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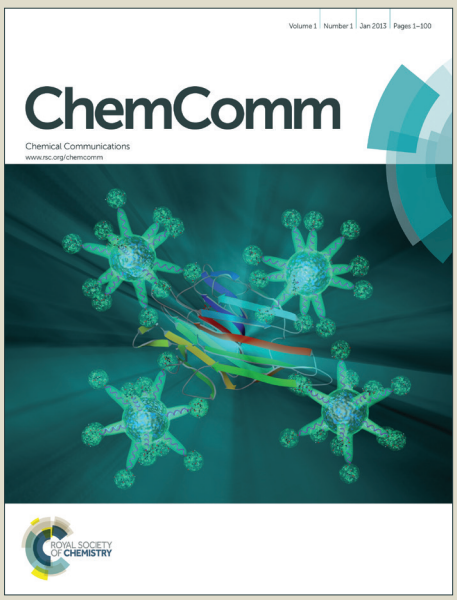

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Emerging Approaches for the Synthesis of Triazoles: Beyond Metal-Catalyzed and Strain-Promoted Azide-Alkyne Cycloaddition

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Metal-free 1,3-dipolar cycloaddition reactions have proven to be a powerful tool for the assembly of key heterocycles, in particular diversely functionalized 1,2,3-triazoles. A number of metal-free (3+2)-cycloaddition approaches have been developed up to date with the aim to circumvent the use of metal catalysts allowing these reactions to take place in biological systems without perturbation of the naturally occurring processes. This feature article specifically provides an overview of emerging metal-free synthetic routes, and their mechanistic features, in the formation of functionalized 1,2,3-triazoles .

1. Introduction

Click chemistry has emerged in the past decade as an important tool for rapid and efficient assembly of a wide variety of molecules.[1] In 2001 Sharpless and co-workers defined the term "click chemistry", and identified the copper-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and alkynes, to access 1,2,3-triazoles, to be a prime example.[2] This conceptually new approach of generating functionalized triazoles, often exhibiting biological or pharmacological activities,[3] appeared not to be restricted to the biological field, but rapidly extended to other areas of the fine chemical industries, comprising dyes, agrochemicals, corrosion inhibitors and photostabilizers.[4]

The copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC)-based triazole formation is however limited by the fact that only terminal alkynes can be used, hence hampering the diversification of the triazole core structure. Moreover, copper has been associated with cellular toxicity, metabolic disruption and Cu-induced oxidative damage in biological systems.[5,6] As a consequence, significant research efforts have been directed towards the development of metal-free procedures to generate triazoles under mild conditions.[7] Pioneering work in the field of metal-free cycloaddition reactions comes from Bertozzi's lab, where they showed that the reaction between an azide and a strained cyclooctyne, also referred to as strain-promoted azide alkyne cycloaddition (SPAAC), resulted in rapid triazole formation.[8] Soon after, Rutjes and co-workers demonstrated that strained, electron deficient oxanorbornadienes efficiently produced triazoles through a cycloaddition retro-Diels Alder process.[9] These seminal papers marked the off-set of a plethora of exciting new metal-free methodologies.[10] Besides the frequently used cyclooctynes several different dipolarophiles, such as enamines, enolates, activated alkenes, among others have recently been employed to facilitate triazole formation. Enamines, specially, have been receiving much attention and these species are generated *in situ* through the condensation of secondary amines and readily accessible carbonyl compounds.

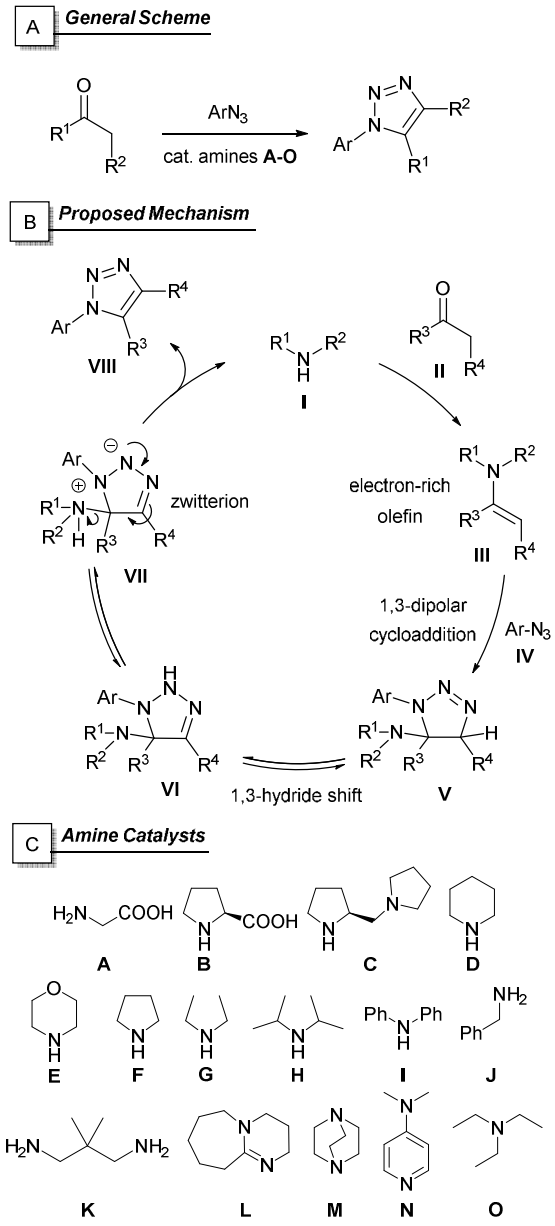
This feature article provides an overview of several alternative metal-free strategies beyond SPAAC that have been designed in the last few years to facilitate the fast and efficient synthesis of highly diverse 1,2,3-triazoles.

2. Enamine and Dienamine/azide (3+2)-cycloaddition

The 1,3-dipolar cycloaddition of enamines and azides constitutes a highly regioselective access to substituted 1,2,3-triazoles (Scheme 1A). As shown in the proposed mechanism (Scheme 1B) enamine **III** can be readily generated *in situ* through the reaction of a carbonyl compound **II** and amine catalyst **I**, which then reacts as a dipolarophile with the azide partner **IV**. The cycloaddition of the enamine and the azide generates the five membered heterocycle triazoline intermediate **V** which is in equilibrium with intermediate **VI** and stabilized zwitterionic intermediate **VII**. The spontaneous elimination occurs under acidic conditions in the final step generating 1,2,3-triazole **VIII**.

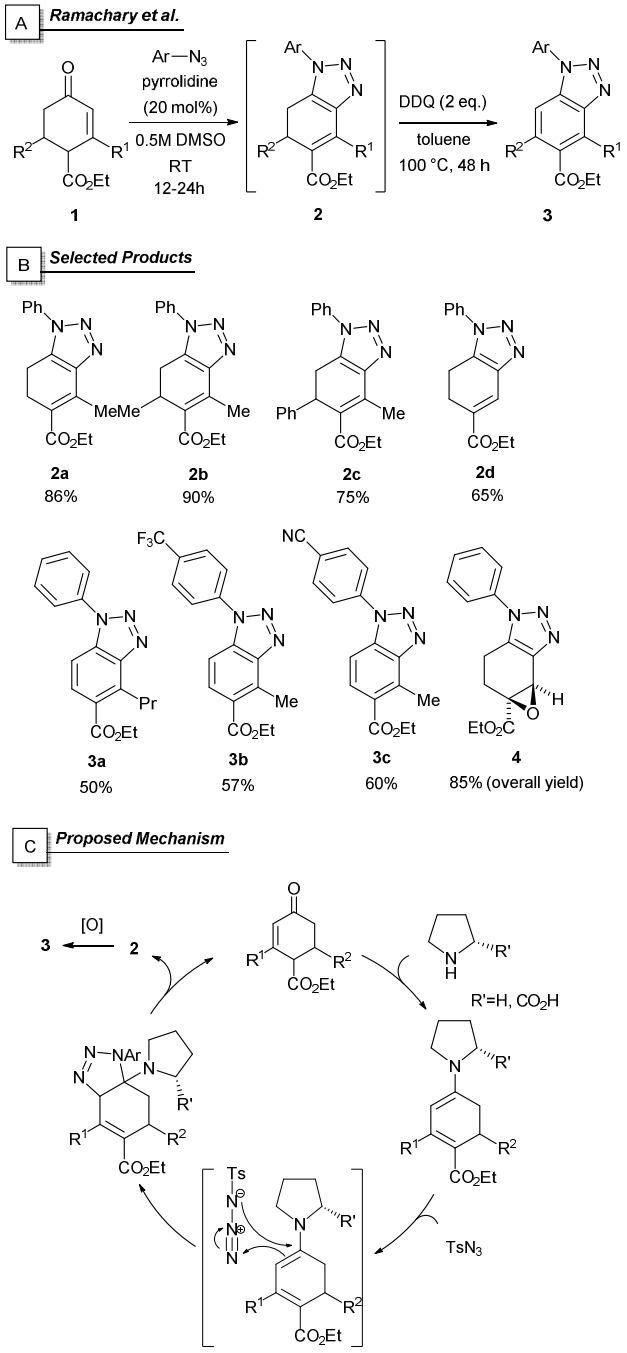
The catalysts evaluated in this reaction are amines and amino-acids (Scheme 1C) with proline **B**, pyrrolidine **F**, and diethylamine **G** typically being the most effective.

The carbonyl compounds to generate enamines acting as dipolarophiles in organocatalyzed 1,3-dipolar cycloadditions can be divided into two categories: a) ***activated***, including Hagemann's esters, β-ketoesters, β-oxo-amines and b) ***unactivated***, which include alkyl/allyl ketones and aldehydes.[11]



Scheme 1. Amine-catalyzed 1,3-dipolar cycloaddition of carbonyl compounds to azides.

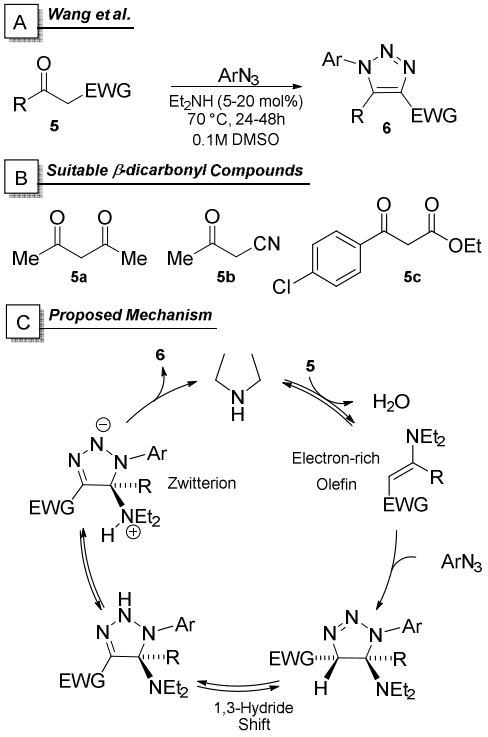
In a seminal paper by Ramachary and co-workers, the metal-free synthesis of 1,2,3-triazoles from activated carbonyl compounds was reported, employing proline as organocatalyst.[12a] In order to accomplish this, the authors successfully established a (3+2)-cycloaddition/hydrolysis sequence in which the products were unprotected *NH*-1,2,3-triazoles. Aiming to broaden the scope and apply a similar protocol for the synthesis of benzotriazoles, they published, in 2013, a highly versatile methodology for the preparation of such molecules. Starting with Hagemann's ester **1**, they were able to synthetize 1,3-cyclohexadienes **2** employing pyrrolidine as catalyst (Scheme 2). This protocol could be successfully applied to a wide range of aryl azides bearing different substitution patterns, however, the reaction times were considerably shorter when electron-poor azides have been employed.



Scheme 2. Synthesis of 1,2,3-triazoles from Hagemann's ester **1** and aryl azides.

Compellingly, the group also showed that the cyclohexadienes **2** could be further manipulated, with the ß-olefin being oxidized with *m*CPBA to generate highly functionalized epoxy triazoles **4**. Moreover, it was shown that subsequent aromatization of the cyclohexadiene moiety using DDQ in a one-pot fashion resulted in the formation of benzo-annulated triazole products **3**.[12b] The scale on which these reactions can be run was up to gram-scale, as exemplified by the 1g synthesis of **3b**.The versatility of this approach seems to be very broad; it is obvious that further applications will be originated by this finding.[12c]

In 2011, Wang et al. reported the organocatalyzed cycloaddition reaction of azides to enamines/enaminone to produce 1,4,5-trisubstituted-1,2,3-triazoles **6** (Scheme 3A).[13]

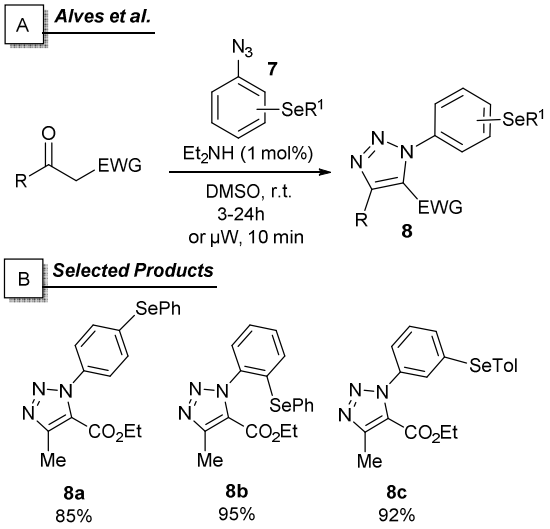


Scheme 3. Organocatalyzed formation of 1,4,5-trisubstituted-1,2,3-triazoles **6**.

Several features accompany this methodology: a) the use of a simple organocatalyst (diethyl amine); b) high yields; c) slightly elevated temperatures; d) regioselectivity and e) high degree of diversity of the products. This approach showed a quite broad functional-group tolerance as can be deduced from the varied of ß-carbonyl compounds (Scheme 3B, e.g. ß-ketoesters **5a** and ß-ketonitriles **5b**) and substituted aryl azides (ranging from electron poor to electron rich aryl moieties) that could successfully be applied.

The proposed mechanistic pathway involves an inverse electron-demand 1,3-dipolar cycloaddition process of the enamine (electron-rich olefinic partner) and the aryl azide. After enamine formation, attack of the aryl azide generates a triazoline intermediate, which undergoes a subsequent 1,3-H shift. Rearrangement of this intermediate to the zwitterions sets the stage for spontaneous aromatization and generation of the triazole.

With the aim to study the biological activity of 1,2,3-triazole moieties bearing organoselenides, Alves et al. utilized an organocatalytic enamide/cyclization cascade to synthesize organylselanyl-1,2,3-triazoles **8** (Scheme 4).[14a]



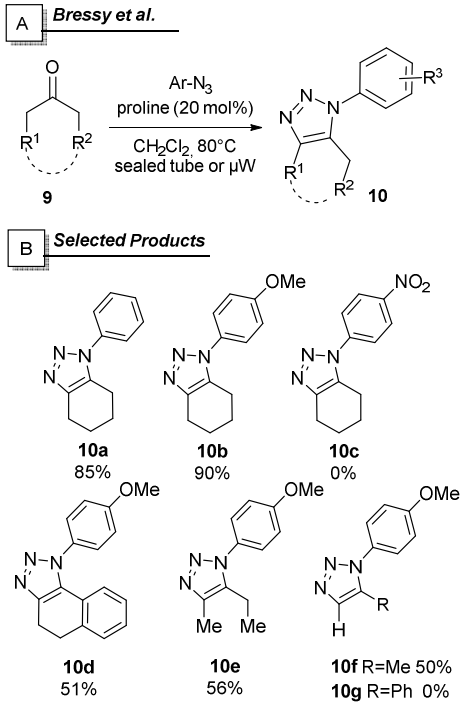
Scheme 4. Organylselanyl-1,2,3-triazoles **8** via *β*-enaminone-azide cycloaddition.

Optimization studies showed that the catalyst loading can be reduced to 1 mol% and that the reaction time could be reduced considerably by applying microwave (μw-) heating (from 3-24 h to 10 min). Different functionalized azidophenyl aryl-selenides, such as 4-(azidophenyl)(phenyl)-selenide, 2-azido-phenyl arylselenides amongst others were tolerated under the optimized reaction conditions, demonstrating that those were insensitive to the electronic effect of the aromatic ring of the arylselanyl moiety. More recently, the same group extended this methodology by employing *β*-oxo-amides as dicarbonyl compound to obtain (arylselanyl)phenyl-1H-1,2,3-triazole-4-carboxamides.[14b]

Besides the β-carbonyl compounds usually employed to form electron-rich enamines/enaminones dipolarophiles, Bressy and co-workers showed that non-activated ketones **9** could also be used for this purpose (Scheme 5).[15] Here, proline was employed as organocatalyst and the reactions were performed either under conventional or μw-heating.

Evaluation of the scope of aryl azides indicated that electron-donating groups on the aromatic ring furnished good results, this in contrast with aryl azides functionalized with electron-withdrawing groups which did not react to **10c**. The type of heating had a dramatic effect in the reaction, since the reactions employing conventional heating typically took 5-6 days, while reactions performed under μw-heating took only one hour to reach similar yields. Acyclic ketones gave considerably lower

yields (**10e**) under the same conditions, whereas acetophenone **10g** turned out to be completely unreactive.



Scheme 5. Organocatalyzed formation of 1,4,5-trisubstituted-1,2,3-triazoles **10** from non-activated ketones **9**.

The methods described thus far for metal-free synthesis of 1,2,3-triazoles all employ organic solvents (e.g. DMSO, CH_2Cl_2), which may be regarded as a limitation for expanding its applications in biological systems. Aiming to develop a biocompatible procedure for activated and non-activated carbonyl compounds, Wang developed a proline-based lipophilic amine catalyst **11** (Figure 1), which proved to be highly suitable for the triazole-formation in water.[16] The yields in water were comparable to those described previously in organic solvents. It was shown that the catalyst required a tertiary amide rather than a secondary amide (in **12**) indicating that the reaction is possibly driven by the formation of catalytic micelles.

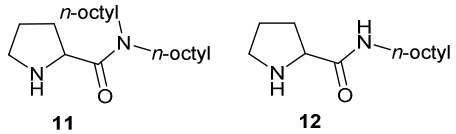
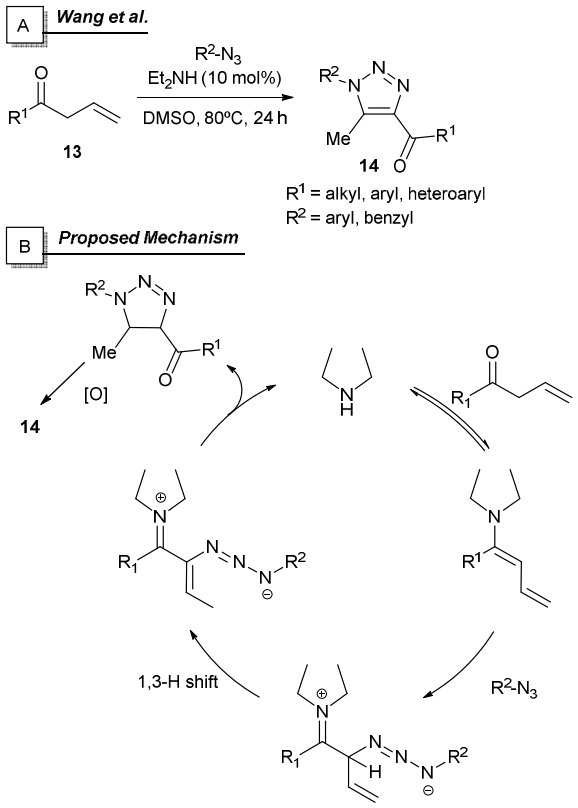


Figure 1. Lipophilic amine catalysts employed by Wang et al. allow the formation of 1,2,3-triazoles in water.

In addition to the non-activated alkyl ketones that could be employed to generate enamines, Wang and co-workers reported the organocatalytic cycloaddition of allyl ketones **13** to aryl azides in the presence of a catalytic amount of a secondary amine (i.e. diethyl amine, Scheme 6).[17]

In this reactions, the desired products **14** were formed through an unusual α,β-reactivity of the dienamine intermediate, which is shown in the proposed catalytic cycle (Scheme 6B).



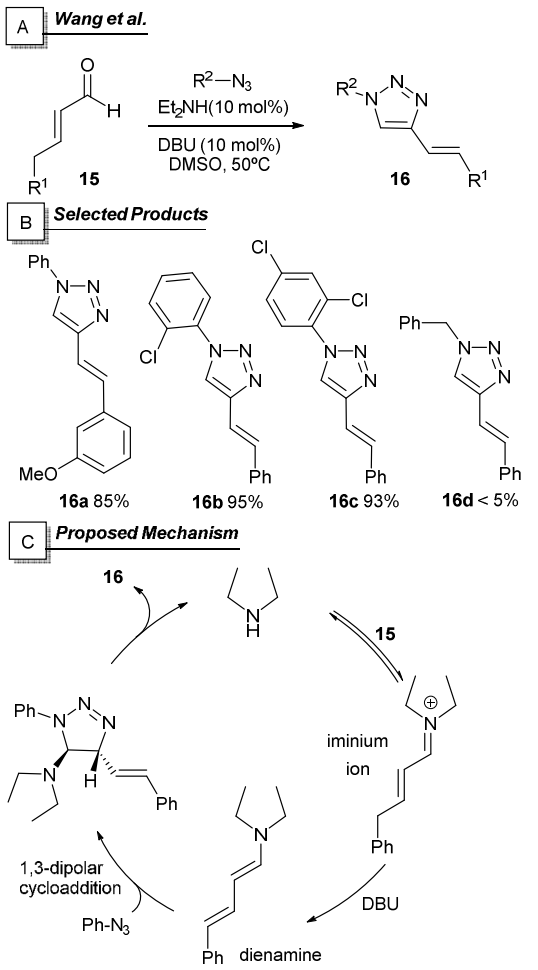
Scheme 6. Amine-catalyzed cycloaddition reaction between allyl ketones **13** and aryl azides.

This methodology could be successfully applied for several allyl aryl ketones bearing electron-donating, neutral and electron-withdrawing groups, as well as for allyl heteroaryl ketones and allyl alkyl ketones. The electronic effects of the substituents on the aryl ring of aryl azides also did not affect the outcome of the reaction, and alkyl azides were also tolerated.

Similarly, the same authors described the use of α,β-unsaturated aldehydes to generate a dienamine species which could also be used as dipolarophiles (Scheme 7).[18]

The proposed catalytic cycle (Scheme 7C) starts with the generation of the iminium ion through the condensation of α,β-unsaturated aldehyde **15** with the amine catalyst. The iminium ion is then converted into a dienamine in the presence of a strong organic base (DBU). The dienamine further acts as the electron-rich olefinic partner to react with aryl azides via an 1,3-dipolar cycloaddition process to produce the cyclized product. The desired product **16** is formed after an elimination step regenerating the catalyst.

As shown in Scheme 7B, the reaction afforded high yields for a wide range of α,β-unsaturated aromatic aldehydes and aryl azides bearing both electron-donating and electron-withdrawing functional groups (applies to both reagents). In the presence of benzylic azides the reaction, however, did not proceed.

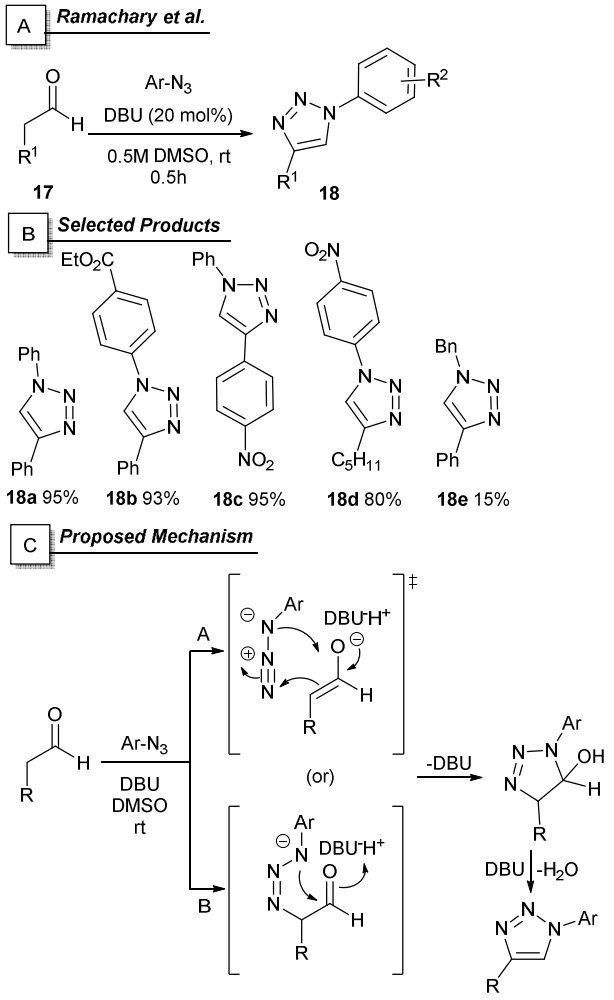


Scheme 7. Triazoles **16** generated from azides and α,β-unsaturated aldehydes **15**.

3. Enolates as dipolarophiles

In a similar but complementary approach, enolates have been successfully employed as dipolarophiles in the metal-free synthesis of triazoles as was demonstrated by Ramachary et al. (Scheme 8).[19] In an interesting work published in 2014, the group was able to synthetize 1,4-DTs from enolizable aldehydes and aryl azides employing DBU as catalyst.

The products could be obtained in a highly efficient procedure that took only 0.5 h at room temperature to achieve completion. The protocol could be employed for a wide range of aldehydes and aryl azides (Scheme 8B), wherein 2-arylacetaldehydes bearing both electron-donating and electron-donation groups afforded higher yields. Even alkyl aldehydes, which have less acidic α-methylene groups when compared to the 2-arylacetaldehydes, were tolerated, affording good yields. For the aryl azides, the ones bearing electron-withdrawing groups gave rise to higher yields. Alkyl, acyl and tosyl azides, however, did not produced the desired products. From a mechanistical perspective the aldehyde may react following two different pathways: A) a highly selective and concerted (3+2) cycloaddition or B) a stepwise amination–cyclization reaction, both giving the same 1,2,3-triazoline product (Scheme 8C).

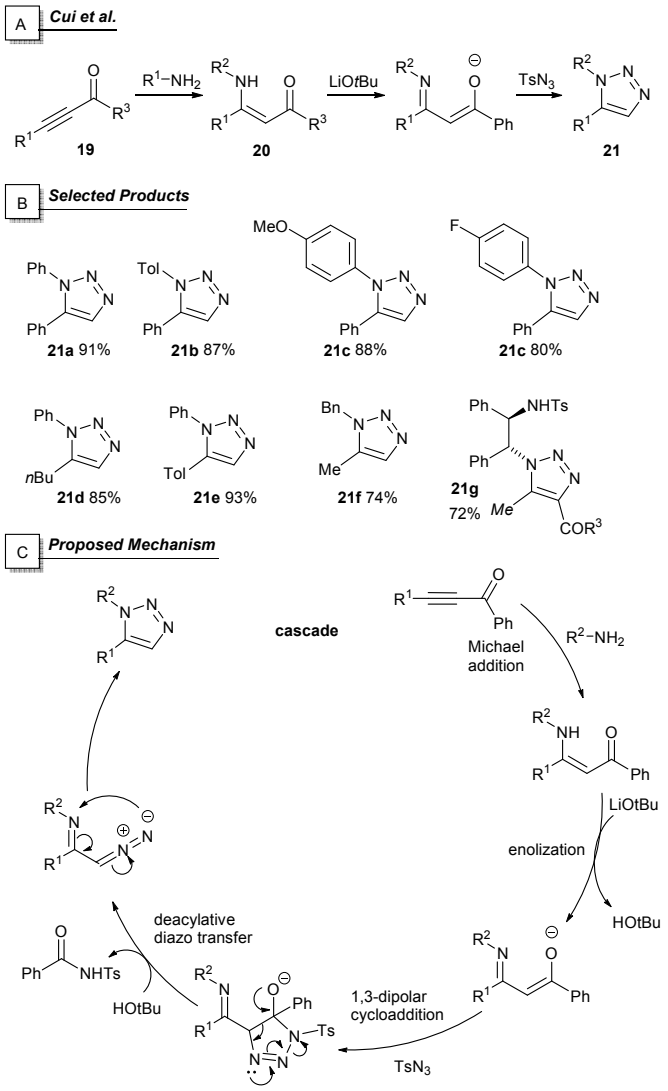


Scheme 8 Organocatalytic enolate-mediated synthesis of 1,2,3-triazoles with DBU as catalyst.

An appealing method for the regioselective generation of 1,5-disubstituted triazoles **21** (1,5-DTs) was provided by Cui et al., who utilized iminoenolates as dipolarophiles in the (3+2)-cycloaddition with azides.[20]

Exploring this concept, an unprecedented methodology was developed comprising a Michael addition/deacylative diazo-transfer/cyclization cascade utilizing primary amines, propynones, and sulfonyl azides in a single transformation (Scheme 9). This one-pot protocol afforded good yields for amines and alkynes functionalized with various functional groups (Scheme 9B). Moreover, several N-aryl enaminones **20** functionalized with electron-donating or electron–withdrawing groups could be successfully employed to form the corresponding 1,5-DTs in good to excellent yields (71-99%).

The proposed mechanism is initiated by Michael addition between the primary amine and the propynone to produce enaminone **20** (Scheme 9C). In the next step, deprotonation of **20** by LiO*t*Bu generates an iminoenolate intermediate, that reacts with the tosyl azide through a 1,3-dipolar cycloaddition, and after a diazotransfer and subsequent cyclization, the desired 1,5-DTs **21** are formed. The challenge to form enantiomerically enriched 1,5-DTs was endeavoured by the formation of **24g**, which was sinthetized from enantiomerically pure monoprotected diamine.

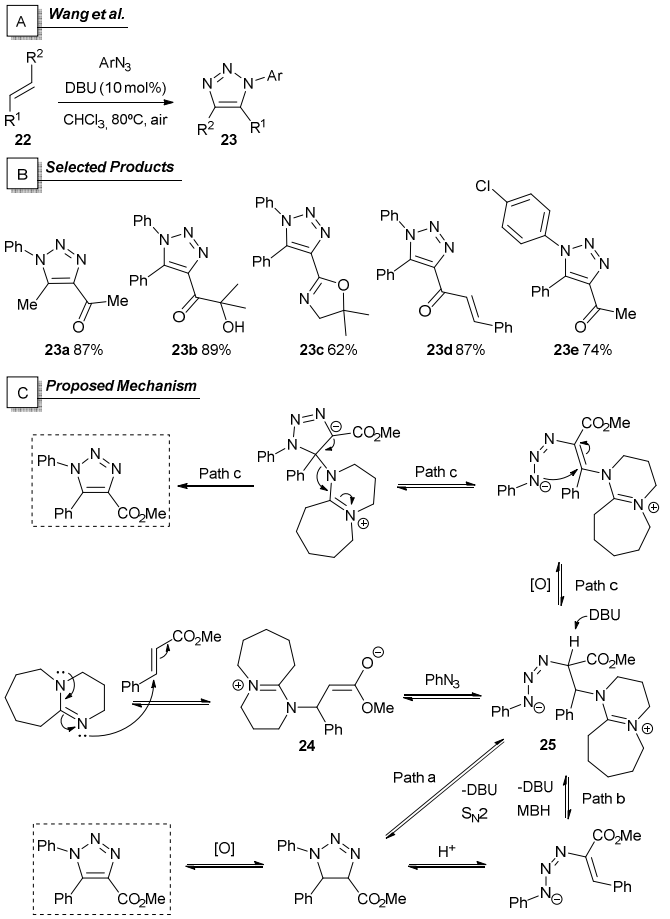


Scheme 9. 1,5-DTs synthesis through a three component reaction of primary amine, propynone and sulfonyl azide.

Recently, Wang and co-workers reported an organocatalytic reaction which involves an intermediate similar to intermediate **20** reported by Cui, (Scheme 10C, intermediate **24**).[21] The methodology described by Wang presented the first example of a metal-free catalytic aerobic oxidative intermolecular azide-zwitterion cycloaddition (AZC) (Scheme 10) whereby the mechanism is associated with the Morita-Baylis-Hillman (MBH) reaction.

The protocol could be successfully applied for a variety of aryl and alkyl azides, as well as a diverse set of α,β-unsaturated esters, affording the products in good yields (62-89%). Ketones, thioesters, amides, dihydrooxazoles were also suitable reactants in this transformation.

The mechanistic pathway proposed for this transformation was corroborated by mass spectrometry studies, whereby the detection of the zwitterion species related to the MBH reactions proved key in unrevealing the mechanism. The reaction starts when DBU is added to cinnamic acid as the α,β-unsaturated ester**,** forming the zwitterion intermediate **24**. The subsequent addition of **24** to phenyl azide forms intermediate **25**, which can generate the final product following three possible pathways, of which "Path c" is the most favoured. Path c involves the aerobic oxidation of intermediate **25**, followed by a 6π electrocyclization and elimination of DBU, forming the 1,4,5-TT.



Scheme 10. Metal-free catalytic aerobic oxidative intermolecular azide-zwitterion cycloaddition reaction.

The ability of enolate chemistry to potentially generate 1,5-distubsituted triazoles makes it a powerful tool for the construction of peptide chimeras with a locked *cis*-peptide mimetic configuration (Figure 2).

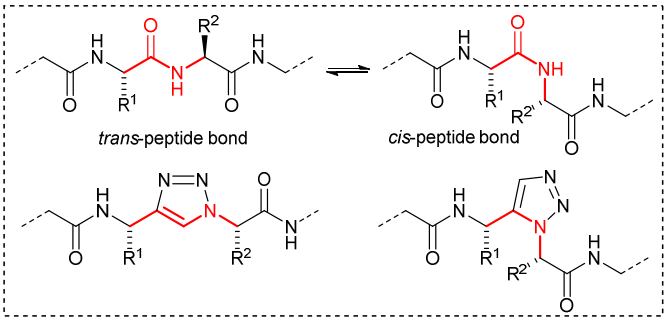
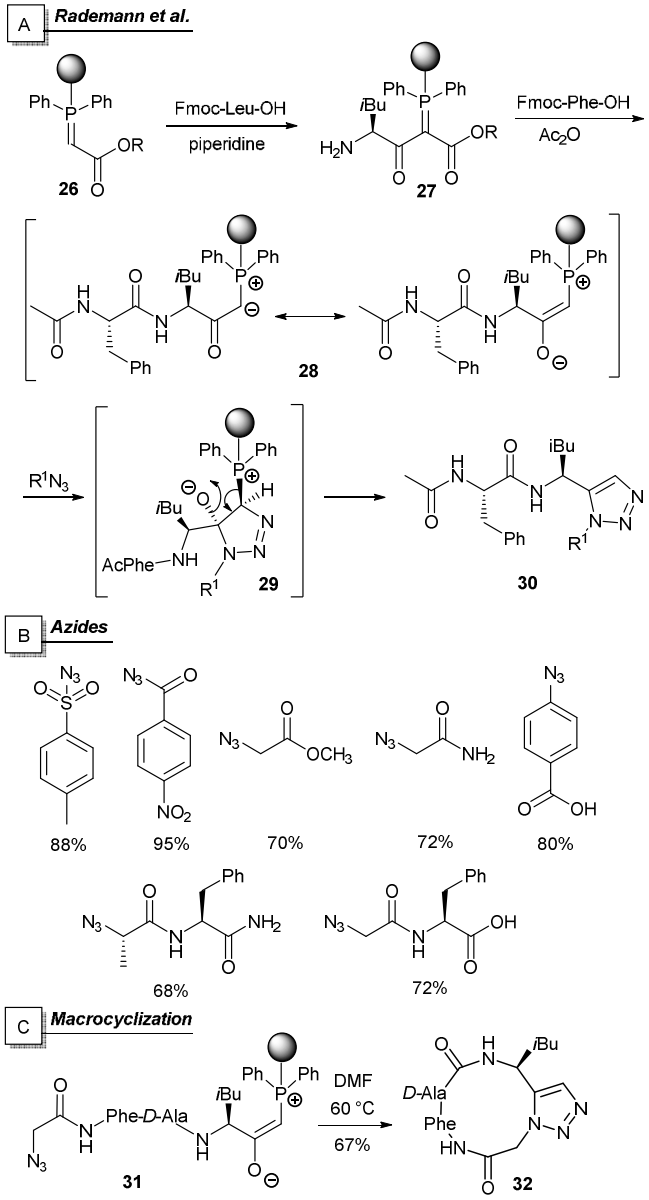


Figure 2. Triazoles as *trans*- and *cis*-peptide bond chimeras.

To this end, Rademann et al. developed a protocol for the solid phase synthesis of peptide chimeras with *cis*-locked peptide bonds with 1,5-disubstituted triazoles (Scheme 11).[22]



Scheme 11. Synthesis of a cyclic peptide chimera with a locked *cis*-peptide bond.

The synthesis was initiated by C-acylation of solid phase bound phosphoranylidene with Fmoc-protected leucine. After chain elongation, e.g. with phenyl alanine, the phosphor ylide/phosphonium enolate tautomers **28** facilitate the cycloaddition with various azides leading to the rapid formation of the desired 1,5-DTs **30**. The scope of the reaction was demonstrated by reacting peptidyl phosphorane **28** with a variety of azides producing the 1,5-DTs in good yields and high regioselectivity (Scheme 11B). Intriguingly, when both triazole forming functionalities (i.e. phosphonium enolate and azide) are present in the same molecule, locked *cis*-peptide macrocyles **32** could be obtained.[23] Overall, this protocol presents several advantages, such as high yields and selectivity and eliminates the requirement of the preparation of amino acid alkynes. However, this methodology was not applied to azides functionalized with strong electron-donating groups, which might limit the scope.

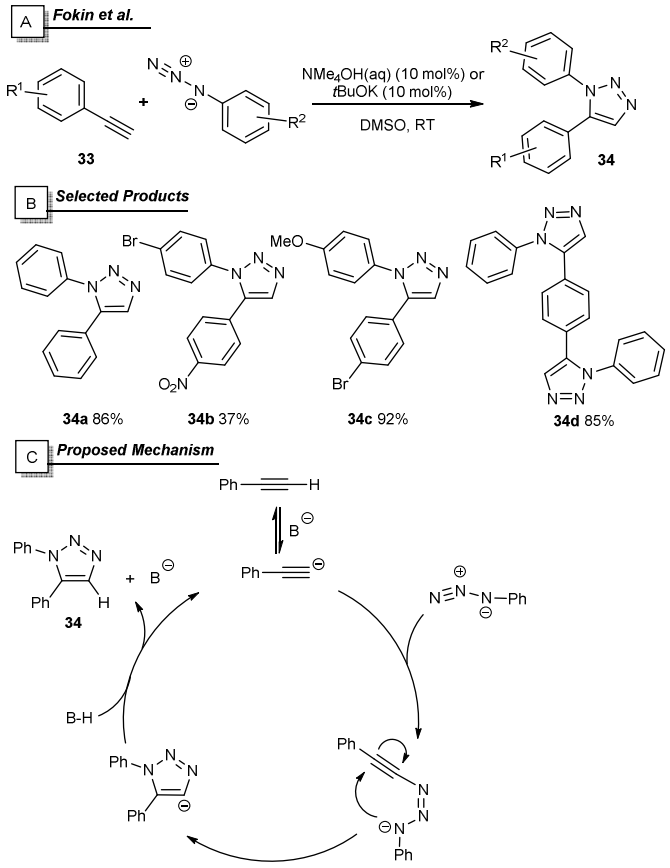
4. Alkynes and alkynes precursors

Alkynes are amongst the most commenly used dipolarophiles in metal-free 1,3-dipolar cycloadditions.[24] Initially, however, the reactions involving alkynes could only be successfully accomplished if strained alkynes or elevated temperatures were employed.[25]

At present, alkynes are still frequently employed to form 1,2,3-triazoles, though continuous research efforts have resulted in alternative cyclization strategies to generate these compounds.[26] Pioneering this field, Fokin et al. reported the use of alkynes to generate reactive acetylide intermediates *in situ,* resulting in the exclusive formation of 1,5-disubstituted triazoles (Scheme 12).[27]

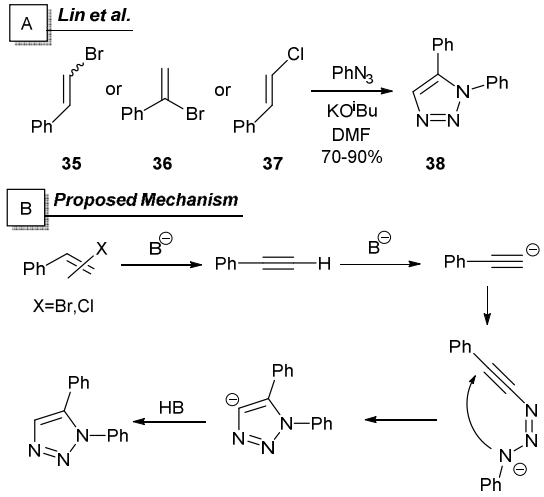
After screening several bases, NMe_4OH was found to be the preferred base, considering the favourable yield and reaction time. The scope of the reaction showed that electron-deficient aryl azides, as well as aryl azides with sterically demanding *ortho*-substituents, afforded lower yields. For the acetylenes, aryl groups containing strong electron-withdrawing groups afforded low yields, possibly due to the reduced nucleophilicity of the acetylide anion. Interestingly, this protocol was found to be tolerant to base-labile functionalities.

The proposed catalytic cycle (Scheme 12C) is initiated by the reversible deprotonation of the terminal alkyne, generating an aryl acetylide. The aryl acetylide then acts as a nucleophile, attacking the terminal nitrogen atom of the aryl azide, forming a triazenide intermediate, which undergoes either a 6π-electrocyclization or a 5-endo-dig cyclization to form 1,5-disubstituted-1,2,3-triazolyl anion. Reprotonation of this intermediate then furnishes the final 1,5-disubstituted triazole **34**.



Scheme 12. Base-catalyzed synthesis of 1,5-DTs from alkynes and azides.

Similarly to this approach, 1,5-DTs can also be synthesized by *in situ* generation of alkynes from vinyl halogenides (Scheme 13). According to Lin et al., the mechanism leading to these products (Scheme 13B) is closely related to the one reported by Fokin et al (see Scheme 12).[28]

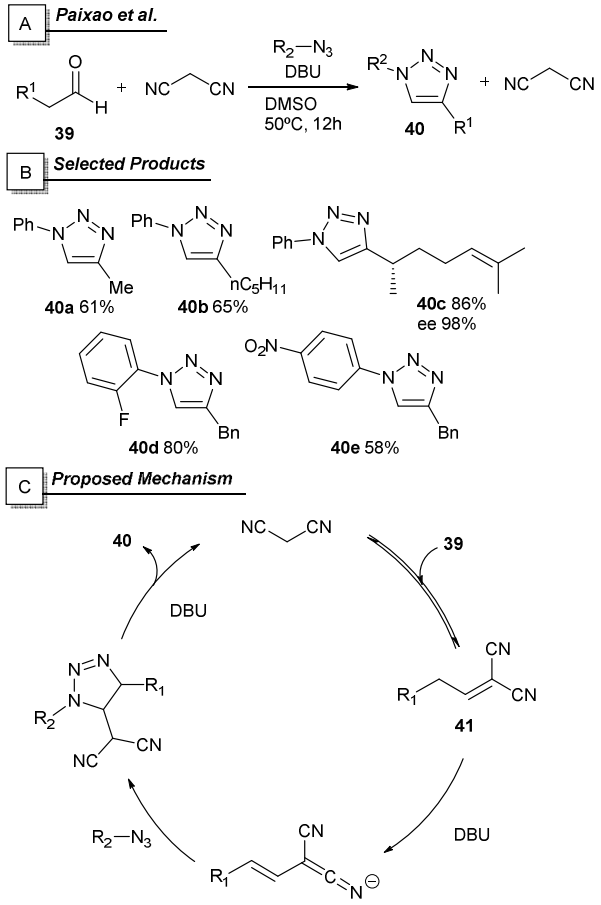


Scheme 13. Synthesis of triazoles **38** starting from vinyl halogenides **35-37**.

The mechanism presumably is initiated by a base-catalyzed dehalogenation (Scheme 13B). As a result of the dehalogenation, this method is only applicable for substrates bearing no acidic CH-protons. In addition to aromatic vinyl halides, aliphatic vinyl halides could also successfully undergo the cycloaddition reaction, however, with a significant decrease in yield.

5. Activated alkenes as dipolarophiles

Another class of compounds that present the ability to react as dipolarophiles in the 1,3-dipolar cycloaddition reaction are the activated alkenes. In (3+2)-cycloadditions with azides, electron-poor or electron-rich activated alkenes can react by normal or inverse electron-demand 1,3-cyclopolar addition, respectively.
Recently, Paixao et al. disclosed an efficient one-pot strategy for the highly regioselective metal-free synthesis of 1,4-disubstituted-1,2,3-triazoles **40** (Scheme 14).[29]
This procedure encompasses an inverse electron demand 1,3-dipolar cycloaddition approach, by which the alkylidene malonitrile **41** is formed *in situ* from an aldehyde and will act as the dipolarophile.



Scheme 14. Inverse electron demand akylidene malononitriles **19** and aryl azides producing 1,4-disubstituted-triazoles **18**.

This practical one-pot procedure could be applied to various alkylidene malononitriles and aromatic azides. Studying the scope and limitations of this procedure furthermore revealed that azides with an α-chiral center can also be employed.

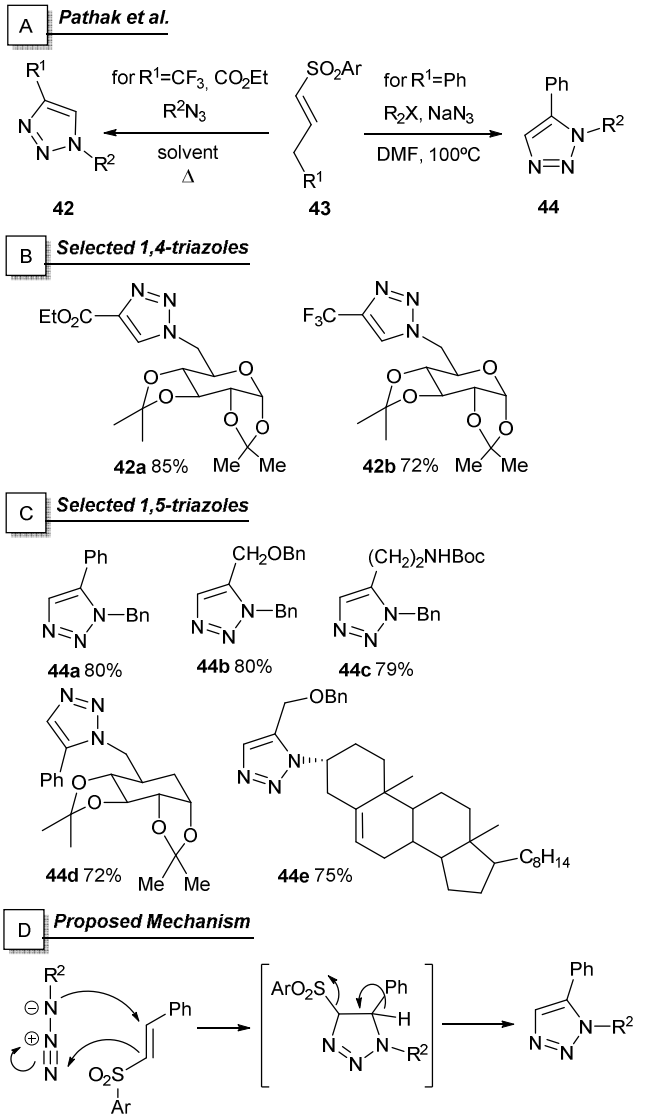
Based on DFT calculations and MS-analysis, a mechanism was proposed in which the reaction is initiated by a Knoevenagel condensation of malononitrile and an aldehyde to generate the alkylidene malononitrile **41** (Scheme 14C). Subsequently, deprotonation with DBU furnishes a vinylogous carbanion, which operates as the electron-rich olefinic partner in the cyclo-addition to azides. Finally, an elimination step delivers the final product and recycles the malononitrile. The aromatization of the triazole ring is the potential driving force of the reaction. Despite being an elegant methodology for the one-pot synthesis of 1,4-disubstituted-1,2,3-triazoles, this protocol is limited by the low tolerability towards aryl azides containing electron-donating groups as well as benzyl azides.

A similar reaction mechanism can be accounted for 4-triflic triazole formation described by Alcaide et al.[30] A highly activated 1,2 Tf_2C=C dipole is generated, which undergoes a stepwise (3+2)-cycloaddition, upon which the triazole formation can be finalized by the elimination of one triflate.

On the other hand, Pathak demonstrated an intriguing methodology in which selective triazole substituent patterns could be obtained through the selection of the appropriate azide (Scheme 15).[31]

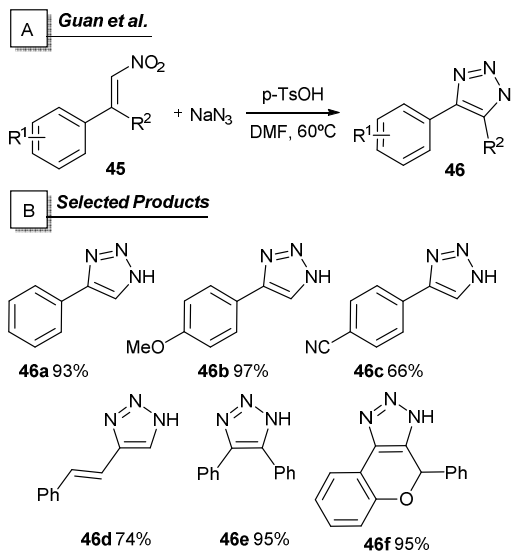
Starting from vinyl sulfones **43**, they accomplished the formation of either 1,4- or 1,5-disubstituted triazoles (Scheme 15A). This type of selectivity has previously been reported for the metal-catalyzed triazole formation using either a Cu- or Ru-catalyst.[32] The reported regioselectivity of this organocatalytic method is directed by the substituents on the (*E*)-vinyl sulfone moiety, which govern the outcome of the reaction. Starting from CF_3- or ester functionalized starting materials 1,4-substituted triazoles **42** are formed (Scheme 15B), whereas aryl, alkyl and heteroalkyl substituents generate 1,5-substituted products **44** (Scheme 15C). In the latter case, the cycloaddition of phenyl vinyl sulfones and organic azides gives the highest yields when the azide is prepared in the same flask. As an example, the azide could be prepared via diazotation of primary amines followed by substitution with NaN_3.

The mechanism is proposed to be initiated by a classical (3+2)-cycloaddition, followed by an elimination of the aryl sulfone moiety to produce the desired 1,2,3-triazole (Scheme 15C).



Scheme 15. Synthesis of 1,4- and 1,5-disubstituted triazoles from vinyl sulfones.

In a similar way, Guan et al. reported the use of nitroalkenes in 1,3-dipolar cycloaddition with azides mediated by tosic acid (TsOH) (Scheme 16).[33]



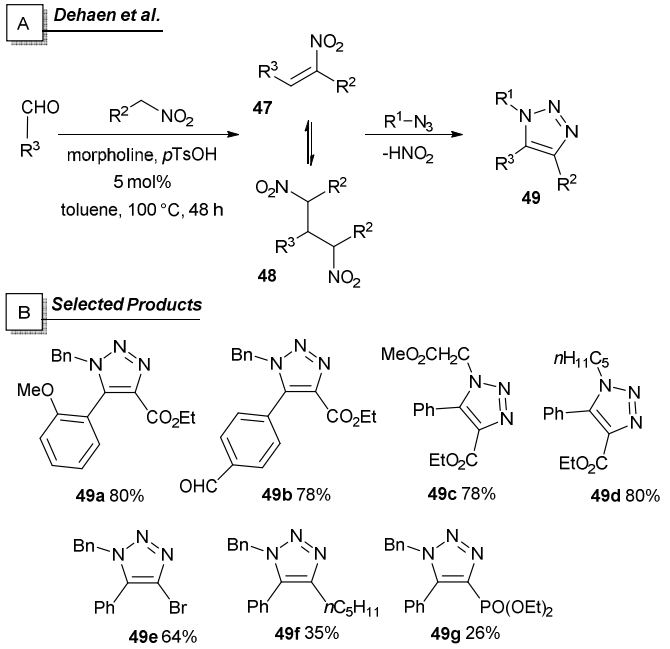
Scheme 16 TsOH catalyzed synthesis of 4-aryl- and 4,5-DTs

By using this strategy, the group was able to synthetize, in good yields, 4-aryl-*NH*-1,2,3-triazoles as well as 4,5-disubstituted triazoles, employing disubstituted nitroolefins in the latter case. The protocol tolerated a wide range of aromatic nitroolefins bearing electron-withdrawing and electron-donating groups and could be applied on gram-scale. At present, this methodology however, is only applicable to aromatic nitroolefins **45**.

Considering that nitroalkenes can be accessed with great diversity starting from aldehydes and nitroalkanes through a Knoevenagel condensation, the scope of this reaction is significant.

As was demonstrated by the Dehaen group, sequential nitroalkene formation and addition of organic azides in a single reaction vessel can generate 1,4,5-TTs.[34] Hence, the entire sequence can be carried out as a multicomponent type reaction (Scheme 17).

As depicted in Scheme 17B, this protocol presents a broad substrate tolerability in terms of aldehydes, nitroalkanes and azides. This method encompasses a variety of highly functionalized starting materials and is therefore highly suitable to construct to diversely decorated 1,2,3-triazoles. Aliphatic aldehydes afforded somewhat lower yields, which was attributed to the undesired aldol condensation under the employed reaction conditions.

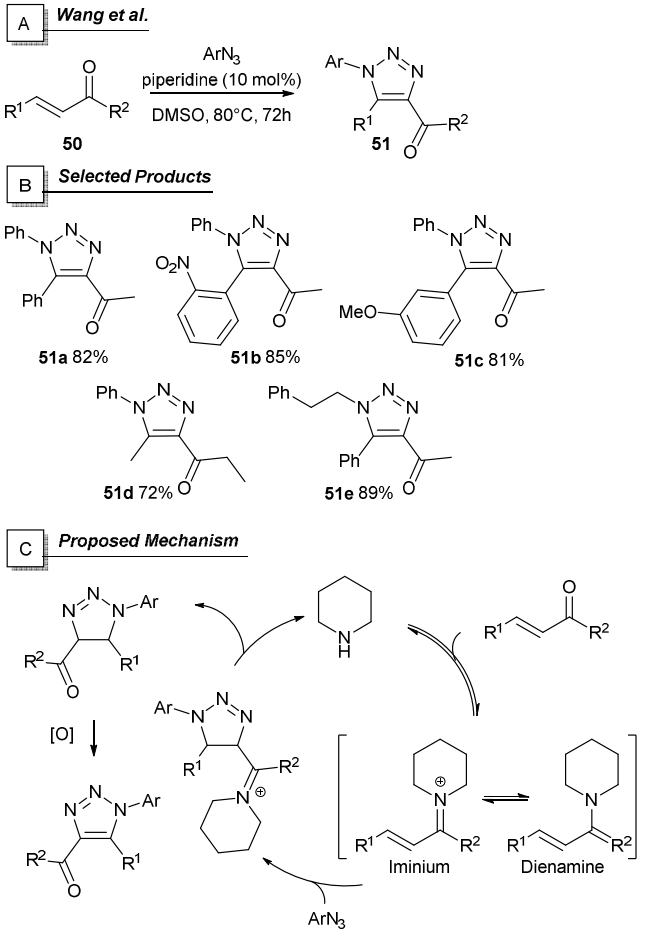


Scheme 17. Three-component synthesis of 1,4,5-TTs **45** from aldehydes, nitroalkanes and azides.

Another interesting paper describes the use of a amine catalyst to obtain diversely substituted 1,2,3-triazoles (Scheme 18).[35] The formation of 1,4,5-TTs was accomplished through a 1,3-dipolar cycloaddition between α,β-unsaturated ketones and azides in the presence of a piperidine catalyst. In this case, even though there is the tautomeric equilibrium between the formed iminium and the dienamine, the iminium is the species that act as dipolarophile, resembling an activated alkene (Scheme 18C). The described methodology worked well for a series of aromatic α,β-unsaturated ketones, showing low sensitivity to the substitution pattern on the aryl ring. Moreover, heterocyclic rings such as furan and thiophene were also tolerated as substrates, as well as less reactive α,β-unsaturated alkyl ketones. As for the azides, a wide range of (hetero)aromatic substrates were tolerated, including aryl azides bearing electron-donating and electron-withdrawing groups, as well as several alkyl azides.

6. Other nucleophiles/dipolarophiles

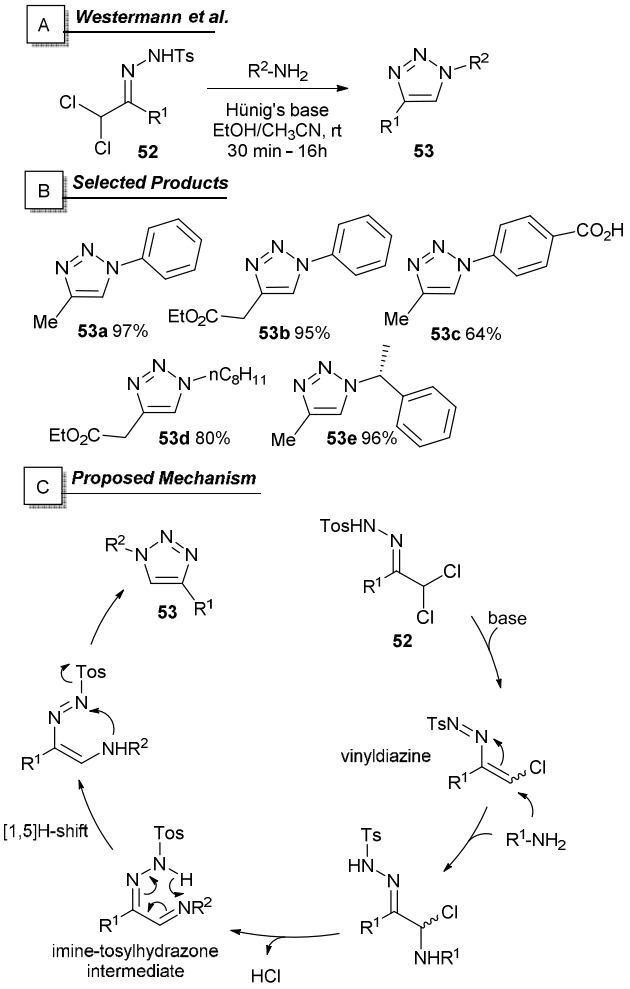
An intriguing method for triazole formation which does not rely on the utilization of either an azide or alkyne to facilitate triazole formation is based on a synthetic methodology developed in 1986 by Sakai et al.[36] It encompasses a condensation of a primary amine and an α,α-dichlorotosylhydrazone to form, regioselectively, 1,4-substituted triazoles under ambient reaction conditions.



Scheme 18. Iminium ion promoted 1,3-dipolar cycloaddition of α,β-unsaturated ketones to azides.

Recently, Westermann and co-workers reported the use of this strategy in the synthesis of a library of 1,4-DTs.[37] As depicted in Scheme 19, a variety of α,α-tosylhydrazones **52** could be utilized to react with a wide range of aromatic amines (electron-rich and electron-poor), as well as aliphatic amines. Interestingly, this methodology is highly chemoselective, hence not requiring a protection strategy for hydroxy-, carboxy- and other functionalities. This feature turned out to be particularly useful in the chemoselective modification of natural products such as phytosphingosine and psychosine. Apart from high chemoselectivity, this reaction also shows high regioselectivity yielding exclusively 1,4-DTs. The scalability of this procedure was demonstrated by Hanselmann and co-workers, producing an antibacterial macrolide on a kilogram scale.[38]

The proposed reaction mechanism starts by base-mediated formation of a vinyldiazine, which is followed by the addition of the amine substrate. After loss of HCl, generating an imine-tosylhydrazone intermediate, a 1,5-H shift is most likely to take place providing the amino nucleophile for intramolecular cyclization. As a result of the mild reaction condition for the Sakai reaction, as compared to most of the organocatalytic cycloaddition reactions, this methodology possibly allows for reactions to be performed under physiological conditions.

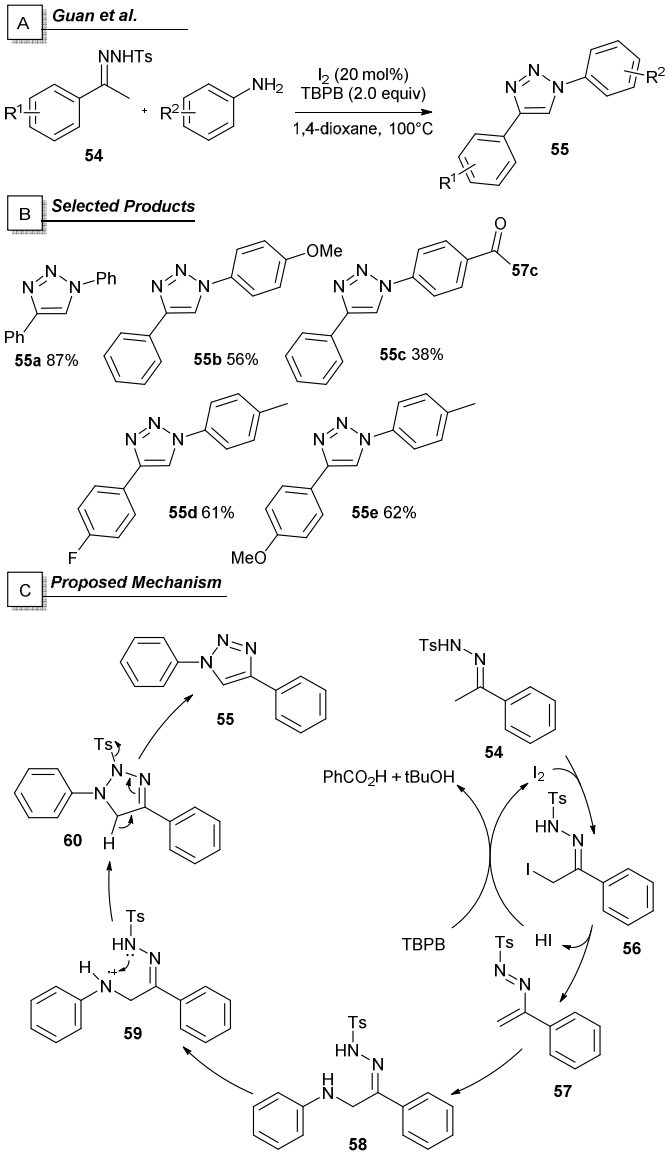


Scheme 19. Synthesis of 1,4-DTs based on the Sakai methodology.

In 2014, applying a similar strategy, Guan et. al reported another azide-free methodology for the construction of 1,4-DTs.[39] Their approach differs from the others by employing N-tosylhydrazones in combination with I_2/TBPB to promote the reaction (Scheme 20). The methodology was successfully applied to a wide range of anilines and N-tosylhydrazones **54**, showing broad functional group tolerance.

The mechanic pathway proposed for this transformation starts with the conversion of N-tosylhydrazone **54** into the substituted intermediate **56**. This intermediate then gives rise to azoalkene **57** through the loss of HI, which is oxidized back to I_2 by TBPB in a coinciding catalytic cycle. Next, the addition of the aniline to intermediate **57** gives rise to intermediate **58**. After oxidation under basic conditions, generating radical cation **59**, intramolecular cyclisation takes place. Further oxidation generates the final 1,4-disubstituted 1,2,3-triazole **55**. This protocol, which consists of an oxidative formal (4 + 1) cycloaddition of N-tosylhydrazones and anilines via C−N/N−N bond formation, provides yet another interesting alternative for the synthesis of 1,4-DTs. However, the requirement of stoichiometric amounts of co-catalyst (TBPB) and elevated

temperatures possibly hamper broad application of this methodology.



Scheme 20 I_2/TBPB mediated synthesis of 1,4-DTs.

Conclusions

For a long time, the copper(I)-catalyzed azide-alkyne cycloaddition reaction has been the method of choice for the construction of 1,4-disubstituted triazoles. Although the CuAAC reaction is still frequently applied in the synthesis of numerous biological relevant 1,2,3-triazoles, new methodologies have emerged and have demonstrated to be powerful alternatives. A landmark in the development of so-called copper-free methodologies has been the (re)introduction of the strain-promoted azide-alkyne cycloaddition reactions, typically utilizing functionalized cyclooctynes as the preferred dipolarophile. Although a plethora of cyclooctynes has been developed, their synthesis often remains challenging, hence creating a window of opportunities for novel methodologies that make use of different types of dipolarophiles. Beside the use of various dipolarophiles (e.g. enamines, enolates, vinyl sulfones, peptidyl phosphoranes and iminoenolates), other types of reactions besides 1,3-dipolar cycloadditions have been investigated in order to generate highly diverse triazoles.

Applying these different dipholarophiles in so-called organocatalytic (3+2)-cycloaddition reactions[40] have great potential to become the next generation preferred tool in metal-free triazole formation. Currently, enamines/enaminones as well as enolates are the most frequently explored dipolarophiles since they can be easily produced by the condensation of amines and carbonyl compounds, which can be categorized as *activated* or *unactivated*. While holding great promise, the applicability of these dipolarophiles is restricted to the synthesis of 1,4,5-TTs, and most protocols are still limited to the use of aryl azide. Other promising methodologies, though not relying on (3+2)-cycloaddition reaction, are those based on the Sakai reaction, which involves the condensation of a primary amine and a α-functionalized-tosylhydrazone. Generally affording high yields and high regioselectivities, the Sakai reaction is an excellent alternative for the synthesis of 1,4-DTs.

Although recent years have brought about exciting new methodologies for the synthesis of 1,2,3-triazoles, there is still significant room for improvement, both in terms of substrate scope as well as reaction conditions. In particular, the latter will play a pivotal role in the development of methodologies that will allow reactions to take place under physiological conditions, thereby enabling the access to new research areas.

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Notes and references

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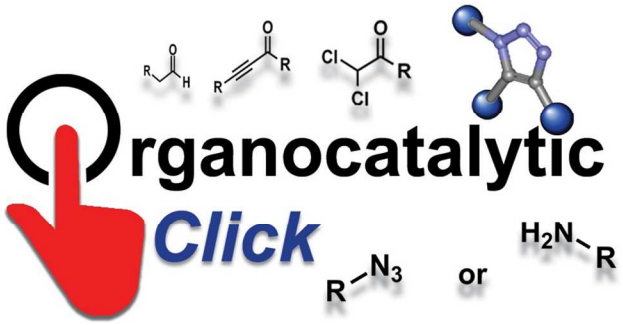
Graphical abstract



Organocatalytic click reactions to 1,4- and 1,5-disubstituted triazoles are rapidly emerging as most valuable alternatives to other triazole-forming protocols. Here the latest developments are discussed leading to very intriguing synthetic possibilities.

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Carolina Lima obtained her Bachelor in Chemistry degree in 2010 from Federal University of Goiás, Brazil and M.S. in Chemistry in 2012, from the same university. In 2012 she joined Paixão's group at Federal University of São Carlos, Brazil, where she is currently conducting her PhD studies. Her research interests include "semi-heterogeneous" catalysis, organic synthesis and green chemistry, as well as asymmetric organocatalysis.

Akbar Ali is currently working as a PhD fellow at Federal University of São Carlos, Brazil under the guidance of Prof Dr. Marcio Weber Paixão. He completed his Master in the subject of organic chemistry from University of Malakand K.P.K Pakistan in 2007 and then his M.Phil in the same subject from Hazara University K.P.K Pakistan in 2011 under the supervision of Prof. Dr. Wajid Rehman and cosupervisor Prof Dr Muhammad Raza Shah (International Centre for Chemical and Biological Sciences, H.E.J. Research Institute of Chemistry.W.H.O. Collaborating Centre University of Karachi, Pakistan). His interests include organic synthesis, click chemistry and asymmetric organocatalysis.

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Prof. Dr. Bernhard Westermann obtained his Diploma degree at the University of Paderborn (Germany, Prof. F. Seela). At the same university, he received his Ph.D. in 1989, working with Profs. W. Sucrow and H.-J. Altenbach. After a postdoctoral stay at the University of Toronto (Prof. J. B. Jones) from 1990 to 1991, he started his independent scientific career at the University of Paderborn mentored by Prof. K. Krohn. After his habilitation in 1998, he stayed at this university as an associate professor. In 2004 he moved to the Leibniz-Institute of Plant Biochemistry, where he continues to work on topics dealing with natural product synthesis, method development with regard to multicomponent reactions, and ligation strategies.

Márcio Weber Paixão was born in Cachoeira do Sul, RS, Brazil, in 1979. He received his B.S. in Chemistry in 2003 from the Federal University of Santa Maria (Brazil). In 2007, he completed his Ph.D. at the same university under the supervision of Prof. A. L. Braga, working with catalytic enantioselective synthesis. He immediately started postdoctoral studies at the University of São Paulo (Brazil) and then at the Center for Catalysis, University of Aarhus, DK, where he worked under guidance of Prof. Karl A. Jørgensen. Since 2010 he has started his independent career at the Federal University of São Carlos, Brazil. In 2012 he worked as visiting professor in the Group of Prof. Carlos F. Barbas III at The Scripps Research Institute (TSRI). His research interests focus on the development of new catalytic methodologies.