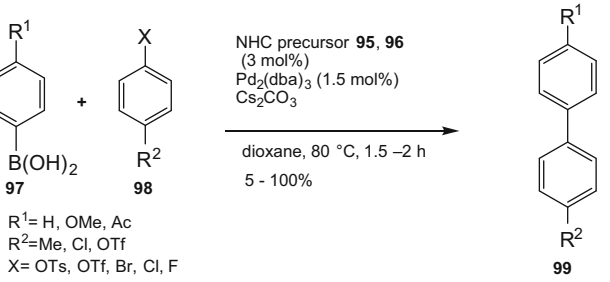


100

1,2,3-Triazol-5-ylidene complexes **100** with iridium or ruthenium have found application as catalysts in olefin metathesis [109], water oxidation [110–112], as



Scheme 28 Synthesis of TADDOL catalysts tagged with 1,2,3-triazolium salts



Scheme 29 Suzuki–Miyaura cross-coupling reaction catalysed by catalyst **95**, **96**

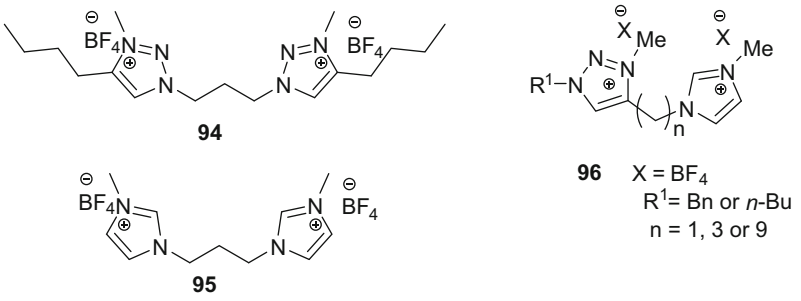
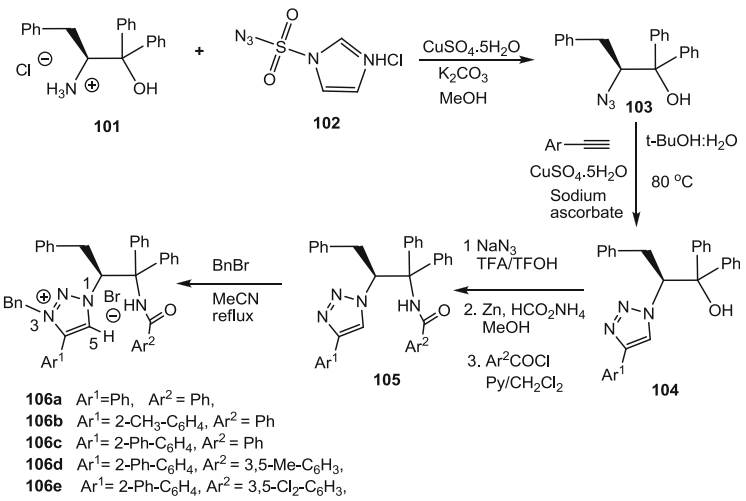


Fig. 2 IL tag for N-heterocyclic carbenes



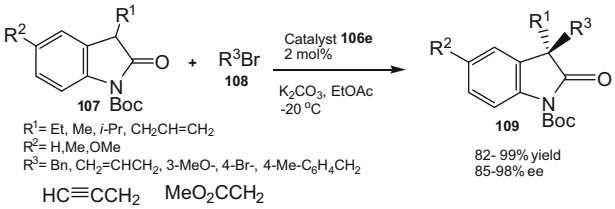
Scheme 30 Synthesis of phenylalanine derived anion-recognizing catalysts

photo sensitizers [113, 114], in oxidation of alcohols and in oxidative coupling of amines to imines or amides [115, 116]. 4,4′-bis(1,2,3-triazolium) salts served as precursors for bidentate ligands for Rh and are promising for potential application in asymmetric catalysis [24].

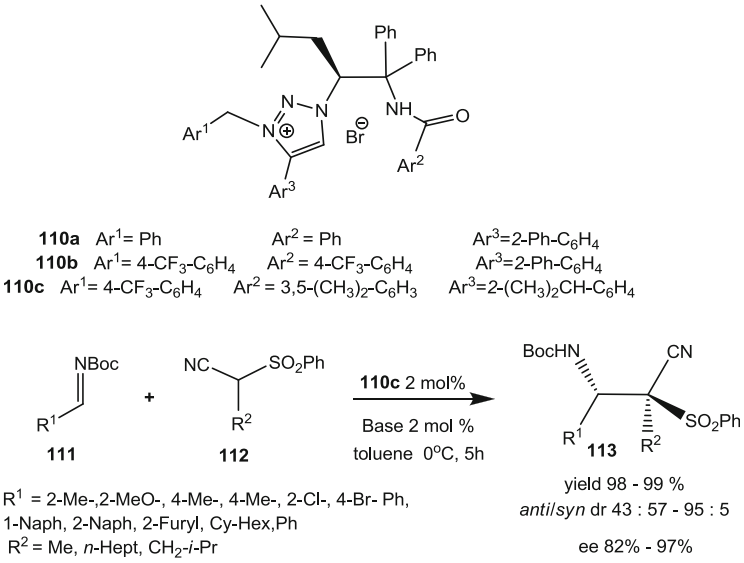
A very recent application of 1,2,3-triazolium salts as catalysts utilizes the ability of the 1,2,3-triazolium ring to engage in hydrogen bonding by its hydrogen atom at position 5 for anion recognition. The ability of 1,2,3-triazoles to form hydrogen bonds has long been exploited in peptide mimetics where the proton on carbon 5 serves as a hydrogen bond donor while the nitrogen at position 3 serves as hydrogen bond acceptor. The transformation of 1,2,3-triazoles to 1,2,3-triazolium salts by alkylation increases their hydrogen bonding ability due to an increased polarization of the C–H bond [59, 117, 118]. The ability of forming H–bonds can be exploited not only in catalysis but also in recognition of anions and in formation of supramolecular systems.

1,2,3-Triazolium-tagged organocatalysts **106** were synthesized starting from Boc protected phenylalanine, which was converted to 2-amino-1,1,3-triphenylpropane-1-ol hydrochloride **101** by Grignard reaction and deprotection. Diazo transfer provided the azidoalcohol **103** used for CuAAC and the resulting triazole **104** was transformed into the 1,2,3-triazolium salts **106** by OH-substitution and benzylation (Scheme 30).

The 1,2,3-triazolium salts **106** were found to be very efficient as catalysts (2% catalyst loading) for asymmetric carbon–carbon bond forming reactions between oxindoles **107** and alkyl bromides **108** in a wide scope providing oxindoles **109** with a quaternary carbon atom in excellent enantioselectivities (85–98%) and high yields (>82%) (Scheme 31). The reaction showed a wide scope. The catalytic activity and stereoselectivity was explained by formation of two H–bonds of the chiral 1,2,3-triazolium salt by the 5–H and the amide NH with the halide leaving group of the alkylating reagent as confirmed by X-ray diffraction analysis and NMR comparison between 1,2,3-triazolium salts with different counter anions.



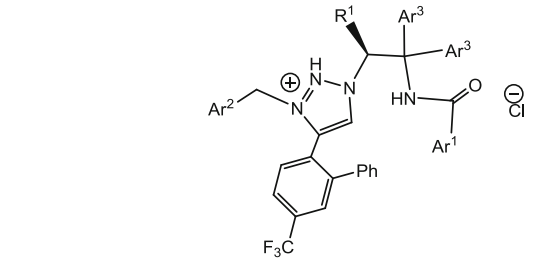
Scheme 31 Asymmetric alkylation of oxindoles catalysed by the 1,2,3-triazolium bromide **106e**



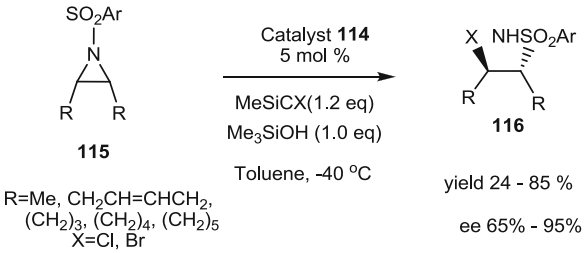
Scheme 32 Application of catalyst **110** in Mannich-type reaction of cyanosulphones

Similar chiral 1,2,3-triazolium salts such as **110** with anion recognition ability were proved to act as catalyst for asymmetric Mannich-type reaction of α-cyanosulphones with *N*-Boc imines (Scheme 32) [73]. Here, the hydrogen bonding occurred to a sulphonyl carbanion. The efficiency of the catalytic system was improved by choosing appropriate substituents, which were optimal in case of **110c** leading to excellent yields, anti/syn ratios up to $>$ 95:5 and ee up to 97% of the products **113**.

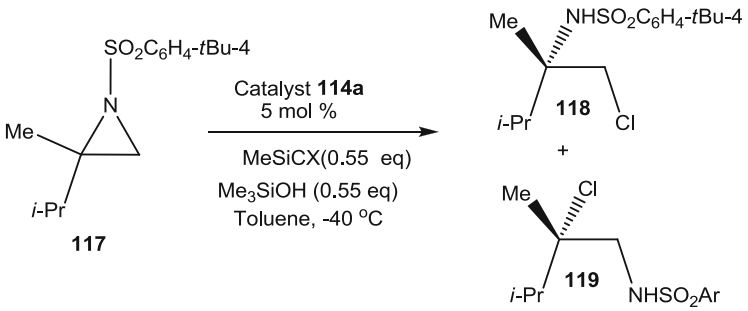
Structurally similar 1,2,3-triazolium salts **114** and others were found to catalyse enantioselective ring opening of *meso*-aziridines **115** by halides using trimethylsilyl halides (chloride or bromide) as halide source. A hypervalent chlorosilicate (formed by the addition of the chloride anion from 1,2,3-triazolium salt to trimethylsilyl chloride) was proposed as reactive intermediate. The structure of the catalytic 1,2,3-triazolium salts **114** was optimized by providing high anion binding ability to the hypervalent silicate and thus improving the asymmetric induction reaching 95% ee (Scheme 33) [72].



114a Ar^1= 4-NO_2-C_6H_4 Ar^2 = 4-CF_3-C_6H_4 Ar^3 = 4-Cl-C_6H_4 R^1= CH_2*i*-Pr
114b Ar^1= 4-NO_2-C_6H_4 Ar^2 = 4-CF_3-C_6H_4 Ar^3 = 4-Cl-C_6H_4 R^1= CH_2c-Hex



Scheme 33 Catalytic asymmetric ring openings of *meso*-aziridines with halides catalysed by **114**



Scheme 34 Kinetic resolution of 2,2-disubstituted aziridines mediated by 1,2,3-triazolium ionic liquid **114a**

The same 1,2,3-triazolium salts **114** were also applied in kinetic resolution of racemic aziridines, e. g. **117** (Scheme 34) [72]. When the aziridines **117** were treated with Me_3SiCl (0.55 equiv) in the presence of **114a** (5 mol%) and Me_3SiOH (0.55 equiv) in toluene at −40°C a regioisomeric mixture of the chlorinated products **118** and **119** arising from the stereo-invertive ring opening of the (*R*)-aziridine was isolated. The combined yield was 48% (131/132 = 80:20) with 90% enantioselectivity of the major β-chloroamine derivative **118**, while the (*S*)-**117** was recovered in 46% yield in enantiopure form [72].

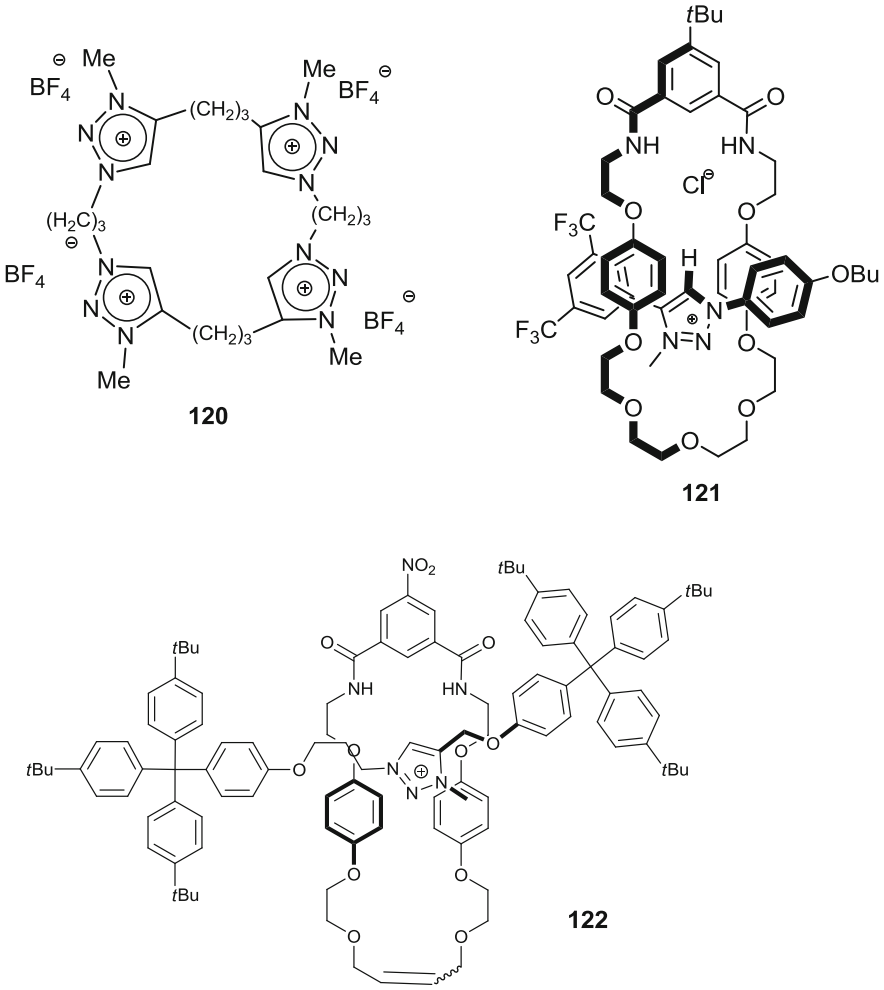


Fig. 3 1,2,3-Triazolium salts **120** and triazolium salt containing rotaxanes **121** and **122** with anion binding properties

5 Miscellaneous

1,2,3-Triazolium salts have entered the field of supramolecular chemistry and even of molecular machines. Here again, often the ability of forming H–bonds via the hydrogen atoms found at position 4 or 5 is involved. Thus, the cyclic tetra-1,2,3-triazolium salt **120** acted as a strong anion binder [64]. The pseudorotaxanes **121** and **122** with 1,2,3-triazolium-containing threads served as hosts for anions and were able to recognize halides (chloride or bromide) selectively [118].

An analogue of **122** with an iodo-substituent at the triazolium ring showed an unusual specific recognition for iodide [119] (Figs. 3 and 4).

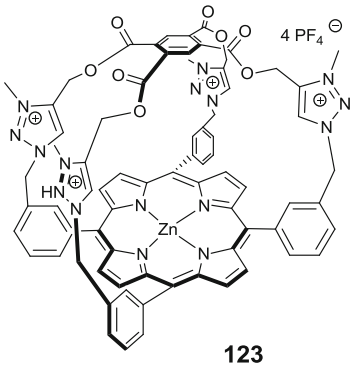


Fig. 4 1,2,3-triazolium-porphyrin cage **123** with selective sulphate anion recognition properties

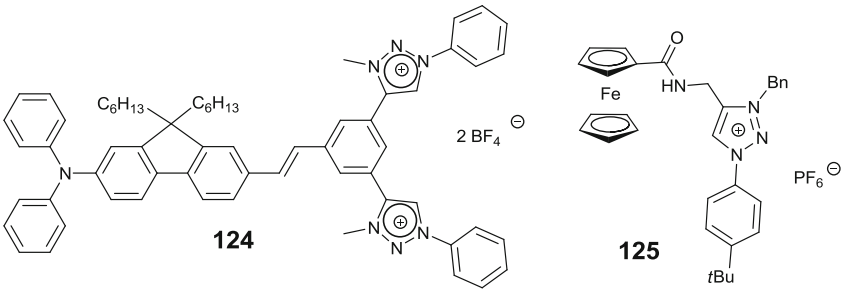


Fig. 5 1,2,3-Triazolium salts **124** and 1**25** with fluoride sensing properties

The 1,2,3-triazolium-porphyrin cage **123** exhibited a strong preference to include sulphate ions in the presence of halide ions [120].

The fluorene derivative **124** with two 1,2,3-triazolium units represents a highly selective fluoride sensor [121]. A marked electrochemical selectivity again for fluoride was found with a ferrocene-based anion receptor **125** containing a 1,2,3-triazolium donor group [122] (Fig. 5).

The 1,2,3-triazolium ring was also introduced into a nanomachine component **126** wherein it causes pH-sensitive two station shuttling by protonation of an amino group [123] (Fig. 6).

The 1,2,3-triazolium unit played a double role in the "lasso-based" molecular switch **127** by acting as a bulky gate for the cycle and a second molecular station [124] (Fig. 7).

The di-1,2,3-triazolium salt **128** was used as a component in a molecular "double-leg elevator" operating by the same principle [125] (Fig. 8).

Two molecules of the triazolium-containing chain compound **129** were involved in the construction of two-station [3]-rotaxane with an oligoethyleneglycol ether-containing rings [126]. Again, deprotonation/protonation of an amino group caused the movement of the molecular threads (Fig. 9).

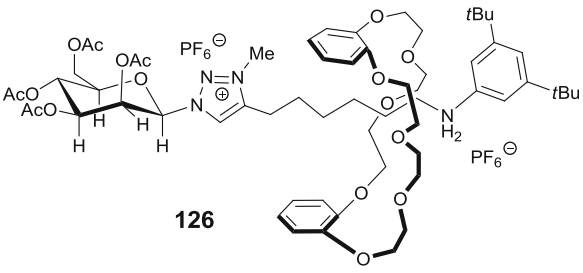


Fig. 6 1,2,3-triazolium salt containing nanomachine component

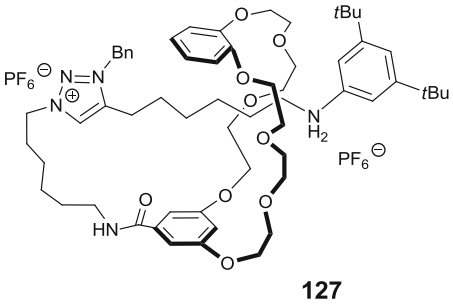


Fig. 7 Molecular switch **127** containing a 1,2,3-triazolium salt

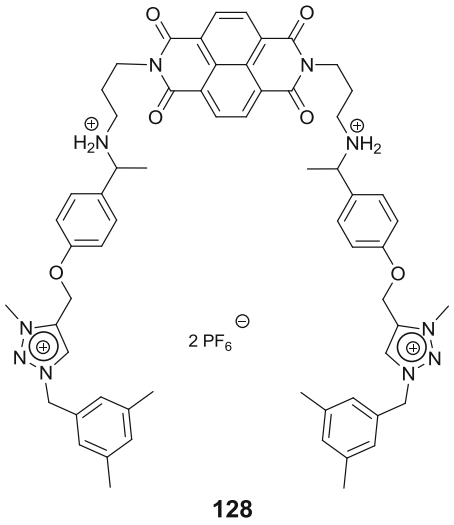


Fig. 8 1,2,3-Triazolium salt **128** as component for a molecular machine

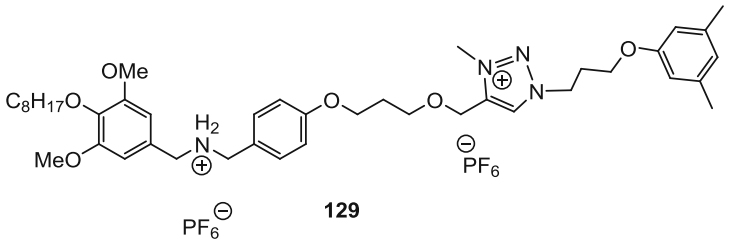


Fig. 9 1,2,3-triazolium salt **129** as a thread for a switchable two-station rotaxane

6 Summary

1,2,3-Triazolium salts have developed from being a common type of heterocycles to an impressive class of ILs. Their synthesis is straightforward including the CuAAC, *N*-alkylation and eventual salt metathesis in most cases. It also has a wide scope and thus allows to tune the properties of the 1,2,3-triazolium ILs as well as to functionalize them by one or more applicatory groups. The latter property is mainly exploited in catalysis so far. In addition to the use of the 1,2,3-triazolium moiety as a support for catalysts there is recent impressive application as precursors for unusual NHC ligands for metals providing catalytic properties better than conventional NHC. 1,2,3-Triazolium ILs also provides perspectives in other fields, such as in supramolecular chemistry and molecular switches or machines. The impact of 1,2,3-triazolium ILs would heavily increase if such materials will be produced in an industrial scale and become commercially available.

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Mesoionic 1,2,3-Triazoles and 1,2,3-Triazole Carbenes

Jesus M. Aizpurua, Maialen Sagartzazu-Aizpurua, and Zaira Monasterio

Abstract Routine access to 1,2,3-triazoles through the copper-catalyzed azide-alkyne "click" cycloaddition reaction has promoted the rapid development of 1,2,3-triazolylidenes as ligands for transition metals. The organometallic complexes containing this kind of *N*-heterocyclic carbene ligands (NHCs) have shown to possess unique structural characteristics, including a relatively high covalent contribution to the metal–NHC bond, a strong donor ability, and a mesoionic character. Complexes of mesoionic triazolylidene carbenes (MICs) are readily available, among other methods, by metallation of N3-substituted 1,2,3-triazolium salts, usually followed by transmetallation reactions. A diverse array of monodentate, polydentate, and bridged ligands containing the 1,2,3-triazolylidene motif has been described, and the structures of complexes containing them have been characterized in detail. Promising applications in organometallic catalysis involving C–C and C–X bond formation and redox reactions have emerged in recent years for 1,2,3-triazolylidene metal complexes, and, owing to the modular and multiple functionalization possibilities around the 1,2,3-triazole scaffold, novel applications are expected in upcoming years.

Keywords 1,2,3-Triazolium salts · 1,2,3-Triazolylidenes · Carbenes · Homogeneous catalysis · Mesoionic compounds · Metallation · Transition metal complexes

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Abbreviations

Ac	Acetyl
adam	Adamantyl
Ag	Silver
Ar	Aryl
Au	Gold
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bpy	2,2′-Bipyridyl
Bu	Butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
cat	Catalyst
cod	Cyclooctadiene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
Cu	Copper
CuAAC	Copper-accelerated azide-alkyne cycloaddition
CV	Cyclic voltammetry
Cym	Cymene
d	Day(s)
DBU	1,8-Diazabicyclo [5.4.0]undec-7-ene
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine

Dipp	2,6-Diisopropylphenyl
DMAP	4-(Dimethylamino)pyridine
DMB	3,4-Dimethoxybenzyl
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Dtm	Di(4-tolyl)methane
EDA	Ethyl diazoacetate
ee	Enantiomer excess
equiv	Equivalent(s)
Et	Ethyl
eV	Electron volt
GII	Grubbs' second-generation catalyst
h	Hour(s)
HMPA	Hexamethylphosphoric triamide
HOMO	Highest occupied molecular orbital
*i*Pr	Isopropyl
Ir	Iridium
KHMDS	Potassium hexamethyldisilazane, potassium bis(trimethylsilyl)amide
LUMO	Lowest unoccupied molecular orbital
M	Metal(s)
m.p.	Melting point
Me	Methyl
Mes	Mesityl, 2,4,6-trimethylphenyl
MIC	Mesoionic carbenes
min	Minute(s)
MLCT	Metal-to-ligand charge transfer
mol	Mole(s)
Ms	Methanesulfonyl (mesyl)
MS	Mass spectrometry
mV	Millivolt
Na Asc	Sodium ascorbate
NHC	*N*-heterocyclic carbene
Nu	Nucleophile
PA_1	Proton affinity
Pd	Palladium
Ph	Phenyl
Pr	Propyl
py	Pyridine
RCM	Ring-closing metathesis
Re	Rhenium
Rh	Rhodium
ROMP	Ring-opening metathesis polymerization
rt	Room temperature

Ru	Ruthenium
s	Second(s)
*t*Bu	*tert*-Butyl
Tf	Trifluoromethanesulfonyl (triflyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Tipp	2,4,6-Triisopropylphenyl
tmeda	*N*,*N*,*N*′,*N*′-tetramethylenediamine
TMS	trimethylsilyl
TMSD	(Trimethylsilyl)-diazomethane
Tol	4-Methylphenyl
TON	Turnover number
Tpy	2,2′,6′,2″-Terpyridine

1 Introduction

N-Heterocyclic carbenes (NHCs) comprise a family of heterocyclic molecules containing a neutral divalent carbon with two unshared valence electrons stabilized by one or several nitrogen atoms in the ring. Unquestionably, the most popular NHCs are the 1,3-imidazole-based carbenes, which have been extensively crafted to form a wide variety of transition metal complexes, since their discovery by Arduengo two decades ago [1].

1,2,3-Triazoles can also form several kinds of triazolylidene structures including triazol-5-ylidenes **I** and **II** and triazol-4,5-diylidenes **III** (Fig. 1). The term "mesoionic" is assigned to carbenes that require additional charges in their resonance forms [2–6]. For example, neutral carbenes **I** can only be represented by Lewis structures containing positive and negative charges, whereas carbenes **II**, derived from 2*H*-1,2,3-triazoles, posses an uncharged Lewis structure and are not mesoionic. Analogously, anionic dicarbenes **III** can be represented without a positive charge. This review covers the synthesis, structural characteristic, and chemical applications of fully mesoionic and related carbenes comprising the 1,2,3-triazolylidene motif.

Triazolylidenes, specially the mesoionic ones, are excellent ligands for transition metal ion coordination to form complexes. Such MIC complexes can be classified according to the coordination ability of the carbene ligand, the number of triazole units included in the ligand, and the chelating or open character of the coordination bonds formed with the metal. Combining these criteria, we have defined five main families of monodentate, polydentate, and bridged triazolylidene complexes (Fig. 2). Herein, we examine the preparation of triazolylidene complexes of types (**A**–**J**), focusing on the synthesis of the mesoionic ligands, their incorporation into transition metal complexes, and their use in organometallic catalysis.

Despite its recent creation, the chemistry of triazolylidene complexes is currently one of the most promising and fastest developing areas in *N*-heterocyclic

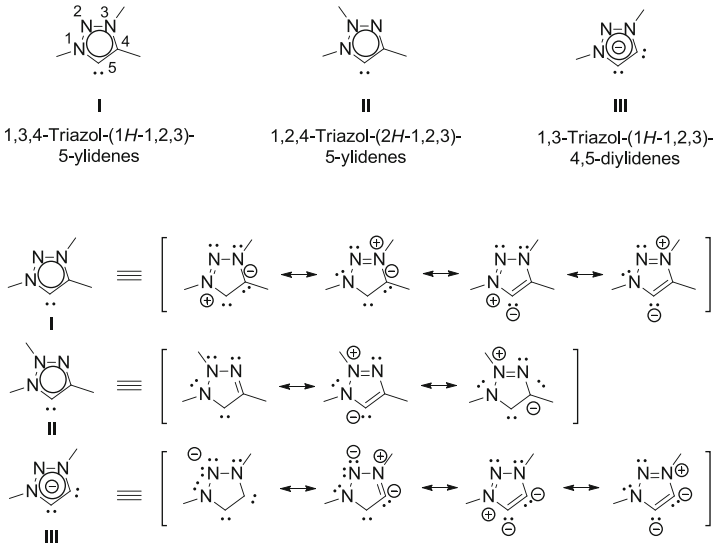


Fig. 1 *Top*: *N*-heterocyclic carbenes comprising the 1,2,3-triazole motif. *Bottom*: representative Lewis structures of mesoionic (**I**) and normal (**II**, **III**) 1,2,3-triazolylidene carbenes

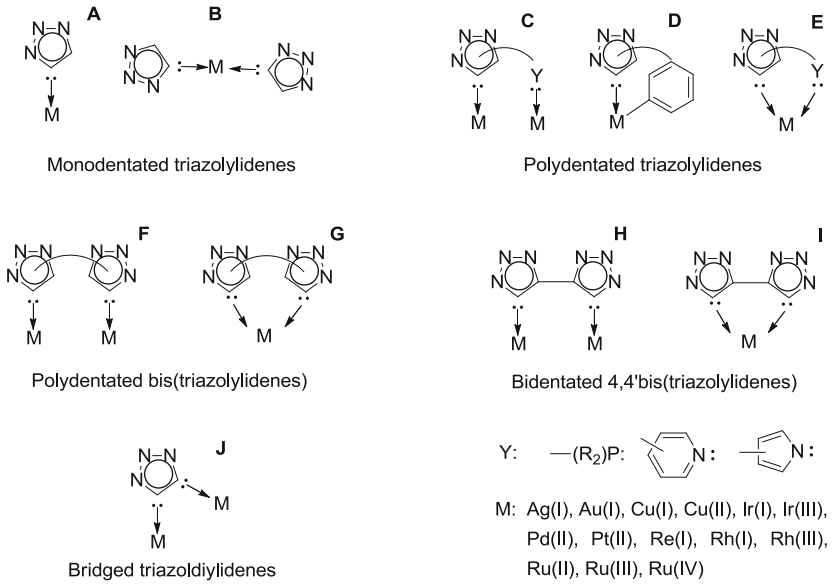
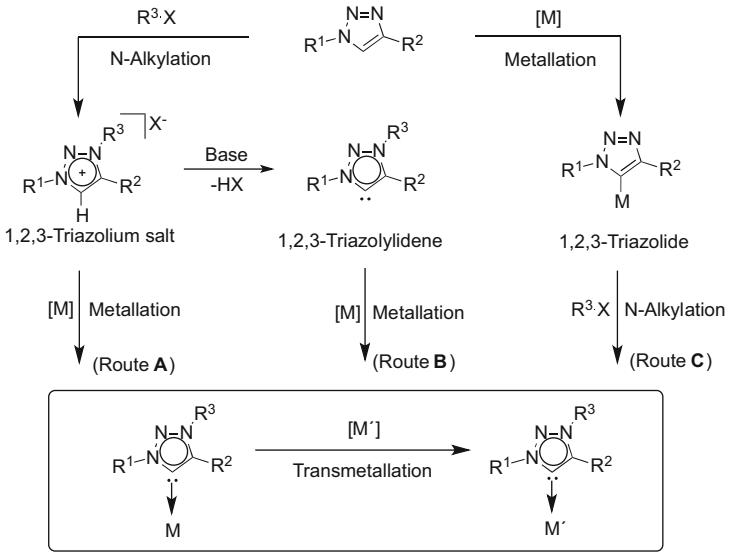


Fig. 2 Main molecular architectures of metal carbene complexes containing 1,2,3-triazolylidene ligands covered in this review

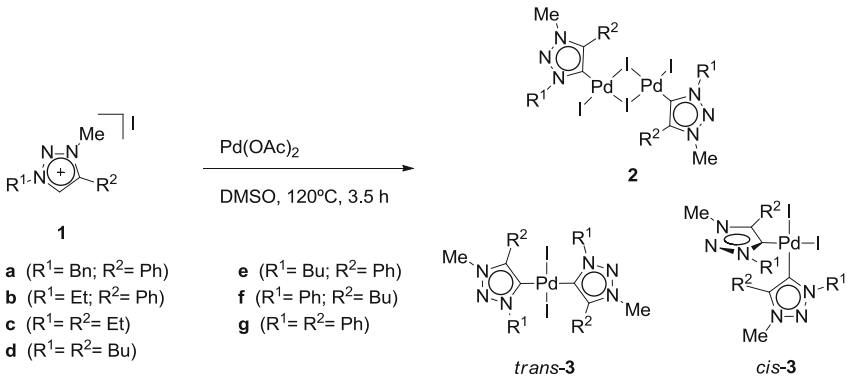


Scheme 1 Synthetic approaches to 1,2,3-triazolylidene complexes

carbenes. The topic has been surveyed by Albrecht in an excellent review covering aspects related to the preparation, donor properties, and catalytic activity of 1,2,3-triazolylidenes [7]. Crabtree has also partially reviewed the subject [8].

2 Synthetic Routes to Metal Triazolylidene Complexes

Transformation of 1,4-disubstituted 1,2,3-triazoles into 1,2,3-triazolylidene metal complexes can be achieved formally following the synthetic routes depicted in Scheme 1. 1,2,3-Triazoles are regioselectively *N*-alkylated at position N3 upon treatment with strong alkylating agents such as methyl iodide, alkyl triflates, or Meerwein salts (R_3OBF_4) to afford 1,3,4-trisubstituted triazolium salts. The preparation and chemical properties of such compounds are comprehensively covered in this book [98]. Triazolium salts can be directly metallated to triazolylidene complexes employing transition metal salts carrying basic anions (route A). Alternatively, they can be deprotonated to free triazole carbenes with strong bases and further metallated to the complexes in two separate steps (route B). The transformation sequence can be inverted metallating first the C5 position of the parent triazoles and then *N*-alkylating the resulting triazolide anions to the carbene complexes (route C). Finally, the range of accessible triazolylidene complexes can be considerably expanded by transmetallation of appropriate metal carbenes (typically silver carbenes) with exchange complexes of other metals.



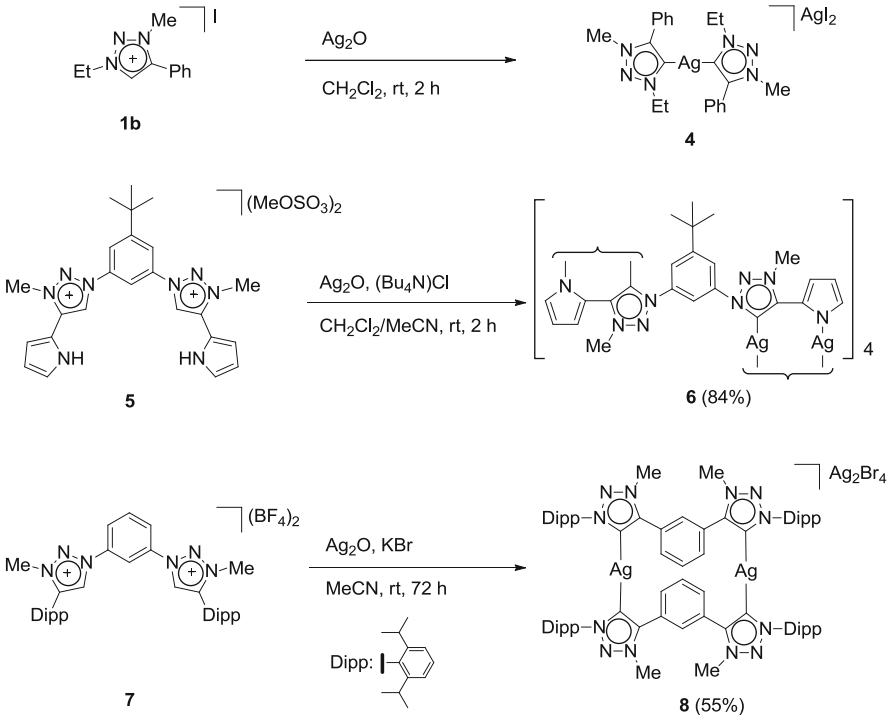
Scheme 2 Direct metallation of 1,2,3-triazolium salts with $Pd(OAc)_2$

Different research groups have pioneered the synthetic routes (A–C) outlined above to prepare triazolylidene metal complexes from 1,2,3-triazoles. Albrecht described the first triazolylidene metal complex in 2008 using the *N*-alkylation/metallation route and also paved the way for the application of transmetallation reactions to 1,2,3-triazolylidene complexes [9]. Bertrand, on the other hand, succeeded to isolate and characterize the first free triazolylidene, demonstrating its coordination with transition metal complexes [2]. Finally, Gandelman recognized C5-metallated 1,2,3-triazolide anions as potential precursors of triazolylidene complexes by *N*-alkylation of the heterocyclic ring [10].

In the next Sects. (2.1)–(2.4) some illustrative synthetic examples to prepare 1,2,3-triazolylidene metal complexes from 1,2,3-triazoles are presented, focusing the discussion on their scope and limitations.

2.1 Direct Metallation of 1,2,3-Triazolium Salts

A direct, albeit not straightforward, method to form triazolylidene complexes involves the metallation of triazolium salts employing metals with basic ligands. For example, when the thermally induced metallation of triazolium salts **1** is carried out with $Pd(OAc)_2$, a mixture of products is obtained comprising the dimeric monocarbenes **2** and biscarbenes **3**, the latter as *cis*/*trans* and *syn*/*anti* isomers (Scheme 2) [9, 11]. Sequential extraction and fractional crystallization of the reaction products derived from the triazolium salt **1b** allowed for isolating the corresponding pure complexes **2b**, *trans*-**3b**, and *cis*-**3b** (Similar mixtures of dimetallic and monometallic complexes have been reported in the palladation of imidazolium salts: [12]). Attempts to improve the reaction selectivity by adding an excess of iodide ligand (KI) or a base (NaOAc) resulted in a significant increase of the ratio of the dimeric complexes **2** (up to 8:1), but alternative attempts to improve



Scheme 3 Metallation of 1,2,3-triazolium salts to silver triazolylidene complexes with Ag_2O

the ratio of biscarbenes **3** failed. Luckily, applying a two-step transmetallation route provided more successful results (see Sect. 4.2).

Metallation at the C5 position of triazolium cations can be conducted under milder conditions with Ag_2O following the method developed by Lin for 1,3-imidazolium salt [13]. The silver *N*-heterocyclic carbene complexes can be obtained as ionic and neutral compounds. Depending on the solvent employed, the metal to triazolium salt molar ratio and the presence of additive salts (e.g., KBr, Bu_4NCl, etc.), the silver complexes may present a large variety of structures. For example, the metallation of the triazolium salt **1b** with Ag_2O at room temperature yielded exclusively the cationic biscarbene **4**, which slowly decomposed in solution but was stable enough to be characterized by NMR and MS analysis (Scheme 3) [9]. Most silver triazolylidene complexes are unsuitable for isolation and purification using standard laboratory protocols, but their formation can be easily accessed by NMR analysis checking the disappearance of the low field triazolium H5 proton, the downfield shift of the C5 signal in the ^{13}C NMR spectrum and the coupling of the latter with ^{107}Ag.

Aided by the steric effects of their bulky ligands, only two stable silver triazolylidene complexes, **6** and **8**, have been isolated to date and their structures determined by X-ray crystallography (Fig. 3) [14, 15]. In one complex, derived

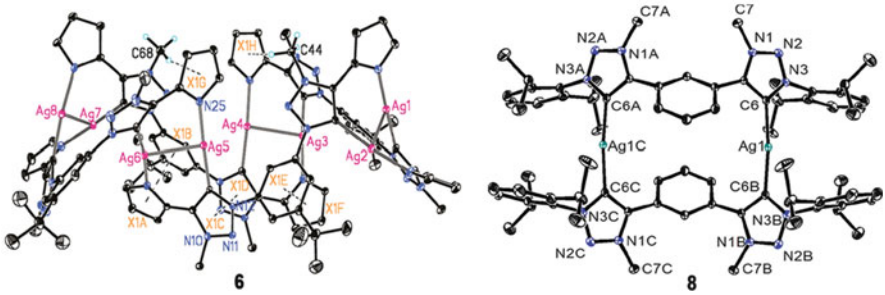


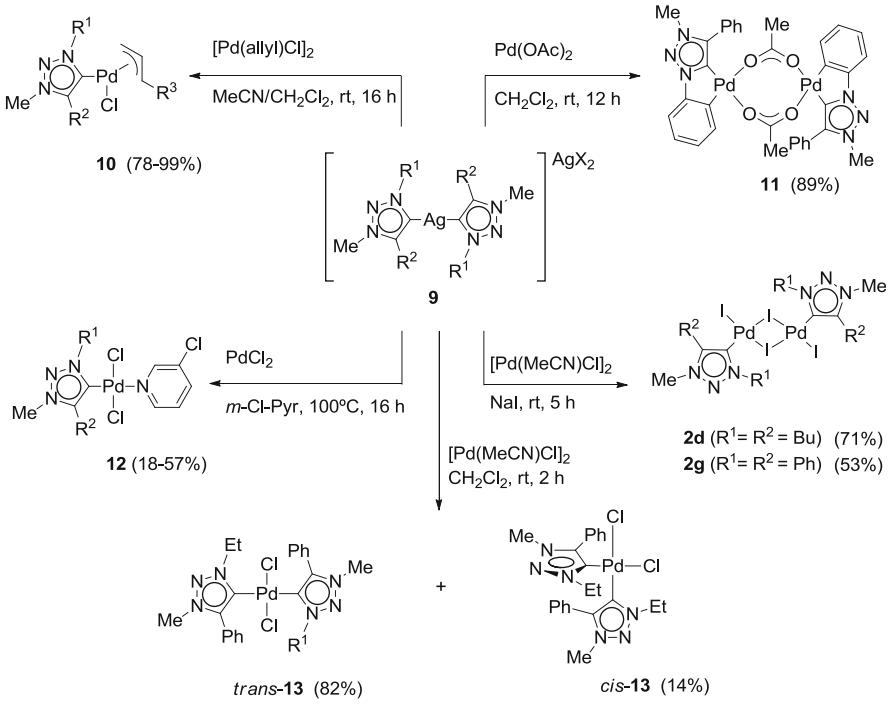
Fig. 3 X-ray structures of the neutral octanuclear silver triazolylidene **6** and the cationic dinuclear carbene complex **8**. Figure partially reprinted from [14, 15], © 2011, 2012 ACS

from the pyrrole-functionalized ditriazolium salt, **6**, each silver cation is bound to one triazolylidene and one deprotonated pyrrolyl ligand in a *trans* configuration. Due to the four bonding sites of each ligand precursor, a macrocyclic structure is obtained, comprised of four ligands, eight Ag(I) centers, and various weak interactions, including Ag–Ag contact pairs. In contrast to this formally neutral complex, the silver carbene **8** is cationic and features two Ag biscarbene moieties. This complex is derived from the related ditriazolium salt **7** that lacks additional stabilizing pyrrole substituents.

As mentioned above, the direct metallation approach to prepare 1,2,3-triazolylidene metal complexes from triazolium salts is often thwarted by the obtention of complex reaction mixtures when the transformation needs to be carried under thermal conditions. Furthermore, there are only a limited number of metal complexes available with basic ligands strong enough to promote the in situ deprotonation of the cationic heterocycle. Transmetallation of silver carbene complexes offers a solution to these drawbacks and is currently the most widely employed method to prepare triazole carbene complexes.

2.2 *Transmetallation of 1,2,3-Triazolylidene Complexes*

Transmetallation of silver carbenes with suitable transition metal complexes, specially bridged dimeric species (e.g., $[Rh(cod)Cl]_2$, $[Ir(Cp^*)Cl_2]_2$, $[Ru(cym)Cl_2]_2$, or $PdCl_2$), provides a general and clean metal exchange procedure working under mild reaction conditions. It also allows for the preparation of otherwise inaccessible 1,2,3-triazol-5-ylidene metal complexes. The transformation is achieved in two steps, preparing first the silver carbene as outlined in Sect. (2.1) and then performing the in situ carbene transfer to another metal. Successful triazolylidene transmetallations have been achieved with a variety of transition metals including Au(I), Cu(I), Pd(II), Rh(I), Ir(I), and Ru(II). The whole process is thermodynamically favored by the addition of halide salts (typically R_4NX) or by the selection of transfer metal

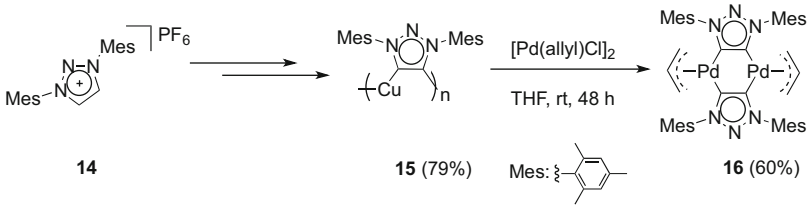


Scheme 4 Ligand dependence on transpalladation reaction products from silver triazolylidene complex **9**

complexes containing halide ligands (e.g., $Pd(MeCN)Cl_2$, $Pt(cod)Cl_2$, or CuCl) to promote the precipitation of AgX salts.

As outlined by Albrecht, the choice of metal precursor and metallation procedure determines the selectivity of product formation during the transmetallation of silver carbene complexes [16, 17]. For example, transpalladation of the silver carbene **9** with a dimeric palladium chloride source, such as $[Pd(allyl)Cl]_2$ or $PdCl_2$, in the presence of another coordinating ligand affords the monocarbene triazolylidene complexes, **10** and **12** (Scheme 4). Addition of $Pd(OAc)_2$ to the silver carbene complex selectively affords the dimeric palladium species **11** [18]. It is notable that cyclopalladation of the ligand occurs in this case (see Sect. 5.2 for more details). In contrast, $Pd(RCN)_2Cl_2$ favors the formation of the biscarbenes, *trans*-**13** and *cis*-**13**, with the *trans* isomer as the major species. Both forms exist as *syn* and *anti* conformers. Finally, performing the carbene transfer in the presence of NaI selectively yields the dimeric palladium species **2** with bridging iodide groups.

Transmetallation by using coinage metal complexes other than silver is well documented [19], and Bertrand has described recently the first extension of this concept to 1,2,3-triazol-4,5-diylidenes (Scheme 5) [20]. Accordingly, the requisite polymeric copper dicarbene complex **15** was obtained in 79% yield by sequential



Scheme 5 Transmetallation reaction of copper 1,2,3-triazoldiylidene complexes

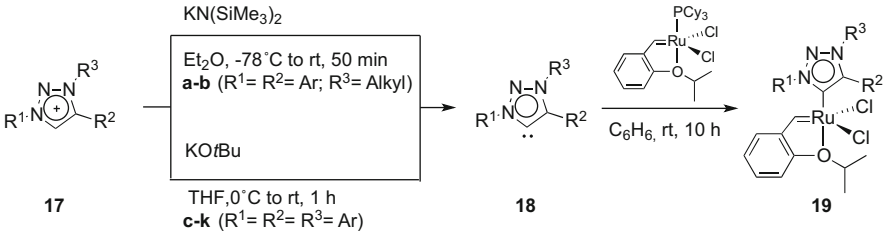
deprotonation and metallation with CuCl of the triazolium salt **14**. The latter was reacted with dimeric allylpalladium chloride to give the dimetallic dicarbene complex **16** in 60% yield (see also Sect. 8).

2.3 Metallation of Free 1,2,3-Triazole Carbenes or Carbene Adducts

Conceptually, the simplest and more elegant method to obtain triazolylidene metal complexes involves the preparation and isolation of free carbenes, followed by complexation with suitable metal carriers. Bertrand and coworkers have implemented this idea to the synthesis of ruthenium complexes **19** [3]. First, they prepared the free 1,2,3-triazolylidenes **18** by deprotonation of the triazolium salts **17** using $KN(SiMe_3)_2$ or KO*t*Bu as non-nucleophilic bases (Scheme 6).

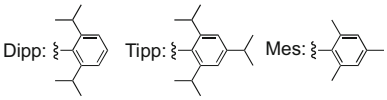
The deprotonation of N3-alkyl triazolium salts **17a–b** required the strong base $KN(SiMe_3)_2$ ($pK_a = 26$), whereas N3-aryl carbenes **18c–k** were better obtained with the weaker base KO*t*Bu ($pK_a = 22$) [2, 3]. However, both methods failed to form the free carbenes derived from N1, N3-dialkyl triazolium ions. To overcome the operational difficulties arising from the isolation and manipulation of free triazole carbenes, the deprotonation-metallation sequence can be accomplished in a one-pot operation. Sarkar and coworkers [21] have successfully implemented this method in the formation of triazolylidene copper(I) complexes **20** from the triazolium salts **1** with KO*t*Bu base and CuI at low temperature (Scheme 7). Many mechanistic details of this transformation (e.g., direct C5-H proton abstraction versus Cu(O*t*Bu) formation) remain unexplained [2].

When applying conventional deprotonation routes to 1,2,4-trisubstituted triazolium salts **21**, only mixtures of decomposition products were isolated, or, in the presence of suitable metal precursors, very small amounts of metal carbenes were formed (Scheme 8). Kühn reported a solution to this problem by trapping in situ the free carbenes as ammonia adduct (**22**), which can be safely stored in THF at −30°C for several months without decomposition. The same author has demonstrated that this carbene adduct undergoes direct metallation reactions with Ir(I), Rh(I), Cu(I), and Au(I) complexes, resulting in 1,2,4-trisubstituted triazolylidene complexes **23** [22].

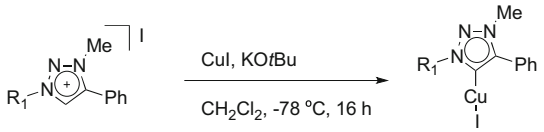


18a (R^1= Dipp; R^2= Ph; R^3= Me) (55%)
18b (R^1= Dipp; R^2= Ph; R^3= *i*Pr) (39%)
18c (R^1= Dipp; R^2= Ph; R^3= Dipp) (90%)
18d (R^1= Dipp; R^2= Mes; R^3= Dipp) (77%)
18e (R^1= R^2= R^3= Dipp) (88%)
18f (R^1= Dipp; R^2= Tipp; R^3= Dipp) (99%)
18g (R^1= Dipp; R^2= *t*Bu; R^3= Dipp) (69%)
18h (R^1= Dipp; R^2= Cy; R^3= Dipp) (69%)
18i (R^1= Dipp; R^2= OEt; R^3= Dipp) (83%)
18j (R^1= Mes; R^2= Ph; R^3= Mes) (98%)
18k (R^1= R^2= R^3= Mes) (99%)

19c (R^1= Dipp; R^2= Ph; R^3= Dipp) (49%)
19d (R^1= Dipp; R^2= Mes; R^3= Dipp) (21%)
19f (R^1= Dipp; R^2= Tipp; R^3= Dipp) (50%)
19j (R^1= Mes; R^2= Ph; R^3= Mes) (17%)



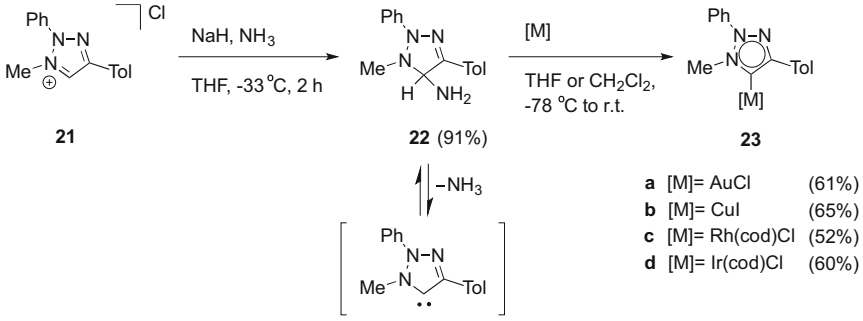
Scheme 6 Preparation of free triazolylidenes and further metallation to ruthenium(II) complexes



1a R^1= Bn
1h R^1= C_6H_4-SMe-*o*

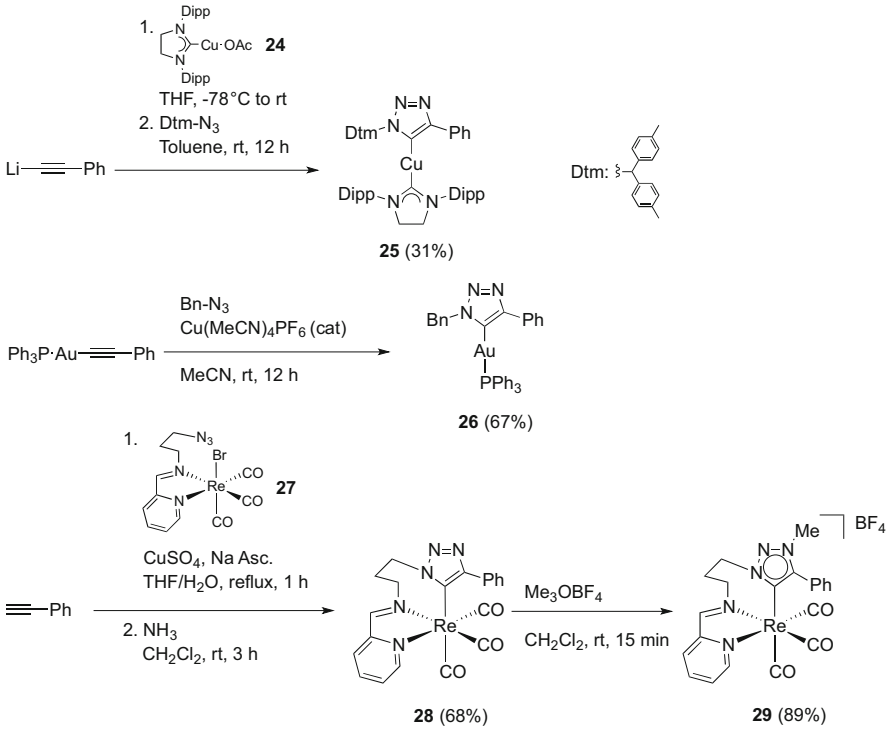
20a (60%)
20h (75%)

Scheme 7 Direct cupration of 1,2,3-triazolium salts in the presence of KOtBu base



a [M]= AuCl (61%)
b [M]= CuI (65%)
c [M]= Rh(cod)Cl (52%)
d [M]= Ir(cod)Cl (60%)

Scheme 8 1,2,4-Trisubstituted triazolylidene complexes from the ammonia-carbene adduct **22**

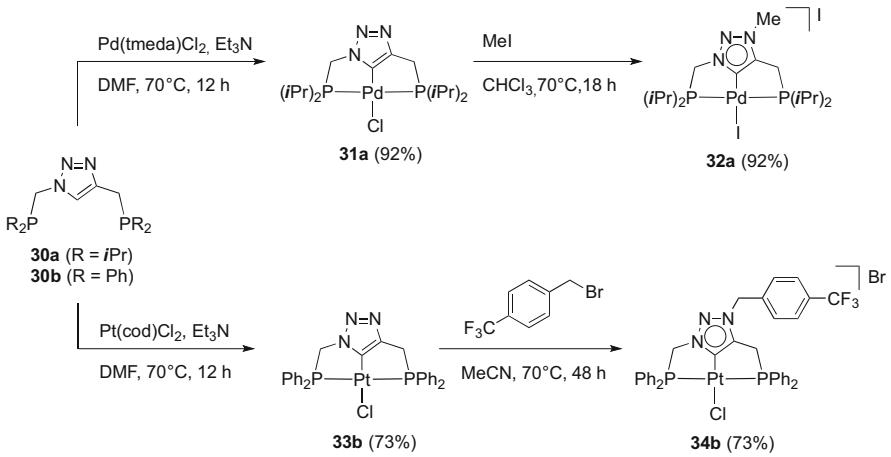


Scheme 9 Preparation of copper(I) triazolide complexes from CuAAc reactions

2.4 N-*Alkylation of 1,2,3-Triazolide Carbanions*

Straub and coworkers succeeded to isolate the first stable copper(I) 1,4-disubstituted-1,2,3-triazolide complex **25** by reacting a bulky NHC-stabilized copper(I) acetylide, generated in situ from lithium phenylacetylide and the carbene cuprate **24**, with azido-di(4-tolyl)methane in toluene (Scheme 9) [23]. Complex **25** was stable in air and water, and its molecular structure was confirmed by X-ray crystallography. The copper(I) 1,2,3-triazolide species is presumed to be an intermediate in the catalytic cycle of the CuAAC reaction. Straub also showed that protonolysis of the triazolide cuprate **25** with acetic acid in dichloromethane at room temperature leads to the corresponding 1,4-disubstituted-1,2,3-triazole and the NHC-Cu-OAc complex **24**.

Gray has synthesized a family of stable gold(I) 1,4-disubstituted-1,2,3-triazolide complexes (e.g., **26**) in moderate to good yields using the copper(I)-catalyzed [3+2] cycloaddition reaction of gold(I) alkynyls with benzyl azide [24]. The reaction protocol tolerated a broad range of functionalities on the alkynyl moiety, and the resulting complexes were air and water stable. The gold(I)-1,2,3-triazolide

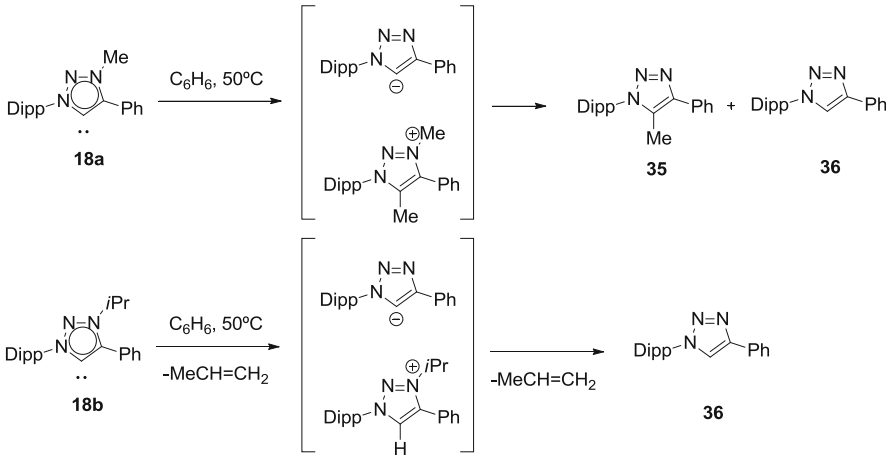


Scheme 10 Triazolylidene metal complexes by alkylation of metal triazolide precursors

complexes of the type **26** were luminescent and displayed both singlet- and triplet-state emissions. Neither the copper complexes **25** nor the gold complexes **26** were submitted to *N*-alkylation to prepare the corresponding MIC complexes. In contrast, Miguel and coworkers have reported the first example of the preparation of a triazolylidene complex **29** taking advantage of a remarkable CuAAC reaction between phenylacetylene and the azide **27**, which involved a spontaneous copper to rhenium transmetallation during the formation of the triazolide anion complex **28** [25]. Selective *N*-alkylation of the triazole ring in **28** with Me_3OBF_4 afforded the MIC complex **29**.

Gandelman and coworkers have taken advantage of the particular chelating ability of triazole pincer ligands **30** to promote their facile C5 metallation using tertiary amine bases and suitable palladium(II) and platinum(II) complexes, avoiding in this way the in situ preparation of the 1,2,3-triazolide core with a CuAAC reaction from alkynes and azides (Scheme 10) [10, 26–28].

Triazolide *N*-alkylation of **31a** and **33b** with methyl iodide and *p*-trifluoromethylbenzyl bromide, respectively, led to the formation of the triazolylidene carbenes **32a** and **34b** in 92% and 73% yields. Both complexes showed a square-planar geometry around the Pd(II) and Pt(II) metals as ascertained from their X-ray crystal structures. Furthermore, the C5–Pd bond length shortened from 1.929 Å in **31a** to 1.902 Å in **32a**, indicating the increased contribution of carbene character of this bond. ^{195}Pt NMR also proved useful in observing changes in the electronic environment of the platinum center. Alkylated cationic complex **34b** exhibited a double doublet-platinum resonance due to its coupling to two nonsymmetric phosphines at $\delta = -4{,}347$ ppm. This was an effective upfield shift of approximately 100 ppm relative to starting neutral complex **33b**.



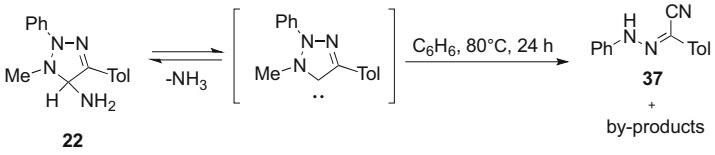
Scheme 11 Thermal decomposition of 3-alkyl-1,4-diaryltriazolylidenes

3 Stability and Reactivity of Metal Triazolylidene Complexes

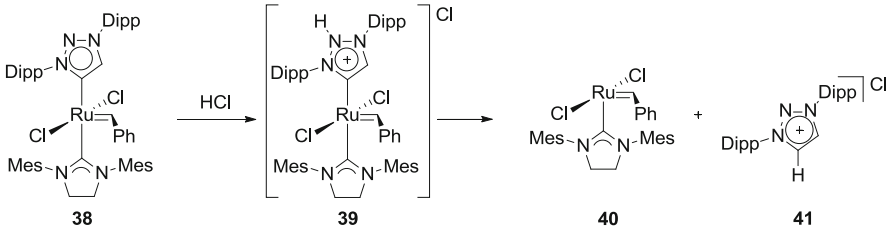
This section covers the transformations of free 1,2,3-triazole carbenes and/or their metal complexes into noncarbene compounds. Related transformation preserving the C5–M carbene metal bond, such as ligand exchange reactions or cyclometallation reactions, is covered in Sect. 5.

3.1 Thermal Stability of Free Triazolylidenes

Thermal stability of free triazole carbenes is strongly dependent on the steric bulkiness of the ring substituents [2, 3]. For example, in the solid state, with the exclusion of oxygen and moisture, free 3-methyl-1,2,3-triazol-5-ylidene **18a** (m.p. 50–52°C) remained stable for several days at −30°C and for a few hours at room temperature (Scheme 11). By contrast, **18b** (m.p. 110–112°C), bearing a bulkier N3-isopropyl substituent, was significantly more stable showing no sign of decomposition after 3 days at room temperature in the solid state. Upon heating in a benzene solution for 12 h at 50°C, **18a** decomposed to give a mixture of the C5-methylated triazole **35** and the protonated analog **36**. The methylated product **35** could result from a nucleophilic attack of the carbon lone pair of **18a** on the methyl group of a second molecule of **18a**. In agreement with this hypothesis, MIC **18b**, which contains the less-electrophilic isopropyl group at the N3 position, would give a propylene elimination reaction to provide only compound **36**.



Scheme 12 Thermal decomposition of 1,2,4-trisubstituted ammonia-triazolylidene adduct 22



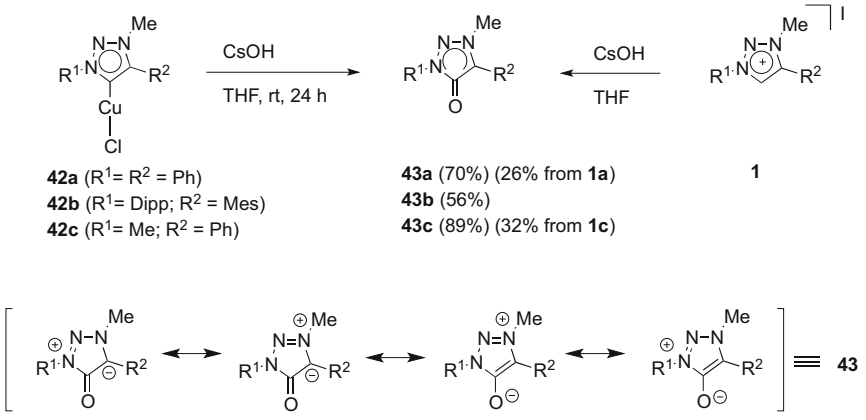
Scheme 13 Protonolysis of a mixed ruthenium(II) triazole(MIC)-imidazole(NHC) complex

Analogous nonmesoionic 1,2,4-trisubstituted free carbenes are less stable than their mesoionic 1,2,3-substituted triazolylidene counterparts and cannot be isolated. However, their ammonia-carbene adducts (e.g., **22**) were stable in C_6D_6 solution for days at room temperature and slowly decomposed only when heated to 80°C for 24 h (Scheme 12). Hydrazonoyl cyanide **37** could be isolated from the resulting mixture. Interestingly, the methyl group was absent in **37**, suggesting intermediate carbene formation and subsequent alkyl rearrangement [22].

3.2 Protonolysis of Triazolylidene Complexes

Triazolylidene–metal bonds (C5-M) have been reported to be stable under acidic conditions. For example, palladium complexes **2f–g** (see Scheme 2) survived the exposure to HI for several days without any degradation [11]. Likewise, the iridium complexes **82** (see Scheme 36, Sect. 5.2) tolerated aqueous 1 M HCl for several days [29].

Grubbs and Bertrand have studied the Brønsted acid-promoted protonolysis of the ruthenium complex **38** containing an unhindered 5H-unsubstituted triazolylidene (MIC) and an *N*-heterocyclic carbene (NHC) (Scheme 13) [30]. The cleavage of the Ru–MIC bond was observed to generate an extremely active metathesis catalyst **40** and the triazolium salt **41**, demonstrating that a MIC ligand may act as a leaving group, allowing an otherwise inactive complex **38** to enter the metathesis catalytic cycle. Previously reported density functional theory calculations suggest that N2 nitrogen atom on the MIC ligand **38** has the second-highest proton affinity after the carbene itself [3]. Thus, it is likely that protonolysis could involve the triazolium salt **39**.



Scheme 14 Oxidative transformation of copper(I) triazolylidene complexes

3.3 Oxidation

The only example of the oxidative transformation of triazole carbenes to mesoionic sydnone analog compounds **43** has been reported by Albrecht, starting from the corresponding triazolylidene cuprous salts **42** and CsOH (Scheme 14) [31]. Identical products are formed while treating the triazolium salts **1** with the same hydroxide, albeit in lower yields and contaminated with minor amounts of the de-methylated triazoles. The reaction from the copper complex presumably occurs via reductive carbene hydroxide elimination from a putative [Cu(triazolylidene)OH] intermediate.

The synthetic methodology is remarkably general and provides facile access to a wide range of mesoionic compounds that have potential in their own right, e.g., as new structural motifs in active pharmacological ingredients and also as a new class of ligands with a high degree of electronic flexibility.

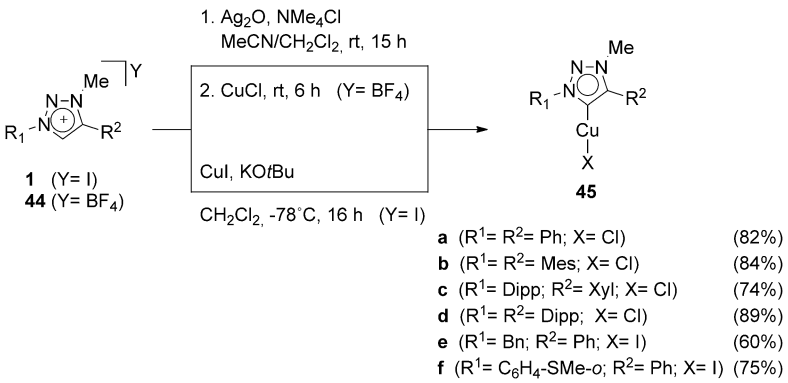
The next Sects. (4)–(8) collect the synthesis, main structural details, and chemical applications of the different triazolylidene metal complexes **A**–**J** (Fig. 2) classified following the different transition metal groups.

4 Monodentate 1,2,3-Triazolylidene Complexes

4.1 Monocarbene Complexes (Type A)

4.1.1 Copper

Fukuzawa and coworkers have described the first synthesis of copper complexes **45a**–**d** bearing a 1,2,3-triazole carbene ligand [32, 33]. Simultaneously, Sarkar prepared copper complexes **45e**–**f** in a different way [21]. Complexes **45** are



Scheme 15 Synthesis of monodentate copper(I) triazolylidene complexes

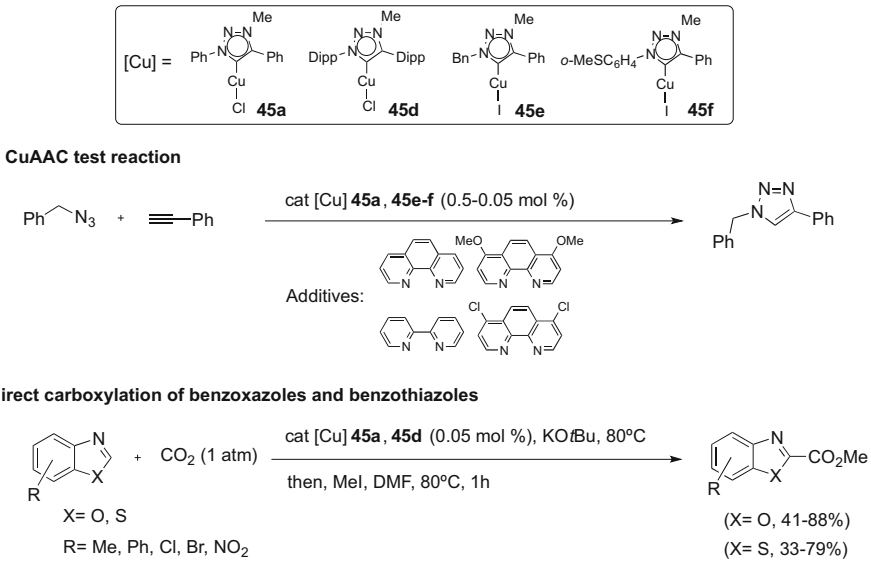
versatile catalysts for the CuAAC "click" cycloaddition of a wide range of alkynes and azides and for the direct carboxylation of benzoxazoles and benzothiazoles.

The air-Stable 1,2,3-triazol-5-ylidene-copper(I) complexes **45a–d** were obtained treating the corresponding triazolium tetrafluoroborate salts **44** with Ag_2O and tetramethylammonium chloride, followed by transmetallation with CuCl at room temperature. Complexes **45e–f**, on the other hand, were prepared by direct deprotonation-metallation of the triazolium iodide salts **1** with KO*t*Bu and CuI at low temperature (Scheme 15).

Cuprous triazolylidene complexes **45** showed characteristic signals attributable to the metal-bonded carbene carbon around 160–170 ppm in the ^{13}C NMR spectrum. X-ray analysis of a single crystal of complex **45c** showed that bond distance and angles were similar to those in the previously reported copper imidazole carbene complex Cu(ImPr)Cl [34]. The C-Cu-Cl and C-Cu-I angles in **45c** and **45f** were linear and the Cu–Cl and Cu–I bond lengths were 2.115(15) Å and 2.236(2) Å, respectively. Lastly, the C–Cu bond lengths for **45c** and **45f** were 1.879(5) Å and 1.89(1) Å, respectively.

Triazolylidene complexes **45** acted as efficient catalysts for azide-alkyne [3+2] cycloaddition reactions at very low loads of catalyst (typically 0.5–0.05 mol%) (Scheme 16) [32].

Functional groups such as alcohols, esters, and pyridines were well tolerated, while primary amines containing alkynes were not coupled efficiently and produced mixtures. The best of the series, complex **45a**, was more active than 2-imidazolylidene copper analogs in a test reaction and performed well in reactions where classical catalysts tend to fail. For example, the coupling of sterically bulky alkynes with bulky azides (e.g., Dipp-CCH with Dipp-N_3) proceeded with high conversion, albeit after long reaction times (18 h). Gautier and coworkers have reported that the scope of the Cu(I) (MIC) catalysts **45a–f** can be extended by adding aromatic *N*-donor ligands such as 1,10-phenanthroline or 4,7-dichloro-1,10-phenanthroline [35]. Using the latter additive, the solubility of the catalyst was



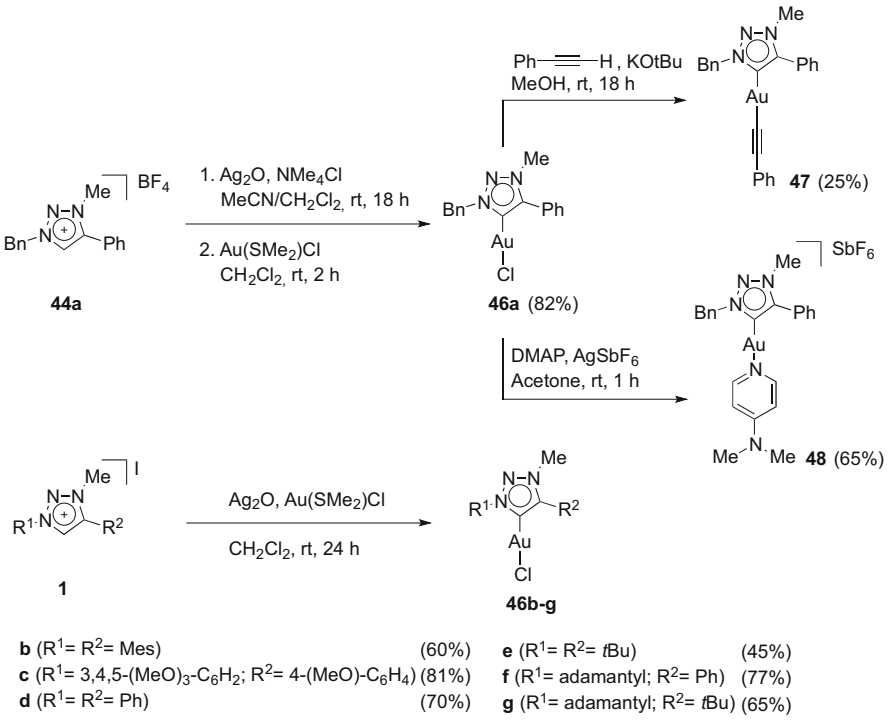
Scheme 16 CuAAC and direct carboxylation reactions catalyzed with copper(I) MIC complexes

improved in various solvents and the cycloaddition rate increased dramatically. Fukuzawa also performed the direct transformation of benzoxazoles and benzothiazoles into the corresponding 2-methoxycarbonyl heterocycles using carbon dioxide as the electrophile under low loads of copper triazolylidene complexes **45a** and **45d**. The same author developed a similar method for the C-thiolation of benzothiazoles and benzoxazoles with thiophenols and alkylthiols [36].

4.1.2 Gold

Crowley and coworkers have prepared several triazolylidene gold complexes and have demonstrated their usefulness as highly active catalyst precursors for carbene insertion and cyclization reactions [37]. For example, the triazolium salt **44a** was readily metallated with Ag_2O and transmetallated with $Au(SMe_2)Cl$ to provide the gold(I) 1,2,3-triazolylidene chloride complex **46a** in 82% yield. The chloride anion of **46a** could be replaced by other ligands to give the neutral phenylacetylide **47** or the cationic *N*,*N*′-dimethylaminopyridine complex **48** (Scheme 17). In a similar development Albrecht prepared the gold(I) triazolylidene complexes **46b–g** starting from triazolium iodides **1** rather than tetrafluoroborate salts, avoiding the use of alkylammonium salt additives [38]. Complex **46a** was air and moisture stable in solution and in the solid state.

Gold(I) 1,2,3-triazolylidene complexes **46–48** showed typical chemical shifts of the carbene carbons between δ_C 174 and 155 ppm in the ^{13}C NMR spectra, similar to other reported 1,2,3-triazolylidene metal carbenes, but significantly lower than



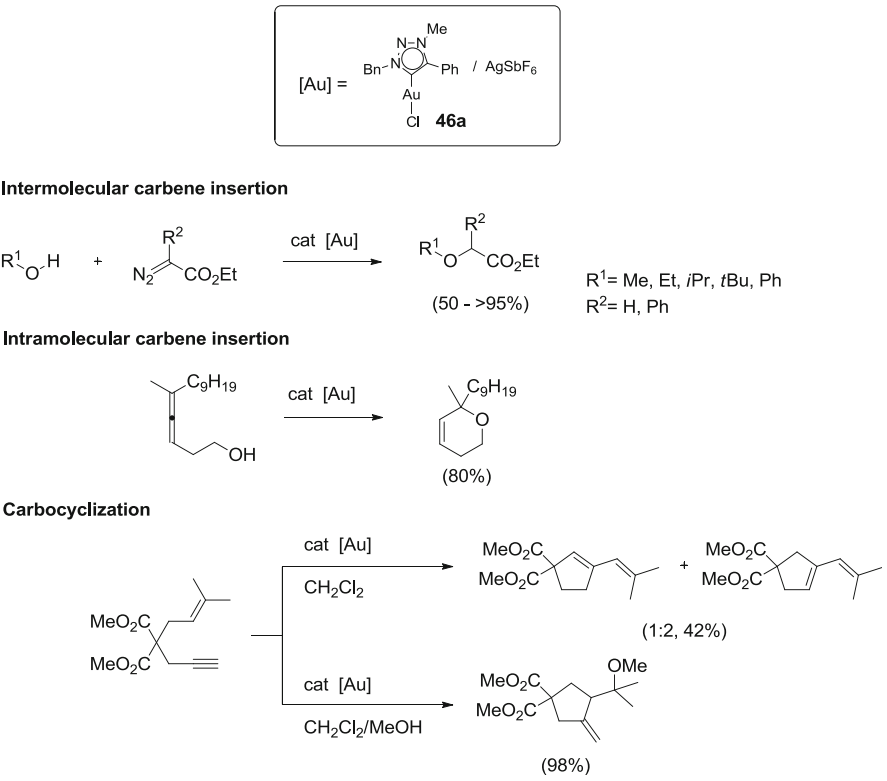
Scheme 17 1,3,4-Trisubstituted gold(I) triazolylidene complexes

those observed for previously reported gold(I) imidazole carbene complexes [39, 40]. X-ray crystal structure of **46**–**48** showed gold(I) ions coordinated in a linear fashion with L–Au–C bond angles ranging from 173.6° to 177.2°. The Au–C and Au–L bond lengths were similar to those reported for other gold(I) imidazole carbene complexes [39–42].

Triazolylidene gold complex **46a** precatalyst in combination with $AgSbF_6$ was a highly active catalyst for carbene insertion and cyclization reactions (Scheme 18).

For example, the cationic auric catalyst generated in situ from **46a** promoted the insertion of the carbene derived from α-azidoesters into O–H bonds of primary, secondary, and tertiary alcohols. Insertion into phenolic O–H bonds or into N–H bond of aniline was less efficient. Likewise, using larger carbene precursors than ethyl diazoacetate (e.g., ethyl α-diazophenylacetate) was not clean, though still feasible. Similar intramolecular insertion reactions were also catalyzed by the complex **46a**/$AgSbF_6$ system when using allenes instead of diazo precursors of carbene. Finally, the carbocyclization of enynes has also been demonstrated using the same catalyst.

Kühn and coworkers have synthesized a series of gold(I) complexes coordinated to "normal" 1,2,3-triazolylidene ligands and examined their feasibility in catalysis (Scheme 19). Accordingly, chloride complexes **50** were prepared using the

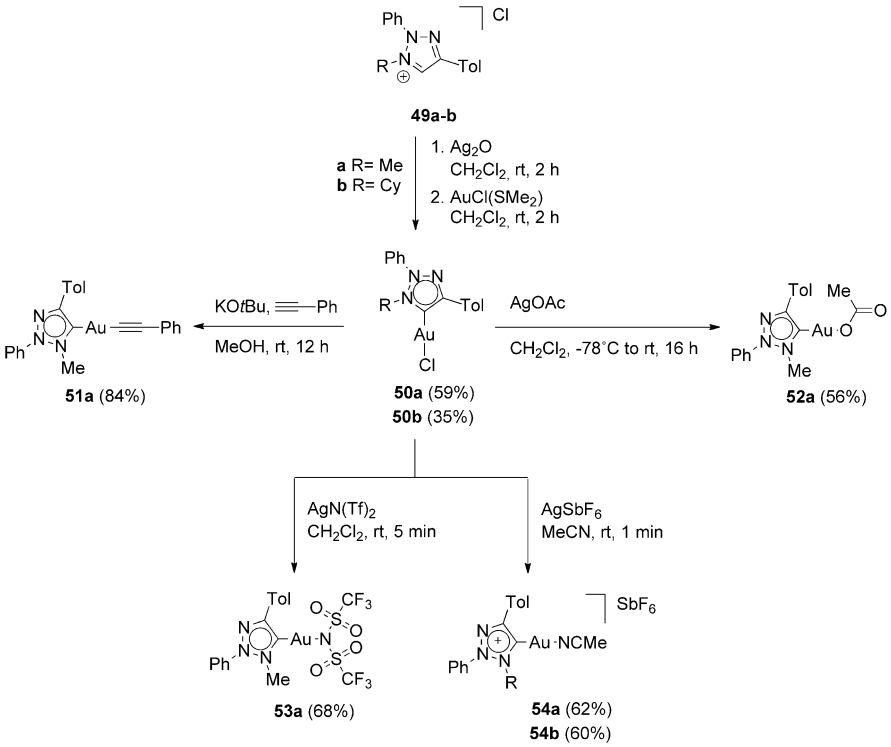


Scheme 18 Gold(I) triazolylidene-catalyzed carbene insertion and carbocyclization reactions

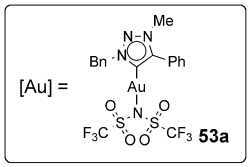
transmetallation procedure from the triazolium salts **49** [43]. Different gold(I) compounds **51**–**54** with a variety of ligands were synthesized in order to avoid the use of silver salt additives for halide dissociation during catalysis.

The X-ray crystal structure of **50a** showed in the unit cell a close Au-Au contact of 3.499 Å, which is well within the range of typical aurophilic interactions [44]. The Au–Cl bond length of **50a** was 2.290(1) Å, comparable to bond lengths observed in the related triazolylidene compound of Lee and Crowley (2.2940(10) Å), in [Au(ImPr)Cl] (2.2698(11) Å), or in [Au(ImCy)Cl] (2.306(3) Å, 2.281(3) Å) described by Nolan [45].

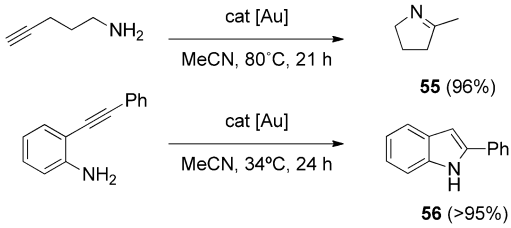
Complexes **50**–**51** were air and moisture stable, compounds **52**–**53** were stable for hours under similar conditions, and complexes **54a**–**b** appear to be less stable, but were storable in the solid under argon at low temperature. All synthesized compounds **50**–**54** were screened as catalysts for the hydroamination of 4-pentyn-1-amine, to yield the ring-closing product **55** (Scheme 20). The catalyst **51a** turned out to be the least active, followed by complexes **50b**, **52a**, and **50a**. Better-performing precatalysts contained more labile substituents, such as acetonitrile (**54a**–**b**) and, especially, triflamide **53a** which catalyzed the formation of the



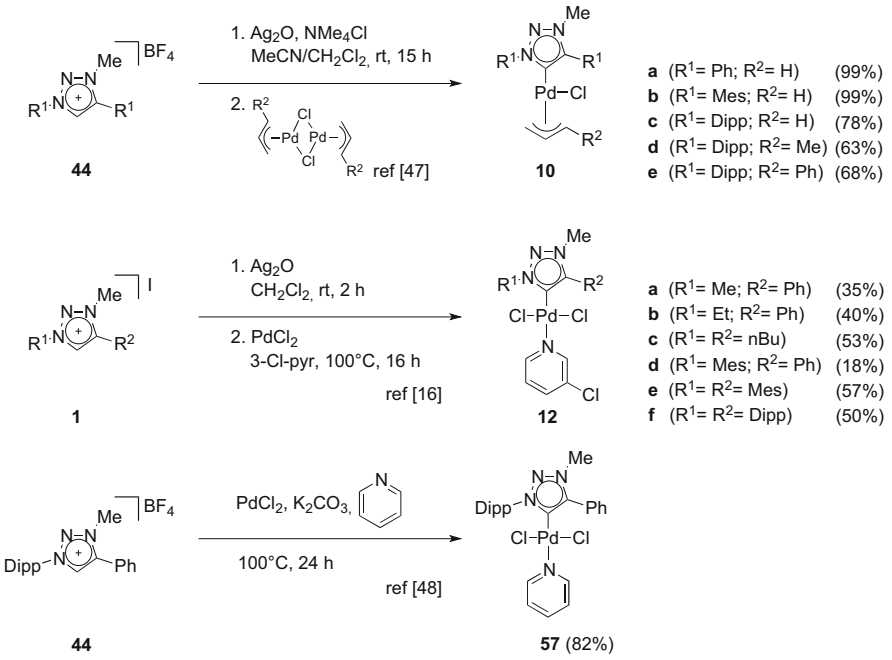
Scheme 19 Synthesis of gold(I) 1,2,4-substituted triazolylidene complexes



Intramolecular hydroamination of alkyne-amines



Scheme 20 Gold(I) triazolylidene-catalyzed dehydroamination of alkyne amines



Scheme 21 Synthesis of palladium(II) triazolylidene complexes

aliphatic ring-closing imine **55** in a 96% yield after 21 h in refluxing acetonitrile. Triazolylidene complex **53a** also catalyzed the hydroamination reaction of 2-(2-phenylethynyl)aniline containing an internal alkyne to the indole **56** in virtually quantitative yield at room temperature. Compounds **54** seemed at first most promising for catalysis applications due to their rather labile acetonitrile substituent, but in practice they were much less active than complex **53a**.

4.1.3 Palladium

Palladium currently enjoys preeminent status in cross-coupling reactions. Hence, it is not surprising that many triazolylidene palladium complexes have been investigated as catalyst precursors for Suzuki–Miyaura cross-coupling. In particular, the superior donor ability of triazolylidenes compared to phosphines and imidazole carbenes was expected to improve the aryl halide insertion to palladium(0) intermediates, in less reactive aryl chlorides. Several monodentate monomeric MIC-palladium complexes prepared to this end are shown in Scheme 21.

Fukuzawa and coworkers [46] have prepared Pd(II) monotriazolylidene complexes **10** considering to be more preferable active catalysts than the bis (triazolylidene)metal complex analogs. Complexes **10a–e** were prepared following

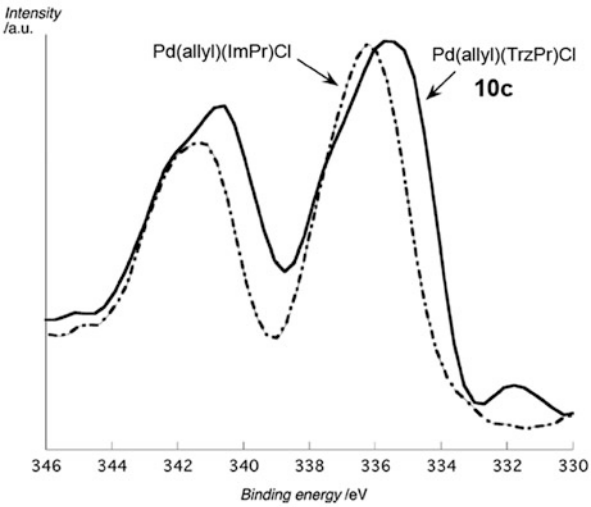
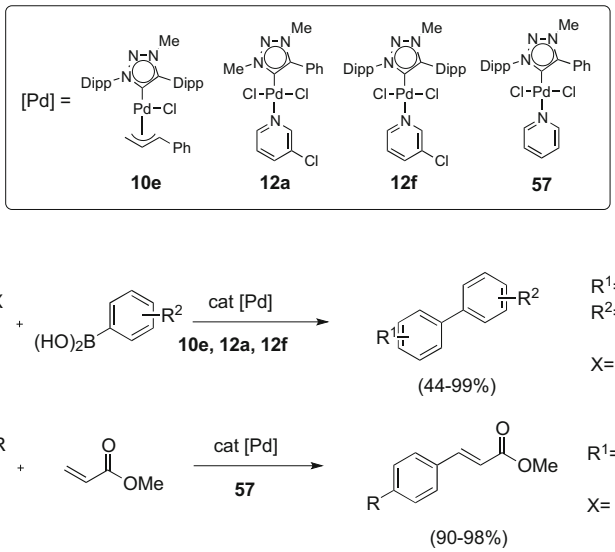


Fig. 4 XPS spectra (palladium 3d level) for **10c** (*solid line*) and (allyl)(ImPr)PdCl. Figure partially reprinted from [46], © 2013 VCH

the transmetallation procedure with Ag_2O and $[Pd(allyl)Cl]_2$ in CH_2Cl_2 at room temperature. Concomitantly, and inspired by the PEPPSI concept (pyridine-enhanced precatalyst preparation, stabilization, and initiation), Albrecht [16] synthesized the complexes **12** containing an easily cleavable 3-chloropyridine ligand by metallation of the triazole iodide salts **1** with Ag_2O and subsequent transpalladation in 3-chloropyridine as the solvent. The PEPPSI-type palladium complexes **12** were air- and moisture-stable solids. Finally, Crudden [47] synthesized the complex **57** by direct deprotonation-metallation of the triazolium tetrafluoroborate salt **44** with $PdCl_2$ in pyridine in the presence of potassium carbonate.

The strong donor properties of the triazole carbenes **10** were confirmed by X-ray photoelectron spectroscopy (XPS) (Fig. 4) [48, 49]. A comparison between the triazole carbene complex **10c** and a complex sterically identical to the imidazole complex, e.g., Pd(allyl)(ImPr)Cl, showed that the Pd 3d electron-binding energies in the former were 0.5 eV less than those in the latter [**10c**: 335.7 eV; Pd (allyl)(ImPr)Cl: 336.2 eV] indicating that the triazole carbene was a stronger donor than the imidazole analog.

Complexes **12b–d** were analyzed by single-crystal X-ray diffraction. In all instances, the ligands around the square-planar palladium center adopted the expected *trans* arrangement. The (MIC)C5-Pd bond length in all complexes was 1.96(1) Å, which is in line with those of related triazolylidene palladium complexes. The pyridine N–Pd bond length was weakly affected by the substitution pattern on the triazolylidene ligand and increased slightly in the series **12b**<**12c**<**12d**. The most pronounced distinction between the three complexes pertains to the different twist angle of the heterocycles out of the palladium coordination plane, with an almost perpendicular arrangement in **12d**, probably a direct consequence of the shielding properties of the *ortho*-methyl groups of the



Scheme 22 Palladium(II) triazolylidene catalysts for Suzuki–Miyaura and Heck reactions

mesityl substituent. Finally, in the X-ray structure of complex **57** were observed several weak noncovalent C-H-Cl interactions occurring between one of the Pd-bound chlorine atoms and the *meta*-hydrogen of the pyridine of a neighboring molecule.

Complexes **10** and **12** have been investigated as Suzuki–Miyaura reaction catalysts (Scheme 22). Complex **10e**, containing Dipp wingtip groups and featuring a cinnamyl ligand, yielded the most active catalytic system. This complex showed high activity in the room temperature reaction with aryl chlorides; regardless of the electronic and steric properties of the substituents, it was effective in the reaction with sterically crowded arylboronic acids, and, furthermore, the reaction could be carried out with a low catalyst load (1–0.1 mol%). Sterically less demanding catalyst **12a**, on the other hand, gave moderate yields only with aryl bromides, whereas aryl chlorides led to conversions not exceeding 60%. Besides, the reaction outcome was very sensitive to the temperature due to the formation of heterogeneous Pd(0) colloids. Hong succeeded to alleviate this problem by using the more hindered catalyst **12f** [50]. The Heck reaction was finally screened for catalyst **57** to give aryl-substituted cinnamates from aryl bromides or iodides and methyl acrylate in excellent yields, following a heterogeneous reaction pathway.

Mechanistic studies conducted to compare precatalysts **12a** and **12b** using mass spectrometry (MS) and transmission electron microscopy (TEM) have revealed the formation of ligand-free Pd(0) clusters and particles in the 3–5 nm range under catalytic conditions, suggesting a heterogeneous process (Fig. 5) [16]. Formation of colloidal palladium may further explain the delicate role of the temperature, since

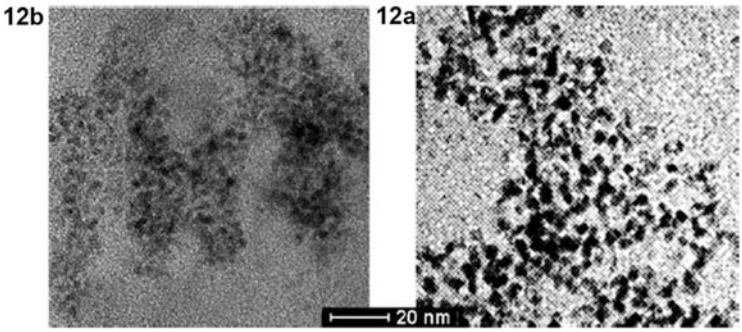
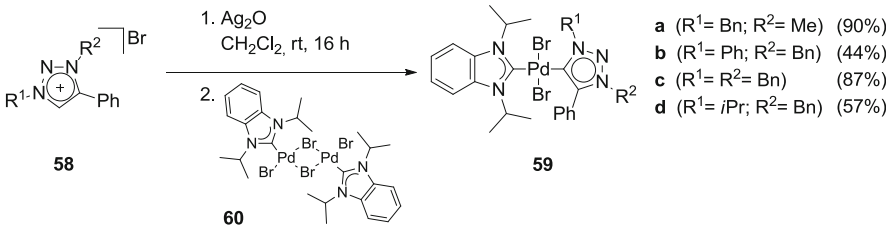


Fig. 5 TEM micrographs of post-reaction mixtures after the Suzuki–Miyaura reaction with **12b** and bromoanisole and **12a** and chlorobenzaldehyde. Figure partially reprinted from [15] © 2012 VCH



Scheme 23 Synthesis of palladium(II) (NHC)-/(MIC)-mixed complexes

elevated temperatures accelerated colloid formation and eventually led to aggregation into large particles that cannot easily expel a palladium atom.

Some palladium(II) imidazole-triazole hetero-bis(carbene) complexes **59** have been designed and prepared by Huynh and coworkers to introduce a new method that employs a ^{13}C NMR spectroscopic evaluation of the relative donating ability of the triazole carbene ligand [51]. One-pot bridge-cleavage reactions of the dimeric benzimidazole complex **60** with two equivalents of triazole ligand precursor **58** and 1.2 equiv. of Ag_2O in CH_2Cl_2 yielded the desired hetero-bis(carbene) complexes **59** (Scheme 23).

In the ^{13}C NMR spectra of complexes **59a–d**, two carbene signals were observed as expected. The downfield signals ranging from 180.3 to 181.2 ppm were assigned to the imidazole carbene, whereas those ranging from 157.9 to 160.6 ppm were attributed to the 1,2,3-triazole-derived carbenes. It was empirically found that the ^{13}C carbenoid signal of the constant benzimidazole probe was sensitive to the transoid ligand L, whereby stronger donating ligands would lead to a more downfield shift [52–55]. An extension of this methodology to other ligand systems is shown in Fig. 6. A closer inspection of the *i*Pr_2-bimy chemical shifts among the four triazolylidene complexes **59a–d** revealed increasing downfield shifts in the order **59b** (180.3 ppm) < **59a**/**59c** (180.8 ppm) < **59d** (181.2 ppm), reflecting a stepwise

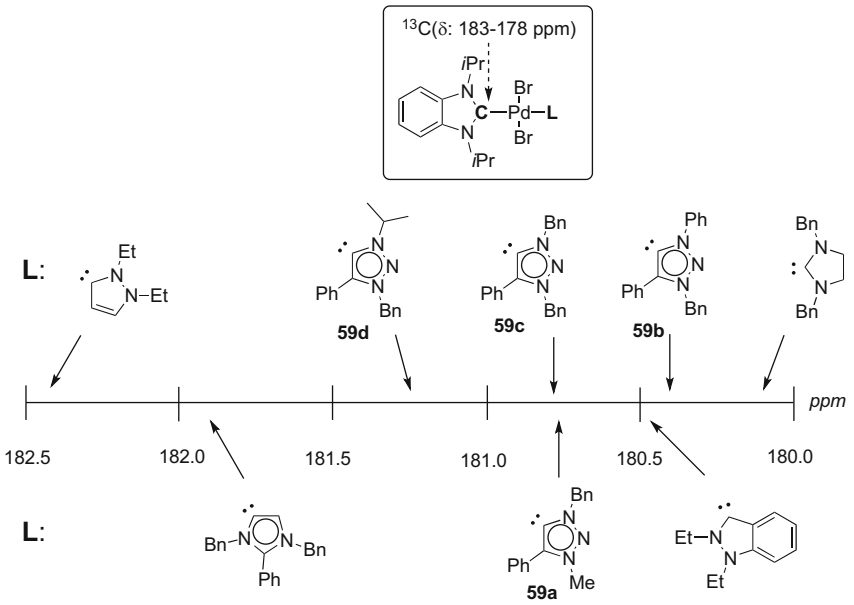


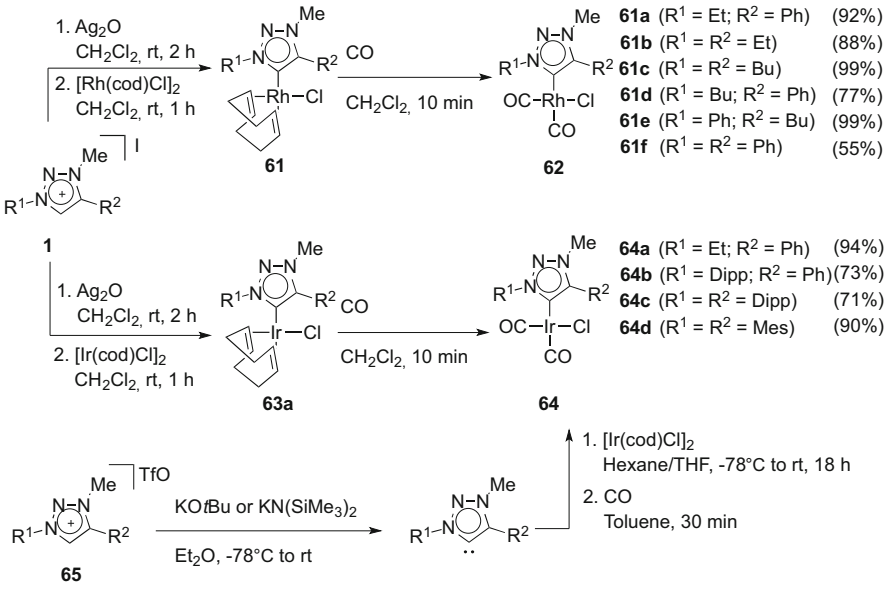
Fig. 6 Evaluation of the increasing donating ability of carbene ligands L by downfield shift of the benzimidazole carbene ^{13}C NMR signal (shown in ppm)

increase of the triazolylidene ligands donor ability. Because complexes **59b–d** differ only in the N1 substituent of the triazole ligand, the determined order also correctly reflected the increasing positive inductive effects of the groups Ph < Bn < *i*Pr. It must be highlighted that the lower sensitivity of common IR-based methodologies is not sufficient to discern electronic influences brought about by different substituents.

Finally, the mixed triazolylidene benzimidazolylidene complexes **59** were also used as precatalysts for the arylation of pentafluorobenzene with aryl bromides by direct C–H bond activation. The catalytic activity was higher at low catalyst loading (1–0.5%) than with higher concentrations of **59**. This behavior, together with the rather high operation temperature (120°C) and the incidental observation of palladium black, pointed to a possibly heterogeneous mechanism as established for the PEPPSI-type triazolylidene complexes **12** and **57**.

4.1.4 Rhodium and Iridium

Albrecht and coworkers [9, 11] have prepared several rhodium complexes **61–62** in order to evaluate the donating ability of triazolylidene ligands, first by NMR spectroscopy due to the $I = 1/2$ spin of ^{103}Rh and second by measuring the CO stretch vibration in the corresponding rhodium carbonyl complexes (translating into



Scheme 24 Carbonylation reaction of (cod) ligands in rhodium(I) and iridium(I) triazolylidene complexes

Tolman electronic parameters, TEPs). Accordingly, the rhodium complexes **61** were prepared using classical transmetallation procedures involving Ag_2O as a basic silver salt and $[Rh(cod)Cl]_2$ as transmetallating agent (Scheme 24). Exposure of complexes **61** to a CO-saturated environment afforded the corresponding carbonyl analogs **62** in essentially quantitative yield [56, 57]. Twin iridium complexes **64** were also prepared in high yields using either the transmetallation procedure (**64a**) [2] or the free carbene trapping method for aryl-substituted complexes (**64b–d**) [9, 46].

The ^{13}C NMR chemical shift of the rhodium-bound triazolylidene carbon showed an apparent correlation with the nature of the wingtip group [11]. With alkyl wingtip groups, the doublet ($^1J_{RhC} = 46.5 \pm 3$ Hz for all complexes) appeared at highest field (δ_C 168.5 and 168.6 for **61b** and **61c**, respectively), while the presence of one phenyl group as in **61d** and **61e** induced a downfield shift (δ_C 170.4 for both complexes) when considering the $^1J_{RhC}$ coupling constant of rhodium with the *trans*-CO, an increase of $^1J_{RhCO}$ was observed upon reduction the wingtip donating ability.

The CO stretch vibrations occurred in the IR spectrum at 1,983 and 2,065 cm^{-1} for all complexes **62** except for **62f** (ν_{CO} = 1,988 and 2,068 cm^{-1}). Depending on the applied linear regression [58, 59], these values translated into a TEP in the range 2,035–2,042 cm^{-1}. Because of the identical CO absorption energies, the calculated TEPs for the triazolylidene ligands in complexes **62b–e** were obviously the same,

which may indicate some limitation of this method for evaluating ligand donor properties [60–62]. TEP variations recorded for iridium-triazolylidene complexes **64** followed essentially the same trend of their rhodium analogs **62** [46].

4.1.5 Ruthenium

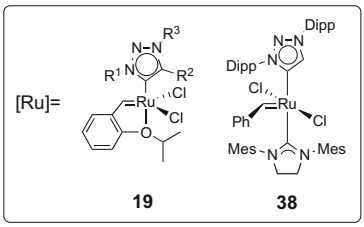
Bertrand and Grubbs have explored various triazolylidene ruthenium complexes (e.g., **19** and **38**) in olefin metathesis [3, 30]. The complexes were prepared as described in Scheme 6 (Sect. 2.3) starting from robust N1,N3,C4-triarylated or N1, N3-diarylated triazolium salts [2, 63]. The stability of triazolylidene ruthenium complexes to oxidative conditions was of utmost importance to design effective catalysts for olefin metathesis and oxidation reactions. Related complexes with an alkyl substituent at N3 have been noted to be unstable, and, for this reason, polyarylated triazole carbene ligands are strongly preferred.

Complexes **19c** and **19f** were characterized by single-crystal X-ray diffraction and their characteristic bond lengths were very similar to the analogs Grubbs' second-generation imidazole catalyst. For instance, the carbene–Ru bond length (1.99 Å versus 1.98 Å in the imidazole complex), the benzylidene C–Ru bond length (1.82 Å versus 1.82 Å), and the O–Ru bond length (2.27 Å versus 2.26 Å) were largely conserved across the three species. Notably, the smaller aryl substituent (on C4 in **19c** and N1 in **19f**) is positioned above the Cl-Ru-Cl plane in order to minimize steric interactions with the chloride ligands, while the larger substituent is positioned above the benzylidene group.

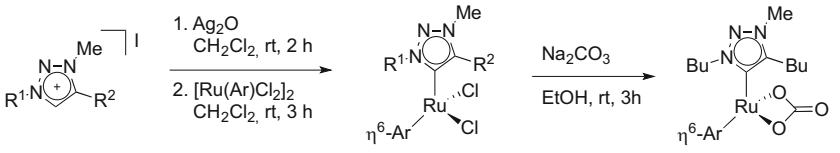
All complexes **19** except **19f** displayed high activity in ring-opening metathesis polymerization (ROMP) of cyclooctadiene (Scheme 25). Kinetic studies indicated that catalyst **19d** performed very efficiently with similar activity to the Grubbs' second-generation catalyst (GII). Ring-closing metathesis (RCM) followed related trends. Complex **19f** was essentially inactive, while **c**omplex **19j** performed best and displayed fast initiation as well as catalytic activity similar to GII. Interestingly, metathesis screens revealed that **38** was completely inactive, but acidolysis of the Ru–triazolylidene bond was demonstrated to yield a highly active Ru(NHC) species (see Sect. 3.2), which catalyzed the RCM reaction of test dienes to reach 100% conversion within a few minutes.

Ruthenium NHC carbene complexes designed to catalyze dehydrogenative oxidation of alcohols and amines have been usefully applied to the preparation of carbonyl compounds, imines, and amides [64, 65]. The new ruthenium(II) triazolylidene complexes **66** and **67** bearing η^6-arene ligands were prepared by Albrecht [66, 67] according to the established transmetallation and halogen ligand exchange protocols from the corresponding triazolium salt **1d** (Scheme 26).

Both complexes **66** and **67** were checked as catalysts precursors for the dehydrogenative oxidation of alcohols and amines (Scheme 27). Primary and secondary benzylic alcohols were readily oxidized in refluxing toluene with 5 mol% catalyst **66b**, though electron-withdrawing substituents needed longer



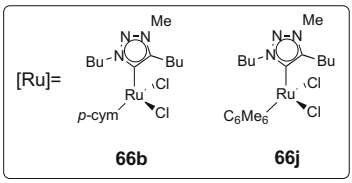
Scheme 25 Ruthenium(II) triazolylidene catalysts for olefin metathesis reactions



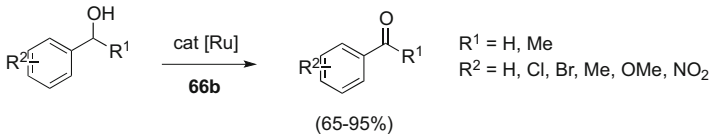
a (R^1= Et; R^2= Bu; η^6-Ar= *p*-cym) (83%)
b (R^1= Bu; R^2 = Bu; η^6-Ar= *p*-cym) (71%)
c (R^1= Hex; R^2= Hex; η^6-Ar= *p*-cym) (74%)
d (R^1= Me ; R^2= Ph; η^6-Ar= *p*-cym) (40%)
e (R^1= Et; R^2= Ph; η^6-Ar= *p*-cym) (85%)
f (R^1= Bu; R^2= Ph; η^6-Ar= *p*-cym) (99%)
g (R^1= Bu; R^2= Mes; η^6-Ar= *p*-cym) (72%)
h (R^1= Mes; R^2= Ph; η^6-Ar= *p*-cym) (70%)
i (R^1= Mes; R^2= Mes; η^6-Ar= *p*-cym) (77%)
j (R^1= ; R^2= ; η^6-Ar= C_6Me_6) (62%)

Scheme 26 Synthesis of ruthenium(II) η^6-arene triazolylidene complexes

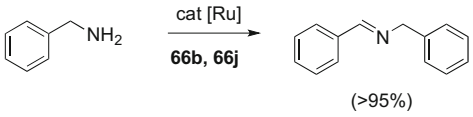
reaction times. Aliphatic alcohols such as 2-phenylethanol and 1-octanol were poor substrates. The oxidation of benzylic amines generated homocoupled imines due to condensation of the initially formed imine with residual amine. Slightly higher reaction temperatures (150°C) were needed than for the analogous alcohol oxidation. When alcohol and amine oxidation were combined, amides were formed in the presence of a base. For instance, reaction of benzyl alcohol with benzylamine in the presence of a catalytic amount of **66b** and NaH afforded the corresponding *N*-benzyl benzamide.



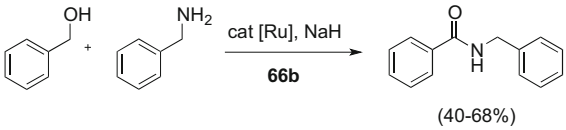
Alcohol dehydrogenation



Oxidative homocoupling of amines



Amide formation from alcohol and amines

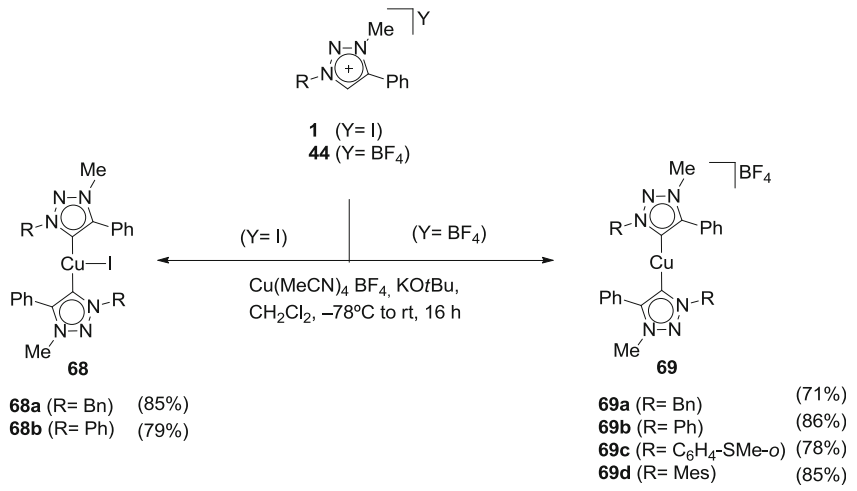


Scheme 27 Ruthenium(II) η^6-arene catalysts for dehydrogenative oxidation of alcohols and amines

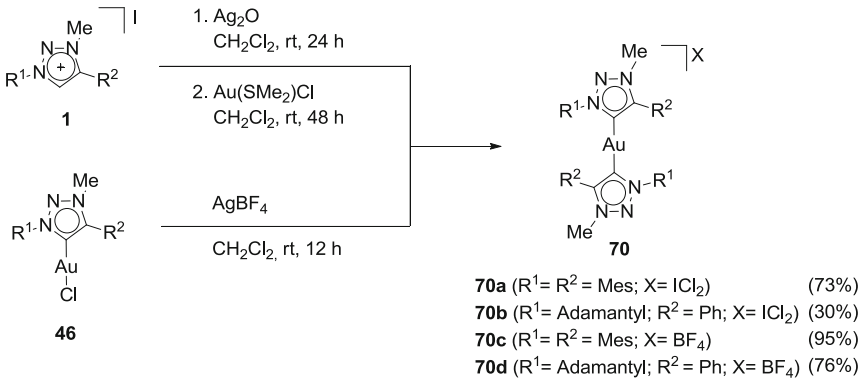
4.2 Dicarbene Complexes (Type B)

4.2.1 Copper

Halide-containing bis(triazolylidene) copper complexes **68** and halide-free congeners **69** could be selectively synthesized as demonstrated by Sarkar (Scheme 28) [68]. Direct metallation of triazolium iodides **1** with $Cu(MeCN)_4BF_4$ in the presence of KO*t*Bu base afforded the halogenated neutral complexes **68** in excellent yields, whereas tetrafluoroborate salts **44** yielded under the same conditions the cationic compounds **69**. The structures of compounds **68a** and **69d** were unequivocally ascertained by X-ray crystallographic analysis. As expected, cationic complexes **69c–d** catalyzed the CuAAC reaction under low loads (0.5 mol%), proving to be clearly superior to the neutral iodinated complexes **68a–b**.



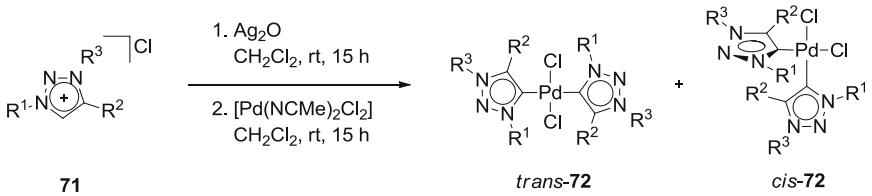
Scheme 28 Synthesis of copper(I) bis(triazolylidene) complexes



Scheme 29 Synthesis of gold(I) bis(triazolylidene) complexes

4.2.2 Gold

Transmetallation of triazolium salts **1** with only 0.5 equiv. of $Au(SMe_2)Cl$ has been demonstrated by Albrecht to provide homoleptic gold(I) biscarbene complexes **70** (Scheme 29) [38]. Alternatively, the same gold complexes were formed by reacting the monodentate complexes **46** with $AgBF_4$. This procedure afforded the bis (carbene) complexes **70** in higher yields. Silver-assisted formation of complexes **70** from **46** implies a carbene transfer from one Au center to another, indicating that the carbene–Au bond is not very strong in the presence of Ag^+ ions and that dissociation is facile. The kinetic lability of the carbene ligand in the triazolylidene



71 *trans*-**72** *cis*-**72**

a (R^1= Et; R^2= Ph; R^3= Me) (96%)
b (R^1= Dipp; R^2= Ph; R^3= Me) (75%)
c (R^1= R^2= Mes; R^3= Me) (98%)
d (R^1= R^2= Ph; R^3= Me) (88%)
e (R^1= Me; R^2= R^3= Ph) (54%)
f (R^1= Me; R^2= Ph; R^3= Bn) (60%)
g (R^1= iPr; R^2= Ph; R^3= Bn) (67%)
h (R^1=  ; R^2= Ph; R^3= Me) (67%)

Scheme 30 Synthesis of palladium(II) bis(triazolylidene) complexes

gold complexes was further demonstrated by mixing **70c** and the gold complex **46f** (see Scheme 17 in Sect. 4.1). Upon addition of $AgBF_4$ (10 mol%), formation of the carbene gold complex **46c** was indicated in 40% by NMR analysis, along with the new heteroleptic gold biscarbene complex [Au(trzMes_2)(trzPh(adam))].

4.2.3 Palladium

Palladium(II) bis(triazolylidene)dichloride complexes **72** can be prepared under appropriate transmetallation conditions without the concomitant formation of dimeric monocarbenes through linear silver biscarbene intermediates (see Sects. 2.1 and 2.2). Starting from diversely substituted chloride triazolium salts **71**, various authors have developed this synthetic route to prepare the mesoionic biscarbene compounds **72** [11, 18, 47, 69–71], including the Sankararaman's first chiral palladium triazolylidene complex **72h** containing a (*S*)-prolinol moiety (Scheme 30) [72]. Mixtures of *cis*/*trans* isomer complexes **72** were formed depending on the triazole substituents. Isomer proportions could be monitored using NMR spectroscopy by assuming that the *trans* configuration is expected to alleviate steric congestion around the metal coordination sphere and may therefore be more easily accessible than *cis* isomers. Dynamic *cis*/*trans* isomerization equilibria were often observed upon heating the mixtures of complexes **72**, and, for example, a *cis*/*trans* isomerization barrier of $\Delta G^{\ddagger} = 70$ kJ mol^{-1} was calculated for complex **72a** using variable temperature NMR spectroscopy. Sankararaman recently reported on the unexpected stabilization of the *cis*-bis(4-hydroxymethyl-1-phenyl-1,2,3-triazolylidene) palladium dichloride complex taking advantage of the hydrogen bonding of the hydroxyl group and the chloride ligands [73].

Complexes **72** showed the Pd center in a distorted square-planar environment as is typical of such compounds and can be illustrated by the X-ray diffraction

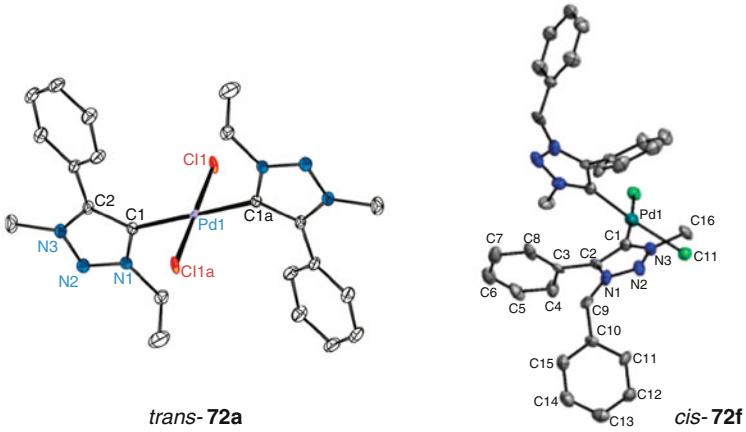
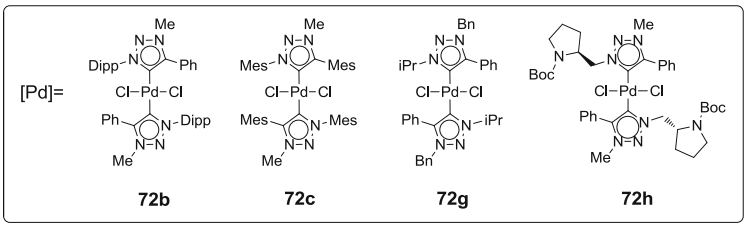


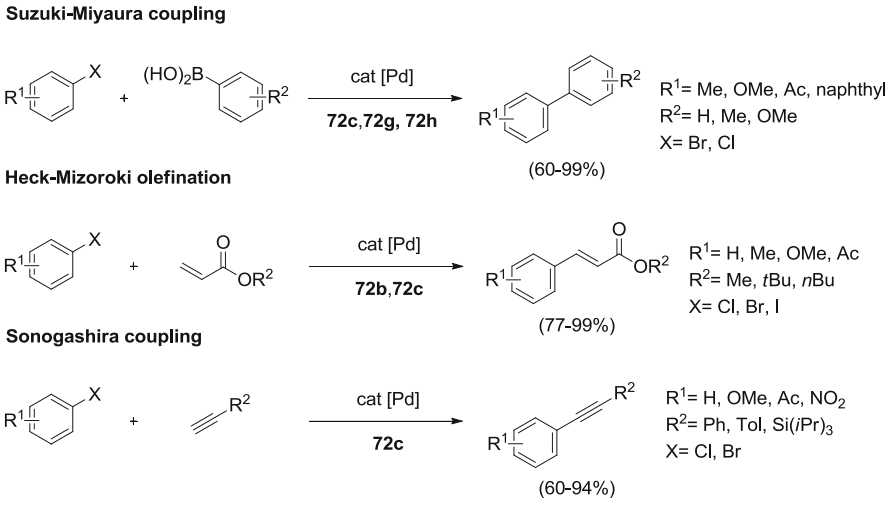
Fig. 7 X-ray structures of palladium(II) bis(triazolylidene) complexes *trans*-**72a** and *cis*-**72f**. Figures partially reprinted from [10] and [70], © 2011 VCH and 2013 RSC

structures of complexes *trans*-**72a** and *cis*-**72f** (Fig. 7). For *trans*-**72a** the Pd–$C_{carbene}$ and Pd–Cl bond lengths were 2.037(3) and 2.3534(8) Å, respectively, and the dihedral angle was 88.8(1), while for *cis*-**72f** the Pd–$C_{carbene}$ and Pd–Cl bond lengths were 1.99(1) and 2.373(3) Å and the angle was 54.0(5).

Palladium(II) biscarbene complexes **72** proved to be very effective for cross-coupling reaction catalysis (Scheme 31). When tested for the Suzuki–Miyaura diarylation reaction, the complexes **72e–g** showed excellent activity with aryl bromide substrates. In each case, yields exceeding 90% were observed within 5 h at room temperature with a catalyst loading of 0.5 mol% in the environmentally benign solvent water. However, with aryl chlorides no product formation was observed under these conditions. Nevertheless, in dry 1,4-dioxane at 120°C and using 1 mol% of the catalyst, yields of about 70% were obtained with **72g** and **72c**. The latter **72c**, which turned out to be the more efficient, catalyzed the Suzuki–Miyaura coupling reaction with aryl and heteroaryl chlorides successfully to give biaryls in excellent yields, particularly for the sterically hindered reaction between *o*-substituted arylchlorides and *o*-substituted phenylboronic acids. Furthermore, it was shown to be very active for multiple Suzuki–Miyaura coupling of polybromoarenes [74].

In an attempt to prepare optically active *ortho*-disubstituted biaryl compounds, Sankararaman observed diaryl formation when using the chiral triazolylidene palladium complex **72h** catalyst for the coupling of different aryl bromides with arylboronic acids. At 75°C and with 2–5 mol% **72h**, activated aryl bromides were converted in high yield over several hours. Unfortunately, sterically more demanding substrates, e.g., naphthyl bromides, were poorly converted with phenylboronic acid and were not cross-coupled to naphthylboronic acid, thus preventing the evaluation of a potential asymmetric induction of the chiral ligand **72h**.

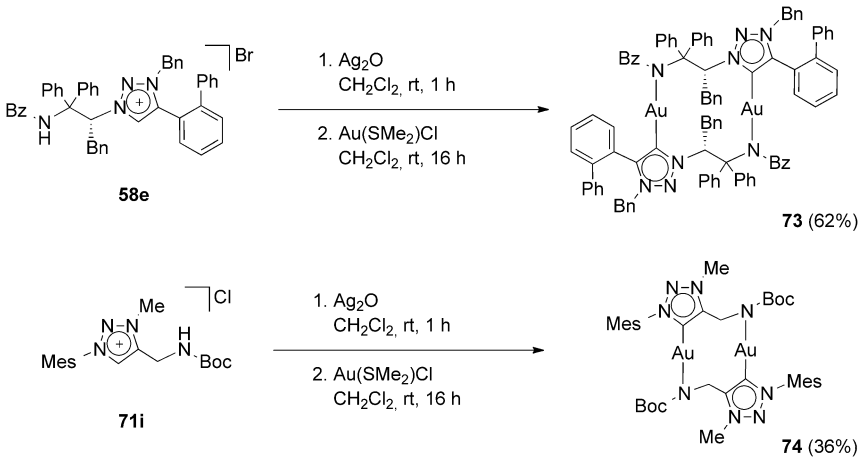




Scheme 31 Catalytic activity of palladium(II) bis(triazolylidene) complexes in cross-coupling reactions

Fukuzawa and coworkers have described the olefin arylation reaction (Heck–Mizoroki coupling) using **72b–c** as catalysts [75]. The triazolylidene palladium complex **72c** with mesityl wingtip groups induced higher activity than phenyl substituents. Aryl bromides were converted well, but aryl chlorides gave much lower yields and were only converted if activated by an electron-withdrawing group. Heteroatoms and *ortho* substituents constituted a further limitation to this catalyst system. Interestingly, mesoionic complex **72c** was more active than the corresponding 2-imidazolylidene analogs, e.g., $[Pd(ImMes)_2Cl_2]$.

Complex **72c** was also effective in the arylation of alkynes (Sonogashira coupling). The reaction was only practical for electron-poor aryl bromides, while electron-donating substituents on the aryl halide induced moderate to low conversion. Conversely, a variety of terminal alkynes were successfully coupled, validating complex **72c** as a catalyst that outperforms the analogous imidazole carbene complex comprising two ImMes ligands. The efficiency of complex **72c** both in the Heck–Mizoroki and the Sonogashira coupling has been exploited to perform tandem reactions. Thus, a sequential Heck-arylation with *tert*-butyl acrylate and



Scheme 32 Synthesis of bidentate dimetallic gold(I) triazolylidene complexes

subsequent Sonogashira coupling of *p*-bromo-iodobenzene with phenylacetylene has been developed to generate the desired product in 69% yield [71].

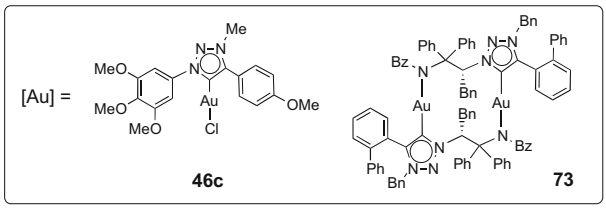
5 Polydentate 1,2,3-Triazolylidene Complexes

5.1 Bidentate Bimetallic Complexes (Type C)

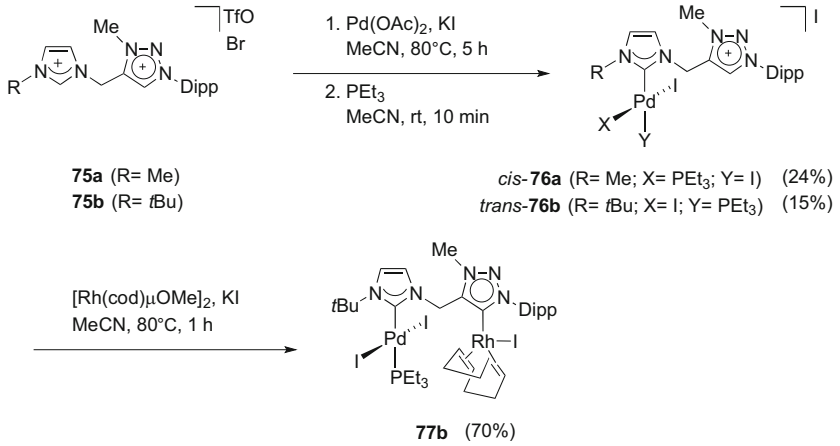
5.1.1 Gold

Amide-functionalized triazolium salts **58e** and **71i** were used by Albrecht to prepare dimetallic gold(I) complexes **73** and **74** bearing bidentate triazolylidene ligands (Scheme 32) [38]. A single-crystal X-ray analysis of complex **74** confirmed the dimeric connectivity pattern.

The monodentate gold complex **46c** (see Scheme 29) and the chiral bidentate complex **73** have been studied as catalysts for the aldol condensation of aldehydes and methyl isocyanoacetate in the presence of $AgBF_4$ and diisopropylethylamine base (Scheme 33) [38]. With a catalyst load of 1 mol%, benzaldehydes with electron-donating and withdrawing substituents were converted into 1,3-oxazolines as *cis*/*trans* diastereomeric mixtures ranging from 40/60 to 15/85. Bulky *t*BuCHO was poorly converted, presumably due to steric limitations, but in substantially better *cis*/*trans* proportion (5/95). Despite the use of the chiral catalyst **73**, no appreciable asymmetric induction was noted for the aldol reaction in any instance.



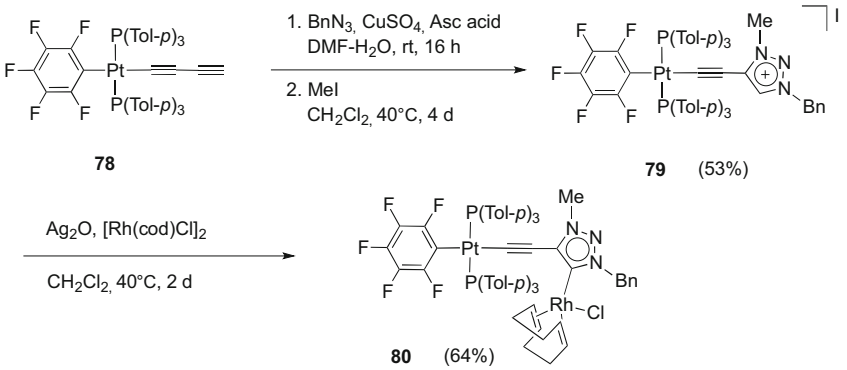
Scheme 33 Gold(I) triazolylidene catalysts for the aldol condensation of aldehydes and methyl isocyanoacetate



Scheme 34 Synthesis of bidentate mixed dimetallic palladium(II)/rhodium(I) imidazolylidene/triazolylidene complexes

5.1.2 Rhodium

Cowie synthesized the first mixed Pd(II)/Rh(I) bimetallic dicarbene complex based on the *N*-heterocyclic/mesoionic carbene framework (Scheme 34) [76]. Following a direct metallation strategy, the dicationic salts **75** were palladated exclusively at the 1,3-imidazole moiety using $Pd(OAc)_2$ in the presence of potassium iodide. The pendent PdI_3 group of the intermediate imidazolylidene carbene was further functionalized through iodide substitution with triethylphosphine, which adopted a preferential *cis* or *trans* disposition in the complexes **76**, depending on the bulk of the R group anchored to the imidazole. Finally, a second metallation at the triazole



Scheme 35 Synthesis of a dimetallic platinum(II)/rhodium(I) triazolylidene complex

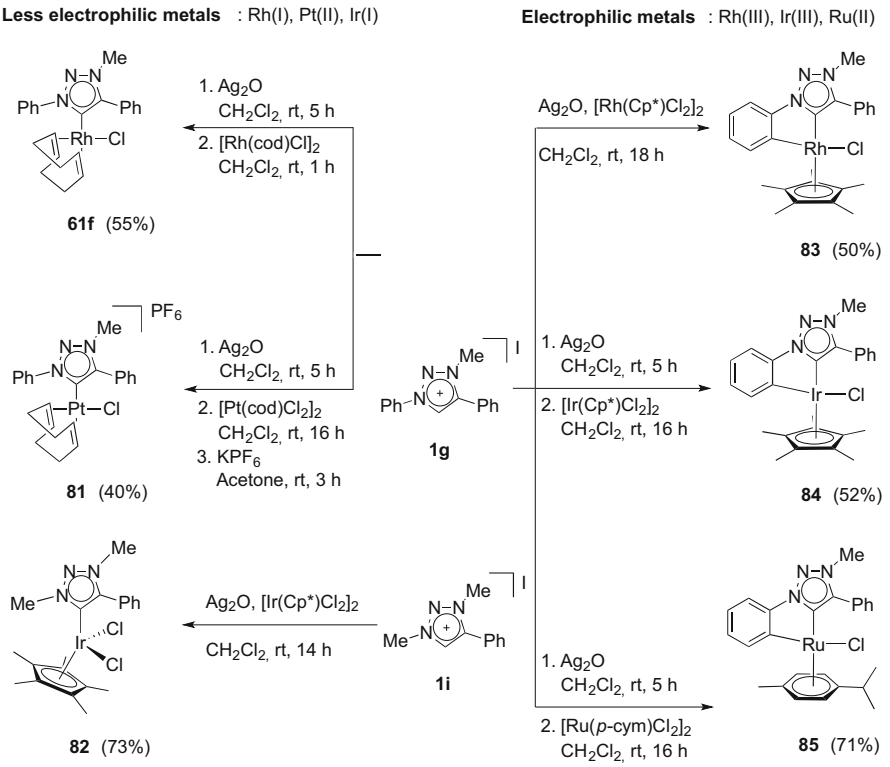
moiety in *trans*-**76b** using [Rh(cod)μOMe]$_2$ and KI led to the hybrid complex **77b** in good yield.

In an effort to incorporate a maximum of metal coordination spheres around the triazolylidene moiety, Gladysz has prepared the bimetallic Pt/Rh complex **80** (Scheme 35) [77]. The requisite triazolium salt **79** was prepared by clicking the diyne **78** with benzyl azide, followed by *N*-methylation with methyl iodide. Finally, a one-pot transmetallation reaction with Ag_2O and [Rh(cod)Cl]$_2$ yielded the complex **80**.

5.2 *Cyclometallated Complexes (Type D)*

Triazolylidene complexes featuring a metal coordinated to a mesoionic carbene ligand with an additional chelating aryl–metal bond (type D complexes, see Fig. 2) are mostly accessible by cyclometallation reactions as demonstrated by Albrecht [78]. Thus, metallation of 1,4-(di)aryl-substituted triazolium salts (e.g., **1g**) with Ag_2O, followed by transmetallation with electrophilic metal center carriers [e.g., Rh(III), Ir(III), or Ru(II)] usually results in a spontaneous and chemoselective cyclometallation reaction involving C–H bond activation of the *N*-bound aryl group exclusively (cf. **83**–**85**) (Scheme 36).

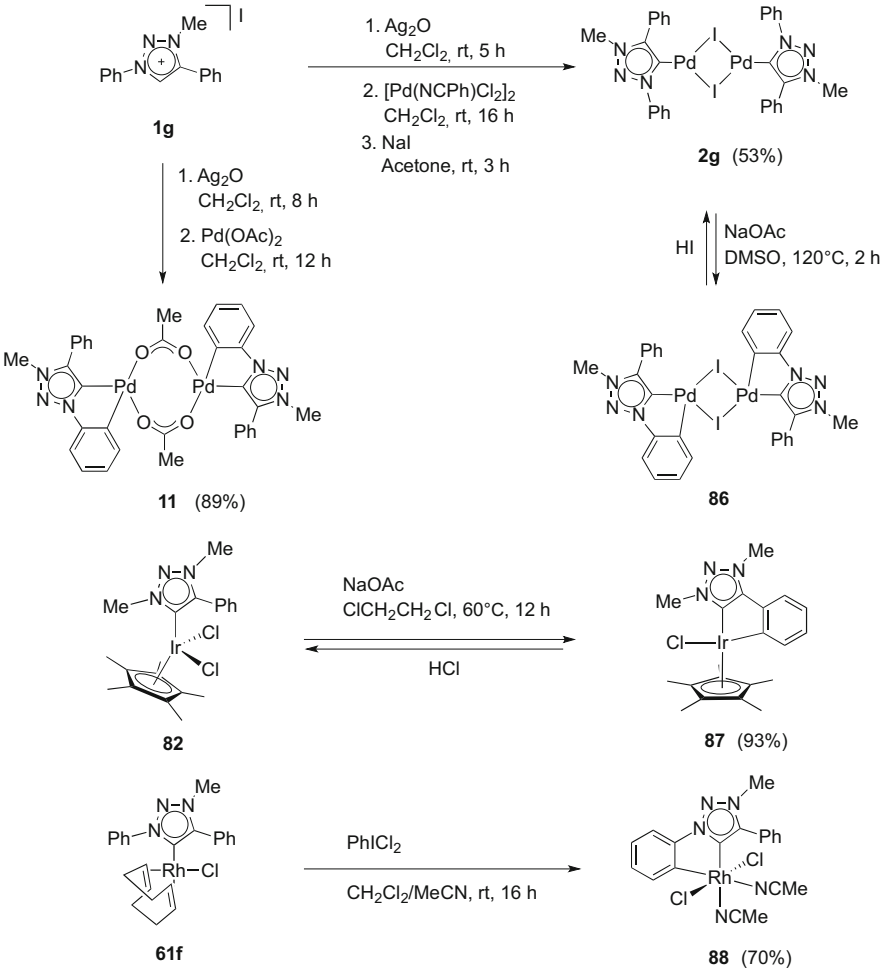
The metallacycles in complexes **83**–**85** were remarkably robust and gave no ring opening upon treatment with HCl in methanol at room temperature during 24 h. Likewise, no deuterium incorporation was detected when complexes **83**–**85** were treated with DCl/*i*PrOD-d_8 at reflux for 10 min. Upon prolonged heating, slow decomposition was noted as the only reactivity pattern. Cyclometallation is substantially easier with electron-rich phenyl rings, e.g., aniline-type arenes that are bound to the N1 nitrogen of the heterocyclic carbene. Less-electrophilic metals such as Rh(I), Ir(I), or Pt(II) yield normal transmetallation complexes (cf. **61f**, **81**),



Scheme 36 Metal electrophilicity and spontaneous cyclometallation of N1-aryl-triazolylidene complexes

but not cyclometallation products. Likewise, 4-aryltriazolium salts without *N*-aryl substituents (e.g., the N1, N3-dimethyl salt **1i**) also give monodentate complexes (e.g., **82**), even when strongly electrophilic metals are used [79]. Similarly, triazolium tetrafluoroborates with *ortho*-disubstituted *N*-aryl groups (e.g., 2,6-dimethylphenyl) or with *N*-benzyl groups also failed to give the cyclometallation reaction [80].

Acetate base [81], but not Et_3N, effectively assisted cyclometallation in borderline metal Pd(II) complexes and in activated Ir(III) mesoionic N1, N3-dialkyl complexes (e.g., **82**) with a C-aryl group (Scheme 37). For example, Sankararaman prepared the dinuclear acetate-bridged derivative complex **11** in high yields treating the silver carbene complex generated in situ from the triazolium salt **1g** with Pd $(OAc)_2$ [18]. In the absence of acetate base, the palladium triazolylidene complex **2g** was formed with no cyclopalladation, but, upon addition of sodium acetate, it cleanly underwent cyclopalladation at room temperature to produce complex **86** [11]. In contrast, rhodium complex **61f** and the platinum analog **81** (Scheme 36) were inert to acetate base under a variety of reaction conditions, including the use of AgOAc as a combined proton and halide scavenger.



Scheme 37 Deprotonation- and oxidation-promoted cyclometallation reactions of aryl-triazolylidene complexes

Metallacycle formation is fully reversible. When exposing complex **86** to excess HI, complex **2g** was recovered in high yield. The iridium(III) complexes **82** and **87** behave in a similar way. Complex **82** was converted into a chelate complex **87** increasing pH at moderate temperature and the reaction was reversed treating the cyclometallated complex with anhydrous HCl. Rather than directly forcing a C-H activation, the rhodium(I) complex **61f** was stirred in the presence of dichloro (phenyl)iodine(III), which induced rhodium oxidation and spontaneous cyclometallation to give the rhodium(III) complex **88**. Despite the limited stability of this complex and the formation of detectable amounts of triazolium salt as side

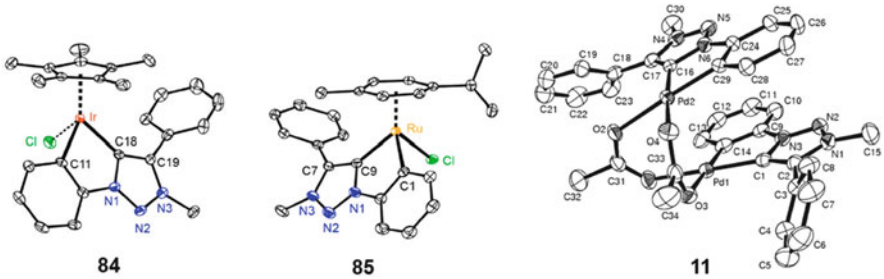


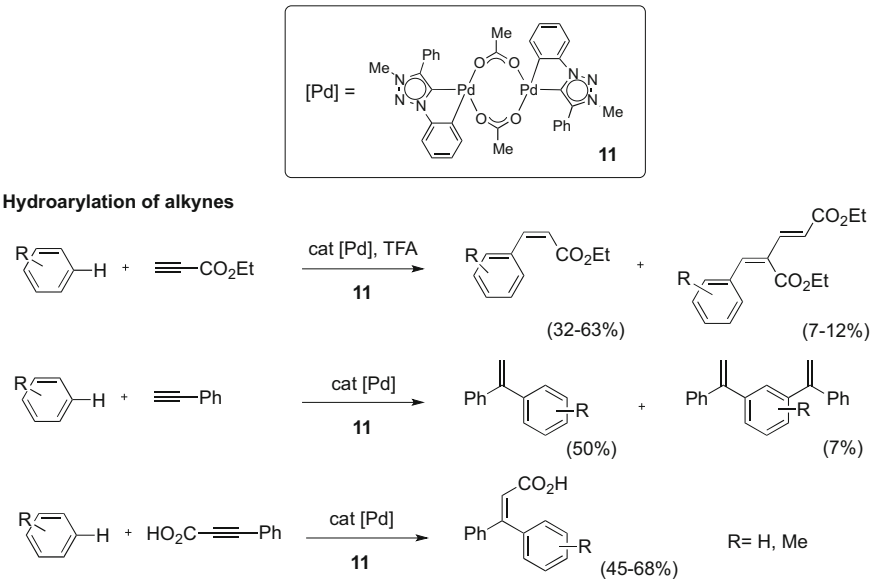
Fig. 8 X-ray diffraction crystal structures of cyclometallated triazolylidene complexes **84**, **85**, and **11**. Figures partially reprinted from [18, 78], © 2011, 2012 ACS

product, unambiguous evidence for the formation of **88** was obtained from NMR spectroscopic analysis. The ^{1}H NMR spectrum revealed a diagnostic desymmetrization of the N-bound phenyl group into four distinct resonances. Moreover, the phenyl carbon bound to the rhodium center appeared as a doublet at 149.5 ppm ($^{1}J_{RhC} = 28.9$ Hz).

X-ray analysis of cyclometallated Ir(III) and Ru(II) complexes **84** and **85** (Fig. 8) showed that metal-triazole carbene bond lengths were not significantly affected by the bidentate bonding mode (2.01–2.03 Å) and the triazolylidene plane coincided with the planar metallacycle. The X-ray structure of the palladium dimeric complex **11** clearly showed a Pd–Pd distance of 2.870 Å, much larger than the Pd–Pd bond distance of 2.56 Å reported earlier for a similar binuclear Pd cyclic complex with acetate bridges [81]. The geometry around each palladium was square planar and the stereochemistry was *cis* with respect to the two triazolylidene and two acetate units. The two tricyclic rings thus formed were within a π-stacking distance of 3.4–3.5 Å. The molecule possessed a C2 axis of symmetry passing through the center of the two palladium atoms.

Complex **11** catalyzed the hydroarylation of alkynes, though less efficiently than the normal imidazole Pd analogs (Scheme 38) [82]. For example, reaction of mesitylene with ethyl propiolate produced the corresponding vinylarene stereoselectively, forming only the Z-isomer and the double addition product. The reaction worked well for low catalyst loading (0.5%) in the presence of excess TFA in CH_2Cl_2. In the absence of TFA, only propiolate polymerization took place. Evaluation of the scope of catalyst **11** indicated high activity with electron-rich arenes, while 4-*tert*-butylphenol produced 6-*tert*-butylcoumarin as the single product resulting from an intramolecular transesterification. Phenylacetylene also induced a mixture of mono- and dihydroarylation products. With phenyl propiolic acid, only a single insertion was observed.

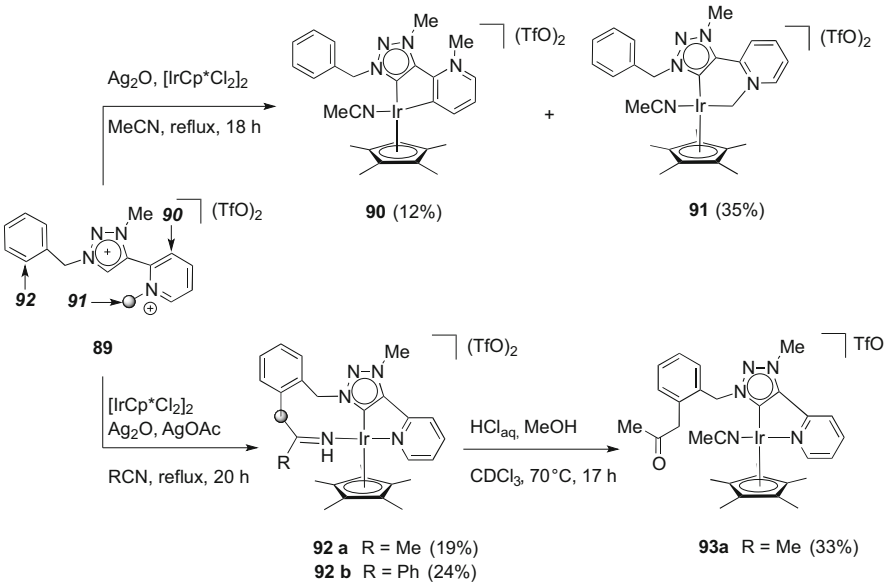
Albrecht and coworkers have conducted an elegant study on the cyclometallation of the triazolium salt **89**, bearing a *N*-benzyl group and a C-(*N*′-methyl)pyridyl substituent, to put into evidence the selective activation of up to three different C–H bonds depending on the iridium transmetallation reaction



Scheme 38 Catalytic activity of palladium(II) dimer complex **11** on the hydroarylation of alkynes

conditions (Scheme 39) [83]. In the absence of acetate base, iridium(III) bidentate complexes **90** and **91** were readily favored from the pyridinium triazolium salt **89** via Ag_2O-mediated proton abstraction and in situ metallation with $[Ir(Cp^*)Cl_2]_2$ in a one-pot procedure. The transformation involved the activation of two C–H bonds in the *N*-methyl pyridine moiety. Complex **90** comprised two different abnormally bound *N*-heterocyclic carbene ligands, that is, a triazolylidene and a 3-pyridylidene, while complex **91** featured a rare ylide bonding mode of the pyridinium ligand precursor, along with the mesoionic triazolylidene.

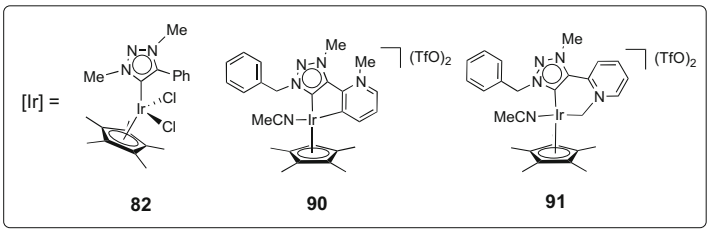
Mechanistic studies supported on the detailed NMR analysis established that complex **90** did not undergo a thermally induced isomerization to yield complex **91** and, hence, the pyridylidene bonding mode in **90** was not an intermediate on the route to the ylide complex **91**. More likely, complexes **90** and **91** shared a common, monodentate triazolylidene iridium intermediate. An unprecedented reactivity was observed when the *N*-benzyl-triazolium salt **89** was metallated with $[Ir(Cp^*)Cl_2]_2$ in the presence of silver acetate. After formation of the triazolylidene–iridium bond, a methylene group was selectively transferred from the pyridinium fragment to the aryl unit of the N-bound benzyl group with concomitant activation of a solvent molecule to yield complex **92** comprising a N,C,N-tridentate triazolylidene chelate. Formation of **92** involves C–H and C–N bond cleavage and formation of two new $C(sp^2)$-$C(sp^3)$ bonds within the iridium coordination sphere. Isotope labeling experiments unambiguously confirmed the selective transfer of the pyridine-bound carbon. Formally, complex **92a** was the product of a methylene shift from the pyridinium fragment to the benzyl group, and subsequent insertion of a MeCN



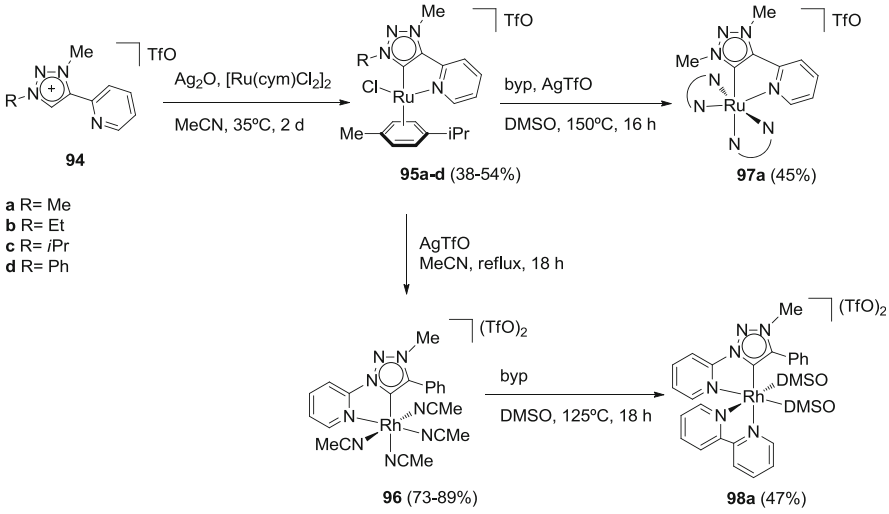
Scheme 39 Cyclometallation diversity for iridium(III) *N*-benzyl-*N*′-methyl-pyridyl triazolylidene complex **89**

molecule. Support for solvent activation was obtained by carrying out the reaction in benzonitrile (PhCN) instead of MeCN, which yielded complex **92b**.

Owing to the multistep redox processes involved in water oxidation, Albrecht and coworkers considered 1,2,3-triazole carbenes to be advantageous spectator ligands for complexes aimed to catalyze such reaction. Mesoionic carbenes have large contributions from zwitterionic resonance forms, which may assist in stabilizing different metal oxidation states when coordinated to an appropriate transition metal (Scheme 40). In addition, the ligands may serve as a transient reservoir of both positive and negative charge, thus providing synergistic effects similar to those observed in bi- and multimetallic complexes [29, 79]. Iridium(II) complex **82** displays high potential as a water oxidation catalyst. In CAN-mediated oxidation, high turnover numbers were achieved, even though the catalytic performance gradually ceased over extended periods of time (several days). Detailed analysis of the O_2 evolution rate indicated that O_2 production was essentially constant over the first 60 h. The initial turnover frequency (120 h^{-1}) was substantially lower when compared with the activity of chelated species **90**, indicating a beneficial role of the chelate on the catalytic performance. Within 5 days, the TON for complex **90** had nearly reached 10,000, which is the largest number reported to date for water oxidation (TON_{max} for complex **91** is 8350). This productivity corresponds to the formation of almost 1.2 L O_2 per mg of iridium. A detailed study of the evolution of iridium-based catalysis during water oxidation with CAN has been conducted recently by Grotjahn [84].



Scheme 40 Water oxidation reaction catalyzed by iridium(III) triazolylidene complexes

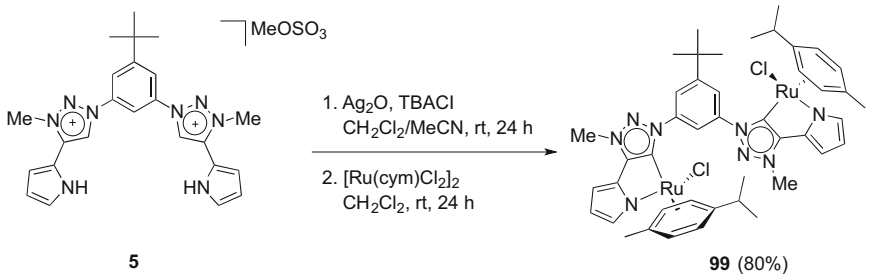


Scheme 41 Synthesis of ruthenium(II) triazolylidene pyridyl complexes

5.3 Chelated Ruthenium Complexes (Type E)

Llobet and Albrecht have developed a new family of ruthenium-based water oxidation catalysts containing a pyridine-functionalized triazolylidene ligand (Scheme 41) [85].

The ruthenium complexes **95** were prepared in moderate yields from the readily accessible pyridine-substituted triazolium salts **94** with Ag_2O and the transmetallating complex $[Ru(cym)Cl_2]_2$. Halide abstraction from **95** with AgOTf



5 **99** (80%)

Scheme 42 Synthesis of the bidentate ruthenium(II) triazolylidene complex 99

and thermal cymene dissociation in refluxing acetonitrile afforded the dicationic complexes **96** in good yields. Subsequent displacement of the *p*-cymene and chloride ligands in **95** with 2,2-bipyridine (bpy) was accomplished by heating a dimethylsulfoxide (DMSO) solution of the complex in the presence of bpy and AgOTf to afford the highly air- and water-stable complex **97a** [86]. Complex **98a** featuring two solvent ligands was prepared similarly from complex **96a**.

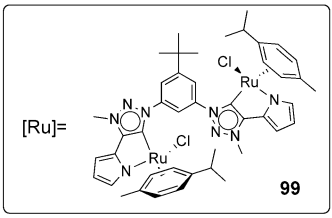
Electrochemical analysis of complexes **95** and **96** revealed a quasireversible oxidation at +1.42 V for complexes **95** and at a slightly lower potential for complexes **96** (+1.35 V). Complex **95d** comprising a withdrawing Ph substituent displayed the highest oxidation potential (1.445 V) and this potential decreased with increasing the donor ability of the substituent R. A different trend was observed in the dicationic complexes **96** with the oxidation potential increasing from Me < *i*Pr < Et << Ph.

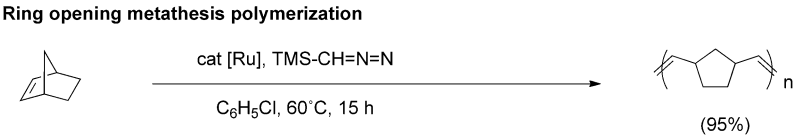
Complexes **95** and **96** were all active in the oxidation of water using Ce(IV) as a sacrificial oxidant. The cymene containing complexes **95** generated substantial amounts of CO_2 along with O_2 according to mass spectrometric analysis of the products. The relative CO_2 portion gradually increased over time and was considerably higher with bulkier N-substituents, increasing in the order Me < Et < *i*Pr < Ph. In contrast, the dicationic complexes **96** produced O_2 exclusively.

Bielawski, Sessler, and coworkers [14] have reported the first structurally characterized bis-ruthenium complex **99** supported by a pyrrole-containing bis (1,2,3-triazolylidene) ligand identified by an overall 1:2 ligand-to-metal stoichiometry and featuring a discrete ruthenium bimetallic structure (Scheme 42).

The bis(triazolium) salt **5** was subjected to metallation with silver oxide in the presence of tetrabutylammonium chloride and the resulting intermediate silver carbene **6** (see Scheme 3, Sect. 2.1) was reacted with [Ru(*p*-cym)Cl_2]$_2$ to give the bis-ruthenium(II) complex **99**, containing two triazolylidene donor groups in 80% overall yield.

Complex **99** catalyzed the ring-opening metathesis polymerization (ROMP) of norbornene when activated by trimethylsilyldiazomethane, although less strained cyclic olefins such as 1,5-cyclooctadiene or cyclopentene were not efficiently polymerized (Scheme 43). The norbornene polymerization reaction was carried





Scheme 43 Ring-opening metathesis polymerization reaction catalyzed by the ruthenium (II) triazolylidene complex **99**

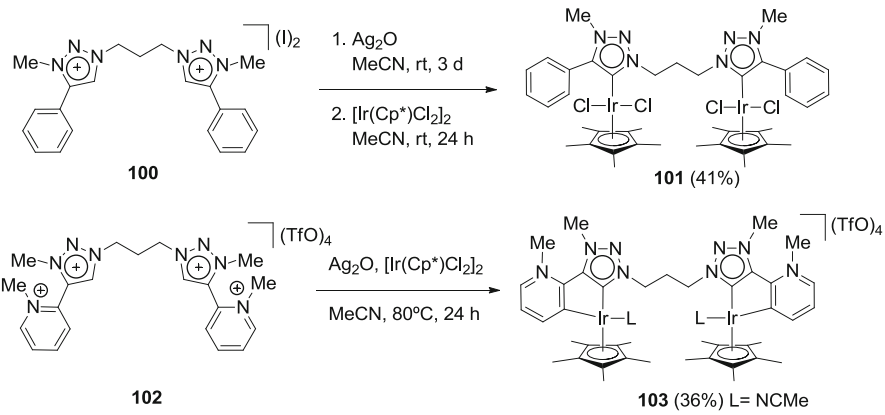
out in chlorobenzene under an atmosphere of nitrogen at 60°C for 15 h with 0.5 mol % of **99** and 3.0 mol% of trimethylsilyldiazomethane (TMSD). Under these conditions, a 95% yield of polynorbornene was obtained.

6 Polydentate Bis(1,2,3-Triazolylidene) Complexes

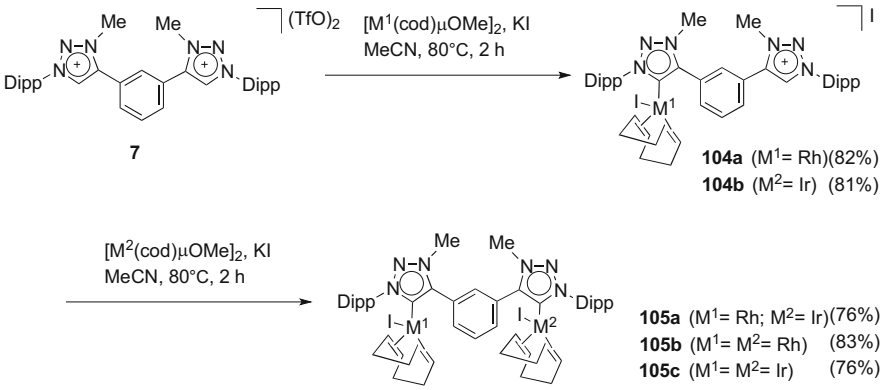
6.1 Iridium and Rhodium Complexes (Type F)

Bimetallic diiridium-triazolylidene complexes **101** and **103** were investigated by Bernhard and Albrecht to get highly soluble and stable catalysts for water oxidation (Scheme 44) [87]. The reaction of bis(triazolium) salt **100** with Ag_2O for prolonged time at room temperature followed by transmetallation with stoichiometric quantities of $[Ir(Cp^*)Cl_2]_2$ afforded the desired complex **101**. In parallel, the bimetallic chelating complex **103** was synthesized by adding simultaneously Ag_2O and the iridium precursor salt and performing the metallation at 80°C to promote the double cyclometallation of the two pyridine ligands. Both complexes were orange, air-stable compounds that dissolved well in MeCN, water, and MeOH. In contrast to the ionic complex **103**, the neutral diiridium complex **101** was also very soluble in chlorinated solvents. Chelation in **103** was unambiguously deduced from the resonance pattern of the pyridylidene ring, which featured two doublets ($\delta_H = 8.71$ and 8.29 ppm) and a triplet ($\delta_H = 7.60$ ppm), in agreement with the activation of one pyridine C–H bond.

The electrochemical properties of complexes **101** and 1**03** did not differ significantly from the monometallic model compounds and from related species when evaluated as catalysts for the oxidation of water in the presence of sacrificial CAN.



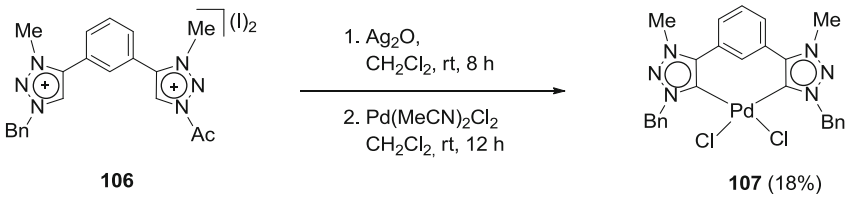
Scheme 44 Synthesis of iridium(III) bis(triazolylidene) complexes



Scheme 45 Synthesis of (rhodium(I)/iridium(I) bis(triazolylidene) heterobimetallic complexes 105

However, contrary to the monometallic analogs, the activity was improved when water oxidation was performed under dilute catalyst concentrations.

Cowie has demonstrated that heterobimetallic complex **105a** bridged with a bis (triazolylidene) ligand could be obtained by sequential metallation of the aromatic bistriazolium salt **7** with $[M(cod)\mu OMe]_2$ (M = Rh; Ir) in the presence of an excess KI to force an iodide product upon metallation (Scheme 45) [88]. Deprotonation of the triazolium moiety was promoted by the basic methoxy ligands of the metallating agents, bypassing the need for the generation of a silver transfer intermediate. The method was suitable only for similarly oxidized metals (e.g., Rh/Ir), but attempts to prepare similar Pd/Rh or Pd/Ir complexes failed.



Scheme 46 Synthesis of the chelated palladium(II) bis(triazolylidene) complex 107

6.2 Palladium and Ruthenium Complexes (Type G)

6.2.1 Palladium

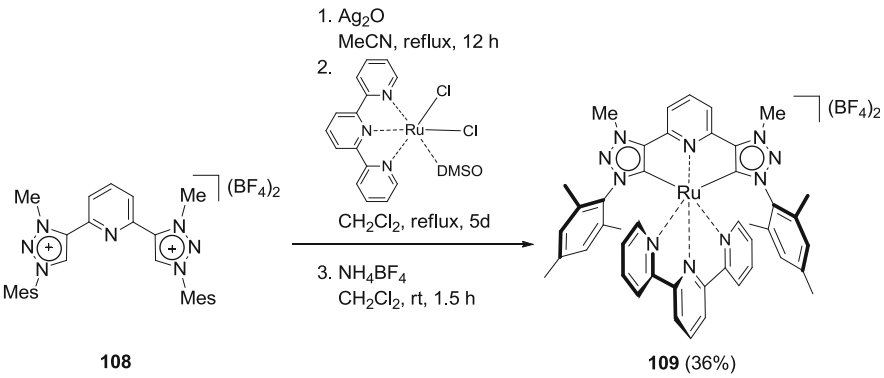
Sankararaman [72] has reported the first example of a pincer palladium complex **107** bearing a MIC ligand based on bis(1,2,3-triazolydene) precursors. Double palladation of **106** was conducted uneventfully following a transmetallation protocol involving treatment with Ag_2O followed by metal exchange with Pd $(MeCN)_2Cl_2$ to afford complex **107** in low yield (Scheme 46).

Complex **107** was tested for its catalytic activity in Suzuki coupling. Coupling of 4-bromonitrobenzene and 4-bromobenzonitrile with phenylboronic acid yielded 4-nitro- and 4-cyanobiphenyl, respectively, in >90% yields (see also Sect. 4.2).

6.2.2 Ruthenium

González, Schubert, and coworkers have exploited the superior σ donating of mesoionic carbenes to prepare the heteroleptic ruthenium(II) complex **109** as a promising candidate for photosensitizer applications (Scheme 47) [89]. Complex **109**, comprised of a C,N,C-tridentate coordinating bis(triazolylidene)-pyridine ligand as a tpy analog (tpy = 2,2′,6′,2″-terpyridine), was synthesized under mild reaction conditions with a high selectivity and acceptable overall yield. A stable silver(I) carbene was first prepared from the bis(triazolium) tetrafluoroborate **108** by utilizing Ag_2O. For the subsequent transmetallation, ruthenium(II) complex *cis*-$[Ru(tpy)(DMSO)Cl_2]$ proved to be a sufficiently selective and reactive precursor to afford the corresponding tpy complex, which was finally treated with excess NH_4BF_4 to exchange the anion affording the dicationic complex **109**.

Luminescence and electrochemical studies conducted by the authors showed that the longest wavelength metal-to-ligand charge transfer MLCT absorption of **109** occurred at the tpy ligand, whereas the triplet metal-centered ^{3}MLCT emission emerged from the carbene ligand. Increased energy levels of ^{3}MLCT states due to the strongly donating triazolylidene ligands in complex **109** efficiently diminished radiationless deactivation, which is an important requisite for photosensitizer applications. Recently, Schubert and Berlinguette have developed a second generation of Ru(tpy)bis(triazolylidene) complexes incorporating terminal carboxylate and



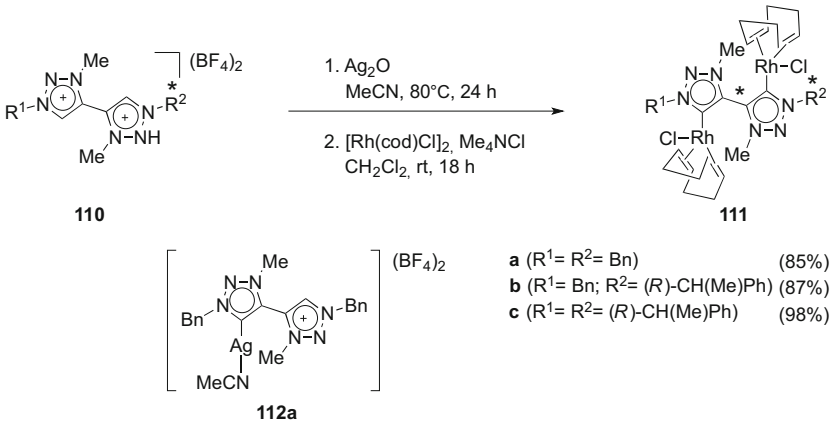
Scheme 47 Synthesis of a chelated ruthenium(II) bis(triazolylidene) complex

phosphonate groups to achieve a robust cooperative anchoring onto TiO_2 surfaces [90, 91].

7 Bidentate 4,4′-Bis(1,2,3-triazolylidene) Complexes

7.1 Rhodium Complexes (Type H)

Aizpurua and coworkers have demonstrated for the first time the potential of 4,4′-bis(1,2,3-triazol)-5,5′-diylidene ligands as atropoisomeric components for the preparation of enantiopure dirhodium(I) complexes **111** featuring configurationally stable axial chirality (Scheme 48) [92]. The method required the use of nonsymmetrically *N*-substituted 4,4′-bis(1,2,3-triazolium) salts **110** as carbene precursors, which were accessible in a totally site-controlled manner by Cu(I)-catalyzed "click" [2+3] cycloaddition of 3-alkyl-4-ethynyl-1,2,3-triazolium salts with alkyl or aryl azides [93]. Submitting the chiral bistriazolium salt **110b** to metallation with Ag_2O under usual room temperature conditions followed by transmetallation with $[Rh(cod)Cl]_2$ afforded complex reaction mixtures, whereas carrying the formation of the silver dicarbene in refluxing acetonitrile for 24 h cleanly led to the final dirhodium complex **111b** in high yield. ^{1}H NMR monitoring evidenced a slow thermodynamic equilibration of the two possible silver dicarbene diastereomers around the C4–C4′ biaryl bond to a single complex. Subsequent transmetallation with $[Rh(cod)Cl]_2$ to afford the rhodium complexes **111** occurred with total axial configuration integrity and virtually complete diastereomeric excess in each case. The absolute configuration of the newly created C4–C4′ chiral axis for the enantiopure atropoisomeric dirhodium complexes **111b–c** was established as (*R*) from the X-ray crystallograms (Fig. 9).



Scheme 48 Synthesis of rhodium(I) 4,4′-bis(triazole)diylidene chiral complexes

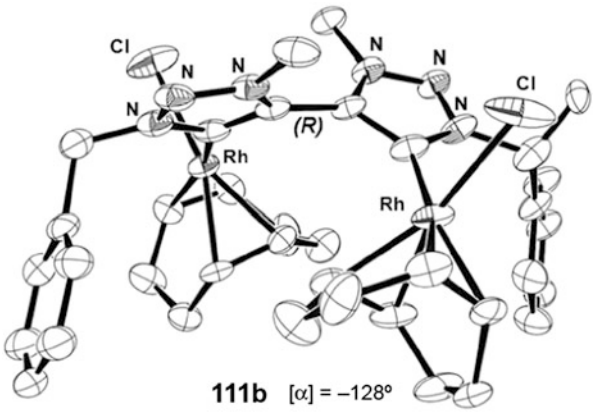
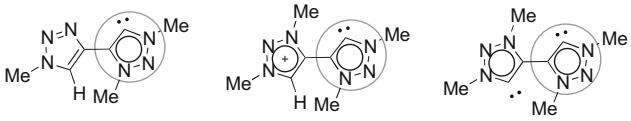


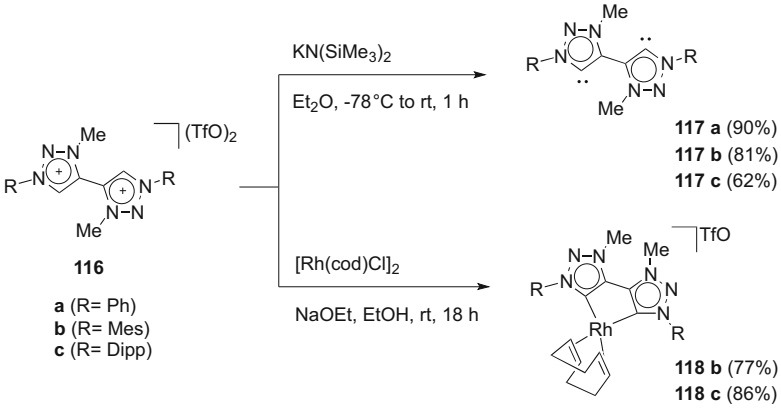
Fig. 9 X-ray structure of the enantiopure rhodium(I) complex **111b**. Figure partially reprinted from [92], © 2012 ACS

A mechanistic study of the formation of silver dicarbene complexes from the bistriazolium salt **110a** allowed for the spectroscopic detection, though no isolation, of the unprecedented monometallated carbene cation complex **112a**. This clearly suggested a strong electronic stabilization of the carbene moiety by the contiguous triazolium cationic ring in **110a** throughout conjugative effects. Cyclic voltammetry analysis of **110a** in the absence of metal cations allowed for the detection of two reduction peaks at −1.6 and −1.3 V assigned to the dicarbene and monocationic carbene species, respectively. Ab initio computational calculations conducted on the model bistriazole structures **113–115** further supported the exceptional stability of mesoionic cation carbenes of the type **114** (Fig. 10).



	113	**114**	**115**
HOMO (eV)	-4.11	-8.30	-4.51
HOMO/LUMO gap (Kcal·mol^{-1})	54.5	42.4	57.3
Proton affinity PA_1 (Kcal·mol^{-1})	280.0	181.1	269.7

Fig. 10 Stabilization of cation carbene **114** by conjugative effects estimated by ab initio calculations (Gaussian09; BP86/def2-SVP)



Scheme 49 Synthesis of chelated rhodium(I) 4,4′-bis(triazolylidene) complexes

7.2 Rhodium Complexes (Type I)

Following the free carbene isolation strategy, Bertrand has reported the first preparation of a metal-free mesoionic dicarbene and has demonstrated its incorporation as a bidentate chelating ligand into rhodium(I) complexes (Scheme 49) [94]. Accordingly, deprotonation of triazolium salts **116** with KHMDS in diethyl ether or tetrahydrofuran at −78°C allowed for the isolation of the free species **117** in good to excellent yields. Alternatively, the direct metallation of bis(triazolium) salts **116b–f** with the basic ligand bearing rhodium dimer complex $[Rh(cod)(OEt)]_2$ afforded the chelated complexes **118b–c** in 77–86% yield.

The X-ray structure of the free dicarbene **117a** featured two triazolylidene rings adopting antiperiplanar geometry with a torsion angle (C1–C2–C3–C4) of 166.1° (Fig. 11).

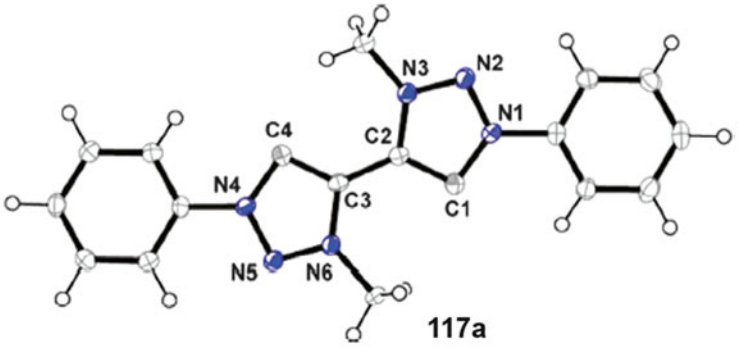


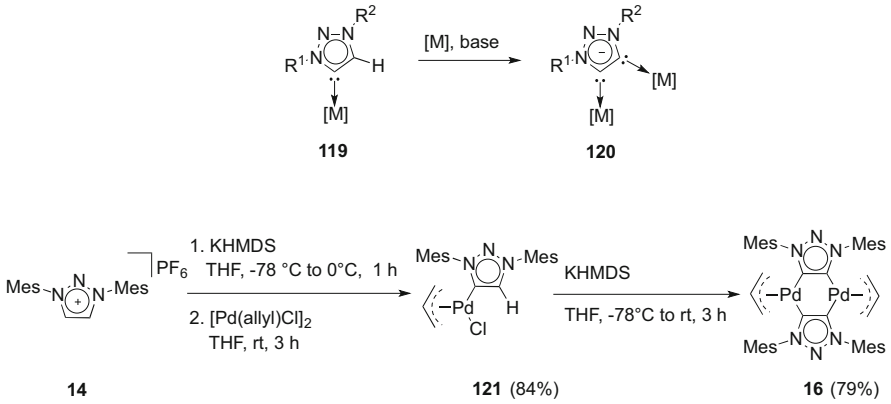
Fig. 11 Crystal structure of the free 4,4′-bis(1,2,3-triazol-5-ylidene) dicarbene **117a**. Figure partially reprinted from [94], © 2011 ACS

8 Bridged 1,2,3-Triazol-4,5-diylidene Complexes (Type J)

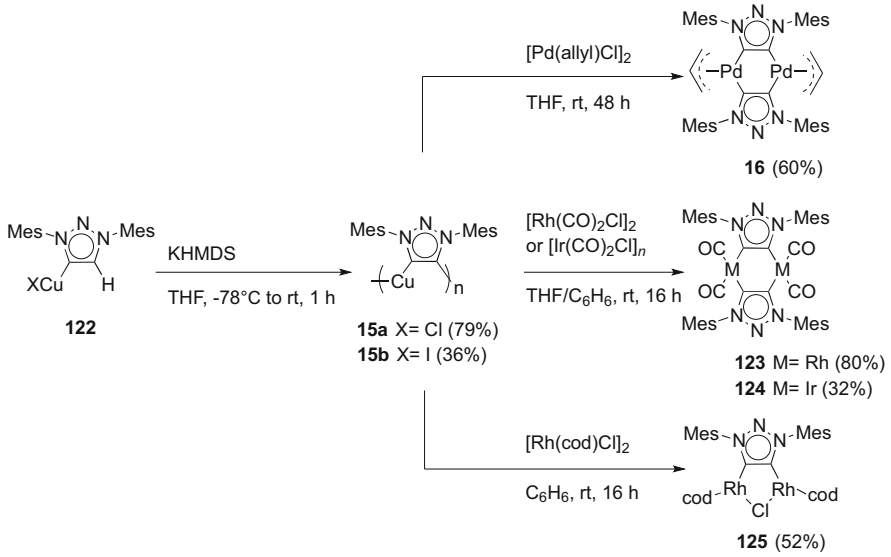
Inspired by the preparative method of pyrazolate complexes [95], Bertrand and coworkers have envisioned that deprotonation of the 4-position of triazolylidene-transition-metal complexes **119**, followed by metal coordination, would give anionic 1,2-dicarbene dimetalic 1,2-dihapto complexes **120** [20]. To implement this idea, the starting triazolium salt **14** was deprotonated by KHMDS followed by direct palladation to yield the mesoionic triazolylidene allylpalladium complex **121**, which was treated with KHMDS again to afford exclusively the bridged palladium complex **16** (Scheme 50).

The ^{13}C NMR spectrum of **16** showed only one set of mesityl signals and a single carbene peak at $\delta = 169.5$ ppm. An X-ray diffraction study demonstrated that **16** was a dimetallic complex and adopted a boat conformation. The Pd–C_{allyl} bond lengths [2.005(11)–2.061(11) Å] were significantly longer than that in pyrazolate allylpalladium complexes [2.10–2.13 Å], indicating the stronger electron-donating capabilities of the anionic dicarbene.

The same sequential synthetic route was applied to copper complexes **15** (Scheme 51), which were obtained as oligomeric or polymeric complexes. When **15** was treated with dimeric allylpalladium chloride or $[M(CO)_2Cl]_2$, (M= Rh, Ir), bridged bistriazolic complexes **16**, **123**, and **124** were formed. Conversely, treatment of copper complex **15** with $[Rh(cod)Cl]_2$ at room temperature gave **125**. The ^1H NMR showed the cyclooctadiene and the MIC in a 2:1 ratio, indicating that **125** was not a dimeric complex, but was comprised of two metal centers coordinated to a single triazolediylidene ligand. A single-crystal X-ray diffraction study demonstrated that the two rhodium atoms were bridged by a chloride and a triazole dicarbene to form a five-membered Rh_2C_2Cl ring, which adopted an envelope conformation with a short Rh-Rh distance (3.226 Å) (Fig. 12).



Scheme 50 Synthetic route to anionic 1,2-dicarbene complexes



Scheme 51 Synthesis of bridged dimetallic complexes by copper carbene transmetallation

9 Conclusions and Outlook

The chemistry of mesoionic 1,2,3-triazole-based carbenes has experienced a remarkable and fast growth since the first report of a stable transition metal complex with a triazolylidene ligand in 2008. Mirroring the abundant prior information available for imidazole NHCs [96], and taking advantage of the efficiency and simplicity of the copper-catalyzed azide-alkyne "click" chemistry to prepare the

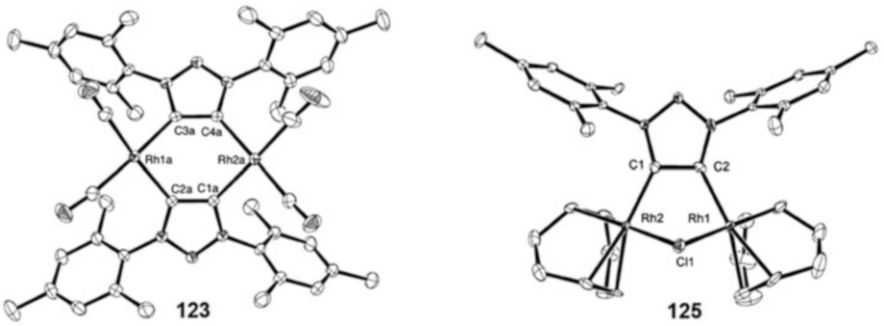


Fig. 12 Crystal structures of the rhodium(I) complexes **123** and **125**. Figures partially reprinted from [20], © 2012 VCH

1,2,3-triazole ligand precursors, a systematic quest for novel triazolylidene structures and metal complexes thereof has been launched in recent years. By far, the triazolium ion/silver carbene/transmetallation route has demonstrated to be the method of choice to synthesize a large variety of triazolylidene carbene complexes, encompassing monodentate, polydentate, chelated, and bridged ligands. On the other hand, organometallic catalysis has been the favorite field of application for most novel mesoionic carbene complexes, together with the technologically appealing catalytic water oxidation for energy storage purposes and photosensitizer development for advanced photovoltaic applications.

Mesoionic carbene complexes incorporating task-specific or chiral wingtips to their triazole core will represent an exciting new frontier in the realm of organometallic compounds that hold promise as catalysts for asymmetric synthesis. In addition, recent developments of 1,2,3-triazolium-containing ionic liquids and polymer materials [97] open the way to immobilized catalysts containing such mesoionic metal complexes. In coming years, a subtle balance in complexity, specificity, and robustness in novel mesoionic triazoles should allow these compounds to reach their maturity not only in the field of organometallic chemistry but also in catalysis, material science, or bioinorganic chemistry.

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Multicomponent and Domino Reactions Leading to 1,2,3-Triazoles

N.T. Pokhodylo

Abstract In most cases, application of multicomponent and domino reactions in organic synthesis allows solving complex problems in a simple synthetic way, involving the saving of materials, ensuring of a safe work environment, and the abatement of the number of processes and manipulations performed. In general, these processes are more environmentally friendly and economically profitable. The usage of such reactions in triazole chemistry, which is directly linked with the work with dangerous, explosive, and toxic reagents, facilitates the obtaining of derivatives with valuable properties and opens new opportunities to their widespread application for medical and industrial purposes. This review highlights the key strategies and tactical approaches for the use of multicomponent and domino reactions in the recent reports that clearly demonstrate the advantages of their application in molecular design of the triazole derivatives.

Keywords 1,2,3-Triazoles · Alkynes · Azides · Condensation · Cycloadditions · Domino reactions · Multicomponent reactions

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Abbreviations

aq.	Aqua
AAC	Azide-alkyne cycloaddition
AAIL	Amino acid ionic liquids
Ac	Acetyl
Ar	Aryl
Bn	Benzyl
BMIM	1-Butyl-3-methylimidazolium
Boc	Tert-butoxycarbonyl
Bt	Benzotriazole
BTC	Benzene-1,3,5-tricarboxylate
CAN	Ceric ammonium nitrate
Cp	1,2,3,4,5-Pentamethylcyclopentadiene
CuAAC	Copper(I)-catalyzed azide-alkyne cycloaddition
dppf	1,1-Bis(diphenylphosphanyl)ferrocene
DCM	Dichlormethane
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMEDA	*N*,*N*′-dimethyl-1,2-ethylenediamine
DMF	Dimethylformamide
DMSO	Dimethyl sulphoxide
DTBB	4,4′-Di-tert-butylbiphenyl
ee	Enantiomer excess
eq.	Equivalent(s)
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

Gly	Glycine
His	Histidine
Hmim	1-Methyl-1*H*-imidazolium
HTIB	[Hydroxy(tosyloxy)iodo]benzene
IAAC	Intramolecular Azide-alkyne cycloaddition
MAO	Methylaluminoxane
MAP	Mitogen-activated protein kinases
MCM	Mobil Composition of Matter
MeCN	Acetonitrile
MCR	Multicomponent reaction
MW	Microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
Nf	Nonafluorobutanesulphonyl
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
Orn	Ornithine
PEG	Polyethylene glycol
Ph	Phenyl
PIP	Piperidine
PIFA	Phenyliodine bis(trifluoroacetate)
PMDTA	$[Me_2N(CH_2)_2]_2NMe$
RCM	Ring-closing metathesis
RT	Room temperature
S_N	Nucleophilic substitution
TBA	Tetra-*n*-butylammonium
TCR	Three component reaction
TEA	Triethylamine
TMEDA	Tetramethylethylenediamine
$TMSN_3$	Trimethylsilyl azide
Ts	Tosyl

1 Introduction

Multicomponent reactions (MCRs) and domino reactions are increasingly important in organic and medicinal chemistry and are very powerful synthetic processes, because they allow to achieve both complexity and diversity of compounds in a single and simple experimental step with a high efficiency and atom economy, economies of time, labour, resource management, and waste generation. They offer significant advantages over conventional linear-type syntheses. The applicability of MCRs and domino reactions has been widely demonstrated in the synthesis of natural products and in medicinal chemistry. In recent years, several books and reviews have appeared, dealing with this issue [1–5].

By definition, multicomponent reactions are those reactions, where more than two reactants combine in a sequential manner, giving highly selective products where basically all or most of the atoms contribute to the newly formed product. In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally come together into an irreversible step yielding the product. The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reaction channels into the main product and does not yield side products. Such considerations are of particular importance in connection with the design and discovery of novel MCRs [6].

Unfortunately, there is no clear definition for domino reactions and similar meaning terms such as "cascade reactions" or "tandem reactions" are often used in the literature. Different authors use various definitions as to what constitutes a cascade process, although efforts have been made to restore order to this area of reaction terminology [7–13]. We consider the three most used definitions of "one-pot" multistage reaction processes. In such reactions, the substrate contains many functional groups that take part in chemical transformations one at the time. Firstly, if in a one-pot process two or more reactions proceed independently by different reaction centres, in such cases the term "tandem" is to be used. Secondly, if the reactions occur consistently without generating new reaction centres, these types of reactions are named cascade. Often a functional group is generated in situ from the previous chemical transformation. Such a process should be named as "domino type." Although there is no unambiguous definition, it may safely be said that these reactions occur by the domino effect by pushing each other. Nevertheless, we believe that all of the above descriptions are an appropriate association of one group of domino reactions. A cascade reaction or tandem reaction or domino reaction is a consecutive series of intramolecular organic reactions which often proceed via highly reactive intermediates.

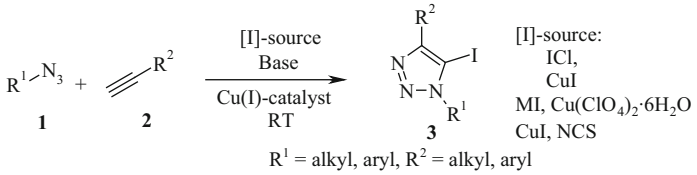
In conclusion, it is worth noting that MCRs and domino reactions have much in common and can be considered to fall under the concept of "green chemistry," as savings are involved when one carries out several transformations in one synthetic operation [14, 15]. Moreover, in this review, we do not characterize all the benefits of these reactions but emphasize, in our opinion, their main advantages such as atom-economy, time-economy, more ecological-friendliness, facile handling and less hazards, because separation of the explosive, hazardous, and toxic intermediates and reagents is avoided. Finally, MCRs and domino reactions are perhaps the most promising and powerful methods for the generation of large molecule libraries in a parallel manner.

2 One-Pot Azide-Alkyne Cycloaddition with Subsequent Triazole Functionalization

We begin with a review of perhaps the largest section of the reactions, which are widely studied. Triazole chemistry, based on the philosophy and methodology of click reactions proposed by K. Barry Sharpless, received a very broad application [16]. The term "click chemistry" is proposed for the high yielding reactions that allow to create products that can be removed without chromatography, are stereospecific, simple to perform, and can be conducted in easily removable or benign solvents. The azide-alkyne Huisgen cycloaddition with the use of a copper (Cu) catalyst at room temperature to a large extent falls under the click chemistry concept. Recently, a significant number of reviews, dedicated to the chemistry, different aspects of the synthesis and application of 1,2,3-triazoles, prepared by click reactions, have been published [17–27].

2.1 One-Pot Azide-Alkyne Cycloaddition and Substituent Introduction of Substituents in Position 5

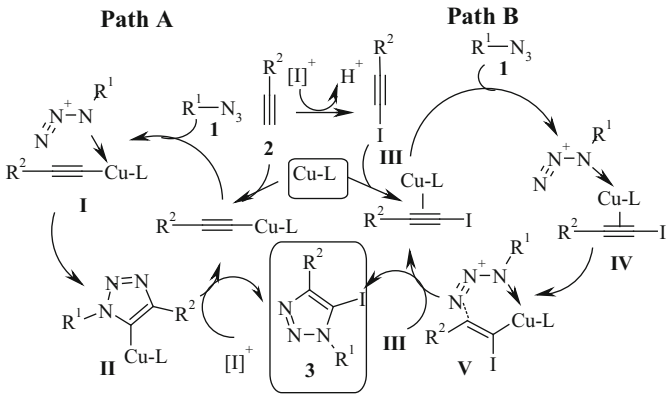
Obviously, taking into account an interest in triazole chemistry, based on a copper (I)-catalysed azide-alkyne cycloaddition (CuAAC), the philosophy of multicomponent one-pot processes should be used extensively. Indeed, a classic example of such a strategy is one-pot introduction of the substituent into the 5 position of triazole under the CuAAC conditions. One of the first examples representing this approach is a regiospecific synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazole **3** from azides **1** and alkynes **2** (Scheme 1). Such transformations are possible due to the fact that the intermediate copper(I) acetylide or Cu(I) salt of 1,2,3-triazole formed in CuAAC can be trapped by an electrophile [28]. In this way, a library of 5−iodinated 1,2,3-triazoles with aliphatic and aromatic substituents at the 1- and 4-positions in the presence of a variety of functional groups in the initial substrates were synthesized [19–33]. Iodination with ICl was selected for design, synthesis, and biological evaluation of 4,5-substituted 1,2,3-triazole derivatives, which are potential inhibitors of p38a MAP kinase. The starting azides were converted into the 4-aryl substituted 5-iodo-1,2,3-triazoles via the Cu(I)-catalysed [3 + 2] cycloaddition with 4-halogenated ethynylbenzene in THF–DCM and simultaneous iodination with ICl. It is to be noted that the reactions proceeded smoothly overnight in good yields (41–67%) as a one-pot two-step reaction with no intermediate purification [34]. This tactic applies to a large number of examples of different substituted azides, agents for the introduction of iodine, copper catalysts, and reaction conditions. For instance, the system of CuI and NBS was found to provide both I^+ and Cu^+ for an efficient preparation of 5-iodo-1,4-disubstituted-1,2,3-triazoles. It is claimed that the high tolerance of various sensitive groups revealed the potential applications of this method in organic synthesis and drug



Scheme 1 Three-component synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazoles

discovery [35]. A significant number of studies were carried out by Fokin and colleges, dedicated to the synthesis of 5-iodo-1,2,3-triazoles via the regioselective reaction of iodoalkynes, prepared in situ with azides, using catalytic copper (I) iodide and a tris((1,2,3-triazolyl)methyl)amine ligand, such as tris((1-benzyl-1*H*-1,2,3-triazolyl)methyl)amine (TBTA). The 1-iodoalkyne was partially purified by filtration through neutral alumina prior to the introduction of the azide component. This method gave 5-iodotriazoles with efficiency comparable to that observed with the isolated 1-iodoalkynes [36, 37]. Moreover, it was shown that the above obtained 5-iodo-1,2,3-triazoles (Scheme 1) underwent facile substitution reactions with fluoride salts, thus providing ready access to 5-fluorotriazoles. The latter can be further elaborated with various nucleophiles to furnish fully substituted 1,2,3-triazole compounds [38]. Further elaboration can be used for the synthesis of a variety of 1,4,5-trisubstituted-1,2,3-triazole derivatives.

Smith et al. found that the identity of the organic base, as well as the concentration of the alkyne, could play major roles in determining the product nature in the CuI-promoted alkyne-azide cycloaddition (AAC). Low concentrations of the alkyne and the use of DMAP led to the formation of 5-I-triazoles as the only cycloaddition products [39]. Brotherton, Clark, and Zhu described the synthesis of 5-iodo-1,2,3-triazoles mediated by in situ generated copper(I) catalyst and electrophilic triiodide ion. Mixing copper(II) perchlorate and sodium iodide solutions results in copper(I) species and the electrophilic triiodide ions, which collectively mediate the cycloaddition reaction of organic azide and terminal alkyne to afford 5-iodo-1,4-disubstituted-1,2,3-triazoles. One molar equivalent of an amine additive is required for achieving a full conversion into 5-iodo-1,2,3-triazole by promoting the formation of 5-unsubstituted-1,2,3-triazole. Based on the preliminary kinetic and structural evidence, a mechanistic model is formulated in which a 5-iodo-1,2,3-triazole is formed via iodination of a copper(I) triazolide intermediate by the electrophilic triiodide ions (and possibly triethyliodoammonium ions). The experimental evidence explains the higher reactivity of the in situ generated copper (I) species and triiodide ion in the formation of 5-iodo-1,2,3-triazoles than that of the pure forms of copper(I) iodide and iodine [40]. An improved method has been developed for the preparation of 5-iodo-1,2,3-triazoles by a reaction mediated by copper(I) and iodinating agents generated in situ. The major methodological advance of the current procedure is that it provides a high conversion and good iodo/proto selectivity with a broad range of substrates without using an excess of the alkyne. The copper(II) perchlorate hexahydrate, used in the described work, was dried at 40–70°C in a vacuum oven overnight to remove adsorbed moisture (but not

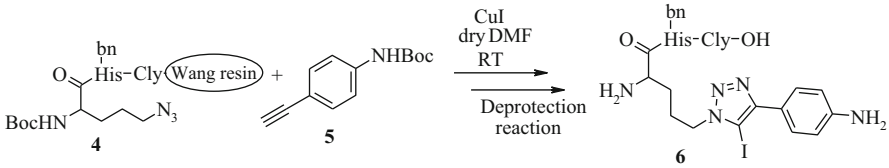


Scheme 2 Proposed mechanisms for the CuAAC including iodation reaction

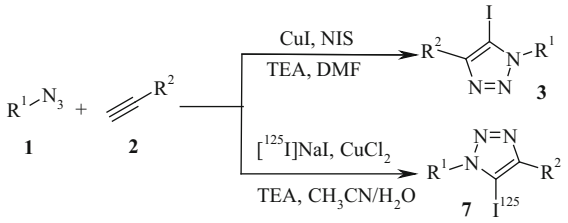
crystalline water) and subsequently stored in a dry keeper. The recommended procedure begins with the dissolution of the azide in tetrahydrofuran to give a 0.2 M solution. LiI (four equiv), $Cu(ClO_4)_2 \cdot 6H_2O$ (two equiv), triethylamine (one equiv), and the alkyne (one equiv) are then added sequentially. Coupling of an organic azide with a terminal alkyne in the presence of copper(II) perchlorate and an alkali metal iodide under mild conditions gives the corresponding 5-iodo-1,2,3-triazole. With the addition of the accelerating ligand TBTA (10 mol%), this procedure can tolerate a wide variety of functional groups, including carboxyl or hydroxy groups. Aliphatic and aromatic azides and alkynes can be readily converted into 5-iodo-1,2,3-triazoles with high to exclusive iodo/proto selectivity [41].

A possible mechanism for cascade cyclization and iodation was proposed by a number of chemists. The most accepted mechanism, outlined in Scheme 2, includes two pathways. One possible pathway (path A) is similar to that proposed for the CuAAC [27, 42, 43] and involves the formation of the σ-acetylide complex **I** as the first key intermediate. Coordination of the azide through the proximal nitrogen centre and subsequent cyclization yielded the cuprated triazoles **II**. Copper exchange through σ-bond metathesis with iodoalkyne **III** completes the cycle, thus liberating iodotriazole **3** and regenerating acetylide **2**. Alternatively (path B) [36], copper may activate the iodoalkyne **II** through the formation of a π-complex intermediate, which then engages the azide to produce complex **IV**. Cyclization then proceeds via a vinylidene-like transition state **V** to give iodotriazole **3**. A similar transition state has been proposed to explain the involvement of dicopper intermediates in the CuAAC reaction. The distinctive feature of this pathway is that the C–I bond is never severed during the catalysis.

Such a strategy is useful for the creation of complicated biocompounds. For instance, an efficient self-activating click reaction between azide- and acetylene-containing peptides on solid-phase has also been achieved by introducing the Nim-benzylhistidine residue on the reacting peptides. The reaction of Boc-Orn



Scheme 3 Representative example of solid-phase CuAAC-iodination reaction for peptide couplings

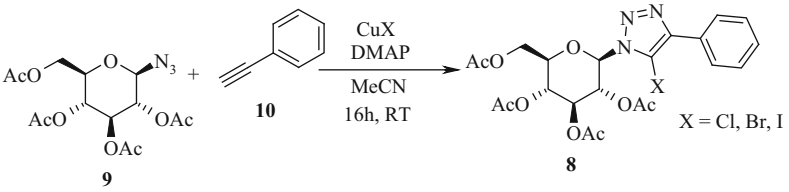


Scheme 4 One-pot three-component radiochemical synthesis of ^{125}I-labeled 1,2,3-triazoles

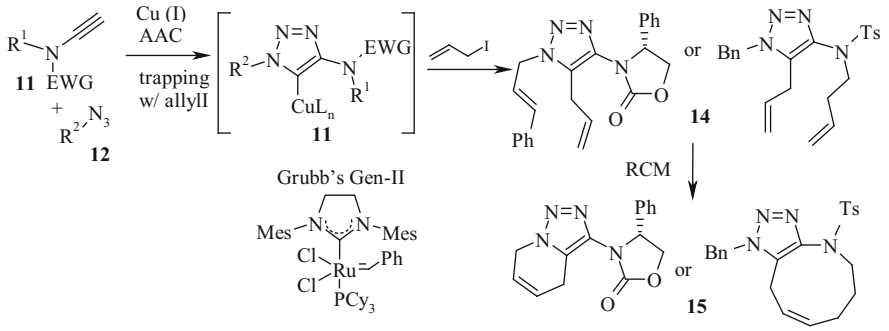
(N_3)-His(Bn)-Gly-OR **4** with N-Boc-4-ethynylaniline **5** provided the corresponding triazole **6** quantitatively (Scheme 3). The histidine-activated click reaction was applied to self-activating peptide couplings on solid-phase under additive-free conditions (Scheme 3) [44].

Furthermore, a one-pot three-component copper(II)-mediated reaction of azides **1**, alkynes **2**, and [^{125}I]iodide to yield 5- [^{125}I]iodo-1,2,3-triazoles **7** (Scheme 4) has been reported. Using a selection of azides and alkynes in a combinatorial approach, a library of structurally diverse ^{125}I-labeled triazoles, functionalized with bioconjugation groups, fluorescent dyes, and biomolecules, was created. Preliminary biological evaluation suggested that 5-[^{125}I]iodo-1,2,3-triazoles were resistant to deiodination in vivo, both as small molecular probes and as antibody conjugates. The ability to incorporate radioactive iodide into triazoles directly from the parent azides and alkynes makes the method broadly applicable and offers the potential to rapidly assemble molecular probes from an array of structurally diverse and readily available building blocks. The added flexibility of trisubstituted triazoles and their apparent resistance to metabolic deiodination has the potential to transform the development of tracers for biomedical imaging and therapeutic applications [45].

The above described method found a new accomplishment and development by using other electrophilic agents, including halogens. For example, a new synthetic protocol for the one-pot preparation of 5-halo-1,4-disubstituted-1,2,3-triazoles is provided by rational combination of a CuAAC reaction and an oxidative halogenation reactions. CuI-*N*-chlorosuccinimide (NCS) and CuBr-NCS reaction systems were developed, respectively, for effective preparation of 5-iodo-1,4-disubstituted-1,2,3-triazoles and 5-bromo-1,4-disubstituted-1,2,3-triazoles under mild conditions with a high tolerance of various sensitive groups [46, 47]. Moreover, new triazole-based compounds in accordance with the pocket binding requirements of human



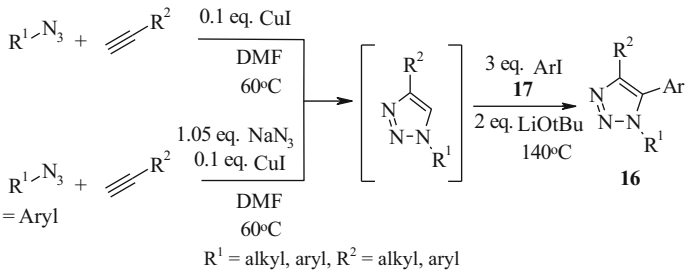
Scheme 5 Synthesis of 5-halogenated 1,2,3-triazoles 8 using stoichiometric amounts of Cu(I)–halides



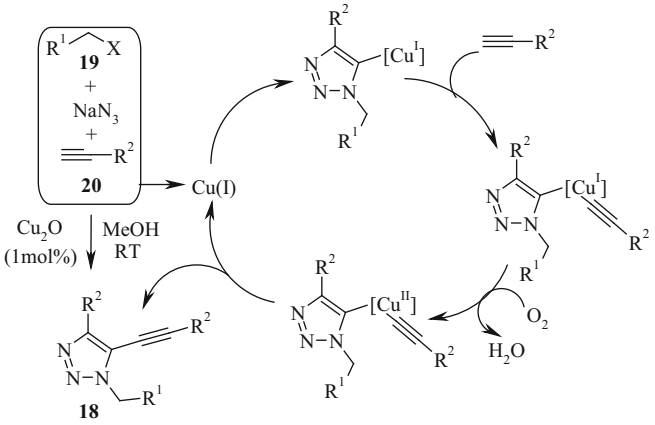
Scheme 6 Fused triazoles via AAC (involving triazole alkylation with allyl iodide)

mPGES-1 were designed. Docking results, in agreement with ligand efficiency values, suggested the synthesis of compounds that at least in theory was shown to be more efficient in inhibiting mPGES-1. Biological evaluation of the selected compounds has disclosed three new potential anti-inflammatory drugs [48]. It is noteworthy that while catalytic amounts of copper halides provide specifically the 5-proto-1,2,3-triazoles, the introduction of an excess of CuX must be carefully controlled. Application of this synthetic methodology for the formation of 5-halogenated 1,2,3-triazoles **8** from azide **9** and phenylacetylene **10** in high yields (>74%) and under smooth conditions was reported for the design of potential glycogen phosphorylase inhibitors through Pd-catalysed C–C couplings (Scheme 5) [49].

Carbon–carbon bonds could also be formed in the course of the CuAAC reactions. The triazole copper intermediate **11** was generated in situ from azide **12** and alkyne **13** via [3 + 2] cycloaddition. The feasibility of trapping the intermediate **11** by allyl/propargyl iodide provided the preparation of 5- allyl/propargyl triazoles **14** in good yields. Such system can serve as a new template for ring-closing metathesis (RCM) to construct de novo fused triazoles **15**, which are otherwise non-trivial to access. The prepared triazoles **14** were examined in ring-closing metathesis using Grubb's Gen-II17 as a catalyst at room temperature yielding fused triazole **15** in excellent yield (Scheme 6) [50].



Scheme 7 Sequent CuAAC and direct arylation



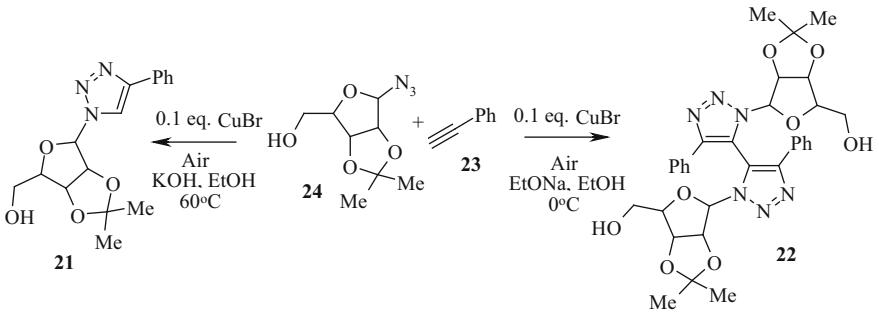
Scheme 8 One-pot synthesis of 5-alkynyl 1,2,3-triazoles **18** and proposed catalytic cycle

Lately, modular one-pot multicomponent synthesis of fully decorated triazoles **16** through a sustainable "click" reaction and direct arylation with iodoarenes **17** using inexpensive copper catalysts (Scheme 7) has been shown [51].

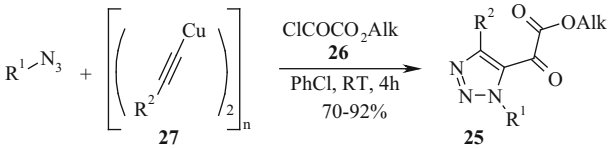
Moreover, copper(I) oxide was found to effectively catalyse the multicomponent click synthesis of fully substituted 5-alkynyl-1,2,3-triazoles **18** from organic halides **19**, sodium azide, and terminal alkynes **20** in methanol under ambient conditions. A possible mechanism of carbon–carbon bond formation was also proposed (Scheme 8) [52].

Angell and Burgess [53] have studied the condensation of acetylenes with various azides in the presence of Cu powder/$CuSO_4$ and aq. Na_2CO_3 in acetonitrile under air atmosphere at room temperature to obtain bistriazoles. A similar protocol was proposed for the controllable preparation of 1,2,3-triazoles **21** and bis(1,2,3-triazole)s **22** from alkyne **23** and azide **24** under different temperatures with good yields (63–91%). The reaction was successfully applied for nucleoside analogue synthesis (Scheme 9) [54].

Recently, a novel one-pot three-component method has been discovered for an efficient preparation of 1,4,5-trisubstituted 5-(2-alkoxy-1,2-dioxoethyl)-1,2,3-triazoles **25** via methodology by which the Cu–C bond in the 5-Cu(I)-1,2,3-triazole

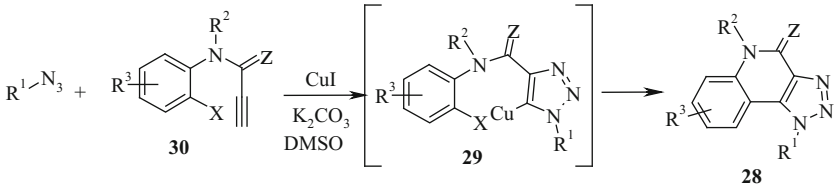


Scheme 9 Temperature effect controlled synthesis of bis(1,2,3-triazole)s or 5-alkynyl-triazoles



R^1 = alkyl, R^2 = vinyl, aryl, Alk=Et, Me.

Scheme 10 Preparation of 1,4,5-trisubstituted 5-(2-alkoxy-1,2-dioxoethyl)-1,2,3-triazoles

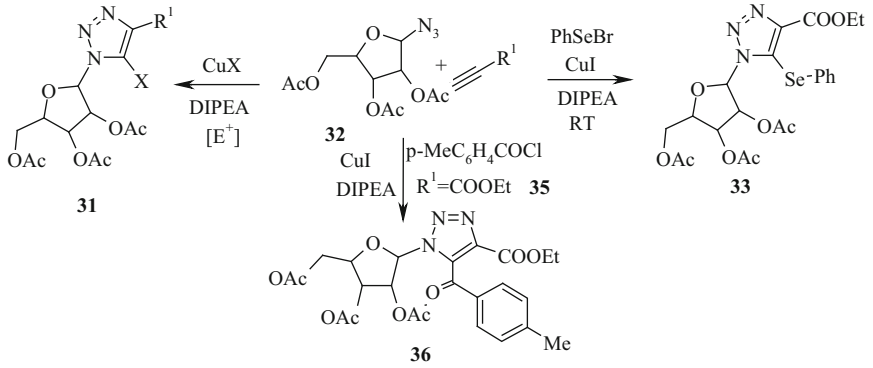


R^1 = alkyl, aryl R^2 = H, alkyl, R^3 = H, alkyl, MeO, Hal, NO_2, COOEt, CN, X=Br,I Z=O, H_2

Scheme 11 Tandem CuAAC/Ullmann coupling reactions of azides with N-(2-iodoaryl)-propiolamides or 2-iodo-N-(prop-2-ynyl)-benzenamines

intermediate (in situ formed) was trapped selectively by alkoxalyl chloride **26** in the presence of 1-Cu-alkyne (pre-made) **27**. It is important to note that the initial 1-Cu (I)-alkyne **27** does not react with alkoxalyl chloride **26** in solvent under base-free and ligand-free conditions since it is a metal cluster and has extremely high chemical stability (Scheme 10) [55].

The first combination of CuAAC and intramolecular Ullmann C–C coupling was reported for developing novel tandem reactions leading to the formation of 1*H*-[1,2,3]triazolo[4,5-*c*]quinolin-4(5*H*)-ones **28**. This occurred by the trapping of the C–Cu intermediate **29** produced in the CuAAC reaction (Scheme 11). The process proceeded efficiently when a variety of *N*-(2-iodoaryl)-propiolamides or 2-iodo-*N*-(prop-2-ynyl)benzenamines **30** were used, and it displayed a wide range of functional group compatibility (Scheme 11) [56].



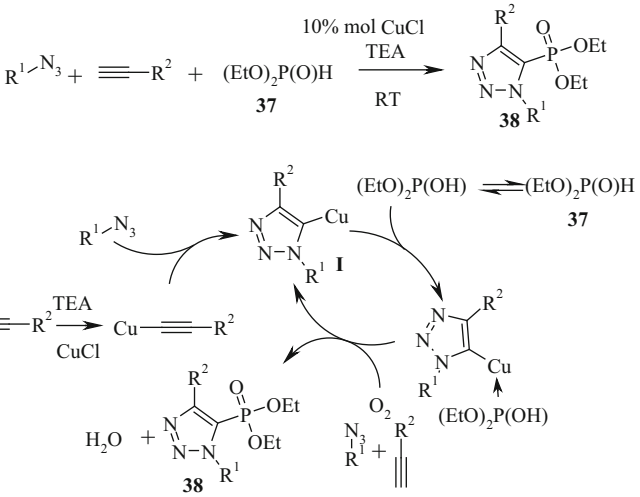
R^1 = COOEt, aryl, X=Cl,Br,I [E^+]=NCS, NBS, I_2 CAN.

Scheme 12 The CuAAC–electrophilic addition tandem process

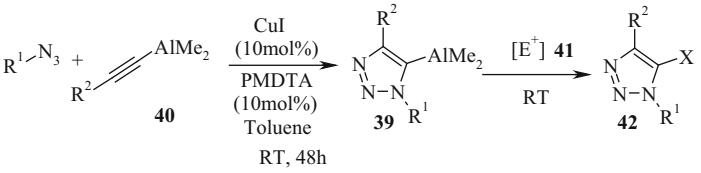
Malnuit and co-workers described a one-pot three-component approach to a new family of 4,5-functionalized triazolyl-nucleosides (Scheme 12). The method relies on a one-pot AAC/electrophilic addition tandem reaction, which affords good yields of the corresponding 4,5-disubstituted nucleosides **31**. In general, all reactions of NIS, NBS, and NCS with various azido-sugars **32** (α- and β-deoxy-ribose, D- and L-ribose and pyranose series) were performed. The CuCl/NCS and CuBr/NBS couples were used as sources of Cl^+ and Br^+, respectively. It has also been found that this three-component reaction was applicable to other electrophiles. Thus, PhSeBr was used in the reaction for the 5-phenylselenide-substituted triazole **33** preparation in moderate yield, which is probably due to the low reactivity of the electrophile. Moreover, the reaction of azido-ribose **34**, ethyl propiolate **35** and toluoyl chloride, which was used as the electrophile, led to 5-toluoyl-triazolyl-nucleoside **36** in excellent yield [57].

Furthermore, by using a strategy of aerobic oxidative coupling, Cu/triazole complex **I** was successfully trapped by nucleophilic H-phosphonates **37** in a controlled manner to generate a variety of 1,2,3- triazolyl-5-phosphonates **38** (Scheme 13). This is the first example of the direct construction of a Csp^2-P bond at room temperature through aerobic oxidative coupling reactions. In view of a high regioselectivity and efficiency, mild conditions, and applicability to a broad range of substrates bearing sensitive functional groups, this CuAA[P]C reaction (direct incorporation of P as accompanying a "click reaction") provides a facile new protocol for the preparation of structurally sophisticated phosphorus compounds [58].

Finally, to make this current strategy more variable a way to the fixed Cu-triazole intermediate was demonstrated. Micouin et al. obtained aluminotriazoles **39** in a fully chemo- and regioselective manner by a copper-catalysed cycloaddition of organic azides with mixed-aluminum acetylides **40** (Scheme 14). The carbon–aluminum bond, unaffected by the first transformation, is still able to react further with different electrophiles **41** and enables a rapid and simple access to 1,4,5-trisubstituted triazoles **42** [59].



Scheme 13 Domino synthesis of 1,2,3-triazolyl-5-phosphonates and proposed catalytic cycle

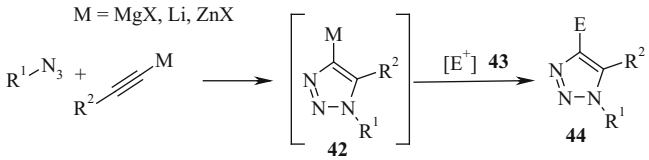


R^1 = alkyl, aryl R^2 = alkyl, aryl, $[E^+]$= DCl, D_2O; NCS, NBS, NIS, $ClCO_2Alk$; X=D, Cl, Br, I, CO_2Alk

Scheme 14 Synthesis of 1,4-disubstituted-5-alumino-1,2,3-triazoles and their one-pot transformation into 1,4,5-trisubstituted-1,2,3-triazoles

2.2 One-Pot Azide-Alkyne Cycloaddition and Substituent Introduction of Substituents in Position 4

The regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles can be produced via the Huisgen cycloaddition of bromomagnesium acetylides to azides [60–62]. In 2004 Sharpless and co-workers upon the reexamination of an old process showed that the intermediates **42** of that reaction can be trapped with different electrophiles **43** and can regioselectively form 1,4,5-trisubstituted 1,2,3-triazoles **44** in a one-pot procedure (Scheme 15). The results of quenching of the 4-halomagnesio-1,5-diphenyl-1,2,3-triazole **43** with nine different electrophiles showed that yields are usually good, but in cases when trace acid impurities are hard to avoid, the product of protonation at C-4 is formed (E = H in Scheme 15). It was also underlined that not all electrophilic compounds are suitable for this capture process. For example, the use of sulphamoyl and sulphonyl chlorides



R^1 = alkyl, aryl, RSO_2; R^2 = alkyl, aryl, $[E^+]$= DCl, D_2O; I_2, CO_2, $ClCO_2Me$, PhCOH, PhNCO; E= D; I, CO_2H, CO_2Me, PhCHOH, PhNHCO.

Scheme 15 Synthesis of fully substituted 1,2,3-triazoles via the addition of bromomagnesium acetylides to azides with the following electrophilic attack

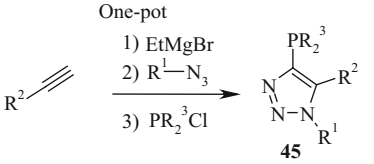
results in partial chlorination of the triazole ring at C-4. Although iodination with elemental iodine is an efficient process, the use of bromine promotes the formation of oxidatively coupled 4,4′-bis-triazoles in significant amounts, along with the 4-bromotriazole analogues. Because of the very strong basicity of 4-magnesiotriazoles, reactions with electrophiles, which also possess acidic C–H bonds, usually fail as a result of competing protonation at C-4 (Scheme 15) [63, 64]. In addition, it was found out that the reaction of lithium acetylides with sulphonyl azides, followed by trapping putative triazole anion with various electrophiles, yielded 1,4,5-trisubstituted sulphonyl triazoles **44** ($R^1 = RSO_2$ in Scheme 15) [65]. In both cases, the metallotriazole can react with several electrophiles, leading to 1,4,5-triazoles in a regioselective manner. The proposed mechanism involves a nucleophilic addition of the metal acetylide, followed by a ring closure to the metallotriazole. Moreover, the reaction of alkynylzinc or zincates with azides was reported to deliver metallotriazoles which can be further functionalized using a Negishi coupling reaction [66].

Lately, a simple one-pot three-step procedure, which allows the synthesis of a number of new members of mono(triazolyl)-phosphane ligands, has been reported. In the first step, the Grignard reagents were used to form the corresponding magnesium salts starting from an alkyne at low temperature. Subsequent addition of aryl or alkyl azides at slightly elevated temperature forms the triazolyl-magnesium salt. Direct treatment of these salts with various diarylchloro-phosphanes furnished the triazoles **45** in moderate to good yields (Scheme 16) [67]. It is noteworthy that such triazole-based monophosphines **45** have been prepared previously via a multi-step procedure and studied as ligands in palladium complexes providing highly active catalysts for Suzuki–Miyaura coupling and amination reactions [68, 69].

3 One-Pot Generation of Azides and Subsequent AAC Reactions

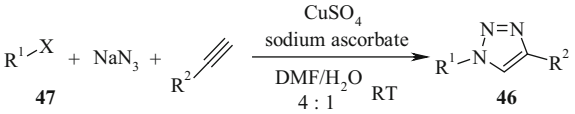
Synthesis, extraction, and purification of organic azides are dangerous, and difficult to handle procedures, so more advantageous and desirable are the methodologies in which the organic azides are generated in situ, avoiding their isolation. Such

Scheme 16 One-pot procedure towards 1,5-disubstituted-1*H*-1,2,3-triazol-4-ylphosphanes



R^1 = alkyl, aryl R^2 = alkyl, aryl, R^3 = Ph, C_6F_5

Scheme 17 One-pot synthesis of 1,2,3-triazoles from alkyl halides, NaN_3, and alkynes



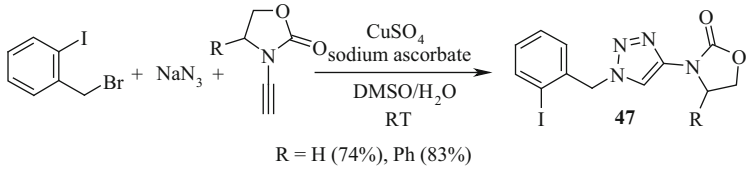
R^1 = alkyl, R^2 = alkyl, aryl, X = Cl, Br, I.

reactions are safer because hazards derived from their isolation and handling are minimized and time consuming and waste generating additional synthetic step is avoided. This is especially practical for small molecules with several azide functionalities.

3.1 Generation of Azides by the Nucleophilic Substitution or Addition Reaction Sand Subsequent AAC

One of the first multicomponent reactions, which avoided utilization of organic azides, was carried out by Fokin et al. [70]. By a convenient one-pot procedure, 1,4-disubstituted 1,2,3-triazoles **46** were obtained in excellent yields from a variety of readily available aromatic and aliphatic halides **47** without isolation of potentially unstable organic azide intermediates. Aliphatic azides can be readily prepared from the corresponding halides by nucleophilic displacement or, in case of aryl and vinyl azides, by a Cu(I)-catalysed reaction (vide infra) with sodium azide. The substitution is especially facile when activated halides, such as allylic, propargylic, and benzylic, are used (Scheme 17). Moreover, when this process was performed under microwave irradiation, the time of the reaction was significantly reduced [71].

This safe and efficient method for the synthesis of 1,4-disubstituted 1,2,3-triazoles became quite popular and widely used [72, 73]. A number of articles, where a variety of reagents and catalysts were tested in such an approach, have been published. For example, a one-pot synthesis of 1,2,3-triazole-linked glycoconjugates [74] or [1,2,3]-triazol-1-yl-trifluoroborates [75] from saccharide acetates or haloalkyltrifluoroborates correspondingly was performed. Afterward, tandem azidation– and hydroazidation–Huisgen[3 + 2]cycloadditions, employing chiral ynamides, were described [76] for the synthesis of chiral amide-substituted triazoles **47** (Scheme 18). It was noted that tandem processes are highly regioselective and chemoselective in the case of the hydroazidation of ynamides



Scheme 18 A one-pot synthesis of amide-substituted triazoles from alkyl bromides and ynamides

[77]. A one-pot multicomponent click reaction was used to synthesize novel "drug-like" 1,2,3-triazoles in the eco-friendly conditions PEG-400/water (1:1, *v*/*v*) [78].

This reaction has been studied under different conditions varying the structure of the catalyst [79, 80]. For example, ultrasound-acceleration in water at room temperature, using CuI as a catalyst, was studied for such three-component reactions to form 1,4-disubstituted 1,2,3-triazoles. The authors claim that using water as the solvent and the purity of the recovered products makes it attractive not only for large-scale synthesis of this class of biologically active molecules but also for the synthesis of screening libraries for drug discovery [81]. Furthermore, a library of new 1,4-disubstituted 1,2,3-triazoles, with a variety of additional functional groups in their structure, from an in situ generated benzyl azide and different alkynes and dialkynes, was obtained by means of microwave-assisted synthesis in higher yields and in shorter times [82]. Later on, a new tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol ligand **48** (Fig. 1) was prepared by a triple Cu(I)-catalysed alkyne-azide 1,3-dipolar cycloaddition (CuAAC). Ligand **48** forms a stable complex with CuCl, which catalyses the Huisgen 1,3-dipolar cycloaddition in water or under neat conditions. Low catalyst loadings, short reaction times at room temperature, and compatibility with free amino groups make **48**·CuCl an outstanding catalyst for CuAAC in a one-pot process [83]. Looking for new catalysts, the protocols, where scientists use the cheap and easy-to-prepare $Cu(PPh_3)_2NO_3$ [84] and commercially available [$CuBr(PPh_3)_3$] [85] complexes, were elaborated. These systems are active at room temperature, with catalyst loadings of 0.5 mol% or less, in the absence of any additive, and it does not require any purification step to isolate pure triazoles. Moreover, it was shown [86] that a structurally well-defined copper(I) isonitrile complex **49** (Fig. 1) was an efficient, heterogeneous catalyst for a three-component preparation of 1,4-disubstituted 1,2,3-triazoles. The catalyst can be readily recovered by precipitation and filtration and recycled for at least five runs without significant loss of activity and applied to the cycloaddition reaction of electron-rich, electron-poor, hindered alkynes and dialkynes at room temperature in water to give the corresponding triazoles in high yields [86]. Finally, Garcia-Alvarez and co-workers demonstrated a new family of iminophosphorane Cu^I complexes related to **50** (Fig. 1), which exhibited a versatile and efficient catalytic activity in Huisgen three-component cycloaddition reaction of 1-iodoalkynes with azides in aqueous media under mild conditions. *N*-Thiophosphorylated iminophosphorane ligand was prepared by the treatment of water-soluble phosphanes 1,3,5-triaza-7-phosphaadamantane (PTA) and diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (DAPTA) with an equimolecular amount of azides $(RO)_2P(=S)N_3$ (R = Et, Ph) [87].

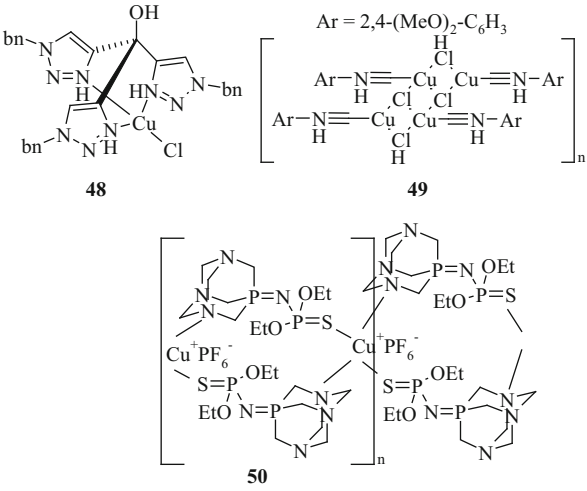


Fig. 1 Structure of some catalysts for multicomponent CuAAC

The new catalytic systems enabled the development of regioselective, efficient, modular, mild, and eco-friendly multicomponent synthesis of diversely decorated 1,2,3-triazoles, contributing to expand the scope and versatility of the Cu-catalysed 1,3-dipolar cycloaddition. Application of ionic liquids in triazole multicomponent synthesis is interesting for green chemistry. It was shown that treatment of a copper (I) catalyst in a mixture of the ionic liquid [bmim][BF_4] and water can effect three-component reaction [88]. Moreover, it was found that the ionic liquid/H_2O is a good reaction medium for the synthesis of 1,2,3-triazoles using either halides at sp^3-hybridized carbon atoms or halides at sp^2-hybridized carbon atoms. This procedure permits extensive recycling of the solvent without substantial loss in activity within five times [88]. In addition, another one-pot procedure for 1,2,3-triazole preparation, catalysed by copper(I) and amino acid ionic liquid (AAIL) in [BMIM]BF_4, was developed by Jincan and Lei. It is noteworthy that CuI, AAIL, and [BMIM]BF_4 could be recovered after six consecutive trials without significant loss of activity. The reaction medium was prepared from [BMIM]OH and an appropriate amino acid such as L-proline, *trans*-4-hydroxy-L-proline, and *N*,*N*-dimethylglycine at room temperature, and the solution was then evaporated and dried in vacuo to generate the desired amino acid ionic liquids (AAILs) [89].

It is known that copper heterocyclic carbene complexes are a dynamically developing class of catalysts for the click reactions. These versatile and highly efficient catalysts for the Huisgen cycloaddition are represented in a number of articles. It was first demonstrated that in situ generated azides led to 1,2,3-triazoles with differently substituted alkynes in the presence of a [(NHC)CuBr] complex **51** (Fig. 2) (NHC = *N*-heterocyclic carbene) with extremely high reaction rates and excellent yields. Furthermore, for the first time an internal alkyne was successfully used in this copper-catalysed cycloaddition reaction. DFT calculations on this particular system allowed for the proposition of a new mechanistic pathway for disubstituted alkynes [90]. The use of a catalytic system, easily prepared in situ

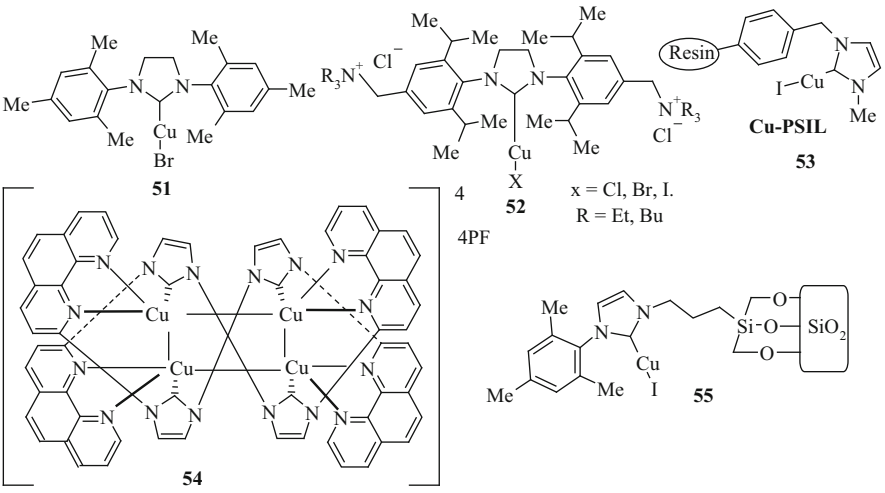


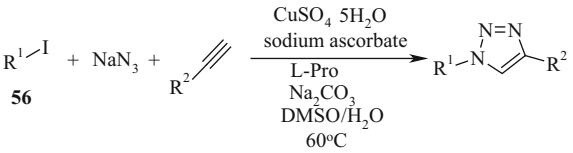
Fig. 2 Some copper heterocyclic carbene complexes for the CuAAC catalyst

from Cu(I) and Cu(II) species, in combination with benzimidazole salts in water medium provided many corresponding 1,2,3-triazole derivatives via a simple methodology [91]. Moreover, a series of ammonium salt-tagged SIPr ((SIPr = *N*, *N*¢-bis(2,6-diisopropylphenyl)-imidazolidin-2-ylidene))–Cu(I) complexes **52** (Fig. 2) were conveniently synthesized, and it was observed that they were highly active toward three-component reaction (3CR). The current catalyst could be efficiently used at least four times with an 84% isolated yield of the desired triazole in the last run [92]. Moreover, Merrifield resin-supported copper (Cu-PSIL) and silica dispersed CuO (CuO/SiO_2) were selected as catalytic systems for the 3CR AAC. It was found that immobilized copper catalysts Cu-CPSIL **53** (Fig. 2) exhibited excellent catalytic activity for one-pot reactions. The X-ray photoelectron spectroscopy (XPS) results suggested that the supported Cu(II) catalysts were reduced to catalytic Cu(I) species via alkyne homocoupling reaction [93]. A rare macrocyclic tetranuclear copper (I) complex ($[Cu_4(\mathbf{2})_2](PF_6)_4$) **54** (Fig. 2) of phenanthroline-based NHC ligand was prepared and found to exhibit high catalytic activity in the CuAAC reaction in an air atmosphere at room temperature in a $MeCN/H_2O$ mixture solution [94]. Furthermore, 1,2,3-triazole derivatives were synthesized in one-pot procedure in the presence of 0.5 mol% silica-immobilized NHC–Cu(I) catalyst **55** (Fig. 2). The copper catalyst immobilized on silica gel was readily prepared in a three-step procedure [95].

Solid state, silica functionalized nanoparticles and polymer supporting catalysis are also effective and useful for in situ azide generation and subsequent AAC reaction. For example, the dicopper-substituted γ-Keggin silicotungstate with bis-μ-1,1-azido ligands $TBA_4H_2[\gamma\text{-}SiW_{10}O_{36}Cu_2(\mu\text{-}1,1\text{-}N_3)_2]$ (**I**, TBA) tetra-*n*-butylammonium) was used as an efficient precatalyst for the regioselective one-pot synthesis of various kinds of 1,4-disubstituted-1,2,3-triazole derivatives.

The catalyst effect, kinetic, mechanistic, and computational studies showed that the reduced dicopper core plays an important role in the present 1,3-dipolar cycloaddition [96, 97]. Furthermore, silica functionalized Cu(I) is reported as a green and recyclable heterogeneous catalyst for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles via Huisgen 1,3-dipolar cycloaddition in water at room temperature. Silica functionalized Cu(I) could be recovered by simple filtration and recycled up to seven consecutive runs without loss of significant activity [98]. The mixed catalyst $Cu(OAc)_2$ on mobil composition of matter (MCM-41) showed a high catalytic activity and possibilities for the development of better catalysts supported on siliceous materials. These materials have a high surface area ($1{,}000\ m^2\ g^{-1}$), a large pore volume, and an ordered hexagonal pore array with pore diameters that can be tuned between 20 and 100 Å [99]. New supported catalysts have been prepared by immobilization of copper species on commercially available polymeric matrices incorporating the 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) template. The synergic exploitation of the exceptional copper chelating ability and basicity profile of the TBD framework, in addition to ensuring effective immobilization and stabilization of copper species, allows the implementation of three-component strategies [100]. Nanoferrites, post-synthetically modified by ligands, were used to immobilize nanometals (Cu, Pd, Ru, etc.), which enabled the development of efficient, sustainable, and green procedures for AAC. The beneficial attributes of such catalysts are an easy separation by an external magnet and their recovery and reuse. 1,4-Disubstituted 1,2,3-triazoles were synthesized by using magnetically separable and reusable copper ferrite nanoparticles ($CuFe_2O_4$) in high yields. The present method is simple, facile, and can be applied to a wide range of substrates with a high functional group tolerance [101]. The nm size range of these particles facilitates the catalysis process as an increased surface area is available for the reaction [102]. In addition, the copper nanoparticles on silica-coated maghemite nanoparticles (MagSilica®) were prepared under mild conditions by fast reduction of anhydrous $CuCl_2$ with lithium sand and a catalytic amount of DTBB (4,4′-di-tert-butylbiphenyl) as electron carrier, in the presence of the magnetic support [103]. The 1,2,3-triazoles were synthesized in water using magnetically recoverable heterogeneous Cu catalyst via one-pot multicomponent reaction using microwave irradiation [104]. A group of authors [105] demonstrated that a copper vial and copper ball can be used in lieu of a traditional homogenous copper catalyst to conduct the CuAAc reaction. As a catalyst for subsequent reactions, the recycled copper(II) sulphate, supported on ten alumina (Cu/Al_2O_3) under ball-milling in the absence of any solvent and additive, was used. This protocol offers a broad scope for an access to a variety of diversely substituted 1,2,3-triazoles in general with high yield. Several functional groups, such as F, Br, NO_2, CN, OMe, CO_2Et, CF_3, and CHO, are compatible under the reaction conditions. No rigorous extraction of the product by solvent and work-up are necessary [106]. For the first time, the potential of CuI-doped zeolites as heterogeneous catalysts was evaluated [107]. Furthermore, Cu^I-zeolites were found to be efficient heterogeneous catalysts for triazole synthesis [108]. At the same time, a lot of studies are dedicated to the

Scheme 19 One-pot synthesis of 1,2,3-triazoles from aryl and vinyl halides, NaN_3, and alkynes



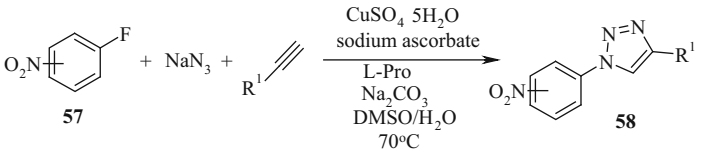
R^1 = vinyl, aryl R^2 = alkyl, aryl.

use of polymer supported copper nanoparticles. For instance, poly(4-vinyl pyridine) supported nanoparticles of copper(I) iodide were reported as green and recyclable catalysts, which can be recovered by a simple filtration and recycled up to eight consecutive runs without any loss of their efficiency [109, 110]. Moreover, self-assembly of copper sulphate and a poly- (imidazole − acrylamide) amphiphile was found to provide a highly active, reusable, globular, solid-phase catalyst for 3CR. The surface of the catalyst was covered with globular particles tens of nanometers in diameter, and those sheet-like composites were layered to build an aggregated structure. The imidazole units in the polymeric ligand coordinate with $CuSO_4$ to give a self-assembled, layered, polymeric copper complex. The catalyst was readily reused without loss of catalytic activity to give the corresponding triazoles quantitatively [111]. Finally, 3CR was performed in the presence of 1 mol% nanoparticles copper/carbon (Cu/C) catalyst [112]. It is noteworthy that zinc was also reported as a catalyst for 3CR AAC [113]. Moreover, it was shown that charcoal, impregnated with this zinc catalytic system, could tolerate a large variety of functional groups, including electron-rich and electron-poor substrates and heterocyclic alkynes [114].

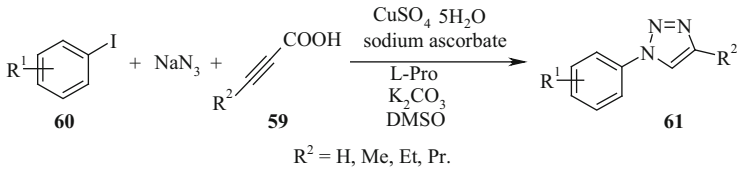
It is worth noting that the S_N-CuAAC approach has a disadvantage that nucleophilic replacement of halides proceeds easily only in the case of activated halides, e.g., in benzylic or anomeric positions. A three-component one-pot S_N/click reaction was explored by employing aromatic compounds. Obviously, aryl azides can also be generated in situ using a modified Ullmann-type reactions and nucleophilic substitution in the aromatic ring (S_NAr) reactions. The advantage of such a protocol is that both steps are catalysed by Cu(I). This reaction has been first demonstrated by Fokin et al. [70]. Aryl **56a**, heteroaryl **56b**, and vinyl **56c** halides readily participate in this process (Scheme 19) [115–117].

Otherwise, activated fluorobenzenes **57** reacted with azide nucleophile by the classic nucleophilic aromatic substitution (S_NAr) mechanism resulting aryl azides, which underwent in situ Huisgen cycloaddition with alkynes for a rapid one-pot access to 1,4-substituted triazoles **58** (Scheme 20). The reactions are generally regioselective and various commonly employed protecting groups are found to be compatible with the employed conditions [118].

Ullmann-type reactions, including copper-catalysed nucleophilic aromatic substitution, have found wide application in three-component one-pot procedures. Such studies illustrate the feasibility and broad applicability of tandem catalysis processes. For instance, a tandem catalysis protocol was found based on decarboxylative coupling of alkynoic acids **59**. 1,3-Dipolar cycloaddition of



Scheme 20 One-pot S_NAr–click reaction

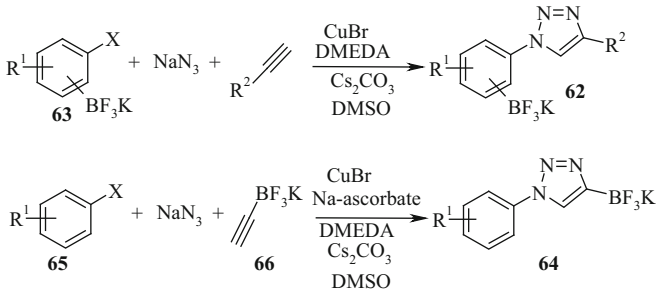


Scheme 21 Tandem low molecular weight alkynes and aryl azides generated in situ for the synthesis of 1,2,3-triazoles

alkynes **59** and azides, prepared from aryl iodides **60**, enables the synthesis of a variety of functionalized 1,2,3-triazoles **61** (Scheme 21). The method avoids usage of gaseous or highly volatile terminal alkynes, reduces handling of potentially unstable and explosive azides to a minimum, and furnishes target structures in excellent yields and a very good purity without the need for additional purification. The decarboxylative protocol was found to tolerate a variety of structural patterns and yielded almost quantitative amounts of the target structures **61** in excellent purity. Substrates bearing either electron-donating or -withdrawing groups or even one of each type underwent smooth conversion, and the method turned out to be insensitive to unprotected carboxylic acid, amino, and phenol groups [119].

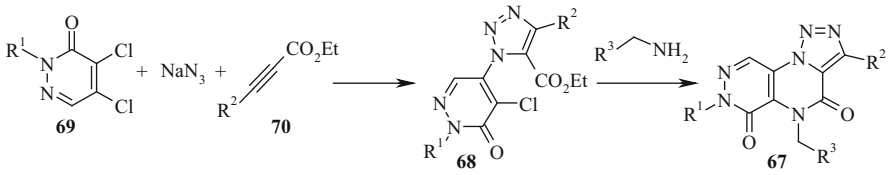
This type of reactions was expanded by the use of trifluoroborate reagents. Kim et al. elaborated a method for the regiospecific preparation of organo-[1,2,3]-triazol-1-aryl-trifluoroborates **62** from haloaryltrifluoroborates **63** via a one-pot 1,3-dipolar cycloaddition reaction (Scheme 22). It should be mentioned that the use of either electron-rich or electron-deficient haloaryltrifluoroborates led to the desired cycloaddition products with good to excellent yields [120]. Furthermore, a novel series of 1,4-disubstituted 1,2,3-triazole-containing potassium trifluoroborates **64** were prepared in good to excellent yields from the corresponding organohalides **65** and potassium ethynyltrifluoroborate **66** (Scheme 22). This method allows a convenient access to versatile triazole-containing trifluoroborate reagents, a class that can be difficult to obtain by other means [121]. Subsequent Suzuki–Miyaura cross-coupling of these 1,2,3-triazolo trifluoroborates with aryl and alkenyl bromides was demonstrated.

In addition, copper nanoparticles on activated carbon were found to effectively catalyse the multicomponent synthesis of 1,2,3-triazoles from different azide precursors, such as organic halides, diazonium salts, anilines, and epoxides in water [122]. The activity of different catalysts was tested in the cycloaddition of benzyl bromide and phenylacetylene. It was determined that the best results were obtained



X= Br, I. R^1 = H, Me, MeO, Cl. CF_3, OH, NH_2.

Scheme 22 One-pot preparation of 1-aryl-1*H*-1,2,3-triazoles containing a potassium trifluoroborate moiety



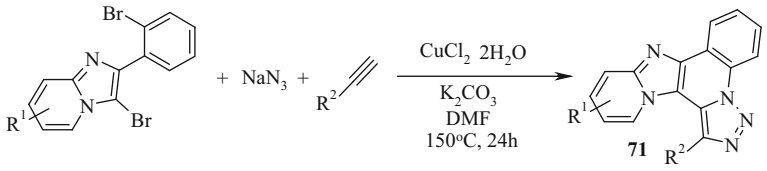
R^1 = alkyl, Ar. R^2 = TMS, COOEt.

Scheme 23 One-pot synthesis of the substituted [1,2,3]triazolo[1′,5′:1,6]pyrazino[2,3-*d*] pyridazine-4,6(5*H*,7*H*)-dione

with SiO_2, Al_2O_3, Al silicate, magnetite, graphite, multi-walled carbon nanotube, and activated carbon. Among them, the activated carbon exhibited the highest activity (>99% yield, 3 h), giving triazole in quantitative yield after reuse in a second cycle [123].

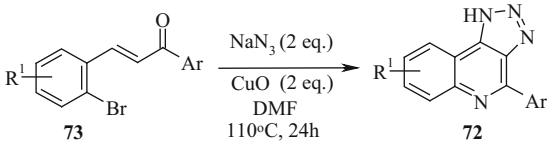
The proposed multicomponent strategy S_NAr-AAC is suitable for the synthesis of fused aromatic rings. For example, [1,2,3]triazole-fused pyrazinopyridazinedione tricycles **67** were synthesized in a four-component stepwise condensation with 42–73% isolated yields (Scheme 23). The key step in this one-pot process was a thermal [3 + 2] triazole **68** formation (by 3CR from 4,5-dichloropyridazinones **69**, sodium azide, diethyl acetylenedicarboxylate **70**), which activated the adjacent position and set the stage for a subsequent tandem nucleophilic aromatic substitution/cyclization sequence. It should be noted that a limitation of this protocol was observed with more sterically demanding primary amines, such as t-butyl amine and α-methylbenzylamine [124].

On the other hand, a ligand-free copper-catalysed tandem CuAAC, Ullmann-type C–N coupling, and intramolecular direct arylation were described. Such a protocol led to a novel triazole-fused azaheterocycle framework. The reaction gave good yields of 1,2,3-triazole-fused imidazo[1,2-a]pyridines **71** in a single step (Scheme 24) [125].



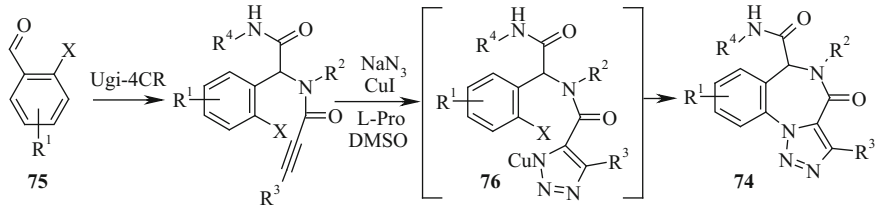
R^1 = H, Me, F. R^2 = Alkyl, Aryl.

Scheme 24 Tandem synthesis of 1,2,3-triazole-fused imidazo-[1,2-*a*]pyridines



R^1 = H, MeO, F, Cl.

Scheme 25 One-pot synthesis of 4-substituted 1*H*-[1,2,3]triazolo[4,5-*c*]quinolines



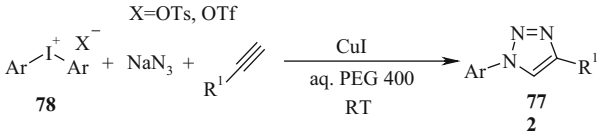
R^1 = H, MeO, F, Cl. R^2 = Alkyl, Bn. R^3 = H, Me, Aryl, R^4 = Alkyl

Scheme 26 Tandem CuAAC/Ullmann C–N coupling for the synthesis of triazolo[1,5-*a*][1,4] benzodiazepinones

Furthermore, a protocol for the synthesis of 4-substituted-1*H*-[1,2,3]triazolo [4,5-*c*]quinolines **72** through a CuO-promoted tandem cyclization reaction was developed from the readily available (*E*)-3-(2-bromoaryl)-1-arylprop-2-en-1-ones **73** and sodium azide (Scheme 25) [126].

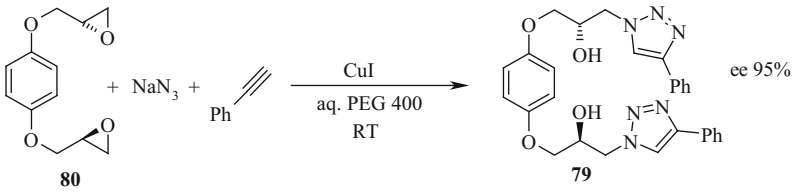
An attractive synthetic way, as a combination of the tandem azide–alkyne cycloaddition/Ullmann C–N coupling with Ugi 4-component reaction, was elaborated and is shown in Scheme 26. The methodology is compatible with various functional groups and allows the construction of triazolo[1,5-*a*][1,4]benzodiazepinones **74** starting from 2-haloarylcarbaldehydes **75** in good yields by the intramolecular trapping of the N–Cu intermediate **76**, formed by the CuAAC, by Ullmann coupling leading to the formation of the C–N bond [127].

Besides the halides, several other function groups could be used for three-component one-pot S_N-click reaction. Kumar and Buchi Reddy described the synthesis of 1,4-diaryl-1*H*-1,2,3-triazoles **77** via the reaction of diaryliodonium salts **78**, sodium azide, and terminal alkynes (Scheme 27). The best result for the in situ



78 77 2

Scheme 27 One-pot synthesis of 1,4-diaryl-1*H*-1,2,3-triazoles from diaryliodonium salts



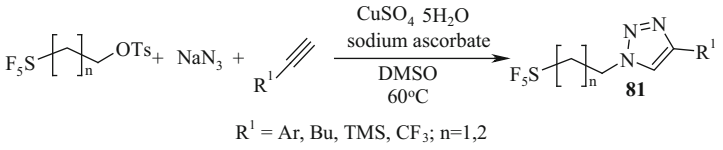
80 79

Scheme 28 One-pot synthesis of aryloxy α-hydroxy triazoles

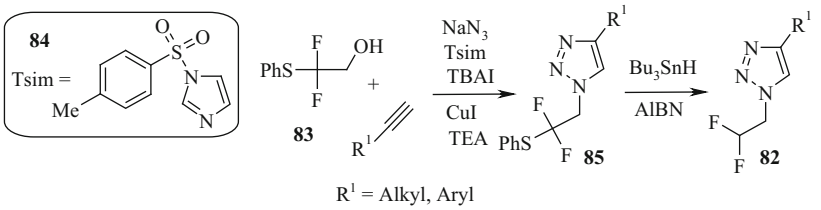
generation of phenyl azide was obtained using copper(I) iodide in PEG 400–water (1:1, *v*/*v*) solution at room temperature. Notably, as a result of the weak nucleophilicity of the counter anions and their high solubility, both diphenyliodonium triflate and diphenyliodonium tosylate salts were suitable and equally reactive starting materials for the in situ generation of azides in good yield [128].

Epoxides are commonly used as starting materials in 1,2,3-triazole preparation. For example, the synthesis of α-hydroxy or *N*-tosylamino 1,2,3-triazoles **79** via azidation of epoxides **80** or *N*-tosylaziridines with sodium azide followed by AAC using PEG-400 as a reaction medium in the presence of 5 mol% of CuI, was described (Scheme 28) [129]. Enantiomerically pure epoxide and *N*-tosylaziridines were obtained in high yield with excellent *ee* values maintaining stereospecificity [130]. The efficiency of the reaction can be increased by using a new heterogeneous catalyst. For example, the latter was prepared by simple and successful impregnation of the catalyst onto activated multi-walled carbon nanotubes [131]. Additionally, copper(I)-modified zeolites, especially CuI–USY, proved to be very efficient catalysts in multicomponent reactions of epoxides [132].

Furthermore, compounds containing mesyl- or tosyloxy function groups are simple and convenient precursors for a one-pot regioselective synthesis of 1,4-disubstituted-1*H*-1,2,3-triazoles. For instance, fused triazoles with a bis-azahomotwistane skeleton were prepared via tandem reactions of the activated *cinchona* alkaloids with azide ion in a subsequent intramolecular alkyne-azide cycloaddition (IAAC) [133]. Moreover, a wide range of α-tosyloxy ketones and acetylenic compounds were tested for preparation of the assembly of a diverse set of 1,4-disubstituted-1*H*-1,2,3-triazoles [134]. In the same manner, 1,2,3-triazoles **81** containing the pentafluorosulphanylalkyl group were synthesized in good to excellent yields. Noteworthy, isolation of such azides as SF_5-ethyl azide is hazardous due to its low boiling point and high nitrogen content (Scheme 29) [135].



Scheme 29 One-pot preparation of 1,4-disubstituted 1,2,3-triazoles via click chemistry



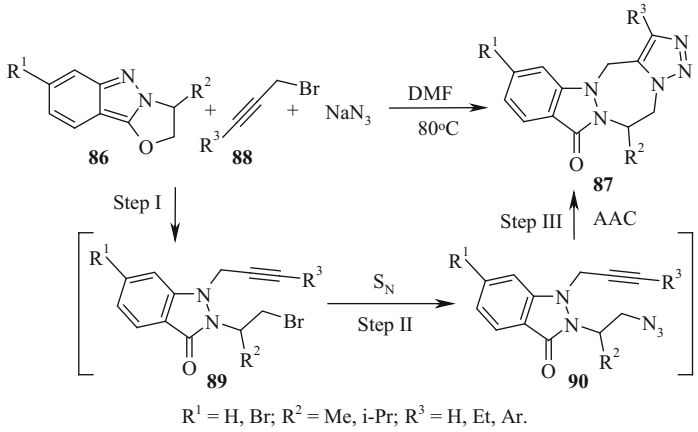
Scheme 30 N-(p-Toluenesulphonyl)imidazole activator for S_N-AAC reaction

Moreover, fourteen difluoromethyl-containing 1,4-disubstituted 1,2,3-triazoles **82** were synthesized via the reaction of 2,2-difluoro-2-phenylsulphanylethanol **83**, sodium azide and terminal alkynes in the presence of *N*-(p-toluenesulphonyl) imidazole **84**, tetrabutylammonium iodide and triethylamine, followed by reductive cleavage of the phenylsulphanyl group in **85** using tributyltin hydride and azobisisobutyronitrile (Scheme 30) [136].

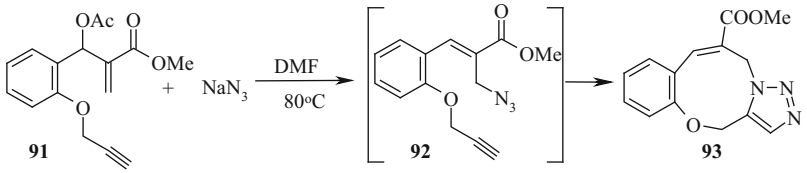
Conrad and co-workers developed a one-pot three-step method for the conversion of oxazolino-2*H*-indazoles **86** into triazolotriazepinoindazolones **87** with three points of diversity. Step one of this process involves a propargyl bromide **88**-initiated ring opening of the oxazolino-2*H*-indazoles **86** (available by the DavisBeirut reaction) to give an N^1-(propargyl)-N^2-(2-bromoethyl)-disubstituted indazolone **89**, which then undergoes CH_2Br to CH_2N_3 displacement (step two, **90**) followed by an uncatalysed intramolecular azide-alkyne 1,3-dipolar cycloaddition (step three) to form the target heterocycle **87** (Scheme 31) [137].

Acetylated Baylis–Hillman adducts were found to be useful starting materials for 3CR, leading to 1,4-disubstituted 1,2,3-triazoles [138, 139]. Recently, Baylis–Hillman adducts have been used to provide IAAC, which led to fused triazoles. Novel tricyclic [1,2,3]-triazolo-[1,4]-benzoxazonine derivatives were obtained from the Baylis-Hillman acetates **91** by the treatment with sodium azide followed by heating the resulting azido-alkyne **92** for 2 h at 110°C in the same solvent to provide **93** in overall 55% isolated yield in the absence of any copper salts (Scheme 32). However, authors emphasized that the two-pot operation process, with the second step using toluene as a solvent (under reflux), gave high yields [140].

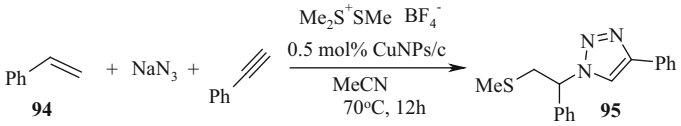
Alkenes could alsobe used as starting materials in one-pot protocols for 1,2,3-triazole synthesis. For instance, by the Michael addition of azide ion to α,β-unsaturated ketones and subsequent 1,3-dipolar reaction, 1,2,3-triazoles were prepared in very short times (30 min to 1 h) and satisfactory yields



Scheme 31 One-pot three-step synthesis of variously substituted triazolotriazepinoindazolones



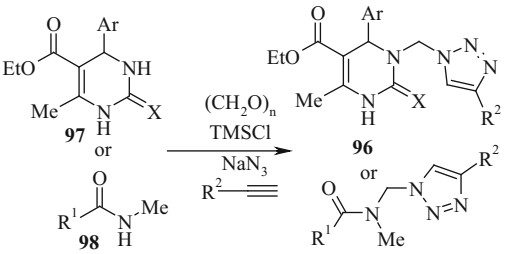
Scheme 32 One-pot synthesis of [1,2,3]-triazolo-[1,4]-benzoxazonine



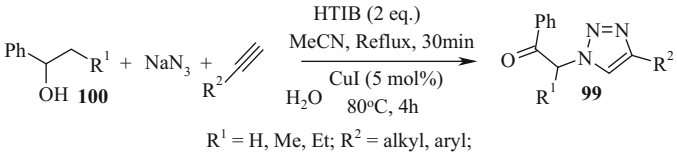
Scheme 33 One-pot protocol for the synthesis of 1,2,3-triazoles starting from inactivated alkenes

[141]. Furthermore, starting from inactivated alkenes **94**, and using a one-pot two-click process, the azidosulphenylation of the carbon–carbon double bond and the CuAAC led to the β-methylsulphanyl triazoles **95**, which were obtained using CuNPs/C as a catalyst (Scheme 33) [142]. The versatility of the methylsulphanyl group has been demonstrated through a series of synthetic transformations, including the direct access to 1-vinyl and 4-monosubstituted triazoles.

Recently, a one-pot CuAAC reaction combined with a Mannich addition has been reported. A series of N-functionalized 1,2,3-triazoles **96** with 3,4-dihydropyrimidione or amide fragment was prepared by the Cu(I) (generated in situ from $Cu(OAc)_2$ $3H_2O$/sodium ascorbate) catalysed one-pot MCR of 3,4-dihydropyrimidiones **97** or amides **98**, paraformaldehyde, sodium azide, and alkynes (Scheme 34) [143].



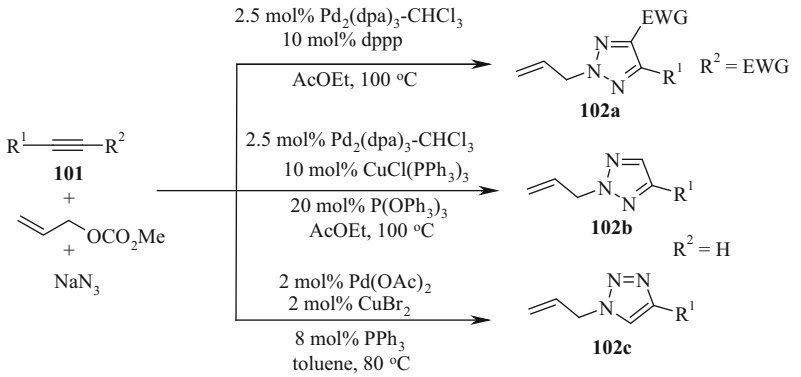
Scheme 34 Sequential Mannich-CuAAC synthesis of functionalized 1,2,3-triazoles



Scheme 35 Synthesis of β-keto-1,2,3-triazoles from secondary alcohols

An efficient method for the synthesis of 1,2,3-triazoles (β-keto-1,2,3-triazoles) **99** in good to excellent yields by successive treatment of secondary alcohols **100** with [hydroxy(tosyloxy)iodo]benzene (Koser's reagent) and sodium azide, followed by AAC, was described (Scheme 35). The reaction includes the direct conversion of an alcohol with HTIB into a tosyloxyketone intermediate, which, without isolation, was treated with sodium azide and phenylacetylene, using copper(I) iodide as a catalyst to furnish the β-keto-1,2,3-triazole in an one-pot operation. It was underlined that water plays an important role in this reaction for (a) quenching of HTIB; (b) formation of azide nucleophile; and (c) formation of copper acetylide from copper iodide and acetylene without any amine base [144].

Finally, Yamamoto et al. proposed a unique synthetic route for 2*H*-1,2,3-triazoles using a multicomponent protocol. By the palladium-catalysed 3CR of alkynes **101**, allyl methyl carbonate and trimethylsilyl azide 2-allyl-1,2,3-triazoles **102 a**,**b** were prepared (Scheme 36) [145]. For example, the reaction of phenylacetylene with allyl methyl carbonate and $TMSN_3$ was carried out in AcOEt at 100°C under the $Pd_2(dba)_3$-$CHCl_3$-$P(OPh)_3$-$CuCl(PPh_3)_3$ catalyst system. The reaction was completed in 10 h to afford 2-allyl-4-phenyl-1,2,3-triazole in 83% yield [146]. Notably, the cooperative activity of palladium and copper catalysts plays an important role in the present transformations. To accomplish the regioselective synthesis of the allyltriazoles, proper choice of two different catalyst systems is needed. The combination of $Pd_2(dba)_3 \cdot CHCl_3 - CuCl(PPh_3)_3 - P(OPh)_3$ catalyses the formation of 2-allyl-1,2,3-triazoles **102b**, while the combination of $Pd(OAc)_2 - CuBr_2 - PPh_3$ promotes the formation of 1-allyl-1,2,3-triazoles **102c** (Scheme 36). Authors also proposed a plausible mechanism for the allyltriazole forming reaction using a Pd(0)-Cu(I) bimetallic catalyst



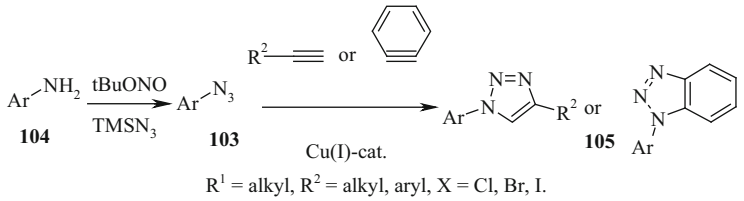
Scheme 36 Synthetic route for allyl 1,2,3-triazoles using MCR

[147]. In conclusion, fully substituted triazoles were synthesized via the four-component coupling reaction of unactivated silylacetylenes, two equivalents of allyl carbonates, and trimethylsilyl azide in the presence of a Pd(0)–Cu (I) bimetallic catalyst [148].

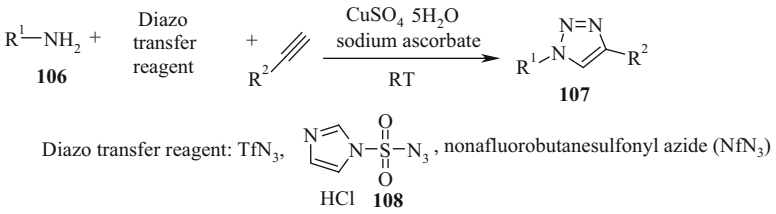
3.2 *One-Pot Generation of Azides from Amines and CuAAC Reactions*

Another convenient class of precursor for the preparation of organic azides preparation are amino derivatives. It is not surprising that they are also used in multicomponent processes. A simple and highly efficient procedure for the conversion of aromatic amines into their corresponding azides is using stable and non-explosive reagents, such as *tert*butyl nitrite (*t*-BuONO) and azidotrimethylsilane ($TMSN_3$). Barral and co-workers elaborated a methodology for a one-pot preparation of azides **103** from amines **104** and subsequent "click-reaction," enabling an access to 1,2,3-triazoles **105** without the need to isolate the corresponding aromatic azide. This procedure should prove to be especially useful when unstable low molecular weight and polyvalent aromatic azides are needed (Scheme 37) [149]. Moreover, a modification of this methodology, using microwave radiation to significantly enhance the rate of formation of 1,4-disubstituted triazoles, was reported [150]. The above methodology was also used for the synthesis of substituted benzotriazoles (Scheme 37). In addition, it was found that heating the reaction with microwave irradiation dramatically decreased reaction times from hours to minutes with yield increase in some cases [151].

Another widely used approach to the synthesis of azides is the diazo transfer reaction. In 2007, Beckmann published a one-pot two-step procedure involving generation of azides in situ from primary amines **106** via Cu(II)-catalysed diazo



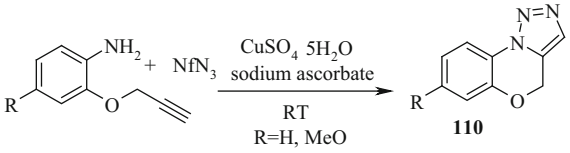
Scheme 37 Conversion of aromatic amines into azides by using of *t*-BuONO and $TMSN_3$



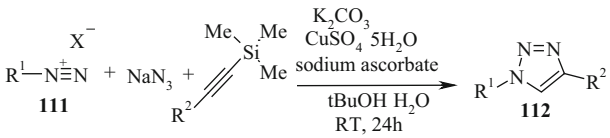
Scheme 38 One-pot diazo transfer-CuAAC reactions

transfer and Cu(I)-catalysed azide-alkyne 1,3-dipolar cycloaddition, which led to 1,2,3-triazoles **107**. The first step was the preparation of series of azides from various primary amines using triflic azide (TfN_3) in combination with copper (II) sulphate and solid sodium bicarbonate. After complete conversion into azide, acetylene and the reducing agent were added directly without any work-up procedure to provide the CuAAC reaction [152]. Later, as an effective heterogeneous catalyst for tandem diazo transfer process, click reactions mediated by trifluoromethanesulphonyl azide and copper-in-charcoal (Cu/C) were proposed [153]. Smith et al. underlined several practical limitations for the use of TfN_3 and focused on its explosive nature. The latter makes difficult to apply the reagent in parallel or combinatorial synthesis. On the contrary, it was proposed to utilize the inexpensive, shelf-stable diazo transfer reagent imidazole-1-sulphonyl azide hydrochloride **108** in a one-pot procedure for the regioselective synthesis of the functionalized 1,4-disubstituted 1,2,3-triazoles from primary amines (Scheme 38). The procedure is experimentally simple and suitable for parallel chemistry [154]. In addition, the diazo transfer approach allows to synthesize fused triazole derivatives. Nonafluorobutanesulphonyl azide is an efficient, shelf-stable, and cost-effective diazo transfer reagent for the synthesis of azides from primary amines. The nonafluorobutanesulphonyl azide was successfully applied to a one-pot regioselective synthesis of 1,2,3-triazoles, including intramolecular variants leading to polycyclic derivatives **110**, from primary amines by sequential diazo transfer and azide–alkyne 1,3-dipolar cycloaddition process (Scheme 39) [155].

Lately, Fletcher and Reilly have examined whether the commercially available diazonium salts **111** could be used as efficient aromatic azide precursors in one-pot multi-step click transformations. Seven different diazonium salts, including Fast Red RC, Fast Blue B, Fast Corinth V, and Variamine Blue B, were surveyed under



Scheme 39 One-pot synthesis of 4*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazine from amine

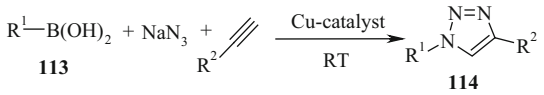


Scheme 40 Diazonium salts as aromatic azide precursors for 3CR CuAAC

aqueous click reaction conditions of $CuSO_4$/Na ascorbate catalyst with 1:1 t-BuOH/H_2O solvent and led to 1,2,3-triazoles **112** in 61–88% yields (Scheme 40). These findings establish diazonium salts as new and practical additions to a recently evolving class of synthons able to generate organic azide intermediates in situ [156].

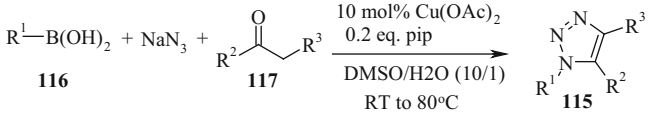
3.3 Generation of Azides from Boronic Acids and the Following Triazole Formation

Synthesis of azides from boronic acids is a relatively new, but very promising and convenient approach for three-component 1,2,3-triazoles preparation. Recently, such an approach has been used to synthesize aryl and vinyl azides from the corresponding boronic acids **113** and a one-pot approach has been applied to synthesize 1-aryl- and 1-vinyl-1,2,3-triazoles **114** (Scheme 41). It was found that the proposed azidation reaction occurred smoothly in the presence of several different Cu salts including $Cu(OAc)_2$, $CuSO_4$, CuI, and CuCl [157]. Various reaction conditions and catalytic systems can be used in such a reaction. For example, montmorillonite KSF clay supported CuO nanoparticles found to be efficient catalysts in one-pot aromatic azidonation of aryl boronic acids followed by the CuAAC reaction producing corresponding 1-aryl-1,2,3-triazole derivatives at room temperature [158]. Finally, magnetically recoverable and reusable $CuFe_2O_4$ nanoparticles were shown to be highly efficient catalysts for a one-pot synthesis of biologically important 1,4-diaryl-1,2,3-triazoles. Usage of aqueous reaction medium at room temperature, the low cost and facile recovery of the catalyst by application of an external magnetic field, and consistently high catalytic efficiency for at least three consecutive cycles render the protocol operationally attractive [159].



R^1 = vinyl, aryl, R^2 = alkyl, aryl.

Scheme 41 Synthesis of 1,4-diaryl-1,2,3-triazoles from boronic acids



R^1 =, aryl, R^2 = Me, Ph, CF_2H, CF_3; R^3 = CN, COOEt, COMe.

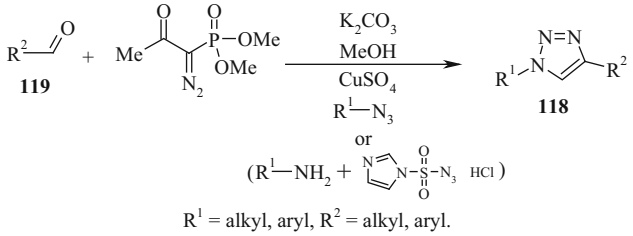
Scheme 42 One-pot synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from boronic acids

One of the main advantages of using boronic acids as azide precursor is the possibility to use them in cyclocondensation reactions with β-keto esters. The latter, in contrast to alkynes, are much less studied and allow regioselective introduction of substituents at position 5 of the triazole ring. Thus, a series of 1-aryl-5-trifluoromethyl (or difluoromethyl) 1,4,5-trisubstituted 1,2,3-triazoles **115** were synthesized in high yield by a novel one-pot three-component reaction of arylboronic acids **116**, sodium azide, and active methylene ketones **117**, such as ethyl 4,4-difluoroacetoacetate or ethyl 4,4,4-trifluoroacetoacetate in the presence of $Cu(OAc)_2$ and piperidine using a DMSO/H_2O (10/1) mixture as a solvent (Scheme 42) [160].

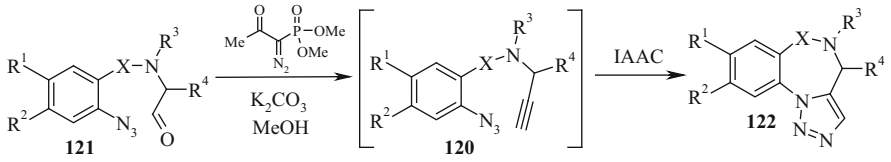
In summary, the reaction of in situ generated azides followed by CuAAC is a useful synthetic approach helping in the creation of compounds directed at different targets. For example, recently the generation of alkyl, benzyl, or aryl substituted bi- and tridentate pyridyl-1,2,3-triazole ligands [161], compounds with cytotoxicity activity [162], and other compounds assigned for biological activities screening research have been prepared [163, 164].

4 Generation of Alkynes with a Following AAC Reaction

Besides multicomponent strategies relying on in situ generation of the azido group, there are a large number of reports, focusing on the creation or modification of triple bonds or functionalization of substrates containing reactive groups for the synthesis of triazoles.



Scheme 43 One-pot reaction of terminal alkynes generation-AAC reaction



Scheme 44 Synthesis of 1,2,3-triazolo fused 1,4-benzodiazepines, 1,2,5-benzothiadiazepines, pyrrolobenzodiazepines, and pyrrolobenzothiadiazepines from the corresponding aldehydes

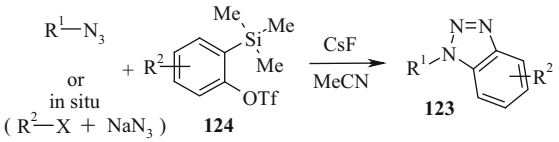
4.1 Tandem Ternary Bond Formation in AAC Reactions

The usage of the Ohira–Bestmann reagent (dimethyl-1-diazo-2-oxopropylphosphonate) in the Seyferth–Gilbert homologation reaction for the generation of terminal alkynes at low temperatures allows to combine this methodology in a one-pot AAC protocol. Such a reliable and operationally simple one-pot reaction for a one-carbon homologation provided 1,4-disubstituted 1,2,3-triazoles **118** in good to excellent yields from a variety of readily available aldehydes **119** without the need for isolation of the alkyne intermediates (Scheme 43) [165]. The reaction has a broad scope, allows the formation of new bioconjugates, and has been applied for the synthesis of new boronic acid-based fluorescent sensors [165], fluorescent amino acid derivatives as well as glycoconjugate mimetics [166]. The above-mentioned approach was used for the synthesis of triazolyl boronates [167].

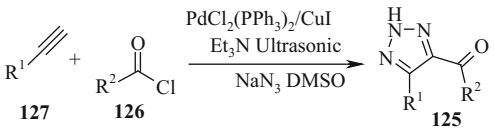
Furthermore, intramolecular 1,3-dipolar cycloaddition between alkynes **120**, usually obtained as transient intermediates, by treatment of the corresponding aldehydes **121** (derived from α-amino acids) with the Bestmann–Ohira reagent, and an azide leads to series of 1,2,3-triazoles **122** fused with 1,4-benzodiazepines, 1,2,5-benzothiadiazepines, pyrrolobenzodiazepines, and pyrrolobenzothiadiazepines (Scheme 44) [168].

Other methods of triple bond generation for 1,2,3-triazole synthesis were also published. For example, benzotriazoles **123** were prepared by the two-component [169] and three-component [170] classic or microwave-assisted [3 + 2] cycloadditions of sodium azide to benzyne generated from the reaction of an

Scheme 45 Benzotriazoles preparation via MCR



Scheme 46 One-pot Sonogashira coupling-1,3-dipolar cycloaddition reactions



R^1 = alkyl, aryl, Th, R^2 = aryl, furan, cyclohe-1en.

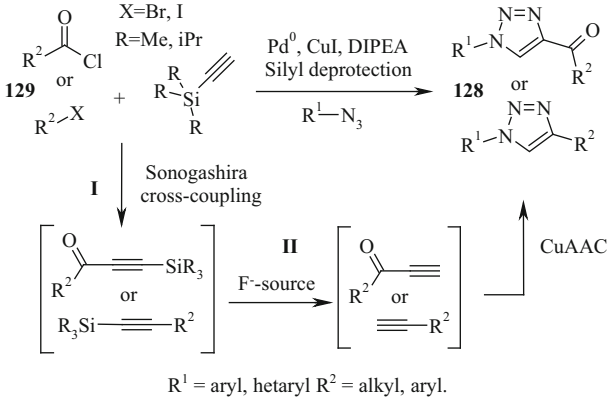
o-(trimethylsilylaryl) triflate **124** in the presence of arylmethyl halides with either CsF or KF/18-Crown-6. Good to excellent yields of benzotriazoles were obtained in 15–20 min when the microwave-assisted reactions were carried out at 125°C (Scheme 45). These reaction times are significantly faster than similar reactions carried out using conventional heating [170].

4.2 One-Pot Chemical Modification of Alkyne Functional Group Before CuAAC Reaction

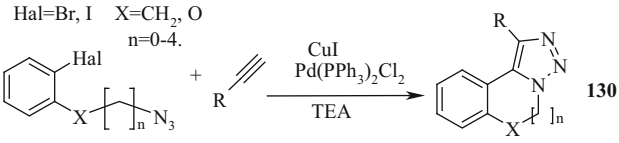
The terminal alkynes, before AAC reaction, may also undergo chemical transformations such as alkylation, arylation, and acylation. This approach allows to functionalize the desired 1,2,3-triazoles in a simple one-pot procedure. For instance, a novel and efficient one-pot way of 4,5-disubstituted-1,2,3-(NH)-triazoles **125** synthesis through palladium-catalysed and ultrasonic promoted Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides **126**, terminal acetylenes **127**, and sodium azide in one-pot (Scheme 46). The procedure is suitable for many substrates, and various 1,2,3-triazoles can be conveniently produced with excellent yields in a short time using cheap and easily available starting materials [171].

Another example of a one-pot synthetic approach was demonstrated for the synthesis of 1-substituted 4-acyl-1*H*-1,2,3-triazoles **128** [172, 173]. The reaction involves an initial preparation of TMS-protected or triisopropylsilyl (TIPS)-protected ynones from acid chlorides **129** and TMS or TIPS-acetylene **I**, followed by a TBAF/CuI, CuF_2,or AgF-mediated silanes deprotection **II** and Cu-catalysed Huisgen cycloaddition (Scheme 47). The increased chemical stability of TIPS-protected ynones is an important factor in the high overall product yield [173].

In 2005, the first successful palladium–copper catalysed reaction for the synthesis of fused triazoles **130** was described [174]. The mechanism of the reaction involved the catalytic cycle, which began with the formation of active Pd(0) species accompanied by the formation of an acetylenic dimer. Then coupling through the Sonogashira reaction could lead to the formation of an acylic precursor, which was



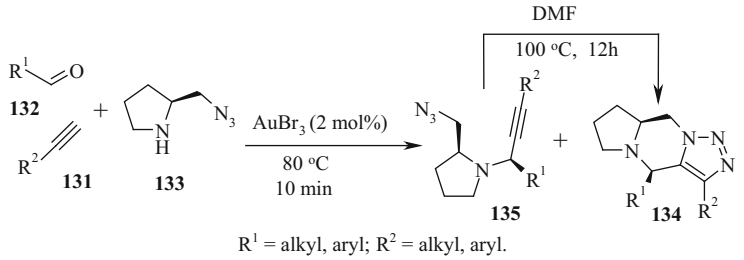
Scheme 47 One-pot three-step synthesis involving cross-coupling-CuAAC processes



Scheme 48 Palladium–copper catalysed reaction for the synthesis of fused triazoles

converted into the cyclic product through IAAC. Recently, a cascade palladium–copper catalysed procedure has been applied for the preparation of fused triazoles by using a bifunctional metal organic framework catalyst containing palladium and copper(II) benzene-1,3,5-tricarboxylate – MOF-Cu (BTC)-[Pd]. This catalyst enables the performance of the tandem Sonogashira/click reaction starting from 2-iodobenzylbromide, sodium azide, and alkynes to produce 8*H*-[1,2,3]triazolo[5,1-*a*]isoindoles with good yields under mild reaction conditions [175]. Moreover, such an approach allows to synthesize 1,2,3-triazoles **130** fused with five-, six-, seven-, and eight-membered benzoheterocycles, including isoindoline, tetrahydroisoquinoline, benzoazepine, and benzoazocine in one-pot as shown in Scheme 48 [176, 177]. The reactions are experimentally simple and utilize easily accessible substrates of different types.

Chen and co-workers attempted to combine, in a one-pot coupling reaction, terminal alkynes **131**, aldehydes **132**, and amines **133** with AAC reaction for the synthesis of several new 4,6,7,8,8*a*,9-hexahydropyrrolo[1,2-*a*][1,2,3]triazolo[1,5-*d*]pyrazines **134** (Scheme 49). The first step involves the $AuBr_3$-catalysed TCR of terminal alkynes, aldehydes, and amines under solvent-free conditions to provide the requisite propargylamines **135**, which undergo catalyst-free IAAC reactions to give the target triazoles. Unfortunately, in one-pot procedure pyrrolo[1,2-*a*][1,2,3]triazolo[1,5-*d*]pyrazine **134** was formed only in very low yields, so it was decided to perform the synthesis in a two-pot protocol, which diastereoselectively gave products in good to excellent yields in short reaction times [178].



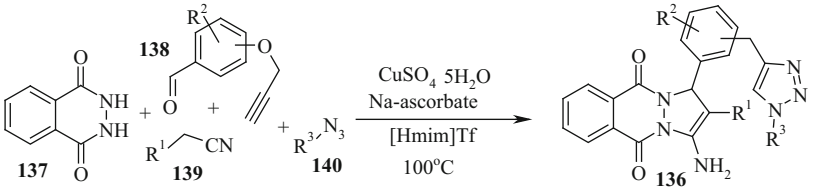
Scheme 49 Synthesis of propargylamines and 4,6,7,8,8*a*,9-hexahydropyrrolo[1,2-*a*][1,2,3]triazolo[1,5-*d*]pyrazines

4.3 Reaction Between Functional Groups in Substrates Containing Azido and Alkyne Moieties and Subsequent AAC Reaction

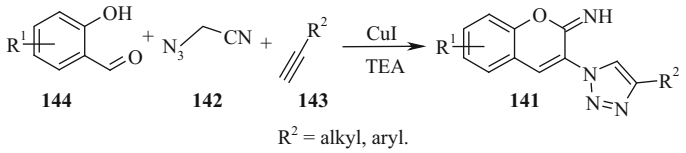
The chemoselectivity of the AAC reaction allows to carry out many parallel reactions, such as alkylation, acylation, and condensation. between a variety of functional groups of substrates containing azido and/or alkyne moieties. For instance, a copper(I)-catalysed 3CR of amines, propargyl halides, and azides forming 1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines in water was demonstrated [179]. Moreover, the application of combined enzyme-metal catalysed methodology allowed to obtain more sophisticated peptides and azides as substrates for the efficient generation of peptidomimetics in a one-pot fashion. For example, CAL-B (*Candida antarctica* lipase B) immobilized on an acrylic resin (Novozyme® 435) was found to catalyse the aminolysis of methyl esters with propargyl amine, furnishing propargyl amides which were consecutively transformed into amide ligated 1,2,3-triazoles using CuAAC, in good to excellent yields [180].

A simple and efficient method was proposed for preparation of 1-{[(1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives **136** in good to excellent yields by a one-pot four-component condensation reaction of phthalohydrazide **137**, a (propargyloxy)benzaldehyde **138**, an active methylene compound **139** (malononitrile or ethyl cyanoacetate), and an azide **140** in the presence of $Cu(OAc)_2$/Na-ascorbate as a catalyst and 1-methyl-1*H*-imidazolium trifluoroacetate ([Hmim]Tf) as an ionic liquid medium (Scheme 50). It is noteworthy that this domino reaction involved the formation of one C–C and four C–N bonds and of two heterocyclic scaffolds in a highly selective manner [181].

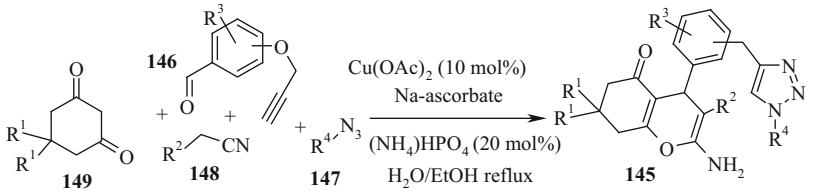
Continuing the above highlighted approach, a variety of 3-triazolyl-2-iminochromenes **141** were synthesized in a one-pot combined Cu(I)-catalysed cycloaddition between 2-azidoacetonitrile **142** and an acetylene **143** forming a triazole and the activated neighbouring methylene group, inducing an aldol-cyclization-dehydration sequence in the presence of a salicylaldehyde **144** (Scheme 51) [182].



Scheme 50 One-pot four-component synthesis of 1-[(triazolylmethoxy)phenyl]-1*H*-pyrazolo [1,2-*b*]-phthalazine-5,10-diones



Scheme 51 One-pot synthesis of 3-triazolyl-2-iminochromenes

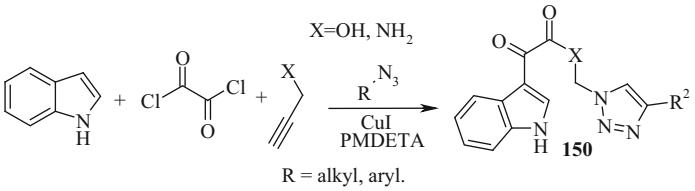


Scheme 52 One-pot synthesis of (1,2,3-triazolyl) methoxyphenyl tetrahydro-5-oxo-4*H*-chromene

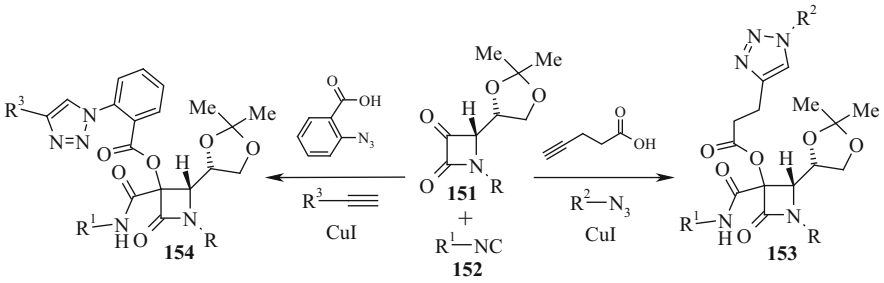
Furthermore, a one-pot procedure was described for the synthesis of (1,2,3-triazolyl) methoxyphenyl tetrahydro-5-oxo-4*H*-chromene derivatives **145** by concurrent reaction of aryloxy propargylated aldehydes **146**, various azides **147**, active methylene compounds **148**, and 1,3-cyclohexanediones **149** using catalytic amounts of $Cu(OAc)_2$/sodium ascorbate and diammonium hydrogen phosphate in aqueous ethanol media (Scheme 52) [183].

Stefani and co-workers developed a method for the synthesis of indole-3-glyoxyl-1,2,3-triazole derivatives **150** in a one-pot procedure shown in Scheme 53. Typically, the reactions were carried out in dry tetrahydrofuran by mixing indole, oxalyl chloride, a propargyl alcohol or amine and DIPEA at room temperature. Subsequent addition of organic azide, CuI, and PMDETA led to the formation of triazoles **150** [184].

During the last years, the application of the Passerini (P-3CR) and Passerini-Smiles reactions combined with CuAAC has drawn attention as a promising approach for the creation of combinatorial libraries for drug searching. Alcaide and co-workers demonstrated that the Passerini reaction could be coupled with CuAAC using the corresponding alkynes and azides to afford a family of mono-, bis-, and



Scheme 53 One-pot multicomponent synthesis of indole-3-glyoxyl triazoles

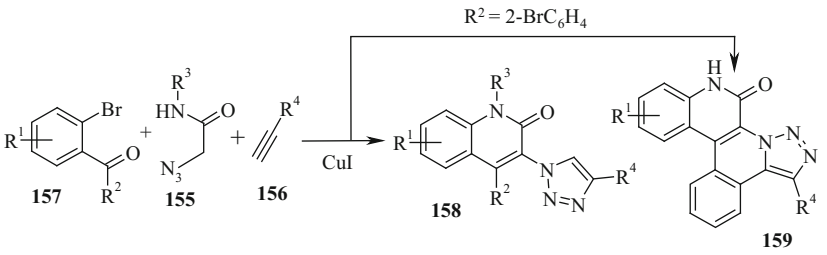


R =PMP, Aryl; R^1 = alkyl, aryl; R^2 = alkyl, aryl, Ts; R^3 = alkyl, aryl.

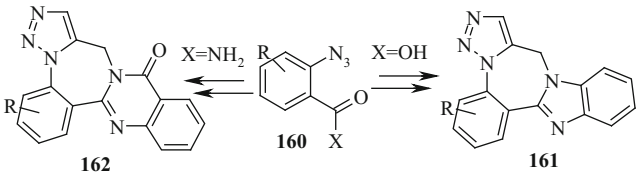
Scheme 54 Tandem Passerini-Smiles CuAAC reactions

tris(β-lactam-triazole) hybrids regioselectively. For both one-pot reactions Cu(I) salts were used under anhydrous conditions. For example, the treatment of azetidine-2,3-dione (+) **151** and isocyanide **152**, with 4-pentynoic acid and azides or 2-azidobenzoic acid with alkynes under CuI catalyst and 2,6-lutidine as base at room temperature afforded the corresponding β-lactam triazoles **153**, **154** in moderate to excellent yields (Scheme 54) [185].

Recently, a one-pot domino sequence azide–alkyne cycloaddition, a Goldberg amidation, Camps cyclization, and C–H arylation have been performed for rapid construction of complex heterocycles from three simple components under mild conditions. The proposed possible reaction steps included a CuAAC between a 2-azidoacetamide **155** and acetylene **156** leading to a triazole, in which the adjacent methylene group was activated. Then, in the presence of an *ortho*-carbonyl-substituted aryl halide **157**, the same catalytic system should enable an intramolecular Goldberg amidation, followed by the Camps cyclization (intramolecular aldol–dehydration sequence) to form the 2-quinolinone ring **158**. In case of more reactive electrophiles, such as 2-bromobenzaldehyde, an alternative sequence involving the Knoevenagel condensation followed by intramolecular N-arylation is also possible and leads to the same product **158**. When the R^2 substituent in **157** is the 2-bromoaryl group, a domino sequence should continue to evolve, as the triazolyl group is now perfectly positioned for an intramolecular copper-mediated C–H arylation to afford a pentacycle **159** (Scheme 55) [186].



Scheme 55 One-pot domino sequence AAC, Goldberg amidation, Camps cyclization, and C–H arylation



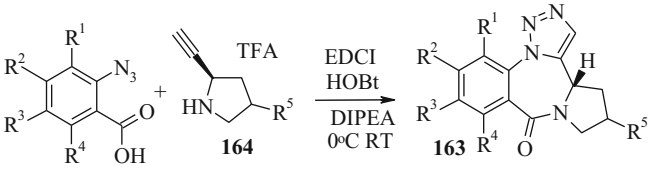
Scheme 56 Synthesis of polycyclic triazoles fused with the benzimidazole and quinazoline ring

4.4 Reaction Between Functional Groups in Substrates Containing Azido and Alkyne Moieties and Subsequent AAC Reaction Leading to the Formation of Polycyclic Compounds with the Fused Triazole Ring

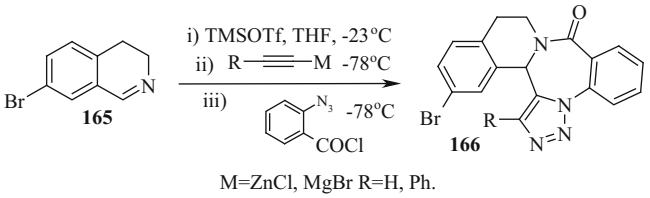
In this section, we focus on the class of reactions leading to the formation of the fused triazoles with unique structures. Typically, these reactions provide new heterocyclic systems, which are difficult or impossible to obtain by other methods or in multi-step manner.

One of the most convenient reagents for these reactions is *ortho*-substituted aromatic azides. For instance, at the end of the eighties of the last century Mohiuddin et al. suggested to use 2-azidobenzoic acid derivatives **160** for the synthesis of polycyclic triazoles fused with the benzimidazole **161** and quinazoline ring **162** in a simple way (Scheme 56) [187, 188].

Since then tandem reaction of *ortho*-substituted carboxylic azides became a very popular and effective strategy. For example, a one-pot synthesis of [1,2,3]triazolo [1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones was described starting from readily available anthranilic acids. The reaction involved amide bond formation employing polymer supported carbodiimide and subsequent 1,3-dipolar cycloaddition reaction. In addition, a number of reagents were tested to activate the *ortho*-azido benzoic acids towards amide bond formation using conventional solution phase methods (DCCI, EDCI, HOBt, etc.), but it was found that in none of the cases the desired adduct was isolated in pure form. In most instances only traces of the



Scheme 57 One-pot amide coupling and IAAC under catalyst-free conditions

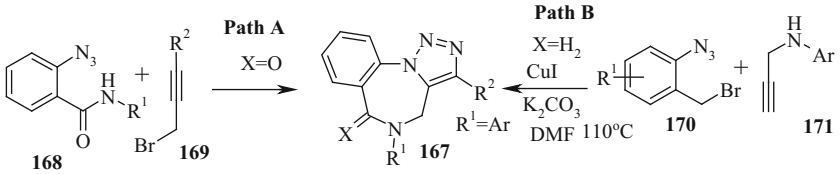


Scheme 58 One-pot synthesis of triazole scaffolds bearing the tetrahydroisoquinoline core

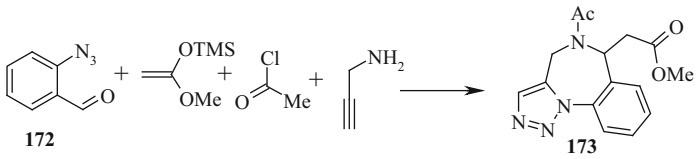
dipolar cycloaddition products were found, even after using excess amine and elevated temperatures [189]. Another example, demonstrated by Molteni et al., is the reaction between 2-methoxycarbonyl-3-thenylazide (3) and propargylamine, which led to the thieno[2,3-*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepine derivative in 25% yield [190]. Using cyclic amines, a one-pot synthesis of novel tetracyclic scaffolds, which incorporate a fusion of a proline, the 1,2,3-triazole ring with the [1,4]-benzodiazepin-8(4H)-one ring systems, was elaborated (Scheme 57). The key step of the reaction is the peptide bond formation followed by in situ 1,3-dipolar cycloaddition in the absence of any catalyst to form triazole **163**. Coupling between aromatic azido acid **160** and TFA salt of amine **164** was carried out in the presence of EDCI, HOBT, and DIPEA in dry DMF. These triazole compounds have been analysed for their efficacy as enzymatic protease inhibitors like serine protease, cysteine protease, and aspartase protease [191].

A novel multicomponent process was developed for the assembly of triazole scaffolds bearing the tetrahydroisoquinoline core. Isoquinolines **165** were allowed to react with either zinc phenylacetylide or ethynylmagnesium bromide in the presence of TMSOTf (Scheme 58) and then trapped with o-azidobenzoyl chloride. At room temperature, the amide thus produced readily underwent a dipolar cycloaddition to furnish the novel triazolo-1,5-benzodiazepin-2-ones **166** in 80–93% yields [192].

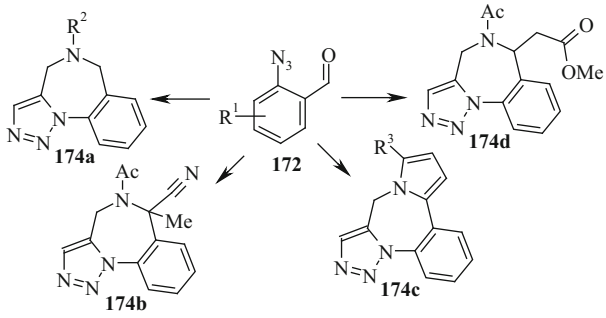
As shown above, intramolecular AAC reaction often takes place regioselectively without the use of a catalyst. Majumdar et al. reported a catalyst-free, one-pot strategy for the synthesis of 1,2,3-triazole-fused 1,4-benzodiazepinone derivatives **167** in good to excellent yields from N-substituted 2-azidobenzamides **168** and propargyl bromide **169**, in the presence of base, via N-alkylation followed by a 1,3-dipolar cycloaddition (Scheme 59, Path A) [193]. The current approach was modified by the use of o-azidobenzylbromide **170** and N-propargylated aniline



Scheme 59 Domino strategies for the synthesis of 1,2,3-triazole-fused 1,4-benzodiazepinones



Scheme 60 Tandem MCR/AAC procedure

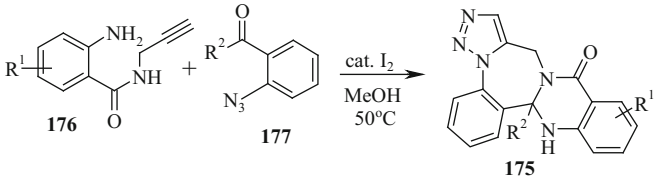


Scheme 61 Synthesis and diversification of 1,2,3-triazole-fused 1,4-benzodiazepines

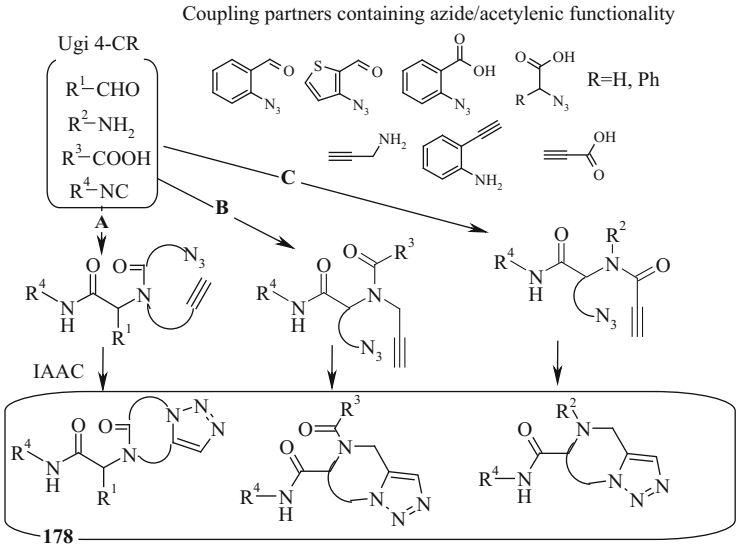
derivatives **171** in the presence of CuI and base. According to this strategy, triazolo [1,5-*a*][1,4]benzodiazepines **167** with methylene instead of the carbonyl group were prepared (Scheme 59, Path B) [194].

Replacement of the carboxyl group by an aldehyde functionality, in *ortho*-substituted aromatic azides, has provided a new design of domino reactions. Thus, cascade reactions were constructed involving condensation of 2-azidobenzaldehyde **172** with propargyl amine furnishing an imine that was treated with acetyl chloride and a ketene acetal to furnish the triazole **173** via a [3 + 2] dipolar cycloaddition (Scheme 60). The key element of the strategy is a one-pot process incorporating four components [195].

Recently, a substituted heterocyclic scaffold, comprising a 1,4-benzodiazepine fused with a 1,2,3-triazole ring **174a–d**, was synthesized from 2-azidobenzaldehyde **172** employing a reductive amination or amination combined with nucleophilic addition, followed by a thermally induced, intramolecular Huisgen cycloaddition (Scheme 61) [196]. Furthermore, it was shown that this strategy was suitable for the



Scheme 62 One-pot two-step cascade synthesis of quinazolinotriazolobenzodiazepines

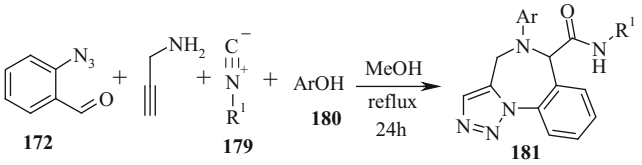


Scheme 63 Fused triazole derivatives by the sequential Ugi and IAAC

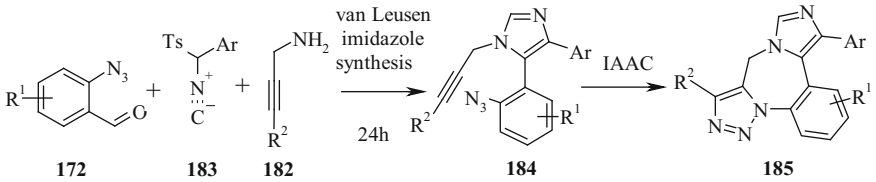
preparation of diverse libraries of compounds, tested in a wide range of biological assays [197].

A one-pot two-step cascade method was developed to afford quinazolino[1,2,3]triazolo[1,4]benzodiazepines **175** via sequential quinazolinone-forming condensation and IAAC reactions. Step one consists of an anilinoketo condensation to form a Schiff base and subsequent nucleophilic attack by the amide nitrogen onto the imine to form an aminal (quinazolinone). These two iodine-promoted condensations preorganize the alkyne (from **176**) and azide (from **177**) groups for an intramolecular 1,3-dipolar cycloaddition (step two) to form a complex pentacyclic system (Scheme 62) [198].

Akritopoulou-Zanze and co-workers elaborated the facile construction of fused triazole derivatives **178** by a sequential Ugi and IAAC. The synthetic sequence is described in Scheme 63. A variety of six- and seven-membered ring systems fused to triazoles have been synthesized as the authors successfully used coupling partners containing an azide functionality on the carboxylic acid (Route A) or aldehyde



Scheme 64 Tandem four-component Ugi-Smiles-type AAC reactions



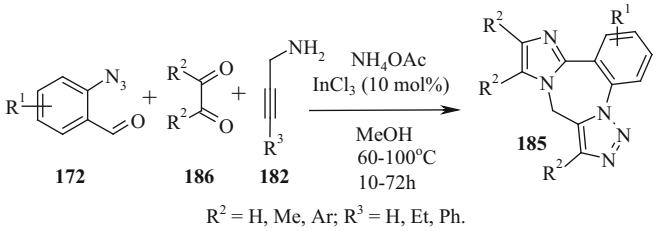
Scheme 65 Sequential van Leusen/alkyne-azide cycloaddition reactions

inputs (Routes B and C) and acetylenic functionalities on the amine (Routes A and B) or carboxylic acid (Route C) inputs [199].

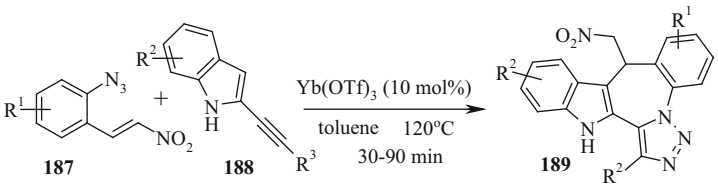
Moreover, it was shown that the use of 2-azidobenzaldehyde **172** and propargylamine in a Ugi-Smiles coupling gave an easy access to 4,5-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine derivatives **181**. The approach is based on the reaction between 2-azidobenzaldehyde, propargylamine, isocyanides **179**, and nitrophenols **180** in methanol under reflux conditions without using additional reagents or catalysts (Scheme 64). In addition, two possible reaction mechanisms were proposed. The first mechanism supposes that the formation of Ugi adduct takes place before AAC; while according to the second mechanism, the cyclization reaction and the formation of the benzodiazepine ring are prior to the Ugi reaction [200].

Furthermore, a fused triazolo imidazole derivative synthesis was reported with good overall yields by a van Leusen/alkyne–azide cycloaddition synthetic sequence from simple starting materials in an expedient fashion (Scheme 65). The use of azide **172** containing the aldehyde moiety, alkyne **182** containing the amine, and isocyanide **183** resulted in a four-component Ugi-Smiles-type reaction providing the intermediate for the van Leusen reaction which led to substrate **184**. Subsequent cyclization via the IAAC allows access to the fused triazolo imidazole scaffolds **185** [201].

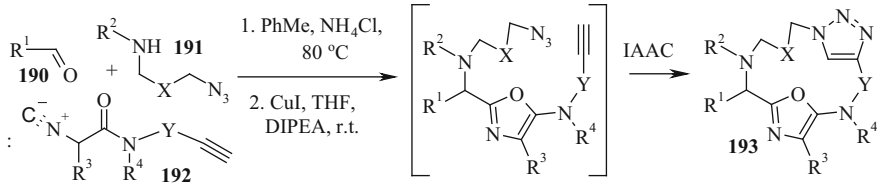
Another example of a fused imidazotriazolobenzodiazepines derivatives **185** synthesis was demonstrated via the transformation, incorporating α-diketones **186**, o-azidobenzaldehydes **172**, propargylic amines **182**, and ammonium acetate via indium(III)-catalysed reaction (Scheme 66). This process involves tandem $InCl_3$-catalysed cyclocondensation and IAAC reaction. A series of transition metal Lewis acids [$Cu(OAc)_2$, $FeCl_3$, $Zn(ClO_4)_2$, $Sc(OTf)_3$,$CeCl_3$, $InCl_3$, $InBr_3$] were examined for their ability to activate 1,2-dicarbonyl electrophiles **186** [202].



Scheme 66 Imidazotriazolobenzodiazepines via indium(III)-catalysed MCRs



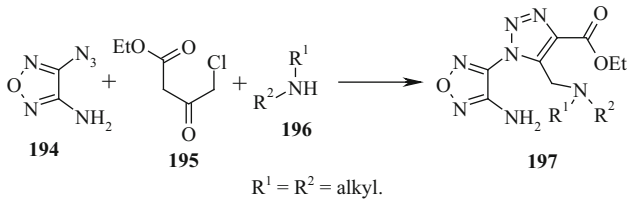
Scheme 67 Cascade Michael addition–IAAC reactions



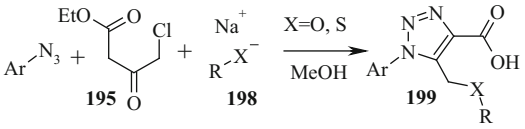
Scheme 68 One-pot synthesis of macrocycles by a three-component reaction/[3 + 2] cycloaddition

Moreover, the 2-nitrovinyl moiety (compound **187**) was used as synthetic equivalent of the aldehyde group. Such a replacement allows to synthesize indole-based polyheterocycles via a sequential Lewis acid catalysed Michael addition and an IAAC reaction. As a result of such a strategy, tetracyclic indolo[2,3-*c*][1,2,3]triazolo[1,5-*a*][1]benzazepines **189** were synthesized in good yields under mild reaction conditions from indole **188** in a one-pot reaction (Scheme 67) [203].

In addition, a straightforward synthesis of complex macrocycles was described from readily accessible starting materials by a tandem process involving a three-component reaction between an aldehyde **190**, an ω-azido amine **191**, and an isocyanoacetamide **192** and subsequent IAAC, which led to macrocyclic 1,2,3-triazoles **192** in good yields (Scheme 68) [204].



Scheme 69 N-nucleophiles in subsequent SN-azides cyclocondensation reactions



Scheme 70 S-, O-nucleophiles in subsequent SN-azides cyclocondensation reactions

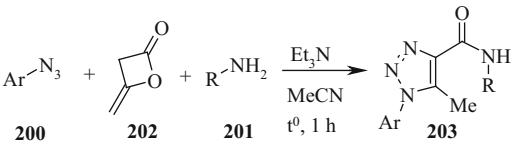
5 One-Pot Multi-Step Triazole Synthesis Involving Azide Reactions with Activated Acetonitriles or Ketomethylenic Compounds and Subsequent Triazole Function Group Transformation

The reactions of azides with active methylene reagents are less studied than the AAC, but they also were amenable to multicomponent strategies. For instance, the 1-(4-aminofurazan-3-yl)-5-dialkylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acids **197** were prepared by a one-pot procedure using 3-azido-2-amino-1,2,5-oxadiazole **194**, ethyl chloroacetoacetic acid **195** and an excess of the appropriate amines **196** (Scheme 69) and tested in a GSK-3 inhibition assay [205].

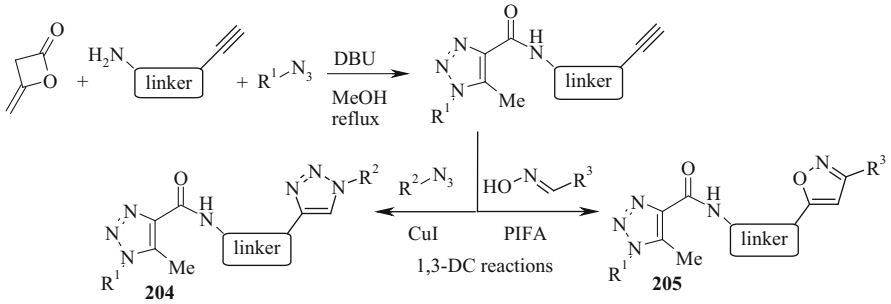
For diversification of such a strategy, O- or S-nucleophiles **198** were used and the optimization of reaction conditions led to substituted 1*H*-1,2,3-triazole-4-carboxylic acids **199**. The reaction of azide with **195** and O-nucleophile (methylate anion) was carried out under strict control of temperature to avoid undesirable reactions, and yields of triazoles **199** were moderate (Scheme 70) [206].

In 2009, Pokhodylo and co-wokers elaborated a convenient synthetic protocol for the creation of combinatorial libraries of 1-(R^1-phenyl)-5-methyl-*N*-R^2-1*H*-1,2,3-triazole-4-carboxamides **203** from commercially available or readily prepared azides **200**, amines **201**, and diketene **202**. It was noted that the reaction of diketene with highly nucleophilic amines and reactive azides proceeded at room temperature, and the yields of the reaction increased with an increase of amine basicity (Scheme 71) [207].

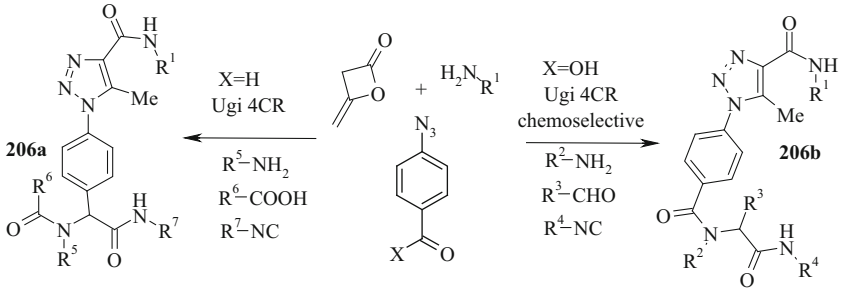
Recently, this strategy has been combined with 1,3-dipolar cycloaddition to an efficient chemoselective methodology for the syntheses of unsymmetrical bis (1,2,3-triazole) (**204**) [208] and isoxazole (**205**) [209] derivatives (Scheme 72). This protocol utilizes alkynyl-substituted amines as bifunctional linkers to conjoin a



Scheme 71 One-pot multicomponent synthesis of 1-aryl-5-methyl-*N*-R^2-1*H*-1,2,3-triazole-4-carboxamides



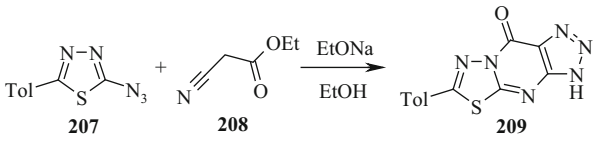
Scheme 72 Chemoselective preparation of 1,2,3-triazole-triazole/isoxazole peptidomimetics



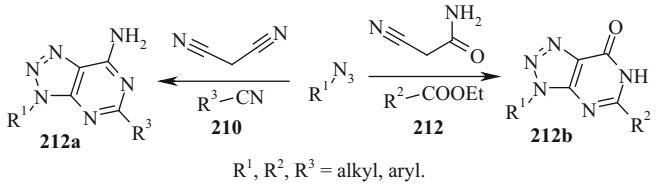
Scheme 73 The 3CR synthesis of 5-methyl-1*H*-1,2,3-triazoles combined with Ugi four-component reaction

copper-free three-component cycloaddition with a cycloaddition in a one-pot procedure. In particular, this methodology is suitable for the synthesis of unsymmetrical bisfunctional-modified peptidomimetics by the combination of MCRs in a sequential process, which allows direct access to complex structures from simple building blocks.

Furthermore, the protocol for a three-component synthesis of 5-methyl-1*H*-1,2,3-triazoles was combined with the Ugi four-component reaction, which allowed to construct diversified 5-methyl-1*H*-1,2,3-triazole modified peptidomimetics **206a**,**b**. The protocol can be useful in biochemistry and medicinal discovery (Scheme 73) [210].



Scheme 74 Domino transformation leading to [1,3,4]thiadiazolo[3,2-a][1,2,3]triazolo[4,5-d] pyrimidine



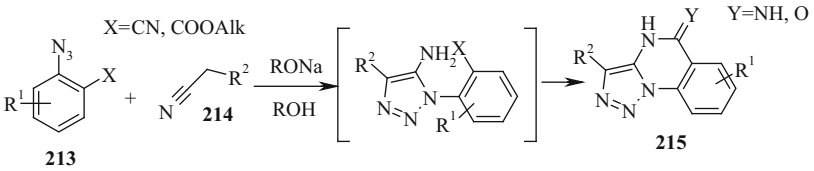
Scheme 75 Subsequent triazole formation and pyrimidine ring annulation

Base catalysed azide reactions with activated acetonitrile occur quite rapidly, allowing to obtain triazoles with a functional group capable for subsequent one-pot domino transformations. For example, 6-(4-methylphenyl)-[1,3,4] thiadiazolo[3,2-*a*][1,2,3]triazolo[4,5-*d*]pyrimidin-9(1*H*)-one **209** was prepared from 2-azido-5-(4-methylphenyl)-1,3,4-thiadiazole **207**, ethyl cyanoacetate **208** and sodium ethoxide as a catalyst (Scheme 74). The reaction involves triazole formation, the Dimroth rearrangement, and thiadiazole acylation by the carboxylic group [211].

Another multicomponent methodology was elaborated for the synthesis of azapurine-related compounds **212** starting from azides, malononitrile or cyanacetic derivatives and an aliphatic or aromatic nitrile **210** or ester **211**. The approach involves the formation of a triazole containing amino and either a carbonyl, amide or nitrile group that undergo the following tandem transformation to annulated pyrimidines (Scheme 75) [212–220].

6 Domino Reactions of *Ortho*-Substituted Azides with Active Methylene Compounds

The reactions of *ortho*-substituted aromatic azides with activated acetonitrile were the first examples of domino strategies, which led to 1,2,3-triazole preparation. In 1966, G. Tennant showed that o-azidobenzoic acid **213a** condensed with phenylacetonitrile **214a** in methanolic sodium rnethoxide to give 4,5-dihydro-5-oxo-3-phenyl-l,2,3-triazolo[l,5-*a*]quinazoline **215** (Scheme 76) [221]. This work has inspired a series of similar transformations, which allowed obtaining new complex fused heterocyclic systems with various substituents for the study of their properties. For

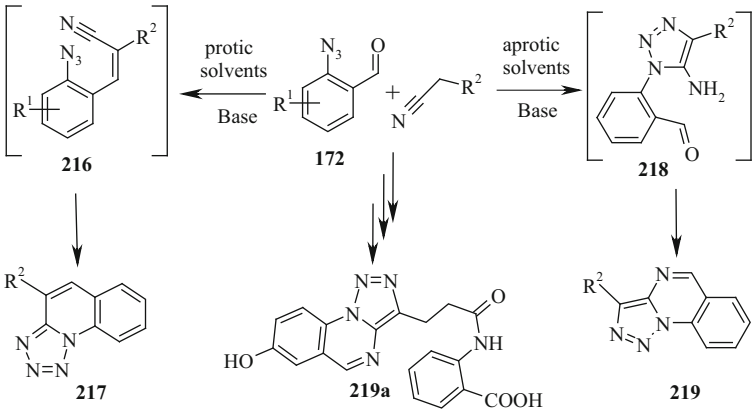


R^2 = Ar, COOEt, CONR, COHet, SO_2Ar, isooxazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, thiazol-2-yl.

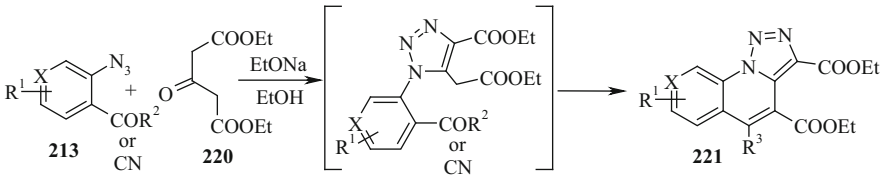
Scheme 76 Domino reactions of *ortho*-CN or COOR aryl azides with activated acetonitrile

instance, such a base-catalysed condensation of the substituted o-azidobenzonitrile **213b** was studied with active methylene compounds containing a cyanogroup, such as arylacetonitrile, arylsulphonylacetonitriles, cyanoacetic acid, ethyl cyanoacetate, cyanoacetamide, and malononitrile, giving high yields of triazolo[l,5-*a*]quinazolines **215** (Scheme 76) [222–224]. Moreover, novel 3-substituted-1,2,3-triazolo[1,5-*a*] quinazolinones **215** were synthesized in high yields via anionic domino reaction with acetonitriles activated by the thiazole, benzothiazole, 1,3,4-oxadiazole, and 1,2,4-oxadiazole rings. It was shown that acetonitriles exhibited high reactivity and were convenient methylenic compounds for such reactions providing rapid structural variation [225–227]. Further applications of such reactions included the reaction of the homolog of amino benzoic este, leading to the formation of 4*H*-[1,2,3]triazolo [1,5-*a*][1,3]benzodiazepin-5(6*H*)-ones [228]. Recently, some 3-ethoxycarbonyl or 3-phenyl-substituted 1,2,3-triazolo[1,5-*a*]quinazolines have been synthesized using domino reaction as a key step, and the biological affinity towards benzodiazepine and A1 and A2A adenosine receptors was evaluated [229]. 3-Arylsulphonyl-[1,2,3] triazolo[1,5-*a*]quinazolines were synthesized as targocil analogues and tested as Wall Teichoic Acid biosynthesis inhibitors [230, 231]. Additionally, a combinatorial library consisting of the substituted 3-phenylsulphonyl-[1,2,3]triazolo[1,5-*a*] quinazolines was created and a study of the relation of their structure with 5-HT6 receptor antagonistic activity was undertaken [232].

When replacing the carboxyl group at the aldehyde moiety in starting azide component the possibility of alternative Knoevenagel condensation appears instead of 1,2,3-triazolo[l,5-*a*]quinazoline formation. However, condensation of malononitrile with 2-azidobenzaldehyde **172** yielded cyano-l,2,3-triazolo[l,5-*a*] quinazoline **219** or tetrazolo[l,5-a]quinoline **217** depending on the base and reaction conditions. In protic solvents, 2-azidobenzaldehyde **172** undergoes a base-catalysed condensation with cyanide-stabilized carbanions to generatethe corresponding intermediate **216**, which then forms tetrazolo[l,5-*a*]quinolines **217**, whereas in aprotic media intermediate **218** leads to 1,2,3-triazolo[l,5-*a*]quinazolines **219** (Scheme 77). The attack of cyanide-stabilized carbanions on azide functions led to the formation of 1,2,3-triazole **219** [233]. This approach was used for the preparation of tricyclic agonists **219a** for the high affinity niacin receptor G-protein-coupled receptor (GPR) 109A [234, 235]. The use of *ortho*-keto azides in domino reactions also was studied in several reports. For example, regioselective attack of cyanide-stabilized carbanions at the azide instead of carbonyl group of



Scheme 77 Aromatic *ortho*-aldehyde azides in domino reaction



Scheme 78 Domino reaction of 1,3-acetonedicarboxylate with *ortho*-substituted azides

2′-azidoacetophenone led to the formation of 5-methyltriazolo[l,5-*a*]quinazolines [233]. Recently, synthesis and purification of aryl azides were reported to be incorporated into a multistep flow sequence to generate triazolo[l,5-*a*]quinazoline directly from aniline starting materials in a fully automated fashion [236].

Smalley and Teguiche reported the preparation of 1,2,3-triazolo[1,5-*a*]quinoline-4,5-dicarboxylates **221** by the action of the diethyl 1,3-acetonedicarboxylate **220** anion on *ortho*-substituted aryl azides o-azidoacetophenones, o-azidobenzaldehyde **172** and methyl o-azidobenzoate **213a**. The anion was formed using either sodium alkoxide in the appropriate alcohol or by an ion-exchange resin [Amberlite IRA-400 (OH)]. Furthermore, the authors demonstrated application of heterocyclic azides. It was found out that 3-azido-4-cyanopyridine **213b** and ethyl 3-azidopyridine-4-carboxylate **213c** behaved similarly with activated acetonitriles to produce the amino/oxy-l,2,3-triazolo[1,5-*a*][1,7]naphthyridine **221** respectively (Scheme 78) [237].

Westerlund reported the first synthesis of a new system 1,2,3-triazolo[1,5-*a*] thieno[3,2-*d*]pyrimidine **222** by the reaction of active methylene nitriles with 3-azido-2-substituted thiophenes [238]. Recently, thienopyridines have been prepared from 3-cyanopyridine. An anionic domino reaction with nitriles, possessing an active methylene group, gave a new polycyclic system. The reaction takes only a few minutes and products are obtained in high yields after crystallization from the reaction mixture without further purification. This approach allows the synthesis of

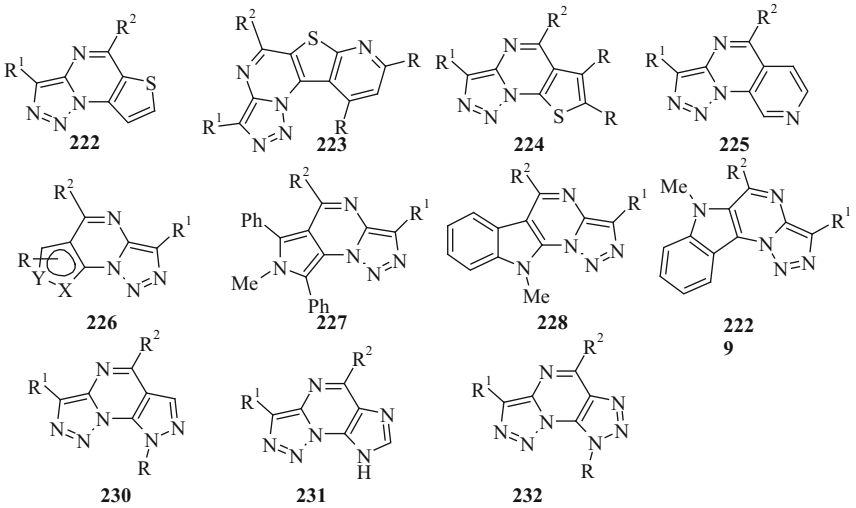
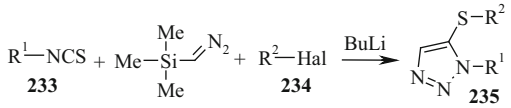


Fig. 3 Heterocyclic [1,2,3]triazolo[1,5-*a*]pyrimidine via domino reaction

derivatives of the new heterocyclic system pyrido[3′,2′:4,5]thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **223** [239]. Such heterocyclic systems became main scaffolds for evaluation of biological activity and a domino reaction is generally used for the creation of the corresponding compounds libraries. For instance, representatives of thieno[3,2-*d*][1,2,3]triazolo[1,5-*a*]pyrimidine **222** were selected for anticancer screening against a panel of 60 human tumour cell lines [240]. A number of 3-(phenylsulphonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines were prepared and their 5-HT6 receptor binding affinity and ability to inhibit the functional cellular responses to serotonin were evaluated [241]. Furthermore, by high-throughput screening, a triazolothienopyrimidine UT-B inhibitor that selectively and reversibly inhibited urea transport with $IC_{50} = 25.1$ nM and reduced urinary concentration in mice was identified [242]. In addition, a novel class of triazolothienopyrimidine (TTPM) compounds was identified as potent HIV-1 replication inhibitors during a high-throughput screening campaign that evaluated more than 200,000 compounds using a cell-based full replication assay [243]. Pokhodylo and co-workers reported the synthesis of derivatives of a new ring system thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **224** in high yields via an anionic hetero-domino reaction. It was found out that 2-azidothiophenes reacted with acetonitriles in sodium methoxide methanol solution with appreciable exothermal effect and the reaction was completed within 1–2 min. Notably in general the product of the reaction was formed immediately after mixing the reagents except for phenylacetonitrile, which reacted slower [244]. This method is not working for shielded carbonyl starting materials. In this case, reaction stopped at the formation of the intermediate aminotriazole, instead going to the expected thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine (Fig. 3) [245].

Scheme 79 Non-azidic multicomponent triazole synthesis



R^1 = alkyl, aryl; R^2 = alkyl.

Lauria and co-workers have reported several examples of the use of these domino reactions to obtain five-membered nitrogen heterocycles.. Firstly, derivatives of the new ring system pyrrolo[3,4-*e*][1,2,3] triazolo[1,5-*a*]pyrimidine **226**, **227** were prepared in high yields by a one-step reaction of azidopyrrole and substituted acetonitriles [246, 247]. Then the derivatives of the new ring system indolo[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **228** were easily prepared from 2-azidoindole. It was the first example of an anionic domino reaction in the indole series [248]. Later, indolo[2,3-e][1,2,3]triazolo[1,5-*a*]pyrimidine derivatives **229** were obtained from 3-azidoindoles. It was also noted that all the fused [1,2,3] triazolo[1,5-*a*]pyrimidines can be used as models for the design of DNA-interactive compounds [249, 250]. The reaction is used for pyrazole **230**, imidazole **231**, and triazole **232** azides leading to pyrazolo[3,4-d][1,2,3]triazolo[1,5-*a*]pyrimidines [251, 252], 8*H*-[1,2,3]triazolo[5,1-*b*]purines [253] and triazolo[4,3-*e*]-v-triazolo [l,5-*a*]pyrimidines [254–256].

7 Non-Azidic Multicomponent Triazole Synthesis

In this final section attention is drawn to the fact that not only azides may be precursors in the synthesis of triazoles **235** via multicomponent strategies. Unfortunately, alternative reactions are less studied, since in many cases the use of azides is favourable due to the high accessability. However, attention may be given to trimethylsilyldiazomethane as triazole precursor. In several reports, one-pot synthesis of 1-substituted-5-alkylthio-1.2.3-triazoles was demonstrated by the treatment of isothiocyanates **233** with lithium trimethylsilyldiazomethane, prepared from $TMSCHN_2$ and n-butyllithium, followed by quenching with alkyl halides **234** (Scheme 79) [257–260].

8 Conclusion

From the reviewed reports it appears obvious that the high rate of azide reactions with alkynes, as well as with methylene active compounds, in combination with a high chemoselectivity of these reactions, makes it possible to combine them with a variety of organic reactions in a one-pot procedure to provide multicomponent domino reactions. By such reactions, the preparation of 1,2,3-triazoles with unique structure, valuable properties in a convenient, economical, and safe way is possible.

9 Addendum

This review covered the field up to November 30, 2013.

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1,2,3-Triazoles Fused to Aromatic Rings

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Abstract The structure, synthesis, reactivity and applications of 1,2,3-triazoles fused to aromatic rings are described. These compounds have been classified in two groups by a structural approach: (a) fused 1,2,3-triazoles without a bridgehead nitrogen atom and (b) fused 1,2,3-triazoles with a bridgehead nitrogen atom. Although both systems present a similar structure, the synthetic procedures and their reactivity are different.

Keywords 1,2,3-Triazoles · Benzotriazoles · Triazolopyridines · Triazolopyrimidines

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Abbreviations

2-PyCHO	2-Pyridylcarboxyaldehyde
AIBN	Azobisisobutyronitrile
ArNs	Aromatic nucleophilic substitution
Boc	Tertbutoxycarbonyl
Bt	1*H*-1,2,3-Benzotriazol
BuLi	Butyllithium
Cod	Cyclooctadiene
DMAD	Dimethyl acetylenedicarboxylate
DMF	Dimethylformamide
El	Electrophile
Et	Ethyl
FVT	Flash vacuum thermolysis
LDA	Lithium diisopropylamide
LiTMP	Lithium tetramethylpiperidine
NBS	*N*-Bromosuccinimide
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
NOS	Nitric oxide synthase
Nu	Nucleophile
OAc	Acetoxy
Ph	Phenyl
THF	Tetrahydrofuran
TMSCN	Trimethylsilyl cyanide
$TMSN_3$	Trimethylsilyl azide
Tp	[1,2,3]triazolo[1,5-*a*]pyridine
TPT	Triazolopyridine-pyridine-triazolopyridine
TsN_3	Tosyl azide

1 Introduction

Fused 1,2,3-triazoles represent a large family of compounds that are applied in different scientific fields, covering from organic synthesis until copper conservation or highly energetic materials. The scope of the fused triazoles treated in this chapter involves systems with two aromatic rings of which one is a 1,2,3-triazole ring and the other is a six-membered aromatic ring. Such compounds have extensively been reviewed in the Comprehensive Heterocyclic Chemistry collection [1, 2]. In order to classify these compounds a structural approach has been reported: (a) Compounds without any bridged nitrogen atom, and the simplest structure is benzotriazole (**Bt**, **1**) reported by Chattaway and Orton in 1901 [3] (Fig. 1). This compound was initially named as azimido benzene. (b) Compounds with one of the three nitrogen acting as a bridge atom, with [1,2,3]triazolo[1,5-*a*]pyridine (**Tp**, **2**) as

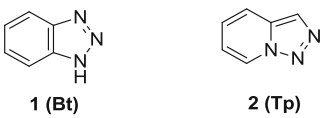


Fig. 1 1,2,3-Triazoles fused to aromatic rings

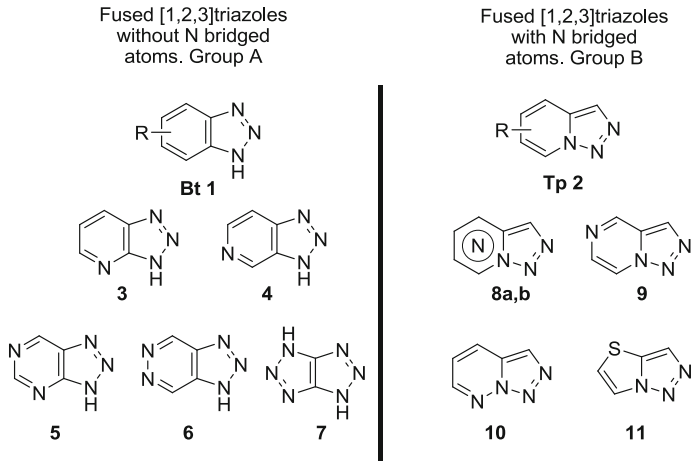


Fig. 2 Fused 1,2,3-triazoles classification

the simplest compound of the group. The first report concerning this structure was the corresponding protonated compound reported in 1953 by Kuhn and Munzing [4]. Although both systems present a similar structure, the synthetic approaches towards them and their reactivity show themselves to be completely different.

2 1,2,3-Triazoles Fused to Aromatic Rings, Structure and Classification

Fused 1,2,3-triazoles having no nitrogen bridge atoms are a large family of compound with benzotriazole **1** as the most studied. The fusion of 5- and 6-membered aromatic rings, with the former 1,2,3-triazole, allows the possibility of another heterocyclic ring (i.e. pyridine) replacing benzene. [1,2,3]Triazolo[4,5-*b*] pyridine (**3**) or [1,2,3]triazolo[4,5-*c*]pyridine (**4**) are the closest systems to **1** reported in the literature (Fig. 2). [1,2,3]Triazolo[4,5-*d*]pyrimidine (**5**) and [1,2,3]-triazolo[4,5-*d*] pyridazine (**6**) systems are also included in this group (Fig. 2). Although these compounds represent the majority of the reported structures, some examples of fused 5+5 aromatic ring 7 can also be found in the literature; however, they are rare structures not deeply investigated compared to the 5+6 family.

The second family of fused 1,2,3-triazoles involves the sharing of one of the 1,2,3-triazole nitrogen atoms by both aromatic rings (either 6+5 or 5+5). As

mentioned before, the simplest compound of this group is [1,2,3]triazolo[1,5-*a*] pyridine (**2**, **Tp**). In this family, pyrimidine [1,5-*a*] (**8a**) and [1,5-*c*] (**8b**), pyrazine (**9**) and pyridazine (**10**) derivatives have also been reported and even some examples of 5+5 systems **11**. This family has been significantly less applied in comparison to the benzotriazole analogues, although they have interesting properties due to the presence of the nitrogen atom in both aromatic rings.

3 Group A: Fused 1,2,3-Triazoles Without a Bridgehead Nitrogen Atom

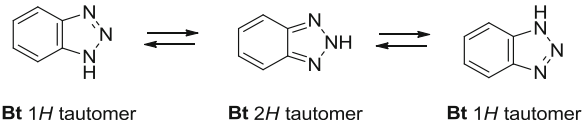
3.1 Structure: Tautomerism and Ring-Chain Isomerization

The particular arrangement of the three nitrogen atoms of benzotriazole gives rise to a special feature for these compounds. Firstly, benzotriazole shows proton tautomerism (Scheme 1). 1*H* and 2*H* **Bt** structures are in equilibrium. Wofford et al. reported in 1982 that in solution the 1H tautomer is the major compound [5]. However, several studies indicate that the 2H tautomer is observed in the gas phase at 0°K, with tautomer 1H increases its population at higher temperature. In terms of lone pair repulsion, it is clear that the 2H tautomer is more stable; however, theoretical calculations indicate that the more stable is the 1H tautomer [6].

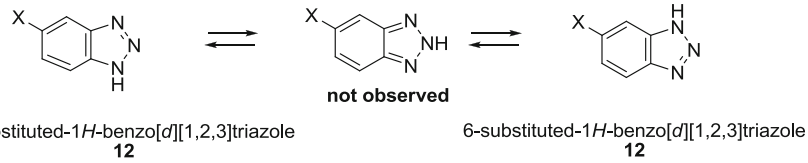
This particular characteristic has consequences for the benzotriazole nomenclature, and as long as two 1*H* structures are possible (Scheme 2), the mixture of them must be specified, for example, 5(6)-substituted-1*H*-benzotriazole (**12**).

This kind of phenomena is also present in *N*-alkylated benzotriazoles (Scheme 3). Known as cationtropic tautomerism and initially reported by Katritzky, this peculiarity allows the equilibrium between 1N and 2N alkylated **Bt**. *N*-Dialkylmethyl-aminobenzotriazole **13** exists as the N1 isomer in the solid state; however, in solution (in nonpolar solvents) or the gas phase, both isomers are present in a 2:1 ratio [7]. Analogues with oxygen **14a** [8] or sulphur **14b** have also the same feature [9]; however, with these heteroatoms, the interconversion is less fast and both 1N and 2N systems can be isolated.

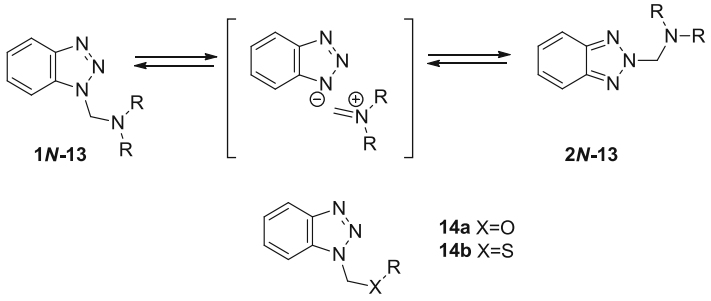
Benzotriazoles also present a particular property in their structures that has been less studied. Indeed they present an opened form in equilibrium with a closed form. Normally this equilibrium is completely on the closed form because of its larger stability. The open form may correspond to a molecule with resonance structures like an ortho-quinoid diazoimine and a benzene ring with a diazonium and an amide as substituents (Scheme 4). Although the detection of the opened forms remains difficult, Katritzky has reported one example with a compound that requires this form as the intermediate to explain the observed equilibrium between the two structures. The only possibility to go from structure **15A** to structure **15B** is through such opened form [10]. This isomerization, being anecdotic in the benzotriazole family, is very common in triazolopyridines (Scheme 4).



Scheme 1 Benzotriazole tautomerism



Scheme 2 Substituted benzotriazole tautomerism



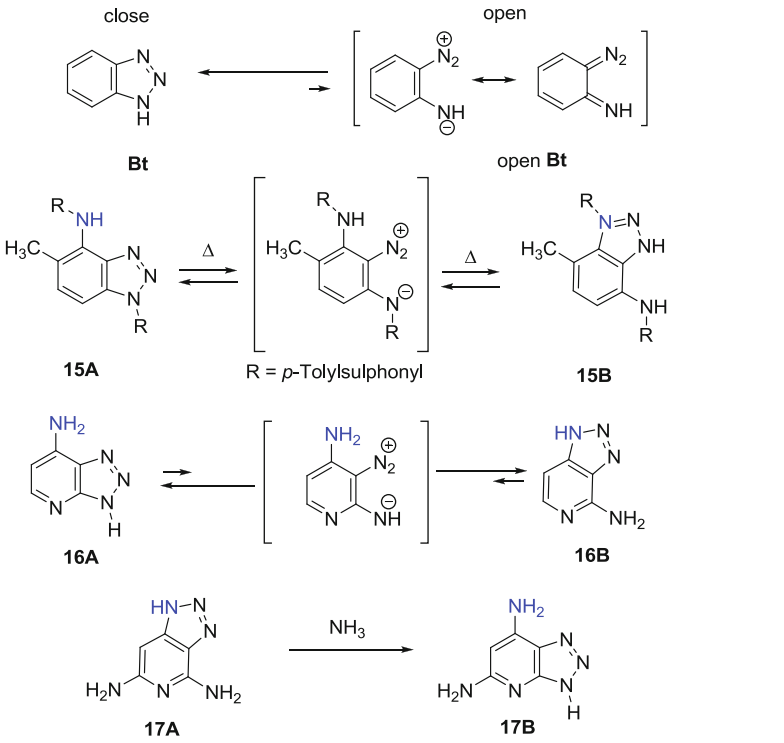
Scheme 3 Cationtropic tautomerism

For example, compound **16** is in equilibrium between **A** and **B** forms; hence it must be necessary to go through the open form [11]. Compound **17A** is also a good example of this ring-chain isomerization. In the presence of ammonia at 150°C, it converts into **17B** by means of an opened diazo system [12, 13].

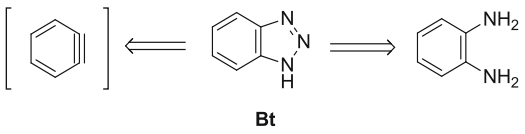
3.2 Synthesis of Benzotriazoles and Triazolopyridines

The preparation of benzotriazole can be realized by different strategies, either by [2+4] cycloaddition from an aryne or by the azotation of ortho-disubstituted diaminobenzene (Scheme 5). Interestingly, the most employed methodology relies on the use of ortho-diaminobenzenes as building blocks. Peterson reported in 1940 the protocol that has been employed for the preparation of benzotriazole and substituted benzotriazoles [14].

Some examples report the use of ortho-nitro anilines that are in situ reduced to obtain the diamine. Oxygenated derivative **18** was obtained during the formation of the triazole ring with hydrazine from 2-chloronitrobenzene [15].



Scheme 4 Ring-chain isomerization

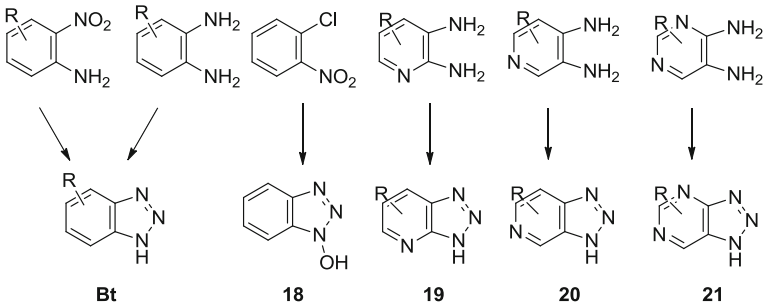


Scheme 5 Retrosynthetic approach

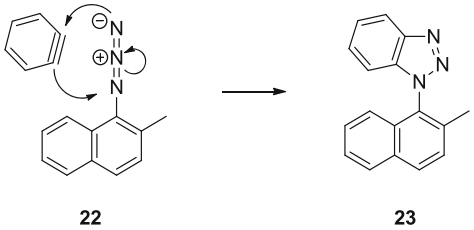
Applying a similar approach with the corresponding diamino derivatives, pyridine (**19**, **20**) and pyrimidine (**21**) derivatives were also obtained [16–19] (Scheme 6). This strategy can be applied to a large family of compounds and has allowed the preparation of more complex molecules derived from diamino pyridines [19, 20].

In the literature there are a few examples involving the aryne approach; however, they remain less employed. This 2+4 cycloaddition to obtain benzotriazoles was first reported by Kulagowski [21] (Scheme 7). Azide derivative **22** reacts with the corresponding aryne to form benzotriazole **23**.

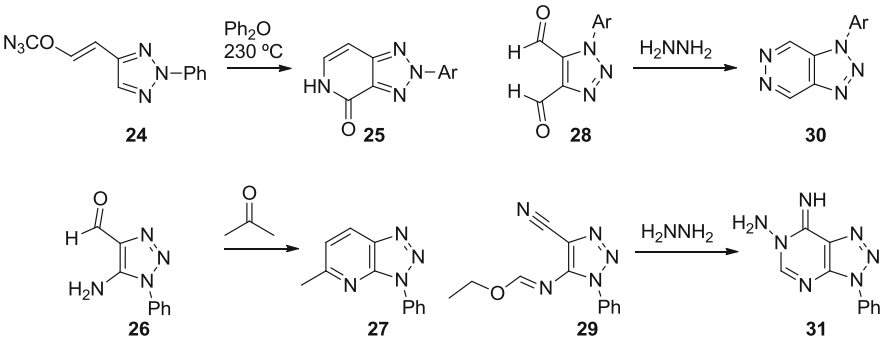
Despite these two strategies being the most common, some alternatives are possible with more complex heterocyclic compounds, based on the initial presence of the triazole ring in the reagent (Scheme 8). For example, triazole **24** undergoes cyclization to form compound **25** [22]. Treatment in acetone of compound **26** allows the formation of triazolopyridine **27** [23]. When 2 heteroatoms are present on the



Scheme 6 Synthons for benzotriazoles and triazolopyridines



Scheme 7 Benzotriazole synthesis through arynes

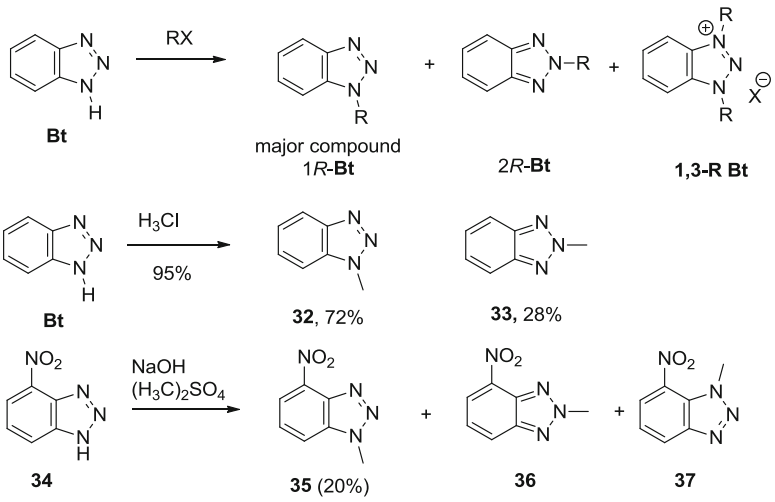


Scheme 8 Alternative approach

6-membered ring, other strategies can be employed. In Scheme 8 we show that 1,2,3-triazoles **28** and **29** react with hydrazine to afford compounds **30** [24] and **31** [25].

3.3 Reactivity of Benzotriazoles and Triazolopyridines

The chemical reactivity of benzotriazoles and triazolopyridines can be presented in two parts: (1) functionalization of the triazole ring and the (2) functionalization of the benzene or heterocyclic (commonly pyridine) ring.



Scheme 9 Alkylation of benzotriazoles

3.3.1 Functionalization of the Triazole Ring

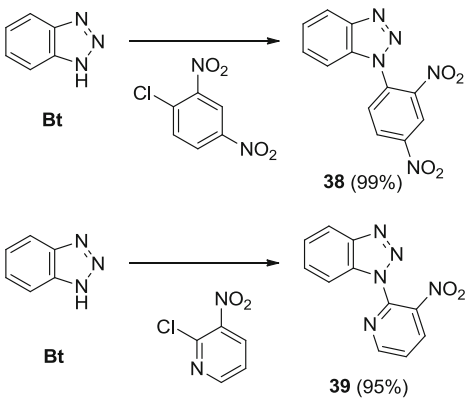
Alkylation

When **Bt** is reacted with alkyl halides, up to three compounds can be observed (Scheme 9): compounds derived from monosubstitution at position 1/3N (major) or 2N and, in some cases, 1,3-disubstituted compounds. Direct methylation of **Bt** affords with high yield (95%), a mixture between 1N-**32** and 2N-**33** methylated compounds in a 72/28 ratio [26]. However, the complexity of these reactions increases when benzotriazole has different substituents on the benzene ring (i.e. nitro substituent, compound **34**) (Scheme 9). In this compound N1 and N3 are no longer the same and the simplest reaction (i.e. methylation) affords at least 3 different compounds **35**, **36** and **37** [27].

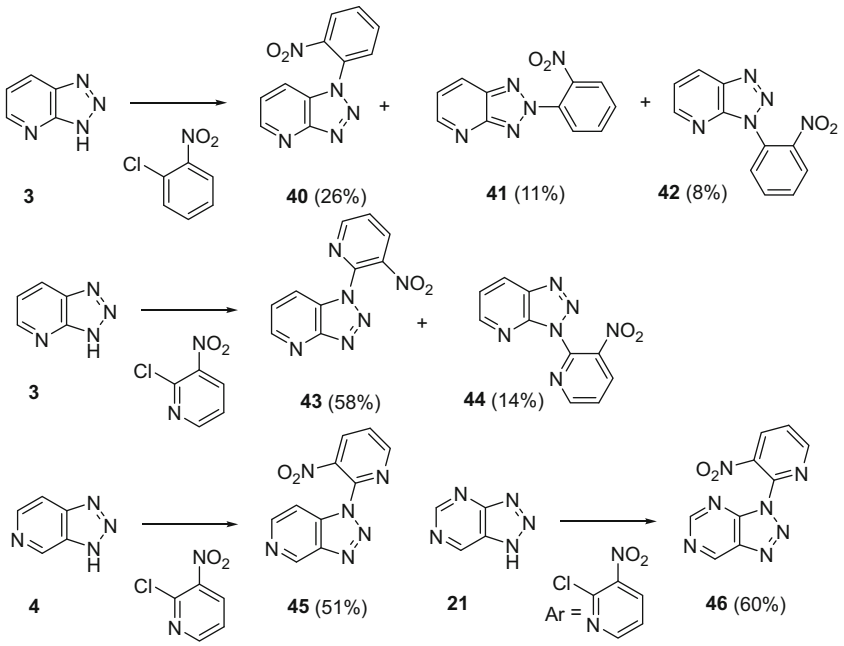
Arylation

Bt acts as a nucleophile in aromatic nucleophilic substitution; exclusive substitution at 1N is observed. Reactions with chloronitrobenzenes are described, affording compounds **38** and **39** in high yields (Scheme 10) [28, 29].

With triazolopyridine derivatives, this behaviour has also been observed. Although no direct reaction with methylene iodide has been reported, reactions with chloronitrobenzene or chloronitropyridine are present in the literature (Scheme 11). Triazolopyridine **3** reacts with either chloronitrobenzene or chloronitropyridine to form compounds **40**, **41** and **42** or **43** and **44** [30, 31]. In both cases the nitrogen atom from the triazole ring is more reactive than the one on the pyridine nitrogen. Triazolopyridine **4** reacts under similar conditions affording



Scheme 10 Benzotriazole as nucleophile in ArNs

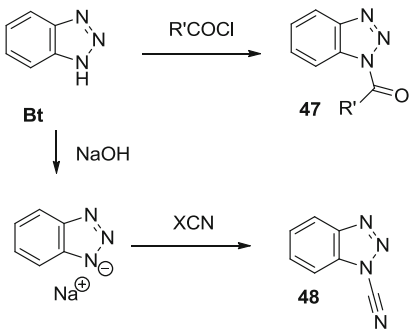


Scheme 11 Triazolopyridines and triazolopyrimidines as nucleophiles in ArNs

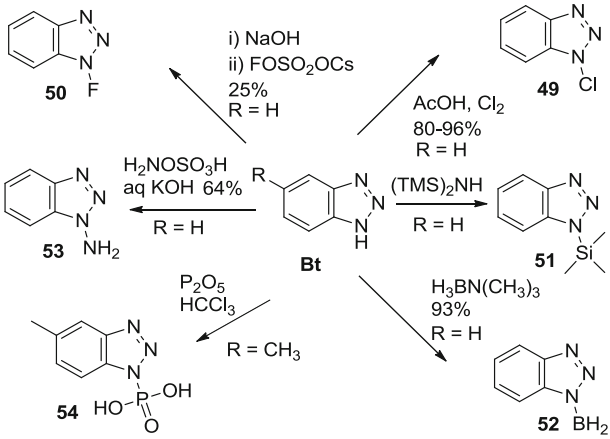
exclusively compound **45**. Triazolopyrimidine **21** affords **46** as a single compound in 60% [24].

N1 Functionalization by Different Substituents

Reaction of **Bt** with acyl chlorides allows the preparation of ketones/amides **47** [32]. Even the introduction of a cyano substituent has been achieved. When the



Scheme 12 N1 functionalization



Scheme 13 N1 functionalization of **Bt** and methyl derivative

corresponding sodium salt of **Bt** is treated with ClCN [33] or BrCN [34], compound **48** is obtained (65 and 90%) (Scheme 12).

The introduction of other atoms has also been reported at position 1 (Scheme 13). Chlorination affords compound **49** in good yield [35]; fluorination [36] takes place with moderate yields affording **50** in 25%. Silylation and borylation have also been reported in the literature to form compounds **51** and **52** with moderate to good yields [37]. Amino and phosphorus derivatives **53** and **54** have also been reported in moderate to good yield [38, 39].

Some of these types of reactions have also been reported with triazolopyridines; shown in Fig. 3 are some of these less common compounds [38–42]. Compounds **55**–**57** are in agreement with the regioselectivity indicated before (Scheme 10).

At this point of the chapter, it is important to remark that almost all applications of **Bt** in organic synthesis deal with *N*-substituted **Bt**. Katritzky has reported many of these original contributions (more than 700) and has written several reviews covering the preparation and application of these compounds [32].

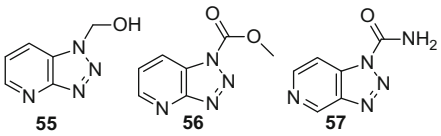
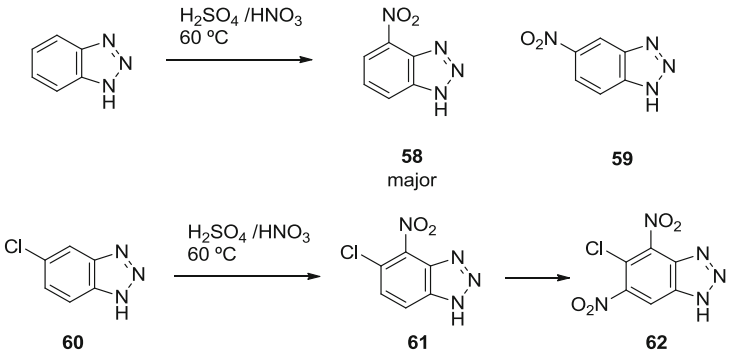


Fig. 3 Triazolopyridine derivatives



Scheme 14 Nitration of **Bt**

3.3.2 Functionalization of the Benzene or Pyridine Ring

The introduction of functional groups on the benzotriazole trends to be performed on the benzene ring prior to the formation of the triazole ring. Nevertheless there are some reactions that are carried out on the benzotriazole ring that allow the functionalization of the benzene ring.

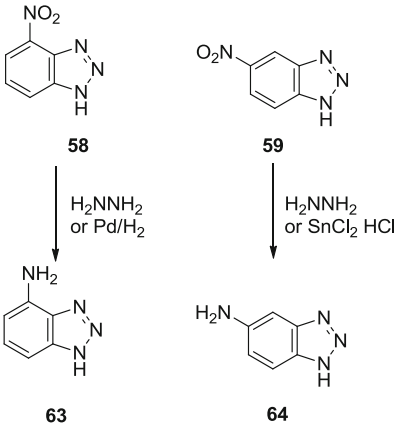
Nitration

Direct nitration of benzotriazole does indeed proceed at positions 4 and 5 with preference at the 4th position [10, 43]; thus compound **58** is the major isomer compared to **59** (Scheme 14). With chlorine-substituted systems **60**, mononitration [44] and dinitration [45] can be realized by increasing the temperature from 60 to 120°C, leading to compounds **61** and **62**. None of these reactions have been reported in the literature for triazolopyridines.

Amination

It remains essential to remark that no direct amination has been reported with benzotriazole. The reduction of nitro groups is the most employed strategy towards the synthesis of amino benzotriazoles (Scheme 15). Hydrazine or Pd/H_2 reductions are the most common methodologies to prepare 4-aminobenzotriazole **63** [10]. The

Scheme 15 **Bt** amino derivatives



derivative at position 5 compound **64** is less common and has been reported by reduction either with hydrazine or with $SnCl_2$ under acid medium [44, 46]. Those reduction conditions did not affect the benzene ring.

Halogenation

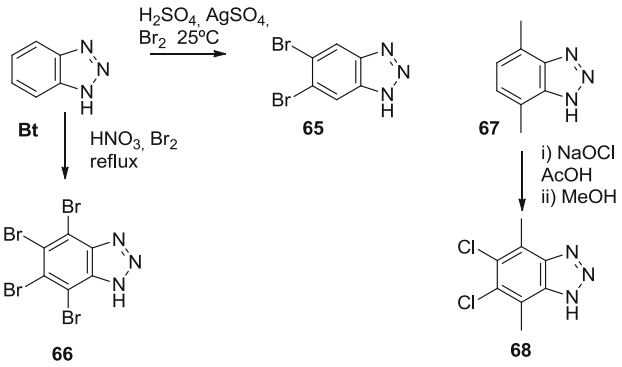
Direct halogenation has been mainly achieved with bromine leading either to dibromation at positions 5 and 6 (Scheme 16, compound **65**) or tetrabromation (compound **66**) with the harshest conditions [47]. The only example reported of chlorination is the reaction of 4,7-dimethyl benzotriazole **67** with NaOCl in acid medium [48]. Compound **68** is obtained under these conditions. No direct fluorination or iodination is reported.

An alternative approach towards the preparation of iodo derivatives relies on diazonium salts. Treatment of **64** with $NaNO_2$ affords the corresponding diazonium salt **69** that undergoes reaction with potassium iodide yielding the monoiodine derivative **70** in low yield (32%) (Scheme 17) [49].

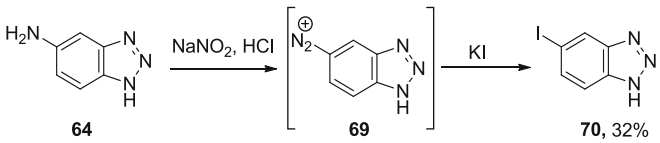
Oxidation and Reduction

Oxidation and reduction are performed on the substituents attached to the benzotriazole ring. It has been reported that strong oxidation of 5-methyl benzotriazole **71** leads to the corresponding acid **72** in good yield (Scheme 18) [50]; however, extreme oxidant conditions can result in the complete destruction of the benzene ring as it will be shown later.

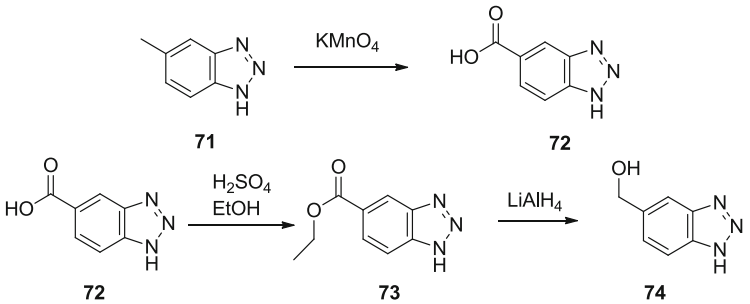
The structure of benzotriazole resists classical Fischer esterification conditions (H_2SO_4). Thus ester **73** has been reported [51]. Furthermore typical reduction reagents like $LiAlH_4$ allow reduction of functional groups without modification of the aromatic core, affording compound **74** [51] (Scheme 18).



Scheme 16 Halogenation of **Bt**



Scheme 17 Iodation of aminobenzotriazole



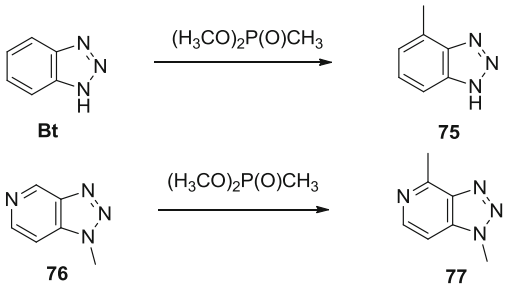
Scheme 18 Oxidation and reduction of benzotriazoles

Methylation

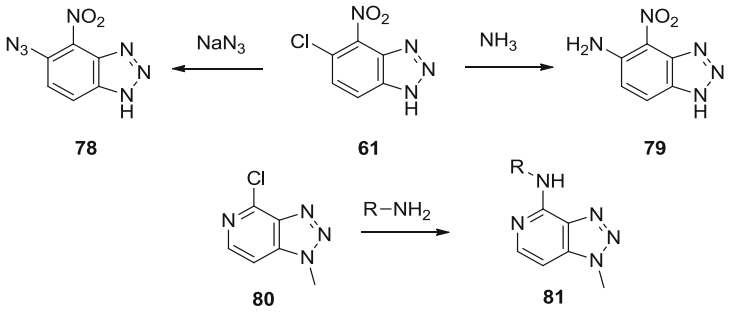
Methylation of benzotriazole has also been achieved in 80% yield by reaction with $(H_3CO)_2P(O)CH_3$ yielding to compound **75** (Scheme 19) [52]. These kinds of reactions are rarely reported in the literature with triazolopyridines; however, the regioselective methylation of compound **76** towards **77** [53, 54] has been described.

Aromatic Nucleophilic Substitution

Aromatic nucleophilic substitution has also been achieved with benzotriazoles but almost all examples required nitro groups to activate the system [45]. Compounds



Scheme 19 Methylations of **Bt** and methyl triazolopyridine **76**



Scheme 20 Aromatic Nucleophilic Substitution

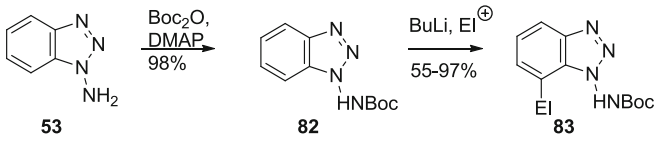
78 and **79** are obtained by means of this reaction (Scheme 20). Some examples are also reported with chlorinated triazolopyridines. Compound **80** undergoes aromatic nucleophilic substitution with primary amines leading to **81** [54].

Lithiation

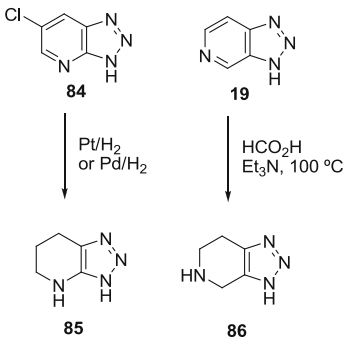
Benzotriazole can also be functionalized by reaction with BuLi; however, it requires Boc protection of 1N (Scheme 21). The only reported example is from compound **53**. After Boc protection (compound **82**), regioselective lithiation and subsequent trapping have been performed, affording compound **83** [38].

Hydrogenation

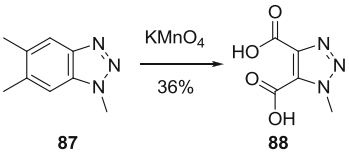
As apparent from the examples above, the benzene ring from **Bt** resists many different conditions. No references concerning the hydrogenation of this compound or derivatives have been reported. However, triazolopyridine derivatives undergo hydrogenation under particular conditions (Scheme 22). Compounds **84** and **19** under reducing conditions result in triazolopiperidines **85** and **86** [16, 56].



Scheme 21 Lithiation of compound **53**



Scheme 22 Hydrogenation of triazolopyridines



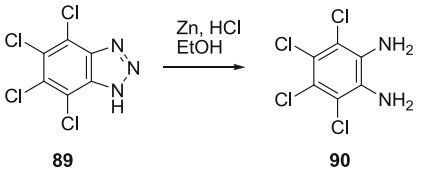
Scheme 23 Oxidation of benzene ring

3.3.3 Triazole Ring-Opening Reaction

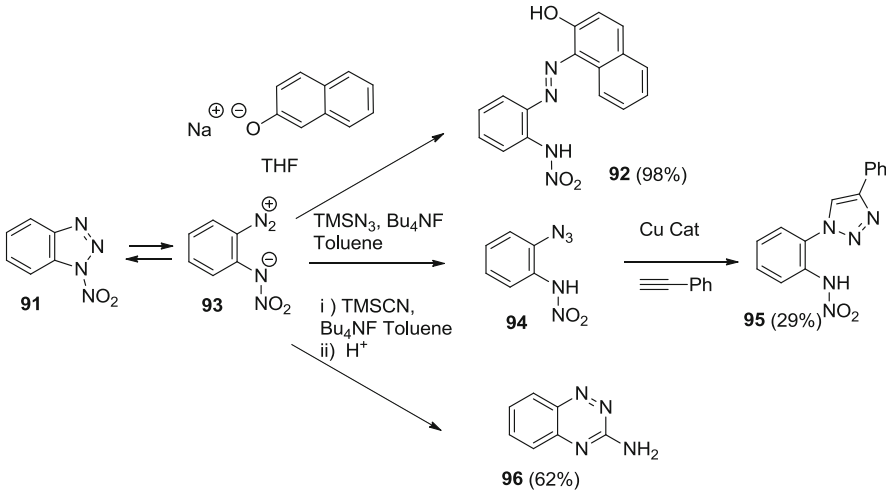
The triazole ring in **Bt** is very stable as it can be seen by means of the reaction conditions reported in the previous examples. As an example, it is interesting to show that extreme oxidative conditions lead to the destruction of the benzene ring instead of the triazole one. Compound **87** affords triazole **88** under strongly oxidative conditions (Scheme 23) [57].

However, some reactions are reported that involve the destruction of the triazole ring leading to a benzene system. For example, tetrachlorobenzotriazole **89** reacts under strongly reducing conditions, affording the corresponding diamine **90** [58] (Scheme 24).

A second example of a ring-opening reaction starts from nitro compound **91** [59]. The presence of the nitro substituent destabilizes the triazole ring, and some ring-opening reactions have been reported [60]. Adduct **92** can be obtained in excellent yield via azo coupling reaction of intermediate diazonium salt **93** with the basic form of napht-2-ol. The formation of this compound can be explained



Scheme 24 Opening of the triazole ring in **89**



Scheme 25 Opening of the triazole ring in **91**

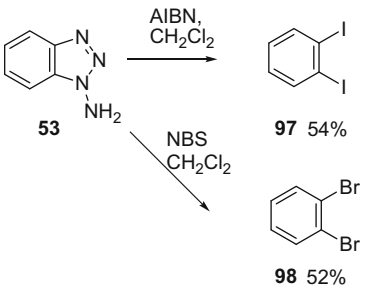
through an open form of **91** with the structure **93**. This ionic form can undergo direct ArNs, leading to compound **94** that was subsequently transformed into a triazole by means of click chemistry (compound **95**). Finally, compound **91** has also been reported as a precursor of exotic heterocyclic compounds like **96** (Scheme 25).

1-Aminobenzotriazole **53** has a particular and interesting behaviour [61, 62] (Scheme 26) giving diiodobenzene **97** and dibromobenzene **98** in moderate yields by radical reactions.

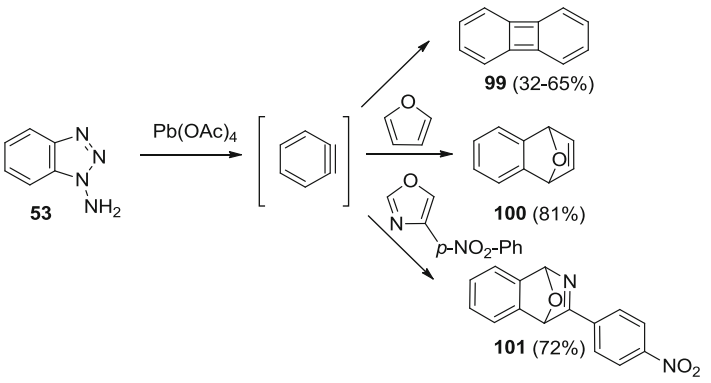
This amino derivative allows the generation of an aryne as the intermediate in the presence of lead acetate (Scheme 27). Despite not being the most employed aryne source, some examples have been reported [63–65]. Adduct **99** that combines two arynes can be obtained in moderate yield. In a similar way, reaction with furan or oxazole leads to the corresponding cycloaddition adducts **100** and **101** in good yields.

Even more surprisingly, diaminobistriazole **102** also shows this behaviour [66] (Scheme 28). This compound performs double-aryne generation, affording more complex structures in moderate to good yields. Adducts **103** and **104** are obtained with good yields.

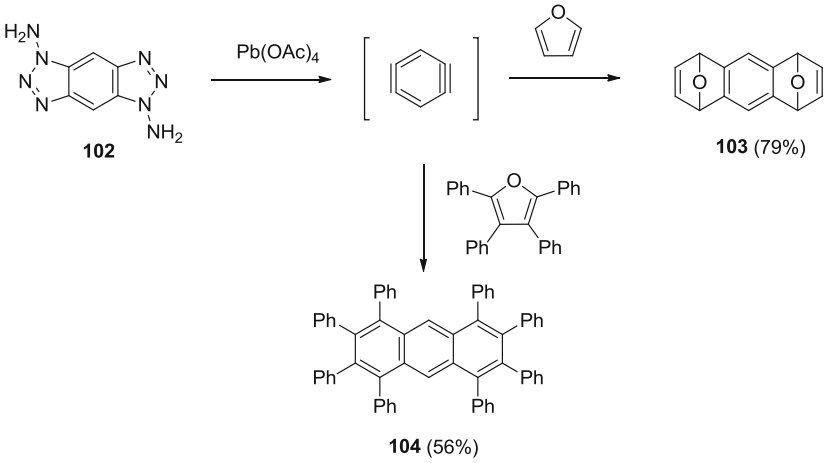
Another approach towards the cleavage of the triazole ring relies on the preparation of salts. Grignard addition to compound **105** generates intermediate **106** that



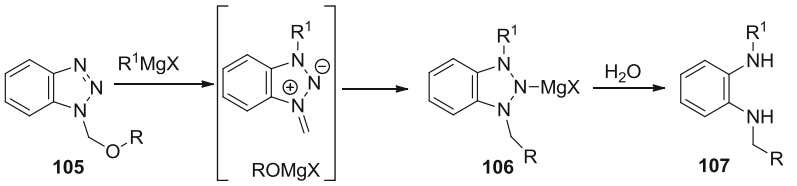
Scheme 26 Triazole ring opening in 1-aminobenzotriazole **53**



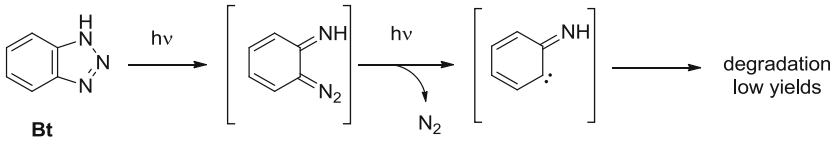
Scheme 27 Aminobenzotriazole **53** as aryne source



Scheme 28 Diaminobistriazol **102** as double-aryne source



Scheme 29 Benzodiamine **107** preparation from benzotriazole **105**



Scheme 30 Photochemical decomposition of **Bt**

in the presence of water decomposes towards the diamine derivative **107** (Scheme 29) [67]. However, the presence of the ether moiety is required for this reactivity.

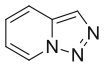
An alternative towards the activation of the triazole ring is the photochemical approach; nevertheless, benzotriazole shows itself to be extremely stable, and low yields are obtained of the corresponding photodegradation products from nitrogen elimination [68] (Scheme 30).

4 Group B: Fused 1,2,3-Triazoles with a Bridgehead Nitrogen Atom

Fused 1,2,3-triazoles with a bridgehead nitrogen atom are those systems when one of the three nitrogen atoms from the triazole ring belongs also to the second aromatic ring. As it has been outlined before, these compounds are represented by the parent [1,2,3]triazolo[1,5-*a*]pyridine (Fig. 4). This compound **Tp** is the simplest member of this family, and although having similar features like benzotriazole, it has also particular characteristics that are not present in the **Bt** family.

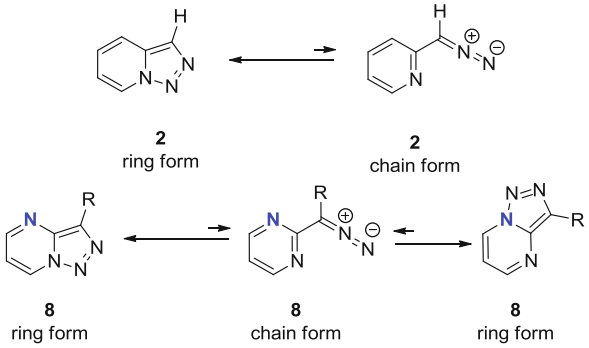
4.1 Structure: Tautomerism and Ring-Chain Isomerization

Compared to the benzotriazole family, these compounds do not present H-tautomerism. However, they indeed show also a ring-chain isomerization. This phenomenon is even more common than in the **Bt** family (Scheme 31) [69]. The

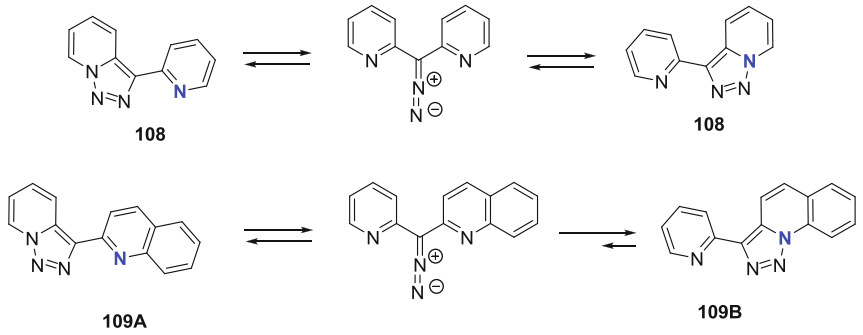


2

Fig. 4 Parent compound of the [1,2,3]triazolo[1,5-*a*]pyridine family



Scheme 31 Ring-chain isomerization in triazolopyridine **2** and triazolopyrimidine **8**

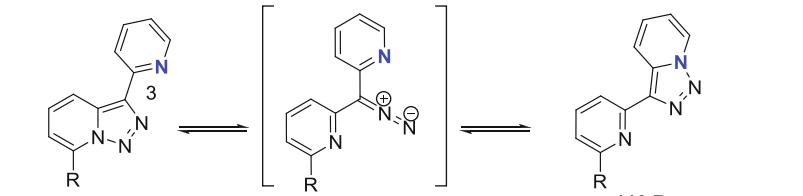


Scheme 32 Ring-chain isomerization in triazolopyridines **108** and **109**

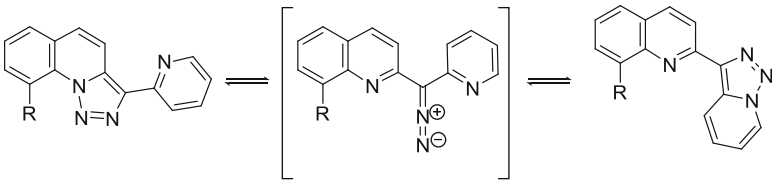
open chain form of these systems is a classic diazo compound. Triazolopyrimidine **8** also presents this equilibrium [70]. As it will be described later, these compounds can react like a diazo compound.

This phenomenon became even more interesting when the substituent R is a 2-pyridyl [71] **108** or 2-quinolyl [72] **109**, because then there are 2 structures in equilibrium. Through an open intermediate with a diazo structure, the cyclization can take place, involving one of the two different nitrogen atoms. Similarly to what has been reported with **Bt**, the most electron-rich nitrogen (or the less hindered) is preferred for the triazole ring formation (Scheme 32).

For 3-(2-pyridyl)-triazolopyridine **108**, both structures are exactly the same; however, in the case of potential equilibrium **109A** and **109B**, there is an interesting difference in the structure of both isomers. There are some studies about the



Scheme 33 Ring-chain isomerization in 7-substituted -3-(2′-pyridil)-triaolopiridines **110**

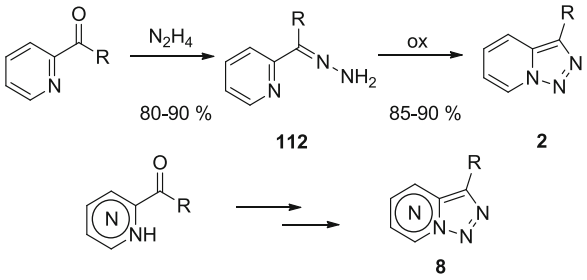


Scheme 34 Ring-chain isomerization in 9-substituted -3-(2′-pyridil)-triazoloquinolines **111**

ring-chain isomerism of 7-substituted-3-(2-pyridyl)-triazolopyridines **110** and 9-substituted-3-(2-pyridyl)-triazoloquinolines **111** [71, 72].

Traditionally these structures had been noted as **A** compounds for those bearing the substitution on the triazolopyridine (or triazoloquinoline) ring and **B** for those obtained after the isomerization. In compound **110** with a methyl group as substituent, a mixture of **A/B** products is observed, and although they can easily be identified by NMR (Scheme 33), these systems cannot be separated because they isomerize at room temperature. Theoretical calculations support these findings. Electronic properties of the substituent were found determinant. Electron-withdrawing substituents favour a **B** structure. Electron donors tend to result in the **A** structure.

Triazoloquinolinepyridines **111** behave similarly. However, initially both **A** and **B** structures are nonequivalent and only **A** is observed (Scheme 34). The introduction of a substituent modifies the **A/B** ratio. Also in this case, electron-withdrawing and bulky substituents afford the **B** structure, and small and donor substituents afford the **A** structure.



Scheme 35 General approach towards the synthesis of **2** and **8**

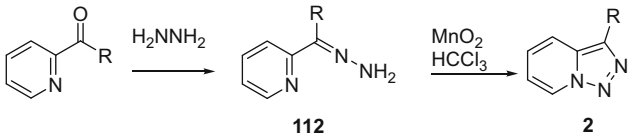
4.2 Synthesis

All examples concerning the synthesis of these compounds involve the preparation of alpha-substituted pyridines. Indeed pyridines are the major starting reagents for the preparation of **Tp**. There are several methodologies reported. The most common approach involves 2-pyridyl aldehydes or ketones that react with hydrazine leading to hydrazone **112** that then is submitted to oxidation (analogous to the Staudinger approach to diazo compounds) affording the desired compounds **Tp 2** (Scheme 35). This strategy is also employed for the other members of the families like triazolo[1,5-*a*] or [1,5-*c*]pyrimidines **8** [70, 73].

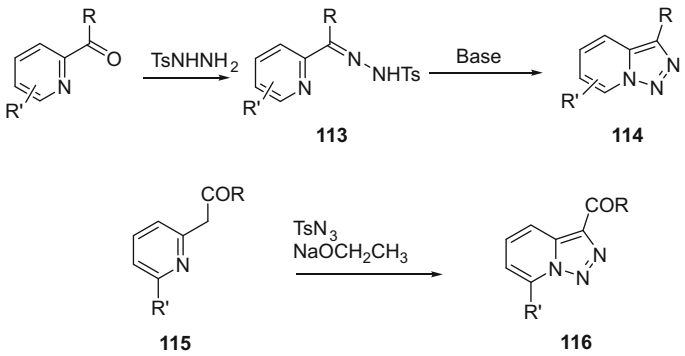
Boyer et al. [74] published the first synthesis of [1,2,3]triazolo[1,5-*a*]pyridines of type **2**. Hydrazones **112** were oxidized using Ag_2O to give the diazo intermediates which undergo an intramolecular cyclization, affording [1,2,3]triazolo[1,5-*a*] pyridines **2**. Although Ag_2O provided triazolopyridines in good yields, Boyer and Ramage [75] replaced it by potassium ferrocyanide. However, along with **Tp** several side reaction products were obtained. Many other oxidants, like nickel peroxide, lead tetraacetate and copper (I) salts, have been tested [76, 77]. Comparing all published synthetic ways to obtain [1,2,3]triazolo[1,5-*a*]pyridines using this methodology, the oxidation with manganese (IV) oxide (MnO_2) due to its low cost and the good and reproducible yields made it the reagent of choice. Manganese oxide was successfully employed by Abarca [78] to prepare triazolopyridines on gram scale (Scheme 36).

In order to avoid the oxidation step that can show incompatibilities with other functional groups, Boyer and Goebel [79] developed another variant of Bamford-Stevens approach to obtain triazolopyridines. They were synthesized after condensation of tosylhydrazine with the corresponding 2-pyridyl aldehydes or ketones. This reaction led to tosylhydrazones **113**. Following a basic treatment with NaOH or KOH, derivatives **114** were obtained. In this way, they succeeded in the synthesis of 3-phenyl, 3-picolinoyl and [1,2,3]triazolo[1,5-*a*]pyridines in high yields without use of oxidizing agent (Scheme 37). Other bases like morpholine were also employed to prepare, for example, 7-methyltriazolopyridine [80], 5-methoxytriazolopyridine [81] or their bromine analogues [82].

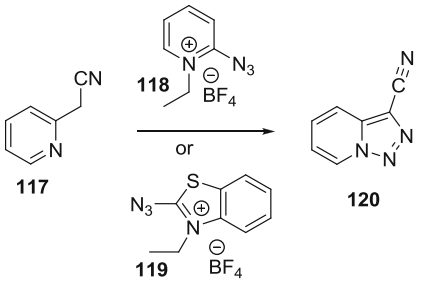
A third original approach relies on the reaction with azides. From 2-acylmethylpyridines **115** with tosylazide (TsN_3) in the presence of sodium



Scheme 36 Abarca approach to **Tp**



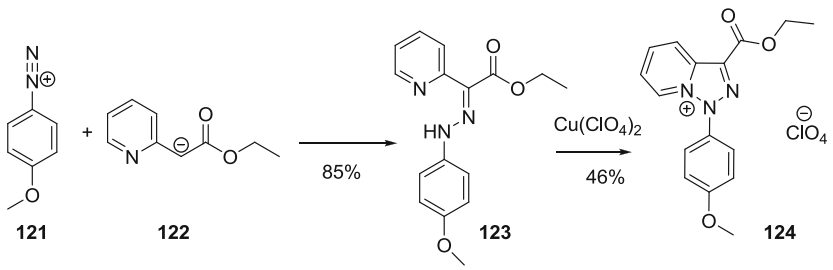
Scheme 37 Tosylhydrazine and Tosylazide approaches



Scheme 38 Preparation of **120**

ethoxide, Regitz obtained triazolopyridine derivatives with moderate to high yields (50–80%) [83, 84], compounds **116** were obtained by this procedure. From compound **117** and other different azides, like 2-azido-1-ethylpyridinium tetrafluoroborate **118** [85] or 2-azido-3-ethylbenzothiazolium tetrafluoroborate **119**, the cyano derivative **120** was obtained (Scheme 38) [86].

The previous strategies are the most commonly employed; however, some alternatives have also appeared that allow the formation of the 1,2,3-triazole ring with substitution at N1 [87]. This approach employs a diazo compound **121** that reacts with the anion **122** leading to a substituted hydrazine **123**. Oxidation with copper (II) perchlorate leads to the 1-subtituted triazolopyridinium perchlorate salt **124** in moderate yield (Scheme 39).



Scheme 39 Preparation of 1-subtituted triazolopyridinium **124**

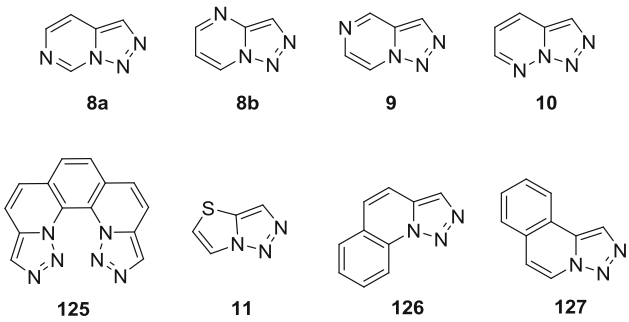


Fig. 5 Different structures of **B** family

These strategies have been applied with different starting reagents. Although the number of examples synthesized is significantly smaller that in **Bt** family, some interesting structures **8–11** and **125 –127** have been reported [70, 73, 74, 88–90] (Fig. 5).

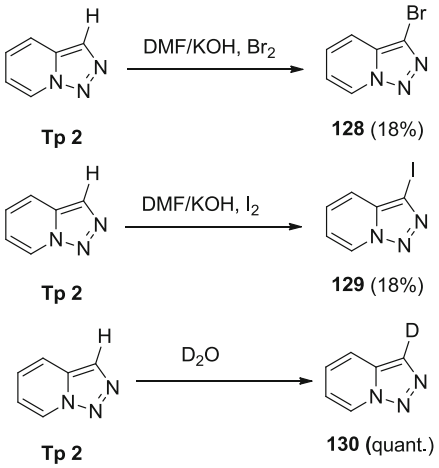
4.3 Reactivity of the Triazolopyridines Family

4.3.1 Functionalization of the Triazole Ring

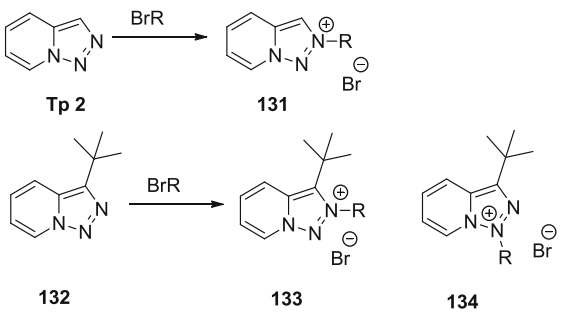
Halogenation

This family has significant differences in terms of reactivity regarding **Bt**. Triazolopyridine with no substituent at position 3 can be bromated or iodinated in basic medium, giving compounds **128** and **129** with moderate yields [91, 92]. It is also important to remark that the proton in position 3 is acidic and exchanges with deuterium just by heating in D_2O, leading to compound **130** (Scheme 40).

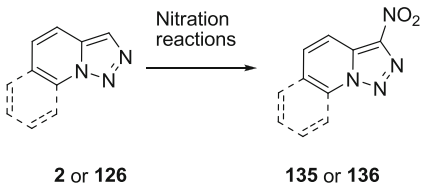
Scheme 40 Substitution at position **3** of parent compound **2**



Scheme 41 Alkylation of **Tp**



Scheme 42 Nitration of **2** and **126**



Alkylation

Alkylation to give triazolopyridinium salts has also been reported on these systems. Normally they are alkylated at nitrogen 2, obtaining structures like compound **131**. However, with large substituents at position 3 [93, 94], like tert-butyl derivative **132**, mixtures of **133** (N2) and **134** (N1) alkylated products are observed (Scheme 41).

Nitration

Nitration of these systems with no substitution at position 3 can also be performed, affording nitrotriazolopyridines **135** [95] and nitrotriazoloquinolines **136**

[96]. However, these reactions gave low yields and side products derived from the opening of the triazole ring (Scheme 42) (see 4.3.3).

4.3.2 Functionalization of the Pyridine Ring

Lithiation

This family of compounds presents a general reactivity that is completely different from benzotriazoles. Indeed all triazolopyridines undergo regioselective metallation at position 7 with butyllithium [80]. Trapping with electrophiles allows the preparation of 7-substituted derivatives **137**. This regioselectivity can be explained by the directed effect by N1 towards peri-metallation (Scheme 43).

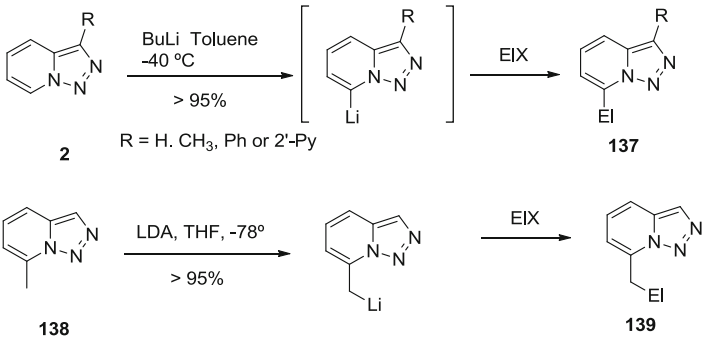
The regioselective metallation at position 7 has been employed for the preparation of a large variety of compounds. This includes also all compounds that were studied in the ring-chain isomerization (see Sect. 4.1 Schemes 33 and 34). This position is extremely activated, undergoing lithiation even when a methyl group is at this place, for example, in compound **138** leading to **139** [80, 97]. This result indicates how different can be the reactivity of **Bt** and **Tp** families. Some studies have been performed [81] by introducing *ortho*-directing groups to metallation on the triazolopyridine ring, like compound **140**, trying to get lithiation in different positions. Nevertheless the metallation with LDA provided exclusively 7-substitued triazolopyridines **141** (Scheme 44).

So far, only few examples of metallation at other positions were described in the literature. Nevertheless, in 1995, Jones reported the reaction of 3-cyano-[1,2,3]triazolo[1,5-*a*]pyridine **120** with LDA [98]. Although this reaction provides a complex mixture of products after trapping with trimethylsilyl chloride, 4-substituted triazolopyridine **142** was identified. However, the low yield remained an important drawback from a synthetic point of view (compound from dimetallation **143** was also isolated and some other side products like **144** and **145**) (Scheme 45).

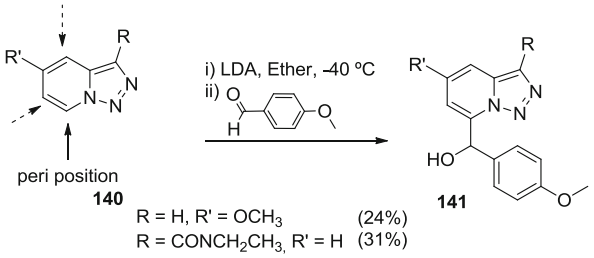
As reported also by Jones, 4-substitution could be achieved with 7-trimethylsilyl-3-carboxamide-[1,2,3]triazolo[1,5-*a*]pyridine (**146**) but lead to compound **147** in very low yield (5%) [98] (Scheme 46).

One important reaction reported with lithium derivatives is the dimerization. Under specific conditions, heterocyclic π-deficient compounds can undergo dimerization. This kind of aryl–aryl coupling is known, but it was not intensively investigated. The reaction of dimerization of [1,2,3]triazolo[1,5-*a*]pyridines was observed by Abarca and Ballesteros for the first time in 1997 (Scheme 47). When 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine (**148**) was treated with LDA at −40°C in THF followed by trapping with 2-pyridylcarboxaldehyde, expected compound **149** was obtained. However, the corresponding dimer **150** was also obtained as a side product [99].

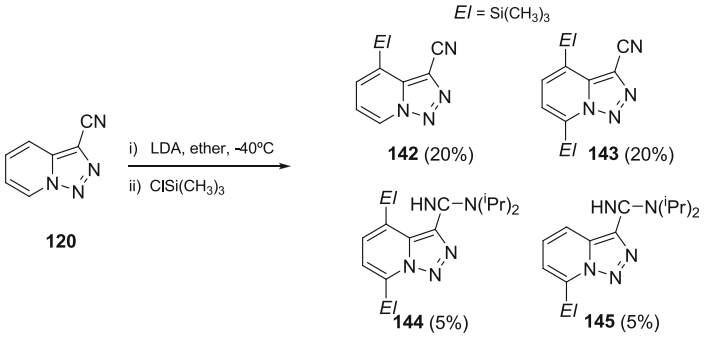
Due to the interesting structure of this dimer, the authors modified the reaction conditions in order to favour dimerization [82]. They found out that the optimal



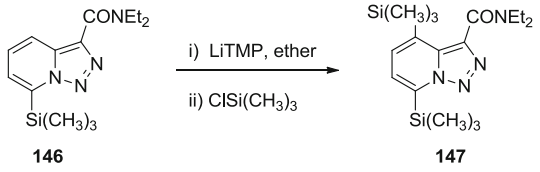
Scheme 43 Regioselective metallation of **Tp**



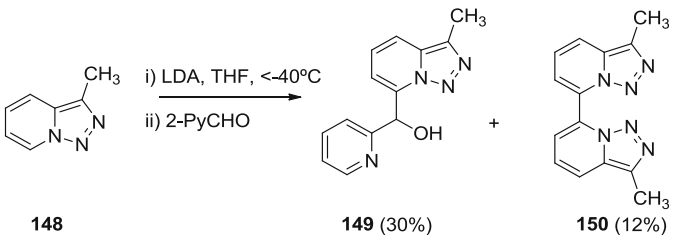
Scheme 44 Regioselective metallation of substituted **Tp**



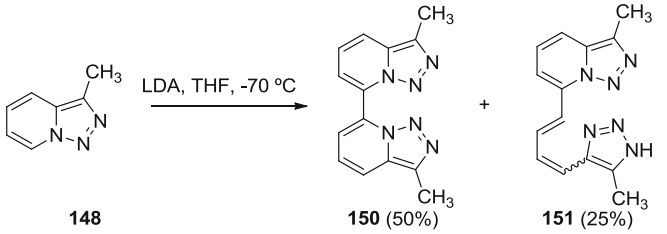
Scheme 45 Metallation of **120**



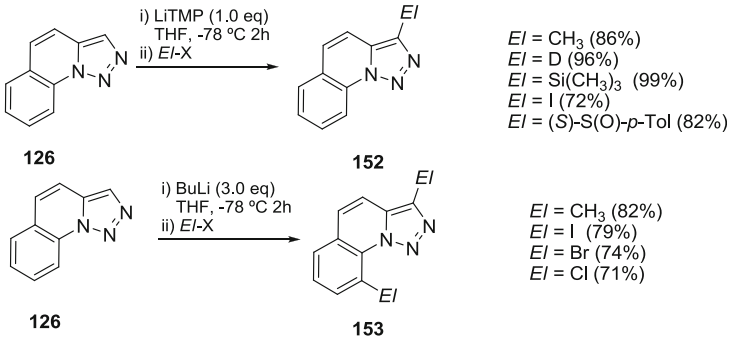
Scheme 46 Metallation of **146**



Scheme 47 First synthesis of **150**



Scheme 48 Optimized synthesis of **150**

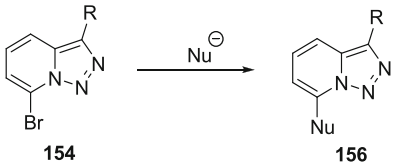


Scheme 49 Mono- and dimetallation of **126**

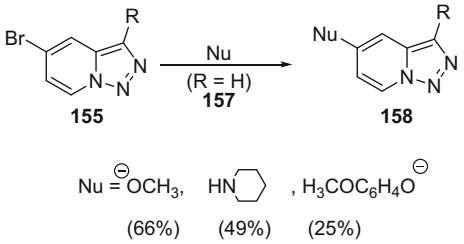
conditions were LDA (1 eq)/THF/−70°C. After 9 h, the dimer **150** was obtained in a 50% yield, but surprisingly, another side product (1-(3-methyl-[1,2,3]triazolo [1,5-*a*]pyridin-7-yl)-4-(5-methyl-1*H*-1,2,3-triazol-4-yl)-1,3-buta-dienyl) (**151**) was formed in a non-negligible amount (25%) (Scheme 48).

Other compounds of this group of fused 1,2,3-triazoles with a N-bridgehead tend to have particular reactivity. Indeed triazoloquinolines **126** can be metallated at position 3 with LiTMP giving compounds **152**, after trapping with electrophiles, in good yield. However, when 3 equiv. of BuLi are employed, double lithiation can be achieved, affording, after trapping, 3,9-disubstituted triazoloquinolines **153** [100] (Scheme 49).

Scheme 50 Aromatic nucleophilic substitution in C7



Scheme 51 Aromatic nucleophilic substitution in C5



Reactions with Nucleophiles

The [1,2,3]triazolo[1,5-*a*]pyridines do not react directly with nucleophiles. However, some ArNs reactions with the halogenated derivatives 7-bromo-3-substituted-[1,2,3]triazolo[1,5-*a*]pyridines (**154**) and 5-bromo-3-substituted-[1,2,3]triazolo[1,5-*a*]pyridines (**155**) are described [82, 101]. Compounds **154** react with nucleophiles like sodium methoxide, sodium 4-methoxyphenolate or sodium benzenethiolate in DMF at 90°C to give substituted compounds **156** in high yields. Also, in ethanol at 80°C, sodium hydrazine and sodium piperidine afforded substitution products **156** in respectively 60 and 65% yield. No reaction occurs with sodium azide and potassium cyanate [101] (Scheme 50).

5-Bromotriazolopyridine **157** reacts with nucleophiles allowing the functionalization at the C5 position leading to compounds like **158** [82] (Scheme 51). No reaction occurs when the reaction is carried out with the chlorinated derivative or with 6-bromo-[1,2,3]triazolo[1,5-*a*]pyridine.

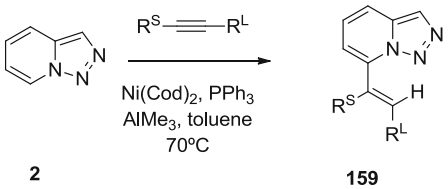
Position 7 of **Tp 2** has also been reported as suitable for direct CH activation in the presence of $Ni(COD)_2$ and disubstituted alkynes leading to compounds **159** in good yields (85–90%) [102] (Scheme 52).

Hydrogenation Reactions of Triazolopyridines

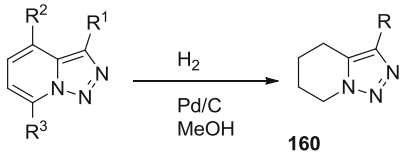
In 1999, Abarca et al. published a study on the hydrogenation of several triazolopyridines **2** by means of heterogeneous catalysis under mild conditions (Pd/C, methanol, 25°C, atmospheric pressure) and obtained 4,5,6,7-tetrahydrotriazolopyridines **160** as indicated in Scheme 53 [103]. This particular feature is completely different from benzotriazoles where the hydrogenation remains difficult and only was reported with some pyridine derivatives.

When the triazolopyridine is substituted by a methyl group in position 3, the reactions lead to the formation of the tetrahydro derivative in good yield. However,

Scheme 52 Direct 7-CH activation (R^S small substituent, R^L large substituent)

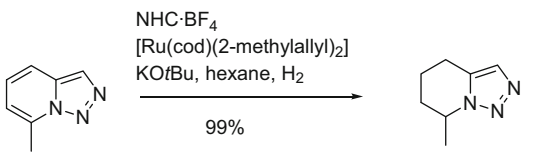


Scheme 53 Heterogeneous hydrogenation



$R^1 = R^2 = R^3 = H$	R = H (90%)
$R^1 = CH_3$, $R^2 = R^3 = H$	R = CH_3 (100%)
R^1 = 2-Py, $R^2 = R^3 = H$	R = 2-Py (46%)
R^1 = 2-Th, $R^2 = R^3 = H$	R = 2-Th (32%)
$R^1 = H$, $R^2 = CH_3$, $R^3 = H$	No reaction
$R^1 = R^2 = H$, $R^3 = CH_3$	No reaction
$R^1 = COOC_2H_5$, $R^2 = R^3 = H$	R = $COOC_2H_5$ (50%)
$R^1 = CN$, $R^2 = R^3 = H$	R = CH_2NH_2 (30%)

Scheme 54 Homogeneous hydrogenation

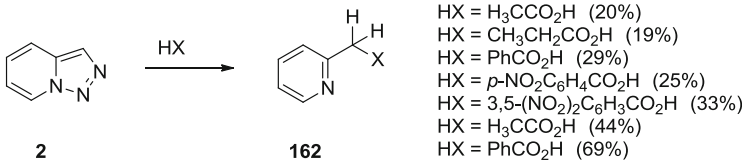


if the methyl group is on the pyridine ring, no hydrogenation product was observed and the starting material was recovered. When the pyridine is substituted with a thiophene at position 3, the 4,5,6,7-hydrogenated product was obtained in low yield (32%) even with increased catalyst charge. This can be explained by the poisoning effect of sulphur towards palladium. On the other hand, the authors highlighted that the presence of electron-withdrawing substituents at the C3 position decreases the reactivity towards hydrogenation.

Recently Glorius has reported a homogeneous hydrogenation of substituted triazolopyridines **138** in excellent yields and high enantiomeric ratio (*e.r*) by means of Ru NHC complexes to obtain triazolopiperidines **161** (Scheme 54) [97].

4.3.3 Opening Reactions of the Triazole Ring in Triazolopyridines

Triazolopyridine **2** and its derivatives undergo triazole ring-opening reaction with loss of dinitrogen in many different conditions. These compounds tend to afford pyridines in the presence of acids. The first paper about this was published by Boyer



Scheme 55 Triazole ring-opening reaction with organic acids

and Wolford in 1958. In their study [104], with carboxylic acids at high temperature, the triazole ring degrades with loss of dinitrogen to provide pyridine esters **162** in moderate yields (Scheme 55).

Jones performed an exhaustive and methodological study [105] about the ring-opening reaction with loss of nitrogen molecule with electrophiles like sulphuric acid, acetic acid, halogens (Cl_2 and Br_2) and selenium dioxide (Table 1).

Reaction with bromine and iodine has also described with compound **163**, giving the formation of the corresponding derivatives **164** and **165** [106] (Scheme 56).

Abarca and Ballesteros also studied the ring-opening reaction of triazolopyridine dienic derivatives **166** and **167** in sulphuric acid, acetic acid and selenium (IV) oxide [99] (Scheme 57). These reactions afford the corresponding alcohols **168** and **169** with sulphuric acid; esters **170** and **171** were obtained with acetic acid. With selenium oxide, however, compound **166** does not react, but **167** gives the corresponding ketone **172**.

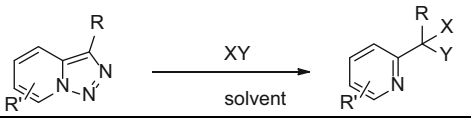
As it has been noted before, the triazolopyridines can be in equilibrium with an opened form. This form is a diazo compound; thus reactivity similar to diazo compounds should be observed. This behaviour was initially reported by Wentrup in the 1960s–1970s [91]. Flash vacuum thermolysis of compound **173** affords complex compound **174** that is explained by means of the chemistry of diazo form **175** (Wolff rearrangement) [107] (Scheme 58).

Other reaction reported in the literature by Wentrup is the thermal treatment of **2** in presence of fumaronitrile, leading to cyclopropane **176**. This result can be explained by the formation of a carbene intermediate from the diazo derivative [108], (Scheme 59).

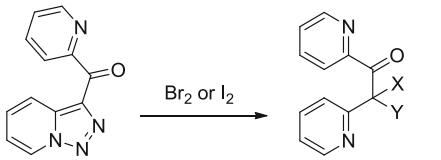
Abarca and Ballesteros also reported of the generation of carbenes in the course of their study on the thermal decomposition of 7-bromotriazolopyridine **177** [109]. The carbene intermediate can be generated by loss of dinitrogen in the corresponding diazo compound before electrophile attack, as indicated in Scheme 59. In this work traces of compound **178** were isolated, and cyclopropanes **179** and **180** were also formed probably by "cyclopropanation" between the carbene and **178** (Scheme 60).

More recently Gevorgyan reported the reaction of 7-chlorotriazolopyridine **181** with rhodium acetate and alkynes or nitriles to afford indolizines **182** and imidazopyridines **183**. Its formation is explained through a diazo intermediate [110] (Scheme 61).

Table 1 Systematic study of the ring-opening reaction in different conditions



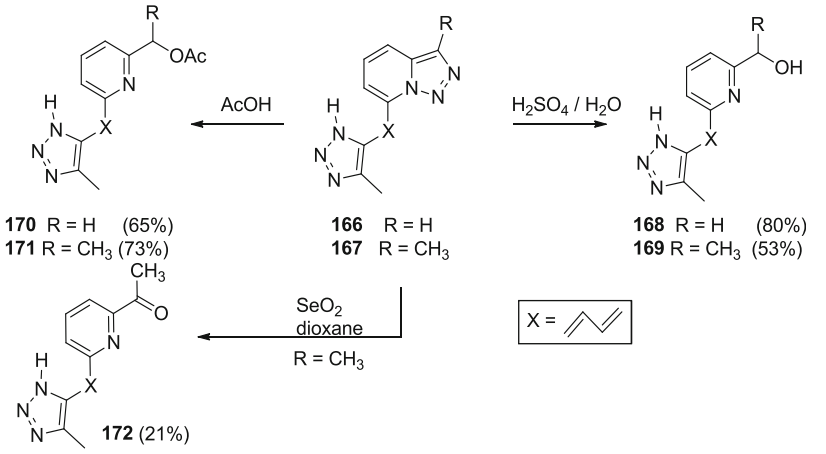
Entry	R	R′	XY	Solvent	X	Y	Yield (%)
1	H	H	Cl_2	CCl_4	Cl	Cl	67
2	H	H	Br_2	CCl_4	Br	Br	75
3	H	H	NBS	CCl_4	Br	Br	79
4	H	H	Hg(OAc)	AcOH	HgOAc	OAc	60
5	H	5–OCH_3	Br_2	CH_2Cl_2	Br	Br	30
6	H	5-OCH_3	H_2SO_4	H_2O	H	OH	78
7	H	7-(*p*-$MeOC_6H_4CHOH$)	Br_2	CH_2Cl_2	Br	Br	98
8	H	7-$(C_6H_5)_2CHOH$	Br_2	CH_2Cl_2	Br	Br	76
9	H	H	H_2SO_4	H_2O	H	OH	78
10	H	H	AcOH	AcOH	H	OAc	70
11	H	H	SeO_2	Dioxane	=O Ketone		89
12	CH_3	H	H_2SO_4	H_2O	H	OH	69
13	CH_3	H	AcOH	AcOH	H	OAc	98
14	CH_3	H	SeO_2	Chlorobenzene	=O Ketone		84
15	H	4-CH_3	Br_2	CCl_4	Br	Br	58
16	H	5-CH_3	Br_2	CH_2Cl_2	Br	Br	30
17	H	5-CH_3	H_2SO_4	H_2O	H	OH	80
18	H	6-CH_3	AcOH	AcOH	H	OAc	98
19	H	7-CH_3	SeO_2	Dioxane	=O Ketone		<10
20	H	7-CH_3	SeO_2	Xylene	=O Ketone		100
21	$CONEt_2$	H	H_2SO_4	H_2O	H	OH	70
22	$CONEt_2$	H	AcOH	AcOH	H	OAc	73
23	$CONEt_2$	H	SeO_2	Xylene	=O Ketone		80
24	H	7-CH_2OH	SeO_2	Xylene	=O Ketone		50
25	H	7-O CH_3	H_2SO_4	H_2O	H	OH	80
26	H	7-O CH_3	SeO_2	Chlorobenzene	=O Ketone		60
27	CH_3	7-(*p*-anysol)	SeO_2	Chlorobenzene	=O Ketone		70
28	CH_3	7-piperidinyl	AcOH	AcOH	H	OAc	75



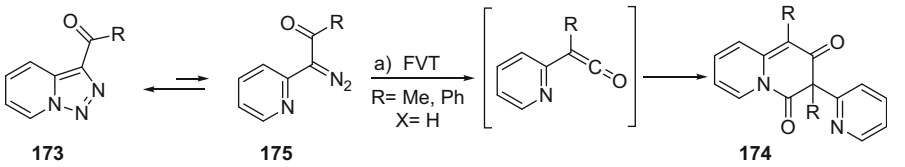
163

164 X = Y = Br
165 X = Y = I

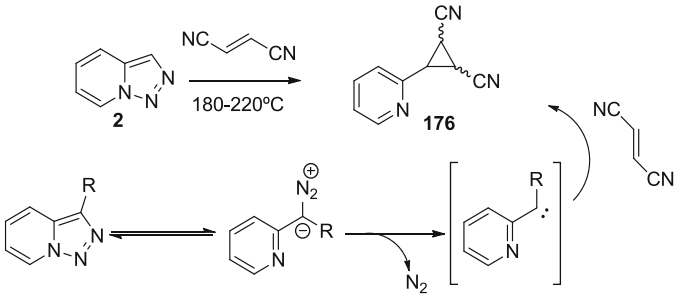
Scheme 56 Triazole ring-opening reaction with bromine or iodine



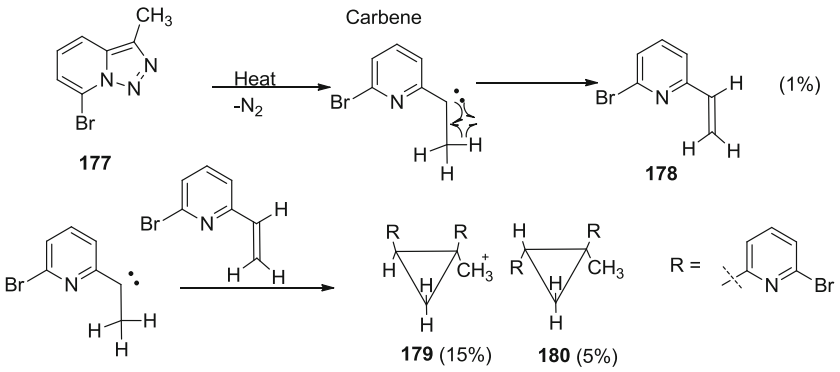
Scheme 57 Triazole ring-opening reactions of **166** and **167**



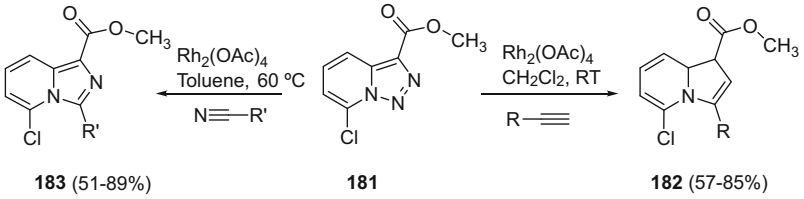
Scheme 58 Diazo compound behaviour of **173**



Scheme 59 Cyclopropane formation from **2**



Scheme 60 Cyclopropane formation from **177**

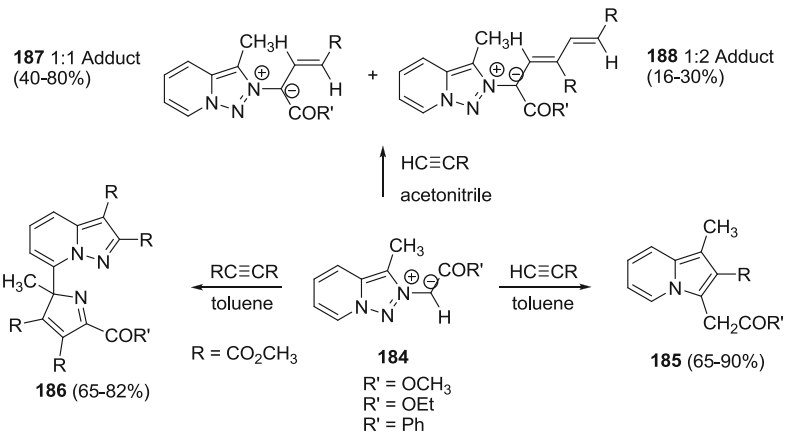


Scheme 61 Rhodium mediated **181** decomposition through a diazo intermediate

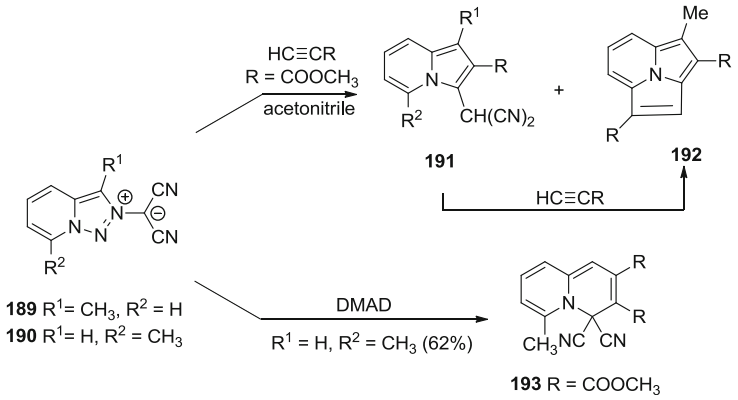
There are also some examples of triazole opening reaction with triazolopyridinium ylides. Initially, these experiments were performed with [1,2,3]triazolo[1,5-*a*]pyridinium ylide **184** and acetylenic esters [111–114]. The authors found out that these reactions were extremely solvent polarity dependent and the results could vary according to the acetylenic ester (Scheme 62).

When the synthesis was performed in toluene with methyl propiolate, indolizines **185** were obtained, providing a new way to synthesize this heterocycle [113]. When dimethyl acetylenedicarboxylate (DMAD) was used as dipolarophile in toluene, pyrazolo[1,5-*a*]pyridines **186** were obtained after the addition of two molecules of DMAD. In both cases cleavage of the N^2–N^3 bond occurred, leading to the triazole ring opening, and a 1,3-dipolar cycloaddition was observed. The structure of these compounds was confirmed by single X-ray [112]. However, when acetonitrile was used as solvent, the reaction of the ylides **184** with methyl propiolate gives in each case two products characterized as 1:1 **187** and 1:2 **188** adducts, with ylide structure and without triazole ring opening.

2-Dicyanomethyl-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridinium ylide **189** and 2-dicyanomethyl-7-methyl-[1,2,3]triazolo[1,5-*a*]pyridinium ylide **190** were also studied. The reactivity of these compounds towards acetylenic esters is different depending on the dipolarophile [115], but always produces the triazole ring-opening reaction with loss of nitrogen. 3-Methylated (R^1=CH_3, R^2=H) ylide **189** reacts with methyl propiolate in acetonitrile as solvent to provide indolizine



Scheme 62 Triazole ring-opening reaction of ylide **184**



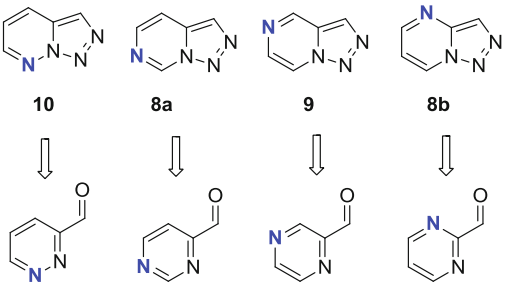
Scheme 63 Ring-opening reactions of **189** and **190**

191 and cyclizine **192**. The reaction performed with the 7-methylated (R^1=H, R^2=CH_3) ylide **190** provided exclusively the indolizine. 7-Methylated ylide reacted with DMAD to afford 4*H*-4,4-dicyan-2,3-dimethoxycarbonyl-6-methylquinolizine **193** (Scheme 63).

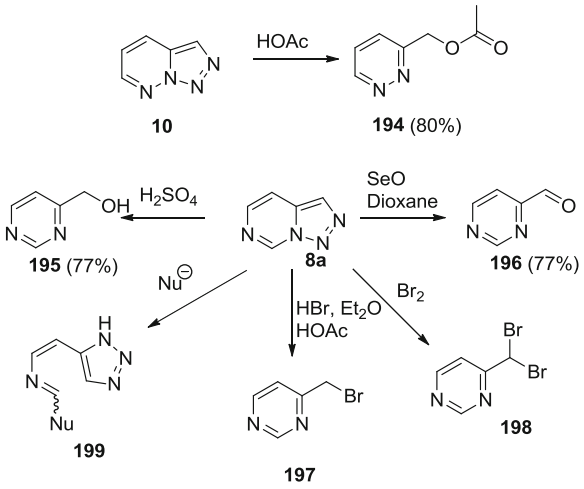
4.4 Reactivity of Triazolodiazines

Triazolodiazines represent a less explored family. These compounds are depicted in Scheme 64. In all cases those compounds are obtained by hydrazine/oxidation methodology of the corresponding aldehyde [70, 73]. Despite of not being

Scheme 64 Four nitrogen atom-containing molecules



Scheme 65 Ring-opening reactions on **10** and **8a**

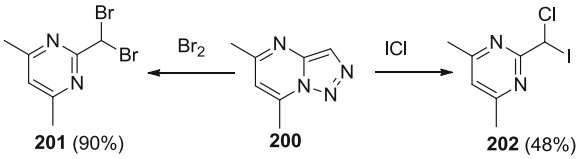


extensively studied from a chemical point of view, many of these structures are evaluated in pharmacological studies.

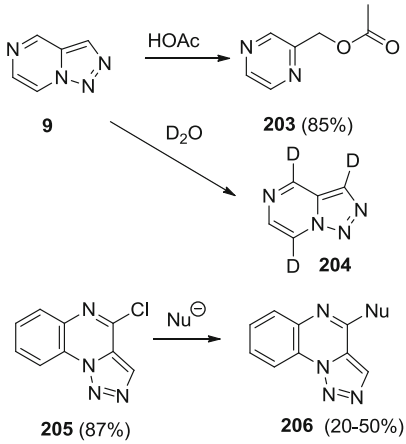
The presence of the two nitrogen atoms in the six-membered ring induces instability of these systems which are, contrary to almost all of the previous examples, water sensitive. For compound **10** only ring-opening reaction with acetic acid has been reported yielding to acetate **194** [73]. Triazolo[1,5-*c*]pyrimidine **8a** has been extensively studied by Abarca and Jones and behaves similar to triazolopyridine **2** [116]. The compound **8a** of acid leads to a ring-opening reaction affording alcohol **195** with H_2SO_4 and ketone **196** with selenium dioxide. Monohalogenation can be achieved with HBr, leading to compound **197**. Jones reported also on the dehalogenation of this molecule with molecular bromine, affording compound **198** [80]. However, in these reactions the presence of a large amount of side products is reported. This has been associated to the instability of these compounds. Indeed, the presence of nucleophiles induces the ring opening of the pyrimidine moiety, leading to triazoles **199** [116] (Scheme 65).

The reactivity of compound **8b** has not been studied; it is only known that dimethyl derivative **200** undergoes ring-opening reaction with bromine, leading

Scheme 66 Reactivity of **200**



Scheme 67 Reactivity of **9** and **205**



to compound **201**. In a similar way, when **200** is treated with ICl, halogenated compound **202** is obtained in moderate yield [117] (Scheme 66).

The reaction of pyrazine **9** with acetic acid has also been reported yielding compound **203** in good yield [73]. Despite not being deeply studied, Wentrup reported on the deuteration of this compound with D_2O [91], being able to introduce 3 deuterium atoms (**204**). Of this particular structure, more conjugated analogues, like compound **205**, have been reported [118]. Compound **205** reacts with nucleophiles in moderate yields affording **206** [119] (Scheme 67).

5 Applications of Fused 1,2,3-Triazoles

5.1 Benzotriazole Applications

Benzotriazoles resist hot sulphuric acid or melted KOH treatment; even strong oxidants or reductants ($KMnO_4$, $LiAlH_4$) do not affect this system. Taking into consideration that benzotriazole is relatively cheap and stable up to 400°C, several applications have been reported in different fields.

5.1.1 Organic Synthesis

Katritzky is the main researcher on the application of these compounds in organic synthesis [32]. Several reviews, patents and research articles are reported in the literature just concerning its application in organic synthesis [120–122]. The key point of benzotriazole is that it can be easily introduced into different molecules by means of different reactions. Substitution [32], addition or even three-component reactions had been reported for this purpose. Once **Bt** is attached to a molecule, it can be used under different approaches: as leaving group [123, 124], *ortho*-directing group [125], as cation stabilizer [67], radical precursor [126], etc. Today more than 1,000 publications employ benzotriazoles as a synthetic tool. Schematic examples about the use of **Bt** in organic synthesis are shown in Fig. 6.

In this field it is important to stress the utility of some benzotriazoles in peptide synthesis [127] (Fig. 7). The compounds used in this synthesis are derivatives of hydroxy triazoles **18** [15, 128]. Compounds **207**, **208** and **209** are commercially available and largely employed for amide bond formation with a high degree of racemization suppression [129–131].

5.1.2 Medicinal Applications

The benzotriazole structure (5+6 aromatic rings) displays similarities with the natural bases adenine and guanine (Fig. 8). For this reason it is not surprising that it is considered as a preferential scaffold in pharmaceutical chemistry as long as it allows subsequent derivatization. In particular pyrimidine derivatives tend to be employed [132–134].

5.1.3 Coordination Chemistry and Metal Organic Frameworks

Benzotriazole and its derivatives had also been applied in coordination chemistry and metal organic frameworks [135–138], in particular, carboxylic derivatives **73** [139] or even more complex molecules **214** [137] (Fig. 9). The particular arrangement of the nitrogen atoms allows coordination with different angles; thus coordination polymers and metal organic frameworks have been obtained. Although this is not the most common nitrogenated ligand employed, its reports reveal particular features that are difficult to obtain with other compounds. Furthermore, these structures are stable.

5.1.4 Photostabilizers, Photographic Application and Sensors

Hydroxyphenylbenzotriazole **215** [140, 141] has been used as photostabilizer of polymers. With the addition of this compound, their stability towards light

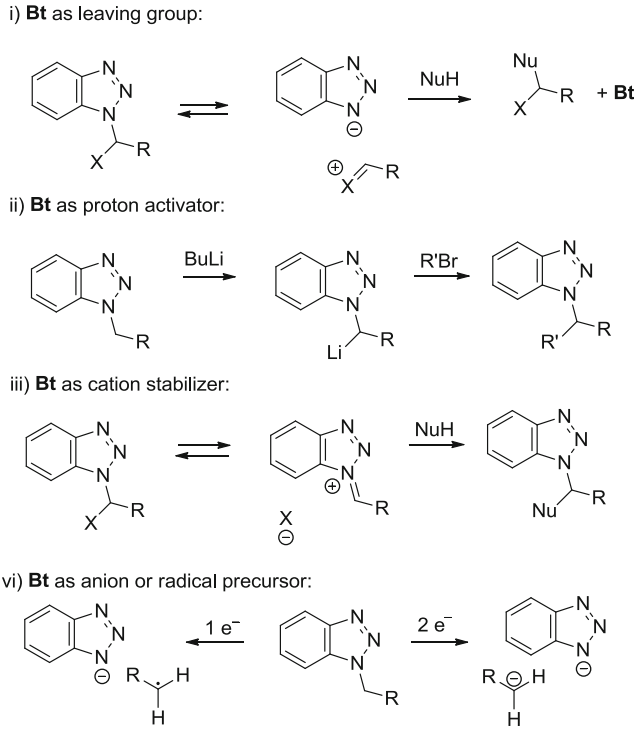


Fig. 6 Benzotriazole in organic synthesis

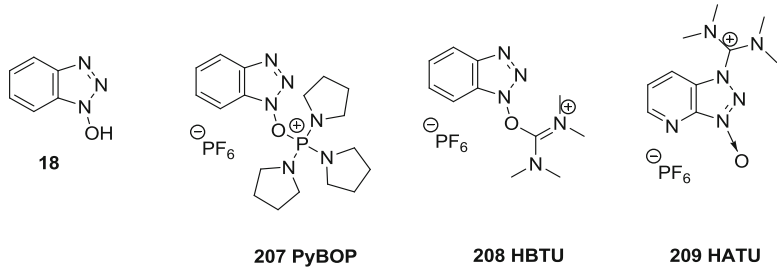


Fig. 7 Benzotriazole-based peptide coupling reagents

increases. In a similar way, compound **216** is employed as a fog inhibitor in the processing of silver photographic material [142] (Fig. 10). The particular facility towards the formation of benzotriazole **218** from the ortho-diamine **217** has been employed as a switch on sensor for NO. The initial molecule presents almost zero emission, but when NO is in the atmosphere, the formation of the benzotriazole ring in **218** leads to a strong emission [143].

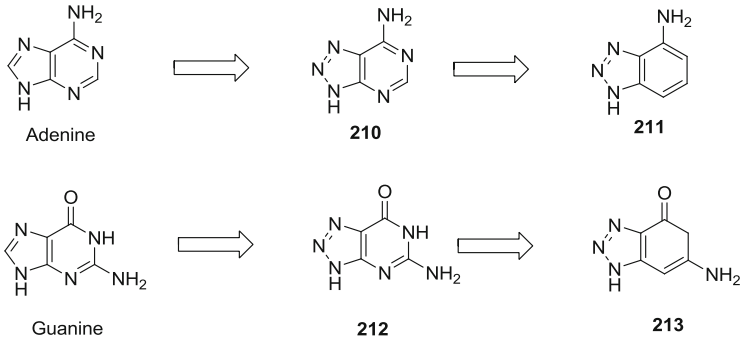


Fig. 8 Analogy between benzotriazole **Bt** and pyrimidinic bases

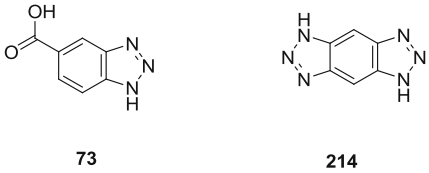


Fig. 9 Benzotriazole-based ligands employed for the preparation of metal organic frameworks

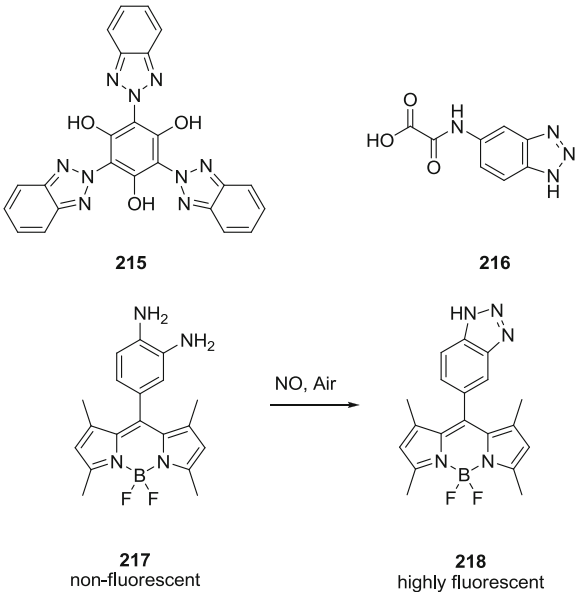


Fig. 10 Benzotriazole-based compounds as photostabilizers and sensors

5.1.5 Copper Conservation

Benzotriazole has been reported as a copper corrosion inhibitor. Indeed copper and copper alloys are treated with a benzotriazole solution [144, 145]. This method has also been applied for brass, steel, cast iron or aluminium to prevent corrosion [146].

5.2 Applications of Triazolopyridines with Nitrogen as Bridgehead Atom

Their reactivity has been shown to be a powerful tool to get access to extremely important compounds in many different yields.

5.2.1 Organic Synthesis

Synthesis of 2,6-Asymmetrically Disubstituted Pyridines and Quinolines

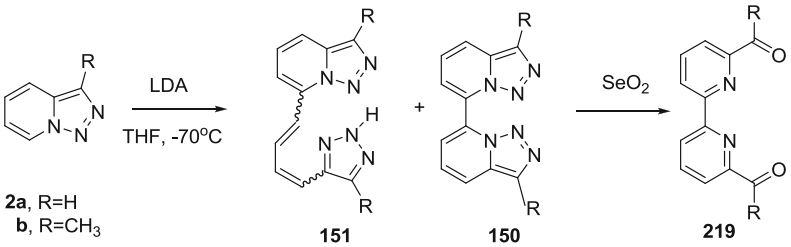
The triazole ring has been employed as an activating and protecting group of 2 aldehyde/ketone pyridines or quinolone. The combination of the triazole ring formation, lithiation, trapping with electrophiles and ring-opening reactions is a powerful strategy to prepare 2,6-asymmetrically disubstituted pyridines or 2,8-asymmetrically disubstituted quinolines. These kinds of molecules are difficult to obtain by other procedures. However, by means of the triazolopyridine chemistry, several compounds have been obtained [80, 82, 100, 147].

A New Route to 2,2′-Bipyridines

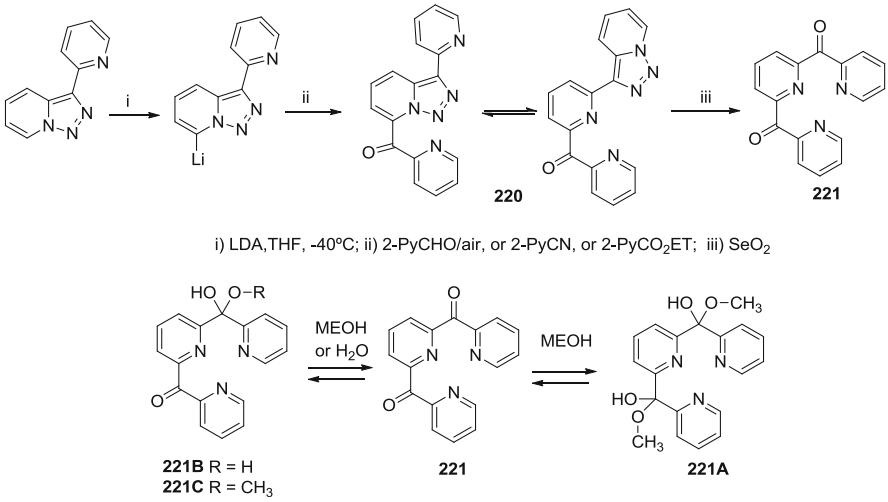
As has been described, the usual reaction between triazolopyridines and lithium reagents at −40°C gives a 7-lithio derivative that can be trapped by electrophiles [80, 147]. This reaction is temperature dependent, and at −70°C in THF as solvent, a new reaction occurs, giving two products, the 7,7′-bitriazolopyridine **150** and the butadiene **151** [82] (see Scheme 48). Like all simple triazolopyridines, bitriazolo-pyridines **150** react with electrophiles to produce 2,2′-bipyridines **219** (Scheme 68). With these reactions, a general route to 2,2′-bipyridines has been discovered with a variety of substituents in the 6 and 6′ positions [82]. These compounds have use in supramolecular chemistry because of their great complexing power for metal ions, and, in particular, 2,2′-disubstituted-6,6′-bipyridines are useful building blocks for oligo-bipyridines, which spontaneously form helical metal complexes [148].

Synthesis of Pyridylcarbonylpyridines

Pyridyl carbonyl pyridyl triazolopyridine **220** is obtained from 3-(2-pyridyl)-triazolopyridine by the typical reaction of lithiation and trapping the lithio



Scheme 68 New synthesis of bipyridines



Scheme 69 Synthesis of bis-(pyridylcarbonyl)pyridine

derivative by 2-PyCHO/air or 2-$PyCO_2Et$ or 2-PyCN. Its triazole ring-opening reaction with SeO_2 formed a bis-pyridylcarbonyl-pyridine **221** [149] (Scheme 69). This compound undergoes hydration or reaction with methanol, leading to compounds **221A**, **221B** and **221C**.

The discovery of this synthesis of compound **221**, using triazolopyridines as building blocks, has been the beginning of a new study looking for new polynitrogenated potential helicating ligands or coordination supramolecular compounds from triazolopyridines with potential magnetic or photochemical properties [150]. The aim of this study was the synthesis of oligopyridylcarbonylpyridines **222** and related compounds. In Fig. 11 there are some examples of the synthesized compounds with this methodology in different conditions [149–152].

Pyridylcarbonylpyridine (PyCOPyCOPy) **221** is a ligand very often used in coordination chemistry to form clusters or helicates with different structures and very interesting magnetic properties. Figure 12 shows the molecular formula of some examples synthesized from **221** and with application in these fields.

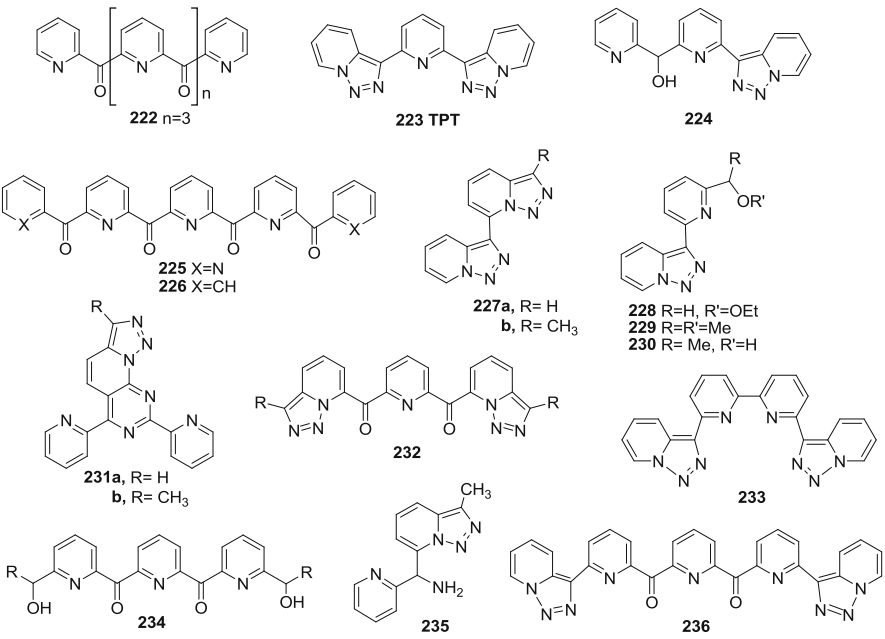


Fig. 11 Oligopyridylcarbonylpyridines and related compounds

Complexes with silver **237** and **238** and copper **239** and **240** [153] and with iron **241**–**244** [154], the first icosanuclear Co cluster exhibiting superparamagnetic relaxation **245** [155], an *S*-shaped pentanuclear Cu^{II} cluster **246** [156], clusters of Cu^{II}_4 **247** and Co^{II}_4 **248** with ferromagnetic interactions [157], a Ni^{II}_5 cluster **249** with a $S = 5$ ground state exhibiting slow magnetic relaxation and a high spin-reversal barrier have been described [158]; complexes **250**–**252** (Cu^{II}_4, Co^{II}_4 and Ni^{II}_6) are also synthesized in the presence of sodium azide with very interesting ferromagnetic intramolecular interactions [159]. Structural, magnetic and spectroscopic studies have been done with **253** (Fe^{III}) [160]. Isomorphous replacement of M^{II} ions in M^{II}-Gd^{II} dimers **254** (M^{II}=Cu^{II} (**a**), Mn^{II} (**b**), Ni^{II} (**c**), Co^{II} (**d**), Zn^{II} (**e**) [161], Fe^{II} (**f**) [162]) has been studied; magnetic susceptibility measures indicate a ferromagnetic interaction for (**a**), antiferromagnetic for (**b**–**e**) and weakly ferromagnetic for (**f**).

There is a second-generation family of ligands derived from metal ion-assisted reactivity of di-2,6-(2-pyridylcarbonyl)pyridine **221**. A $Mn^{II/III}_4$ rhombus was synthesized by nucleophilic attack of the carbanion $^{-}CH_2COCH_3$ at the carbonyl carbon atoms of (py)CO(py)CO(py), in the presence of Mn^{n+} ions under basic conditions; the cationic cluster $[Mn_4(OH)_2(L)_2(H_2O)_2](ClO_4)_4$ **255**, where L^{2-} is the (py)C(CH_2COCH_3)(O^{-})(py)C(CH_2COCH_3)(O^{-})(py) dianion, was synthesized and characterized [163]. Complex **255** is antiferromagnetically coupled with an unusual $S = 2$ ground state resulting from spin frustration effects within the triangular Mn_3 subunits of the cluster.

237 $[\{Ag(\mathbf{121})\}(ClO_4)]_\infty$
238 $[\{Ag(\mathbf{121})(NO_3)\}\cdot CH_3CN]_\infty$
239 $[Cu(\mathbf{121B})]_2(BF_4)_2\cdot 2H_2O$
240 $[Cu(\mathbf{121C})]_2(CLO_4)_2\cdot 2H_2O$
241 $[Fe_3(\mathbf{121A})_2(\mu\text{-}OCH_3)_2Cl_2]\ (FeCl_4)\cdot H_2O$
242 $Fe(\mathbf{121B})Cl_2\cdot H_2O$
243 $Fe(\mathbf{121B})Cl_2\cdot THF$
244 $Fe(\mathbf{121C})Cl_2\cdot THF$
245 $[Co_{20}\ (\mu_3\text{-}OH)_6(O_2CMe)_4(\mu_2\text{-}O_2CMe)_{12}(\mu_3\text{-}O_2CMe)_6(HL)_4(DMF)_2]\cdot 2H_2O\cdot 1.6DMF$, where HL^{3-} = pyC(O)(OH)pyCO$_2$py^{3-}.
246 $[Cu_5(O_2CMe)_6\{pyC(O)(OH)\ pyC(O)(OH)py\}_2]$
247 $[Cu_4\{py(C(O)_2pyC(O)(OEt)py\}(O_2CMe)_5\,(EtOH)_2]$
248 $[Co_4\ \{py(C(O)(OMe)pyC(O)(OMe)py\}_2(O_2CMe)_2(N_3)_2]$
249 $[Ni_5\{pyCOpyC(O)(OMe)py\}_2(O_2CMe)_4(N_3)_4(MeOH)_2]\cdot 2.6MeOH\cdot 2.6H_2O$
250 $[Cu_4(N_3)_2\{pyC(OMe)(O)pyC(OMe)(O)py\}_2(MeOH)_2]\ (ClO_4)\cdot 2MeOH$
251 $[Co_4(N_3)_2(NO_3)\ \{pyC(OMe)(O)pyC(OMe)\ (O)py\}_2]\cdot 0.5MeOH$
252 $[Ni_6(CO_3)(N_3)_6\{pyCOpyC(O)(OMe)py\}_3(MeOH)_2(H_2O)]$-$[Ni_6(CO_3)(N_3)_6\{pyCOpyC(O)(OMe)py\}_3(MeOH)_3](ClO_4)_2\cdot 1.8MeOH$
253 $[Fe2\{pyCO(OMe)pyCO(OMe)py\}_2(MeO)_2](ClO_4)_2.MeOH$
254 $[M^{II}Gd^{II}\{pyCO(OEt)pyC(OH)(OEt)py\}_3(ClO_4)_2.EtOH$ [M^{II} = Cu^{II} (**a**), Mn^{II} (**b**), Ni^{II} (**c**), Co^{II} (**d**), Zn^{II} (**e**), Fe^{II} (**f**).
255 $[Mn_4(OH)_2(L)_2(H_2O)_2](ClO_4)_4$, where L^{2-} is the pyC(CH_2COCH_3)(O^-) pyC(CH_2COCH_3)(O^-)py dianion,

Fig. 12 Molecular formulas of complexes **237–255**

5.2.2 Triazolopyridines as Building Blocks in Supramolecular Chemistry

All triazolopyridines have interesting ligand properties to form polynuclear complexes with different metal ions. These molecules may also have the ability to complex other cationic, neutral or anionic species of biomedical or environmental relevance to form supramolecular compounds, which may have interesting magnetic or fluorescent properties, and could act as luminescent molecular chemosensors.

The following are the preliminary experiments accomplished in supramolecular chemistry, with some of the compounds described in this chapter.

X-ray single-crystal studies and magnetic, photomagnetic and colorimetric measurements of a series of iron(II)-3-(2-pyridyl)-triazolopyridine (**TP**) complexes $[Fe(\mathbf{TP})_3](BF_4)_2$ **256**, $[Fe(\mathbf{TP})_2](NCS)_2\cdot 2CHCl_3$ **257**, $[Fe(\mathbf{TP})_2](NCS)_2\cdot H_2O$ **258** and $[Fe(\mathbf{TP})_2](NCSe)_2$ **259** have been studied and have been characterized as new mononuclear spin crossover compounds [164].

A molecular chemosensor for metal ions, anions and amino acids has been described, the Zn(II) complex of compound **231b** [165]. This system permits the

direct detection of anions without using competitive reactions or dyes. One of the most interesting aspects is the discrimination between nitrite and nitrate anions. The ability of the Zn(II) complex to interact and quantify amino acids has been explored for L-glutamate and L-aspartate.

Triazolopyridine **223** (**TPT**) (Fig. 11) possessing fluorescent properties has been studied as molecular chemosensor for Zn(II), nitrite and cyanide anions. The fluorescence behaviour of **TPT** was checked in the presence of the divalent transition metal ions Co^{2+}, Ni^{2+} and Cu^{2+} and of the post-transition metal ions Zn^{2+}, Cd^{2+} and Pb^{2+}. Zn(**TPT**)$^{2+}$ 1:1 complex in solution was checked with different monovalent anions (F^-, Cl^-, Br^-, I^-, CN^-, SCN^-, NO_2^-, NO_3^-). In all cases, quenching of the emission was produced. Complex Zn(**TPT**)$^{2+}$ is a sensor for anions specially cyanide and nitrite [166].

A tetranuclear complex of Cu(II) with compound **110B** (R = 2-PyCO-) with magnetic properties has been described; the structure shows a cubane tetrameric complex of copper(II) with the hemiacetalate of the 2-pyridyl-[1,2,3]triazolo[1,5-*a*] pyrid-7-ylmethanone and a S_4 symmetry. The Cu_4O_4 core corresponds to a distorted cubane [167]. The magnetic behaviour of the complex is typical for compounds displaying significant intramolecular antiferromagnetic coupling.

5.2.3 Pharmacological Studies

There are no [1,2,3]triazolo[1,5-*a*]pyridines used as pharmaceutical compounds. This section reports preliminary studies of the pharmacological interest of some triazolopyridines.

Synthesis and Evaluation of 7-Arylhydroxymethyltriazolopyridines as Potential Cardiovascular Agents

7-Arylhydroxymethyltriazolopyridines might be considered as structural analogues of benzyltetrahydroisoquinoline and bisbenzyltetrahydroisoquinoline alkaloids that have the ability to block calcium channels and/or antagonize α_1-adrenoreceptors, and may have applications in the treatment of cardiovascular disorders. A series of these triazolopyridine derivatives **260** have been synthesized (Fig. 13), and the activity as relaxants of vascular smooth muscle has been tested in isolated aortic rings precontracted by noradrenaline looking for activity as antagonists of the α_1-adrenoreceptors present in this tissue and stimulated by noradrenaline. The lack of a relaxant action excludes the possibility that these compounds act as α_1-adrenoreceptors antagonists.

Addition of depolarizing solution to the aortic ring induces a sustained contractile response in the absence of endothelium. In these conditions, opening of voltage-sensitive calcium channels and calcium entry promotes this contractile response. Subsequent addition of these compounds in cumulative concentrations, once the contractile plateau induce by depolarizing solution had been reached, did

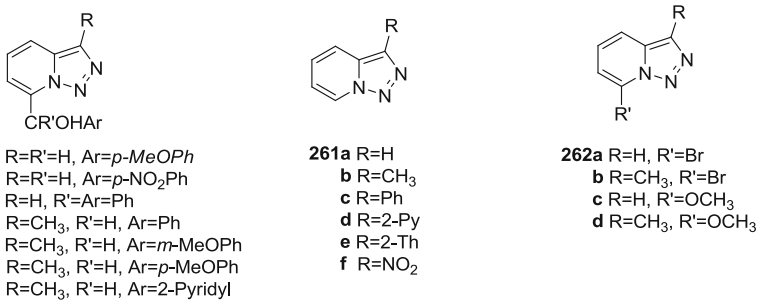


Fig. 13 Triazolopyridines with potential pharmacological activity tested

not modify the tone, thus suggesting that none of the compounds tested can block calcium entry through voltage-dependent calcium channels [168].

Biological Evaluation of [1,2,3]Triazolo[1,5-*a*]pyridines as New Neural Nitric Oxide Synthase Inhibitors

The importance of nitric oxide (NO) as a biological messenger in numerous physiological processes has been demonstrated to a growing extent over the last decades. This molecule is indeed involved in various fundamental functions such as neurotransmission [169], blood pressure and blood flow regulation [170] and platelet aggregation and inflammation [171]. Overproduction of nitric oxide plays a role in a variety of disorders. Nitric oxide is synthesized in several cell types from L-arginine by different isoforms of nitric oxide synthase (NOS).

A series of inhibitors of this enzyme is constituted by heterocycles such as substituted indazoles or imidazoles. The 3- or 7-substituted indazoles are potent nNOS inhibitors [172, 173]. [1,2,3]Triazolo[1,5-*a*] pyridines can be considered as aza-analogues of indazoles, and some studies have been done to test the possibility that the triazolopyridines can be (NO) synthase inhibitors. A number of 3- and 7-substituted triazolopyridines **261** and **262** (Fig. 13) have been synthesized and have been tested [174]. The triazolopyridines evaluated have small activity, and the results indicate that a NH group is necessary for the interaction with the NOS.

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