Ruthenium-Catalyzed Azide Alkyne Cycloaddition Reaction: Scope, Mechanism, and Applications

CHEMICAL REVIEWS

Review

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Ruthenium-Catalyzed Azide Alkyne Cycloaddition Reaction: Scope, Mechanism, and Applications

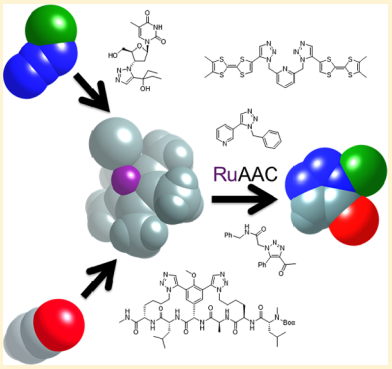
Johan R. Johansson,*[,†] Tamás Beke-Somfai,*[,‡] Anna Said Stålsmeden,[§] and Nina Kann*[,§]

[†]Cardiovascular and Metabolic Diseases, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Pepparedsleden 1, SE-43183 Mölndal, Sweden

[‡]Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar tudósok krt. 2, H-1117 Budapest, Hungary

[§]Chemistry and Biochemistry, Department of Chemistry and Chemical Engineering, Chalmers University of Technology, SE-41296 Göteborg, Sweden

ABSTRACT: The ruthenium-catalyzed azide alkyne cycloaddition (RuAAC) affords 1,5-disubstituted 1,2,3-triazoles in one step and complements the more established copper-catalyzed reaction providing the 1,4-isomer. The RuAAC reaction has quickly found its way into the organic chemistry toolbox and found applications in many different areas, such as medicinal chemistry, polymer synthesis, organocatalysis, supramolecular chemistry, and the construction of electronic devices. This Review discusses the mechanism, scope, and applications of the RuAAC reaction, covering the literature from the last 10 years.



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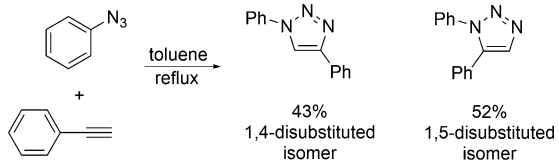
1. INTRODUCTION

Nitrogen-containing heterocycles are ubiquitous in nature, being components of many important biomolecules, such as RNA and DNA, peptides and proteins, and vitamins and cofactors, and found in natural products such as alkaloids. Because of the diversity of properties displayed by nitrogen heterocycles, members of this class such as triazoles are widely applied in the pharmaceutical industry,[1,2] and synthetic methods for these building blocks are thus of importance. This Review will focus on 1,2,3-triazoles. While earlier methods for preparing these molecules often required harsh reaction conditions,[3] this changed in 2002 when Meldal and co-workers and Fokin, Sharpless, and co-workers independently reported mild and direct methods for accessing 1,4-disubstituted 1,2,3-triazoles in one step from an organic azide and an alkyne, using Cu(I) catalysis.[4,5] This copper-catalyzed azide alkyne cycloaddition (CuAAC) has since found widespread use even outside the chemistry community.[6−11] However, a method to form the corresponding 1,5-disubstituted 1,2,3-triazole isomer was also needed. In 2005 this problem was solved by Fokin, Jia, and co-workers,[12] who showed that, by exchanging copper for ruthenium, this class of isomers could also be accessed. While this ruthenium-catalyzed azide alkyne cycloaddition (RuAAC) has as yet not found as prevalent use as the CuAAC reaction, reports of its application are increasing rapidly. Although the RuAAC reaction has been briefly mentioned in several reviews on triazole formation[13−23] and metal-catalyzed reactions,[24−26] a comprehensive survey focused solely on RuAAC is now essential. This Review covers the initial reports of the ruthenium-catalyzed azide alkyne cycloaddition from 2005[12] and 2008,[27] as well as the synthetic development, mechanistic studies, and applications of the RuAAC reaction up until September 2016.

2. BACKGROUND

The 1,3-cycloaddition of organic azides to alkynes to form 1,2,3-triazoles is generally referred to as the Huisgen cycloaddition, due to Huisgen's extensive studies of the mechanism and kinetics of dipolar cycloadditions in the 1960s.[28−30] The first report of such a transformation dates back even further, to 1893, when Michael described the reaction of phenyl azide with dimethyl acetylenedicarboxylate.[31] However, many cycloadditions involving azides are impractically slow at ambient temperature,[32] and mixtures of 1,4- and 1,5-disubstituted triazoles are formed in the reaction with alkynes (Scheme 1).[28]

Scheme 1. Thermal Cycloaddition of Organic Azides with Alkynes Affords Isomeric Mixtures[28,33]

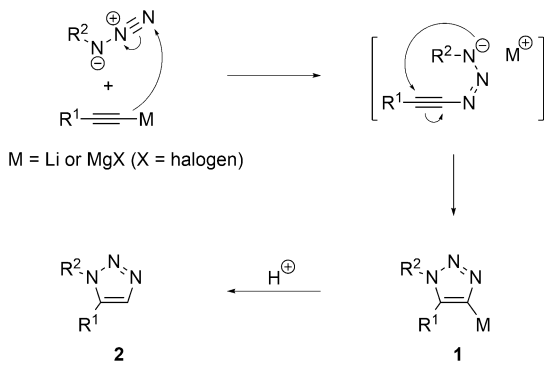


In 2002, both Meldal and co-workers at the Carlsberg Laboratory in Copenhagen[4] and Fokin, Sharpless, and co-workers at the Scripps Research Institute in La Jolla[5] independently reported that Cu(I) can catalyze the 1,3-cycloaddition of alkynes to organic azides to selectively form 1,4-disubstituted 1,2,3-triazoles under mild reaction conditions. Meldal and co-workers applied this reaction toward the solid-phase synthesis of triazole-based peptidomimetics, using copper(I) iodide as the catalyst.[4] The report from Scripps, meanwhile, provides a procedure for the reaction in solution, employing convenient in situ reduction of copper(II) sulfate with ascorbic acid to form the necessary Cu(I) species.[5] This Cu-catalyzed azide alkyne cycloaddition (CuAAC) has since been applied to a great extent,[9−11,34,35] not only in chemistry but also in related areas such as biology[36−38] and new materials,[39] mainly due to the experimental simplicity of the reaction, as well as its robustness and the high yields obtained. The reaction is tolerant of almost every functional group; can be performed in a wide range of solvents, including water; and has a very favorable atom economy[40] as all ingoing components are, at least in theory, incorporated into the product. Triazoles are stable compounds with interesting properties,[1] but an important application of this reaction has also been as a method for connecting or "clicking together" two molecules with each other, providing an alternative to amide bond formation, which has traditionally filled this role. Although "click chemistry", in the original definition,[41] includes a wider range of transformations,[42,43] CuAAC is normally the first reaction that springs to mind when this expression is employed.[44]

As mentioned, different isomers can be obtained in the cycloaddition of alkyl and aryl azides with alkynes. While the original Huisgen reaction afforded mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles[32] and CuAAC selectively produced the 1,4-isomer,[4,5] there was a lack of robust methods for the exclusive formation of 1,5-disubstituted triazoles. Such compounds can be of interest in their own right, as the positioning of the two substituents on adjacent atoms can be advantageous in cyclization reactions, and the rigid cyclic structures of these products can be exploited in materials science applications. However, in many of the studies discussed in this Review, the main focus has been to compare the properties of 1,4- and 1,5-disubstituted 1,2,3-triazoles in different contexts, and this is especially true in the area of medicinal chemistry and studies of bioactive compounds.

In looking at methods for the preparation of 1,5-triazole isomers, selected metal acetylides (Sn, Ge, Si, and Na) had early on been reported to produce 4-metalated 1,5-disubstituted triazoles,[45,46] and Akimova et al. studied the reactions of lithium and magnesium acetylides in detail in the 1960s.[47−49] These latter reactions are proposed to involve nucleophilic attack of the lithium or magnesium acetylide on the azide followed by ring closure to form metallotriazole **1** (Scheme 2). Quenching of the reaction then afforded the 1,5-disubstituted 1,2,3-triazole **2**. However, the yields were low and the reaction was accompanied by the formation of byproducts.

Scheme 2. Proposed Mechanism for Triazole Formation Using Li and Mg Acetylides[47−50]



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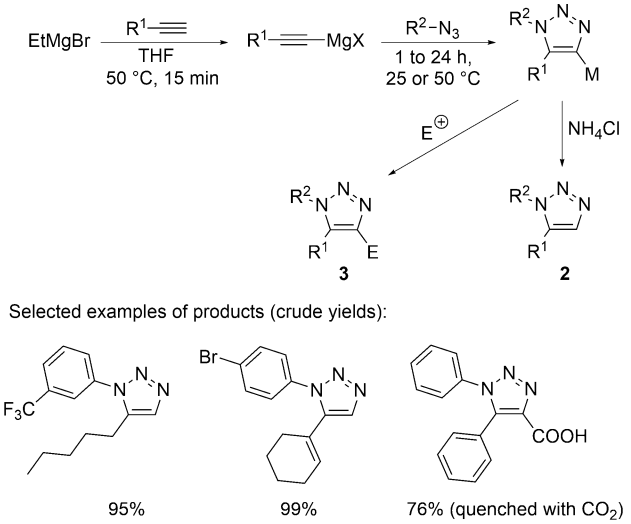
Krasiński et al., together with Fokin, Sharpless, and co-workers, returned to these early reports by Akimova et al. to see if the magnesium-mediated reaction could be improved.[50] They found that the original procedure described by Akimova et al. provided 1,5-disubstituted 1,2,3-triazole **2** in substantially higher yields than earlier reported (Scheme 3). In addition, the scope of

Scheme 3. 1,5-Disubstituted and 1,4,5-Trisubstituted 1,2,3-Triazoles from Magnesium Acetylides[50]



substrates applied in the reaction was increased. The 4-metalated triazole intermediate could also be trapped with other electrophiles than protons, providing access to 1,4,5-trisubstituted 1,2,3-triazoles **3**.

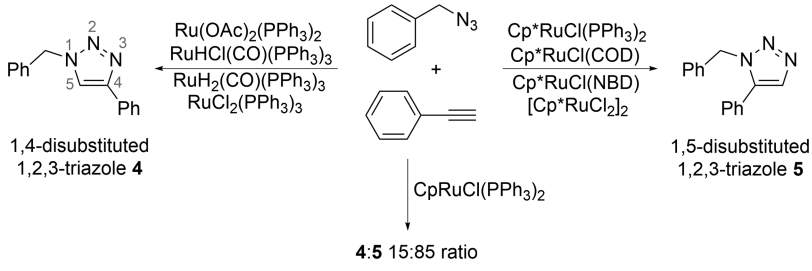
However, the use of magnesium acetylides requires stoichiometric amounts of metals, and such reagents are incompatible with a number of functional groups. A catalytic alternative to CuAAC that provides access to 1,5-disubstituted 1,2,3-triazoles would be preferable. As Ru(II) is known to catalyze reactions involving alkynes,[51] Fokin, Jia, and co-workers reasoned that a ruthenium(II) complex could perhaps be applied toward the synthesis of 1,2,3-triazoles via a cycloaddition reaction using an alkyne in a similar manner to the CuAAC reaction.[12] Initial catalyst screening, using the reaction of benzyl azide with phenylacetylene as a test system, showed that triazoles were indeed formed when heating all components in benzene at 80 °C for 4 h. Complexes such as $Ru(OAc)_2(PPh_3)_2$, $RuCl_2(PPh_3)_3$, and $RuHCl(CO)(PPh_3)_3$ afforded the 1,4-disubstituted 1,2,3-triazole (**4**, Scheme 4) with varying degrees of conversion, and this type of selectivity is discussed in more detail in section 4.5.2.

However, a complex containing a cyclopentadienyl ligand, $CpRuCl(PPh_3)_2$, did encouragingly produce the 1,5-isomer **5**, albeit accompanied by some of the 1,4-disubstituted derivative. By switching to the more sterically hindered pentamethylcyclopentadienyl derivative $Cp^*RuCl(PPh_3)_2$, complete selectivity for the 1,5-disubstituted triazole was obtained. Several other Ru(II) catalysts containing the [Cp*RuCl] unit were also useful in effecting this transformation, i.e., Cp*RuCl(COD) (COD = cyclooctadiene), Cp*RuCl(NBD) (NBD = norbornadiene), and $[Cp^*RuCl_2]_2$. A full investigation of the scope and limitations of this reaction was then carried out as part of this initial report[12] as well as in an ensuing publication a few years later, where also $RuH_2(CO)(PPh_3)_3$ was reported to afford the 1,4-regioisomer.[27] Certain aspects of these initial studies, concerning the substrate scope as well as the catalysts that have been evaluated, are covered in more detail in other sections below, but a summary of these two seminal papers will be given here.

The initial conditions employed 5 mol % catalyst, but this could be reduced to 1 mol % in most cases. Heating to 60−80 °C did provide a more rapid reaction for $Cp^*RuCl(PPh_3)_2$, but ambient temperature could be applied by running the reaction for a longer time at higher catalyst loading. For the more-reactive complex Cp*RuCl(COD), the reaction gave high yields at room temperature even after 30 min. Both polar and nonpolar solvents could be employed, including benzene, toluene, dioxane, tetrahydrofuran, dimethylformamide, and 1,2-dichloroethane. Yields were substantially lower if the reaction was performed in protic solvents such as water and alcohols, but trace amounts of water in nonprotic solvents did not affect the reaction. As oxygen may react with the Cp*RuCl(COD) catalyst, it is recommended to perform the reaction under an inert atmosphere in this case to avoid degradation of the complex.[52] However, the $Cp^*RuCl(PPh_3)_2$ catalyst did not appear to be very sensitive in this system, and excellent conversions were obtained even if oxygen was not excluded.[27] A striking feature of the reaction is the high tolerance toward many functional groups, such as alkyl and aryl chlorides, boronic ester, alkenes, and polyalcohols, in both the azide and the alkyne reaction partners. Figure 1 shows some of the products formed using either $Cp^*RuCl(PPh_3)_2$ or Cp*RuCl(COD) as the catalyst.

In contrast to the CuAAC reaction, which is limited to terminal alkynes, the RuAAC reaction was found to tolerate internal alkynes, providing access also to 1,4,5-trisubstituted 1,2,3-triazoles.[12,27] The Cp*RuCl(COD) catalyst was found to be well-adapted to this task, allowing reactions to be performed at ambient temperature in order to access a wide range of different trisubstituted triazoles. This aspect of the reaction, as well as the observed regiochemistry for this class of alkyne substrates, is

Scheme 4. Regiochemical Outcome Using Different Ru Catalysts[a12]



[a]Conditions: 5 mol % catalyst, benzene, 80 °C, 4 h. Reactions with $Ru(OAc)_2(PPh_3)_2$, $RuHCl(CO)(PPh_3)_3$, and $CpRuCl(PPh_3)_2$ afforded low yields.

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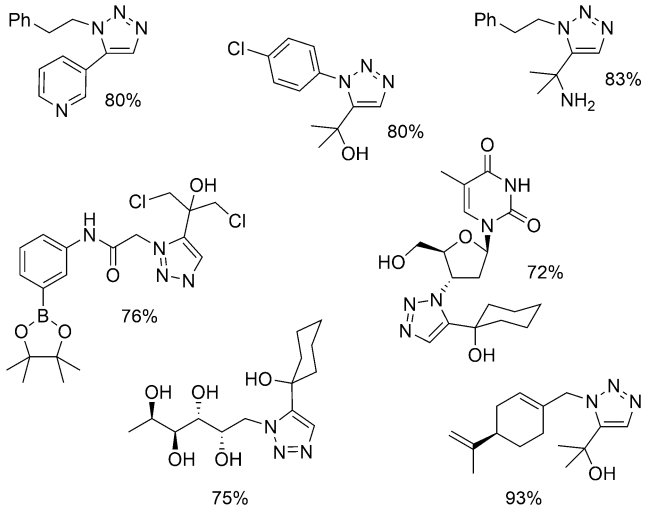

Figure 1. Selected products from the original reports of the RuAAC reaction.[12,27]

discussed in more detail in section 4.4.2. The reactivity of internal alkynes is also an indication that the reaction does not proceed via a ruthenium acetylenide, in contrast to the CuAAC reaction that involves an intermediate copper acetylenide.[53] Mechanistic proposals for this reaction are summarized in the next section.

3. MECHANISTIC AND THEORETICAL STUDIES

Regarding the mechanism of triazole formation, numerous studies have appeared addressing the reaction steps throughout the cycloaddition. These rely on both experimental techniques, employing, e.g., mass spectrometry, NMR spectroscopy, and single-crystal X-ray diffraction, as well as on quantum mechanical (QM) calculations using mainly density functional theory (DFT). We here mostly focus on the Ru-catalyzed azide alkyne cycloaddition; for studies on the Cu-catalyzed azide/alkyne 1,3-cycloaddition reaction (CuAAC), the reader is directed to papers by Rostovtsev et al. and Himo et al.[5,53] Note that other transition metal complexes can be used in the chemistry of organic azides; these reactions are covered in a detailed review by Cenini et al.[54] The atomic-level insight by computations into the chemical reorganization provides an important contribution in understanding the steric and energetic aspects of the reaction. However, calculations quite often provide several alternative routes, where it is not trivial to select the most likely reaction pathway. Furthermore, the accuracy of energetic descriptions can often be undermined due to solvent effects, temperature, and other parameters. Consequently, capturing key intermediates and determining conversion rates by experimental methods provide important contributions to selecting the most probable reaction mechanism. Accordingly, in this section we concentrate on the steric and energetic details of the Ru-catalyzed cycloaddition provided by theoretical methods, but we reflect also on their correlation with experimental investigations.

The general mechanism of the azide alkyne 1,3-cycloaddition reaction (AAC) was described in an early study by Himo et al.[53] The authors employed the B3LYP hybrid functional and considered the cycloaddition for both 1,4- and 1,5-regioisomers.[53] The reaction without any catalyst has a rather high barrier for both 1,4- and 1,5-regioisomers, with relative energies of 25.7 and 26.0 kcal/mol, respectively. Both reaction pathways were reported to be highly exothermic with >60 kcal/mol, not accounting for entropy effects.[27,53] The general mechanism was further investigated by Jones and Houk, who addressed substituent effects in detail and also the reversibility of the 1,3-dipolar cycloadditions involving azides and either alkenes or alkynes.[55] Jones and Houk employed complete basis set (CBS) calculations, which allow energetic predictions with very high accuracy.[56] Their results indicated that azide 1,3-dipolar cycloadditions with alkenes and alkynes have similar reaction barriers, but for the latter the products are more exothermic by ~30−40 kcal/mol. They also concluded that azide cycloadditions with alkynes and most alkenes are irreversible. Note that the calculations also provided the single, so far only theoretical, prediction that the reaction of methanesulfonylazide with *N,N′*-dimethylvinylamine may be reversible at micromolar reactant conditions.

Focusing more on the ruthenium catalysts, Boren et al. employed DFT calculations using methyl azide and propyne as model reactants with [CpRuCl].[27] These calculations demonstrated that in principle four different relative orientations are possible for the methyl azide and propyne, with rather small relative energy differences between them (Figure 2).[27,57]

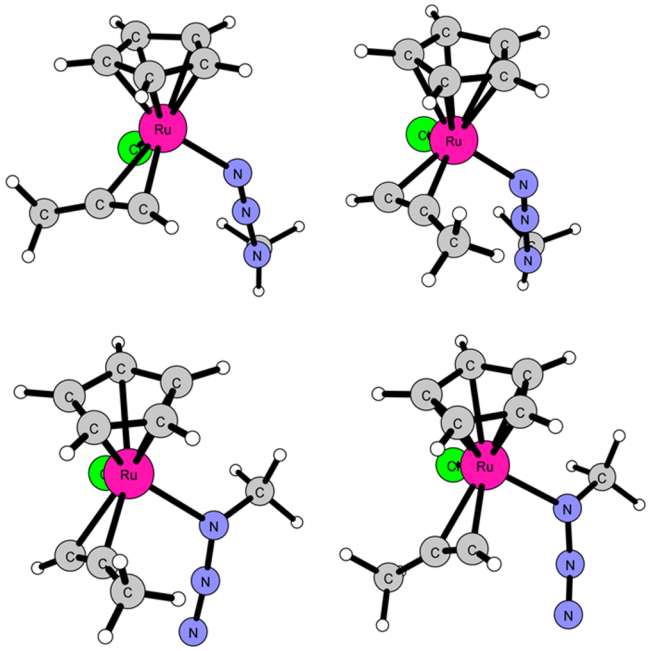

Figure 2. Four possible orientations of the reactants in their initial complexes. Structures are reproduced from original optimized coordinates provided by the authors.[27]

Although two of these alternative orientations would eventually lead to 1,4-regioisomers, three pathways were ruled out due to either much higher barrier heights or steric repulsions in the product states. The lowest-energy pathway had its highest barrier at 13 kcal/mol, much lower than the barrier height for the same path without a catalyst. This shows that Ru is an efficient catalyst, reducing the rate of the reaction by several orders of magnitude. The calculated results (Figure 3) fit well to the experimental observations, explaining the 1,5-regioselectivity and also providing a reasonable energetic explanation for the reaction rate. The reaction was later revisited in detail by using alternative substrates including Cp*, which confirmed the reaction paths determined earlier but further explained the effect of different substituents on the reaction rate and the product ratio of 1,4- and 1,5-regioisomers.[58] On the basis of these results,

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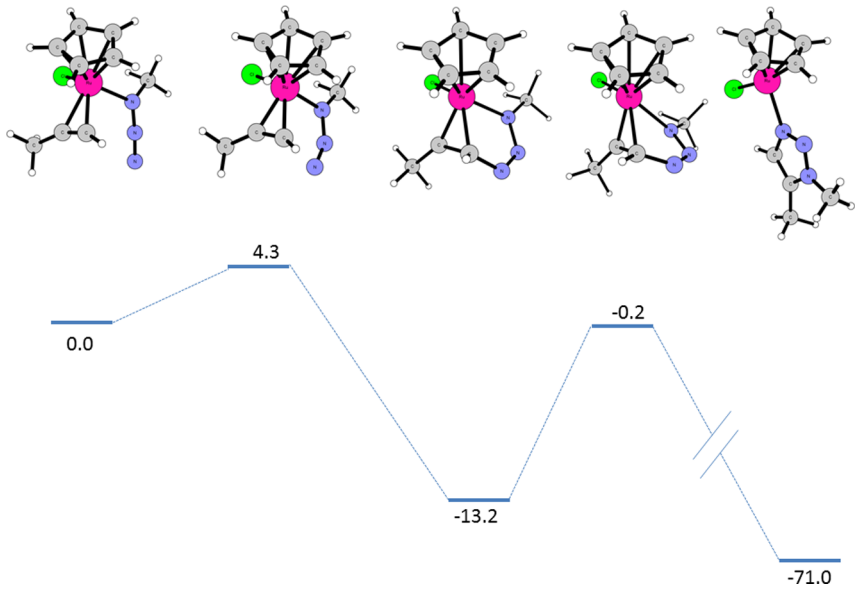

Figure 3. Simplified schematics of the reaction pathway obtained for the lowest-energy pathway using DFT calculations.[27] Structures were reproduced from optimized coordinates provided by the authors; relative energies are in kcal/mol.

Boren et al. proposed that the mechanism involves an irreversible oxidative coupling, which is a nucleophilic attack of the coordinated alkyne on the terminal electrophilic nitrogen of the azide, and this is followed by a reductive elimination.

The mechanism was also addressed by Hou et al.,[59] who again confirmed the irreversibility of the reaction and further investigated the molecular orbitals of the C−N bond-forming transition state using DFT calculations and Bader's atoms-in-molecules theory.[60,61] The latter analyzes interactions of atoms by topological mapping of the surrounding electron density. They found that, when using larger substrates, the transition state involves the electron donation from the alkynyl carbon to the π^* orbital of the N═N group from the azide, opening the way to formation of a transient cyclic structure where the π electrons delocalize from the alkynyl to the azido group. It is worth noting that, for internal alkynes, both Boz and Tüzün[58] and Hou et al.[59] showed a higher-energy transition state for the C−N bond-forming step than observed initially for small substrates and terminal alkynes.

Besides 1,5-substituted 1,2,3-triazoles, selective synthesis of 1,4-substituted compounds can also be achieved with high yield using Ru complexes lacking Cp ligands (see section 4.5.2). Liu et al. have demonstrated that, among other catalysts, RuH(η^2-BH_4)(CO)(PCy_3)$_2$ and Ru(C≡CPh)$_2$(CO)(PCy_3)$_2$ were the most active.[62] In addition to mass spectrometry, X-ray diffraction, and NMR spectroscopy, the authors have also used DFT calculations to elucidate the mechanism of the reaction. The presence of the triazolide intermediate (structure provided by X-ray, Figure 4) indicates that the Ru center actively takes part in the reaction, forming even a Ru···H−C interaction with one hydrogen of the CMe_3 group in the triazolyl ligand.[62] In their DFT studies using methyl azide and propyne as model substrates, the authors have determined that the reaction starts with a Ru complex that coordinates the internal nitrogen in the azide. The triazolide intermediate is then reached via a metathesis step, which is also the rate-determining step at 11.5 kcal/mol. The pathway for these complexes lacking Cp ligands to 1,5-disubstituted products has a much higher barrier, 21.5 kcal/mol, which explains their selectivity toward 1,4-disubstitution. The

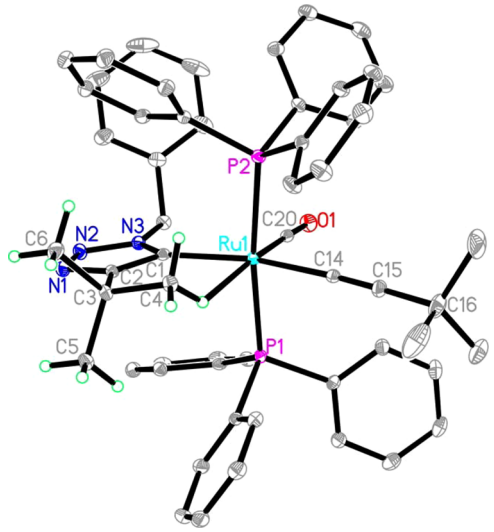

Figure 4. Structural evidence for the formation of a triazolide intermediate in the reaction of benzyl azide with Ru(C≡CCMe$_3$)$_2$(CO)(PPh_3)$_3$. Reproduced with permission from ref 62. Copyright 2012 American Chemical Society.

structural explanation is that coordination of the internal (−N−Me) nitrogen from the azide on the Ru complex results in an intermediate and a transition state (TS) with conjugated bond systems; thus, the barrier of the TS for the rate-determining step lowers significantly. In contrast to Cp-containing Ru catalysts, the final Ru complex with the formed triazole product has a much lower energy gain with a −38.6 kcal/mol relative energy. Overall, the lowest-energy reaction pathway for the Ru complexes lacking Cp ligands is rather similar to those with a Cu catalyst.

To provide a systematic overview on alternative Ru complexes, Nolan and co-workers have investigated the effect of substituents in Ru complexes that result in unsaturated 16-electron configurations in the general form of Cp*Ru(L)Cl.[63] Here L was a sterically demanding ligand, either phosphine or an N-heterocyclic carbene (NHC), where the nitrogens contained adamantyl- (IAd), diisopropyl- (IPr), or cyclohexyl groups

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(ICy).[63] They chose sterically large substrates to model the reaction, using benzylazide and phenylacetylene to afford the 1,5-disubstituted 1,2,3-triazole compound. Mechanistic insights were gained by NMR experiments combined with DFT calculations. Catalysts with phosphines, Cp*Ru(P*i*Pr$_3$)Cl and Cp*Ru(PCy$_3$)-Cl, showed the best catalytic activities, having 89% and 87% conversion rates, respectively, while the best catalyst with an NHC-based ligand was IAd, showing a somewhat lower conversion of 67%. In terms of mechanism, this clearly hints that the behavior of the Ru complexes cannot be directly correlated to the steric size of the L ligands. The authors have also demonstrated that the anionic Cl ligand makes an important contribution to the conversion rate.[63] While Cp*Ru(P*i*Pr$_3$)Cl had a rate of 89%, the alkoxo complex Cp*Ru(P*i*Pr$_3$)-(OCH$_2$CF$_3$) produced only traces of the product. They have also found that addition of the alkyne prior to addition of the azide lowered the conversion by 6-fold, whereas adding the azide first and the alkyne second did not show any significant difference relative to adding the mixture of the two substrates. In line with the above, the calculations have shown that excess phenyl-acetylene results in a complex with two alkyne ligands on the Ru complex, leading to the production of a 1,4-disubstituted metallacycle as predicted earlier.[64] A similar scenario was also investigated using excess phenyl azide, which could potentially lead to a stable tetraazametallacyclopentene ring. However, the highest barriers are rather low for the former, below 10 kcal/mol, while several barriers are well above 20 kcal/mol in the latter case. These give an explanation for the experimental behavior of the studied Ru complex in excess of one of the substrates. In contrast to the species based on [Cp*RuCl], here the extrusion of ligands to create the coordinative unsaturation at the Ru center is of importance. The calculations have demonstrated that, out of the activated catalysts having the original Cp*Ru(P*i*Pr$_3$)Cl and either phenylacetylene or the internal- or terminal N-coordinated benzylazide, only the Cp*RuCl(η^2-HCCPh)(P*i*Pr$_3$) complex favors phosphine dissociation over that of the bound substrate. This is also in agreement with the NMR studies that observed this intermediate complex at low temperatures. These results suggest that activation of the catalyst should proceed through initial coordination of an alkyne substrate, and thus alkyne binding precedes azide coordination. Starting from the activated catalyst, the reaction for the investigated complex then progresses on the same pathway as observed by Boren et al.[27]

4. METHODOLOGY, SUBSTRATES, AND CATALYSTS

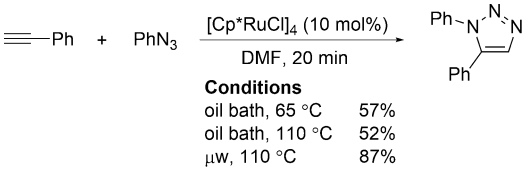
This section will look at the general conditions that can be applied for the RuAAC reaction, summarize the catalysts that have been employed in different studies, and report on more specialized studies where the focus has been on the reaction itself rather than on the applications of the target molecules.

4.1. General Methodology

A typical RuAAC procedure involves the reaction of an alkyne with an organic azide in the presence of catalytic amounts of a ruthenium(II) complex containing a [Cp*RuCl] unit in a nonprotic solvent. A variety of solvents can be used for the reaction, where the most commonly used are aromatic solvents, like benzene or toluene, or ethers such as tetrahydrofuran (THF) and dioxane. Certain polar solvents can also be applied, i.e., dimethylformamide (DMF) and dimethylacetamide (DMA), while reactions using dimethyl sulfoxide (DMSO) have been reported to be problematic,[65] which is most likely related to the ability of DMSO to act as ligand to ruthenium.[66] Protic solvents are not suitable, giving low yields and a high degree of byproduct formation.[27,52] Most reported RuAAC reactions employ either Cp*RuCl(PPh$_3$)$_2$ or Cp*RuCl(COD) as the catalyst, using between 1 and 5 mol % catalyst, and both of these complexes are commercially available. For full details of the catalyst scope, see section 4.5. Although heating is generally employed to shorten reaction times, reactions at ambient temperature are also possible, especially when using a catalyst with high reactivity such as Cp*RuCl(COD).[27] A typical procedure for the RuAAC reaction has been described by Oakdale and Fokin in *Organic Synthesis* and involves the reaction of benzyl azide with phenyl acetylene in dichloroethane at 45 °C, using 1 mol % Cp*RuCl(COD) as the catalyst.[52] The high tolerance to a wide range of functional groups has already been mentioned in section 2; these include alcohols and polyols, amines and pyridines, alkyl and aryl halides, ethers, aldehydes and ketones, esters, amides, sulfonamides, carbamates, and boronic esters.[12,27] However, acidic functionalities such as carboxylic acids, boronic acids, and HCl/HBr salts of amines can be problematic.[65] This broad application scope is also one of the reasons why the RuAAC reaction has been extensively applied in the area of medicinal chemistry, where highly functionalized substrates, often including H-bond donors and acceptors, are used. Such applications are covered in more detail in section 5.

The use of microwave heating has been applied in several instances in the CuAAC reaction to accelerate triazole formation[67,68] but is of even more relevance for the RuAAC reaction, where heat is in many cases required to achieve a high conversion in a short time. Fokin and co-workers applied this technology in the RuAAC reaction when investigating aryl azides as substrates (see section 4.3).[69] The authors reportedly opted for a microwave-mediated reaction to facilitate optimization of the reaction conditions but also found that direct comparison of a microwave-assisted reaction with conventional oil bath heating was in favor of the former (Scheme 5). Not only was the yield higher when microwave heating was used, but the conventional method was also fraught with byproduct formation. Looking at other comparisons between conventional and microwave heating, Carvalho and co-workers also report a higher yield by employing microwave-assisted RuAAC in their synthesis of benznidazole analogues,[70] of interest for the treatment of Chagas disease. However, Agrofoglio and colleagues obtained similar results in terms of yield and selectivity when comparing oil bath heating with microwave heating in the synthesis of ribavirin analogues via RuAAC.[71] However, the reaction time was significantly shortened.

Scheme 5. Comparison of Microwave and Conventional Heating[69]



A sequential microwave-assisted, one-pot method to produce triazoles directly from alkyl halides, more easily available than alkyl azides, was described by Johansson et al.[65] Although direct one-pot methods for CuAAC have been reported,[72−74] only trace amounts of product were formed when a solution of benzyl bromide, sodium azide, 3-ethynylpyridine, and Cp*RuCl(PPh$_3$)$_2$

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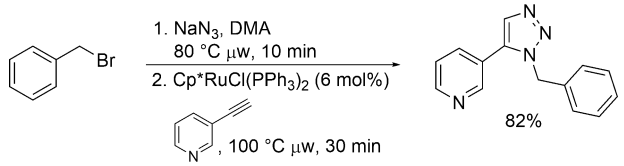
in DMA were subjected to microwave heating at 100 °C for 30 min. Catalyst deactivation or competing reactions are most likely the cause here.[75,76] However, by first heating the alkyl halide with sodium azide for 10 min and then adding the catalyst and the alkyne (Scheme 6), this problem was solved and 14 different

Scheme 6. Microwave-Assisted Sequential One-Pot RuAAC Using Alkyl Halides As Precursors[65]



triazoles were prepared in moderate to excellent yields. Alkyl chlorides as well as iodides could also be used, while acidic functionalities in the alkyne or alkyl halide were not tolerated.

4.2. Structural Assignment

Once the triazole is formed, suitable analytical methods are needed to determine the regioselectivity in the reaction and to confirm that the 1,5-disubstituted isomer is indeed the one formed, as the 1,4- and 1,5-isomers are difficult to differentiate between using simple ^{1}H NMR. In the original report by Fokin, Jia, and co-workers, the structure and 1,5-regioselectivity of selected products were verified by X-ray crystallography (see Figure 5).[12]

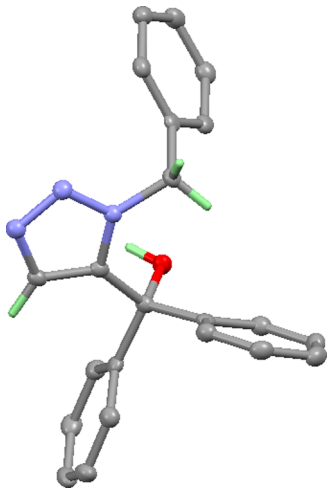


Figure 5. Confirmation of the 1,5-regioselectivity using X-ray diffraction: 1,2,3-triazole formed in the reaction between benzyl azide and a propargylic alcohol. Adapted with permission from ref 12. Copyright 2005 American Chemical Society.

1D or 2D NMR techniques based on the nuclear Overhauser effect (NOE), providing information on interactions through space rather than through bonds, are also convenient tools to differentiate between the 1,4- and 1,5-isomers and have been applied in several instances.[65,77] Creary et al. sought to develop a simpler means of distinguishing between the 1,4- and 1,5-isomers of a 1,2,3-triazole using ^{13}C NMR.[78] Nineteen pairs of triazole isomers bearing a variety of different substituents were investigated, focusing on the signal displayed by the unsubstituted carbon of the triazole ring. As a general trend, the C5 carbon of the 1,4-disubstituted triazole displays a signal around 120 ± 3 ppm, while the corresponding C4 carbon of the 1,5-disubstituted isomer instead appears around 133 ± 3 ppm (Figure 6). For triazoles carrying a carbonyl group, the signals

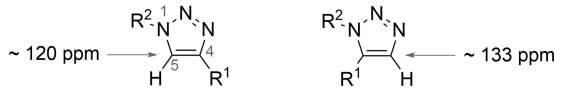


Figure 6. ^{13}C NMR as a tool for distinguishing between 1,4- and 1,5-disubstituted 1,2,3-triazole isomers.[78]

from the unsubstituted carbons are shifted slightly but nevertheless show a clear difference between the two isomers. Ethoxy-substituted isomers also deviated from the norm, with carbon signals for the unsubstituted carbons appearing at 106 ppm for the 1,4-isomer and 114 ppm for the 1,5-isomer. Both these discrepancies are in line with predictions obtained via supportive theoretical studies. The authors employed DFT calculations and used gauge-independent atomic orbitals (GIAOs) to calculate the shielding tensors for the investigated compounds. The theoretical calculations showed the same relative differences for C4 and C5 as in the experiments, although having a consistent 6 ppm upfield shift compared to the experiments.

The heterocyclic ring of triazoles contains three nitrogen atoms that could potentially also be analyzed using NMR. The low natural abundance and sensitivity of ^{15}N has earlier been a limitation in applications of ^{15}N NMR spectroscopy, although probe development and new pulse techniques have greatly facilitated the use of this technology.[79] Alfonso and co-workers[80] instead applied an indirect method, i.e., a gradient-enhanced indirect detection pulse sequence,[81] that makes use of the ^{1}H nucleus to obtain information about ^{15}N NMR shifts in order to differentiate between 1,4- and 1,5-disubstituted 1,2,3-triazole isomers, as well as to distinguish these from the less-common 2,4-disubstituted isomer. The substituted nitrogen appears at a much lower shift (in the range of −120 to −140 ppm) in comparison to the other two nitrogen atoms for all three isomers, allowing the 2,4-substituted isomer to be easily identified. The ^{1}H/^{15}N correlation pattern can then be employed to distinguish the 1,4- and 1,5-disubstituted isomers. To aid interpretation of the experimental results, the GIAO method mentioned above was used with DFT calculations. To reach a consistent data set, the authors have calculated the shielding value for all obtained conformers and used a Boltzmann weighing based on the relative energies of these different conformers. These data showed reasonable agreement with the NMR results and helped in differentiating between the different observed isomers.

4.3. Azides

The highly energetic nature of azides and their toxicity are aspects that need to be considered when working with 1,3-cycloaddition reactions of azides to alkynes, and we recommend that new users of the CuAAC and RuAAC reactions familiarize themselves with the properties of azides before embarking upon experimental work. A treatise by Keicher and Löbbecke on the safety of azides provides some general guidelines.[82] As a rule of thumb, azides with a (C + O)/N ratio of <3 are considered to be highly explosive.

In the initial report of the RuAAC reaction, Fokin, Jia, and co-workers reported that some limitations were found in terms of the azide component.[12] Although primary aliphatic azides functioned well in the reaction, both tertiary azides (*tert*-butyl and adamantyl) and aromatic azides afforded low yields. Reactions of the latter were also accompanied by the formation

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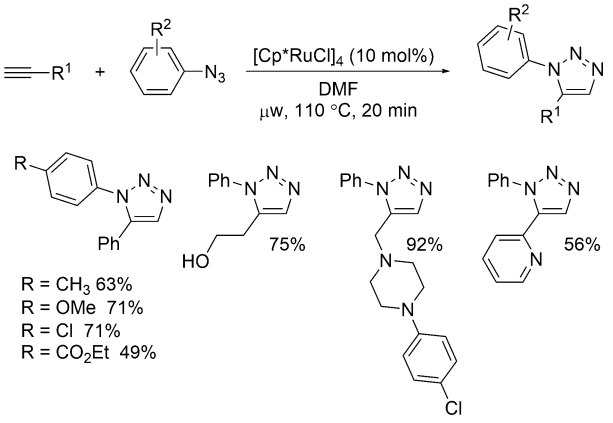
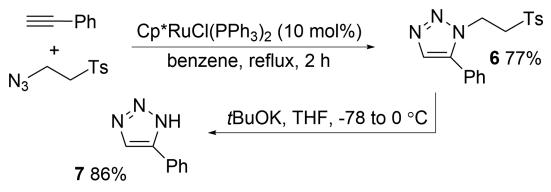
of byproducts. An exception was seen in the reaction of 1-azido-4-methoxybenzene with a tertiary propargylic alcohol, forming the desired triazole in 94% yield. Reactions involving sterically hindered azides could be improved by increasing the catalyst loading to 5% and extending the reaction time. Seeking to find a solution also to the problematic aryl azides, Fokin and co-workers investigated other ruthenium catalysts to see if a more efficient conversion to 1-aryl-substituted 1,2,3-isomers could be attained.[69] During the initial development of the RuAAC reaction, the authors had found that the ruthenium tetramer $[Cp^*RuCl]_4$ performed well in RuAAC reactions of aliphatic azides with alkynes using dimethylformamide as the solvent.[69] This catalyst, prepared by reduction of $[Cp^*RuCl_2]_n$ with $LiBHEt_3$, was thus evaluated with aryl azides and was indeed found to effect the desired transformation efficiently. Microwave irradiation was employed to facilitate optimization of the reaction, and suitable conditions involved the use of 10 mol % catalyst in DMF, heating for 20 min at 110 °C (Scheme 5). Longer reaction times did not provide a higher yield, indicating that catalyst deactivation is a competing reaction. Both electron-rich and electron-poor aryl azides could be employed (Scheme 7), although the authors report that strongly electron-withdrawing groups as well as diortho substituents inhibited the reaction.

Scheme 7. Improved Conditions for Aryl Azides in RuAAC Using Microwave Heating[69]



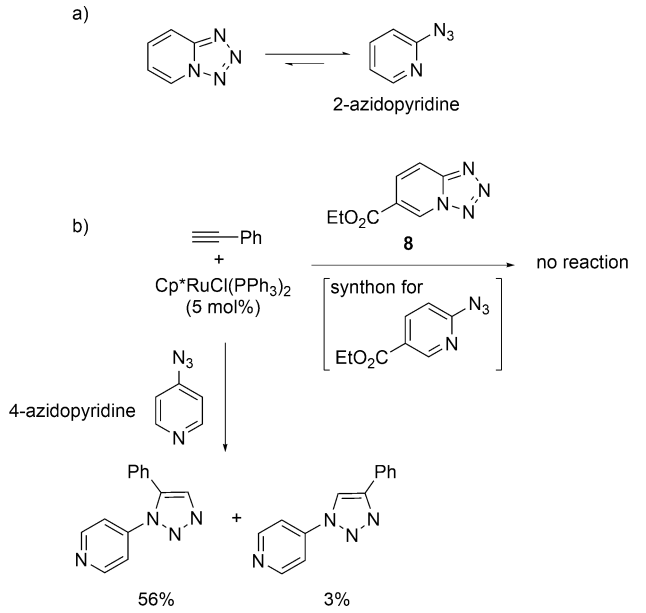
The remainder of this section will look at two reports where the focus has been on the azide component. β-Tosylethylazide can be employed as a synthon for hydrazoic acid, HN_3, in the RuAAC reaction to access 5-substituted 1*H*-1,2,3-triazoles after deprotection (Scheme 8), as shown by Yap and Weinreb.[83] Phenylacetylene was heated with an excess of β-tosylethylazide in the presence of $Cp^*RuCl(PPh_3)_2$, using benzene as the solvent, affording selectively the 1,5-disubstituted triazole **6** in 77% yield. Deprotection of the β-tosylethyl group with potassium *tert*-butoxide in THF at low temperature produced the free 1*H*-1,2,3-triazole **7** via a retro-Michael reaction, providing convenient access to this class of substrates. Internal alkynes were also applicable in this reaction. The β-tosylethylazide reagent was prepared in one step from commercially available *p*-tolylvinyl sulfone and sodium azide, and could be stored at low temperature for an indefinite period of time.

Scheme 8. 5-Substituted 1*H*-1,2,3-Triazole from a β-Tosylethyl-Protected Azide[83]



Fused tetrazoles can be applied as azide surrogates in CuAAC reactions with alkynes to form 1,4-disubstituted triazoles appended with a heterocyclic functionality such as a 2-pyridyl moiety, as demonstrated by Gevorgyan and co-workers.[84] The reaction is based on the equilibrium existing between the closed form of the tetrazole and the corresponding open azide form (Scheme 9a), where the position of this equilibrium can depend on a variety of factors, including the substitution pattern and the reaction conditions. Attempted cyclization of phenylacetylene with tetrazole **8** using $Cp^*RuCl(PPh_3)_2$ was unsuccessful, however (Scheme 9b). The authors speculated that the nitrogen atom of the pyridine could be involved in chelation with the ruthenium complex, resulting in catalyst deactivation. A reaction using 4-azidopyridine, where such chelation is not possible, afforded mainly the 1,5-disubstituted product, indicating that it is indeed the positioning of the 2-azide functionality relative to the pyridine nitrogen that is the problem. Unfortunately, this convenient azide surrogate methodology is not applicable in RuAAC.

Scheme 9. Attempted Use of a Fused Tetrazole as a 2-Azidopyridine Surrogate[84]



4.4. Alkynes

A wide scope of alkynes are compatible with the RuAAC reaction, also including internal triple bonds and alkynes directly connected to a heteroatom. Many of the terminal alkynes employed in RuAAC belong to the category of functionalized terminal alkynes, and in this Review the majority of these alkynes have been classified according to the potential applications of the triazoles produced. In this section, we will discuss various functionalized alkynes where method development has been the focal point of the study.

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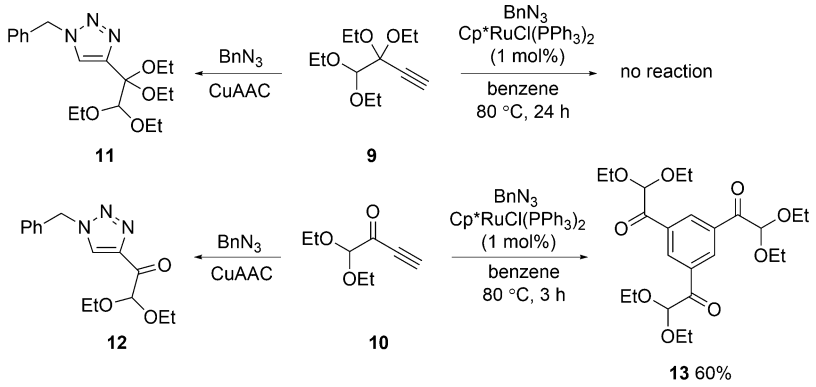
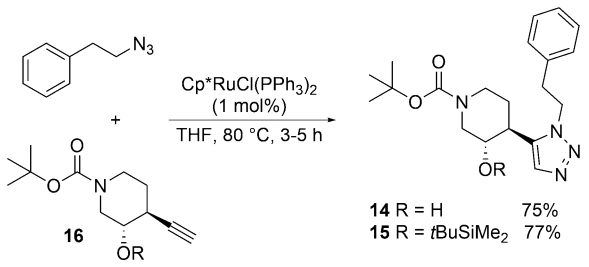
Scheme 10. CuAAC and Attempted RuAAC Using Highly Functionalized Alkynes[85]



4.4.1. Functionalized Terminal Alkynes. Farooq and colleagues have investigated terminal alkynes with oxygen functionalities on both the α- and β-carbons in both CuAAC and RuAAC, with the aim of producing 1,2,3-triazoles with polar substituents for applications in the area of peptidomimetics.[85] Ketal **9** as well as ketone **10** were selected as substrates and reacted with benzyl azide in the presence of $CuSO_4$ to form triazoles **11** and **12** via CuAAC (Scheme 10). Disappointingly, however, treatment of ketal **9** with Cp*RuCl$(PPh_3)_2$ afforded only recovered starting materials upon workup. Ketone substrate **10** did react but produced the aromatic product **13** instead of a triazole, which the authors propose is formed via an ionic cyclotrimerization reaction. The same group also investigated the debenzylation of *N*-benzylated 1,4- and 1,5-disubstituted 1,2,3-triazoles under hydrogenation conditions, showing that both isomers afford the same 1*H*-1,2,3-triazole via tautomerization of the product.[86]

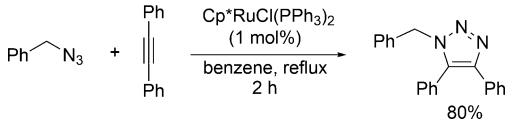
Piperidines are common motifs in natural products as well as in pharmaceuticals. Haug and colleagues prepared a set of 3-hydroxypiperidine triazoles using both CuAAC and RuAAC.[87] 1,5-Disubstituted triazoles **14** and **15** were successfully synthesized from alkynes **16** using 1 mol % of Cp*RuCl$(PPh_3)_2$ as the catalyst (Scheme 11).

Scheme 11. Triazole-Substituted 3-Hydroxypiperidine Derivatives[87]



4.4.2. Internal Alkynes. One advantage of RuAAC compared to CuAAC is that the former allows the use of internal alkynes, while the latter reaction involves the formation of a copper acetylide[53] and thus requires a terminal alkyne. In the original report of the RuAAC reaction, Fokin, Jia, and co-workers included one example of a symmetrical internal alkyne with benzyl azide, showing that, while the ruthenium-catalyzed reaction afforded a 1,4,5-substituted triazole in 80% yield after 2 h of reflux in benzene, the corresponding uncatalyzed reaction showed only trace amounts of product even after 24 h (Scheme 12).

Scheme 12. First Report of an Internal Alkyne in RuAAC[12]



Inspired by this study, Majireck and Weinreb decided to apply unsymmetrical internal alkynes in RuAAC to investigate the regiochemical outcome when different substitution patterns on the alkyne were used.[77] Standard reaction conditions were applied, involving the use of benzyl azide as the azide component and Cp*RuCl$(PPh_3)_2$ as the catalyst in refluxing benzene for 2 h, using an excess of the alkyne relative to the azide. Isomeric ratios were measured by ^{1}H NMR on the crude products, and the regiochemistry of each isolated product was then verified by ^{1}H NMR NOE. A selection of triazoles derived from internal alkynes was also prepared by Fokin, Jia, and co-workers using Cp*RuCl(COD) as the catalyst in toluene at room temperature.[27] Similar trends were seen by both groups (Figure 7), allowing some insight into factors that might govern the regioselectivity. Mixed alkyl-/aryl-substituted alkynes gave

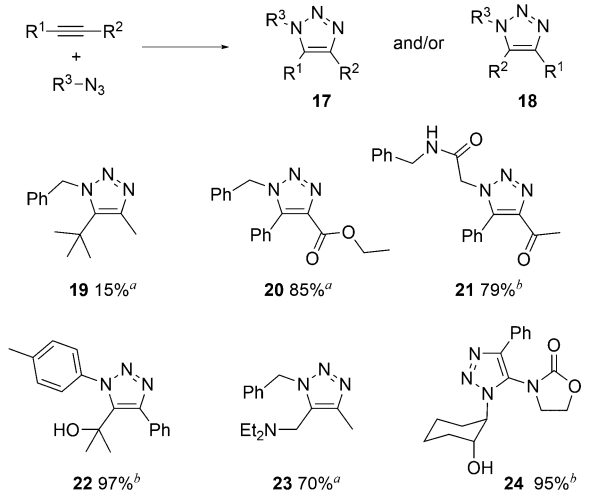


Figure 7. Regiochemistry in reactions of internal alkynes. Conditions: [a]Cp*RuCl$(PPh_3)_2$ (10 mol %), benzene, 80 °C, 2.5–40 h;[77] [b]Cp*RuCl(COD) (2 mol %), toluene, rt, 30 min.[27]

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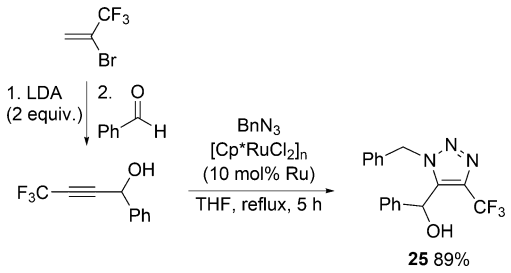
mixtures of regioisomers **17** and **18**, and the same result was seen for alkynes bearing two different alkyl groups. However, an exception to this was seen for the reaction of benzyl azide with 4,4-dimethylpent-2-yne, bearing a methyl group on one of the acetylenic carbons and a *tert*-butyl group on the other, where triazole **19** was obtained with complete regioselectivity, albeit in a rather low yield. Triple bonds with an electron-withdrawing group afforded triazoles with this group in the 4-position with complete selectivity (**20** and **21**). An alcohol or amine in the propargylic position of the alkyne instead resulted in the selective formation of triazole isomers where these substituents are in the 5-position of the triazole (compounds **22** and **23**), explained by hydrogen bonding of −OH or −NH to the chloride ligand of the ruthenium complex.[27] However, a homopropargylic alkyne was found to be unselective,[77] producing a mixture of the regioisomers, indicating that the hydrogen-bond donor needs to be placed in the propargylic position and not further away. Poor regioselectivity when using homopropargylic alcohols has also been noted by Pelly and co-workers.[88] Majireck and Weinreb also found that alkynes containing heteroatoms connected directly to the triple bond also favored the isomer where this heteroatom substituent ends up in the 5-position in the product, as seen in triazole **24**. The regiochemistry can thus be summarized as follows: propargylic hydrogen-bond donors, bulky substituents, and heteroatoms will be found on C5 in the triazole, while electron-deficient groups will be directed to C4.

A more specialized class of internal alkynes was studied by Qing and colleagues,[89] who focused their work on propargylic alcohols with a trifluoromethyl group connected to the alkyne. The precursor alkynes were made by treating 2-bromo-3,3,3-trifluoropropene with LDA followed by the addition of a ketone or aldehyde, to provide four different trifluoromethylated propargylic alcohols to evaluate in RuAAC, using either benzyl azide or *n*-octyl azide, and $[Cp^*RuCl_2]_n$ as the catalyst. Complete selectivity for isomers such as **25** (Scheme 13), with the CF_3

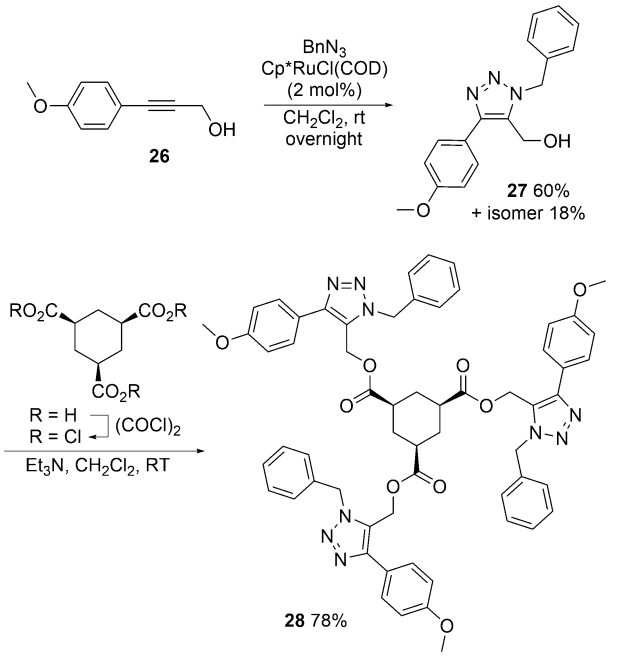
Scheme 13. Trifluoromethylated Propargylic Alcohol in RuAAC[89]



group in the 4-position, was obtained, and the authors propose a polarity effect to explain the regiochemical outcome. A limited study was also performed using other reaction conditions, i.e., a thermal cyclization (80 °C) performed in water and a Pd-catalyzed reaction carried out in refluxing benzene. Mixtures of regioisomers were obtained in both these cases, demonstrating the utility of RuAAC in this context.

C3-Symmetric tripodal triazole-containing ligands for copper(I) complexation have been described by Toth and colleagues.[90] Propargylic alcohol **26** (Scheme 14) was reacted with benzyl azide in the presence of Cp*RuCl(COD), forming a 3:1 mixture of the two possible triazole regioisomers of **27**. Following separation by chromatography, the major isomer was subsequently coupled via esterification to a central cyclohexane

Scheme 14. C3-Symmetric Tripodal Triazole Ligand for Cu Complexation[90]

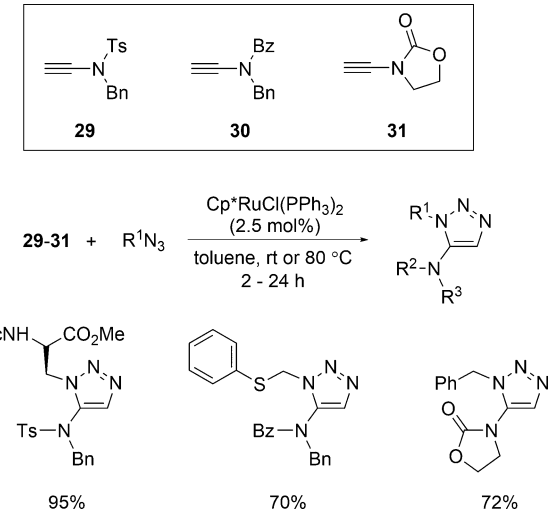


scaffold, affording tripodal ligand **28**, which was found to be an efficient ligand for the CuAAC reaction.

Halogenated internal alkynes can be employed to form 5-halo-1,2,3-triazoles and will be discussed in the next section.[91] An internal bisbithiophenyl alkyne also has been applied in RuAAC with good results.[92]

4.4.3. Heteroatom-Substituted Alkynes. Heteroatom-substituted alkynes have been applied in RuAAC, although there are few examples as yet in the literature. One of the early reports came from Cintrat and colleagues,[93] who applied three different ynamides (**29**−**31**) in RuAAC, providing access to 5-amido-1,2,3-triazoles (Scheme 15). The authors had earlier reported the corresponding CuAAC reaction[94] and now set out to develop methodology providing access to the other triazole isomer. An initial study using benzyl azide and *N*-benzyl-*N*-tosyl ynamide (**29**) with $Cp^*RuCl(PPh_3)_2$ as the catalyst at room temperature

Scheme 15. Ynamides As Alkyne Substrates in RuAAC[93]



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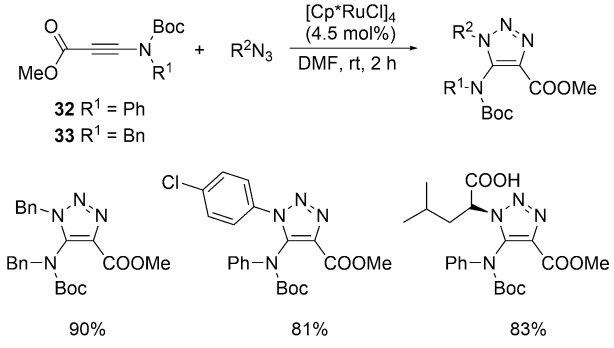
in toluene afforded solely the 1,5-disubstituted triazole isomer; encouraged by these results, the authors screened a wide variety of functionalized azides in reactions with ynamides **29**–**31**. Complete regioselectivity and good-to-excellent yields were obtained in all cases, although certain sterically demanding substrates needed longer reaction times and heating to drive the reaction to completion. One example of an internal alkyne was also included, affording selectively the isomer with the amido substituent in the 5-position of the triazole, following the same trend as for the terminal alkynes.

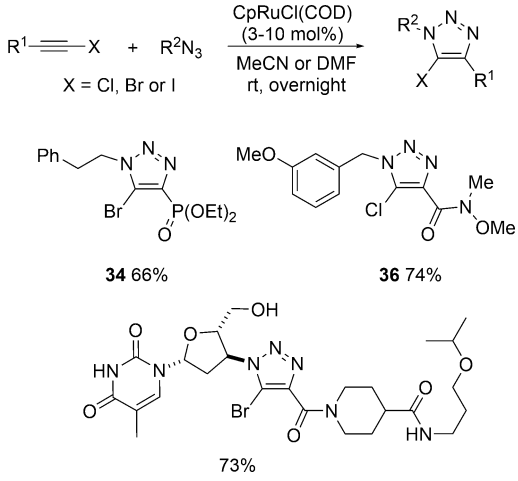
Another example of the use of nitrogen-substituted alkynes comes from Taddei and colleagues, in this case involving *N*-Boc-protected ynamides with a methyl ester functionality at the other end of the alkyne.[95] The purpose was to prepare suitable building blocks for incorporating into triazole peptidomimetics, and these applications are covered in more detail in section 5.1. The authors wished to position the necessary carboxyl and amino functionalities closer to the triazole ring than is normally the case and thus employed an alkyne where these two groups, in protected form, are directly appended to the triple bond. *N*-Boc-ynamides **32** and **33** were prepared in two steps from TIPS-protected bromoacetylene and were subsequently converted to a wide range of functionalized *N*-Boc-5-aminotriazoles in high yields, employing $[Cp^*RuCl]_4$ as the catalyst (Scheme 16). An ynamide-derived 1,5-disubstituted triazole has also been reported by Diaz et al.[96]

Scheme 16. RuAAC Involving Methyl *N*-Boc-Aminopropiolates[95]



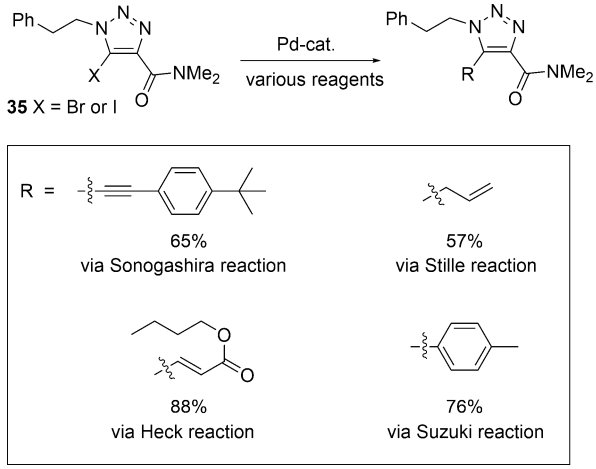
Halogenated internal alkynes have been investigated by Fokin and co-workers, affording 5-halo-1,2,3-triazoles that can be further derivatized using palladium-catalyzed cross-coupling reactions.[91] Cp*RuCl(COD) is commonly employed for room-temperature RuAAC reactions[27] but was found to be inefficient for reactions involving halogen-substituted internal alkynes. However, replacing Cp* with the less-bulky Cp-ligand was found to solve this problem. A variety of alkyl azides reacted with bromo-, chloro-, and iodo-substituted internal alkynes (Scheme 17). Aryl azides were inefficient in the reaction, but apart from this limitation, the reaction was found to tolerate a wide scope of substituents, including even a second heteroatom on the alkyne in the form of a phosphonate as in **34**. Acetonitrile was found to be the most versatile solvent, and many of the reactions could be performed at room temperature, while a few more functionalized or sterically hindered substrates required heating to 50 °C. In general, the highest yields were obtained for chloro-substituted alkynes. The authors also showed that triazoles such as **35** could be employed in palladium-catalyzed transformations such as Sonogashira, Stille, Heck, and Suzuki

Scheme 17. RuAAC Reactions of 1-Haloalkynes[91]

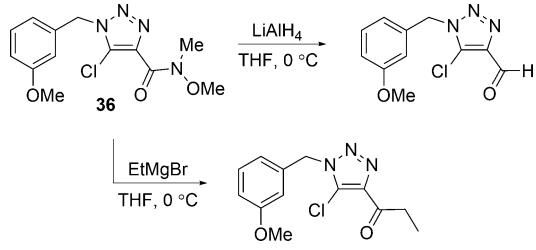


coupling (Scheme 18). Likewise, alkyne precursors substituted with a Weinreb amide as in **36** afforded triazoles that could be

Scheme 18. Halogenated Triazoles in Pd-Catalyzed Cross-Coupling Reactions[91]



Scheme 19. Synthesis of Aldehydes and Ketones from a Triazolyl-Functionalized Weinreb Amide[91]



converted into aldehydes or ketones (Scheme 19). This possibility for further elaboration of the primary products into more complex structures makes this a very versatile methodology indeed. The halogenated alkynes were also employed in conjunction with nitrile oxides to form halooxazoles, as well as in cyclotrimerization reactions affording tribrominated aromatics.

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Sulfur-substituted aryl alkynes were employed by Chen, Guo, and co-workers to prepare (trifluoromethyl)thio-substituted triazoles, potentially useful substrates for medicinal chemistry purposes.[97] Using 10 mol % Cp*RuCl(COD) in benzene, the reaction could be performed at room temperature, and three 1,4,5-trisubstituted triazoles were prepared in 68−85% yields (Figure 8). HMBC (heteronuclear multiple-bond correlation spectroscopy), which can detect heteronuclear coupling over several bonds,[81] was employed to confirm the location of the $-SCF_3$ group at the 5-position of the triazole. Reactions involving 2,2,2-trifluoroethyl-substituted alkynes also afforded the desired triazoles in high yields with the same regioselectivity.

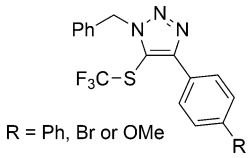

Figure 8. (Trifluoromethyl)thio-substituted triazoles prepared via RuAAC.[97]

4.5. Ruthenium Catalysts

The most commonly applied catalysts for RuAAC are Cp*RuCl-$(PPh_3)_2$ and Cp*RuCl(COD), and a number of examples of their use have already been shown in earlier parts of this Review. Table 1 provides a summary of catalysts for RuAAC, together with selected references to their application, while the remainder of this section deals with more specialized Ru catalysts as well as Ru catalysts that afford the 1,4-disubstituted 1,2,3-triazole isomer.

4.5.1. Ruthenium Catalysts Affording the 1,5-Disubstituted 1,2,3-Triazole. Catalysts employed for the RuAAC reaction are generally 18-electron complexes such as the above-mentioned Cp*RuCl$(PPh_3)_2$ and Cp*RuCl(COD). Nolan and co-workers investigated the effect of using 16-electron ruthenium complexes of the general structure Cp*RuLX in RuAAC, where L was a phosphine or carbene ligand and X was either chloride or alkoxide.[63] The mechanistic aspects of this study have already been described in detail in section 3 and will be mentioned only briefly here. Using the reaction between phenyl acetylene and benzyl azide as a test system, seven different ruthenium complexes were evaluated as catalysts for the cycloaddition at room temperature in dichloromethane, with a reaction time of 40 min. The best results were obtained when L was a phosphine and X was a chloride ligand (Figure 9, **37** and **38**). Replacing chloride with $-OCH_2CF_3$ was detrimental to the reaction, and complex **39** afforded only 2% product. Among complexes with carbene

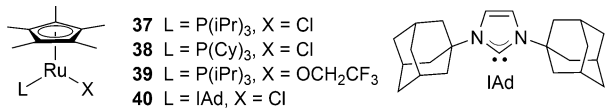

Figure 9. Sixteen-electron ruthenium complexes evaluated in RuAAC.[63]

Table 1. Catalysts for the Synthesis of 1,5-Disubstituted 1,2,3-Triazoles Via the RuAAC Reaction with Examples of Reaction Conditions[a]

catalyst	mol % cat	solvent	temp	ref
Cp*RuCl$(PPh_3)_2$	1−10	benzene	60−80 °C	12, 77, 83, 179, 195, 200, 211, 218, 224
	1−5	dioxane	40−100 °C (incl. μw)	12, 132, 133, 207, 219, 221, 222, 248, 251, 252, 260, 262
	1−28	THF	25−100 °C (incl. μw)	27, 71, 87, 132, 177, 178, 180, 192, 204−206, 212, 213, 217, 220, 223, 225, 229, 231, 253−256, 258, 264, 268, 271, 272
	1−20	toluene	25−120 °C	93, 94, 96, 125, 132, 156, 171, 191, 193, 194, 204, 226, 227
	2−5	DMF	70−120 °C (incl. μw)	111, 142, 202, 209
	2	MeCN	90 °C (incl. μw)	219
	10	DCE	80 °C	237
	10	CH_2Cl_2	50 °C	228
Cp*RuCl(COD)	5−10	benzene	25−80 °C	12, 97, 197
	1−5	DCE	45 °C	52, 196
	2−20	toluene	25−110 °C	27, 88, 120, 122, 129, 132, 191, 227
	4−25	THF	25−66 °C	104, 132, 215, 216, 223, 250, 267, 272
	2−4	dioxane	25−100 °C	120, 132, 169, 190, 208
	20	DMF	60 °C (incl. μw)	112, 270
	6	DMA	100 °C (μw)	189
CpRuCl(COD)	3−10	MeCN	25 °C	91
	3−10	DMF	25 °C	91
CpRuCl$(PPh_3)_2$	3−5	benzene	80 °C	12, 92
	2	THF	75 °C	27
	6	DMA	100 °C (μw)	65
Cp*RuCl(NDB)	5	benzene	80 °C	12
	2	THF	75 °C	27
$[Cp^*RuCl]_4$	2−50	THF	25−120 °C	27, 234, 236, 244, 245
	30	THF/MeOH	50 °C	160, 161
	2.5−10	DMF	25−115 °C (incl. μw)	52, 95, 169, 188, 214, 230, 244, 245, 249, 257
	5−15	toluene	40−110 °C	156, 227, 157, 168
$[Cp^*RuCl_2]_n$	4−10	THF	40−100 °C (incl. μw)	69, 271, 119, 149

[a]For RuAAC reactions on solid phase, see Table 2.

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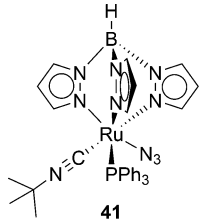
ligands, use of the bulky IAd (**40**), with adamantyl substituents on the carbene, was the most successful, albeit affording a lower yield than that for the phosphine-substituted complexes.

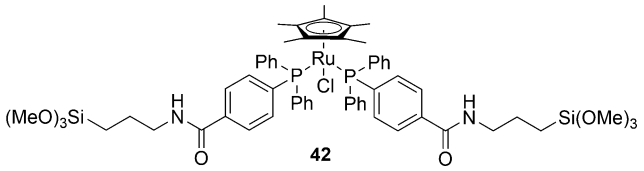
Lo and colleagues prepared several ruthenium azido complexes bearing Tp (trispyrazolylborate) ligands and found that complex **41** (Figure 10) was an efficient catalyst for the RuAAC reaction between benzyl azide and various terminal acetylenes.[98,99] Interestingly, the catalyst gave similar results in toluene and in water.



41

Figure 10. Ruthenium azido complex **41** with Tp ligands for RuAAC reactions in water.[98,99]

A practical approach to RuAAC was reported by Astruc and co-workers, who prepared ruthenium complex **42** (Figure 11) for



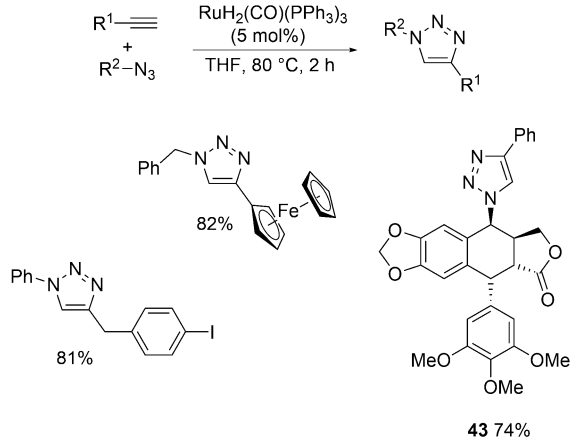
42

Figure 11. Ruthenium catalyst for immobilization on an iron-oxide based magnetic nanoparticle.[100]

immobilization onto magnetic nanoparticles, allowing for facile recycling of the catalyst.[100] A triarylphosphine linker with a pendant trimethoxysilyl group was employed to tether the pentamethylcyclopentadienyl ruthenium(II) catalyst to the surface of a silica-coated γ-Fe_2O_3 nanoparticle. The catalyst was highly selective for the 1,5-disubstituted 1,2,3-triazole isomer and afforded good yields for a range of alkynes and azides, also including an internal alkyne. Facile catalyst recovery was effected using a magnetic field, and the catalyst could be recycled up to five times without substantial loss in selectivity and yield.

4.5.2. Ruthenium Catalysts Affording the 1,4-Disubstituted 1,2,3-Triazole. In the original reports by Jia, Fokin, and co-workers, it was noted that ruthenium catalysts lacking a cyclopentadienyl ligand afforded the 1,4-disubstituted isomer instead of the 1,5-disubstituted 1,2,3-triazole.[12,27] Although such compounds can be accessed via CuAAC, it was nevertheless of interest to evaluate the range of ruthenium catalysts that were applicable in this variant of the cycloaddition as well as to investigate the scope of substrates that could be used. Liu, Jia, and co-workers focused on the most active of the earlier studied catalysts, i.e., $RuH_2(CO)(PPh_3)_3$.[101] Using 5 mol % catalyst in THF at 80 °C, a wide variety of different 1,4-disubstituted triazole products could be produced. Of interest is the synthesis of podophyllotoxin derivative **43** (Scheme 20); derivatization of this natural product via RuAAC also has been reported by Tron and co-workers (see section 5.5), but in this case the triazole replaced the lactone functionality. A one-pot cycloaddition/transfer hydrogenation, using the same catalyst for both reactions, was also described. Liu and co-workers have also

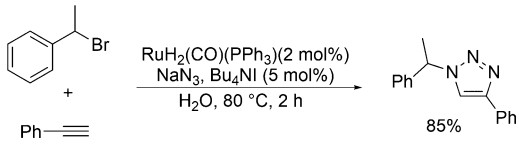
Scheme 20. Formation of 1,4-Disubstituted 1,2,3-Triazoles Using $RuH_2(CO)(PPh_3)_3$[101]



43 74%

shown that the ruthenium-catalyzed cycloaddition can be performed in water using the same catalyst, with a lower catalyst loading (0.2%) than when using an organic solvent.[102] A convenient one-pot method for directly accessing the 1,4-disubstituted triazoles via in situ formation of the azide from the corresponding bromide was also included in this study (Scheme 21).

Scheme 21. One-Pot Cycloaddition Reaction on Water Directly from an Alkyl Bromide[102]



In a later paper by Jia, together with Liu, Fokin, and co-workers, a larger range of ruthenium catalysts was instead explored.[62] Two new catalysts in particular, i.e., $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$ and $Ru(C{\equiv}CPh)_2(CO)(PCy_3)_2$, were found to give both high yields and fast reactions. A wide range of alkynes and three different azides were explored in RuAAC using catalyst $RuH(\eta^2\text{-}BH_4)(CO)(PCy_3)_2$. Although *tert*-butylacetylene as well as an aryl azide were difficult substrates, all other azide/alkyne combinations afforded triazoles in high yields (71−95% yield). Mechanistic studies, also involving DFT calculations, indicate a ruthenium acetylide as a key intermediate.

Porphyrin derivatization is an example of where Ru catalysts that form the 1,4-disubstituted isomer can be put to good use, as the Cu catalyst used for CuAAC can result in copper inserting into the porphyrin. If this is not desired, blocking the central coordination site with Zn(II) is necessary, but this involves extra reaction steps.[103] As part of a study on porphyrin−vitamin B_{12} conjugates, Gryko and co-workers employed $RuH_2(CO)(PPh_3)_3$ to append triazoles onto a central porphyrin scaffold functionalized with an azide (**44**, Scheme 22) or an alkyne.[104] However, although the desired 1,4-disubstituted structures were obtained, this catalyst afforded low yields and substantial amounts of byproduct formation. Thus, this strategy was abandoned, and the authors instead returned to CuAAC, finding after some optimization that $[Cu(phen)(PPh_3)_2]NO_3$ could provide the 1,4-isomers without copper insertion. A set of 1,5-isomers were

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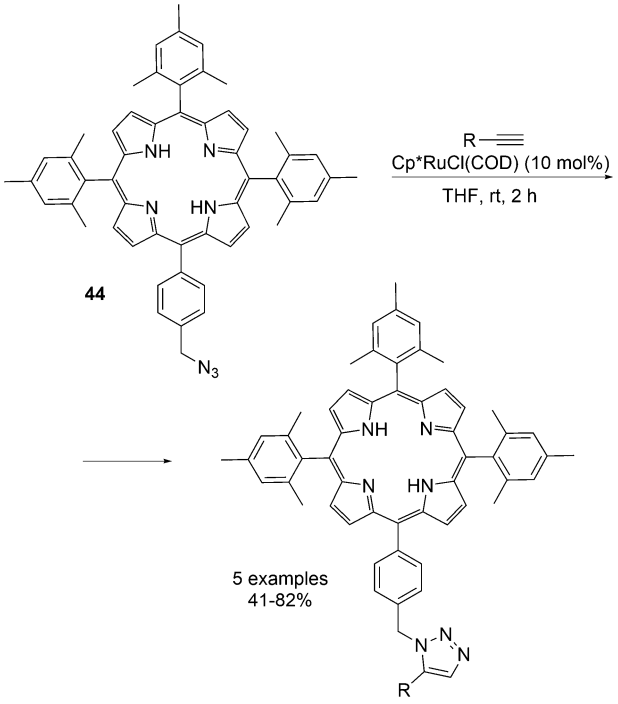
Scheme 22. Ruthenium-Catalyzed Derivatization of Porphyrins[104]



also successfully prepared as part of this study, again with precursor **44** but this time using Cp*RuCl(COD) as the catalyst (Scheme 22). As a point of interest, Gallo and co-workers explored ruthenium porphyrin complexes as catalysts for RuAAC but found that reaction of an aryl azide with an aryl alkyne produced indoles rather than the expected triazoles.[105]

Lee and co-workers employed ruthenium nanoparticles in ruthenium-catalyzed 1,3-cycloadditions reaction, where the catalyst was prepared by calcination of ruthenium hydroxide at 500 °C under a hydrogen atmosphere.[106] The 1,4-triazole isomers were obtained in this case, and of particular interest is the formation of tristriazoles **45** and **46** in 60% and 64% yields, respectively, using this catalyst system (Figure 12). The ruthenium nanoparticles could be recycled three times without any significant change in morphology or catalytic activity.

Another example of a supported catalyst has been described by Tuhina, Islam, and co-workers,[107] in this case employing a polymeric support in contrast to the nanoparticles employed by Astruc and co-workers (section 4.5.1)[100] and Lee and co-workers.[106] The polymer-bound ruthenium(III) catalyst **47** (Scheme 23) was prepared by reaction of $RuCl_3$ with a

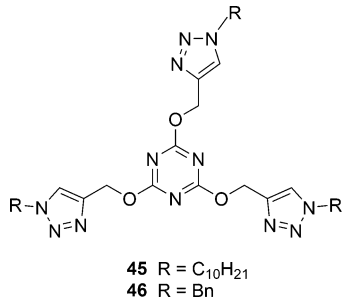
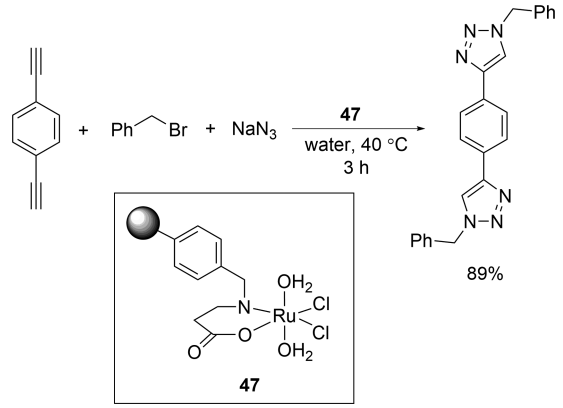


Figure 12. Tristriazoles formed via cycloadditions involving Ru(0) nanoparticles.[106]

Scheme 23. Polystyrene-Supported Ru(III) Complex 47 in One-Pot RuAAC in Water[107]



polystyrene-tethered β-alanine ligand, affording a supported catalyst containing 8.5 wt % ruthenium (determined by AAS). To test the catalyst in RuAAC, phenyl acetylene was mixed with sodium azide and benzyl bromide in the presence of varying amounts of the supported catalyst. By evaluation of the reaction conditions, including exploration of a wide range of organic solvents, the authors concluded that water provided the best medium for this transformation. Employing 2 mol % catalyst and a reaction time of 3 h at 40 °C produced the 1,4-disubstituted 1,2,3-triazole in quantitative yield, after a simple workup involving only filtration, washing with ethanol, and concentration. The substitution pattern of the product is not surprising considering that the catalyst contains neither a Cp nor a Cp* ligand, and thus, this result is in accord with earlier studies by Jia, Fokin, and co-workers.[12,27] The scope of the reaction was further investigated by introducing substituents on the aromatic groups of the precursors, with product yields in the range of 83−94% (see Scheme 23 for an example). The recyclability was investigated and the supported catalyst could be employed up to six times without noticeable reduction in catalytic activity. The polymer-bound catalyst was also investigated in transfer hydrogenation of aromatic and aliphatic ketones with good results.

4.5.3. Ruthenium Catalysts Affording Other Substitution Patterns. An interesting ruthenium-catalyzed tandem reaction has been described by Bhattacharjee and co-workers.[108] In the presence of silver, the ruthenium compound $[Ru(dppp)_2(CH_3CN)Cl][BPh_4]$, prepared from either $RuCl_2(PPh_3)_3$ or $RuCl_3{\cdot}nH_2O$, could effect the homocoupling of alkynes via the formation of silver acetylenides. After heating the reaction for 30 min, sodium azide was added, and after an additional 6−8 h, a product was formed where one of the two triple bonds had participated in a cycloaddition reaction to form a 4,5-disubstituted 1,2,3-triazole (Scheme 24). Five different substrates were isolated in good yields. Attempts to replace NaN_3 with an alkyl azide did not afford any triazole product.

4.6. Solid-Phase RuAAC Reactions

The use of solid-phase synthesis (SPS) can sometimes be advantageous, especially in solid-phase peptide synthesis (SPPS). The RuAAC reaction has been successfully applied using SPS methodology by several groups,[109−113] where SPS RuAAC works under similar conditions as the solution-phase reaction in terms of catalysts, temperature, and solvent. An increased amount of catalyst and slightly prolonged reaction time seems, as expected, to be beneficial due to the slower reaction kinetics on the solid

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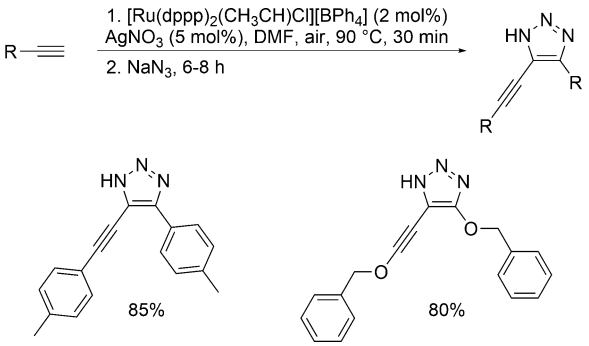
Scheme 24. Tandem Ruthenium-Catalyzed Homocoupling/Cycloaddition Reaction in the Presence of a Silver Salt[108]



phase. Furthermore, a variety of different resins have been employed with good results. The various reaction conditions employed for SPS RuAAC are summarized in Table 2.

5. MEDICINAL AND BIOLOGICAL APPLICATIONS

Since catalysts suitable for RuAAC became commercially available, numerous applications in the fields of medicinal chemistry, biochemistry, and drug discovery have been reported. This section aims to give an overview of different strategies that have been applied in the various fields, with the properties of 1,5-triazoles in mind.

5.1. Peptidomimetics

Compounds that mimic peptides in terms of their secondary structure and/or biological functions, but which can exhibit other beneficial properties such as improved proteolytic stability or improved affinity to a desired target, are known as peptidomimetics.[114] A broad range of different peptidomimetics have been developed, and their use has become a standard tool in medicinal chemistry and drug research today.[115] The field can be broadly divided into three categories, involving scaffold-based peptidomimetics as well as local and global modifications of the parent peptide. The aim of peptidomimetic design is to either maintain or improve biological activity, increase selectivity, and, most importantly, increase proteolytic stability. In this section we will discuss the properties and applications of the RuAAC reaction as a tool for peptidomimetic applications.

5.1.1. *cis*-Amide-Bond Mimetics. In natural peptides and proteins, most of the amide bonds in the peptide backbone are populated in their low-energy trans-conformation, which is used in the construction of α-helices and β-sheets. However, the ability to form a high-energy cis-conformation, especially for *cis*-prolyl peptide bonds (~6% of all Xaa-Pro peptide bonds in nature), may influence the secondary structure, as well as many processes such as the rate of protein folding.[116] In proteins, the cis-conformation can be stabilized by additional intramolecular hydrogen bonds and/or disulfide bonds, which is normally not the case for small peptides. The ability to mimic *cis*-amide bonds governs the possibility to study such biological systems and provides an opportunity for drug design and research. The 1,5-disubstituted 1,2,3-triazole exhibits similar properties to a *cis*-amide bond, particularly concerning the distance between the two adjacent α-carbons (3.2 Å in the 1,5-triazole versus 3.0 Å in a *cis*-amide bond) (Figure 13) and thus constitutes a good mimic for a *cis*-amide bond, despite lacking hydrogen-bond donor abilities.

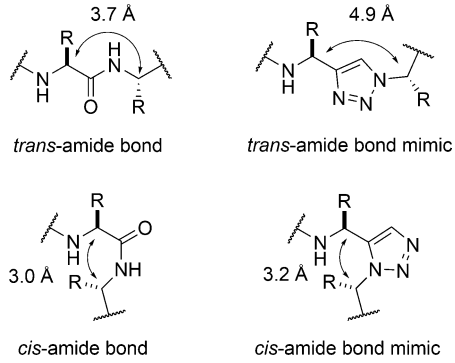


Figure 13. 1,2,3-Triazoles as *trans*- and *cis*-amide bond mimics.[14,117]

Appella and co-workers were among the first to demonstrate the synthesis of a 1,5-disubstituted 1,2,3-triazole amino acid (**48**, Scheme 25) for use as a *cis*-amide bond mimic, albeit not using RuAAC, in order to induce turn formation in an unnatural peptide in aqueous solution.[118] 1,5-Triazole amino acid **48** was synthesized via a noncatalyzed thermal Huisgen cycloaddition in a five-step route with an overall yield of 31%. The synthesis of such derivatives was later improved using the RuAAC reaction, affording the corresponding triazole amino acid protected with Boc instead of Fmoc, in 75% yield over two steps.[119] Insertion of triazole **48** into an unnatural peptide sequence using solid-phase peptide synthesis (SPPS) leads to peptoid **49**, (Scheme 25), which adapts a hairpin-like turn structure as the major conformer in 10 mM sodium phosphate buffer (pH 7.0), as revealed by detailed NMR experiments.

The synthesis and use of 1,5-disubstituted 1,2,3-triazoles as *cis*-prolyl peptide bond mimics has been studied by Raines and co-workers,[120] who found that the Xaa-1,5-triazole-Ala unit mimics an Xaa-*cis*-Pro dipeptide remarkably well. By using the RuAAC reaction, a number of protected Xaa-1,5-triazole-Ala building blocks such as **50** and **51** were prepared in moderate-to-high yields (Scheme 26).

Bovine pancreatic ribonuclease A (RNase A), consisting of 124 residues, was used as a model protein to test the concept of 1,5-triazoles as *cis*-peptide bond mimic. The region Gly112-Asn113-Pro114-Tyr115 in the protein sequence forms a Type VIb reverse turn where Asn113-Pro114 has a *cis*-peptide bond. This

Table 2. Summary of Conditions Reported for the RuAAC Reaction on Solid Phase

resin	catalyst	% cat	solvent	temp (°C)	time (h)	ref
chlorotrityl resin	Cp*RuCl(COD)	20%	toluene	45	16	109
Amphispheres resin[a]	Cp*RuCl(COD)	20%	DMF	60[b]	5	110
Wang resin	Cp*RuCl(PPh_3)$_2$	5%	DMF	70	22	111
TentaGel S AC resin	Cp*RuCl(COD)	20%	DMF	60	5	112
Rink amide	Cp*RuCl(PPh_3)$_2$	NA	THF	70	8	113

[a]Amphispheres 40 HMP resin. [b]Microwave heating.

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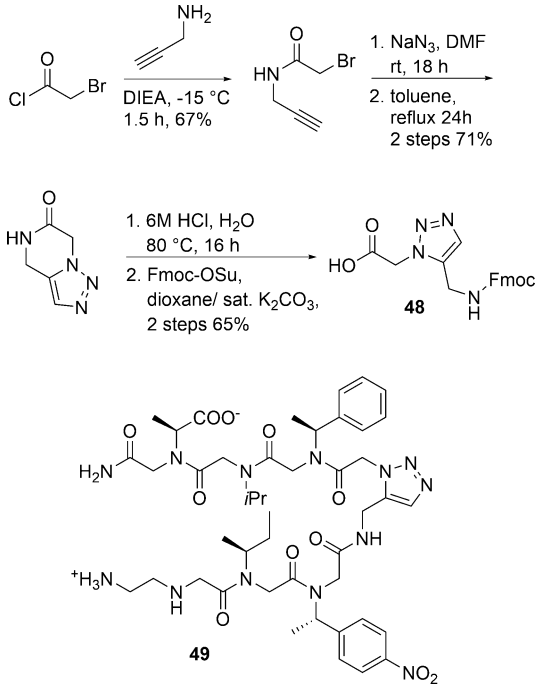
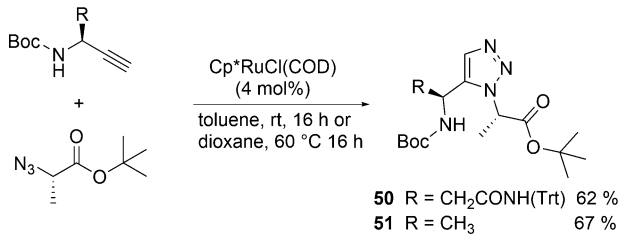
Scheme 25. Synthesis of Amino Acid 48 and Insertion into Peptoid 49[118]



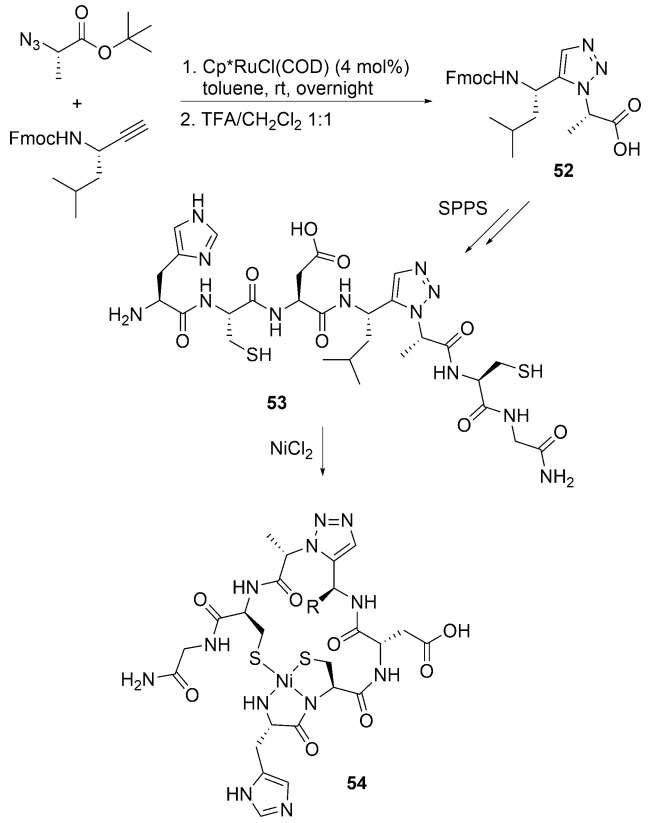
Scheme 26. Synthesis of Xaa-1,5-triazole-Ala Building Blocks Via the RuAAC Reaction[120]



dipeptide segment can be mimicked rather well by Xaa-1,5-triazole-Ala. Triazoles **50** and **51** were incorporated in a peptide sequence corresponding to residues 95−124 by using standard solid-phase peptide synthesis. No epimerization was observed during the basic Fmoc-deprotection steps of the peptide synthesis. Residues 1−94 were created by recombinant DNA methods. After ligation of the two sequence parts, the protein was folded and purified, and the enzymatic activity was compared with the native ones. The two 1,5-triazole-containing enzymes obtained showed catalytic activities comparable to the wild-type analogues. It can be concluded that the Xaa-1,5-triazole-Ala building blocks are efficient mimics of the *cis*-peptide bond conformation in Xaa-Pro residues, as the catalytic activities are closely related to the formed protein tertiary structure.[121]

A similar *cis*-prolyl bond mimetic has also been described by Tietze et al. and applied as a LeuPro *cis*-peptide bond mimetic in the synthesis of a mimic of the nickel superoxide dismutase (NiSOD) metallopeptide.[122] The Fmoc-protected 1,5-triazole amino acid **52** was synthesized using 4% Cp*RuCl(COD) as the catalyst, followed by deprotection of the *tert*-butyl ester, and was then inserted into heptapeptide **53** using standard SPPS. (Scheme 27) Metallopeptide **54** was obtained by treating triazole peptide **53** with 1 equiv of aqueous $NiCl_2$ solution and titration to pH 7.8.

Scheme 27. Synthesis of 1,5-Triazole Amino Acid 52 and Metallopeptide 54[122]



Ferrini et al. have prepared a slightly different 1,5-triazole as a peptide backbone mimetic that exhibits the ability to mimic β-turns.[95] As discussed in section 4.4.3, the 5-aminotriazole was obtained exclusively when using *N*-Boc-aminopropiolates in the RuAAC reaction. These 5-aminotriazoles are appealing as peptide backbone mimetics, as they are equipped with three functional groups that can be used for peptide synthesis or functionalization. Conformational analysis by computational methods (MM, QM, and MD) revealed that triazole **55** (Figure 14) has some populated conformers satisfying reverse turn requirements, and one of the two most stable conformers shows the CO−HN hydrogen bond that is typical for β-turns.

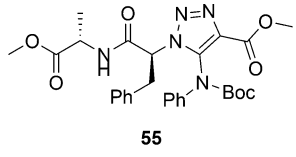


Figure 14. Backbone peptidomimetic based on a 5-aminotriazole structure.[95]

Tischler et al. have also employed a 1,5-triazole as a *cis*-peptide mimic.[112] They targeted the Ile-*cis*-Pro amide bond in the highly potent sunflower trypsin inhibitor 1 (SFTI-1).[123] In the native form, its 14 amino acid backbone GRCTKSIPPICFPD is cysteine bridged and head-to-tail cyclized, and the Ile-*cis*-Pro amide bond is fundamental for bioactivity. By applying RuAAC in standard Fmoc SPPS (see section 4.6), 1,5-triazole *cis*-peptide bond mimics could be prepared, and the disulfide bridge was obtained by DMSO or air-mediated oxidation on the crude peptide. The trypsin-inhibition activity of the mimics was tested,

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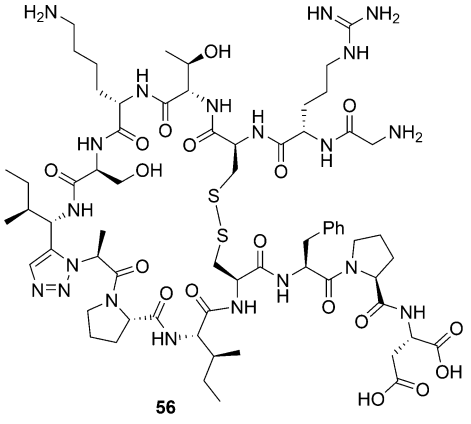


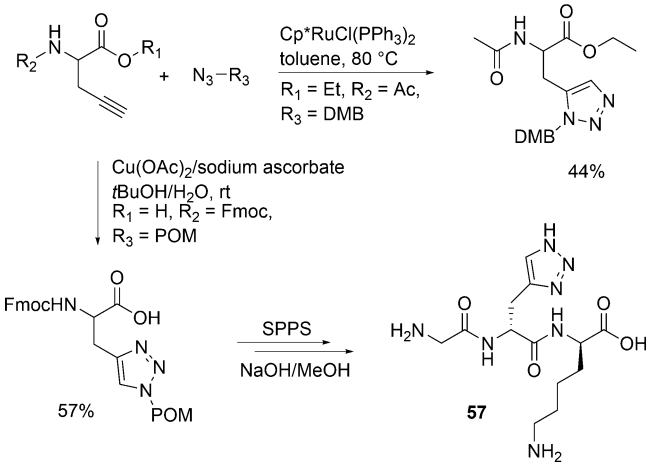
Figure 15. Mimic of the Ile-*cis*-Pro amide bond.[112]

and the most-potent compound, with a K_i of 34 nM, was found to be the triazole-containing **56** (Figure 15).

5.1.2. Peptide Side-Chain Mimetics. In addition to mimetics of the peptide bond and peptide backbone, there are also side-chain mimetics, where the role of such mimetics can be to stabilize interactions or activated species made by the side-chain in the native peptide. Peptide side-chain mimetics are also frequently used to constrain peptide conformations and to stabilize secondary structures such as helices, commonly termed stapled peptides.[124] In this section the use of 1,5-triazoles as side-chain mimetics will be discussed.

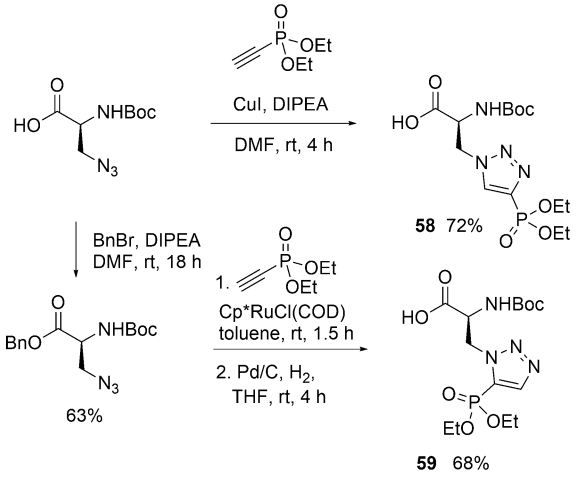
Roux et al. have utilized CuAAC and RuAAC reaction to synthesize orthogonally protected 1,2,3-triazoles as histidine mimetics.[125] Starting from propargyl glycine, various 1,4-protected triazoles and a limited number of 1,5-triazoles were prepared. One could question the motivation for making the protected 1,5-triazoles, as the 1*H*-1,2,3-triazol-4-yl is favored over the 1*H*-1,2,3-triazol-5-yl by 2.0 kcal/mol and will be in an equilibrium shifted toward the 1,4-regioisomer after deprotection irrespective of the route used.[126] Nevertheless, Fmoc- and pivaloyloxymethyl (POM)-protected[127] 1,4-azaHis mimics were utilized in SPPS of Gly-His-Lys (GHK) analogue **57** (Scheme 28). GHK is an endogenous tripeptide known as a growth-modulating factor, a strong activator of wound healing, with copper-chelating properties.[128] However, no biological evaluation of compound **57** was reported.

Scheme 28. Synthesis of 1,5-Triazole-Containing Gly-His-Lys Analogue 57[125]



Interesting stable phosphohistidine (pHis) mimetics and phosphoryltriazolylalanines (pTza) have been developed by Kee et al.[129] A cycloaddition of diethyl ethynylphosphonate with protected azidoalanine under both CuAAC and RuAAC conditions gave the desired pTza derivatives **58** and **59** in 72% and 68% yields, respectively (Scheme 29). According to

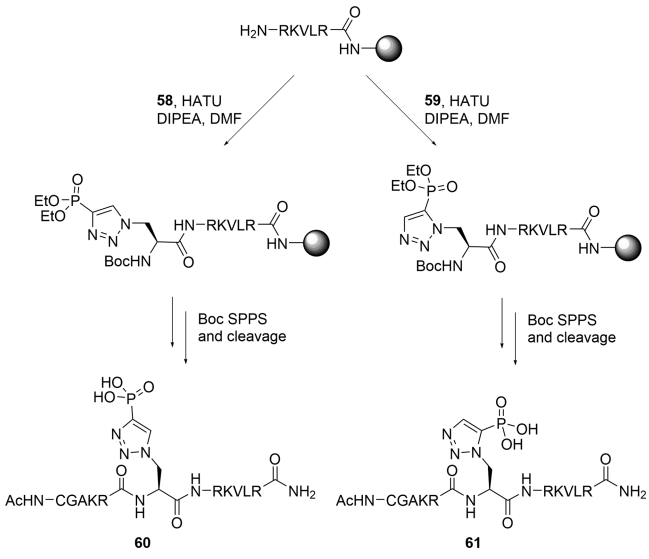
Scheme 29. Synthesis of Stable pHis Mimetics[129]



molecular modeling, these compounds display favorable pHis-mimetic properties in terms of geometry and electronics. Particularly the hydrolytic liability of the original phosphohistidine moiety is overcome by the replacement of the labile N−P bond with a stable C−P bond.

With the two stable pHis isomers pTza **58** and **59** at hand, the possibility to study the function of pHis in biological systems was opened. It is known that histone H4 histidine kinase (HHK) activity is upregulated by 200-fold in human hepatocellular carcinomas compared to normal liver tissue.[130] Stabile pHis analogues could thus be useful tools, enabling the study of histone histidine phosphorylation. Peptides **60** and **61** (Scheme 30) were designed and synthesized by SPPS. These compounds correspond to the N-terminal tail of human histone H4 protein

Scheme 30. Solid-Phase Synthesis of Histone H4 Tail Peptides Containing Stable 3-pHis and 1-pHis Mimics[129]



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(residues 14−23), containing either the 1-pHis or the 3-pHis analogue instead of His18.[131]

Triggered by the possibility that the pTza peptides **60** and **61** could be used in the generation of antibodies that can selectively recognize pHis in phosphoproteins, peptide **60** was employed as an immunogen to obtain rabbit polyclonal antibodies such as Ab-3pHis. Ab-3pHis is an example of an antibody that selectively recognizes a pHis-containing protein. Accordingly, Ab-3pHis was formed and its specificity was determined by peptide dot blot assays with a series of histone H4 tail peptides, harboring the two pTza isomers (**60** and **61**) as well as the His, pTyr, pSer, and pThr analogues. As Ab-3pHis only recognizes **60** and not **61** or the other phosphorylated analogues, no cross-reactivity toward His or other phosphoamino acids was demonstrated. Western blot analysis showed that Ab-3pHis selectively recognizes the histidine-phosphorylated histone H4 but not the nonphosphorylated counterpart.

Buysse et al. have investigated amino triazolo diazepines (Ata, Figure 16) as constrained histidine mimics and demonstrated

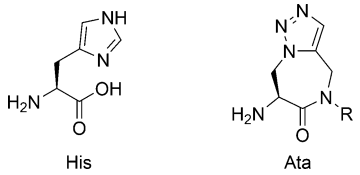
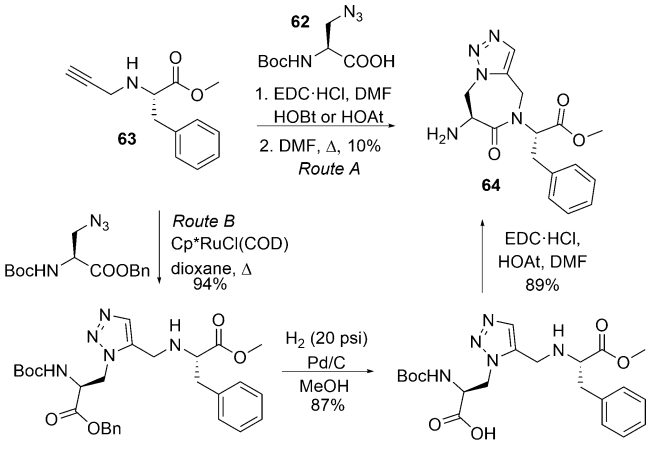


Figure 16. Histidine (left) and amino triazolo diazepine (Ata) (right).[132]

their potential as histidine mimics by replacement of the His-Pro dipeptide in angiotensin IV and subsequent evaluation in two enzyme inhibition assays.[132]

Two different strategies for the synthesis of such Ata-Xaa dipeptidomimetics were explored as seen in Scheme 31. Route A,

Scheme 31. Comparison of Thermal Versus RuAAC Synthesis of Ata-Xaa Dipeptidomimetics 64[132]



involving the initial amide coupling of Boc-β-azido-Ala **62** with *N*-propargyl amino acid methyl ester **63** followed by a thermal Huisgen cycloaddition to form **64**, was found to be unsatisfactory, due to not only low yields but also a considerable degree of epimerization. Route B, employing an intermolecular RuAAC reaction followed by intramolecular lactamization, proved superior both in terms of yield and suppressed epimerization after optimization of the reaction conditions. The Ata-Gly dipeptidomimetic **64** was applied to the angiotensin IV sequence, Val-Tyr-Ile-His-Pro-Phe, using standard SPPS. The activity of this modified sequence was determined by measuring the inhibition of insulin-regulated aminopeptidase (IRAP) and aminopeptidase-N (AP-N). Inhibition activitity of the peptidomimetic was in principle the same as that measured for the original peptide (pK_i IRAP = 7.09 vs 7.14), concluding that Ata functions as a potent mimic for His.

Keller, Pyne, and co-workers have reported the synthesis of mono-, di-, and tripeptidomimetics, introducing a C-terminal triazole as an ester isostere, using both CuAAC and RuAAC.[133] The antibacterial activity of the compounds was evaluated, with a particular focus on the gastric anaerobe *Clostridium difficile*, where two dipeptides with 1,5- and 1,4,5-substitution patterns were among the most active.

5.1.3. α-Helix Mimetics. Among the tremendous number of biological processes that occur in all living cells, a large portion of these involve protein−protein interactions (PPIs). The ability to control and modulate PPIs is of great significance for increased understanding of these processes, as well as for the development of new molecular therapeutics. The discovery of cell-permeable small-molecular inhibitors of PPIs is still a big challenge, partly due to the absence of natural small-molecular ligands, the inherent conformational flexibility of proteins, and also the lack of simple, suitable binding assays. Helical secondary structure motifs are the most abundant forms in proteins and correspond to over 30% of the structures. For that reason, it is rational to imagine that a significant population of PPIs should involve α-helices and that a mimic of a helix recognition face could act as a small-molecular competitive inhibitor.[134−137]

α-Helix mimetics can be divided into three different categories. Type I mimetics are short oligomers that strive to replicate the local topography of an α-helix. These often involve peptide backbone mimetics with the aim to stabilize the helical conformation and to improve proteolytic stability; examples are stapled peptides and foldamers (foldamers are discussed in section 5.1.4). Type II mimetics are small nonpeptidic molecules that bind to a peptide receptor but do not necessarily mimic the original helix structure and rather serve as functional mimetics.[134] Type III mimetics are nonpeptidic scaffolds that mimic the surface formed by nonsequential hot-spot residues of the α-helix.[138−140] Attempts to use 1,5-triazoles in such type III α-helix mimetics have recently been reported by the groups of König[111,141] and Grøtli.[142] Both groups have designed and synthesized mimics bearing three side chains, which by calculated lowest-energy conformation mimic the orientation of the side chains in an α-helix at position *i*, *i*+3, and *i*+7. The König group used Cp*RuCl(PPh_3)$_2$ as catalyst in dioxane at 70 °C to obtain the bistriazole scaffold **65** in good yield (Figure 15). Grøtli and colleagues synthesized the 8-(1,5-triazolyl)-purine scaffold **66** under microwave conditions at 120 °C in DMF, (Figure 17) aiming at fluoroscent PPI inhibitors of the MDM2/p53 interaction. Disappointingly, however, these compounds showed no activity in the fluorescence polarization (FP) assay. Thus, a

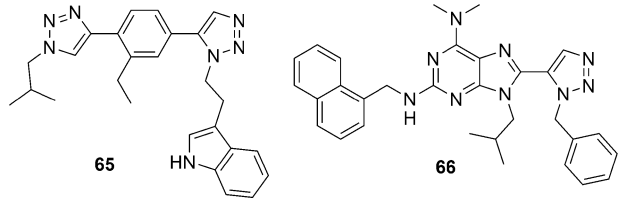


Figure 17. Attempted α-helix mimetics.[111,141,142]

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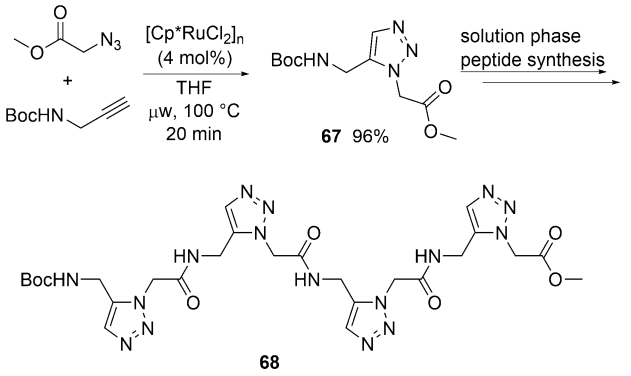
biologically active 1,5-triazole-based α-helix mimetic still remains to be discovered.

5.1.4. Foldamers. In the area of peptidomimetics, non-natural peptidic oligomers having the capacity to mimic structural and folding properties of natural peptides are called "peptidic foldamers" or "foldamers". The field was originally initiated by two parallel papers published by Seebach et al.[143] and Gellman and co-workers in 1996.[144] By now, foldamers demonstrate diverse secondary structures and also very exotic side-chain chemistry for the non-natural amino acid-like building units.[145,146] Peptidic foldamers are useful tools in target validation and can also provide additional modalities when designing drugs for challenging target classes like PPIs.[147] As already mentioned above, because helical and turn structures are easily achieved by employing backbones involving cyclic insertions,[145,146] both the 1,4- and 1,5-substituted 1,2,3-triazole ring coupled with N- and C-terminal groups of amino acids have accordingly come up as novel "triazole amino acids" with an application potential as non-natural insertions into natural amino acid sequences.[14,148] The important abilities, such as stability against degrading enzymes or more controlled secondary structures, also hold for the 1,5-disubstituted 1,2,3-triazole amino acid insertions, which promotes their potential use for creating foldamer oligomers. By applying 4 mol % $[Cp^*RuCl_2]_n$ in the RuAAC reaction, Johansson et al.[119] obtained the 1,5-disubstituted 1,2,3-triazole amino acid **67** in excellent yield (Scheme 32). Accordingly, this amino acid was also oligomerized

Scheme 32. Synthesis of 1,5-Triazole Amino Acid 67 and Tetramer 68[119]



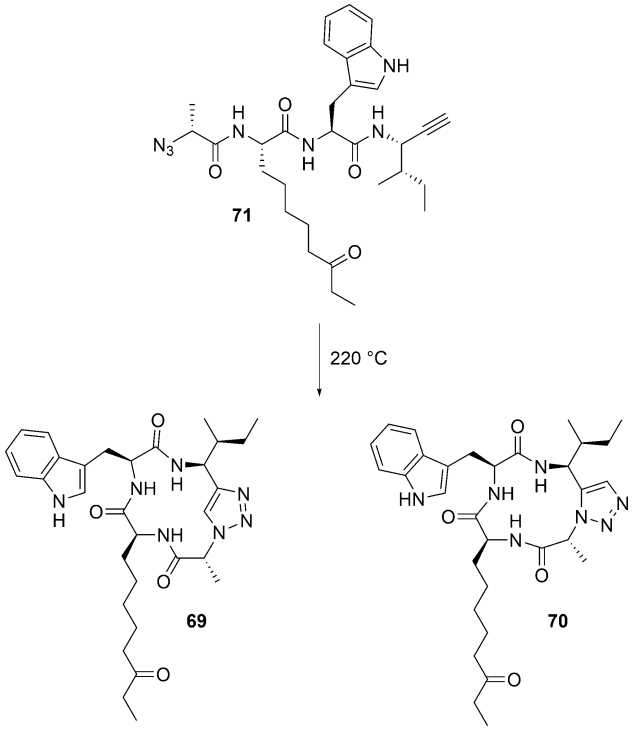
into triazole foldamers, resulting in short δ-peptide trimer and tetramer (**68**) derivatives showing diverse structural properties and having several conformations present simultaneously in solution phase.[119] The relatively rich set of stable conformers for the 1,5-disubstituted triazole amino acids, the on-purpose extended nature of their 1,4-regioisomers,[149] and their applicability in both standard peptide synthesis and expressed protein ligation[120] have already provided some initial studies toward the "foldamer direction".[119,150,151] The latter examples together also foreshadow a rapid increase in the number of new promising triazole foldamer constructs in the near future.

5.2. Macrocycles

In the past decade, the interest for macrocycles as drug leads has grown,[152,153] especially in the case of nonpeptidic macrocycles, due to their generally more-favorable properties, i.e., higher metabolic stability and permeability, which facilitate their use as oral drug candidates. Macrocycles populate a different chemical space than the space traditionally seen as druggable according to Lipinski's rule of five.[154] The turnlike structure of 1,5-disubstituted 1,2,3-triazoles makes them excellent motifs for incorporation into macrocycles.[155] Two different strategies can be employed for the introduction of a 1,5-disubstituted triazole in a macrocycle. Either the triazole formation can be used in the macrocyclization step or the 1,5-triazole moiety can be introduced prior to the cyclization step. Both strategies have been utilized by several groups and will be discussed in this section.

Horne et al. have employed the 1,5-triazole as a *cis*-peptide bond mimetic in a conformational study of apicidin, a naturally occurring cyclic tetrapeptide inhibitor of histone deacetylases (HDACs).[109] They initially tried to apply the triazole formation as the macrocyclization step in order to access both the 1,4- and 1,5-triazoles (**69** and **70**) via the same linear intermediate **71**, as shown in Scheme 33. A 2:1 mixture of 1,5- and 1,4-triazole was

Scheme 33. Microwave-Assisted Thermal Huisgen Macrocyclization[109]



obtained when using thermal Huisgen cycloaddition conditions, but the 1,5-triazole **70** was isolated in only 8% yield. When RuAAC was instead applied to introduce the 1,5-triazole in the middle of the sequence, using solid-phase methodology, subsequent macrolactamization in solution after cleavage from the resin afforded the macrocycles **72**–**74** in 9–10% total yield (based on resin loading) over 8 steps and with >95% yield in the macrocyclization step (Scheme 34). The macrocyclization in this case is greatly favored by the turn conformation of the linear precursor **75** containing the 1,5-triazole, which brings the ends closer together.

Extensive NMR studies of the macrocycles revealed one single conformation in solution for **69**, **72**, and **73**, but **70** and **74** indicated a population of multiple conformations. The solution conformation of macrocycle **69** corresponded well with all-trans conformations of the peptide backbone in apicidin, while **72** overlapped closely with the less present *c-t-t-t* conformation and

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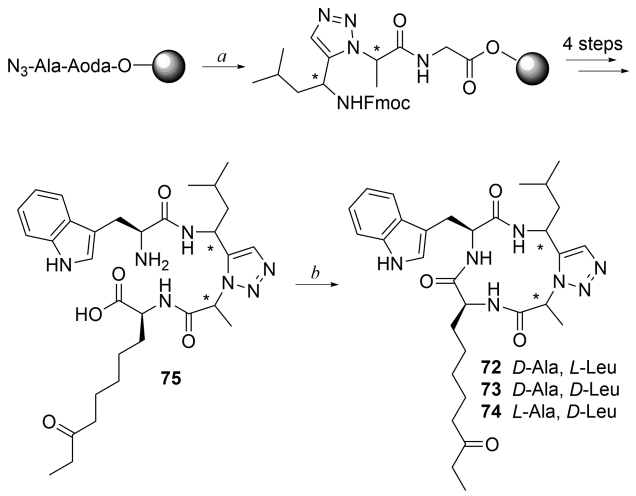
Scheme 34. Synthesis of Macrocycles 72−74 Utilizing the RuAAC Reaction[109]

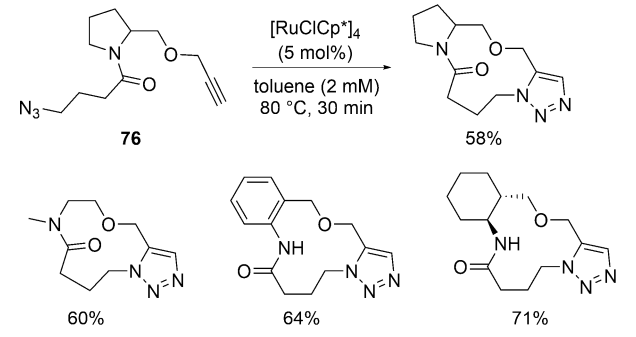


[a]Reaction conditions: Fmoc-L-Leu-CCH or Fmoc-D-Leu-CCH, Cp*RuCl(COD) (20 mol %), toluene, 45 °C, 16 h. [b]HATU, *N*,*N*-diisopropylethylamine (DIPEA), 0.5 mM in DMF, 1.5 h, >95% yield.

73 formed the *c-t-c-t* conformation. The NMR study, together with enzyme activity data, suggests that the less-populated (15%) *c-t-t-t* conformation of apicidin is the more bioactive one.

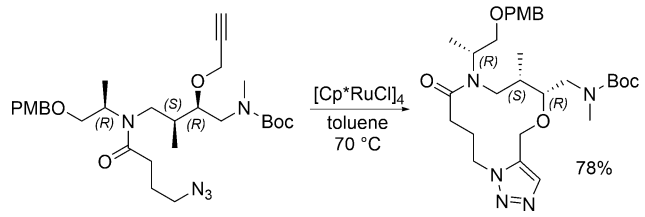
The first report of a successful method for using the RuAAC as the macrocyclization step was published by the Marcaurelle group.[156] They desired a method that could produce nonpeptidic macrocycles, of ring size both *n* and *n*+1, from a single starting material by using different catalysts. After some optimization they found that $[RuClCp^*]_4$ was more advantageous compared to the classic $Cp^*RuCl(PPh_3)_2$ in terms of monomer/dimer ratio. Dimer formation is usually the most common issue in all macrocyclizations in solution. Dilution and increased temperature was also beneficial for the monomer/dimer ratio. The RuAAC conditions were optimized on azido alkyne **76**, and with the optimized conditions in hand, a number of 11-, 12-, and 13-membered macrocycles were synthesized in good yields. Some selected examples are shown in Scheme 35.

Scheme 35. Synthesis of Triazole Macrocycles Using RuAAC as the Macrocyclization Step[156]



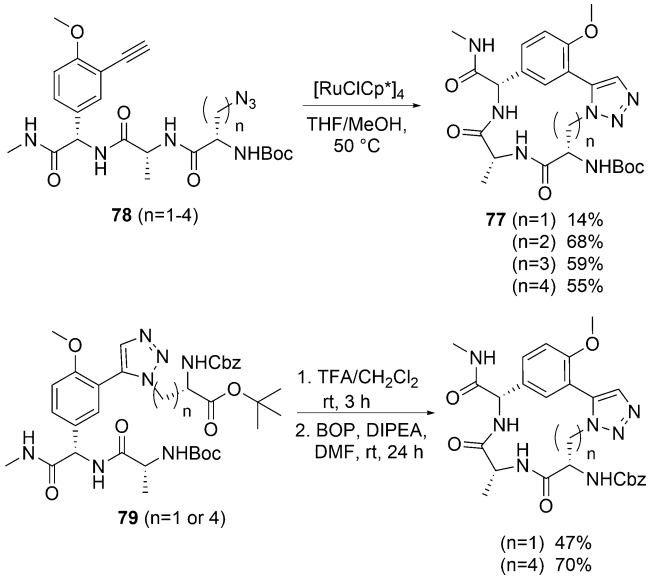
The same group then utilized this method in a large diversity-oriented synthesis (DOS) library in their search for new macrocyclic histone deacetylase inhibitors (HDACs),[157] using a three-phase DOS strategy called build/couple/pair (B/C/P), a method described in more detail in section 5.7.[158] In the pair phase, different macrocyclic structures of a linear intermediate were subjected to different reactions, including RuAAC, to generate a total of 48 macrocyclic scaffolds ranging from 8- to 14-membered ring systems. These 48 scaffolds were then finally further diversified on solid phase by utilizing SynPhase Lantern technology[159] to produce a library of more than 30 000 compounds. The RuAAC macrocyclization reactions were reliable and were routinely performed on 5−10 g scale in 50−80% yield. An example is shown in Scheme 36.

Scheme 36. Macrocyclization by RuAAC Affording 12-Membered Triazole Macrocycles[157]



Zhang et al. studied two different strategies for making triazole macrocycles in their synthesis of macrocyclic vancomycin mimics.[160,161] Macrocyclization by RuAAC was successful but with some difficulty for the smallest ring **77** (*n* = 1), due to the rigidity of the corresponding linear azido alkyne **78** (*n* = 1), giving rise to both dimer and trimer byproducts (Scheme 37).

Scheme 37. Comparison of RuAAC Macrocyclization and Macrolactamization[160]



However, when the 1,5-triazole was introduced in the linear sequence using **79**, and the ring was closed via lactamization instead, the yield of the macrocyclization step was enhanced from 14% to 47% for the smallest ring size. The amount of dimer formation was equal, 28% vs 31%, for the two methods, but the trimer byproduct was not formed during the macrolactamization.

The same group also utilized a RuAAC double-macrocyclization in the synthesis of a 1,5-triazole-bridged vancomycin bicyclic mimic.[161] By treating the linear bisazido alkyne **80** with $[Cp^*RuCl]_4$ in THF/MeOH for 24 h at 50 °C, the bicyclic bistriazole macrocycle **81** in was obtained in 40% yield, which can be considered high for this level of complexity (Scheme 38),

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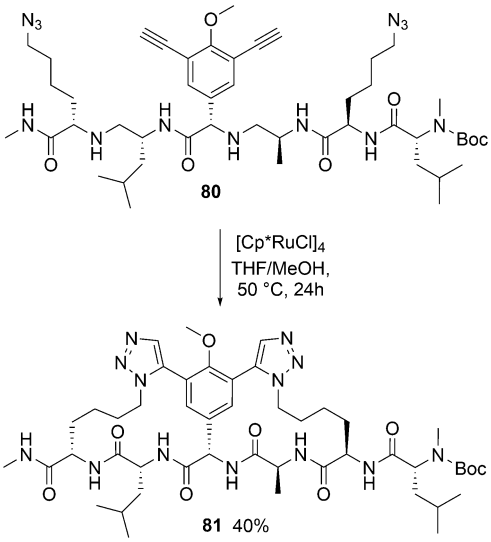
Scheme 38. Double RuAAC Macrocyclization[161]



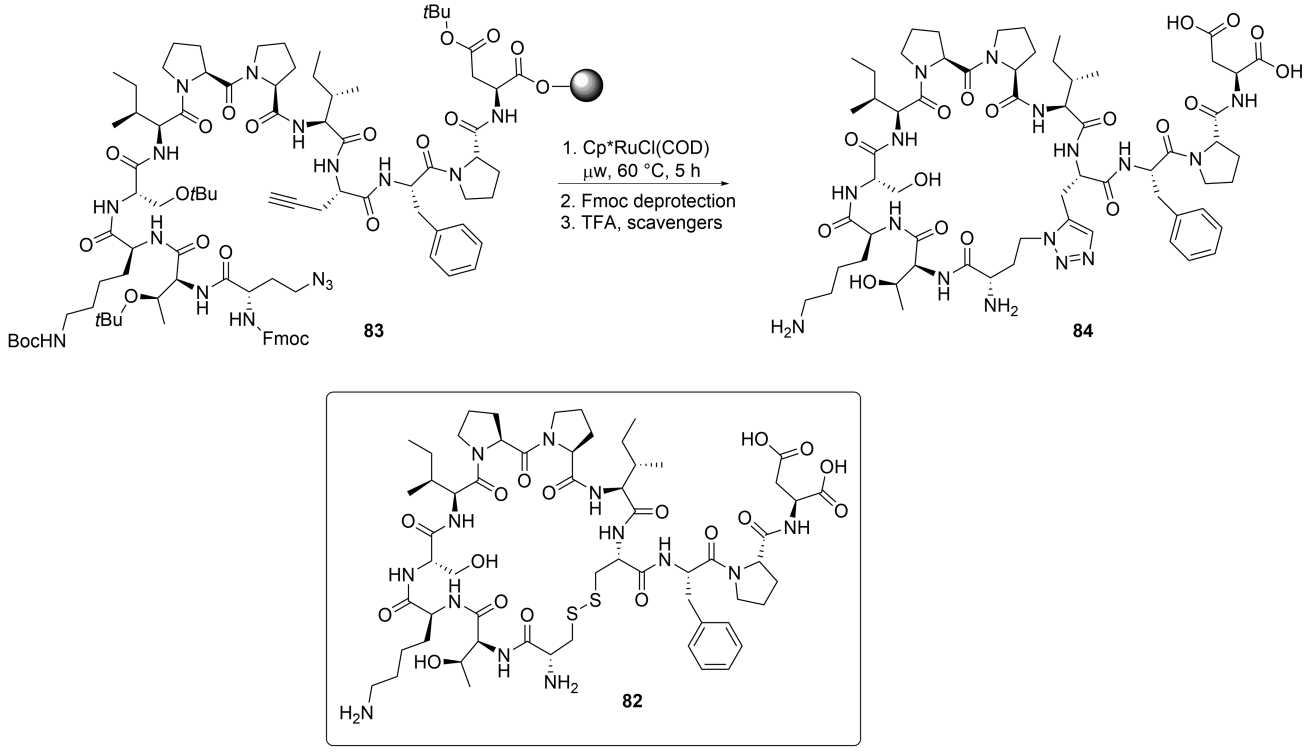
Disulfide bridges are very common and important in oligopeptides and proteins as they contribute to defining tertiary folding and conformational stability of proteins. One special group of naturally occurring peptides are called cysteine knot miniproteins[162] or cyclotides.[163−166] These are cyclic peptides with three cross-linked disulfide bridges. The disulfide bridges provide the cyclotide with extraordinary thermal stability and resistance against protolytic degradation.[167] The in vitro generation of disulfides bridges is usually achieved postsynthetically and is not always straightforward, especially for controlled regiospecific formation of such linkages.

Empting et al. have demonstrated successful mimicking of the disulfide bridge by introducing a 1,5-triazole into an analogue of the sunflower trypsin inhibitor-I (SFTI-1) **82** (Scheme 39).[110] Macrocyclization of the linear azido alkyne **83**, using RuAAC on solid phase, yielded the triazole macrocycle **84** after deprotection and cleavage from the resin. Overlay of energy-minimized models of **84** with a previous solution structure of **82** (PDB code: 1JBN)[123] showed a comparable distance (4.00 vs 4.18 Å) between the two C_α atoms of residue 3 and 11. The inhibition of trypsin-catalyzed proteolysis was also tested, and interestingly no significant drop in activity was seen. This methodology could be useful in the future in controlling folding of peptides where several disulfide formations are possible.

Isidro-Llobet et al. have also utilized the RuAAC reaction as a macrocyclization strategy in a diversity-oriented synthesis of macrocyclic peptidomimetics,[168] applying the three-phase DOS build/couple/pair strategy mentioned earlier.[158] In the pair phase, the RuAAC macrocyclization method developed by the Marcaurelle group[156,157] was employed to cyclize linear compounds **85**−**87** to obtain triazole macrocycles **88**−**90** in good yields and without any epimerization (Scheme 40). The triazole macrocycles were then further diversified by diketopiperazine (DKP) formation using solid-supported *N*-methylmorpholine, acetic acid, and microwave heating.

Krause et al. utilized RuAAC for both macrocyclization and preparation of the linear precursor **91** in their synthesis of the C3-symmetrical tris-1,5-triazole macrocycle **92** (Scheme 41).[169,170] They studied the anion-binding properties of triazole macrocycle **92** by extensive NMR and ITC (isothermal titration calorimetry) experiments and found that **92** binds Cl, Br, I, and sulfate in both protic and aprotic solvents in a 1:1 ratio with high affinity. The synthesis of **92** (Scheme 41) involves three RuAAC reactions and starts with the cycloaddition of freshly prepared

Scheme 39. Solid-Phase RuAAC Synthesis of Macrocycle 84 and Structure of the Sunflower Trypsin Inhibitor-I 82[110]



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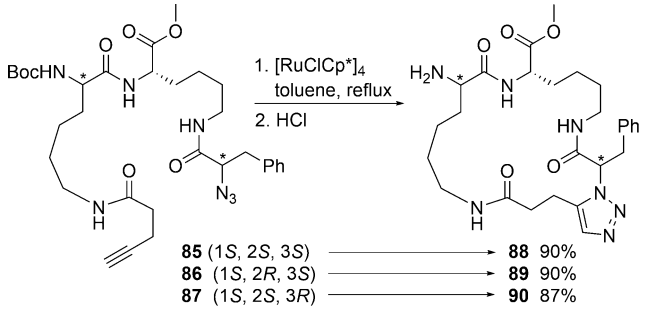
Scheme 40. Synthesis of 21-Membered Triazole Macrocycles by RuAAC Macrocyclization[168]

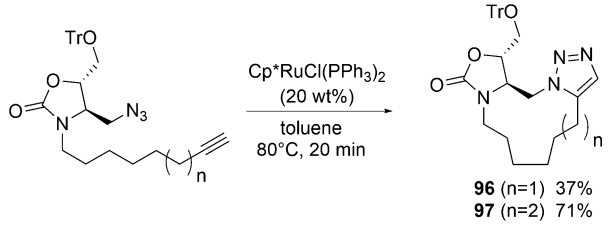


azide **93** to alkyne **94** to form the 1,5-triazole **95** in good yield. Worth mentioning is that azide **93** dimerizes under neat or concentrated solutions upon standing at room temperature, and it is thus crucial to use newly prepared azide **93** to obtain a good yield. The second RuAAC reaction afforded the linear intermediate **91** but required a longer reaction time and benefitted from the addition of triphenylphosphine to keep the catalyst active. Compound **91** was then, after deprotection and azide introduction, macrocyclized to tristriazole macrocycle **92** using $[Cp^*RuCl]_4$ and microwave heating in dilute ~2 mM DMF solution.

Fang et al. used RuAAC for macrocyclization to obtain 11- and 12-membered macrocycles,[171] using previously reported unoptimized conditions[156] but with a slightly higher temperature (Scheme 42). Macrocycles **96** and **97** were obtained in moderate-to-good yield, but it remains uncertain to what degree the yield was reduced by any dimer formation.

To conclude this section on 1,5-triazole-containing macrocycles, one can easily realize the utility of the 1,5-triazole as a building unit due to its natural turn conformation. As discussed in the beginning of this section, the two strategies to introduce the 1,5-triazole either prior to or during macrocyclization are both fruitful, as shown by the many examples discussed. The optimal strategy depends heavily on the nature of the linear precursor for a given macrocycle. In general, introduction of the 1,5-triazole prior to the macrocyclization increases the yield of the macrocyclization step due to its conformational preorganization. However, the use of RuAAC as a macrocyclization reaction can

Scheme 42. RuAAC Macrocyclization Forming 11- and 12-Membered Triazole Derivatives[171]



also be effective, but it is very much dependent on the flexibility of the linear precursor and also the size of the ring to be formed.

5.3. Nucleoside and Nucleotide Analogues

Nucleosides and nucleotides both contain a nucleobase (also called nitrogenous base) connected to a ribose or deoxyribose unit, and in the case of nucleotides also linked to one or more phosphate groups (Figure 18), providing many potential sites for

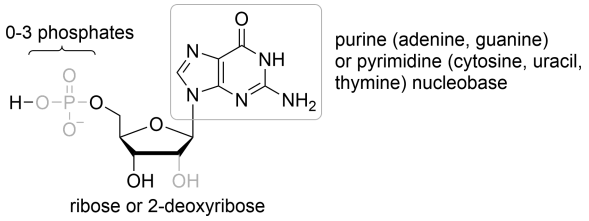
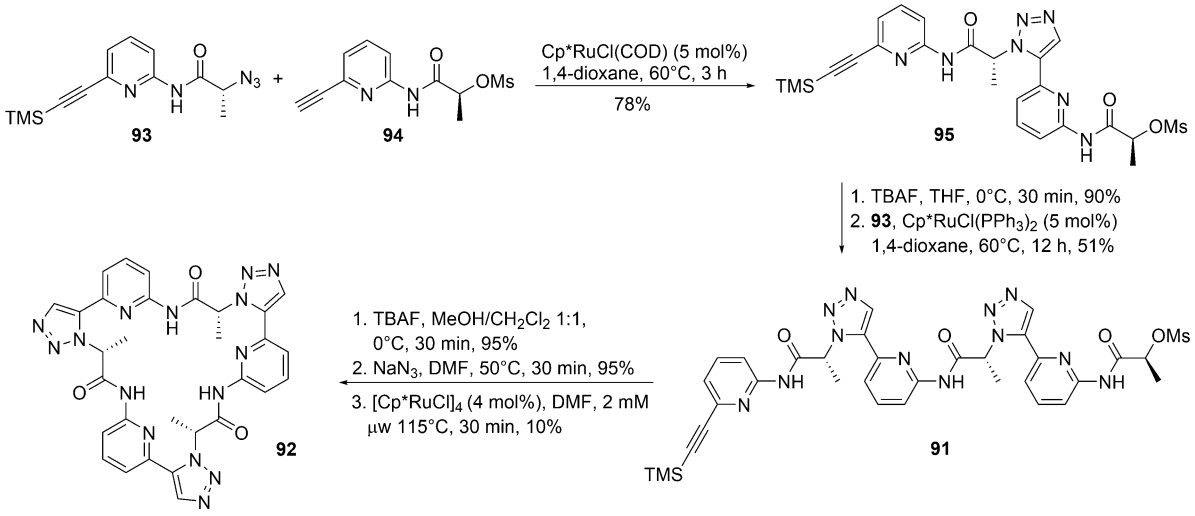


Figure 18. Nucleosides and nucleotides with many potential sites for derivatization.

derivatization. Synthetic compounds of this type are of interest, for instance, in the development of antivirals and anticancer agents.[172−174] A triazole unit can be employed to either derivatize or entirely replace the nucleobase moiety, or it may be appended to the base or to the sugar unit, to afford a nucleoside analogue. Subsequent phosphorylation also provides access to nucleotides. As for many other areas of drug discovery, reported applications of triazole incorporation mainly employ CuAAC,[175] while RuAAC has been less investigated in this context.

5.3.1. Replacing or Derivatizing the Nucleobase via RuAAC. Ribavirin (Scheme 43) is an antiviral agent, mainly used

Scheme 41. Synthesis of an Anion-Binding Tristriazole Macrocycle via Three Sequential RuAAC Reactions[169]



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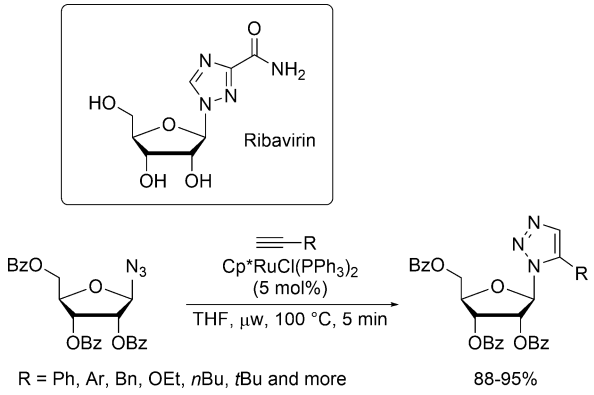
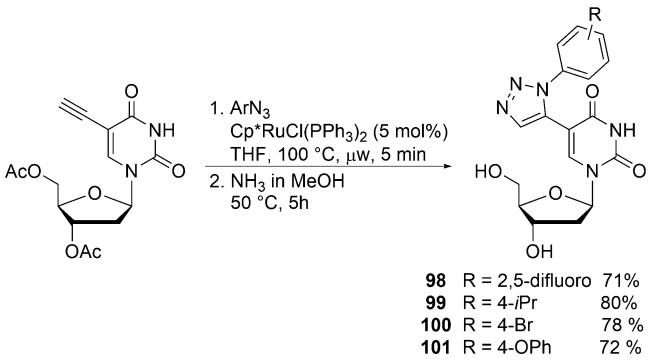
in the treatment of hepatitis, but also used to combat the respiratory syncytial virus (RSV).[176] Agrofoglio and co-workers prepared a set of ribavirin-like compounds by replacing the 1,3-disubstituted 1,2,4-triazole ring in ribavirin with a 1,4- or 1,5-disubstituted 1,2,3-triazole.[71] A benzoyl-protected β-azido ribose was subjected to RuAAC conditions using Cp*RuCl$(PPh_3)_2$ as the catalyst in THF (Scheme 43). Microwave heating was found to be more efficient than thermal heating in this case, and the desired derivatives were obtained in good-to-excellent yields using a reaction time of only 5 min. Minor amounts of the 1,4-disubstituted isomer accompanied the formation of the desired 1,5-isomer, but this byproduct could be removed by chromatography. Unprotected azido ribose could also be applied in the reaction with excellent results. The prepared compounds were not found to display any activity toward the hepatitis C virus (HCV) upon screening, however.[176]

Scheme 43. Ribavirin Analogues with the Nucleobase Replaced by a Triazole[71]



The same group prepared nucleoside derivatives with a triazole appended to the C5 position of a 2′-deoxyuridine structure using the microwave conditions for RuAAC described earlier.[177] Compounds **98**−**101** were obtained in good yields (Scheme 44)

Scheme 44. Triazole Derivatives of 2′-Deoxyuridine[177]



and could be deacetylated using ammonia in methanol. While the corresponding 1,4-disubstituted derivatives, prepared using CuAAC, displayed some antiviral and cytostatic activity, the 1,5-isomers were inactive. Similar triazoles were also reported by Nielsen and co-workers for use in DNA−RNA duplexes.[178]

5.3.2. Derivatization of the Ribose or Deoxyribose Unit via RuAAC. The attachment of a triazole to the sugar moiety instead of the nucleobase in the nucleoside structure has been reported by several groups, and the prepared structures are summarized in Figure 19.[27,93,179−182]

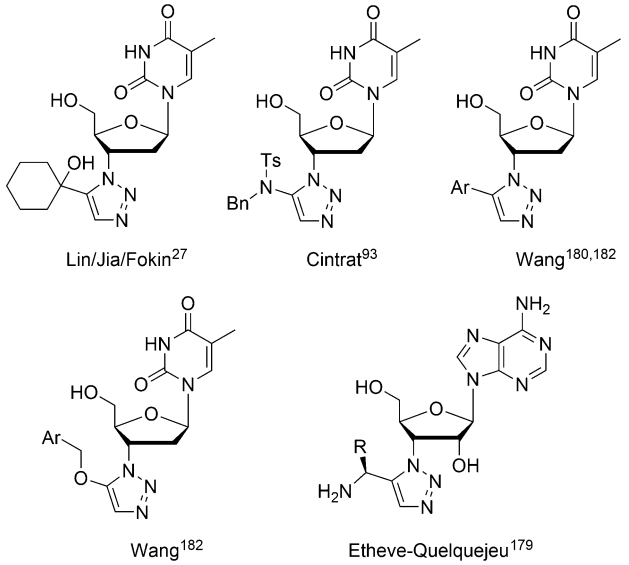


Figure 19. Derivatization of the nucleoside ribose or deoxyribose via RuAAC.

The most extensive study in this area has been reported by Wang and co-workers, with the purpose of investigating the antiviral properties of nucleoside analogues.[180−182] 3′-Azidothymidine (AZT, Figure 20) was one of the earliest drugs employed

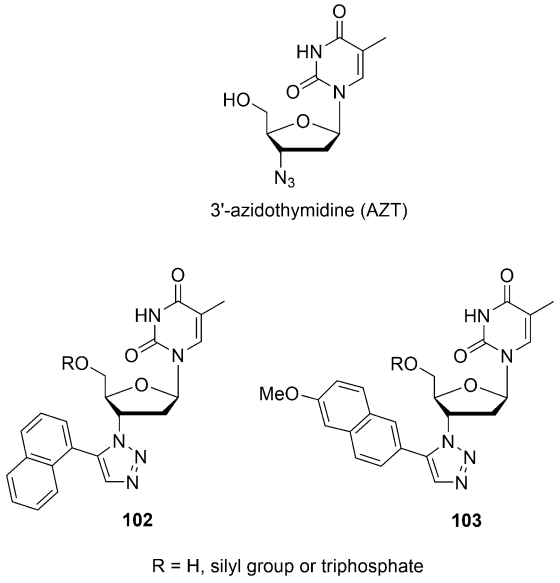


Figure 20. Triazole analogues of AZT.[180]

toward the human immunodeficiency virus (HIV),[183] but treatment with this drug can be accompanied by undesired side effects. As the AZT structure contains an azido functionality already at the outset, a natural strategy for derivatization would be the formation of triazoles via CuAAC or RuAAC. Previous attempts to investigate this pathway toward analogues in general did not afford compounds with antiviral activity, but the explored triazole side chains were in most cases aliphatic. However, aryl-substituted triazole-AZT derivatives were reported to show potent thymidine kinase 2 (TK-2) inhibition.[184] Inspired by this,

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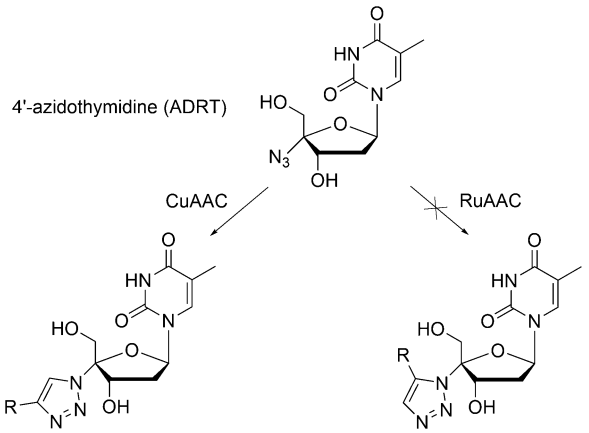
Wang and colleagues prepared a number of both 1,4- and 1,5-disubstituted triazole-AZT derivatives containing aromatic substituents (see Figure 20 for two RuAAC derivatives).[180] Standard conditions ($Cp^*RuCl(PPh_3)_2$, THF, 60 °C) were employed for the RuAAC reaction, but extended reaction times (1−2 days) were required to obtain the products in sufficient amounts. These compounds were then screened toward HIV-1, employing a cytopathic effect (CPE)-based assay. Many of the prepared compounds displayed antiviral activity. Especially 1,5-substituted triazole compounds with bulky substituents, such as the 1-naphthyl derivative **102** (Figure 20), showed promising properties. Triphosphates of selected compounds were also prepared. Interestingly, silylation of the free hydroxyl group in derivatives such as **102** and **103** with *tert*-butyldimethylsilyl chloride afforded compounds displaying antiviral activity toward the Western Nile and Dengue viruses.[182]

Having successfully derivatized the 3′-azidothymidine structure, Wang and colleagues then turned to the corresponding 4′-azidothymidine (ADRT, Scheme 45), but then ran into

Scheme 45. RuAAC Inhibited by Steric Hindrance[181]



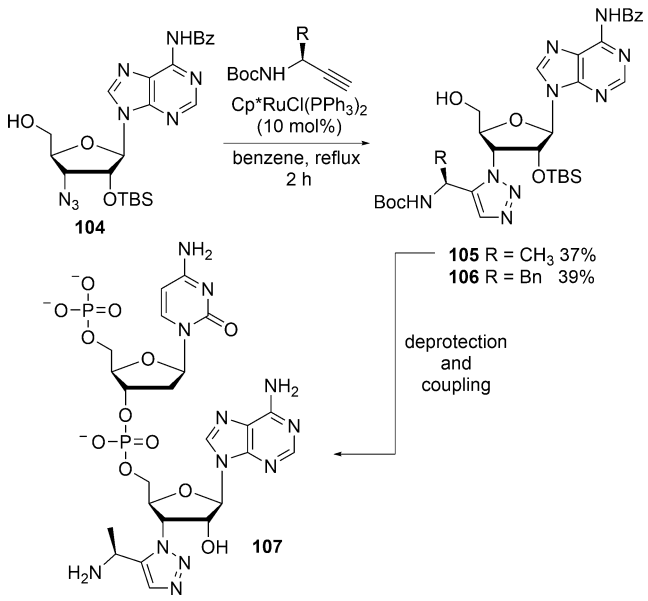
problems.[181] While ADRT could be converted into various compounds using CuAAC, albeit involving long reaction times and heating to 60 °C, the corresponding RuAAC reaction did not proceed at all despite extensive efforts to vary the reaction conditions. The azide in ADRT is tertiary as compared to the secondary azide in 3′-azidothymidine (Figure 18), and steric hindrance is believed to be the cause of this low reactivity.

Etheve-Quelquejeu and co-workers focused on the cycloaddition of 3′-azidoadenosine with chiral alkynes to form analogues of aminoacyl-tRNA.[179] Benzoyl-protected 3′-azidoadenosine **104** (Scheme 46) was reacted with two different chiral propargylic amine derivatives to form triazoles **105** and **106** in 37% and 39% yields, respectively, using standard conditions for the RuAAC reaction. Compound **105** was then coupled with commercially available deoxycytidine phosphoramidite to form dinucleotide **107** after deprotection. Ligation of **107** to an RNA microhelix completed the synthesis to form the desired aminoacyl-tRNA analogue.

5.4. Glycomimetics

Carbohydrates are important structural starting motifs in drug design as they are involved in inter- and intracellular communication in many organisms.[185] Moreover, carbohydrate analogues and mimetics are commonly exploited as transition-state analogues for enzyme inhibition and as tools for understanding enzyme-inhibition mechanisms.[186] The use of

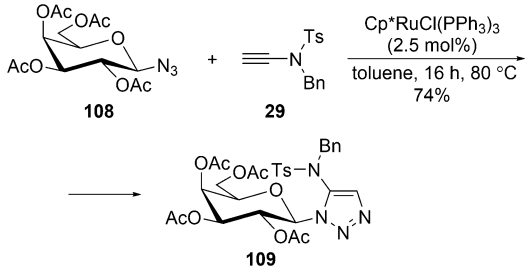
Scheme 46. Synthesis of Aminoacyl-tRNA Analogues Using RuAAC[179]



CuAAC in carbohydrate chemistry has been recently reviewed.[187] The RuAAC reaction has been used as a method to couple carbohydrate moieties to each other as well as to connect saccharides to aromatics or other functionalized units, forming new carbohydrate derivatives. Several of the resulting compounds possess properties that make them promising as future therapeutic lead structures.

The first application utilizing the RuAAC reaction in a carbohydrate context was reported by Cintrat and co-workers,[93] as part of their investigation of ynamides as the alkyne component in the cycloadditions (see section 4.4.3). Included among the azide substrates was acetylated β-D-galactopyranosyl azide **108** (Scheme 47), which reacted with ynamide **29** (Scheme 15) under ruthenium catalysis to afford the 1,5-substituted triazole **109** in good yield.

Scheme 47. Reaction of an Ynamide with a Glycosyl Azide[93]



The RuAAC reaction also can be used to couple two carbohydrate units to each other. The Crich group was the first to exploit the triazole motif as a linker in this manner, to provide a compound resembling a trisaccharide.[188] $[Cp^*RuCl]_4$ was employed as the catalyst in DMF under microwave irradiation at 110 °C to afford an azidomethyl glycoconjugate linked by a 1,5-disubstituted triazole in 75% yield (Scheme 48). The corresponding 1,4-substituted isomer was also synthesized using CuAAC.

A similar strategy has been applied by Opatz and co-workers, who in their search for metabolically stable glycomimetics

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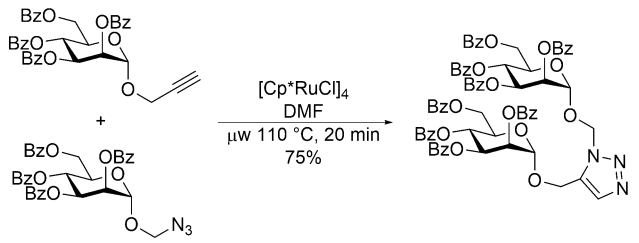
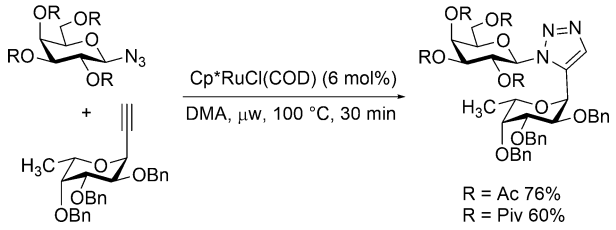
Scheme 48. Connecting Carbohydrates via a Triazole Linker Using RuAAC[188]



demonstrated that pivaloylated and acetylated galactosylazides can be coupled with fucosylacetylene selectively, forming the corresponding 1,5-diglycosylated 1,2,3-triazoles (Scheme 49).[189]

Scheme 49. Coupling of a Galactosylazide with a Fucosylacetylene[189]



Cp*RuCl(COD) was employed as the catalyst under microwave irradiation at 100 °C in DMA. Yields were 76% for the acetylated and 60% for the pivaloylated galactosylazides, respectively. The corresponding 1,4-isomers were obtained using the CuAAC reaction.

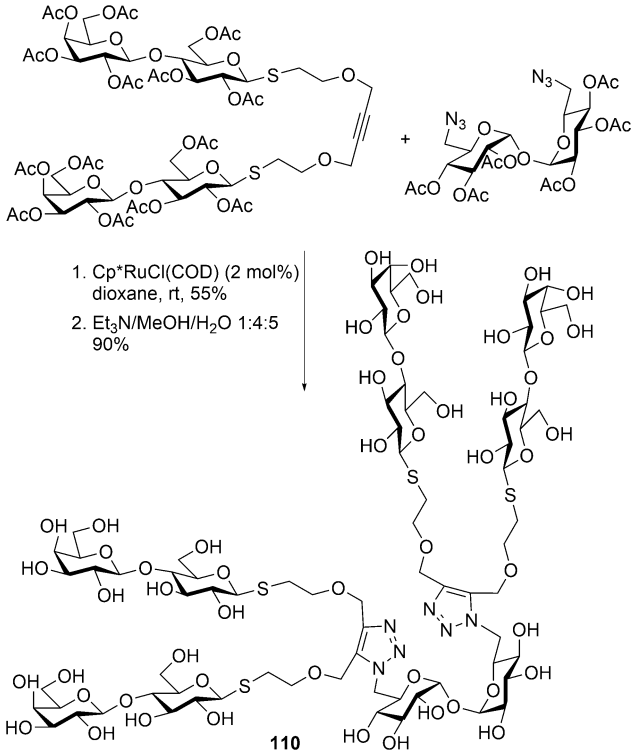
Multivalent glycoclusters can be synthesized by employing the RuAAC reaction as a key step. Uhrig, Kovensky, and co-workers have proved that a variety of multivalent thiogalactosides and thiolactosides can be formed using various azidosugars and carbohydrate-containing alkyne linkers.[190] With the aid of Cp*RuCl(COD) as the catalyst at room temperature in dioxane, a number of different glycoclusters, such as tetravalent compound **110** and even up to octavalent derivatives, were synthesized and evaluated as ligands for peanut lectin (Scheme 50). The yields varied depending on the substrate, stretching from 35% up to 82%.

Furthermore, Supuran, Poulsen, and co-workers have demonstrated the formation of 1-(β-D-glycosyl)-5-benzenesulfonamide-1,2,3-triazole compounds with carbonic anhydrase inhibitory properties.[191] Acetylated sugar azides such as compound **111** were allowed to react with *p*-ethynylbenzenesulfonamide using Cp*RuCl(COD) as the catalyst (Scheme 51). Five different triazoles were prepared, and alkaline hydrolysis of the acetal groups afforded the deprotected structures.

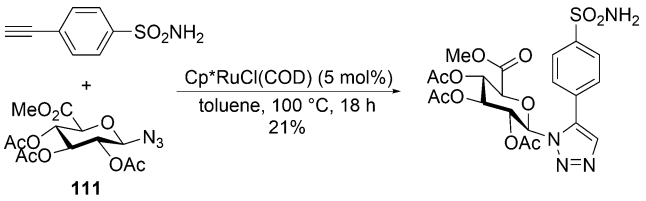
The azide can be located in alternate positions of the saccharide ring. Besra and co-workers prepared triazole derivatives from 6″-azido-6″-deoxy-alpha-galactosyl ceramide (**112**) and phenyl acetylenes in 72−78% yield, employing 5 mol % Cp*RuCl(PPh$_3$)$_2$ as the catalyst (Scheme 52).[192] Both a terminal and a disubstituted internal alkyne were employed, with slightly lower yields for the product from the internal alkyne substrate.

2,3,6-Trideoxysugar triazole hybrids are yet another class of carbohydrate-like compounds that have been examined as potential drugs, more specifically as new broad-spectrum antimicrobial agents. The Shaw group synthesized a library of

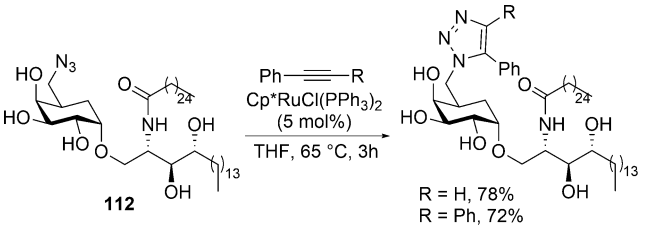
Scheme 50. Formation of Tetravalent Glycocluster 110[190]



Scheme 51. Reaction of a Sugar Azide 111 with *p*-Ethynylbenzenesulfonamide[191]



Scheme 52. Synthesis of Triazole-Containing α-Galactosyl Ceramides[192]



sugar−1,4-triazole conjugates for this purpose[193] and included one example of a 1,5-triazole (Figure 21), using Cp*RuCl-

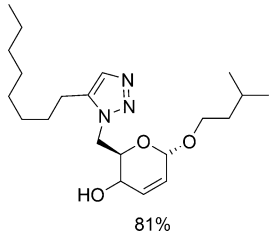


Figure 21. Synthesis of a sugar−1,4-triazole conjugate.[193]

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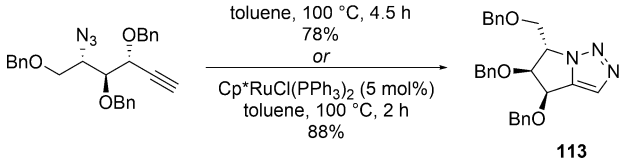
$(PPh_3)_2$ as the catalyst. The same group also synthesized a class of bicyclic iminosugar hybrids, exploiting an intramolecular version of the RuAAC reaction as the key reaction step.[194] Both thermal and ruthenium-catalyzed conditions were examined, where the bicyclic triazole product **113** was produced in both higher yield and shorter reaction time using the Ru-catalyzed reaction (Scheme 53).

Scheme 53. Intramolecular RuAAC Reaction Yielding Bicyclic Iminosugar Hybrids[194]



5.5. Natural Product Analogues

Various natural products have been employed as core structures for triazole-containing analogues, generally with the purpose of evaluating the biological properties of these new target compounds for comparison with the original molecule. Several groups have studied potentially cytotoxic derivatives, based on lignin,[195] alkaloid[196] and natural phenolic[197,198] scaffolds. Tron and co-workers envisaged that the same two building blocks, i.e., piperonyl alcohol and 3,4,5-trimethoxybenzyl alcohol, could be employed to prepare triazole derivatives of the cytotoxic lignans steganacin and podophyllotoxin.[195] RuAAC involving **114** and **115**, using $Cp^*RuCl(PPh_3)_2$ as the catalyst, afforded a precursor that could be oxidatively coupled to form derivative **116** (Figure 22). The same strategy using **117** and **118** instead provided

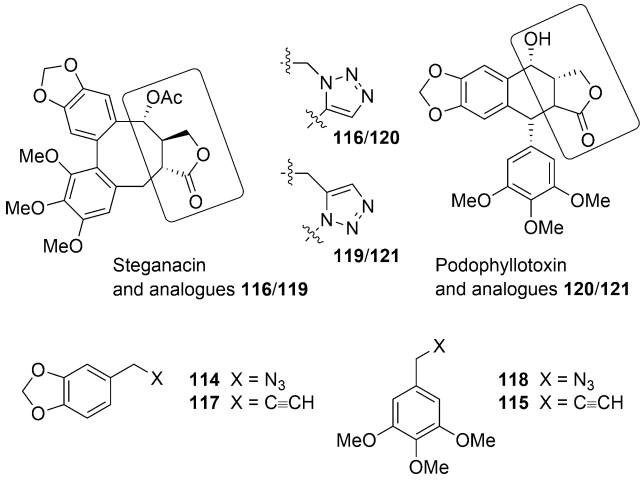
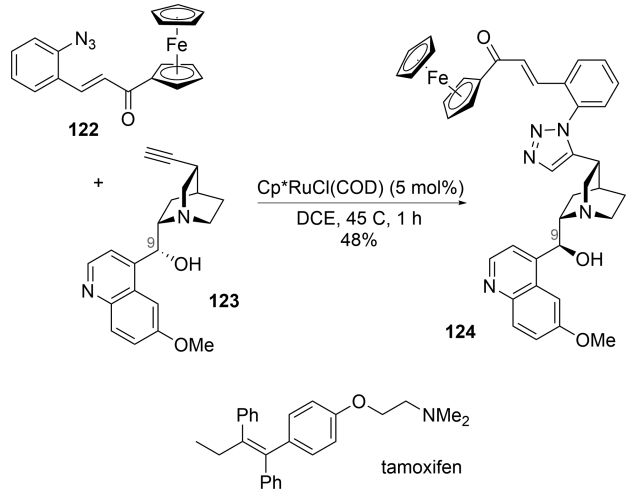


Figure 22. Triazole analogues of steganacin and podophyllotoxin.[195]

analogue **119** in a good overall yield. This methodology was not directly applicable toward the podophyllotoxin analogues, however. A modified reaction sequence involving a Friedel–Crafts reaction to effect the final ring closure allowed the formation of **120**, albeit in a rather low yield, and the remaining compound **121** could not be prepared using either of these strategies. Compounds **116**, **119**, and **120** were all found to display some degree of cytotoxic activity upon screening.

Ferrocene-substituted chalcones have been connected to cinchona alkaloids using both CuAAC and RuAAC as reported by Csámpai and co-workers.[196] The ruthenium-catalyzed cyclization of **122** and **123**, using Cp*RuCl(COD) as the catalyst, was accompanied by Ru-catalyzed epimerization at the C9 position, affording **124** in 48% yield, together with a byproduct where the azide had been reduced to an amino group (Scheme 54). Both **124** and the corresponding 1,4-isomer

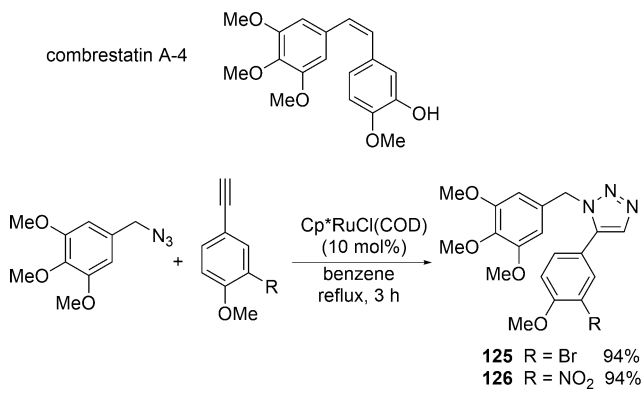
Scheme 54. Cytostatic Ferrocene–Triazole–Cinchona Alkaloid Hybrids[196]



displayed an improved in vivo cytostatic activity toward HepC2 hepatoma and HT-29 colorectal adenocarcinoma human tumor cell lines in comparison to the reference compound Tamoxifen, with the 1,5-isomer **124** being the more active of the two.

Combrestatin A-4 is a cytotoxic natural product isolated from the bark of the tree *Combretum caffrum*, found in South Africa.[199] Hansen and co-workers had earlier prepared analogues of combrestatin, where the cis double bond, necessary for activity, had been replaced by a triazole ring in order to lock the two aromatic rings into a cis relationship. Both 1,4- and 1,5-disubstituted triazoles were included in this previous study,[197] but the 1,5-compounds were prepared using magnesium acetylides. In a more recent study, seeking to investigate the effect of introducing a methylene group between the triazole nitrogen and the trimethoxy-substituted aromatic ring, compounds **125** and **126** were prepared in excellent yields using Cp*RuCl(COD) in refluxing benzene (Scheme 55).[198] Although the 1,5-disubstituted triazole derivatives were found to be more cytotoxic than their 1,4-counterparts, the

Scheme 55. Triazole Derivatives of Combrestatin A-4[198]



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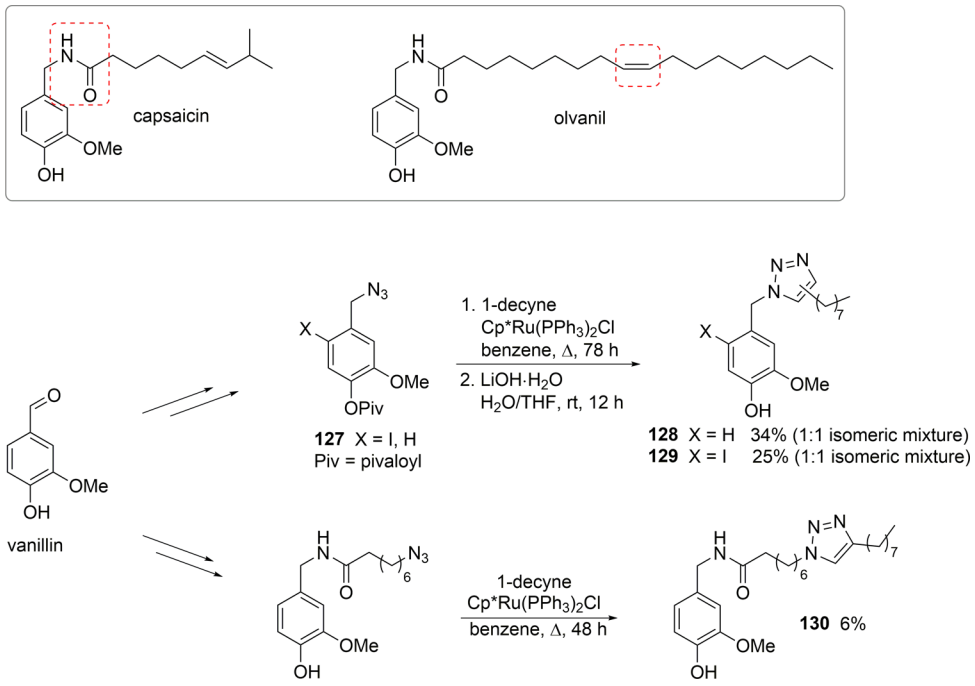
Scheme 56. Derivatives of Capsaicin and Olvanil[200]



introduction of the extra methylene carbon was not found to be beneficial for the biological activity.

Appendino, Di Marzo, and co-workers employed vanillin as a core unit in the preparation of synthetic capsaicinoids, where the amide unit of capsaicin (Scheme 56) was replaced by a triazole moiety to improve stability toward hydrolysis.[200] Vanillin was converted into protected vanillazides **127** and subsequently reacted with 1-decyne under Cu(I) or Ru(II) catalysis. While the copper-catalyzed conversion proceeded with excellent regioselectivity for the 1,4-isomer in both cases, the corresponding ruthenium-catalyzed reaction somewhat surprisingly afforded mixtures of the 1,4- and 1,5-disubstituted isomers of **128** and **129**. The isomers could be separated by preparative high-performance liquid chromatography (HPLC), however, and the activity of the prepared compounds toward vanilloid and cannabinoid receptors was compared to that of capsaicin itself as well as other synthetic derivatives.

The fatty acid side chain of capsaicinoids may contain double bonds, and the presence of at least one such olefin unit in these compounds is believed to be important both for passive transport across cell membranes and for interaction with the vanilloid receptor. Triazoles can act as mimics for the geometrical constraints imposed by double bonds (see section 5.1.1); to investigate this feature, triazole analogues of olvanil, where the double bond was replaced by a triazole, were prepared via CuAAC and RuAAC (Scheme 56, only RuAAC reaction shown), and their vanilloid activity was evaluated. Both the 1,4- and 1,5-isomers were found to be less active than olvanil itself. However, the 1,5-isomer **130** (Scheme 56), which more closely mimics the cis isomer of olvanil, was found to be more active than the corresponding 1,4-isomer, and this is in line with the activity of the two double-bond isomers of olvanil, where the cis isomer is more active than the trans isomer.

Analogues of naamine A, a natural product isolated from calcareous sponges, were prepared by Blache and co-workers, with the purpose of evaluating the ability of these compounds to control the formation of bacterial biofilms.[201] A set of compounds with variation of both the substitution pattern of the aromatic rings as well as the chain length between the triazole and the substituents were prepared from the corresponding azides and alkynes via RuAAC, using $Cp^*RuCl(PPh_3)_2$ as the catalyst. Compound **131** (Figure 23) showed the most interesting antibiofilm activity, while the hydroxylated analogues were found to be inactive.

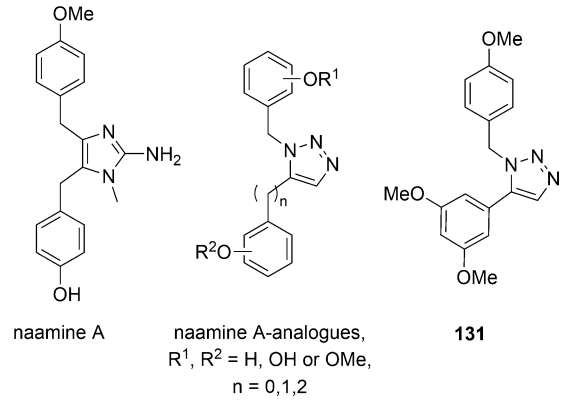


Figure 23. Analogues of naamine A for evaluation of their biofilm inhibitory activity.[201]

1,5-Disubstituted triazole derivatives of the triterpenoid oleanoilic acid have been prepared by Ben Jannet and co-workers using $Cp^*RuCl(PPh_3)_2$ as the catalyst under microwave conditions.[202] The anticancer and anti-inflammatory properties of the compounds were evaluated, and one of the prepared 1,5-isomers was found to show anticancer activity against murine breast and human colon cancer cells.

5.6. Target-Oriented Medicinal Chemistry

Over the last 10 years, the utilization of the RuAAC reaction in drug discovery has been noted as a growing trend in the literature. A diverse set of 1,5-triazole products can be found in

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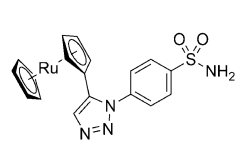
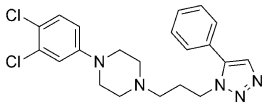
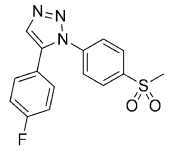
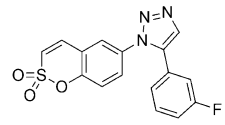
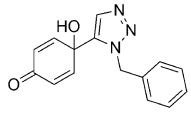
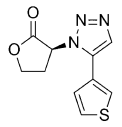

Salmon et al.[191]
CA I, II, IX inhibitor

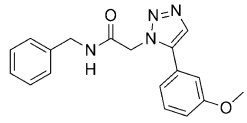

Kwak et al.[219]
D_4 inhibitor

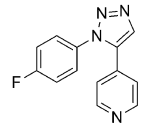

Wuest et al.[204]
COX-1,2 inhibitor

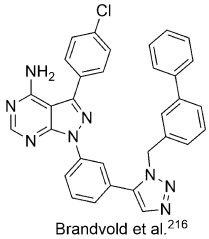

Grandane et al.[209]
hCA IX, XII inhibitor

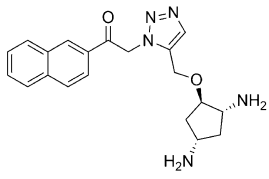

McCarroll et al.[224]
anticancer activity

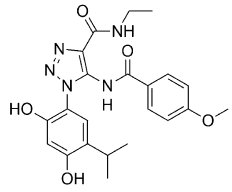

Hansen et al.[229]

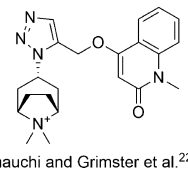

de Andrade et al.[70]
trypanocidal activity

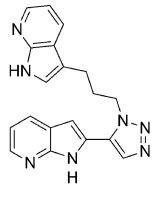

Irie et al.[214]
FLT3 inhibitor

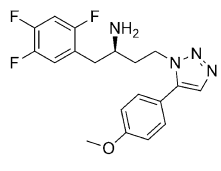

Brandvold et al.[216]
c-Src inhibitor

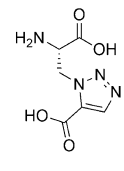

Moumné et al.[223]
$tRNA^{Lys}_3$ ligand

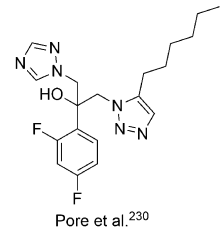

Ferrini et al.[95]
HSP90 ligand

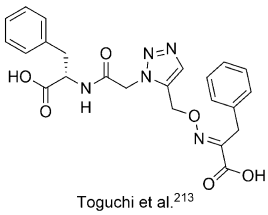

Yamauchi and Grimster et al.[221-222]
α7 nAChR agonist
5-HT_{3A} antagonist

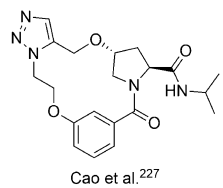

Baltus et al.[217]
CDK2 inhibitor

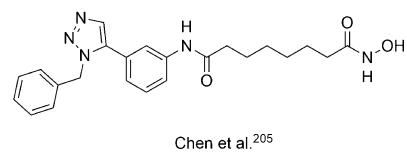

Zhu et al.[212]
DPP4 inhibitor

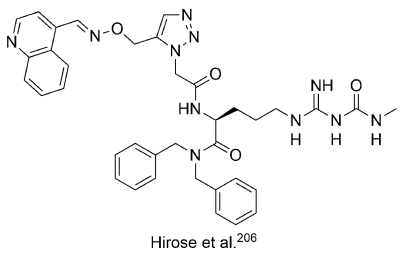

Stanley et al.[220]
weak AMPA ligand

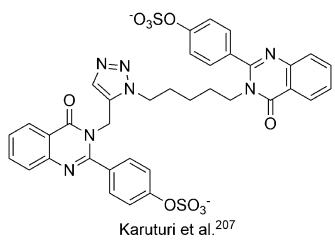

Pore et al.[230]
antifungal activity against *Candida albicans*

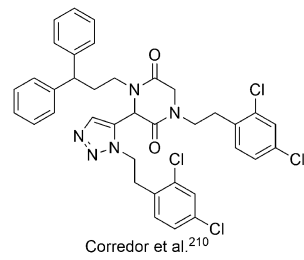

Toguchi et al.[213]
hDAO inhibitor

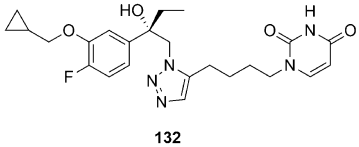

Cao et al.[227]
antiproliferative effect of A549

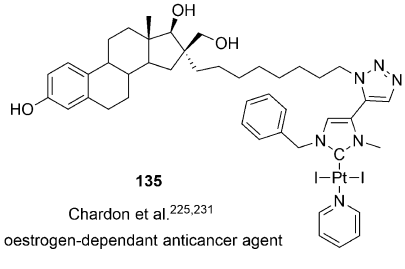

Chen et al.[205]
HDAC pan inhibitor


Hirose et al.[206]
*Sm*ChiA, B inhibitor


Karuturi et al.[207]
FXIa inhibitor


Corredor et al.[210]
inhibitor of aptosome formation


132
Miyakoshi et al.[208]
dUTPase inhibitor


135
Chardon et al.[225,231]
oestrogen-dependant anticancer agent

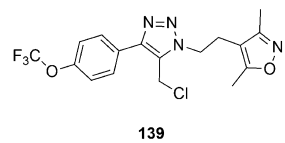

139
Wang et al.[226]
covalent MGMT inhibitor

Figure 24. Selected examples of RuAAC-derived inhibitors and ligands.

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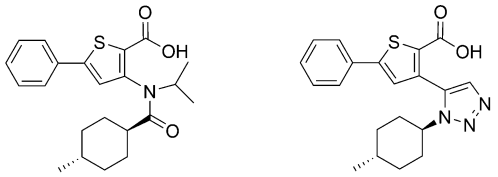
these reports, which cover a wide range of targets and target classes including various enzyme inhibitors,[203−213] kinases,[214−217] proteases,[110,112] antivirals[218] (see also section 5.3), G-protein coupled receptors (GPCRs),[219] ion channels,[220−222] heat shock proteins,[95] and tRNA ligands.[223] 1,5-Triazole derivatives have shown activity against numerous cancer cell lines,[205,215,224−227] as well as against the parasites *Trypanosoma cruzi*[70,228] and *Plasmodium falciparum*.[205] They have also been employed in the search for new antimicrobiotics[229] and antifungal agents.[230] Some selected examples are shown in Figure 24 to demonstrate the broad diversity of 1,5-triazoles in target-oriented medicinal chemistry. Many of these 1,5-triazoles have been made without any rational design but rather to obtain structural diversity or by scaffold hopping. However, some examples have been made with more design in mind, as exemplified by Miyakoshi et al., who applied 1,5-triazole **132** as a mimic of a locked cis-conformation of an amide bond in an early deoxyuridine−triphosphatase (dUTPase) inhibitor hit (Figure 24).[208] Further optimization led to a potent dUTPase inhibitor. Interestingly, in vivo experiments of this triazole together with 5-fluorouracil (5-FU), showed significant enhancement of the antitumor activity of 5-FU against a breast cancer model (MX-1 xenograft) in mice. Yang et al. investigated 1,5-triazoles as replacements for the bioactive *cis*-amide bond of the HCV NS5B polymerase inhibitor **133** (Figure 25).[211] Overlay of

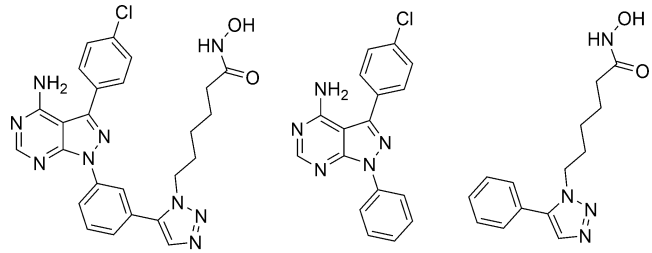


133 IC_{50}, NS5B: 0.028 μM

134 IC_{50}, NS5B: 0.10 μM

Figure 25. 1,5-Triazole as *cis*-amide bond mimic in HCV NS5B inhibitors.[226]

the relevant lower-energy conformation of triazole **134** with an X-ray for the bound structure of **133** displayed potential for a good replacement, although a 3−4-fold drop in inhibition against HCV NS5B was seen. Linking different binders together into conjugates with dual or polypharmacological properties is another emerging area of interest for the pharmaceutical industry, especially in targeting strategies for drug delivery. Two exciting examples using RuAAC as a linkage strategy have been reported. In the first example by Chardon et al.,[225,231] some inspiring results were obtained when the RuAAC reaction was employed to link an ER ligand with a cytotoxic Pt^{II} complex for potential targeting of hormone-dependent diseases (e.g., breast, colon, and ovarian cancers). A 1,5-triazole (**135**, Figure 24) was obtained in 41% yield using 8 mol % $Cp^*RuCl(PPh_3)_2$ in THF at 70 °C overnight. A CuAAC reaction of similar precursors failed to deliver the 1,4-triazole product, most likely because dihalocomplexes of palladium (and platinum) are known to react with terminal alkynes in the presence of a copper(I) catalyst and amine base as a method for preparing acetylide complexes with Sonogashira-type reactivity.[232,233] A 1,5-triazole displayed in vitro cytotoxic activity against several cancer cell lines; however, its selectivity toward positive estrogen receptor cancer cells has not yet been evaluated in vivo. The second example of a 1,5-triazole-linked dual inhibitor is triazole **136** reported by Ko et al. (Figure 26).[215] In this case, the selective c-Src kinase kinase (a



136 K_i, c-Src: 0.138 μM; K_i, HDAC: 0.00026 μM

137 K_i, c-Src: 0.605 μM; K_i, HDAC: >12.5 μM

138 K_i, c-Src: >12.5 μM; K_i, HDAC: 0.045 μM

Figure 26. RuAAC-derived chimeric c-Src/HDAC inhibitor **136**.[215]

key signaling kinase in cancer) inhibitor **137**, reported by Brandvold et al.,[216] was combined with the histone deacetylase (HDAC) inhibitor **138** to afford the chimeric Src/HDAC inhibitor **136**, which is the first-in-class dual c-Src/HDAC inhibitor. Interestingly, both the c-Src and HDAC binding affinities of **136** increased compared to each corresponding smaller inhibitor. Chimera **136** also showed similar or better growth inhibition of several cancer cell lines in the National Cancer Institute's panel screen (NCI-60 panel) compared to vorinostat and dasatinib.[215] Wang et al. has recently published the use of chloromethyl triazoles (CMTs) as a new warhead for covalent inhibitor.[226] A range of CMTs were synthesized using RuAAC, and their activity against O^6-alkylguanine DNA methyltransferase (MGMT) was determined, with **139** (Figure 24) being identified as a potent and selective covalent inhibitor of MGMT. Labeling experiments of the C145A MGMT mutant and wild-type (WT) protein with a probe CMT also showed that these compounds bind exclusively to the active-site cysteine 145.

5.7. Diversity-Oriented Medicinal Chemistry

CuAAC and RuAAC provide convenient methods for elaborating a central molecular scaffold to increase chemical complexity, as use of either an azide or an alkyne as the point of derivatization, in combination with the possibility to vary the metal catalyst, can provide access to four different types of 1,2,3-triazole units appended onto the same scaffold.

The build/couple/pair (B/C/P) strategy,[158] already mentioned in section 5.2, involves the synthesis of molecular scaffolds (build phase), subsequent coupling of different combinations of these scaffolds using the same coupling reaction (couple phase), followed by the pair phase that instead employs different reactions that will define the final structures of the molecules prepared. Spring and co-workers have taken this method one step further in the formation of DOS-derived macrocycles, by employing different reactions in the couple phase, thus allowing for a higher degree of diversification when combining two scaffolds.[234] Macrocycles of a nonpeptidic nature are often difficult to prepare and are thus not well represented in compound collections employed for pharmaceutical-screening purposes. Azido building blocks, of different geometries and containing a fluorous tag to facilitate purification,[235] were constructed and then coupled, not using cycloadditions, but via aza-Wittig-type reactions. The RuAAC and CuAAC reactions were instead reserved for the final macrocyclization step, constituting the pair phase. A total of 73 macrocycles were prepared, and two examples, formed via RuAAC at high dilution in the final step, can be seen in Figure 27. In a later paper,[236] RuAAC was applied in an example of multidimensional DOS, where a functional group introduced during the build/couple/

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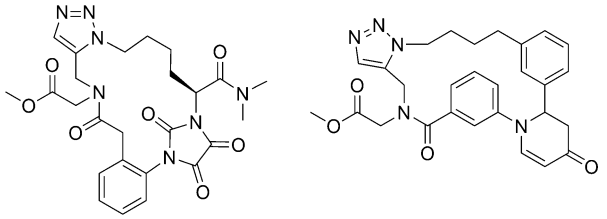


Figure 27. Macrocycles formed via RuAAC using $[Cp^*RuCl]_4$ as the catalyst.[234]

pair phases is reacted further, thus providing an additional possibility for diversification (i.e., build/couple/pair/modify).

Looking more at classical DOS methods involving RuAAC, Park and co-workers have described the synthesis of a benzopyran library,[237] also using solution-phase fluorous-tag chemistry. Described as privileged-substructure-based DOS (pDOS), with the central benzopyran scaffold being considered a privileged structure in drug discovery,[238,239] Park and colleagues prepared a set of 32 benzopyranyl triazoles with a 1,5-substitution pattern in high yields and purities, using $Cp^*RuCl(PPh_3)_2$ as the catalyst (see Figure 28 for selected

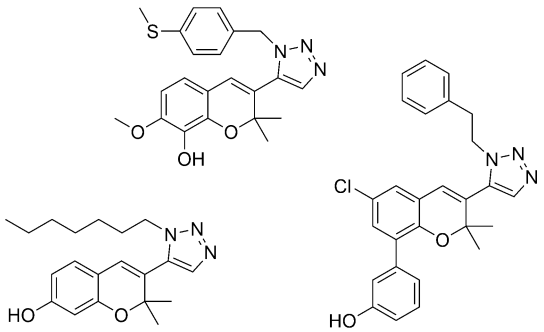


Figure 28. Selected compounds from a 60-membered library of benzopyranyl triazoles.[237]

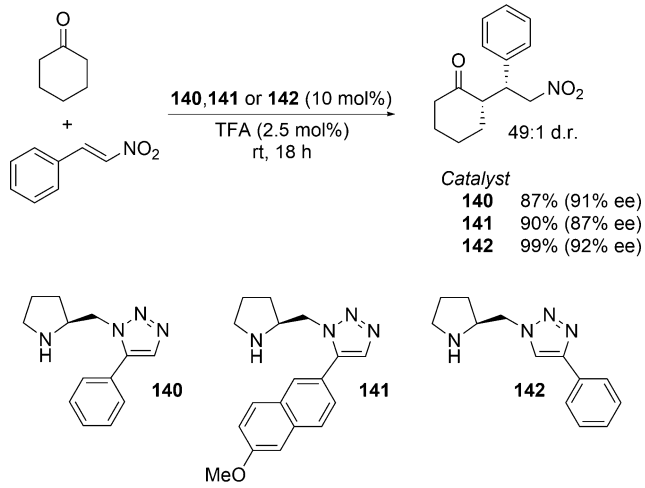
examples). Aryl azides were excluded from the study, as initial experiments showed that these substrates were problematic in RuAAC, in line with earlier reports by Lin, Jia, Fokin, and co-workers[27] (see section 4.3).

Another report on the use of RuAAC for DOS purposes comes from the group of Zondlo,[113] who employed this reaction in the context of proline edition, i.e., modification of a proline residue within a peptide chain with the purpose of studying the steric and stereoelectronic effects of this variation on the peptide conformation. A total of 123 different peptides were prepared by functionalization of a 4-hydroxyproline moiety within a peptide attached to a solid support. Diversification was effected using a wide range of both organic and organometallic reactions and included the formation of two diastereomeric 1,5-disubstituted triazoles following conversion of the 4-hydroxyl unit of prolinol to an azide.

6. ORGANOCATALYSTS

Chiral pyrrolidines are often employed as organocatalysts, with their extensive application triggered by the original discovery by List and co-workers, showing that L-proline itself is an efficient catalyst for asymmetric aldol reactions.[240] Luo, Cheng, and co-workers investigated the organocatalytic asymmetric Michael addition of ketones and aldehydes to nitroolefins.[241] L-proline itself, while a viable catalyst, is known to afford low enantioselectivities in this reaction;[242] there were indications that substituted derivatives such as L-prolinol could be more successful. Seeking a convenient method for derivatizing a proline scaffold, the authors employed CuAAC to produce a library of 1,4-disubstituted triazoles to be used as organocatalysts for screening purposes. Two 1,5-disubstituted triazoles were also prepared (**140** and **141**, Scheme 57), but as this study was

Scheme 57. Triazole-Substituted Pyrrolidines As Organocatalysts in a Michael Addition[241]



published only shortly after the initial report on the RuAAC reaction, the authors here employed the more classical magnesium acetylides (see section 2) to attain the 1,5-isomeric structure instead. Catalysts **140** and **141** both performed well in the reaction between cyclohexanone and 2-nitrovinylbenzene (Scheme 57), but only marginal differences were seen between **140** and the corresponding 1,4-substituted isomer **142**, indicating that the space-shielding effect of the triazole ring itself was more important than the positioning of the substituents. Thiazolidine-based scaffolds were also explored but found to be inefficient as catalysts in the reaction.

Thioureas are also privileged structures in organocatalysis, and the bifunctional organocatalyst **143** (Figure 27), containing this moiety, was originally designed by Takemoto and co-workers for the enantioselective Michael addition of malonates to nitroolefins.[243] The catalyst contains both acidic and basic units and was constructed on the principle that these two sites will activate one reactant each, while simultaneously bringing them into close proximity to facilitate reaction. Seeking to expand this concept toward a trifunctional organocatalyst, Takasu, Azuma, and Takemoto constructed a set of triazole-substituted thioureas employing both RuAAC and CuAAC.[244] Although the RuAAC reaction is compatible with a wide spectrum of functionalities, the sulfur atom in a thiourea can ligate to the ruthenium catalyst, causing deactivation. A synthetic strategy where the thiourea unit was introduced in the last step was thus envisaged, and catalysts of the type **144** (Figure 29) were prepared using a microwave-mediated RuAAC reaction with $[Cp^*RuCl]_4$ as the catalyst, followed by coupling reactions to introduce the thiourea in the final step. Screening of three of the catalysts in the enantioselective conjugate addition of cyclohexanone to *trans*-*β*-nitrostyrene afforded up to 92% ee. In a later study, the scope of aryl-substituted nitroolefins was expanded, with a 2-furyl-substituted nitroolefin affording up to 98% ee using these organocatalysts.[245]

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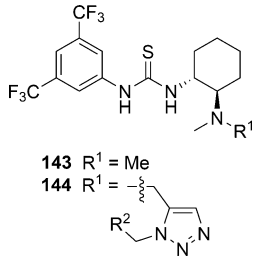


Figure 29. Synthesis of trifunctional organocatalysts for Michael additions to nitroolefins.[244,245]

7. SUPRAMOLECULAR STRUCTURES, NANOCHEMISTRY, AND ELECTRONIC DEVICES

Triazole formation provides a convenient method for elaborating supramolecular structures, which often contain a complex central scaffold and require a simple and high-yielding reaction for the final step. CuAAC has been extensively used for this purpose,[246,247] while examples using RuAAC are more scarce. The aromatic properties of the triazole also make these units well-suited for inclusion into molecules intended for electronic devices or nanochemistry applications, where an extended conjugated system is often desired.

De Cola and colleagues have investigated the effect of introducing triazoles into iridium complexes bearing difluorophenylpyridine (F2ppy) ligands.[248] Metal complexes can be employed in light-emitting diodes (LEDs), acting as phosphorescent dopants and facilitating intersystem crossing from the singlet to the triplet excited state. The colors red, green, and blue are all necessary for applications in color displays, and De Cola and co-workers found that a complex prepared via RuAAC, using $Cp^*RuCl(PPh_3)_2$ as the catalyst, displayed blue emission with high quantum yields (Figure 30).

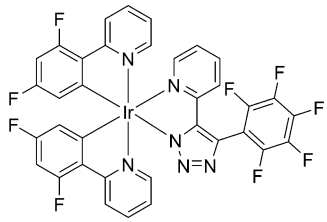
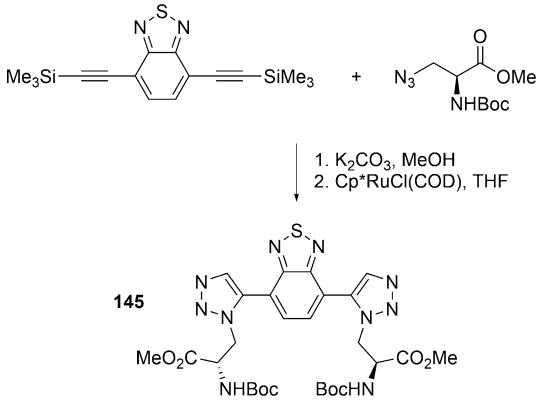


Figure 30. Triazolyl iridium complex with blue-emitting properties.[248]

Theranostic agents combine both diagnostic and therapeutic properties into one entity, and seeking to develop contrast agents for optoacoustic imaging, Franchini and co-workers employed both copper- and ruthenium-catalyzed cycloadditions to link silver nanoparticles (NPs), derivatized with an alkyne unit, to lipophilic azide-functionalized gold nanorods (GNRs).[249] The cycloadducts were subsequently incorporated into PEG-based copolymers to produce polymeric nanoparticles (PNPs). These new constructs were found to display similar electroacoustic and optical behavior to GNR-PNPs without silver NPs, indicating that click-attachment of silver NPs does not disturb the desired properties.

Xie and co-workers employed both CuAAC and RuAAC to derivatize benzothiadiazoles (BTDs) intended for fluorescent chemosensors.[250] Comparing structure **145** with its 1,4-disubstituted counterpart (Scheme 58), the authors found significant differences in the spectral properties of the molecules, where blue-shifts for **145** relative to the corresponding 1,4-

Scheme 58. Triazole-Derivatized Benzothiadiazoles for Fluorescent Chemosensors[250]



isomer in the absorption and emission spectra were attributed to a lesser degree of conjugation in **145**, due to a larger dihedral angle between the triazoles and the central BTD unit. Binding studies to various metal ions were also carried out. Sensors for metal binding have also been reported by Quayle and colleagues, who employed both CuAAC and RuAAC for clicking together a reporter unit (azo dye) with a metal-recognizing moiety (macrocycle) and a carrier molecule (carbohydrate).[251]

Ruthenium(II) polypyridyl complexes, where one or two pyridyl ligands were replaced by 1,5-disubstituted triazoles, were synthesized by Schubert and co-workers,[252] and alkylation of the triazoles with methyl iodide also gave access to ruthenium triazolylidene complexes. The electrochemical and photochemical properties of **146**–**148** (Figure 31) were investigated and complemented by computational studies using DFT. These compounds emit red light and could be of interest in electroluminescence devices, although evaluation in a dye-sensitized solar cell gave modest efficiency in terms of power conversion. Red emissive triazole luminogens have also been prepared by Qin, Tang, and co-workers, using CuAAC and

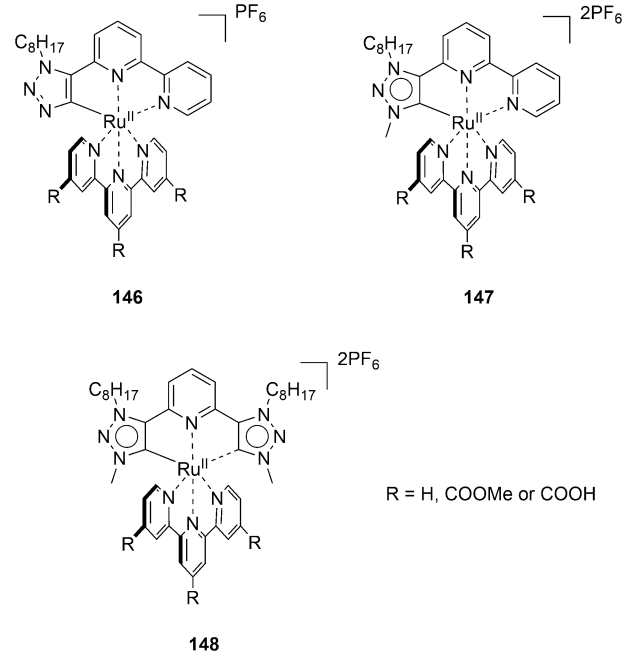


Figure 31. Triazole ruthenium complexes displaying red emission.[252]

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RuAAC to adorn a pyrazine structure.[253] The compounds were shown to have good luminescence properties in the aggregate and solid state, which can be of importance in the development of optoelectronic devices for instance.

Tetrathiafulvalenes (TTFs) are frequently employed for the construction of molecular materials due to their electroactive properties. In a series of reports, Avarvari and co-workers have investigated the structures and properties of a TTF scaffold functionalized with 1,5-disubstituted triazole units.[254−256] By employing a tetrathiafulvalene with one or two appended alkyne units, compounds **149**−**154** (Figure 32) were prepared via

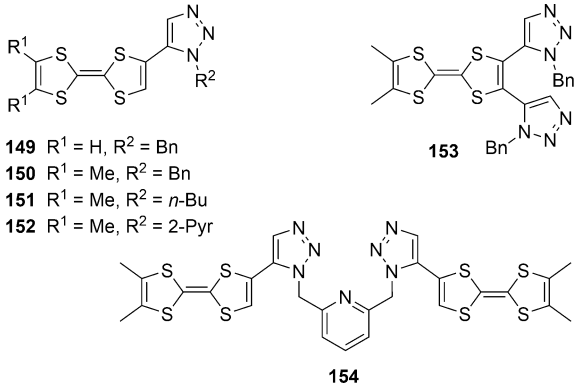
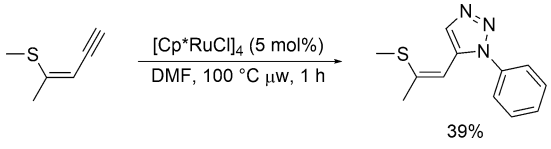


Figure 32. Triazole-containing tetrathiafulvalenes (TTFs).[254−256]

RuAAC, using Cp*RuCl(PPh$_3$)$_2$ as the catalyst in THF at 65 °C.[254] Cyclic voltammetry and DFT calculations showed **149** and **150** to be more electron-deficient and less prone to oxidation than their 1,4-disubstituted counterparts. Cu(II) complexes of these ligands were prepared and characterized by X-ray crystallography, where the triazole N3 atom was found to bind to copper. These metal complexes are predicted to be useful starting materials for paramagnetic molecular conductors. In a second study, the solid-state structure of **149** and analogue **153** were compared. Interestingly, despite their similarities, these compounds crystallize in different fashions, where **150** forms head-to-tail dimers while **153** is arranged in columns with each unit slightly shifted in comparison to the molecule above and below so that the TTF moiety stacks with a triazole unit directly above. The effect of protonation and alkylation of the triazole ring in **149** was also studied,[256] and a triazolium salt was formed via treatment with trimethyloxonium tetrafluoroborate ((Me$_3$O)BF$_4$). A third report focused on chelating pyridine triazole structures, i.e., **152** and **154**, and their ability to act as ligands for metals such as cobalt and cadmium.[255]

Lumpi et al. have also applied the alkyne−azide cycloaddition as a means to prepare new molecular materials, in this case nonlinear optic materials (NLOs) derived from a central enyne scaffold.[257] The majority of structures were formed using CuAAC, but one compound was prepared via microwave-assisted RuAAC using [Cp*RuCl]$_4$ as the catalyst (Scheme 59).

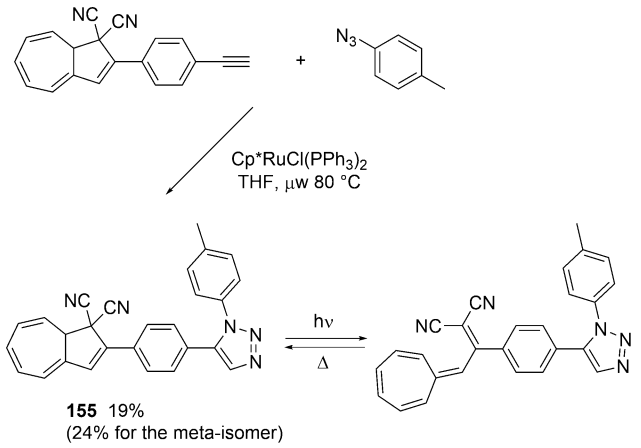
Scheme 59. 1,5-Disubstituted Triazole for Novel Nonlinear Optical Materials[257]



X-ray diffraction showed that this compound crystallized in an enantiomorphic space group and displayed slightly improved nonlinear susceptibility in comparison to the corresponding 1,4-disubstituted isomer.

Dihydrazulenes (DHAs) can act as molecular photoswitches, where irradiation triggers a ring-opening to form a vinyl-heptafulvalene, which can then thermally return to the original structure. This feature, for instance, could be exploited in molecular electronics. Nielsen and co-workers studied the effect that appending a triazole onto the benzene ring of the dihydroazulene had on this isomerization process.[258] Compound **155** as well as its meta isomer were prepared via microwave-assisted RuAAC (Scheme 60). Despite attempts to optimize the

Scheme 60. Triazolyl Dihydroazulenes As Molecular Photoswitches[258]



reaction, the yields were rather low. The rate of ring-closure of these reactions was then measured and employed to determine the Hammett substituent constants for the *meta*- and *para*-tolyl isomers, as well as for the corresponding 1,4-disubstituted triazoles.

8. POLYMERS

CuAAC has found many applications in the area of polymer chemistry and generally has been employed for either "clicking" a molecule onto a polymeric scaffold derivatized with an alkyne or azide or employing the 1,3-cycloaddition for constructing the polymer itself.[259] In comparison with the field of medicinal chemistry, RuAAC as yet has been rather sparingly used in a polymer context, but examples include the synthesis of triazole-containing monomers, polymers, and dendrimers using RuAAC, as well as polymer functionalization.

8.1. Triazole Monomers for Polymerization

Nulwala, Hawker, and co-workers compared the behavior of 1,4- and 1,5-disubstituted vinyl triazoles **156** and **157** in living free radical polymerization (Scheme 61).[260] Monomers **156** were prepared in good yields by applying CuAAC to homopropargylic alcohol, followed by mesylation and elimination to introduce the vinyl functionality. While Fokin and co-workers have reported successful RuAAC reactions with hindered propargylic alcohols,[12,27] Nulwala and co-workers found homopropargylic alcohol to be a problematic substrate in this ruthenium-catalyzed reaction, and low yields of the triazole were obtained. Catalyst deactivation by the substrate was stated as the likely cause. By mesylating the alcohol before the RuAAC reaction, this problem

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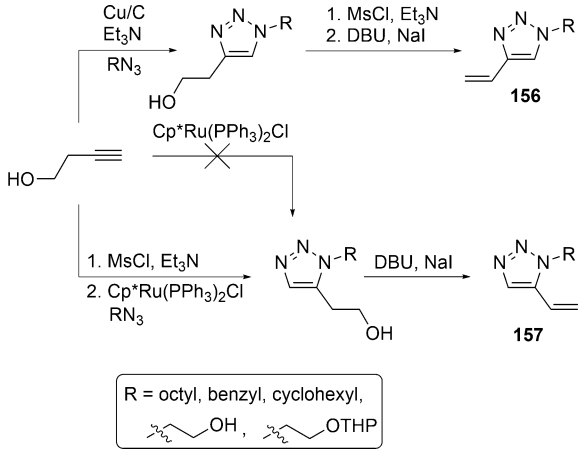
Scheme 61. Synthesis of Vinyl Triazole Monomers for Polymerization[260]



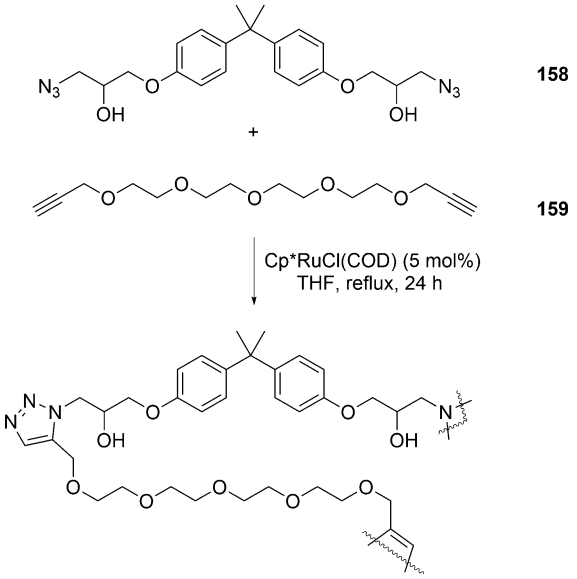
was solved and vinyl triazoles **157** were prepared in reasonable yields. Both monomer types were subsequently polymerized using two different methods, i.e., reversible addition−fragmentation chain transfer (RAFT) polymerization, affording homopolymers, and nitroxide-mediated polymerization (NMP), producing block polymers. As a general trend, the 1,5-isomer produced polymers with a higher glass-transition temperature and lower solubility than their 1,4-isomeric counterparts, indicating a more rigid structure. In a later study, the copolymerization of some of these monomers with styrene was also explored, with the RuAAC-derived monomers showing a higher reactivity than the 1,4-isomers in this case.[261]

A sequential one-pot click-elimination procedure to access the same class of monomers has been reported by Blache and co-workers, starting from 4-bromobutyne and using sodium hydroxide in water to effect the elimination to a vinyl functionality in the final step.[262] Su and Hua have also reported the synthesis of vinyl 1,4-disubstituted triazoles, this time under acidic conditions.[263] Using a bimetallic catalyst system consisting of CuCl and $RuCl_3 \cdot H_2O$, propargylic alcohols were reacted with alkyl, aryl, and benzyl azides and subsequently dehydrated in situ by trifluoroacetic acid present in the reaction mixture. Each of the two catalysts could be used separately, but the bimetallic catalyst increased the yield substantially. Bielawski and co-workers constructed polymer initiators containing 1,4- and 1,5-triazole isomers and subsequently grew poly(methyl acrylate) chains from these structures in order to study the mechanical properties of the formed polymers.[264] Ultrasound irradiation of these structures in acetonitrile resulted in a cycloreversion to the starting azide and alkyne, with a faster reaction rate for the 1,5-isomer in comparison to the 1,4-derivative. A theoretical study of the cycloreversion of 1,4- and 1,5-disubstituted 1,2,3-triazoles has also been reported by Blank and co-workers.[265]

8.2. Polymerization via RuAAC

The azide alkyne cycloaddition reaction can be employed as a method of polymerization itself, by linking monomers functionalized with azide and alkyne units. While this technique has been extensively applied using CuAAC,[259] there are as yet few examples of this type of application employing RuAAC.[266] Storey and co-workers compared the regioselectivity in the reaction of a diazide-functionalized derivative of bisphenol A (**158**) with a dialkyne-substituted tetraethylene glycol derivative (**159**) using thermal cycloadditions as well as CuAAC and RuAAC (Scheme 62).[267] While the copper-catalyzed click reaction could be performed under neat conditions with only the two monomers

Scheme 62. RuAAC Polymerization of a Bisphenol-A Derivative[267]



present, the solubility of Cp*RuCl(COD) in this bulk system at 70 °C was not sufficient and a thermal, nonregioselective reaction was observed instead. However, solution-phase polymerization with the same catalyst in refluxing THF afforded the desired polymer with a 94:6 selectivity for the 1,5-disubstituted triazole compared to the 1,4-isomer.

In another example, Brady et al. employed RuAAC to construct polymers containing Mo−Mo bonds, where the sensitivity of these metal−metal bonds constitutes a problem when conventional polymerization techniques are employed.[268] Building block **160** was first reacted with benzyl azide and with 1,4-bis(azidomethyl)benzene (**161**) in model reactions (Figure 33). Employing Cp*RuCl$(PPh_3)_2$ as the catalyst, complete reaction was attained after 4 h. Reactions with diazide-functionalized polystyrene and polyethylene glycol oligomers (**162** and **163**) were then pursued with good results, affording polymeric structures with the Mo−Mo bond still intact according to analysis of the C≡O bond in IR.

8.3. Polymer Functionalization

Fokin and co-workers have prepared halo-substituted triazoles using ruthenium catalysis, described in detail in section 4.4.3.[91]

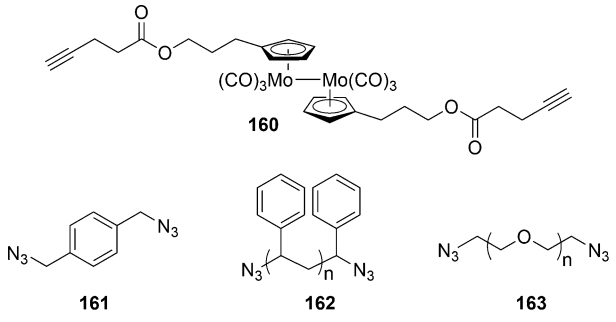


Figure 33. Polymerization of Mo-containing building blocks using RuAAC.[268]

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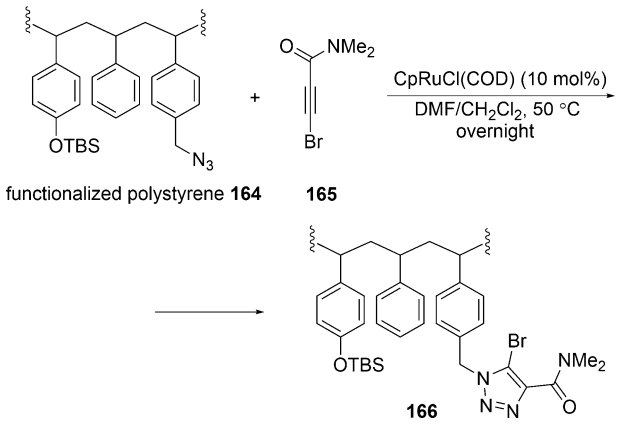
Included in this study also was an example of RuAAC involving a soluble non-cross-linked functionalized polystyrene resin. Polymer **164**, with 7% of the backbone carrying a pendant azide unit, was reacted with an excess of bromoalkyne **165**, affording the bromotriazole-derivatized resin **166** (Scheme 63). IR analysis of the final polymer verified that the azide stretch had indeed disappeared, and ^{1}H NMR confirmed the presence of the amide methyl groups.

Scheme 63. Functionalization of a Soluble Polystyrene Resin via RuAAC[91]



Pola et al. have explored the attachment of peptides to polymeric drug carriers using RuAAC.[269,270] Azide-terminated peptides were reacted with an aminopropargyl-functionalized copolymer of *N*-(2-hydroxypropyl)methacrylamide (HPMA) bearing the anticancer drug doxorubicin. The choice of catalyst was found to be important here. In a test reaction between 5-azidopentanoic acid and the alkyne-functionalized polymer, using Cp*RuCl(PPh$_3$)$_2$ as catalyst at 60 °C afforded only 25% of the polymer conjugate after 12 h. By switching to Cp*RuCl(COD), which can be employed at ambient temperature,[27] full conversion was attained after 6 h, however, and this catalyst was subsequently used for the conjugation reactions.

8.4. Hyperbranched Structures

Tang and co-workers[271] and Brady and Tyler[272] have both targeted dendritic polytriazole structures via RuAAC. Tang and co-workers employed amine-centered triyne **167**, combining this with diazides of different chain lengths, while Brady and Tyler selected 1,3,5-triethynylbenzene (**168**) as the central core for appending metal-containing building blocks, similar in structure to those described in section 8.2 (Figure 34). Tang and co-workers found that Cp*RuCl(PPh$_3$)$_2$, and also the Ru(III) oligomer [Cp*RuCl$_2$]$_n$, could be employed in the coupling of **167** with diazides to produce the desired hyperbranched triazoles in good yields. The degree of branching was determined using ^{1}H NMR, and the ability of the polymers to form films and the photophysical properties of these films were studied also. Brady's attempted coupling of **168** with **169** was unsuccessful, however, affording instead a polymer devoid of molybdenum. The authors propose that a competing cyclotrimerization reaction, not involving **169**, is taking place instead.

9. OTHER METHODS FOR THE FORMATION OF 1,5-DISUBSTITUTED 1,2,3-TRIAZOLES

The use of other metals than Ru and Cu in cycloaddition reactions to form triazoles reaction has been reviewed recently by

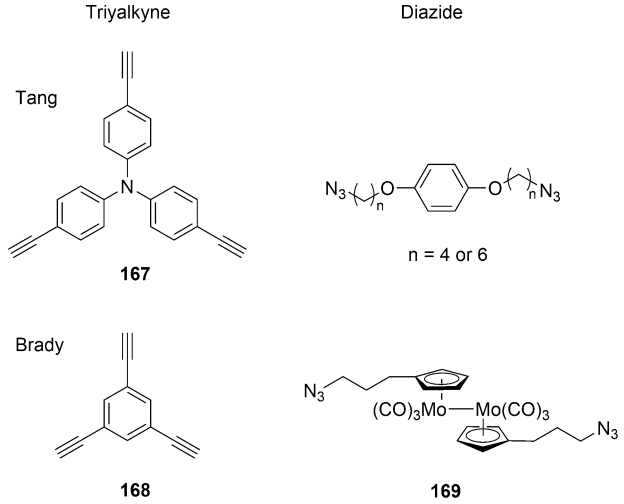


Figure 34. Building blocks for the formation of dendritic polytriazoles.

Astruc and co-workers[21] and will be mentioned only very briefly here. Iridium can catalyze the reactions of bromoalkynes with organic azides to 1,5-isomers with a 4-bromo substituent,[273] as well as can effect the cyclization of internal thioalkynes.[274] Wang et al. reported that cerium could be applied to access 1,5-disubstituted 1,2,3-triazoles, in this case employing a nitroolefin instead of an alkyne together with benzyl or phenyl azide.[275] Ytterbium has been applied in one-pot cascade reactions, affording fused 1,4,5-substituted triazoles,[276] and samarium-catalyzed reactions have been reported to cyclize terminal alkynes with azides to provide the 1,5-isomer.[277] Iron can effect the cyclization of chalcones with sodium azide but affords the 2,4,5-trisubstituted 1,2,3-triazole product.[278] Koguchi and Izawa employed a copper catalyst in ionic liquids in a method that initially affords the 1,4-isomer with a protecting group in the 4-position.[279] This triazole is subsequently alkylated on the 5-position and deprotected to finally afford the 1,5-isomer. Lautens and co-workers used a combination of copper and palladium in a tandem reaction to form 1,4,5-trisubstituted triazoles,[280] while Smith and Greaney reported a zinc-mediated synthesis of 1,5- and 1,4,5-isomers.[281]

1,5-Disubstituted 1,2,3-triazoles can also be formed without the use of a metal. These methods have the advantage that an azide is not necessarily involved, and azide-free methods for 1,2,3-triazole formation have been highlighted recently.[282] A feature article by Dehaen and co-workers summarizes the use of organocatalysis for the formation of substituted 1,2,3-triazoles, and only a few examples will be mentioned here.[283] Azide-free multicomponent reactions have been applied; for instance, Wan et al. describe the use of enaminones with primary amines and tosylhydrazine in the presence of I$_2$.[284] Heating to 110 °C in DMSO afforded triazoles functionalized with an aldehyde or ketone in the 5-position. Another three-component method, albeit not azide-free, has been reported by Dey and Pathak and uses vinyl sulfones in conjunction with alkyl halides and sodium azide.[285] The same group also reports the use of selenium to access 1,4,5-trisubstituted 1,2,3-triazoles.[286] Fokin and co-workers also have reported a robust method for the reaction of aryl azides with terminal aryl alkynes in the presence of catalytic amounts of tetramethylammonium hydroxide at room temperature, affording 1,5-diaryl-substituted 1,2,3-triazoles in good yields.[287] For a full survey of triazole synthesis without employing ruthenium, we refer to the aforementioned reviews.

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10. CONCLUSIONS AND FUTURE OUTLOOK

The ruthenium-catalyzed azide alkyne cycloaddition (RuAAC) provides direct access to 1,5-disubstituted 1,2,3-triazoles and acts as a counterpart to the copper-catalyzed "click" reaction where the 1,4-isomer of the triazole is formed. Many Ru(II) complexes catalyze the reaction, but a pentamethylcyclopentadienyl (Cp*) ligand as well as a chloride bonded to ruthenium are generally required to attain good regioselectivity. Mechanistic studies indicate a different pathway for RuAAC compared to CuAAC, and this is further substantiated by the fact that internal alkynes can be employed in the Ru-catalyzed reaction, which is not the case for CuAAC. Further advantages of RuAAC include the 1,5-disubstitution pattern that can be exploited, for instance, in the formation of macrocycles, where the regiochemistry in the RuAAC reaction is better suited for smaller rings than the 1,4-pattern obtained in CuAAC. The CuAAC reaction, however, has the benefit of using a less-expensive catalyst and can generally be performed at a lower temperature than RuAAC. Both reactions are compatible with a wide range of functional groups, although RuAAC can be problematic when using substrates containing acidic functional groups.

One can easily realize the potential of 1,5-triazoles in various fields of medicinal chemistry and biochemistry, both as tools as well as inhibitors, and the RuAAC reaction has found more widespread use among medicinal chemists than in any other area of research. However, a derivative prepared via RuAAC for clinical purposes has yet to emerge in a drug on the market. Evaluation of the 1,5-disubstituted triazoles as peptide bond or disulfide mimetics, or as α-helix mimetics, is also of interest, and several studies in this area have been reported. Other areas of chemistry are surprisingly underdeveloped in terms of applying the RuAAC reaction, and there is ample scope for further work in many fields, including the development of new materials and electronic devices, as well as the use of 1,5-disubstituted triazoles as ligands in coordination chemistry and catalysis. A commercially available polymer-supported catalyst for RuAAC also could also be of interest. We envisage many new examples of RuAAC applications in the future.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: johan.x.johansson@astrazeneca.com.
*E-mail: beke-somfai.tamas@ttk.mta.hu.
*E-mail: kann@chalmers.se.

Notes

The authors declare no competing financial interest.

Biographies

Johan R. Johansson obtained his M.Sc. from the University of Gothenburg, Sweden, in 2003. In 2004, he joined AstraZeneca R&D, CVGI Medicinal Chemistry, working mainly with library design, synthesis, and lead optimization. In 2013 he obtained his Ph.D. in Organic Chemistry in the group of Prof. Bengt Nordén under the supervision of Prof. Nina Kann at Chalmers University of Technology, Sweden. He then joined the Respiratory, Inflammation and Autoimmune Diseases, Innovative Medicines unit (RIA iMed), of AstraZeneca as a Senior Research Scientist, working on inhalation and new treatments for asthma. In 2016 he joined Eric Valeur's New Modalities Team within the Cardiovascular and Metabolic Diseases Innovative Medicines (CVMD iMed) unit at AstraZeneca Gothenburg. His current research interests include structure-based design, conformational constraints, peptidomimetics, macrocycles, and drug-delivery systems.

Tamás Beke-Somfai is a group leader in the Institute of Materials and Environmental Chemistry at the Research Centre for Natural Sciences (RCNS), Budapest. He obtained his M.Sc. (2001) in chemistry and his Ph.D. in structural chemistry (2007) at Eötvös University, Budapest. He worked as a postdoctoral fellow, and later as a guest researcher, at Chalmers University of Technology, Gothenburg, Sweden (2008–2015). He is currently a Marie-Sklodowska Curie fellow and leads the Biomolecular Self-Assembly group under the Momentum program of the Hungarian Academy of Sciences (HAS). His research field involves theoretical and experimental investigation of natural and non-natural peptide assemblies, enzyme catalysis, polarized light spectroscopy, and membrane–biomolecule interactions.

Anna Said Stålsmeden graduated with a M.Sc. in chemistry from the University of Gothenburg in 2011. She is now pursuing her Ph.D. degree in organic chemistry under the supervision of Prof. Nina Kann at the Department of Chemistry and Chemical Engineering at Chalmers University of Technology. Her research interest is mainly in the development of efficient metal-mediated reactions for the valorization of biomass-derived building blocks and their application in organic synthesis

Nina Kann is professor of Organic Chemistry at Chalmers University of Technology in Göteborg, Sweden. She obtained her Ph.D. at the Royal Institute of Technology in Stockholm (1993) under the supervision of Dr. Tobias Rein and Prof. Björn Åkermark, and she subsequently spent two years as a postdoctoral fellow with Dr. Andrew Greene (Directeur de Recherche, CNRS) at the Université Joseph Fourier in Grenoble, France. Following some years as a researcher at AstraZeneca (Mölndal), she returned to academia in 1999 and became a professor at Chalmers University of Technology in 2010. Her current research interests are green chemistry and applications of organometallics in organic synthesis.

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ABBREVIATIONS

AAC	azide alkyne cycloaddition
AAS	atomic absorption spectroscopy
Ad	adamantyl
ADRT	4′-azidothymidine
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AZT	3′-azidothymidine
Boc	*tert*-butoxycarbonyl
BTD	benzothiadiazole
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate
CA	carbonic anhydrase
CBS	complete basis set
CMT	chloromethyl triazole

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COD	cyclooctadiene
COX	cyclooxygenase
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
CPE	cytopathic effect
CuAAC	Cu-catalyzed azide alkyne cycloaddition
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DFT	density functional theory
DHA	dihydroazulene
DMA	dimethylacetamide
DOS	diversity-oriented synthesis
dppp	1,3-bis(diphenylphosphine)propane
dUTP	2′-deoxyuridine 5′-triphosphate
EDC	1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide
ER	endoplasmic reticulum
Fmoc	fluorenylmethoxycarbonyl
FU	fluorouracil
GHK	Gly-His-Lys
GIAO	gauge-independent atomic orbitals
GNR	gold nanorod
GPRC	G-protein coupled receptor
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo-[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
hCA	human carbonic anhydrase
HDAC	histone deacetylase
HHK	histone H4 histidine kinase
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple-bond correlation spectroscopy
HPMA	*N*-(2-hydroxypropyl)methacrylamide
HOBt	1-hydroxybenzotriazole
HOAt	1-hydroxy-7-azobenzotriazole
HSP	heat shock protein
IRAP	insulin-regulated aminopeptidase
ITC	isothermal titration calorimetry
L	ligand
LDA	lithium diisopropylamide
LED	light-emitting diode
NBD	norbornadiene
NCI	National Cancer Institute
NHC	N-heterocyclic carbene
NOE	nuclear Overhauser effect
NP	nanoparticle
MD	molecular dynamics
MM	molecular mechanics
NiSOD	nickel superoxide dismutase
NLO	nonlinear optical material
NMP	nitroxide-mediated polymerization
PDB	protein data bank
PEG	polyethylene glycol
phen	1,10-phenanthroline
pHis	phosphohistidine
POM	pivaloyloxymethyl
PPI	protein−protein interaction
ppy	phenylpyridine
pTza	phosphotriazolylalanine
QM	quantum mechanics
RAFT	reversible addition−fragmentation chain transfer
RNase A	bovine pancreatic ribonuclease
RuAAC	Ru-catalyzed azide alkyne cycloaddition
SPPS	solid-phase peptide synthesis
SPS	solid-phase synthesis
STFI	sunflower trypsin inhibitor
Su	succinimidyl
TBAF	tetra-*n*-butylammonium fluoride
TFA	trifluoroacetic acid
Tp	trispyrazolylborate
Trt	triphenylmethyl (trityl)
Ts	*p*-toluenesulfonyl
TTF	tetrathiafulvalene

REFERENCES

(1) Agalave, S. G.; Maujan, S. R.; Pore, V. S. Click Chemistry: 1,2,3-Triazoles as Pharmacophores. *Chem. - Asian J.* **2011**, *6*, 2696−2718.

(2) Keri, R. S.; Patil, S. A.; Budagumpi, S.; Nagaraja, B. M. Triazole: A Promising Antitubercular Agent. *Chem. Biol. Drug Des.* **2015**, *86*, 410−423.

(3) Fan, W.-Q.; Katritzky, A. R. 1,2,3-Triazoles. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, U.K., 1996; Vol. *4*; pp 1−126.

(4) Tornoe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: 1,2,3 -Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002**, *67*, 3057−3064.

(5) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(6) Wu, P.; Fokin, V. V. Catalytic Azide-Alkyne Cycloaddition: Reactivity and Applications. *Aldrichimica Acta* **2007**, *38*, 7−17.

(7) Meldal, M.; Tornoe, C. W. Cu-Catalyzed Azide-Alkyne Cycloaddition. *Chem. Rev.* **2008**, *108*, 2952−3015.

(8) Schilling, C.; Jung, N.; Bräse, S. Cycloaddition Reaction with Azides: An Overview. In *Organic Azides: Synthesis and Applications*; Bräse, S., Banert, K., Eds.; John Wiley & Sons: Chichester, U.K., 2010; pp 269−284.

(9) Hein, J. E.; Fokin, V. V. Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) and Beyond: New Reactivity of Copper(I) Acetylides. *Chem. Soc. Rev.* **2010**, *39*, 1302−1315.

(10) Liang, L. Y.; Astruc, D. The Copper(I)-Catalyzed Alkyne-Azide Cycloaddition (CuAAC) "Click" Reaction and Its Applications. An Overview. *Coord. Chem. Rev.* **2011**, *255*, 2933−2945.

(11) Haldon, E.; Nicasio, M. C.; Perez, P. J. Copper-Catalysed Azide-Alkyne Cycloadditions (CuAAC): An Update. *Org. Biomol. Chem.* **2015**, *13*, 9528−9550.

(12) Zhang, L.; Chen, X. G.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. C. Ruthenium-Catalyzed Cycloaddition of Alkynes and Organic Azides. *J. Am. Chem. Soc.* **2005**, *127*, 15998−15999.

(13) Fokin, V. V. Catalytic Dipolar Cycloadditions of Alkynes with Azides and Nitrile Oxides. In *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley-VCH: Weinheim, Germany, 2010; Vol. *2*; pp 917−949.

(14) Pedersen, D. S.; Abell, A. 1,2,3-Triazoles in Peptidomimetic Chemistry. *Eur. J. Org. Chem.* **2011**, *2011*, 2399−2411.

(15) Yubo, J.; Chungxiang, K. Synthesis of 1,2,3-Triazole Derivatives. *Prog. Chem.* **2012**, *24*, 1983−1994.

(16) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. Transition Metal-Mediated Synthesis of Monocyclic Aromatic Heterocycles. *Chem. Rev.* **2013**, *113*, 3084−3213.

(17) Lauria, A.; Delisi, R.; Mingoia, F.; Terenzi, A.; Martorana, A.; Barone, G.; Almerico, A. M. 1,2,3-Triazole in Heterocyclic Compounds, Endowed with Biological Activity, through 1,3-Dipolar Cycloadditions. *Eur. J. Org. Chem.* **2014**, *2014*, 3289−3306.

(18) Das, R.; Majumdar, N.; Lahiri, A. A Review on 1,3-Dipolar Cycloaddition Reactions in Bioconjugation and Its Importance in Pharmaceutical Chemistry. *Int. J. Res. Pharm. Chem.* **2014**, *4*, 467−472.

(19) Hosseinnejad, T.; Fattahi, B.; Heravi, M. M. Computational Studies on the Regioselectivity of Metal-Catalyzed Synthesis of 1,2,3 Triazoles via Click Reaction: A Review. *J. Mol. Model.* **2015**, *21*, 264.

DOI: 10.1021/acs.chemrev.6b00466
Chem. Rev. 2016, 116, 14726−14768

(20) Totobenazara, J.; Burke, A. J. New Click-Chemistry Methods for 1,2,3-Triazoles Synthesis: Recent Advances and Applications. *Tetrahedron Lett.* **2015**, *56*, 2853−2859.
(21) Wang, C. L.; Ikhlef, D.; Kahlal, S.; Saillard, J. Y.; Astruc, D. Metal-Catalyzed Azide-Alkyne "Click" Reactions: Mechanistic Overview and Recent Trends. *Coord. Chem. Rev.* **2016**, *316*, 1−20.
(22) Heravi, M. M.; Tamimi, M.; Yahyavi, H.; Hosseinnejad, T. Huisgen's Cycloaddition Reactions: A Full Perspective. *Curr. Org. Chem.* **2016**, *20*, 1591−1647.
(23) *Click Reactions in Organic Synthesis*; Chandrasekaran, S., Ed.; Wiley-VCH: Weinheim, Germany, 2016.
(24) Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. Catalytic Selective Synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 10954−10990.
(25) Yamamoto, Y. Syntheses of Heterocycles Via Alkyne Cycloadditions Catalyzed by Cyclopentadienylruthenium-Type Complexes. *Heterocycles* **2013**, *87*, 2459−2493.
(26) Palaniraja, J.; Roopan, S. M. Ruthenium Mediated Cycloaddition Reaction in Organic Synthesis. *Chem. Sci. Rev. Lett.* **2014**, *3*, 93−100.
(27) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H. T.; Lin, Z. Y.; Jia, G. C.; Fokin, V. V. Ruthenium-Catalyzed Azide-Alkyne Cycloaddition: Scope and Mechanism. *J. Am. Chem. Soc.* **2008**, *130*, 8923−8930.
(28) Huisgen, R. 1.3-Dipolare Cycloadditionen - Rückschau Und Ausblick. *Angew. Chem.* **1963**, *75*, 604−637.
(29) Huisgen, R. Kinetik Und Mechanismus 1.3-Dipolarer Cycloadditionen. *Angew. Chem.* **1963**, *75*, 742−745.
(30) Huisgen, R. 1,3-Dipolar Cycloaddition. Introduction, Survey and Mechanism. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley Interscience: New York, 1984; Vol. *1*; pp 1−176.
(31) Michael, A. Ueber Die Einwirknng Von Diazobenzolimid Auf Acetylendicarbonsäuremethylester. *J. Prakt. Chem.* **1893**, *48*, 94−95.
(32) Huisgen, R.; Szeimies, G.; Mobius, L. 1.3-Dipolare Cycloadditionen, XXXII. Kinetik Der Additionen Organischer Azide an CC-Mehrfachbindungen. *Chem. Ber.* **1967**, *100*, 2494−2507.
(33) Kirmse, W.; Horner, L. Umsetzung Von Phenylacetylen Mit Aziden Und Diazoverbindungen. *Liebigs Ann. Chem.* **1958**, *614*, 1−3.
(34) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. Cu^{I}-Catalyzed Alkyne-Azide "Click" Cycloadditions from a Mechanistic and Synthetic Perspective. *Eur. J. Org. Chem.* **2006**, *2006*, 51−68.
(35) Sokolova, N. V.; Nenajdenko, V. G. Recent Advances in the Cu(I)-Catalyzed Azide-Alkyne Cycloaddition: Focus on Functionally Substituted Azides and Alkynes. *RSC Adv.* **2013**, *3*, 16212−16242.
(36) Gramlich, P. M. E.; Wirges, C. T.; Manetto, A.; Carell, T. Postsynthetic DNA Modification through the Copper-Catalyzed Azide-Alkyne Cycloaddition Reaction. *Angew. Chem., Int. Ed.* **2008**, *47*, 8350−8358.
(37) El-Sagheer, A. H.; Brown, T. Click Nucleic Acid Ligation: Applications in Biology and Nanotechnology. *Acc. Chem. Res.* **2012**, *45*, 1258−1267.
(38) Yang, M. Y.; Li, J.; Chen, P. R. Transition Metal-Mediated Bioorthogonal Protein Chemistry in Living Cells. *Chem. Soc. Rev.* **2014**, *43*, 6511−6526.
(39) Sumerlin, B. S.; Vogt, A. P. Macromolecular Engineering through Click Chemistry and Other Efficient Transformations. *Macromolecules* **2010**, *43*, 1−13.
(40) Trost, B. M. Atom Economy - a Challenge for Organic-Synthesis - Homogeneous Catalysis Leads the Way. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.
(41) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.
(42) Gil, M. V.; Arevalo, M. J.; Lopez, O. Click Chemistry - What's in a Name? Triazole Synthesis and Beyond. *Synthesis* **2007**, *2007*, 1589−1620.
(43) Becer, C. R.; Hoogenboom, R.; Schubert, U. S. Click Chemistry Beyond Metal-Catalyzed Cycloaddition. *Angew. Chem., Int. Ed.* **2009**, *48*, 4900−4908.
(44) Moses, J. E.; Moorhouse, A. D. The Growing Applications of Click Chemistry. *Chem. Soc. Rev.* **2007**, *36*, 1249−1262.
(45) Himbert, G.; Frank, D.; Regit, M. Investigations on Diazo-Compounds and Azides 0.25. Azide Additions on (Silylethynyl)Amines, (Germylethynyl)Amines, and (Stannylethynyl)Amines. *Chem. Ber.* **1976**, *109*, 370−394.
(46) Boyer, N.; Mack, C.; Goebel, N.; Morgan, L., Jr. Notes - Reactions of Sodium Phenylacetylide and Sodium Alkoxide with Tosyl and Mesyl Azides. *J. Org. Chem.* **1958**, *23*, 1051−1053.
(47) Akimova, G.; Chistokletov, V.; Petrov, A. 1,3-Bipolar Addition to Unsaturated Compounds XVII. The Reaction of Azides with Iotsich Complexes Obtained from Phenyl- and Alkenylacetylenes. *Zh. Obshch. Khim.* **1967**, *3*, 968−974.
(48) Akimova, G.; Chistokletov, V.; Petrov, A. 1,3-Bipolar Addition to Unsaturated Compounds XVIII. Reaction of Aliphatic and Aromatic Azides with the Iotsich Complexes Obtained from Acetylene, Diacetylene, and Their Homologs. *Zh. Obshch. Khim.* **1967**, *3*, 2241−2247.
(49) Akimova, G.; Chistokletov, V.; Petrov, A. 1,3-Dipolar Addition to Unsaturated Compounds XIX. Reactions of Aryl Azides with Lithium Acetylides. *Zh. Obshch. Khim.* **1968**, *4*, 389−394.
(50) Krasiński, A.; Fokin, V. V.; Sharpless, K. B. Direct Synthesis of 1,5-Disubstituted-4-Magnesio-1,2,3-Triazoles, Revisited. *Org. Lett.* **2004**, *6*, 1237−1240.
(51) *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, Germany, 2005.
(52) Oakdale, J. S.; Fokin, V. V. Preparation of 1,5-Disubstituted 1,2,3-Triazoles via Ruthenium-Catalyzed Azide Alkyne Cycloaddition. *Org. Synth.* **2013**, *90*, 96−104.
(53) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. *J. Am. Chem. Soc.* **2005**, *127*, 210−216.
(54) Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. Coordination Chemistry of Organic Azides and Amination Reactions Catalyzed by Transition Metal Complexes. *Coord. Chem. Rev.* **2006**, *250*, 1234−1253.
(55) Jones, G. O.; Houk, K. N. Predictions of Substituent Effects in Thermal Azide 1,3-Dipolar Cycloadditions: Implications for Dynamic Combinatorial (Reversible) and Click (Irreversible) Chemistry. *J. Org. Chem.* **2008**, *73*, 1333−1342.
(56) Montgomery, J. A.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. A Complete Basis Set Model Chemistry. VI. Use of Density Functional Geometries and Frequencies. *J. Chem. Phys.* **1999**, *110*, 2822−2827.
(57) Zhou, Y. B.; Ke, Z. F.; Zhao, C. Y. A Theoretical Study on the Mechanism of Ruthenium(II)-Catalyzed Reaction of Organic Azide with Alkyne. *Acta Chim. Sin.* **2006**, *64*, 2071−2078.
(58) Boz, E.; Tüzün, N. S. Reaction Mechanism of Ruthenium-Catalyzed Azide-Alkyne Cycloaddition Reaction: A DFT Study. *J. Organomet. Chem.* **2013**, *724*, 167−176.
(59) Hou, D. R.; Kuan, T. C.; Li, Y. K.; Lee, R.; Huang, K. W. Electronic Effects of Ruthenium-Catalyzed [3 + 2]-Cycloaddition of Alkynes and Azides. *Tetrahedron* **2010**, *66*, 9415−9420.
(60) Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Oxford University Press: New York, 1990.
(61) Biegler-Konig, F.; Schonbohm, J.; Bayles, D. Software News and Updates - Aim2000 - a Program to Analyze and Visualize Atoms in Molecules. *J. Comput. Chem.* **2001**, *22*, 545−559.
(62) Liu, P. N.; Li, J.; Su, F. H.; Ju, K. D.; Zhang, L.; Shi, C.; Sung, H. H. Y.; Williams, I. D.; Fokin, V. V.; Lin, Z. Y.; et al. Selective Formation of 1,4-Disubstituted Triazoles from Ruthenium-Catalyzed Cycloaddition of Terminal Alkynes and Organic Azides: Scope and Reaction Mechanism. *Organometallics* **2012**, *31*, 4904−4915.
(63) Lamberti, M.; Fortman, G. C.; Poater, A.; Broggi, J.; Slawin, A. M. Z.; Cavallo, L.; Nolan, S. P. Coordinatively Unsaturated Ruthenium Complexes as Efficient Alkyne-Azide Cycloaddition Catalysts. *Organometallics* **2012**, *31*, 756−767.
(64) Zhang, L.; Sung, H. H. Y.; Williams, I. D.; Lin, Z. Y.; Jia, G. C. Reactions of Cp*RuCl(COD) with Alkynes: Isolation of Dinuclear Metallacyclopentatriene Complexes. *Organometallics* **2008**, *27*, 5122−5129.

DOI: 10.1021/acs.chemrev.6b00466
Chem. Rev. 2016, 116, 14726−14768

(65) Johansson, J. R.; Lincoln, P.; Norden, B.; Kann, N. Sequential One-Pot Ruthenium-Catalyzed Azide-Alkyne Cycloaddition from Primary Alkyl Halides and Sodium Azide. *J. Org. Chem.* **2011**, *76*, 2355−2359.
(66) Ferrer, I.; Fontrodona, X.; Rodriguez, M.; Romero, I. Ru(II)-DMSO Complexes Containing Azole-Based Ligands: Synthesis, Linkage Isomerism and Catalytic Behaviour. *Dalton Trans.* **2016**, *45*, 3163−3174.
(67) Kappe, C. O.; Van der Eycken, E. Click Chemistry under Non-Classical Reaction Conditions. *Chem. Soc. Rev.* **2010**, *39*, 1280−1290.
(68) Barge, A.; Tagliapietra, S.; Binello, A.; Cravotto, G. Click Chemistry under Microwave or Ultrasound Irradiation. *Curr. Org. Chem.* **2011**, *15*, 189−203.
(69) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. Ruthenium-Catalyzed Cycloaddition of Aryl Azides and Alkynes. *Org. Lett.* **2007**, *9*, 5337−5339.
(70) de Andrade, P.; Galo, O. A.; Carvalho, M. R.; Lopes, C. D.; Carneiro, Z. A.; Sesti-Costa, R.; de Melo, E. B.; Silva, J. S.; Carvalho, I. 1,2,3-Triazole-Based Analogue of Benznidazole Displays Remarkable Activity against Trypanosoma Cruzi. *Bioorg. Med. Chem.* **2015**, *23*, 6815−6826.
(71) Pradere, U.; Roy, V.; McBrayer, T. R.; Schinazi, R. F.; Agrofoglio, L. A. Preparation of Ribavirin Analogues by Copper- and Ruthenium-Catalyzed Azide-Alkyne 1,3-Dipolar Cycloaddition. *Tetrahedron* **2008**, *64*, 9044−9051.
(72) Feldman, A. K.; Colasson, B.; Fokin, V. V. One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from in Situ Generated Azides. *Org. Lett.* **2004**, *6*, 3897−3899.
(73) Kacprzak, K. Efficient One-Pot Synthesis of 1,2,3-Triazoles from Benzyl and Alkyl Halides. *Synlett* **2005**, 943−946.
(74) Andersen, J.; Bolvig, S.; Liang, X. F. Efficient One-Pot Synthesis of 1-Aryl 1,2,3-Triazoles from Aryl Halides and Terminal Alkynes in the Presence of Sodium Azide. *Synlett* **2005**, 2941−2947.
(75) Taqui Khan, M. M.; Bhadbhade, M. M.; Siddiqui, M. R. H.; Venkatasubramanian, K.; Tikhonova, J. A. Azido(Eta(5)-Cyclopentadienyl)Bis(Triphenylphosphine)Ruthenium(II). *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1994**, *50*, 502−504.
(76) Risse, J.; Scopelliti, R.; Severin, K. Beyond Click-Chemistry: Transformation of Azides with Cyclopentadienyl Ruthenium Complexes. *Organometallics* **2011**, *30*, 3412−3418.
(77) Majireck, M. M.; Weinreb, S. M. A Study of the Scope and Regioselectivity of the Ruthenium-Catalyzed [3 + 2]-Cycloaddition of Azides with Internal Alkynes. *J. Org. Chem.* **2006**, *71*, 8680−8683.
(78) Creary, X.; Anderson, A.; Brophy, C.; Crowell, F.; Funk, Z. Method for Assigning Structure of 1,2,3-Triazoles. *J. Org. Chem.* **2012**, *77*, 8756−8761.
(79) Andersson, H.; Carlsson, A. C. C.; Nekoueishahraki, B.; Brath, U.; Erdelyi, M. Solvent Effects on Nitrogen Chemical Shifts. *Annu. Rep. NMR Spectrosc.* **2015**, *86*, 73−210.
(80) Corredor, M.; Bujons, J.; Messeguer, A.; Alfonso, I. N-15 NMR Spectroscopic and Theoretical Giao-DFT Studies for the Unambiguous Characterization of Disubstituted 1,2,3-Triazoles. *Org. Biomol. Chem.* **2013**, *11*, 7318−7325.
(81) Marquez, B. L.; Gerwick, W. H.; Williamson, R. T. Survey of NMR Experiments for the Determination of ^{n}J(C,H) Heteronuclear Coupling Constants in Small Molecules. *Magn. Reson. Chem.* **2001**, *39*, 499−530.
(82) Keicher, T.; Löbbecke, S. Lab-Scale Synthesis of Azido Compounds: Safety Measures and Analysis. In *Organic Azides: Synthesis and Applications*; Bräse, S., Banert, K., Eds.; John Wiley and Sons, Ltd.: Chichester, U.K., 2010; pp 1−27.
(83) Yap, A. H.; Weinreb, S. M. Beta-Tosylethylazide: A Useful Synthon for Preparation of N-Protected 1,2,3-Triazoles via Click Chemistry. *Tetrahedron Lett.* **2006**, *47*, 3035−3038.
(84) Chattopadhyay, B.; Vera, C. I. R.; Chuprakov, S.; Gevorgyan, V. Fused Tetrazoles as Azide Surrogates in Click Reaction: Efficient Synthesis of N-Heterocycle-Substituted 1,2,3-Triazoles. *Org. Lett.* **2010**, *12*, 2166−2169.
(85) Farooq, T.; Haug, B. E.; Sydnes, L. K.; Tornroos, K. W. 1,3-Dipolar Cycloaddition of Benzyl Azide to Two Highly Functionalized Alkynes. *Monatsh. Chem.* **2012**, *143*, 505−512.
(86) Farooq, T.; Sydnes, L. K.; Tornroos, K. W.; Haug, B. E. Debenzylation of Functionalized 4-and 5-Substituted 1,2,3-Triazoles. *Synthesis* **2012**, *44*, 2070−2078.
(87) Harmsen, R. A. G.; Sydnes, L. K.; Tornroos, K. W.; Haug, B. E. Synthesis of *trans*-4-Triazolyl-Substituted 3-Hydroxypiperidines. *Synthesis* **2011**, *2011*, 749−754.
(88) Pribut, N.; Veale, C. G. L.; Basson, A. E.; van Otterlo, W. A. L.; Pelly, S. C. Application of the Huisgen Cycloaddition and 'Click' Reaction toward Various 1,2,3-Triazoles as HIV Non-Nucleoside Reverse Transcriptase Inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3700−3704.
(89) Zhang, C. T.; Zhang, X.; Qing, F. L. Ruthenium-Catalyzed 1,3-Dipolar Cycloaddition of Trifluoromethylated Propargylic Alcohols with Azides. *Tetrahedron Lett.* **2008**, *49*, 3927−3930.
(90) Neumajer, G.; Toth, G.; Beni, S.; Noszal, B. Novel Ion-Binding C3 Symmetric Tripodal Triazoles: Synthesis and Characterization. *Cent. Eur. J. Chem.* **2014**, *12*, 115−125.
(91) Oakdale, J. S.; Sit, R. K.; Fokin, V. V. Ruthenium-Catalyzed Cycloadditions of 1-Haloalkynes with Nitrile Oxides and Organic Azides: Synthesis of 4-Haloisoxazoles and 5-Halotriazoles. *Chem. - Eur. J.* **2014**, *20*, 11101−11110.
(92) Krompiec, S.; Filapek, M.; Grudzka-Flak, I.; Slodek, A.; Kula, S.; Malecki, J. G.; Malarz, J.; Szafraniec-Gorol, G.; Penkala, M.; Schab-Balcerzak, E.; et al. Multifaceted Strategy for the Synthesis of Diverse 2,2′-Bithiophene Derivatives. *Molecules* **2015**, *20*, 4565−4593.
(93) Oppilliart, S.; Mousseau, G.; Zhang, L.; Jia, G. C.; Thuery, P.; Rousseau, B.; Cintrat, J. C. 1-Protected 5-Amido 1,2,3-Triazoles via Ruthenium-Catalyzed [3 + 2] Cycloaddition of Azides and Ynamides. *Tetrahedron* **2007**, *63*, 8094−8098.
(94) Ijsselstijn, M.; Cintrat, J. C. Click Chemistry with Ynamides. *Tetrahedron* **2006**, *62*, 3837−3842.
(95) Ferrini, S.; Chandanshive, J. Z.; Lena, S.; Comes Franchini, M.; Giannini, G.; Tafi, A.; Taddei, M. Ruthenium-Catalyzed Synthesis of 5-Amino-1,2,3-Triazole-4-Carboxylates for Triazole-Based Scaffolds: Beyond the Dimroth Rearrangement. *J. Org. Chem.* **2015**, *80*, 2562−2572.
(96) Diaz, J. L.; Christmann, U.; Fernandez, A.; Torrens, A.; Port, A.; Pascual, R.; Alvarez, I.; Burgueno, J.; Monroy, X.; Montero, A.; et al. Synthesis and Structure-Activity Relationship Study of a New Series of Selective σ_1 Receptor Ligands for the Treatment of Pain: 4-Aminotriazoles. *J. Med. Chem.* **2015**, *58*, 2441−2451.
(97) Shen, Q.; Han, E. J.; Huang, Y. G.; Chen, Q. Y.; Guo, Y. Synthesis of Fluorinated 1,4,5-Substituted 1,2,3-Triazoles by RuAAC Reaction. *Synthesis* **2015**, *47*, 3936−3946.
(98) Lo, Y. H.; Wang, T. H.; Lee, C. Y.; Feng, Y. H. Preparation, Characterization, and Reactivity of Azido Complex Containing a Tp(^{t}BuNC)(PPh$_3$)Ru Fragment and Ruthenium-Catalyzed Cycloaddition of Organic Azides with Alkynes in Organic and Aqueous Media. *Organometallics* **2012**, *31*, 6887−6899.
(99) Wang, T. H.; Wu, F. L.; Chiang, G. R.; He, S. T.; Lo, Y. H. Preparation of Ruthenium Azido Complex Containing a Tp Ligand and Ruthenium-Catalyzed Cycloaddition of Organic Azides with Alkynes in Organic and Aqueous Media: Experimental and Computational Studies. *J. Organomet. Chem.* **2014**, *774*, 57−60.
(100) Wang, D.; Salmon, L.; Ruiz, J.; Astruc, D. A Recyclable Ruthenium(II) Complex Supported on Magnetic Nanoparticles: A Regioselective Catalyst for Alkyne-Azide Cycloaddition. *Chem. Commun.* **2013**, *49*, 6956−6958.
(101) Liu, P. N.; Siyang, H. X.; Zhang, L.; Tse, S. K. S.; Jia, G. C. RuH$_2$(CO)(PPh$_3$)$_3$ Catalyzed Selective Formation of 1,4-Disubstituted Triazoles from Cycloaddition of Alkynes and Organic Azides. *J. Org. Chem.* **2012**, *77*, 5844−5849.
(102) Siyang, H. X.; Liu, H. L.; Wu, X. Y.; Liu, P. N. Highly Efficient Click Reaction on Water Catalyzed by a Ruthenium Complex. *RSC Adv.* **2015**, *5*, 4693−4697.

DOI: 10.1021/acs.chemrev.6b00466
Chem. Rev. 2016, 116, 14726−14768

(103) Dumoulin, F.; Ahsen, V. Click Chemistry: The Emerging Role of the Azide-Alkyne Huisgen Dipolar Addition in the Preparation of Substituted Tetrapyrrolic Derivatives. *J. Porphyrins Phthalocyanines* **2011**, *15*, 481−504.
(104) Chrominski, M.; Zieleniewska, A.; Karczewski, M.; Gryko, D. Porphyrins as Substrates in CuAAC - Exclusion of Unwanted Copper Insertion into the Macrocyclic Core. *J. Porphyrins Phthalocyanines* **2014**, *18*, 267−281.
(105) Zardi, P.; Savoldelli, A.; Carminati, D. M.; Caselli, A.; Ragaini, F.; Gallo, E. Indoles Rather Than Triazoles from the Ruthenium Porphyrin-Catalyzed Reaction of Alkynes with Aryl Azides. *ACS Catal.* **2014**, *4*, 3820−3823.
(106) Kumar, A. P.; Baek, M. W.; Sridhar, C.; Kumar, B. P.; Lee, Y. I. Synthesis and Catalytic Applications of Ruthenium(0) Nanoparticles in Click Chemistry. *Bull. Korean Chem. Soc.* **2014**, *35*, 1144−1148.
(107) Molla, R. A.; Roy, A. S.; Ghosh, K.; Salam, N.; Iqubal, M. A.; Tuhina, K.; Islam, S. M. Polymer Anchored Ruthenium Complex: A Highly Active and Recyclable Catalyst for One-Pot Azide-Alkyne Cycloaddition and Transfer-Hydrogenation of Ketones under Mild Conditions. *J. Organomet. Chem.* **2015**, *776*, 170−179.
(108) Das, U. K.; Jena, R. K.; Bhattacharjee, M. Synthesis, Structure and Catalytic Properties of $Ru(dppp)_2(CH_3CN)Cl\ BPh_4$ and Isolation of Catalytically Active $Ru(dppp)_2Cl\ BPh_4$: Ruthenium Catalysed Alkyne Homocoupling and Tandem Alkyne-Azide Cycloaddition. *RSC Adv.* **2014**, *4*, 21964−21970.
(109) Horne, W. S.; Olsen, C. A.; Beierle, J. M.; Montero, A.; Ghadiri, M. R. Probing the Bioactive Conformation of an Archetypal Natural Product HDAC Inhibitor with Conformationally Homogeneous Triazole-Modified Cyclic Tetrapeptides. *Angew. Chem., Int. Ed.* **2009**, *48*, 4718−4724.
(110) Empting, M.; Avrutina, O.; Meusinger, R.; Fabritz, S.; Reinwarth, M.; Biesalski, M.; Voigt, S.; Buntkowsky, G.; Kolmar, H. "Triazole Bridge": Disulfide-Bond Replacement by Ruthenium-Catalyzed Formation of 1,5-Disubstituted 1,2,3-Triazoles. *Angew. Chem., Int. Ed.* **2011**, *50*, 5207−5211.
(111) Wrobel, M.; Aube, J.; Konig, B. Parallel Solid-Phase Synthesis of Diaryltriazoles. *Beilstein J. Org. Chem.* **2012**, *8*, 1027−1036.
(112) Tischler, M.; Nasu, D.; Empting, M.; Schmelz, S.; Heinz, D. W.; Rottmann, P.; Kolmar, H.; Buntkowsky, G.; Tietze, D.; Avrutina, O. Braces for the Peptide Backbone: Insights into Structure-Activity Relationships of Protease Inhibitor Mimics with Locked Amide Conformations. *Angew. Chem., Int. Ed.* **2012**, *51*, 3708−3712.
(113) Pandey, A. K.; Naduthambi, D.; Thomas, K. M.; Zondlo, N. J. Proline Editing: A General and Practical Approach to the Synthesis of Functionally and Structurally Diverse Peptides. Analysis of Steric Versus Stereoelectronic Effects of 4-Substituted Prolines on Conformation within Peptides. *J. Am. Chem. Soc.* **2013**, *135*, 4333−4363.
(114) Trabocchi, A.; Guarna, A. *Peptidomimetics in Organic and Medicinal Chemistry: The Art of Transforming Peptides in Drugs*; John Wiley & Sons, Ltd.: 2014.
(115) Scott, D. E.; Bayly, A. R.; Abell, C.; Skidmore, J. Small Molecules, Big Targets: Drug Discovery Faces the Protein−Protein Interaction Challenge. *Nat. Rev. Drug Discovery* **2016**, *15*, 533−550.
(116) Fischer, G. Chemical Aspects of Peptide Bond Isomerisation. *Chem. Soc. Rev.* **2000**, *29*, 119−127.
(117) Angell, Y. L.; Burgess, K. Peptidomimetics via Copper-Catalyzed Azide-Alkyne Cycloadditions. *Chem. Soc. Rev.* **2007**, *36*, 1674−1689.
(118) Pokorski, J. K.; Miller Jenkins, L. M.; Feng, H. Q.; Durell, S. R.; Bai, Y. W.; Appella, D. H. Introduction of a Triazole Amino Acid into a Peptoid Oligomer Induces Turn Formation in Aqueous Solution. *Org. Lett.* **2007**, *9*, 2381−2383.
(119) Johansson, J. R.; Hermansson, E.; Norden, B.; Kann, N.; Beke-Somfai, T. Peptides from RuAAC-Derived 1,5-Disubstituted Triazole Units. *Eur. J. Org. Chem.* **2014**, *2014*, 2703−2713.
(120) Tam, A.; Arnold, U.; Soellner, M. B.; Raines, R. T. Protein Prosthesis: 1,5-Disubstituted 1,2,3 Triazoles as *cis*-Peptide Bond Surrogates. *J. Am. Chem. Soc.* **2007**, *129*, 12670−12671.
(121) Knowles, J. R. Tinkering with Enzymes - What Are We Learning. *Science* **1987**, *236*, 1252−1258.
(122) Tietze, D.; Tischler, M.; Voigt, S.; Imhof, D.; Ohlenschlager, O.; Gorlach, M.; Buntkowsky, G. Development of a Functional *cis*-Prolyl Bond Biomimetic and Mechanistic Implications for Nickel Superoxide Dismutase. *Chem. - Eur. J.* **2010**, *16*, 7572−7578.
(123) Korsinczky, M. L. J.; Schirra, H. J.; Rosengren, K. J.; West, J.; Condie, B. A.; Otvos, L.; Anderson, M. A.; Craik, D. J. Solution Structures by ^1H NMR of the Novel Cyclic Trypsin Inhibitor STFI-1 from Sunflower Seeds and an Acyclic Permutant. *J. Mol. Biol.* **2001**, *311*, 579−591.
(124) Lau, Y. H.; De Andrade, P.; Wu, Y. T.; Spring, D. R. Peptide Stapling Techniques Based on Different Macrocyclisation Chemistries. *Chem. Soc. Rev.* **2015**, *44*, 91−102.
(125) Roux, S.; Ligeti, M.; Buisson, D. A.; Rousseau, B.; Cintrat, J. C. Synthesis of Orthogonally Protected Azahistidine: Application to the Synthesis of a GHK Analogue. *Amino Acids* **2010**, *38*, 279−286.
(126) Ikeda, Y.; Kawahara, S.; Taki, M.; Kuno, A.; Hasegawa, T.; Taira, K. Synthesis of a Novel Histidine Analogue and Its Efficient Incorporation into a Protein in Vivo. *Protein Eng., Des. Sel.* **2003**, *16*, 699−706.
(127) Loren, J. C.; Krasinski, A.; Fokin, V. V.; Sharpless, K. B. NH-1,2,3-Triazoles from Azidomethyl Pivalate and Carbamates: Base-Labile N-Protecting Groups. *Synlett* **2005**, 2847−2850.
(128) Gruchlik, A.; Jurzak, M.; Chodurek, E.; Dzierzewicz, Z. Effect of Gly-Gly-His, Gly-His-Lys and Their Copper Complexes on TNF-Alpha-Dependent IL-6 Secretion in Normal Human Dermal Fibroblasts. *Acta Pol. Pharm.* **2012**, *69*, 1303−1306.
(129) Kee, J. M.; Villani, B.; Carpenter, L. R.; Muir, T. W. Development of Stable Phosphohistidine Analogues. *J. Am. Chem. Soc.* **2010**, *132*, 14327−14329.
(130) Tan, E. L.; Besant, P. G.; Zu, X. L.; Turck, C. W.; Bogoyevitch, M. A.; Lim, S. G.; Attwood, P. V.; Yeoh, G. C. Histone H4 Histidine Kinase Displays the Expression Pattern of a Liver Oncodevelopmental Marker. *Carcinogenesis* **2004**, *25*, 2083−2088.
(131) Schnolzer, M.; Alewood, P.; Jones, A.; Alewood, D.; Kent, S. B. H. In Situ Neutralization in Boc-Chemistry Solid-Phase Peptide-Synthesis - Rapid, High-Yield Assembly of Difficult Sequences. *Int. J. Pept. Protein Res.* **1992**, *40*, 180−193.
(132) Buysse, K.; Farard, J.; Nikolaou, A.; Vanderheyden, P.; Vauquelin, G.; Sejer Pedersen, D.; Tourwe, D.; Ballet, S. Amino Triazolo Diazepines (Ata) as Constrained Histidine Mimics. *Org. Lett.* **2011**, *13*, 6468−6471.
(133) Wales, S. M.; Hammer, K. A.; King, A. M.; Tague, A. J.; Lyras, D.; Riley, T. V.; Keller, P. A.; Pyne, S. G. Binaphthyl-1,2,3-Triazole Peptidomimetics with Activity against Clostridium Difficile and Other Pathogenic Bacteria. *Org. Biomol. Chem.* **2015**, *13*, 5743−5756.
(134) Azzarito, V.; Long, K.; Murphy, N. S.; Wilson, A. J. Inhibition of Alpha-Helix-Mediated Protein-Protein Interactions Using Designed Molecules. *Nat. Chem.* **2013**, *5*, 161−173.
(135) Bullock, B. N.; Jochim, A. L.; Arora, P. S. Assessing Helical Protein Interfaces for Inhibitor Design. *J. Am. Chem. Soc.* **2011**, *133*, 14220−14223.
(136) Edwards, T. A.; Wilson, A. J. Helix-Mediated Protein-Protein Interactions as Targets for Intervention Using Foldamers. *Amino Acids* **2011**, *41*, 743−754.
(137) Saraogi, I.; Hamilton, A. D. Alpha-Helix Mimetics as Inhibitors of Protein-Protein Interactions. *Biochem. Soc. Trans.* **2008**, *36*, 1414−1417.
(138) Davis, J. M.; Tsou, L. K.; Hamilton, A. D. Synthetic Non-Peptide Mimetics of Alpha-Helices. *Chem. Soc. Rev.* **2007**, *36*, 326−334.
(139) Cummings, C. G.; Hamilton, A. D. Disrupting Protein-Protein Interactions with Non-Peptidic, Small Molecule Alpha-Helix Mimetics. *Curr. Opin. Chem. Biol.* **2010**, *14*, 341−346.
(140) Ripka, A. S.; Rich, D. H. Peptidomimetic Design. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441−452.
(141) Ehlers, I.; Maity, P.; Aube, J.; Konig, B. Modular Synthesis of Triazole-Containing Triaryl Alpha-Helix Mimetics. *Eur. J. Org. Chem.* **2011**, 2474−2490.
(142) Pettersson, M.; Bliman, D.; Jacobsson, J.; Nilsson, J. R.; Min, J.; Iconaru, L.; Guy, R. K.; Kriwacki, R. W.; Andreasson, J.; Grøtli, M. 8-

DOI: 10.1021/acs.chemrev.6b00466
Chem. Rev. 2016, 116, 14726−14768

Triazolylpurines: Towards Fluorescent Inhibitors of the MDM2/p53 Interaction. *PLoS One* **2015**, *10*, e0124423.
(143) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. Beta-Peptides: Synthesis by Arndt-Eistert Homologation with Concomitant Peptide Coupling. Structure Determination by NMR and CD Spectroscopy and by X-Ray Crystallography. Helical Secondary Structure of a Beta-Hexapeptide in Solution and Its Stability Towards Pepsin. *Helv. Chim. Acta* **1996**, *79*, 913−941.
(144) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. Beta-Peptide Foldamers: Robust Helix Formation in a New Family of Beta-Amino Acid Oligomers. *J. Am. Chem. Soc.* **1996**, *118*, 13071−13072.
(145) Seebach, D.; Beck, A. K.; Bierbaum, D. J. The World of Beta- and Gamma-Peptides Comprised of Homologated Proteinogenic Amino Acids and Other Components. *Chem. Biodiversity* **2004**, *1*, 1111−1239.
(146) Horne, W. S.; Gellman, S. H. Foldamers with Heterogeneous Backbones. *Acc. Chem. Res.* **2008**, *41*, 1399−1408.
(147) Gopalakrishnan, R.; Frolov, A. I.; Knerr, L.; Drury, W. J., III; Valeur, E. Therapeutic Potential of Foldamers: From Chemical Biology Tools to Drug Candidates? *J. Med. Chem.* **2016**, DOI: 10.1021/acs.jmedchem.6b00376.
(148) Johansson, H.; Pedersen, D. S. Azide- and Alkyne-Derivatised Alpha-Amino Acids. *Eur. J. Org. Chem.* **2012**, *2012*, 4267−4281.
(149) Kann, N.; Johansson, J. R.; Beke-Somfai, T. Conformational Properties of 1,4-and 1,5-Substituted 1,2,3-Triazole Amino Acids - Building Units for Peptidic Foldamers. *Org. Biomol. Chem.* **2015**, *13*, 2776−2785.
(150) Ke, Z. H.; Chow, H. F.; Chan, M. C.; Liu, Z. F.; Sze, K. H. Head-to-Tail Dimerization and Organogelating Properties of Click Peptidomimetics. *Org. Lett.* **2012**, *14*, 394−397.
(151) Sola, J.; Bolte, M.; Alfonso, I. Conformational Promiscuity in Triazolamers Derived from Quaternary Amino Acids Mimics Peptide Behaviour. *Org. Biomol. Chem.* **2015**, *13*, 10797−10801.
(152) *Macrocycles in Drug Discovery*; Levin, J. I., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 2015.
(153) Majumdar, K. C.; Ray, K. Synthesis of 1,2,3-Triazole-Fused Heterocycles via Intramolecular Azide-Alkyne Cycloaddition Reactions. *Synthesis* **2011**, *2011*, 3767−3783.
(154) Matsson, P.; Doak, B.; Over, B.; Kihlberg, J. Cell Permeability Beyond the Rule of 5. *Adv. Drug Delivery Rev.* **2016**, *101*, 42−61.
(155) White, C. J.; Yudin, A. K. Contemporary Strategies for Peptide Macrocyclization. *Nat. Chem.* **2011**, *3*, 509−524.
(156) Kelly, A. R.; Wei, J. Q.; Kesavan, S.; Marie, J. C.; Windmon, N.; Young, D. W.; Marcaurelle, L. A. Accessing Skeletal Diversity Using Catalyst Control: Formation of N and N+1 Macrocyclic Triazole Rings. *Org. Lett.* **2009**, *11*, 2257−2260.
(157) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D.; Liu, H. B.; Lowe, J. T.; Marie, J. C.; et al. An Aldol-Based Build/Couple/Pair Strategy for the Synthesis of Medium- and Large-Sized Rings: Discovery of Macrocyclic Histone Deacetylase Inhibitors. *J. Am. Chem. Soc.* **2010**, *132*, 16962−16976.
(158) Nielsen, T. E.; Schreiber, S. L. Diversity-Oriented Synthesis - Towards the Optimal Screening Collection: A Synthesis Strategy. *Angew. Chem., Int. Ed.* **2008**, *47*, 48−56.
(159) Parsons, J. G.; Sheehan, C. S.; Wu, Z. M.; James, I. W.; Bray, A. M. A Review of Solid-Phase Organic Synthesis on Synphase Lanterns and Synphase Crowns. In *Combinatorial Chemistry, Part B*; Morales, G. S., Bunin, B. A., Eds.; Elsevier: San Diego, 2003; Vol. *369*, pp 39−74.
(160) Zhang, J. Q.; Kemmink, J.; Rijkers, D. T. S.; Liskamp, R. M. J. Cu(I)- and Ru(II)-Mediated "Click" Cyclization of Tripeptides toward Vancomycin-Inspired Mimics. *Org. Lett.* **2011**, *13*, 3438−3441.
(161) Zhang, J. Q.; Kemmink, J.; Rijkers, D. T. S.; Liskamp, R. M. J. Synthesis of 1,5-Triazole Bridged Vancomycin CDE-Ring Bicyclic Mimics Using RuAAC Macrocyclization. *Chem. Commun.* **2013**, *49*, 4498−4500.
(162) Rosengren, K. J.; Daly, N. L.; Plan, M. R.; Waine, C.; Craik, D. J. Twists, Knots, and Rings in Proteins - Structural Definition of the Cyclotide Framework. *J. Biol. Chem.* **2003**, *278*, 8606−8616.
(163) Craik, D. J.; Swedberg, J. E.; Mylne, J. S.; Cemazar, M. Cyclotides as a Basis for Drug Design. *Expert Opin. Drug Discovery* **2012**, *7*, 179−194.
(164) Poth, A. G.; Chan, L. Y.; Craik, D. J. Cyclotides as Grafting Frameworks for Protein Engineering and Drug Design Applications. *Biopolymers* **2013**, *100*, 480−491.
(165) Craik, D. J. Joseph Rudinger Memorial Lecture: Discovery and Applications of Cyclotides. *J. Pept. Sci.* **2013**, *19*, 393−407.
(166) Burman, R.; Gunasekera, S.; Stromstedt, A. A.; Goransson, U. Chemistry and Biology of Cyclotides: Circular Plant Peptides Outside the Box. *J. Nat. Prod.* **2014**, *77*, 724−736.
(167) Kolmar, H. Biological Diversity and Therapeutic Potential of Natural and Engineered Cystine Knot Miniproteins. *Curr. Opin. Pharmacol.* **2009**, *9*, 608−614.
(168) Isidro-Llobet, A.; Murillo, T.; Bello, P.; Cilibrizzi, A.; Hodgkinson, J. T.; Galloway, W.; Bender, A.; Welch, M.; Spring, D. R. Diversity-Oriented Synthesis of Macrocyclic Peptidomimetics. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6793−6798.
(169) Krause, M. R.; Goddard, R.; Kubik, S. Anion-Binding Properties of a Cyclic Pseudohexapeptide Containing 1,5-Disubstituted 1,2,3-Triazole Subunits. *J. Org. Chem.* **2011**, *76*, 7084−7095.
(170) Krause, M. R.; Goddard, R.; Kubik, S. Formation of a Cyclic Tetrapeptide Mimic by Thermal Azide-Alkyne 1,3-Dipolar Cycloaddition. *Chem. Commun.* **2010**, *46*, 5307−5309.
(171) Fang, F.; Vogel, M.; Hines, J. V.; Bergmeier, S. C. Fused Ring Aziridines as a Facile Entry into Triazole Fused Tricyclic and Bicyclic Heterocycles. *Org. Biomol. Chem.* **2012**, *10*, 3080−3091.
(172) Iglesias, L. E.; Lewkowicz, E. S.; Medici, R.; Bianchi, P.; Iribarren, A. M. Biocatalytic Approaches Applied to the Synthesis of Nucleoside Prodrugs. *Biotechnol. Adv.* **2015**, *33*, 412−434.
(173) Pradere, U.; Garnier-Amblard, E. C.; Coats, S. J.; Amblard, F.; Schinazi, R. F. Synthesis of Nucleoside Phosphate and Phosphonate Prodrugs. *Chem. Rev.* **2014**, *114*, 9154−9218.
(174) Hernandez, D.; Boto, A. Nucleoside Analogues: Synthesis and Biological Properties of Azanucleoside Derivatives. *Eur. J. Org. Chem.* **2014**, *2014*, 2201−2220.
(175) Amblard, F.; Cho, J. H.; Schinazi, R. F. Cu(I)-Catalyzed Huisgen Azide-Alkyne 1,3-Dipolar Cycloaddition Reaction in Nucleoside, Nucleotide, and Oligonucleotide Chemistry. *Chem. Rev.* **2009**, *109*, 4207−4220.
(176) Feld, J. J.; Hoofnagle, J. H. Mechanism of Action of Interferon and Ribavirin in Treatment of Hepatitis C. *Nature* **2005**, *436*, 967−972.
(177) Montagu, A.; Roy, V.; Balzarini, J.; Snoeck, R.; Andrei, G.; Agrofoglio, L. A. Synthesis of New C5-(1-Substituted-1,2,3-Triazol-4 or 5-yl)-2′-Deoxyuridines and Their Antiviral Evaluation. *Eur. J. Med. Chem.* **2011**, *46*, 778−786.
(178) Hornum, M.; Djukina, A.; Sassnau, A. K.; Nielsen, P. Synthesis of New C-5-Triazolyl-Functionalized Thymidine Analogs and Their Ability to Engage in Aromatic Stacking in DNA: DNA and DNA: RNA Duplexes. *Org. Biomol. Chem.* **2016**, *14*, 4436−4447.
(179) Chemama, M.; Fonvielle, M.; Arthur, M.; Valery, J. M.; Etheve-Quelquejeu, M. Synthesis of Stable Aminoacyl-tRNA Analogues Containing Triazole as a Bioisoster of Esters. *Chem. - Eur. J.* **2009**, *15*, 1929−1938.
(180) Sirivolu, V. R.; Vernekar, S. K. V.; Ilina, T.; Myshakina, N. S.; Parniak, M. A.; Wang, Z. Q. Clicking 3′-Azidothymidine into Novel Potent Inhibitors of Human Immunodeficiency Virus. *J. Med. Chem.* **2013**, *56*, 8765−8780.
(181) Vernekar, S. K. V.; Qiu, L.; Zacharias, J.; Geraghty, R. J.; Wang, Z. Q. Synthesis and Antiviral Evaluation of 4′-(1,2,3-Triazol-1-yl)-Thymidines. *MedChemComm* **2014**, *5*, 603−608.
(182) Vernekar, S. K. V.; Qiu, L.; Zhang, J.; Kankanala, J.; Li, H. M.; Geraghty, R. J.; Wang, Z. Q. 5′-Silylated 3′-1,2,3-Triazolyl Thymidine Analogues as Inhibitors of West Nile Virus and Dengue Virus. *J. Med. Chem.* **2015**, *58*, 4016−4028.
(183) Broder, S. The Development of Antiretroviral Therapy and Its Impact on the HIV-1/AIDS Pandemic. *Antiviral Res.* **2010**, *85*, 1−18.
(184) Van Poecke, S.; Negri, A.; Gago, F.; Van Daele, I.; Solaroli, N.; Karlsson, A.; Balzarini, J.; Van Calenbergh, S. 3′- 4-Aryl-(1,2,3-Triazol-1-

DOI: 10.1021/acs.chemrev.6b00466
Chem. Rev. 2016, 116, 14726−14768

yl) −3′-Deoxythymidine Analogues as Potent and Selective Inhibitors of Human Mitochondrial Thymidine Kinase. *J. Med. Chem.* **2010**, *53*, 2902−2912.
(185) Dwek, R. A. Glycobiology: Toward Understanding the Function of Sugars. *Chem. Rev.* **1996**, *96*, 683−720.
(186) Gloster, T. M.; Vocadlo, D. J. Developing Inhibitors of Glycan Processing Enzymes as Tools for Enabling Glycobiology. *Nat. Chem. Biol.* **2012**, *8*, 683−694.
(187) Tiwari, V. K.; Mishra, B. B.; Mishra, K. B.; Mishra, N.; Singh, A. S.; Chen, X. Cu-Catalyzed Click Reaction in Carbohydrate Chemistry. *Chem. Rev.* **2016**, *116*, 3086−3240.
(188) Crich, D.; Yang, F. Phenylthiomethyl Glycosides: Convenient Synthons for the Formation of Azidomethyl and Glycosylmethyl Glycosides and Their Derivatives. *Angew. Chem., Int. Ed.* **2009**, *48*, 8896−8899.
(189) Wiebe, C.; Schlemmer, C.; Weck, S.; Opatz, T. Sweet (Hetero)Aromatics: Glycosylated Templates for the Construction of Saccharide Mimetics. *Chem. Commun.* **2011**, *47*, 9212−9214.
(190) Cagnoni, A. J.; Varela, O.; Uhrig, M. L.; Kovensky, J. Efficient Synthesis of Thiolactoside Glycoclusters by Ruthenium-Catalyzed Cycloaddition Reaction of Disubstituted Alkynes on Carbohydrate Scaffolds. *Eur. J. Org. Chem.* **2013**, *2013*, 972−983.
(191) Salmon, A. J.; Williams, M. L.; Maresca, A.; Supuran, C. T.; Poulsen, S. A. Synthesis of Glycoconjugate Carbonic Anhydrase Inhibitors by Ruthenium-Catalysed Azide-Alkyne 1,3-Dipolar Cycloaddition. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6058−6061.
(192) Jervis, P. J.; Graham, L. M.; Foster, E. L.; Cox, L. R.; Porcelli, S. A.; Besra, G. S. New CD1d Agonists: Synthesis and Biological Activity of 6″-Triazole-Substituted Alpha-Galactosyl Cramides. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4348−4352.
(193) Sharma, S.; Saquib, M.; Verma, S.; Mishra, N. N.; Shukla, P. K.; Srivastava, R.; Prabhakar, Y. S.; Shaw, A. K. Synthesis of 2,3,6-Trideoxy Sugar Triazole Hybrids as Potential New Broad Spectrum Antimicrobial Agents. *Eur. J. Med. Chem.* **2014**, *83*, 474−489.
(194) Arora, I.; Kashyap, V. K.; Singh, A. K.; Dasgupta, A.; Kumar, B.; Shaw, A. K. Design, Synthesis and Biological Evaluation of Bicyclic Iminosugar Hybrids: Conformational Constraint as an Effective Tool for Tailoring the Selectivity of Alpha-Glucosidase Inhibitors. *Org. Biomol. Chem.* **2014**, *12*, 6855−6868.
(195) Imperio, D.; Pirali, T.; Galli, U.; Pagliai, F.; Cafici, L.; Canonico, P. L.; Sorba, G.; Genazzani, A. A.; Tron, G. C. Replacement of the Lactone Moiety on Podophyllotoxin and Steganacin Analogues with a 1,5-Disubstituted 1,2,3-Triazole via Ruthenium-Catalyzed Click Chemistry. *Bioorg. Med. Chem.* **2007**, *15*, 6748−6757.
(196) Kocsis, L.; Szabo, I.; Bosze, S.; Jernei, T.; Hudecz, F.; Csámpai, A. Synthesis, Structure and in Vitro Cytostatic Activity of Ferrocene-Cinchona Hybrids. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 946−949.
(197) Odlo, K.; Hentzen, J.; dit Chabert, J. F.; Ducki, S.; Gani, O.; Sylte, I.; Skrede, M.; Florenes, V. A.; Hansen, T. V. 1,5-Disubstituted 1,2,3-Triazoles as *cis*-Restricted Analogues of Combretastatin A-4: Synthesis, Molecular Modeling and Evaluation as Cytotoxic Agents and Inhibitors of Tubulin. *Bioorg. Med. Chem.* **2008**, *16*, 4829−4838.
(198) Odlo, K.; Fournier-Dit-Chabert, J.; Ducki, S.; Gani, O.; Sylte, I.; Hansen, T. V. 1,2,3-Triazole Analogs of Combretastatin A-4 as Potential Microtubule-Binding Agents. *Bioorg. Med. Chem.* **2010**, *18*, 6874−6885.
(199) Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendal, D. Isolation and Structure of the Strong Cell-Growth and Tubulin Inhibitor Combretastatin-A-4. *Experientia* **1989**, *45*, 209−211.
(200) Appendino, G.; Bacchiega, S.; Minassi, A.; Cascio, M. G.; De Petrocellis, L.; Di Marzo, V. The 1,2,3-Triazole Ring as a Peptido- and Olefinomimetic Element: Discovery of Click Vanilloids and Cannabinoids. *Angew. Chem., Int. Ed.* **2007**, *46*, 9312−9315.
(201) Linares, D.; Bottzeck, O.; Pereira, O.; Praud-Tabaries, A.; Blache, Y. Designing 2-Aminoimidazole Alkaloids Analogs with Anti-Biofilm Activities: Structure-Activities Relationships of Polysubstituted Triazoles. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6751−6755.
(202) Chouaib, K.; Romdhane, A.; Delemasure, S.; Dutartre, P.; Elie, N.; Touboul, D.; Ben Jannet, H. Regiospecific Synthesis by Copper- and Ruthenium-Catalyzed Azide−Alkyne 1,3-Dipolar Cycloaddition, Anticancer and Anti-Inflammatory Activities of Oleanolic Acid Triazole Derivatives. *Arabian J. Chem.* **2016**, 10.1016/j.arabjc.2015.12.013.
(203) Salmon, A. J.; Williams, M. L.; Innocenti, A.; Vullo, D.; Supuran, C. T.; Poulsen, S. A. Inhibition of Carbonic Anhydrase Isozymes I, II and IX with Benzenesulfonamides Containing an Organometallic Moiety. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5032−5035.
(204) Wuest, F.; Tang, X. L.; Kniess, T.; Pietzsch, J.; Suresh, M. Synthesis and Cyclooxygenase Inhibition of Various (Aryl-1,2,3-Triazol-1-yl)-Methanesulfonylphenyl Derivatives. *Bioorg. Med. Chem.* **2009**, *17*, 1146−1151.
(205) Chen, Y.; Lopez-Sanchez, M.; Savoy, D. N.; Billadeau, D. D.; Dow, G. S.; Kozikowski, A. P. A Series of Potent and Selective, Triazolylphenyl-Based Histone Deacetylases Inhibitors with Activity against Pancreatic Cancer Cells and Plasmodium Falciparum. *J. Med. Chem.* **2008**, *51*, 3437−3448.
(206) Hirose, T.; Sunazuka, T.; Omura, S. Recent Development of Two Chitinase Inhibitors, Argifin and Argadin, Produced by Soil Microorganisms. *Proc. Jpn. Acad., Ser. B* **2010**, *86*, 85−102.
(207) Karuturi, R.; Al-Horani, R. A.; Mehta, S. C.; Gailani, D.; Desai, U. R. Discovery of Allosteric Modulators of Factor XIa by Targeting Hydrophobic Domains Adjacent to Its Heparin-Binding Site. *J. Med. Chem.* **2013**, *56*, 2415−2428.
(208) Miyakoshi, H.; Miyahara, S.; Yokogawa, T.; Endoh, K.; Muto, T.; Yano, W.; Wakasa, T.; Ueno, H.; Chong, K. T.; Taguchi, J.; et al. 1,2,3-Triazole-Containing Uracil Derivatives with Excellent Pharmacokinetics as a Novel Class of Potent Human Deoxyuridine Triphosphatase Inhibitors. *J. Med. Chem.* **2012**, *55*, 6427−6437.
(209) Grandane, A.; Tanc, M.; Zalubovskis, R.; Supuran, C. T. 6-Triazolyl-Substituted Sulfocoumarins Are Potent, Selective Inhibitors of the Tumor-Associated Carbonic Anhydrases IX and XII. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1256−1260.
(210) Corredor, M.; Bujons, J.; Orzáez, M.; Sancho, M.; Perez-Paya, E.; Alfonso, I.; Messeguer, A. Optimizing the Control of Apoptosis by Amide/Triazole Isosteric Substitution in a Constrained Peptoid. *Eur. J. Med. Chem.* **2013**, *63*, 892−896.
(211) Yang, H. B.; Hendricks, R. T.; Arora, N.; Nitzan, D.; Yee, C.; Lucas, M. C.; Yang, Y. L.; Fung, A.; Rajyaguru, S.; Harris, S. F.; et al. Cyclic Amide Bioisosterism: Strategic Application to the Design and Synthesis of HCV NS5B Polymerase Inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4614−4619.
(212) Zhu, L. R.; Li, Y. Y.; Qiu, L.; Su, M. B.; Wang, X.; Xia, C. M.; Qu, Y.; Li, J. Y.; Li, J.; Xiong, B.; et al. Design and Synthesis of 4-(2,4,5-Trifluorophenyl)Butane-1,3-Diamines as Dipeptidyl Peptidase IV Inhibitors. *ChemMedChem* **2013**, *8*, 1104−1116.
(213) Toguchi, S.; Hirose, T.; Yorita, K.; Fukui, K.; Sharpless, K. B.; Omura, S.; Sunazuka, T. In Situ Click Chemistry for the Identification of a Potent D-Amino Acid Oxidase Inhibitor. *Chem. Pharm. Bull.* **2016**, *64*, 695−703.
(214) Irie, T.; Fujii, I.; Sawa, M. Design and Combinatorial Synthesis of a Novel Kinase-Focused Library Using Click Chemistry-Based Fragment Assembly. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 591−596.
(215) Ko, K. S.; Steffey, M. E.; Brandvold, K. R.; Soellner, M. B. Development of a Chimeric c-Src Kinase and HDAC Inhibitor. *ACS Med. Chem. Lett.* **2013**, *4*, 779−783.
(216) Brandvold, K. R.; Steffey, M. E.; Fox, C. C.; Soellner, M. B. Development of a Highly Selective c-Src Kinase Inhibitor. *ACS Chem. Biol.* **2012**, *7*, 1393−1398.
(217) Baltus, C. B.; Jorda, R.; Marot, C.; Berka, K.; Bazgier, V.; Krystof, V.; Prie, G.; Viaud-Massuard, M. C. Synthesis, Biological Evaluation and Molecular Modeling of a Novel Series of 7-Azaindole Based Tri-Heterocyclic Compounds as Potent CDK2/Cyclin E Inhibitors. *Eur. J. Med. Chem.* **2016**, *108*, 701−719.
(218) Mohammed, I.; Kummetha, I. R.; Singh, G.; Sharova, N.; Lichinchi, G.; Dang, J.; Stevenson, M.; Rana, T. M. 1,2,3-Triazoles as Amide Bioisosteres: Discovery of a New Class of Potent HIV-1 Vif Antagonists. *J. Med. Chem.* **2016**, *59*, 7677−7682.
(219) Kwak, J. M.; Moon, J. S.; Seo, S.; Choi, J. I.; Sampath, V.; Lee, H. Y.; Koh, H. Y. Regioselective Click Chemistry for Construction of

DOI: 10.1021/acs.chemrev.6b00466
Chem. Rev. 2016, 116, 14726−14768

Arylpiperazinyl 1,2,3-Triazole Derivative Libraries as Dopamine D-4/D-3 Receptor Ligands. *Bull. Korean Chem. Soc.* **2014**, *35*, 3675−3678.
(220) Stanley, N. J.; Pedersen, D. S.; Nielsen, B.; Kvist, T.; Mathiesen, J. M.; Brauner-Osborne, H.; Taylor, D. K.; Abell, A. D. 1,2,3-Triazolyl Amino Acids as AMPA Receptor Ligands. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7512−7515.
(221) Grimster, N. P.; Stump, B.; Fotsing, J. R.; Weide, T.; Talley, T. T.; Yamauchi, J. G.; Nemecz, A.; Kim, C.; Ho, K. Y.; Sharpless, K. B.; et al. Generation of Candidate Ligands for Nicotinic Acetylcholine Receptors via in Situ Click Chemistry with a Soluble Acetylcholine Binding Protein Template. *J. Am. Chem. Soc.* **2012**, *134*, 6732−6740.
(222) Yamauchi, J. G.; Gomez, K.; Grimster, N.; Dufouil, M.; Nemecz, A.; Fotsing, J. R.; Ho, K. Y.; Talley, T. T.; Sharpless, K. B.; Fokin, V. V.; et al. Synthesis of Selective Agonists for the Alpha 7 Nicotinic Acetylcholine Receptor with in Situ Click-Chemistry on Acetylcholine-Binding Protein Templates. *Mol. Pharmacol.* **2012**, *82*, 687−699.
(223) Moumne, R.; Larue, V.; Seijo, B.; Lecourt, T.; Micouin, L.; Tisne, C. Tether Influence on the Binding Properties of $tRNA_3^{Lys}$ Ligands Designed by a Fragment-Based Approach. *Org. Biomol. Chem.* **2010**, *8*, 1154−1159.
(224) McCarroll, A. J.; Matthews, C. S.; Wells, G.; Bradshaw, T. D.; Stevens, M. F. G. Synthesis of Antitumour (1H-1,2,3-Triazol-1-yl)-4-Hydroxycyclohexa-2,5-Dien-1-Ones by Copper-Catalysed Huisgen Cycloadditions. *Org. Biomol. Chem.* **2010**, *8*, 2078−2084.
(225) Chardon, E.; Puleo, G. L.; Dahm, G.; Fournel, S.; Guichard, G.; Bellemin-Laponnaz, S. Easy Derivatisation of Group 10 N-Heterocyclic Carbene Complexes and in Vitro Evaluation of an Anticancer Oestradiol Conjugate. *ChemPlusChem* **2012**, *77*, 1028−1038.
(226) Wang, C.; Abegg, D.; Hoch, D. G.; Adibekian, A. Chemoproteomics-Enabled Discovery of a Potent and Selective Inhibitor of the DNA Repair Protein MGMT. *Angew. Chem., Int. Ed.* **2016**, *55*, 2911−2915.
(227) Cao, G. R.; Yang, K.; Li, Y.; Huang, L. J.; Teng, D. W. Synthetic Strategy and Anti-Tumor Activities of Macrocyclic Scaffolds Based on 4-Hydroxyproline. *Molecules* **2016**, *21*, 212.
(228) Bahia, S. B. B. B.; Reis, W. J.; Jardim, G. A. M.; Souto, F. T.; de Simone, C. A.; Gatto, C. C.; Menna-Barreto, R. F. S.; de Castro, S. L.; Cavalcanti, B. C.; Pessoa, C.; et al. Molecular Hybridization as a Powerful Tool Towards Multitarget Quinoidal Systems: Synthesis, Trypanocidal and Antitumor Activities of Naphthoquinone-Based 5-Iodo-1,4-Disubstituted-, 1,4- and 1,5-Disubstituted-1,2,3-Triazoles. *MedChemComm* **2016**, *7*, 1555−1563.
(229) Hansen, M. R.; Jakobsen, T. H.; Bang, C. G.; Cohrt, A. E.; Hansen, C. L.; Clausen, J. W.; Le Quement, S. T.; Tolker-Nielsen, T.; Givskov, M.; Nielsen, T. E. Triazole-Containing N-Acyl Homoserine Lactones Targeting the Quorum Sensing System in Pseudomonas Aeruginosa. *Bioorg. Med. Chem.* **2015**, *23*, 1638−1650.
(230) Pore, V. S.; Jagtap, M. A.; Agalave, S. G.; Pandey, A. K.; Siddiqi, M. I.; Kumar, V.; Shukla, P. K. Synthesis and Antifungal Activity of 1,5-Disubstituted-1,2,3-Triazole Containing Fluconazole Analogues. *MedChemComm* **2012**, *3*, 484−488.
(231) Chardon, E.; Puleo, G. L.; Dahm, G.; Guichard, G.; Bellemin-Laponnaz, S. Direct Functionalisation of Group 10 N-Heterocyclic Carbene Complexes for Diversity Enhancement. *Chem. Commun.* **2011**, *47*, 5864−5866.
(232) Sonogashira, K.; Kataoka, S.; Takahashi, S.; Hagihara, N. Studies of Poly-Yne Polymers Containing Transition-Metals in Main Chain III. Synthesis and Characterization of a Poly-Yne Polymer Containing Mixed Metals in Main Chain, $[trans,trans\text{-}Pt(PBu_3)_2\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}Pd(PBu_3)_2\text{-}C{\equiv}C\text{-}C{\equiv}C]_{N/2}$. *J. Organomet. Chem.* **1978**, *160*, 319−327.
(233) Osakada, K.; Hamada, M.; Yamamoto, T. Intermolecular Alkynyl Ligand Transfer in Palladium(II) and Platinum(II) Complexes with -C⋮CCOOR and -C⋮ph Ligands. Relative Stability of the Alkynyl Complexes and Conproportionation of Dialkynyl and Diiodo Complexes of These Metals. *Organometallics* **2000**, *19*, 458−468.
(234) Beckmann, H. S. G.; Nie, F. L.; Hagerman, C. E.; Johansson, H.; Tan, Y. S.; Wilcke, D.; Spring, D. R. A Strategy for the Diversity-Oriented Synthesis of Macrocyclic Scaffolds Using Multidimensional Coupling. *Nat. Chem.* **2013**, *5*, 861−867.
(235) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. Fluorous Mixture Synthesis: A Fluorous-Tagging Strategy for the Synthesis and Separation of Mixtures of Organic Compounds. *Science* **2001**, *291*, 1766−1769.
(236) Nie, F.; Kunciw, D. L.; Wilcke, D.; Stokes, J. E.; Galloway, W. R. J. D.; Bartlett, S.; Sore, H. F.; Spring, D. R. A Multidimensional Diversity-Oriented Synthesis Strategy for Structurally Diverse and Complex Macrocycles. *Angew. Chem., Int. Ed.* **2016**, *55*, 11139−11143.
(237) Zhu, M.; Lim, B. J.; Koh, M.; Park, S. B. Construction of Polyheterocyclic Benzopyran Library with Diverse Core Skeletons through Diversity-Oriented Synthesis Pathway: Part II. *ACS Comb. Sci.* **2012**, *14*, 124−134.
(238) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. Privileged Structures: Applications in Drug Discovery. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473−493.
(239) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. Natural Product-Like Combinatorial Libraries Based on Privileged Structures. 1. General Principles and Solid-Phase Synthesis of Benzopyrans. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953.
(240) List, B.; Lerner, R. A.; Barbas, C. F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.
(241) Luo, S. Z.; Xu, H.; Mi, X. L.; Li, J. Y.; Zheng, X. X.; Cheng, J. P. Evolution of Pyrrolidine-Type Asymmetric Organocatalysts by "Click" Chemistry. *J. Org. Chem.* **2006**, *71*, 9244−9247.
(242) List, B.; Pojarliev, P.; Martin, H. J. Efficient Proline-Catalyzed Michael Additions of Unmodified Ketones to Nitro Olefins. *Org. Lett.* **2001**, *3*, 2423−2425.
(243) Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673.
(244) Takasu, K.; Azuma, T.; Takemoto, Y. Synthesis of Trifunctional Thioureas Bearing 1,5-Disubstituted Triazole Tether by Ru-Catalyzed Huisgen Cycloaddition. *Tetrahedron Lett.* **2010**, *51*, 2737−2740.
(245) Takasu, K.; Azuma, T.; Enkhtaivan, I.; Takemoto, Y. Synthesis and Properties of Chiral Thioureas Bearing an Additional Function at a Remote Position Tethered by a 1,5-Disubstituted Triazole. *Molecules* **2010**, *15*, 8327−8348.
(246) Juricek, M.; Kouwer, P. H. J.; Rowan, A. E. Triazole: A Unique Building Block for the Construction of Functional Materials. *Chem. Commun.* **2011**, *47*, 8740−8749.
(247) Zabarska, N.; Stumper, A.; Rau, S. CuAAC Click Reactions for the Design of Multifunctional Luminescent Ruthenium Complexes. *Dalton Trans.* **2016**, *45*, 2338−2351.
(248) Orselli, E.; Albuquerque, R. Q.; Fransen, P. M.; Frohlich, R.; Janssen, H. M.; De Cola, L. 1,2,3-Triazolyl-Pyridine Derivatives as Chelating Ligands for Blue Iridium(III) Complexes. Photophysics and Electroluminescent Devices. *J. Mater. Chem.* **2008**, *18*, 4579−4590.
(249) Locatelli, E.; Ori, G.; Fournelle, M.; Lemor, R.; Montorsi, M.; Comes Franchini, M. Click Chemistry for the Assembly of Gold Nanorods and Silver Nanoparticles. *Chem. - Eur. J.* **2011**, *17*, 9052−9056.
(250) Ruan, Y. B.; Yu, Y. H.; Li, C.; Bogliotti, N.; Tang, J.; Xie, J. Triazolyl Benzothiadiazole Fluorescent Chemosensors: A Systematic Investigation of 1,4- or 1,5-Disubstituted Mono- and Bis-Triazole Derivatives. *Tetrahedron* **2013**, *69*, 4603−4608.
(251) Rasheed, O. K.; Lawrence, A.; Quayle, P.; Bailey, P. D. A Modular Approach to Functionalised Dyes. *Synlett* **2016**, *27*, 905−911.
(252) Sinn, S.; Schulze, B.; Friebe, C.; Brown, D. G.; Jager, M.; Altuntas, E.; Kubel, J.; Guntner, O.; Berlinguette, C. P.; Dietzek, B.; et al. Physicochemical Analysis of Ruthenium(II) Sensitizers of 1,2,3-Triazole-Derived Mesoionic Carbene and Cyclometalating Ligands. *Inorg. Chem.* **2014**, *53*, 2083−2095.
(253) Chen, M.; Li, L. Z.; Nie, H.; Shi, Y.; Mei, J.; Wang, J.; Sun, J. Z.; Qin, A. J.; Tang, B. Z. N-Type Pyrazine and Triazole-Based Luminogens with Aggregation-Enhanced Emission Characteristics. *Chem. Commun.* **2015**, *51*, 10710−10713.
(254) Biet, T.; Cauchy, T.; Avarvari, N. Electroactive Tetrathiafulvalenyl-1,2,3-Triazoles by Click Chemistry: Cu- Versus Ru-Catalyzed

DOI: 10.1021/acs.chemrev.6b00466
Chem. Rev. 2016, 116, 14726−14768

Azide-Alkyne Cycloaddition Isomers. *Chem. - Eur. J.* **2012**, *18*, 16097−16103.
(255) Biet, T.; Avarvari, N. Electroactive Tetrathiafulvalene Based Pyridine-Mono and -Bis(1,2,3-Triazoles) Click Ligands: Synthesis, Crystal Structures and Coordination Chemistry. *CrystEngComm* **2014**, *16*, 6612−6620.
(256) Biet, T.; Avarvari, N. Tetrathiafulvalene Mono- and Bis-1,2,3-Triazole Precursors by Click Chemistry: Structural Diversity and Reactivity. *Org. Biomol. Chem.* **2014**, *12*, 3167−3174.
(257) Lumpi, D.; Glocklhofer, F.; Holzer, B.; Stoger, B.; Hametner, C.; Reider, G. A.; Frohlich, J. Systematic Investigations on 1,2,3-Triazole-Based Compounds Capable of Second Harmonic Generation. *Cryst. Growth Des.* **2014**, *14*, 1018−1031.
(258) Lissau, H.; Broman, S. L.; Jevric, M.; Madsen, A. O.; Nielsen, M. B. CuAAC and RuAAC with Alkyne-Functionalised Dihydroazulene Photoswitches and Determination of Hammett Sigma-Constants for Triazoles. *Aust. J. Chem.* **2014**, *67*, 531−534.
(259) Meldal, M. Polymer "Clicking" by CuAAC Reactions. *Macromol. Rapid Commun.* **2008**, *29*, 1016−1051.
(260) Nulwala, H.; Takizawa, K.; Odukale, A.; Khan, A.; Thibault, R. J.; Taft, B. R.; Lipshutz, B. H.; Hawker, C. J. Synthesis and Characterization of Isomeric Vinyl-1,2,3-Triazole Materials by Azide-Alkyne Click Chemistry. *Macromolecules* **2009**, *42*, 6068−6074.
(261) Lartey, M.; Gillissen, M.; Adzima, B. J.; Takizawa, K.; Luebke, D. R.; Nulwala, H. B. Synthesis and Reactivity Ratios of Regioisomeric Vinyl-1,2,3-Triazoles with Styrene. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 3359−3364.
(262) Praud, A.; Bootzeek, O.; Blache, Y. Synthesis of Polymerizable Vinyltriazoles: Development of an Optimized One-Pot Strategy Starting from 4-Bromobutyne. *Green Chem.* **2013**, *15*, 1138−1141.
(263) Su, J.; Hua, R. M. One-Pot Approach to 4-Vinyl-1,2,3-Triazoles by Cycloaddition of Azides with Propargyl Alcohols Catalyzed by Cu(I)/Ru(III)/TFA. *Curr. Org. Synth.* **2012**, *9*, 898−902.
(264) Brantley, J. N.; Konda, S. S. M.; Makarov, D. E.; Bielawski, C. W. Regiochemical Effects on Molecular Stability: A Mechanochemical Evaluation of 1,4-and 1,5-Disubstituted Triazoles. *J. Am. Chem. Soc.* **2012**, *134*, 9882−9885.
(265) Jacobs, M. J.; Schneider, G.; Blank, K. G. Mechanical Reversibility of Strain-Promoted Azide-Alkyne Cycloaddition Reactions. *Angew. Chem., Int. Ed.* **2016**, *55*, 2899−2902.
(266) Qin, A. J.; Lam, J. W. Y.; Tang, B. Z. Click Polymerization. *Chem. Soc. Rev.* **2010**, *39*, 2522−2544.
(267) Brei, M. R.; Hunter Cooke, R., III; Hanson, D. J.; Gray, C. T.; Storey, R. F. NMR and Mass Spectral Analysis of Step-Growth Polymers from Azide Alkyne Cycloaddition and Regioselectivity Afforded by Copper (I) and Ruthenium(II) Catalysts. *J. Macromol. Sci., Part A: Pure Appl.Chem.* **2016**, *53*, 413−423.
(268) Brady, S. E.; Shultz, G. V.; Tyler, D. R. Preparation of Polymers Containing Metal-Metal Bonds Along the Backbone Using Click Chemistry. *J. Inorg. Organomet. Polym. Mater.* **2010**, *20*, 511−518.
(269) Pola, R.; Laga, R.; Ulbrich, K.; Sieglova, I.; Kral, V.; Fabry, M.; Kabesova, M.; Kovar, M.; Pechar, M. Polymer Therapeutics with a Coiled Coil Motif Targeted against Murine BCL1 Leukemia. *Biomacromolecules* **2013**, *14*, 881−889.
(270) Pola, R.; Braunova, A.; Laga, R.; Pechar, M.; Ulbrich, K. Click Chemistry as a Powerful and Chemoselective Tool for the Attachment of Targeting Ligands to Polymer Drug Carriers. *Polym. Chem.* **2014**, *5*, 1340−1350.
(271) Qin, A. J.; Lam, J. W. Y.; Jim, C. K. W.; Zhang, L.; Yan, J. J.; Haussler, M.; Liu, J. Z.; Dong, Y. Q.; Liang, D. H.; Chen, E. Q.; et al. Hyperbranched Polytriazoles: Click Polymerization, Regioisomeric Structure, Light Emission, and Fluorescent Patterning. *Macromolecules* **2008**, *41*, 3808−3822.
(272) Brady, S. E.; Tyler, D. R. A Strategy for Preparing Star Polymers Containing Metal-Metal Bonds Along the Polymeric Arms Using Click Chemistry. *J. Inorg. Organomet. Polym. Mater.* **2013**, *23*, 158−166.
(273) Rasolofonjatovo, E.; Theeramunkong, S.; Bouriaud, A.; Kolodych, S.; Chaumontet, M.; Taran, F. Iridium-Catalyzed Cycloaddition of Azides and 1-Bromoalkynes at Room Temperature. *Org. Lett.* **2013**, *15*, 4698−4701.
(274) Ding, S. T.; Jia, G. C.; Sun, J. W. Iridium-Catalyzed Intermolecular Azide-Alkyne Cycloaddition of Internal Thioalkynes under Mild Conditions. *Angew. Chem., Int. Ed.* **2014**, *53*, 1877−1880.
(275) Wang, Y. C.; Xie, Y. Y.; Qu, H. E.; Wang, H. S.; Pan, Y. M.; Huang, F. P. $Ce(OTf)_3$-Catalyzed 3 + 2 Cycloaddition of Azides with Nitroolefins: Regioselective Synthesis of 1,5-Disubstituted 1,2,3-Triazoles. *J. Org. Chem.* **2014**, *79*, 4463−4469.
(276) Arigela, R. K.; Mandadapu, A. K.; Sharma, S. K.; Kumar, B.; Kundu, B. Cascade Intermolecular Michael Addition-Intramolecular Azide/Internal Alkyne 1,3-Dipolar Cycloaddition Reaction in One Pot. *Org. Lett.* **2012**, *14*, 1804−1807.
(277) Hong, L.; Lin, W.; Zhang, F.; Liu, R.; Zhou, X. $Ln[N(SiMe_3)_2]_3$-Catalyzed Cycloaddition of Terminal Alkynes to Azides Leading to 1,5-Disubstituted 1,2,3-Triazoles: New Mechanistic Features. *Chem. Commun.* **2013**, *49*, 5589−5591.
(278) Kamal, A.; Swapna, P. An Improved Iron-Mediated Synthesis of N-2-Aryl Substituted 1,2,3-Triazoles. *RSC Adv.* **2013**, *3*, 7419−7426.
(279) Koguchi, S.; Izawa, K. Ionic Liquid-Phase Synthesis of 1,5-Disubstituted 1,2,3-Triazoles. *ACS Comb. Sci.* **2014**, *16*, 381−385.
(280) Yamamoto, K.; Bruun, T.; Kim, J. Y.; Zhang, L.; Lautens, M. A New Multicomponent Multicatalyst Reaction (MC)R-2: Chemoselective Cycloaddition and Latent Catalyst Activation for the Synthesis of Fully Substituted 1,2,3-Triazoles. *Org. Lett.* **2016**, *18*, 2644−2647.
(281) Smith, C. D.; Greaney, M. F. Zinc Mediated Azide-Alkyne Ligation to 1,5-and 1,4,5-Substituted 1,2,3-Triazoles. *Org. Lett.* **2013**, *15*, 4826−4829.
(282) Wan, J. P.; Hu, D. Q.; Liu, Y. Y.; Sheng, S. R. Azide-Free Synthesis of 1,2,3-Triazoles: New Opportunity for Sustainable Synthesis. *ChemCatChem* **2015**, *7*, 901−903.
(283) John, J.; Thomas, J.; Dehaen, W. Organocatalytic Routes toward Substituted 1,2,3-Triazoles. *Chem. Commun.* **2015**, *51*, 10797−10806.
(284) Wan, J. P.; Cao, S.; Liu, Y. Y. A Metal- and Azide-Free Multicomponent Assembly toward Regioselective Construction of 1,5-Disubstituted 1,2,3-Triazoles. *J. Org. Chem.* **2015**, *80*, 9028−9033.
(285) Dey, S.; Pathak, T. A General Route to 1,5-Disubstituted 1,2,3-Triazoles with Alkyl/Alkyl, Alkyl/Aryl, Aryl/Aryl Combinations: A Metal-Free, Regioselective, One-Pot Three Component Approach. *RSC Adv.* **2014**, *4*, 9275−9278.
(286) Bhaumik, A.; Samanta, S.; Pathak, T. Enantiopure 1,4,5-Trisubstituted 1,2,3-Triazoles from Carbohydrates: Applications of Organoselenium Chemistry. *J. Org. Chem.* **2014**, *79*, 6895−6904.
(287) Kwok, S. W.; Fotsing, J. R.; Fraser, R. J.; Rodionov, V. O.; Fokin, V. V. Transition-Metal-Free Catalytic Synthesis of 1,5-Diaryl-1,2,3-Triazoles. *Org. Lett.* **2010**, *12*, 4217−4219.

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