



Strategies Towards the Synthesis of N²-Substituted 1,2,3-Triazoles

RODRIGO OCTÁVIO M.A. DE SOUZA and LEANDRO S. DE MARIZ E MIRANDA

Biocatalysis and Organic Synthesis Group, Chemistry Institute, Federal University
of Rio de Janeiro, 21941-909 Rio de Janeiro, RJ, Brazil

Manuscript received on July 23, 2018; accepted for publication on September 26, 2018

How to cite: SOUZA ROMAD AND MIRANDA LSDME. 2019. Strategies Towards the Synthesis of N²-Substituted 1,2,3-Triazoles. *An Acad Bras Cienc* 91: e20180751. DOI 10.1590/0001-3765201820180751.

Abstract: The chemistry of 1,2,3-triazoles gained much attention since the discovery of the copper catalyzed Alkyne-azide cycloaddition (CuAAC) reaction which delivers exclusively the 1,4-regioisomer in high yields. On the other hand there is still no universal methodology capable of delivering the N² substituted regioisomer. The unique properties of these N²-substituted 1,2,3-triazoles have stimulated synthetic efforts on the developments of methodologies capable of delivering it in high yield and selectivity. These efforts are the subject of the presented review.

Key words: 1,2,3-Triazoles, Heterocycles, Regioselectivity, arylation.

INTRODUCTION

Triazoles are five-membered aromatic heterocycles, containing threenitrogen atoms. These atoms can be disposed consecutively or not, being known as 1,2,3-triazoles or 1,2,4-triazoles, respectively (Figure 1).

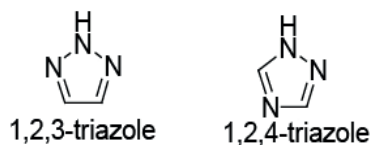


Figure 1 - Structure of isomeric Triazoles.

The structure of 1,2,3-triazoles, as presented in figure 1, may exist as two different tautomers, depending on the position of the N-H bond on the

ring. The NH bond can be on nitrogen 1 (1H) or in nitrogen 2 (2H) (those possible tautomers where H is attached to the carbon atom rather than the nitrogen atom is generally not considered as a function of its high energy). When the 1,2,3-triazole skeleton is substituted at the nitrogen and carbon atoms different regioisomers can be obtained according to figure 2.

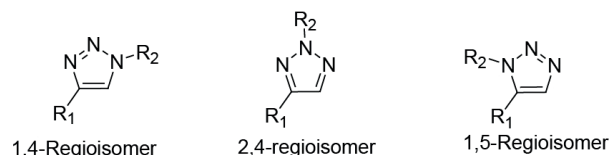


Figure 2 - Different regioisomers of carbon and nitrogen substituted 1,2,3-triazoles.

The 1,2,3-triazole have very distinct properties when compared to its isomeric 1,2,4 isomer, and more importantly the N²substituted has different properties than the N¹ as well as N³, despite structural similarity. An example of this difference can be found in specific applications

Correspondence to: Leandro Soter de Mariz e Miranda

E-mail: leandrosoter@iq.ufjf.br

ORCID: <http://orcid.org/0000-0003-0634-5846>

* Contribution to the centenary of the Brazilian Academy of Sciences.

of N²substituted triazoles, as for example its efficiency as binders in coordination polymers with impressive optical properties (Chen et al. 2015a, b). Differences in basicity between the N¹ and N² isomers can be responsible for their different behavior within biological systems; giving rise to new directions in pharmaceutical research. The N²-1,2,3-triazole core is found in a number of biologically active compounds including dual orexin receptor antagonists (Cox et al. 2010, Baxter et al. 2011) used to treat insomnia, inhibitors of 2,3-oxidosqualene cyclase (Watanabe et al. 2010), α -glycosidase (Gonzaga et al. 2014), and serine hydrolase (Adibekian et al. 2011).

Despite the increase interest in the 1,2,3-triazole core, there is still no universal methodology, except for the 1,4 regioisomer (see below) capable of deliver in the 2,4- and the 1,5 regioisomers in high yield and regioselectivity. However, advances the chemistry of the 2,4-regioisomer have been reported in recent years and are the subject of this review.

PROPERTIES OF 1,2,3-TRIAZOLES.

The discussion concerning the properties and the tautomeric equilibrium of 1,2,3-triazoles is a more complex subject than stated in the previous section. If one consider substitution at the 4 and 5 positions of the ring, as shown in figure 3, the structure with the hydrogen atoms at N¹ and N³ become distinguishable since the N¹-H -tautomer has C_s symmetry and the N²-H tautomer C_{2v} symmetry.

The different tautomers present in figure 3 present distinct physical, chemical and biological properties. For example, according to Begtrup and co-workers (Begtrup et al. 1988), the dipole moment for the unsubstituted N¹-H tautomer is 4.38D, while that of the N²-H tautomer is only 0.218D. Katritzky and co-workers (Alan and Pozharskii 2000), based on the calculated charges for each carbon atom, attribute to the 1H-1,2,3-triazole π system an

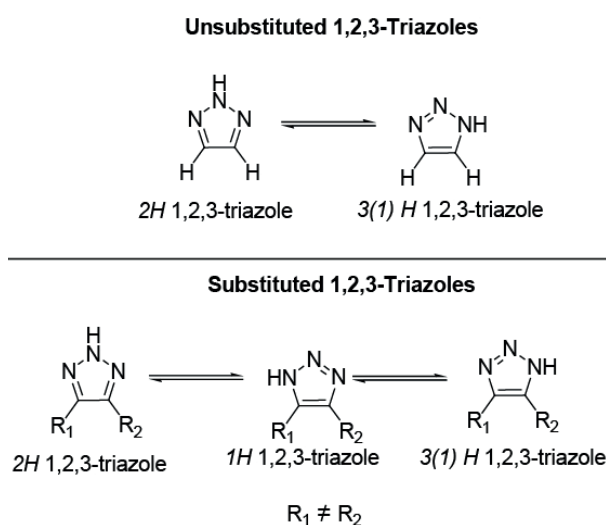


Figure 3 - Different tautomers of substituted and unsubstituted 1,2,3-triazoles.

electron rich character, while for the N²-H tautomer an π electron deficient character.

Compared to others heteroaromatic compounds such as imidazole or pyrrole, the studies in the literature concerning the properties of 1,2,3-triazoles are scarce. Begtrup and co-workers studied by the use of microwave spectroscopy and gas phase electron diffraction on the properties of unsubstituted 1,2,3-triazoles (Begtrup et al. 1988). The experimental data pointed to a ratio of 1:1000 in favor of the N²-H tautomer in the gas phase.

Lunazzi and co-workers, by means of solution Nuclear Magnetic Resonance, studied the same unsubstituted 1,2,3-triazole observed the predominance of the N¹-H tautomer at 175K in toluene solution (Lunazzi et al. 1984). However, the tautomeric equilibrium is reported to be solvent, concentration and temperature dependent, where the relative amount of the other N²-H tautomer increases with decreasing solvent dipole moment, and concentration and increase with temperature. Thus the N²-H tautomer equals more than 97% at 300K at a concentration of 0.05M in toluene. Taylor and co-workers studied the tautomeric equilibrium of 1,2,3-triazoles in aqueous solution (Albert and Taylor 1989).

According to the authors, the N²-H tautomer is the dominant specie in the equilibrium in the aqueous phase by a factor of 2, being attributed the stability of this tautomer to the electronic repulsion between the pairs of electrons of the adjacent hydrogen atoms in the tautomer N¹-H.

Toernkvist and co-workers performed a theoretical study on the 1,2,3-triazoles tautomerism (Toernkvist et al. 1991). By these calculations (MP2 / 6-31G *) the authors determined that the N²-H tautomer is about 21 kJ mol⁻¹ more stable than the N¹-H tautomer. Oziminski and co-workers studied theoretically the properties of substituted 1,2,3-triazoles using the DFT theory level (B3PW91 / 6-311 ++ G **) (Ozimiński et al. 2003). According to the results obtained by the authors, when X= H, the 2H tautomer is 20,52kJ mol⁻¹ more stable than the N¹-H tautomer, in agreement with Toernkvist. The substitution of the triazole implies the study of the N³-H tautomer, in addition to the N¹-H and N²-H. Table I summarizes some of the values obtained by the authors, on substituting the 1,2,3-triazole at carbon with different substituents. The authors observed that in all cases studied the N²-H tautomer to be the most stable. The relative energies of the N³-H and N¹-H tautomers compared to N²-H for different substituent are presented in Table I. It can be observed that the group X has a strong influence on the stabilization of the N¹-H tautomer versus the N³-H.

As can be seen in the Table I, the electron withdrawing or donor behavior of different groups does not translate into differences in the stabilization of the tautomers. The steric interactions and hydrogen bonds between the substituent and the adjacent pyridine like nitrogen atom seem to be the preponderant factor in the stabilization of N¹-H versus N³-H.

Wang and co-workers studied theoretically and experimentally the acidity and gas phase stability values of the three 4-phenyl-1,2,3-triazole tautomers (Wang et al. 2013). According to the

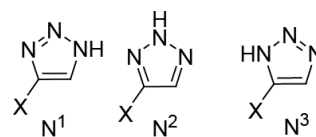


TABLE I
The relative energy of N¹-H and N³-H to N²-H in the presence of different substituents.

| X | ΔE (kJ/mol) | | |
|-------------------|----------------|----------------|----------------|
| | N ³ | N ² | N ¹ |
| NH ₂ | 30.734 | 0 | 22.019 |
| F | 37.059 | 0 | 21.340 |
| Cl | 27,557 | 0 | 20,780 |
| CH ₃ | 20,566 | 0 | 20,080 |
| CN | 22,475 | 0 | 18,004 |
| NO ₂ | 22,194 | 0 | 16,941 |
| CHO | 17,188 | 0 | 15,530 |
| COOH | 12,081 | 0 | 13,261 |
| OH | 35.946 | 0 | 18,578 |
| CONH ₂ | 23,266 | 0 | 10,892 |
| BF ₂ | 12,336 | 0 | 16,966 |
| BH ₂ | 5,547 | 0 | 15,815 |

authors, using the theoretical basis DFT B3LYP / 6-31 + G (d), the N²-H tautomer was obtained as the more stable tautomer by about 16.317 kJ mol⁻¹ compared to N¹-H; the latter being only 3kJ mol⁻¹ more stable than N³-H. As for acidity, in all cases, the most acidic site of the three tautomers is the N-H bond. Among these, the N²-H tautomer is the most acidic ΔH_{acid} = 1410 kJ mol⁻¹, followed by N¹-H ΔH_{acid} = 1393 kJ mol⁻¹ and of N³-H ΔH_{acid} = 1389 kJ mol⁻¹. As for the proton affinity (PA), in the case of N²-H tautomer, the most basic site is N³-H with a PA = 858 kJ mol⁻¹. In the case of the N¹-H tautomer, N³-H is a rather basic center with PA = 916 kJ mol⁻¹. For the N³-H in its protonated form, it has the same structure as the conjugated acid of N¹-H, which makes the proton affinity for N³-H 3kJ mol⁻¹ greater than N¹-H.

SYNTHESIS OF N²-SUBSTITUTED 1,2,3-TRIAZOLES

The main strategy for the synthesis of 1,2,3-triazoles is the reaction between azides and acetylenes, originally described by Huisgen in 1967 (Rolf et al. 1967, Rolf 1963). Originally, this reaction was performed in the presence of organic azides and acetylenes under reflux conditions in toluene, leading to a mixture of 1,4 and 1,5 regioisomers of 1,2,3-triazoles. In 2002, the Sharpless and Medal groups (Tornøe et al. 2002, Haldón et al. 2015) independently reported that, in the presence of copper salts, this transformation occurs at room temperature and provides, in high yields and exclusively the 1,4 regioisomer. This highly selective reaction catalyzed by copper for the synthesis of this 1,2,3-triazoles regioisomer under very mild conditions has allowed its application in the most diverse areas of chemistry, as in the field of material chemistry (Zhou et al. 2005, Li et al. 2010, Peng et al. 2004), medicinal chemistry (Cesare et al. 2008, Aher et al. 2009, Brockunier et al. 2000, Boechat et al. 2011, Dheer et al. 2017, Zhang et al. 2017), bio-conjugation among others (Agard et al. 2004, Wang et al. 2003). It is not the purpose of this paper to discuss the synthesis and properties of the 1,4 (or 1,4,5) substituted 1,2,3-triazoles. About this subject, many reviews are available and the interested reader can consult them (Sandip et al. 2011, Debets et al. 2013, Crowley and McMorran 2012, Thirumurugan et al. 2013, Dheer et al. 2017). On the other hand, there is no strategy, or reaction that provides, in the same terms of the abovementioned reaction developed by Sharpless and medal (for the 1,4, regioisomer) (Sharpless et al. 2001), 2,4-disubstituted 1,2,3-triazoles. With this gap, there is evident lack of information on the properties of these substances, still being an unexplored chemical space in the most diverse areas. However, in the last decades, although timidly, some solutions to this question have

appeared in the literature and are the subject of this review.

The strategy for the synthesis of 1,2,3-triazole derivatives substituted in N² can be divided, in order to facilitate their discussion, in two different strategies: a) the construction of the 1,2,3-triazole skeleton already functionalized in N² and b) the N²functionalization of the 1,2,3-triazole skeleton *a posteriori*.

SYNTHESIS OF THE 1,2,3-TRIAZOLE SKELETON ALREADY FUNCTIONALIZED IN N²

The two most important methodologies for the construction of the triazole skeleton already substituted in N² are the Boulton-Katritzky rearrangement and hydrazine oxidative cyclization reactions, as represented schematically in Figure 4.

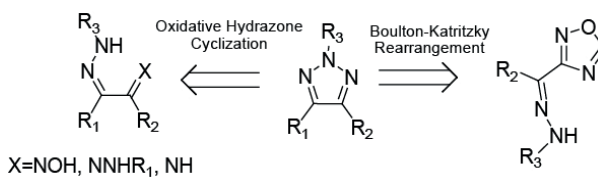


Figure 4 - Major approaches toward the - Synthesis of the 1,2,3-triazole skeleton already functionalized in N²

THE BOULTON-KATRITZKY REARRANGEMENT

The rearrangement observed by Boulton and Katritzky in 1962 involves what is also known as monocyclic rearrangement of heterocycles, which occurs in the presence of both acids or bases (Boulton et al. 1966). In general the rearrangement can be represented according to Figure 5 (“Boulton-Katritzky Rearrangement,”):

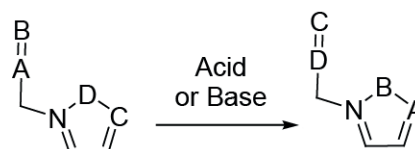


Figure 5 - Schematic representation of monocyclic rearrangement of heterocycles.

In the case of the synthesis of N²-substituted 1,2,3-triazoles, this rearrangement involves the reaction of hydrazones derived from oxadiazoles. This reaction has not found many applications as a tool to construct the N² substituted 1,2,3-triazole skeleton, probably due to difficulties in synthesizing the corresponding oxadiazoles. Some examples of molecules obtained through this approach are presented in Figure 6 (Vincenzo et al. 2014, D'Anna et al. 2005, 2010, Cosimelli et al. 2001).

OXIDATIVE CYCLIZATION OF HYDRAZONES:

The synthesis of N²-substituted 1,2,3-triazoles from the cyclization of bis-arylhydrazones were first reported by Stollè in 1926 (Stollè 1926). Thus, the heating of phenylhydrazones, bis-hydrazones, bis-arylhydrazones or bis-semicarbazones derived from 1,2-dicarbonyl compounds in the presence of oxidizing agents, has been the most commonly used methodology for the synthesis of the N²-substituted 1,2,3-triazolic skeleton. However, this methodology has, as the main disadvantage, the low to moderate yields (Hegarty et al. 1974). The use of copper as catalyst in these cyclizations leads to cleaner and better yielding reactions. Reviews of this reaction can be found in the literature (Shaban et al. 1977, Shaban 1976, Nassr et al. 1985, El Sekily et al. 1977), and for this reason only the recent advances will be discussed in this section. Punniyamurthy and co-workers reported recently the oxidative cyclization of hydrazones in the presence of a copper catalyst and molecular oxygen as final oxidant (Punniyamurthy and Guru 2012) for the synthesis of symmetric N²-substituted 1,2,3-triazoles in good yields, Figure 7.

Wu and co-workers, also using copper catalysis, explored the oxidative intramolecular cyclization of β -ketohydrazones in the presence of ammonium acetate (Wu et al. 2015). In this approach, presented in figure 8, the imine is initially formed, followed by oxidative cyclization to the 1,2,3-triazole skeleton.

Thus, in this reaction there is no aniline formation as a by-product, which occurs when oxidative cyclization of bis-arylhydrazones takes place.

The synthesis of 2-aryl-5-amino-1,2,3-triazoles was recently reported by Kseniya and co-workers (Kseniya et al. 2016). The authors also make use of copper salts as catalyst for the oxidative cyclization, and used, as substrate, α -hydrazono-nitriles to obtain the 1,2,3-triazoles. These nitriles, in the presence of aliphatic amines, lead to the *in situ* formation of 2-(aryl-azo)-ethene-1,1-diamines, which in the presence of copper salts cyclizes to the triazole skeleton. Examples of this approach are found in Figure 9. As can be seen in the Figure this methodology leads to complex structures in moderate to good yields.

The oxidative cyclization between oximes and diazo compounds catalyzed by copper has recently been reported by Jiang and co-workers (Zhu et al. 2018). Important examples of this methodology are highlighted in Figure 10.

Some aspects of this methodology deserved some comments. The first is the possibility of efficiently obtaining 1,2,3-triazole skeletons substituted at the 4 and 2 positions only (R₂=H) or at the 4 and 5 positions. The oxidative cyclization of phenylhydrazones, bis-hydrazones, bis-arylhydrazones or bis-semicarbazones derived from 1,2-dicarbonyl compounds produces efficiently only 1,2,3-triazoles substituted in the 2,4 and 5-positions. Another highlight is the small scope with regard to the diazonium salt. Of all those studied by the author only that derived from 4-methoxy-benzene (PMB) provides satisfactory results.

POST-CYCLOADDITION FUNCTIONALIZATION

As shown in the previous sections, the methodologies available for the synthesis of N²-substituted 1,2,3-triazoles through the construction of the triazole skeleton involves multiple steps,

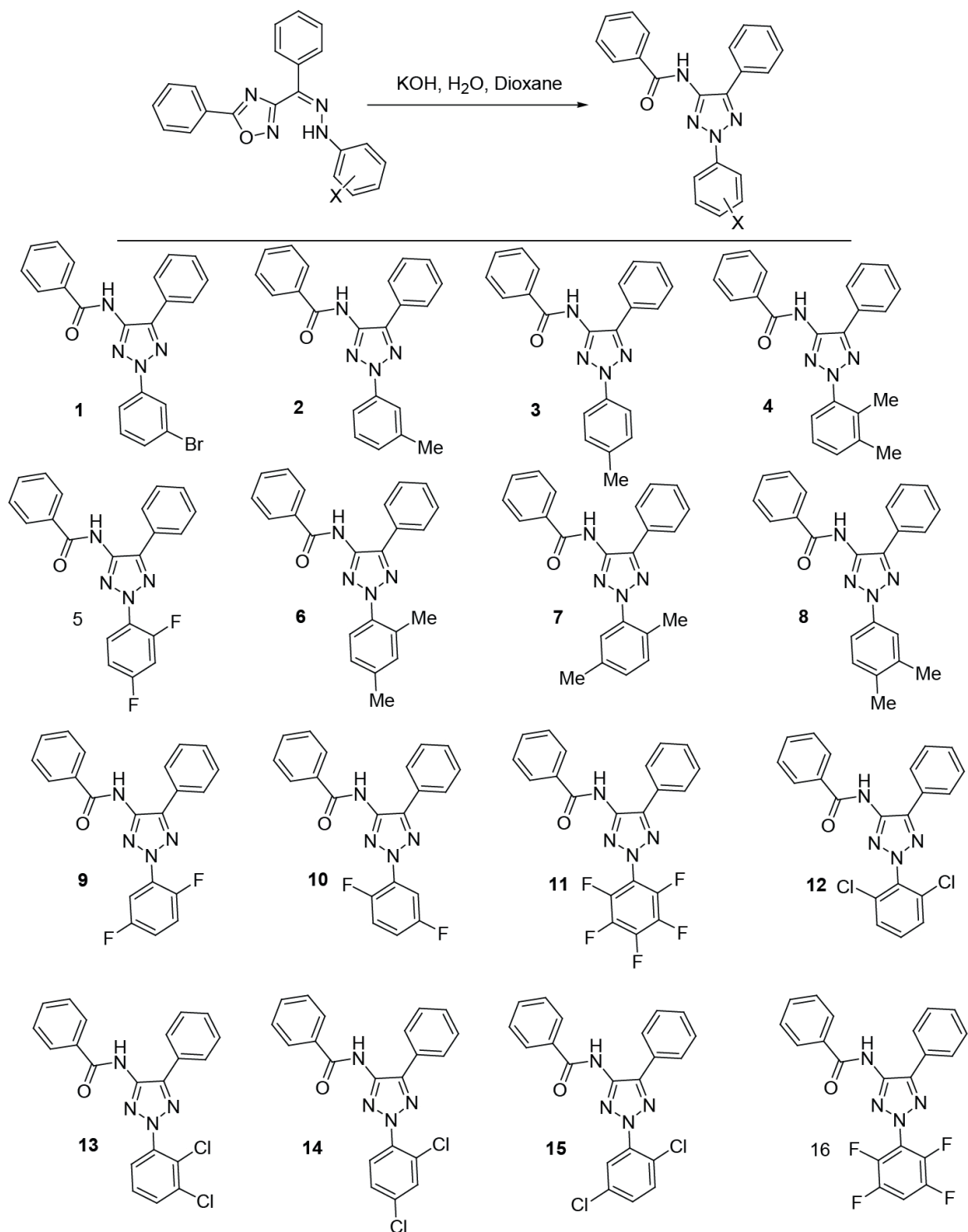


Figure 6 - Examples of molecules obtained through the Boulton-Katritzky rearrangement of oxadiazoles.

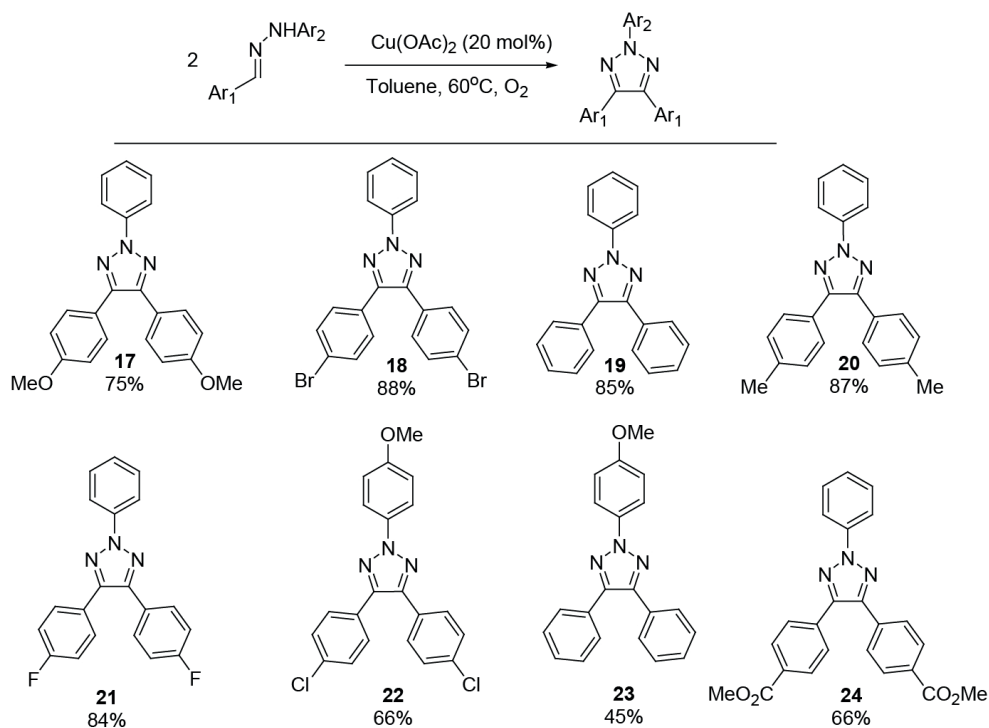


Figure 7 - Synthesis of symmetric N² substituted 1,2,3-triazoles from Aryl-Hydrazones.

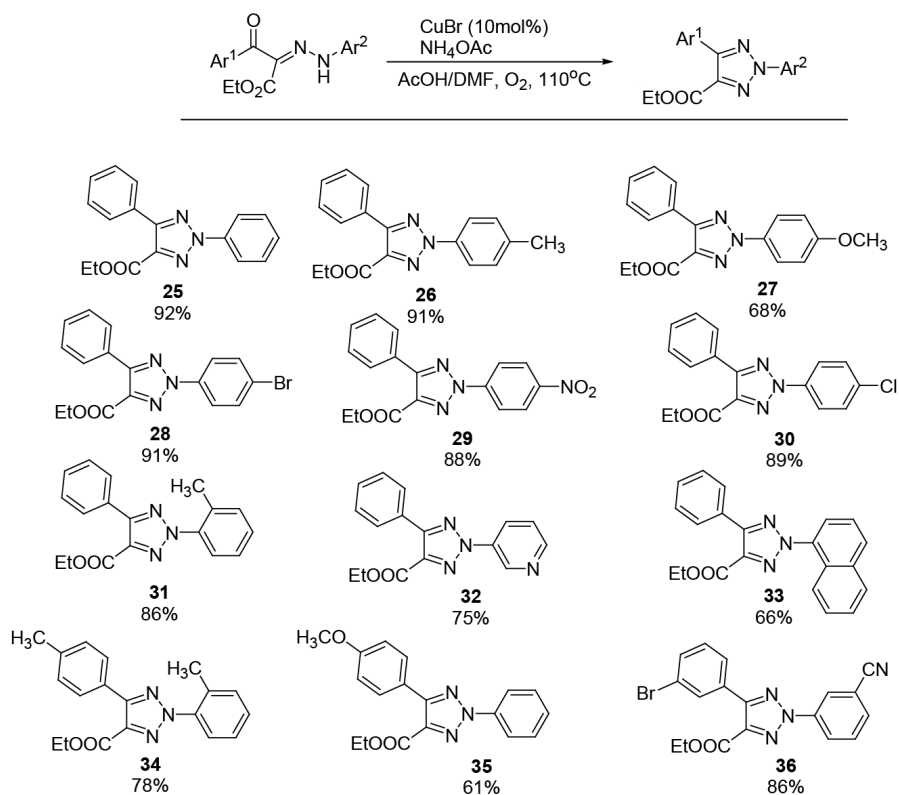


Figure 8 - Intramolecular copper catalyzed cyclization of β -ketohydrazones for the synthesis of N²-Aryl-1,2,3-Triazoles

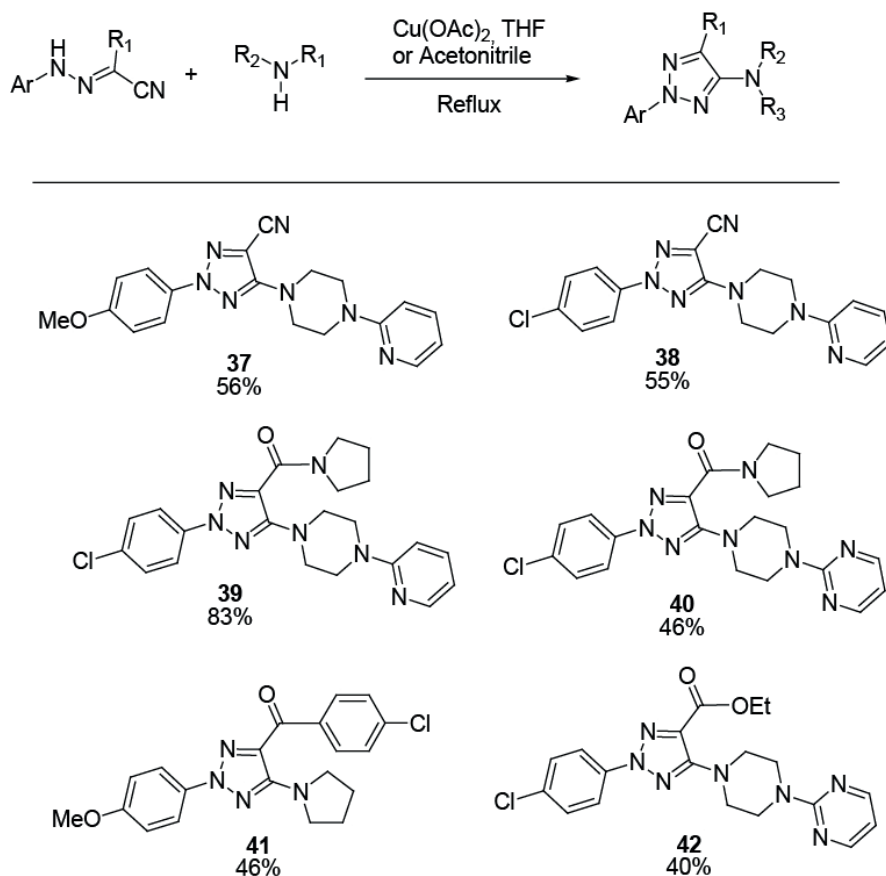


Figure 9 - The synthesis of 2-aryl-5-amino-1,2,3-triazoles from α -hydrazono-nitriles.

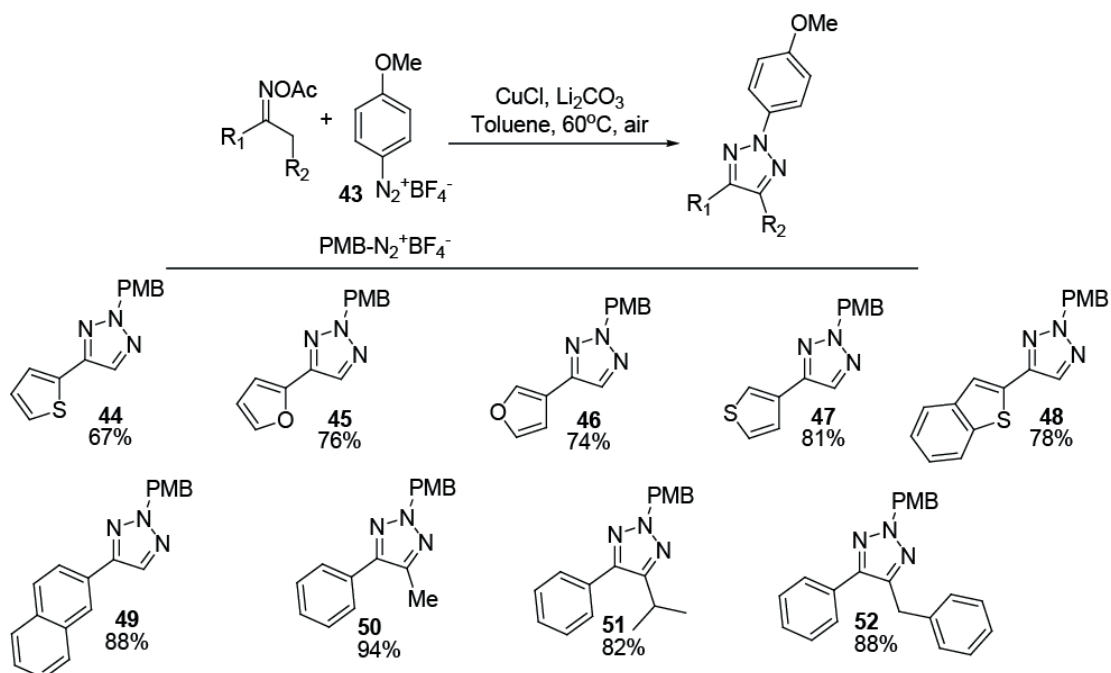


Figure 10 - The copper catalyzed oxidative cyclization between oximes and diazo compounds for the synthesis of N²-PMB-1,2,3-triazoles.

which reduces the efficiency of its production; since the synthesis and purification of the precursors are necessary and it is limited by the availability of the hydrazines, which in many cases are also prepared. In this way, another strategy was developed, in which the 1,2,3-triazole skeleton is prepared prior to its selective functionalization. In general, in this strategy, the synthesis of the triazole skeletons occurs easily and in high yields through the aforementioned copper catalyzed reaction between azides and acetylenes. Once constructed, the triazole skeleton is then functionalized. The functionalization of N² through this strategy is described in the literature for alkylation, acylation and arylation reactions, which may or may not be catalyzed by transition metals such as copper or palladium. The challenge in this approach is derived from the fact that, the 1,2,3-triazole skeleton formed has all three nitrogen atoms as potential nucleophiles which can lead to a mixture of N² and N¹ regioisomers (or N³ when the case). In these cases it is observed that the regioselectivity is a multivariable matter being influenced by the electrophile, solvent, base, catalyst (when present) and temperature. Generally speaking, N¹ alkylation occurs first, due to the higher electron density in this atom. On the other hand, the 1,2,3-triazoles substituted in N² are thermodynamically more stable. Additionally substituent at positions 4 and 5 facilitate N² functionalization. Thus, in general, it is not uncommon in these 1,2,3-triazoles functionalization reactions to observe a mixture of regioisomers (Blass et al. 2006, Estelle et al. 2008, Calderone et al. 2005), and the development of highly selective reactions is still a challenge to be overcome.

ALKYLATION AND ARYLATION (S_N_{AR}) REACTIONS

Miller and co-workers conducted the first systematic study on regioselectivity (N² vs N¹) on the alkylation of 1,2,3-triazoles through the reaction with alkyl

halides and Michael acceptors (Tanaka and Miller 1973). In this study, the reaction of 4-phenyl-1,2,3-triazole with ethyl chloroacetate showed a selectivity of 5:1 in favor of N² regioisomer, using triethylamine as base and dimethylformamide as solvent. In the case of the Michael addition to ethyl propiolate only the product of N² addition was observed, using the same reaction conditions for the reaction with ethyl chloropropiolate.

Sharpless and co-workers reported the synthesis of isomeric hydroxymethyl-1,2,3-triazoles from the reaction, in a single pot, of acetylenes, sodium azide and formaldehyde in the presence of copper and sodium ascorbate (Kalisiak et al. 2008). In this reaction the formed triazole reacts with formaldehyde yielding the product. The selectivity and yields varies from good to excellent as exemplified in Figure 11.

A very interesting solution toward a high yielding and regioselective synthesis of 4-substituted 2-Alkyl-1,2,3-triazoles was described by Wipf and co-workers (Wipf et al. 2010, Wang et al. 2009a, 2010). As previously stated, the potential nucleophilicity of the 3 nitrogen atoms at the triazole core renders a regioselective reaction a very tricky issue. On the other hand, 1,2,3-triazoles substituted at both 4 and 5 positions direct the reaction at the N² position due to disfavored steric interactions at the N¹ or N³ positions with the ligands present at the carbon atoms. With this in mind, the authors developed an alkylation reaction with a 1,2,3-triazole containing bromine atoms at the 4,5 positions, which direct reaction at the N². These bromine atoms can be readily transformed into different groups, allowing the selective synthesis of 4-substituted 2-Alkyl-1,2,3-triazoles. This strategy is present in Figure 12. In the Figure 12I are examples of the structures obtained by such reaction, and in Figure 12II how this bromine atoms can be manipulated to the desired 2,4,5 and 2,4-substituted 1,2,3-triazoles.

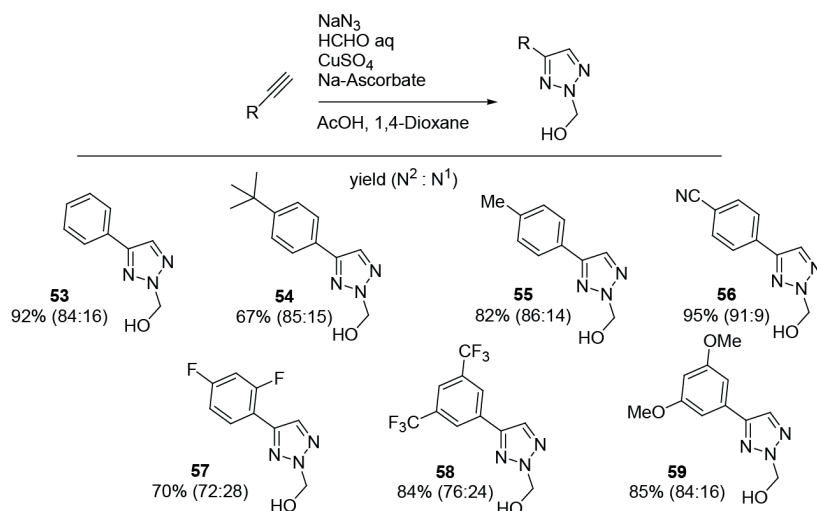


Figure 11 - Synthesis of hydroxymethyl-1,2,3-triazoles.

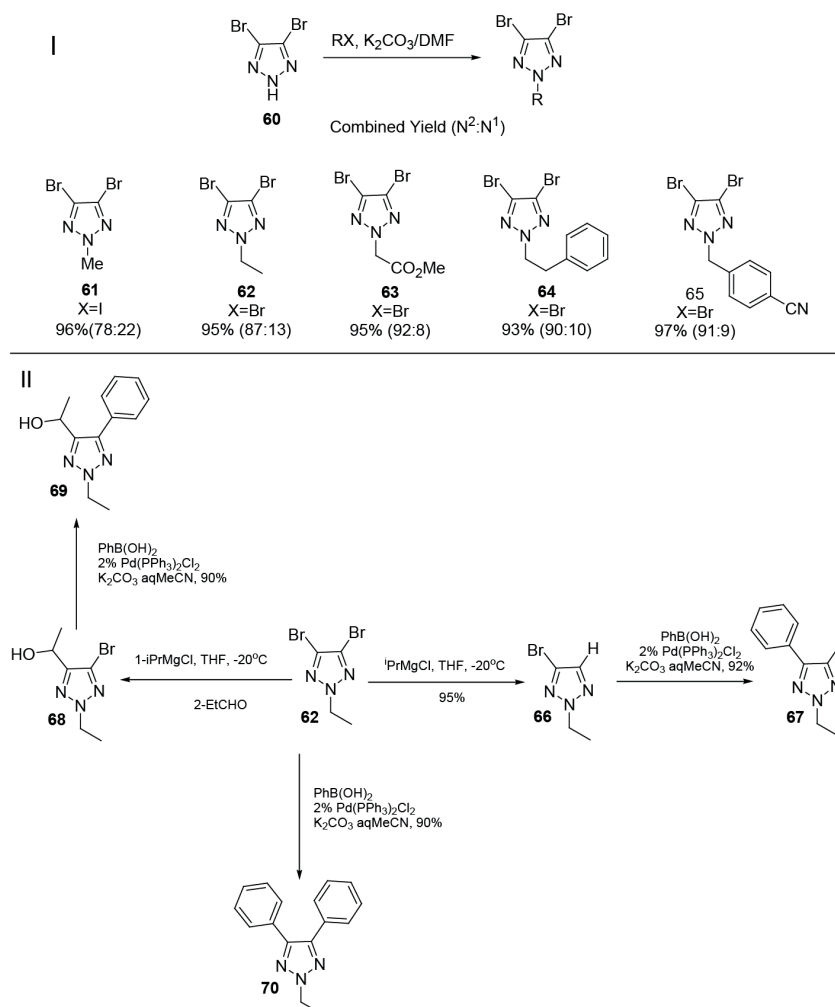


Figure 12 - I- Regioselective alkylation reaction with a 4,5-dibromo-1,2,3-triazole; II-Examples of the transformation of the N²-Alkyl- 4,5-dibromo-1,2,3-triazole into N²-Alkyl-4,5-alkyl(Aryl)-1,2,3-triazoles.

A similar strategy was studied by the same authors concerning the arylation of 4,5-dibromo-1,2,3-triazole with electron deficient arenes and heteroarenes (Wang et al. 2009b). In this approach according to the authors complete selectivity is observed in all cases depicted in Figure 13.

The arylation of 4,5-disubstituted 1,2,3-triazoles was also studied by Chen and co-workers. In this case chloro-nitro benzene were studied, and complete selectivity was also reported for N², probably due to the presence of substituents at the 4 and 5 positions (Li et al. 2009), Figure 14.

Nenajdenko and co-workers studied the regioselective alkylation of 5-aryl-4-fluoro-1,2,3-triazole (Nenajdenko et al. 2017). In this case also complete N² selectivity was observed (only the use of methyl iodide as alkylating agent yields detectable amounts of the N¹ regioisomer, Figure 15).

The interesting point in the present case is that, while in the abovementioned examples the

use of bromine atom can exert steric hindrance to the adjacent nitrogen atom, such effect is not expected for fluorine. Its influence may be exerted by lowering the nucleophilicity of the neighbor nitrogen atom, increasing the N² selectivity.

An asymmetric aza-Michael reaction of 4-aryl-NH-1,2,3-triazoles to cyclic enones under the catalytic influence of chiral bifunctional thiourea organocatalysts for the enantioselective generation of 2,4-disubstituted 1,2,3-triazoles was reported by Bhagat and co-workers (Bhagat and Peddinti 2018). The cinchonine derived thiourea catalyst **91** produce the N²-functionalized 1,2,3-triazoles as major products in good and excellent optical yields, Figure 16. The use of six membered cyclic conjugate ketones furnishes better yields and optical purity than the corresponding five membered rings.

An efficient copper-catalyzed C–N bond formation by N–H/C–H cross-dehydrogenative coupling (CDC) between NH-1,2,3-triazoles

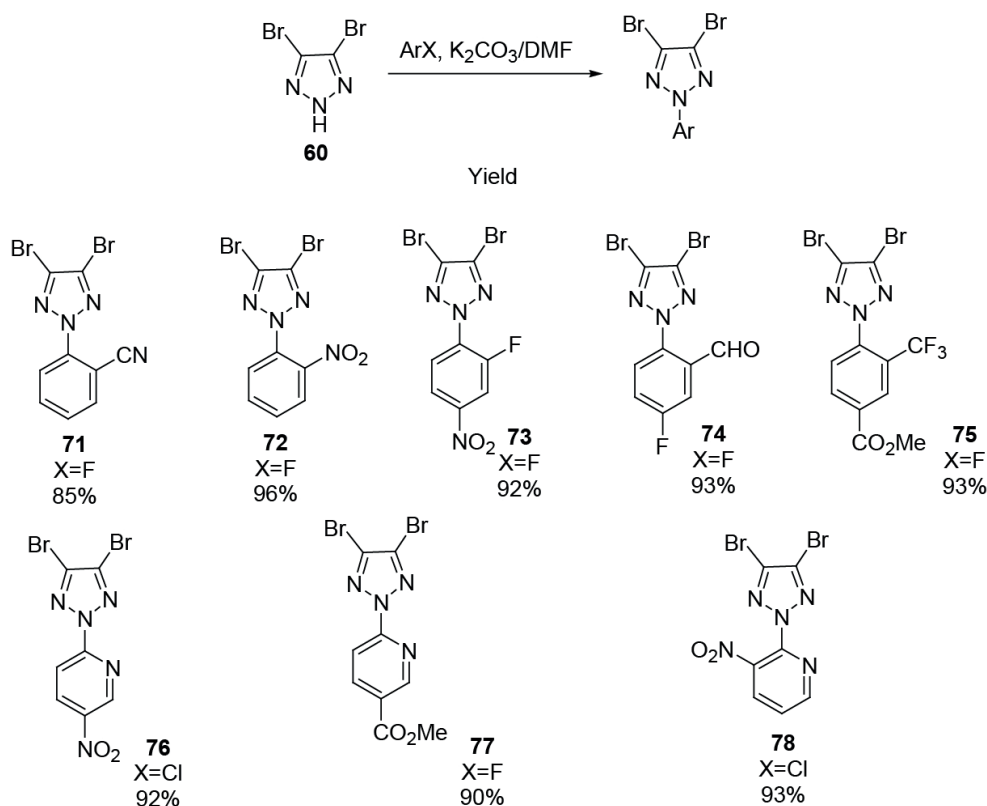


Figure 13 - Arylation of 4,5-dibromo-1,2,3-triazole with electron deficient arenes and heteroarenes.

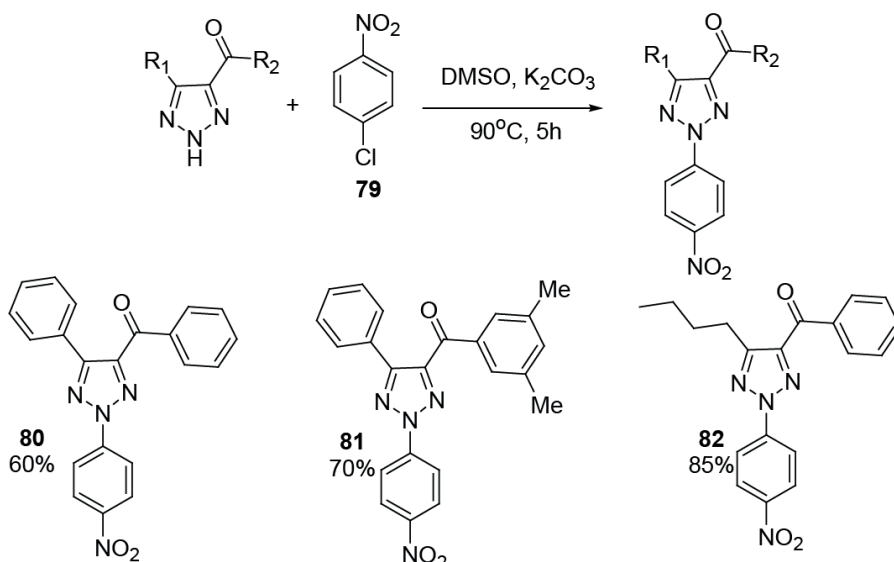


Figure 14 - Complete N²-Regioselective arylation of 4,5-disubstituted 1,2,3-triazoles with chloro-nitro Benzene.

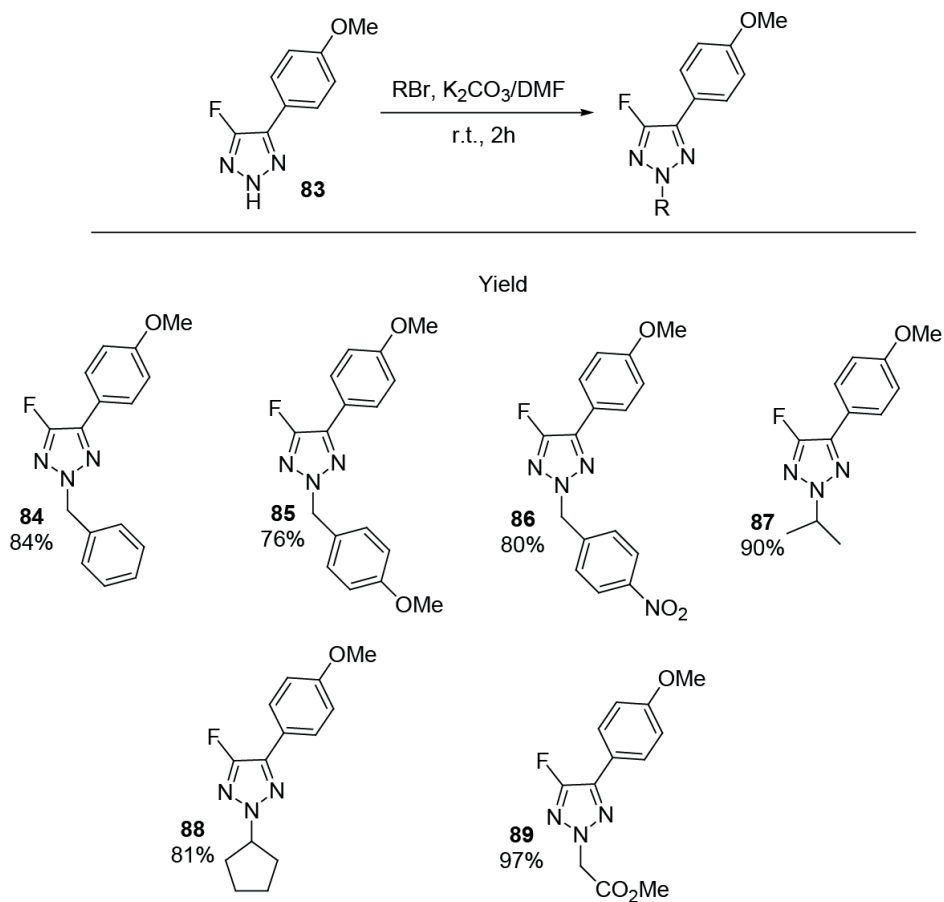


Figure 15 - Highly N²regioselective Alkylation of 5-(4-Methoxy)-Phenyl-4-fluoro-1,2,3-triazole.

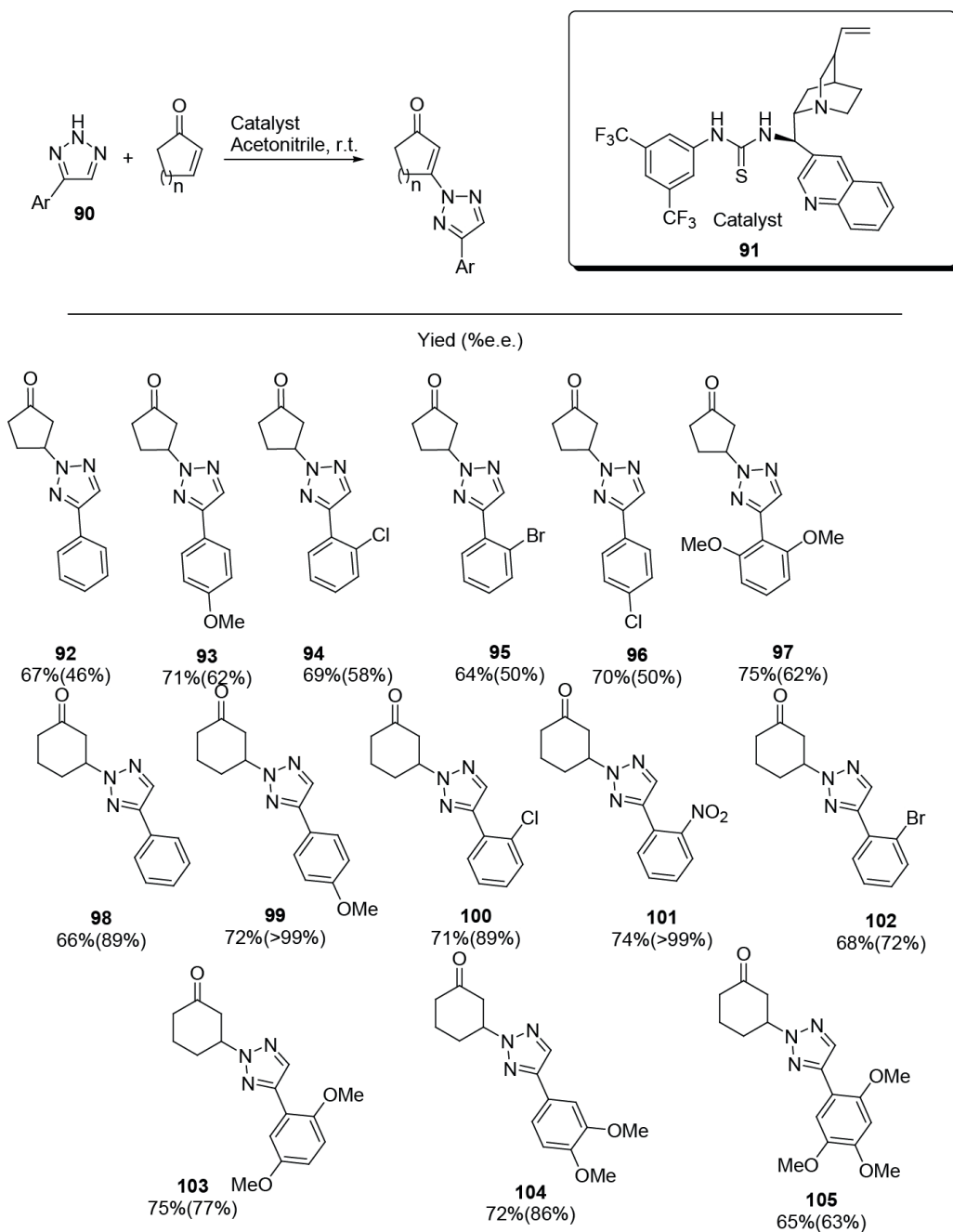


Figure 16 - The regio and enantioselective α -Michael reaction of 4-aryl-NH-1,2,3-triazoles to cyclic enones.

and N,N-dialkyl amides was recently reported by Deng and co-workers (Deng et al. 2017). The developed reaction provides N²-amidoalkylated 1,2,3-triazoles when 4,5-disubstituted NH-1,2,3-triazoles served as the substrates. Examples of this reaction are present in Figure 17.

A very interesting N²-regioselective autocatalytic ditriazolylated reaction of cyclopropanones with N¹-sulfonyl-1,2,3-triazoles was reported recently by Shi and co-workers (Long-Hai et al. 2017). The representative examples of the ditriazolylated reaction of cyclopropanones

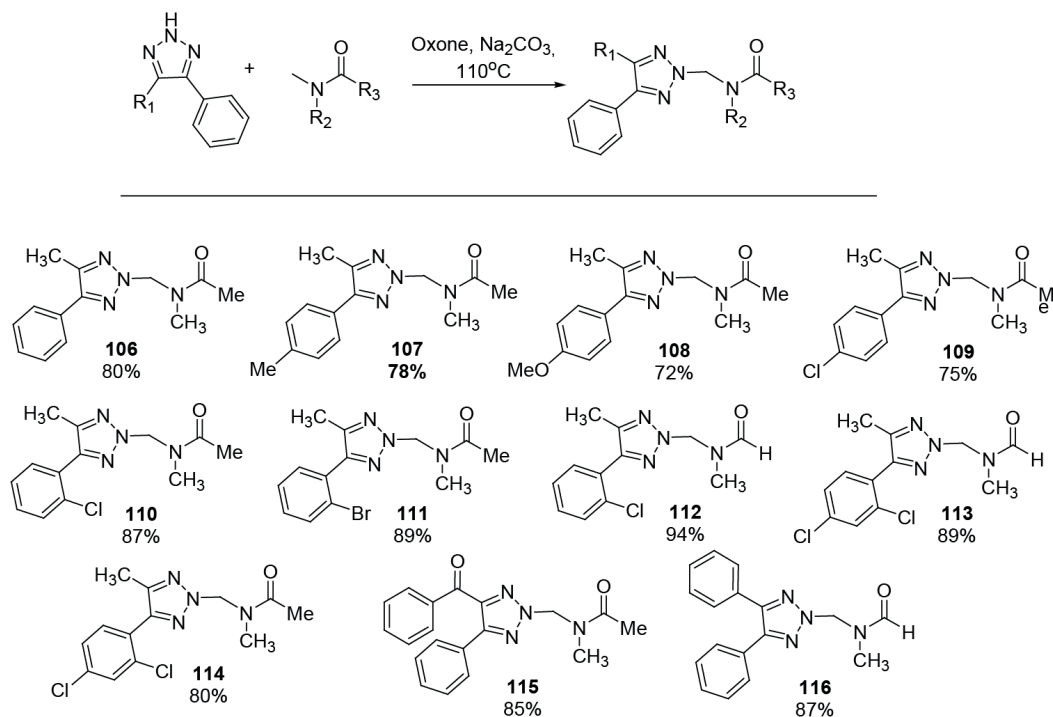


Figure 17 - Regioselective cross-dehydrogenative coupling (CDC) between NH-1,2,3-triazoles and N,N-dialkylamides.

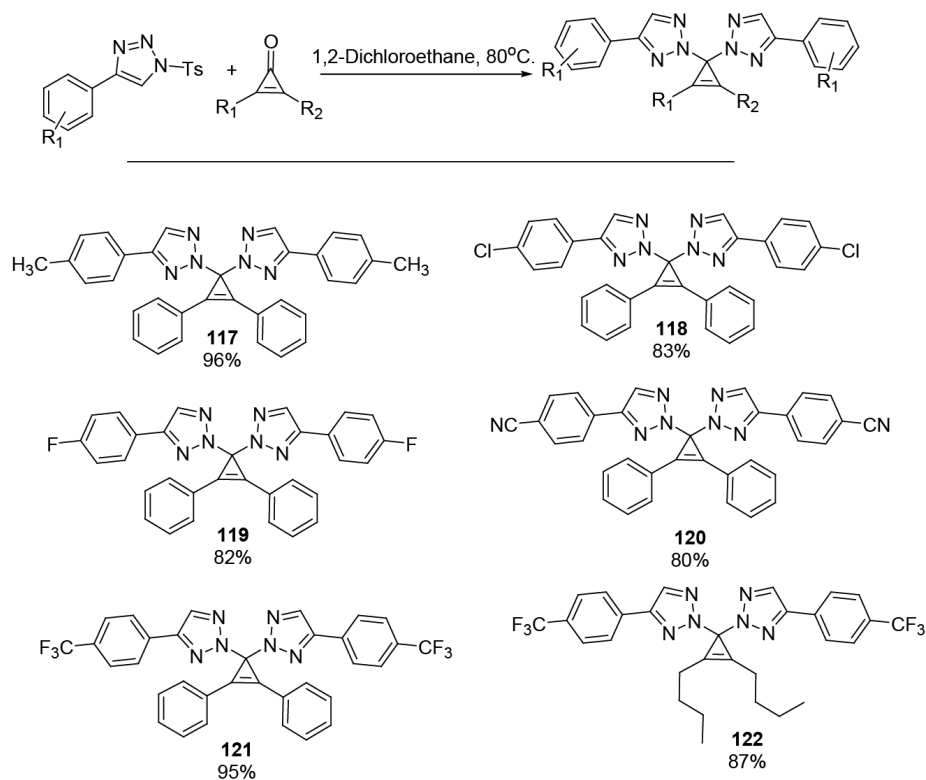


Figure 18 - N²-regioselective autocatalytic ditriazolylation reaction of cyclopropanones with N¹-sulfonyl-1,2,3-triazoles.

are presented in Figure 18. All reactions reported by the authors lead to good yields irrespective the substitution pattern on the triazole and cyclopropanone.

The mechanistic studies conducted by the authors suggest an autocatalytic cycle as the one presented in Figure 19. In this mechanism, the ionization of the N¹-sulfonyl-1,2,3-triazole leads to specie **124**, which reacts with the cyclopropanone to furnish aromatic cation such as **126**. This cation reacts with a second equivalent of the N¹-sulfonyl-1,2,3-triazole yielding the isolated product and the corresponding sulfonyl anhydride. The reaction of the sulfonyl anhydride with another equivalent of the cyclopropanone leads to intermediate **127**, which upon reaction with N¹-sulfonyl-1,2,3-triazole leads again to cation **126** and sulfonyl anhydride, closing then the autocatalytic cycle.

METAL CATALYZED N²ARYLATION OF 1,2,3-TRIAZOLES

The first study of palladium catalyzed N² selective arylation of 1,2,3-triazoles was reported by Buchwald and co-workers (Buchwald et al. 2011). In this study, the use of sterically hindered phosphine ligands such as Me₄tBuXPhos **128** leads to reactions with high selectivity for N² regioisomer with both unsubstituted and 4 (or 4,5)-substituted 1,2,3-triazoles as shown in the Figure 20.

Theoretical calculations show that the selectivity in favor of N² occurs in the reductive elimination step where the transition state for the formation of the arylated product for N² is 3.3 kcal.mol⁻¹ lower than the transition state for the formation of N¹.

The methodology described by Buchwald represented a major advance in triazole chemistry. This methodology enabled a series of subsequent studies, by several authors, where they were able to explore the 2-aryl-1,2,3-triazole skeleton. An important example of these studies is that developed by Tian and co-workers concerning the

selective halogenation reaction of N²-substituted 1,3,2-triazoles by activation of C_{sp²}-H bond (Tian et al. 2013).

This study by Tian presented an important advance to the previous approach reported by Morin on the halogenation of the N²-Phenyl-1,2,3-triazoles where poor selectivities were originally observed, Figure 21A. In this study the palladium-catalyzed halogenation of 2-aryl-1,2,3-triazoles was reported using N-halosuccinimides as a source of halogen. It is important to highlight the wide scope of the reaction regarding the use of aromatic systems with the most diverse substituents. Some examples are present in Figure 21A. In this study, the observed regioselectivity results from the ability of the triazole skeleton to guide *ortho*-palatation of the 2'-position, as summarized in Figure 21B. The constructed frameworks found application in the synthesis the core present in Suvorexant, as shown in Figure 21C.

The ability of the 1,2,3-triazole to orient *ortho*-palatation of the 2'-position of the aromatic system bond to N² also stimulated Wu and co-workers to carry out studies for the ethoxy carbonylation of the 2-Aryl-1,2,3-triazole C2' position, Figure 22. In this reaction, ethyl diazocarboxylate is used as the source of carbamoyl, with the concomitant evolution of N². Such reaction was also applied to the synthesis of Suvorexant.

The methodology developed by Buchwald was also used in the synthesis of novel triazolic C-nucleoside (Lopes et al. 2016). In this work, the use of the same phosphine ligand reported by Buchwald and co-workers led to selectivities lower than originally reported. The use of an even more sterically hindered ligand such as AdBrettPhos was able to rescue the selectivity in the cases studied, as shown in Figure 23. In this work, because of the use of an even more sterically hindered ligand, a reduction in scope has been imposed where halo *ortho*-substituted arenes are not capable of leading to the desired arylated product.

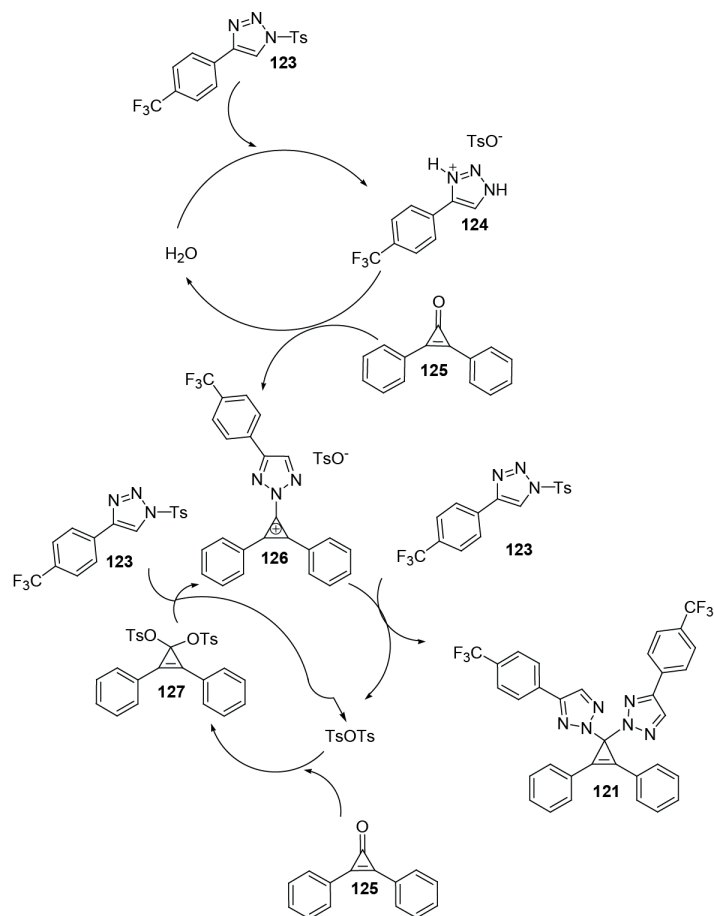


Figure 19 - Proposed autocatalytic mechanism for the ditriazolylation reaction of cyclopropanones.

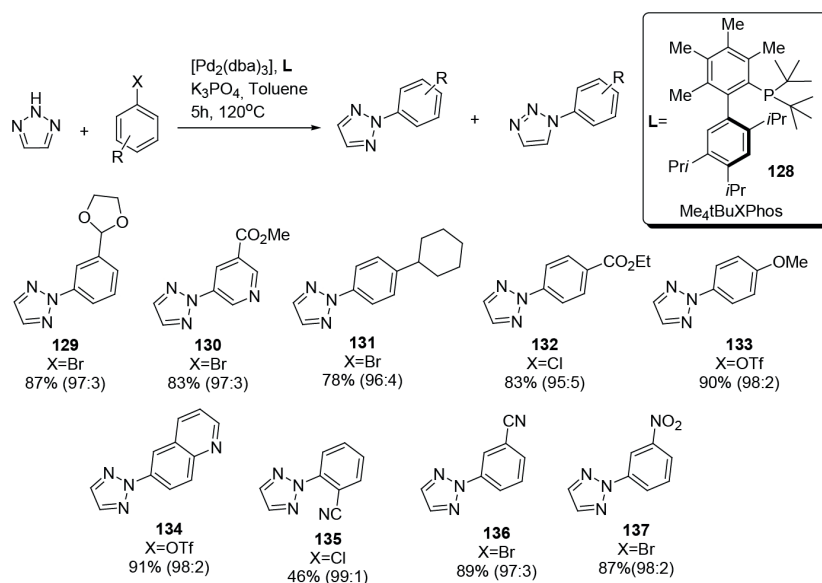


Figure 20 - The Palladium Catalyzed N²-regioselective Arylation of 1,2,3-triazoles.

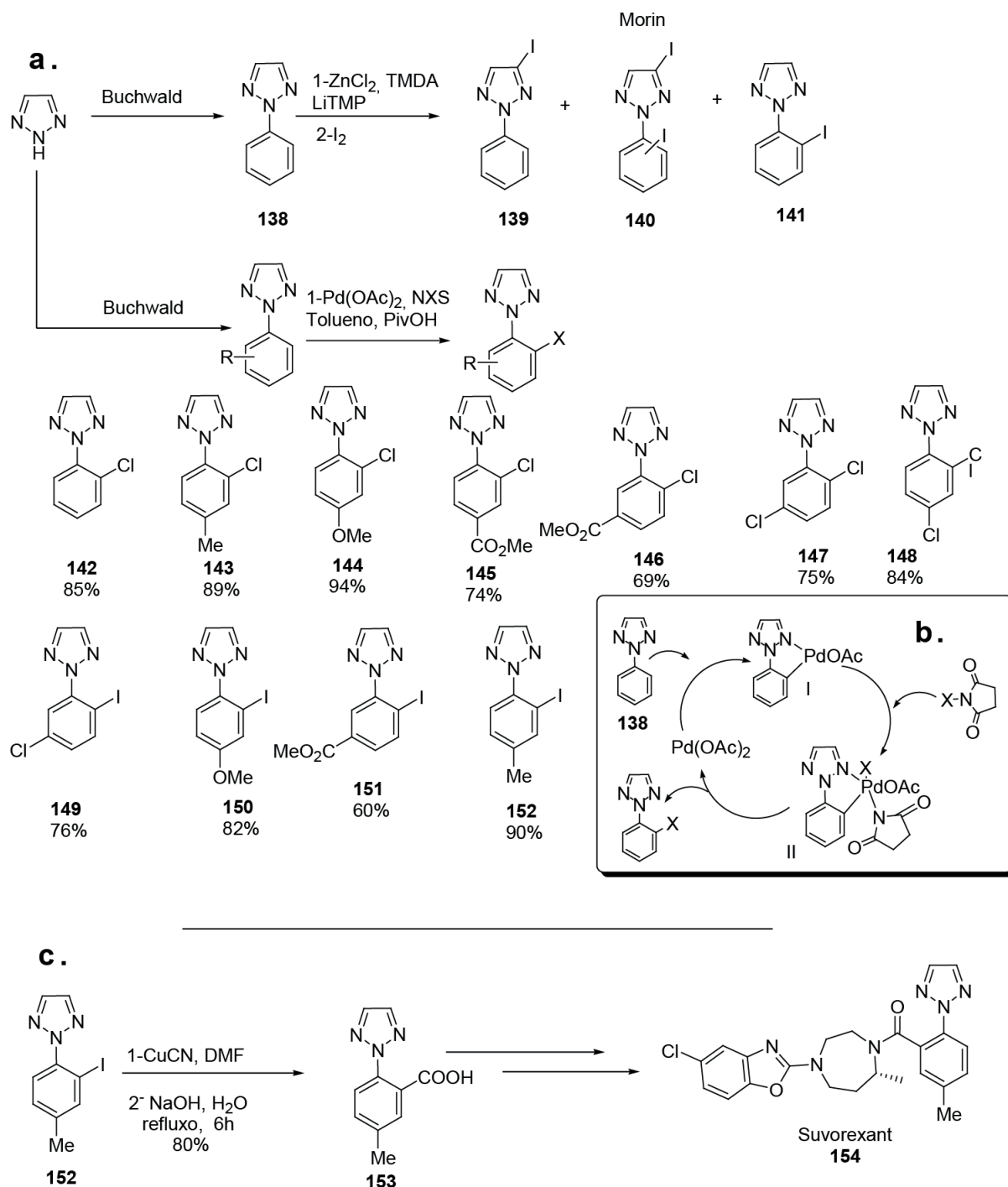


Figure 21 - a) The 2' Halogenation of 2-aryl-1,2,3-triazoles. b) A simplified catalytic cycle showing the *ortho*-palladation directing ability of the 123-triazole core. c) Application of this reaction in the synthesis of the 1,2,3-triazolic core of Suvorexant.

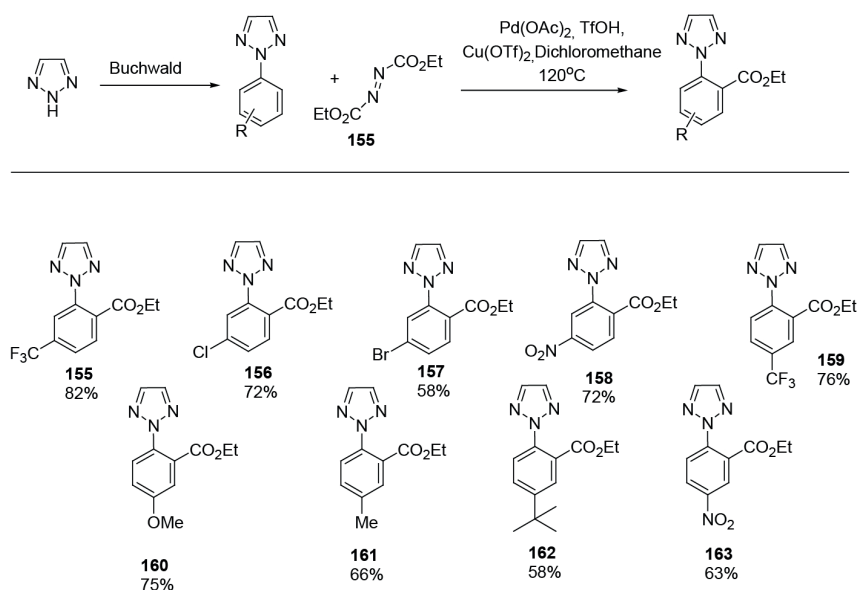


Figure 22 - The Palladium catalyzed C2' ethoxy carbonylation of the 2-Aryl-1,2,3-triazole.

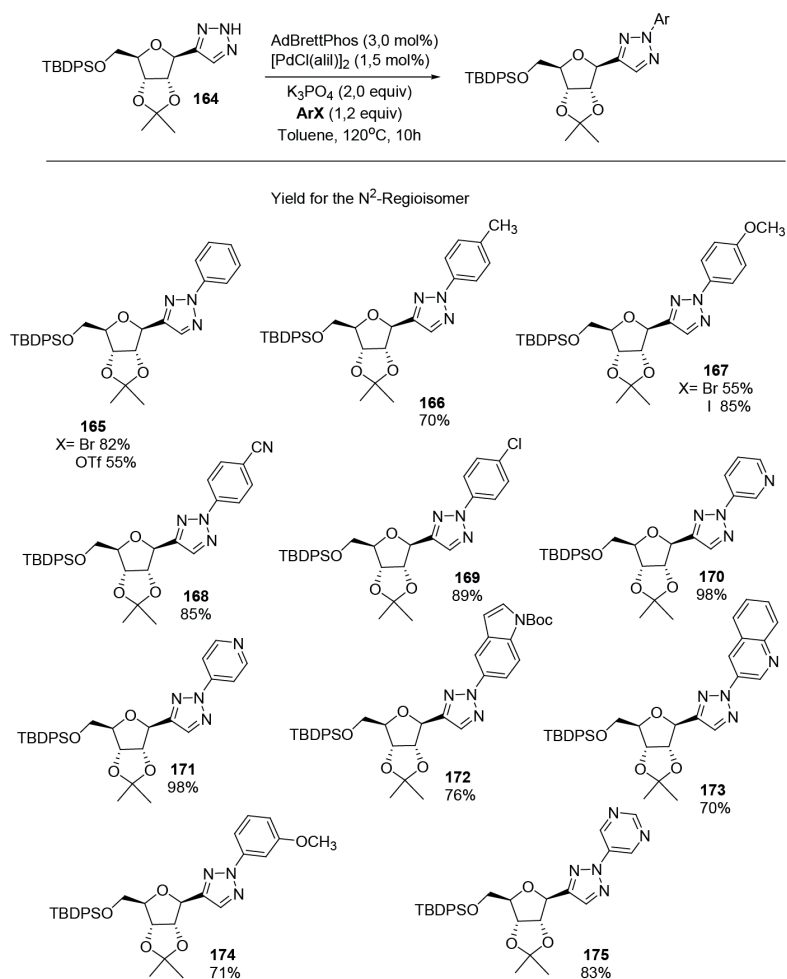


Figure 23 - The Palladium catalyzed N²-Regioselective Arylation of β-Triazoyl Ribosides.

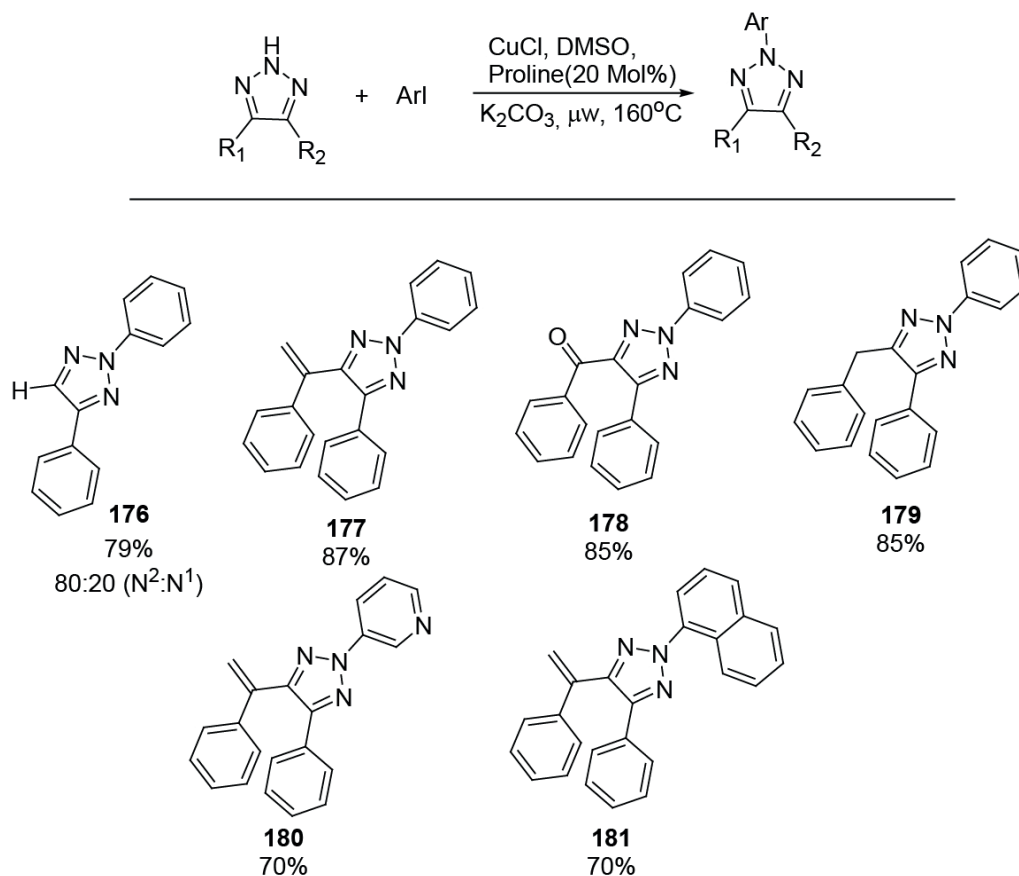
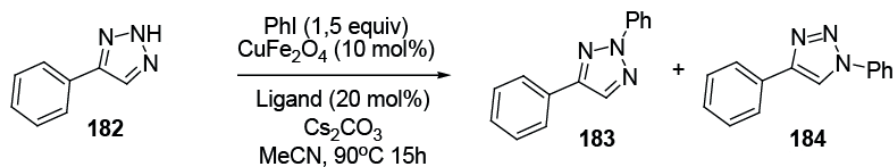


Figure 24 - The copper catalyzed N²Arylation of substituted 1,2,3-triazoles.

The first report on the regioselectivity of copper-catalyzed 1,2,3-triazoles arylation was that described by Liu and co-workers. In their study, the reaction was conducted under microwaves, in the presence of proline as ligand and in DMSO as the solvent (Liu et al. 2008). As shown in Figure 24, the selectivity was studied fundamentally in 4,5-substituted 1,2,3-triazoles which leads to complete regioselectivity for the N² isomer. As described in the previous sections, the selectivity in these cases is facilitated since the presence of these substituents (other than H) exert a steric effect leading to a preferential N² reaction. In the study reported by Liu, in the only example where the reaction is performed on mono substituted triazole the selectivity is 80:20 favoring the N²-Arylated regioisomer.

The first systematic study on the copper-catalyzed of N²-selective arylation reaction of mono substituted triazoles was reported recently by our group (Lopes et al. 2017). In a model reaction using 4-Phenyl-1,2,3-triazole **182**, the different classes of ligands used in copper catalyzed Ullmann coupling were screened in the reaction, and the yield and regioselectivity is present Figure 25.

In this study it was observed that among the different class of ligands screened, amino acids (**186, 188, 190-203, 206-208**) gave the best results in terms of yield and selectivity. Among them secondary amino acids are better than primary amino acids. It was also observed that the group alkylating the nitrogen atom has also profound impact in the outcome of the reaction. The scope was evaluated under the optimized conditions



Ligands Studied

Yield (N²:N¹)

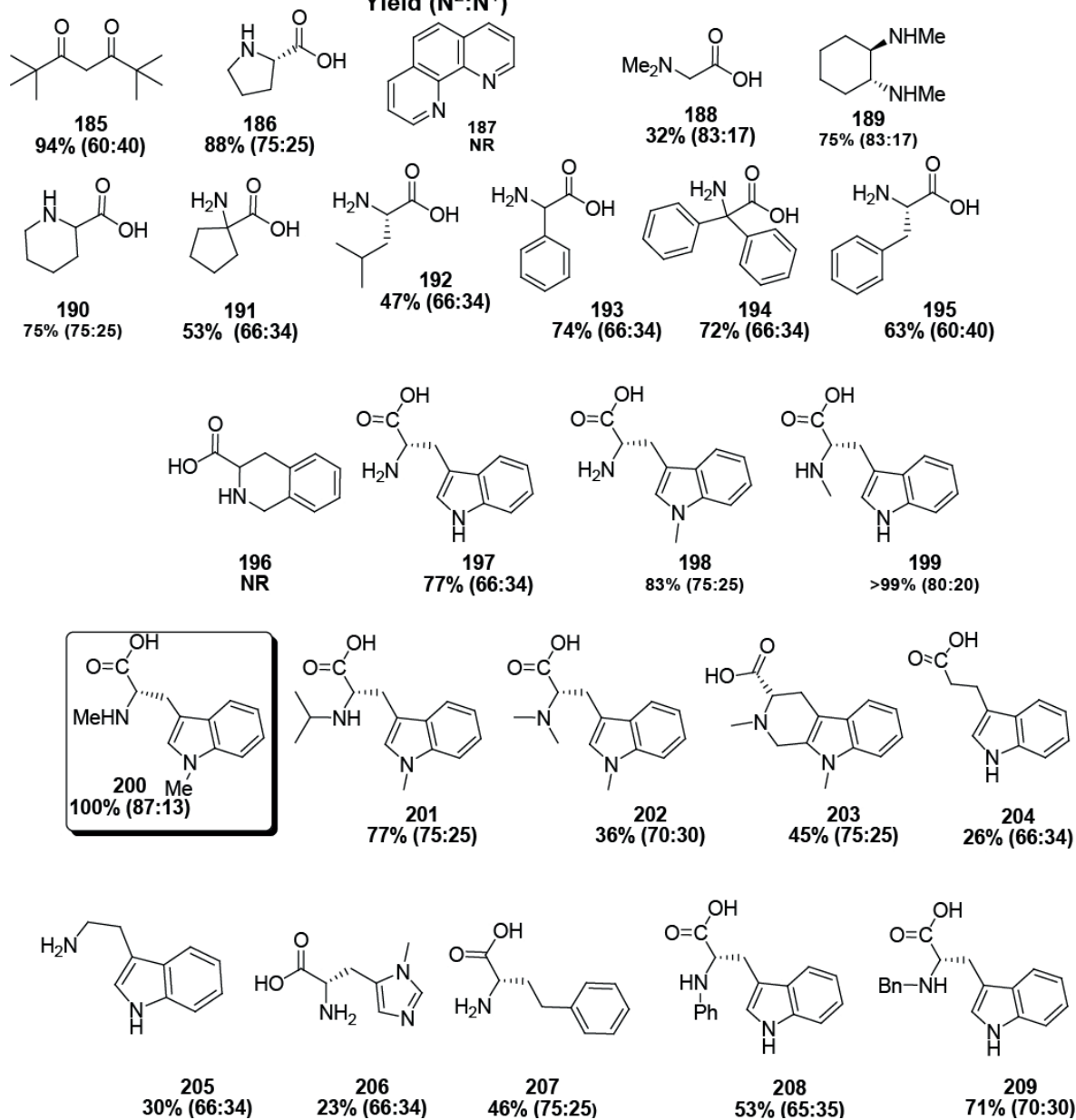


Figure 25 - Data on the yield and regioselectivity of different class of ligands for the copper catalyzed N²-Regioselective arylation of 1,2,3-triazoles.

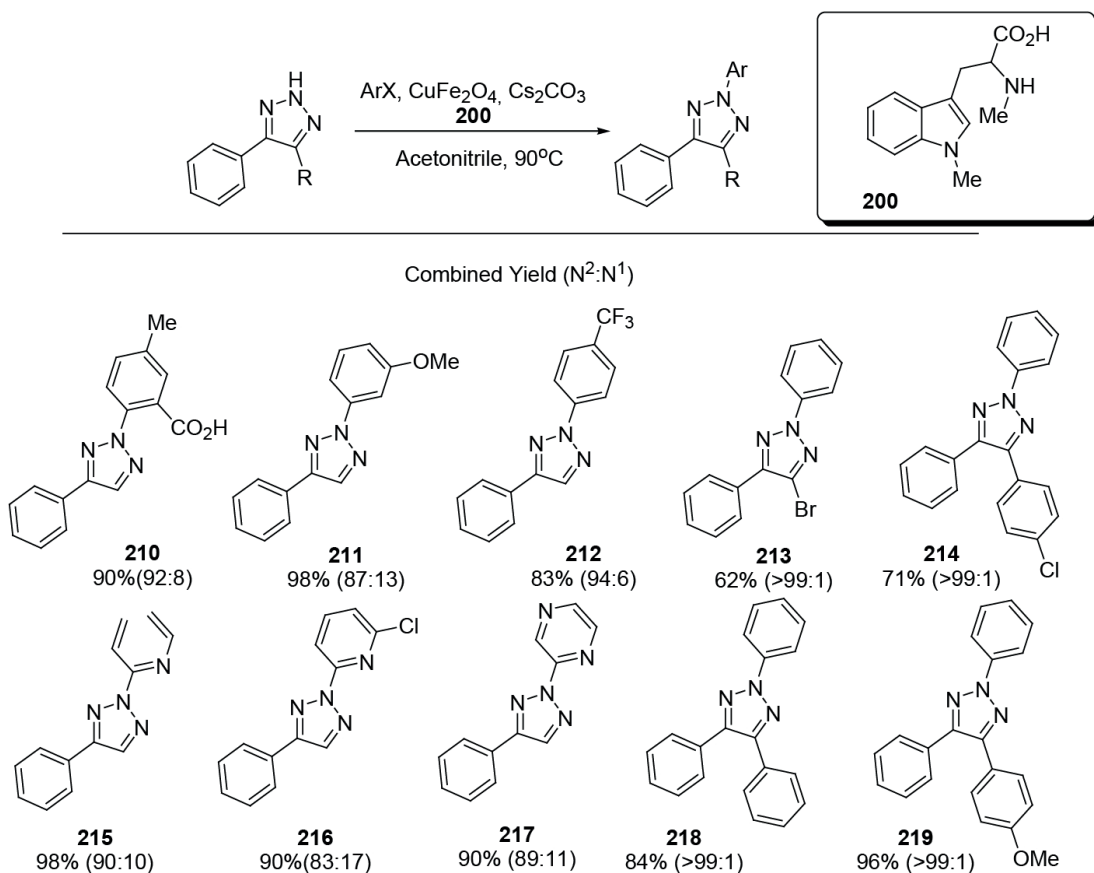


Figure 26 - Scope on the Copper catalyzed N²-Regioselective arylation of 1,2,3-triazoles.

and selectivities up to 92:8 for the N²-regioisomer could be observed under much smoother conditions the one reported by Shi and co-workers (Liu et al. 2008).

CONCLUSIONS

As can be observed in the previous sections, there have been an increased interest in developing new approaches towards the synthesis of the N²-substituted 1,2,3-triazoles. The developments so far achieved represent important advances in the area of the 1,2,3-triazole chemistry, especially those reactions that allow the functionalization of the triazole *posteri*, which enable the synthesis of 2; 2,4 and 2,4,5-substituted 1,2,3-triazole libraries and then to study their properties. However, it is an area where much is still to be done since those reactions

are far from achieving the goals obtained by the CuAAC reaction, i.e high yielding and selective under smooth and even aqueous condition, allowing its application in areas where the properties of the N²-regioisomers is still unknown such as the bioconjugation of biomolecules such as proteins and polysaccharides.

ACKNOWLEDGMENTS

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001. The authors also thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) for their financial support.

REFERENCES

- ADIBEKIAN A, MARTIN BR, WANG C, HSU KL, BACHOVCHIN DA, NIESSEN S, HOOVER H AND CRAVATT BF. 2011. Click-generated triazole ureas as ultrapotent in vivo-active serine hydrolase inhibitors. *Nat Chem Biol* 7: 469.
- AGARD NJ, PRESCHER JA AND BERTOZZI CR. 2004. A Strain-Promoted [3 + 2] Azide-Alkyne Cycloaddition for Covalent Modification of Biomolecules in Living Systems. *J Am Chem Soc* 126: 15046-15047.
- AHER NG, PORE VS, MISHRA NN, KUMAR A, SHUKLA PK, SHARMA A AND BHAT MK. 2009. Synthesis and antifungal activity of 1,2,3-triazole containing fluconazole analogues. *Bioorganic & Medicinal Chemistry Letters* 19: 759-763.
- ALAN RK AND POZHARSKII AF 2000. *Handbook of Heterocyclic Chemistry*. Elsevier Science Ltda.
- ALBERT A AND TAYLOR PJ. 1989. The tautomerism of 1,2,3-triazole in aqueous solution. *J Chem Soc* 2: 1903-1905.
- BAXTER CA, CLEATOR E, BRANDS KMJ, EDWARDS JS, REAMER RA, SHEEN FJ, STEWART GW, STROTMAN NA AND WALLACE DJ. 2011. The First Large-Scale Synthesis of MK-4305: A Dual Orexin Receptor Antagonist for the Treatment of Sleep Disorder. *Org Proc Res Dev* 15: 367-375.
- BEGTRUP M, NIELSEN CJ, NYGAARD L, SAMDAL S, SJOGREN CE AND SORENSEN GO. 1988. The Molecular Structure and tautomer Equilibrium of Gaseous 1,2,3-Triazole Studied by Microwave Spectroscopy, Electron Diffraction and *ab initio* Calculations. *Acta Chem Scand A* 42: 500-514.
- BHAGAT UK AND PEDDINTI RK. 2018. Asymmetric Organocatalytic Approach to 2,4-Disubstituted 1,2,3-Triazoles by N²-Selective Aza-Michael Addition. *The J Org Chem* 83: 793-804.
- BLASS BE ET AL. 2006. Synthesis and evaluation of (2-phenethyl-2H-1,2,3-triazol-4-yl)(phenyl)methanones as Kv1.5 channel blockers for the treatment of atrial fibrillation. *Bioorg Med Chem Lett* 16: 4629-4632.
- BOECHAT N ET AL. 2011. Novel 1,2,3-Triazole Derivatives for Use against Mycobacterium tuberculosis H37Rv (ATCC 27294) Strain. *J Med Chem* 54: 5988-5999.
- BOULTON AJ, GHOSH PB AND KATRITZKY AR. 1966. Heterocyclic rearrangements. Part V. Rearrangement of 4-aryloxy- and 4-nitroso-benzofuroxans: new syntheses of the benzotriazole and benzofurazan ring systems. *J Chem Soc B Phys Org*: 1004-1011.
- BROCKUNIER LL ET AL. 2000. Human β 3-adrenergic receptor agonists containing 1,2,3-triazole-substituted benzenesulfonamides. *Bioorg Med Chem Lett* 10: 2111-2114.
- BUCHWALD SL, SATOSHI U AND MINGJUAN S. 2011. Highly N²-Selective Palladium-Catalyzed Arylation of 1,2,3-Triazoles. *Ang Chem Int Ed* 50: 8944-8947.
- CALDERONE V, GIORGI I, LIVI O, MARTINOTTI E, MARTELLI A AND NARDI A. 2005. 1,4- and 2,4-substituted-1,2,3-triazoles as potential potassium channel activators. *VII. Il Farmaco* 60: 367-375.
- CESARE TG, TRACEY P, A. BR, LUIGI CP, GIOVANNI S AND GENAZZANI AA. 2008. Click chemistry reactions in medicinal chemistry: Applications of the 1,3-dipolar cycloaddition between azides and alkynes. *Med Res Rev* 28: 278-308.
- CHEN Y, SHI W, HUI Y, SUN X, XU L, FENG L AND XIE Z. 2015a. A new highly selective fluorescent turn-on chemosensor for cyanide anion. *Talanta* 137: 38-42.
- CHEN Y, WU J, MA S, ZHOU S, MENG X, JIA L AND PAN Z. 2015b. Syntheses, structures and properties of Zn(II) and Cu(II) complexes based on N²-2-methylenepyridinyl 1,2,3-triazole ligand. *J Mol Struct* 1089: 1-8.
- COSIMELLI B, GUERNELLI S, SPINELLI D, BUSCEMI S, FRENNA V AND MACALUSO G. 2001. On the Synthesis and Reactivity of the Z-2,4-Dinitrophenylhydrazones of 5-Amino-3-benzoyl-1,2,4-oxadiazole. *J Org Chem* 66: 6124-6129.
- COX CD ET AL. 2010. Discovery of the Dual Orexin Receptor Antagonist [(7R)-4-(5-Chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (MK-4305) for the Treatment of Insomnia. *J Med Chem* 53: 5320-5332.
- CROWLEY JD AND MCMORRAN DA 2012. "Click-Triazole" Coordination Chemistry: Exploiting 1,4-Disubstituted-1,2,3-Triazoles as Ligands. In: Košmrlj J (Ed), *Click Triazoles*, Berlin, Heidelberg: Springer Berlin Heidelberg, p. 31-83.
- D'ANNA F, FERRONI F, FRENNA V, GUERNELLI S, LANZA CZ, MACALUSO G, PACE V, PETRILLO G, SPINELLI D AND SPISANIR R. 2005. On the application of the extended Fujita-Nishioka equation to polysubstituted systems. A kinetic study of the rearrangement of several poly-substituted Z-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole into 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazoles in dioxane/water. *Tetrahedron* 61: 167-178.
- D'ANNA F, FRENNA V, LANZA CZ, MACALUSO G, MARULLO S, SPINELLI D, SPISANIR AND PETRILLO G. 2010. On the use of multi-parameter free energy relationships: the rearrangement of (Z)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole into (2-aryl-5-phenyl-2H-1,2,3-triazol-4-yl)ureas. *Tetrahedron* 66: 5442-5450.
- DEBETS MF, VAN HEST JCM AND RUTJES FPJT. 2013. Bioorthogonal labelling of biomolecules: new functional handles and ligation methods. *Org Biomol Chem* 11: 6439-6455.

- DENG X, LEI X, NIE G, JIA L, LI Y AND CHEN Y. 2017. Copper-Catalyzed Cross-Dehydrogenative N²-Coupling of NH-1,2,3-Triazoles with N,N -Dialkylamides: N-Amidoalkylation of NH-1,2,3-Triazoles. *J Org Chem* 82: 6163-6171.
- DHEER D, SINGH V AND SHANKAR R. 2017. Medicinal attributes of 1,2,3-triazoles: Current developments. *Bioorg Chem* 71: 30-54.
- EL SEKILY M, MANCY S, EL KHOLY I, EL ASHRY ESH, EL KHADEM HS AND SWARTZ DL. 1977. Reactions of the 3-oxime 2-phenylhydrazone and mixed bishydrazones of dehydro-L-ascorbic acid: Conversion into substituted triazoles and pyrazolinediones. *Carb Res* 59: 141-149.
- ESTELLE M, PASCAL L AND CHRISTINE G-C. 2008. F-Amphiphilic 1,2,3-Triazoles by Unexpected Intramolecular Cyclisation of Vinyl Azides. *Eur J Org Chem* 2008: 2232-2239.
- GONZAGA D, SENGER MR, DA SILVA FDC, FERREIRA VF AND SILVA FP. 2014. 1-Phenyl-1H- and 2-phenyl-2H-1,2,3-triazol derivatives: Design, synthesis and inhibitory effect on alpha-glycosidases. *Eur J Med Chem* 74: 461-476.
- HALDÓN E, NICASIO MC AND PÉREZ PJ. 2015. Copper-catalysed azide-alkyne cycloadditions (CuAAC): an update. *Org Biomol Chem* 13: 9528-9550.
- HEGARTY AF, QUAIN P, O'MAHONY TAF AND SCOTT FL. 1974. Mechanism of cyclisation of N-(1,2,4-triazol-3-yl)hydrazonyl bromides to mixtures of isomeric triazolotriazoles. *Journal of the Chemical Society, Perkin Transactions 2*: 997-1004.
- KALISIAK J, SHARPLESS KB AND FOKIN VV. 2008. Efficient Synthesis of 2-Substituted-1,2,3-triazoles. *Organic letters* 10: 3171-3174.
- KSENIYA GD, LESOGOROVA SG, SUKHORUKOVA ES, SUBBOTINA JO, SLEPUKHIN PA, BENASSI E BELSKAYA NP. 2016. Synthesis of 2-Aryl-1,2,3-triazoles by Oxidative Cyclization of 2-(Arylazo)ethene-1,1-diamines: A One-Pot Approach. *Eur J Org Chem* 2016: 2700-2710.
- LI J, WANG D, ZHANG Y, LI J AND CHEN B. 2009. Facile One-Pot Synthesis of 4,5-Disubstituted 1,2,3-(NH)-Triazoles through Sonogashira Coupling/1,3-Dipolar Cycloaddition of Acid Chlorides, Terminal Acetylenes, and Sodium Azide. *Org Lett* 11: 3024-3027.
- LI YC, QI C, LI SH, ZHANG HJ, SUN CH, YU YZ AND PANG SP. 2010. 1,1'-Azobis-1,2,3-triazole: A High-Nitrogen Compound with Stable N₈ Structure and Photochromism. *J Am Chem Soc* 132: 12172-12173.
- LIU Y, YAN W, CHEN Y, PETERSEN JL AND SHI X. 2008. Efficient Synthesis of N-2-Aryl-1,2,3-Triazole Fluorophores via Post-Triazole Arylation. *Org Lett* 10: 5389-5392.
- LONG-HAI L, YU J, JIAN H, YIN W AND MIN S. 2017. N²-Selective Autocatalytic Ditrizoloylation Reactions of Cyclopropenones and Tropone with N¹-Sulfonyl-1,2,3-triazoles. *Adv Synt Catal* 359: 3304-3310.
- LOPES AB, WAGNER P, DE SOUZA ROMA, GERMAIN NL, UZIEL J, BOURGUIGNON JJ, SCHMITT M AND MIRANDA LSM. 2016. Functionalization of 2H-1,2,3-Triazole C-Nucleoside Template via N² Selective Arylation. *J Org Chem* 81: 4540-4549.
- LOPES AB, WAGNER P, KÜMMERLE AE, BIHEL F, BOURGUIGNON JJ, SCHMITT M AND MIRANDA LSM. 2017. Development of a L-Tryptophan-Based Ligand for Regioselective Copper Catalyzed N²-Arylation of 1,2,3-Triazoles. *Chem Select* 2: 6544-6548.
- LUNAZZI L, PARISI F AND MACCIANTELLI D. 1984. Conformational studies by dynamic nuclear magnetic resonance spectroscopy. Part 27. Kinetics and mechanism of annular tautomerism in isomeric triazoles. *J Chem Soc* 2: 1025-1028.
- NASSR MAM, SOUSAN E-BM AND SMABAN MAE. 1985. Reactions of Aroylhydrazones, IV: Synthesis of Nitrogen Heterocycles from Opianic Acid Hydrazones. *J Chin Chem Soc* 32: 65-73.
- NENAJDENKO VG, MOTORNOV VA, TABOLIN AA, NOVIKOV RA, NELYUBINA YV, OFFE SLI AND SMOLYAR IV. 2017. Synthesis and Regioselective N-2 Functionalization of 4-Fluoro-5-aryl-1,2,3-NH-triazoles. *Eur J Org Chem* 2017: 6851-6860.
- OZIMIŃSKI WP, DOBROWOLSKI JC AND MAZUREK AP. 2003. DFT studies on tautomerism of C5-substituted 1,2,3-triazoles. *J Mol Struct* 651-653: 697-704.
- PENG W, FELDMAN AK, NUGENT AK, HAWKER CJ, SCHEEL A, VOIT B, PYUN J, FRÉCHET JM, SHARPLESS KB AND FOKIN VV. 2004. Efficiency and Fidelity in a Click-Chemistry Route to Triazole Dendrimers by the Copper(I)-Catalyzed Ligand of Azides and Alkynes. *Ang Chem Int Ed* 43: 3928-3932.
- PUNNIYAMURTHY T AND GURU MM. 2012. Copper(II)-Catalyzed Aerobic Oxidative Synthesis of Substituted 1,2,3- and 1,2,4-Triazoles from Bisarylhidrazones via C-H Functionalization/C-C/N-N/C-N Bonds Formation. *J Org Chem* 77: 5063-5073.
- ROLF H. 1963. 1,3-Dipolar Cycloadditions. Past and Future. *Ang Chem Int Ed* 2: 565-598.
- ROLF H, GÜNTHER SAND LEANDER M. 1967. 1,3-Dipolare Cycloadditionen, XXXII. Kinetik der Additionen organischer Azide an CC-Mehrfachbindungen. *Chem Ber* 100: 2494-2507.
- SANDIP AG, MAUJAN SR AND PORE VS. 2011. Click Chemistry: 1,2,3-Triazoles as Pharmacophores. *Chem Asian J* 6: 2696-2718.
- SHABAN M, NASSR M, EL ASHRY E AND MUSTAFA M. 1977. Reactions of Aroylhydrazones. III: Oxidative

- cyclization of cyclohexane-1,2-dione bis(arylhydrazones) to substituted 1,2,3-triazoles. *Org Prep Proc Int* 9: 117-124.
- SHABAN MAE. 1976. Reactions of Arylhydrazones. II. Oxidative Cyclization of Benzil Bis(arylhydrazones) to Substituted 1,2,3-Triazoles. *Bull Chem Soc Japan* 49: 2606-2608.
- SHARPLESS KB, KOLB HC AND FINN MG. 2001. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew Chem Int Ed* 40: 2004-2021.
- STOLLÉ R. 1926. Über die Konstitution der Osotetrazine und Amino-osotriazole. *Berichte der deutschen chemischen Gesellschaft (A and B Series)* 59: 1742-1747.
- TANAKA Y AND MILLER SI. 1973. Selectivities in 1,2,3-triazolide displacements of halides and additions to alkynes. *Tetrahedron* 29: 3285-3296.
- THIRUMURUGAN P, MATOSIUK D AND JOZWIAK K. 2013. Click Chemistry for Drug Development and Diverse Chemical–Biology Applications. *Chem Rev* 113: 4905-4979.
- TIAN Q, CHEN X, LIU W, WANG Z, SHI S AND KUANG C. 2013. Regioselective halogenation of 2-substituted-1,2,3-triazoles via sp² C-H activation. *Org Biomol Chem* 11: 7830-7833.
- TOERNKVIST C, BERGMAN J AND LIEDBERG B. 1991. Correlated ab initio geometries and vibrations of 1H- and 2H-1,2,3-triazole. *J Phys Chem* 95: 3123-3128.
- TORNØE CW, CHRISTENSEN C AND MELDAL M. 2002. 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* 67: 3057-3064.
- VINCENZO F, ANTONIO PP, BARBARA C, FRANCO G AND DOMENICO S. 2014. The Boulton–Katritzky Reaction: A Kinetic Study of the Effect of 5-Nitrogen Substituents on the Rearrangement of Some (Z)-Phenylhydrazones of 3-Benzoyl-1,2,4-oxadiazoles. *Eur J Org Chem* 2014: 7006-7014.
- WANG K, CHEN M, WANG Q, SHI X AND LEE JK. 2013. 1,2,3-Triazoles: Gas Phase Properties. *J Org Chem* 78: 7249-7258.
- WANG Q, CHANTR, HILGRAF R, FOKIN VV, SHARPLESS KB AND FINN MG. 2003. Bioconjugation by Copper(I)-Catalyzed Azide-Alkyne [3 + 2] Cycloaddition. *J Am Chem Soc* 125: 3192-3193.
- WANG XJ, SIDHU K, ZHANG L, CAMPBELL S, HADDAD N, REEVES DC, KRISHNAMURTHY D AND SENANAYAKE CH. 2009a. Bromo-Directed N-2 Alkylation of NH-1,2,3-Triazoles: Efficient Synthesis of Poly-Substituted 1,2,3-Triazoles. *Org Lett* 11: 5490-5493.
- WANG XJ, ZHANG L, LEE H, HADDAD N, KRISHNAMURTHY D AND SENANAYAKE CH. 2009b. Highly Regioselective N-2 Arylation of 4,5-Dibromo-1,2,3-triazole: Efficient Synthesis of 2-Aryltriazoles. *Org Lett* 11: 5026-5028.
- WATANABE T, UMEZAWA Y, TAKAHASHI Y AND AKAMATSU Y. 2010. Novel pyrrole- and 1,2,3-triazole-based 2,3-oxidosqualene cyclase inhibitors. *Bioorg Med Chem Lett* 20: 5807-5810.
- WIPF P, WANG XJ, ZHANG L, KRISHNAMURTHY D AND SENANAYAKE CH. 2010. General Solution to the Synthesis of N-2-Substituted 1,2,3-Triazoles. *Org Lett* 12: 4632-4635.
- WU L, GUO S, WANG X, GUO Z, YAO G, LIN Q AND WU M. 2015. Tandem synthesis of 2-aryl-1,2,3-triazoles from α -arylhydrazonoketones with NH₄OAc via copper-catalyzed aerobic oxidation. *Tetrahedron Lett* 56: 2145-2148.
- ZHANG S, XU Z, GAO C, REN QC, CHANG L, LV ZS AND FENG LS. 2017. Triazole derivatives and their anti-tubercular activity. *Eur J Med Chem* 138: 501-513.
- ZHOU Z, LIS, ZHANG Y, LIU M AND LI W. 2005. Promotion of Proton Conduction in Polymer Electrolyte Membranes by 1H-1,2,3-Triazole. *J Am Chem Soc* 127: 10824-10825.
- ZHU C, ZENG H, CHEN F, LIU C, ZHU R, WU W AND JIANG H. 2018. Copper-catalyzed coupling of oxime acetates and aryldiazonium salts: an azide-free strategy toward N-2-aryl-1,2,3-triazoles. *Org Chem Front* 5: 571-576.