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Review

Azides in the Synthesis of Various Heterocycles

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Abstract: In this review, we focus on some interesting and recent examples of various applications of organic azides such as their intermolecular or intramolecular, under thermal, catalyzed, or non-catalyzed reaction conditions. The aforementioned reactions in the aim to prepare basic five-, six-, organometallic heterocyclic-membered systems and/or their fused analogs. This review article also provides a report on the developed methods describing the synthesis of various heterocycles from organic azides, especially those reported in recent papers (till 2020). At the outset, this review groups the synthetic methods of organic azides into different categories. Secondly, the review deals with the functionality of the azido group in chemical reactions. This is followed by a major section on the following: (1) the synthetic tools of various heterocycles from the corresponding organic azides by one-pot domino reaction; (2) the utility of the chosen catalysts in the chemoselectivity favoring C−H and C-N bonds; (3) one-pot procedures (i.e., Ugi four-component reaction); (4) nucleophilic addition, such as Aza-Michael addition; (5) cycloaddition reactions, such as [3+2] cycloaddition; (6) mixed addition/cyclization/oxygen; and (7) insertion reaction of C-H amination. The review also includes the synthetic procedures of fused heterocycles, such as quinazoline derivatives and organometal heterocycles (i.e., phosphorus-, boron- and aluminum-containing heterocycles). Due to many references that have dealt with the reactions of azides in heterocyclic synthesis (currently more than 32,000), we selected according to generality and timeliness. This is considered a recent review that focuses on selected interesting examples of various heterocycles from the mechanistic aspects of organic azides.

Keywords: organic azides; click reaction; catalysis; five membered rings; six membered rings; organo-metal heterocycles

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1. Introduction

Organic azides are organic compounds containing the azide (N_3) functional group. Due to the hazards associated with their use, few azides are commercially used, although

they display interesting applications in organic chemistry. Organic azides have four mesomeric structures (**1a**–**1d**, Figure 1), and their structure is also described as isoelectronic with carbon dioxide.

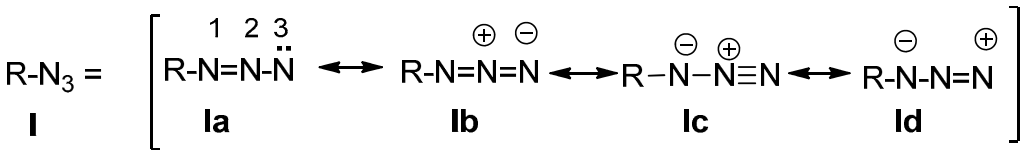


Figure 1. Mesomeric structures of organic azides.

The polar character of the azido group has a remarkable effect on their bond lengths and angles. In methyl azide, as an example, the angles of CH_3-N^1–N^2N^3 and CH_3N^1–N^2–N^3 are approximately 115.28 and 172.58 Å, respectively [1]. Aromatic azides show slightly shorter bond lengths between N^2 and N^3 [1]. Accordingly, an almost linear azide structure is present, with sp^2 hybridization at N^1. The polar resonance structures **Ib**–**Id** illustrated that strong IR absorption by a band at nearly 2114 cm^{-1} (phenyl azide [2]). Alkyl azides show absorption in the UV region at 287 nm and 216 nm [2]. They also exhibit weak dipole moment (1.44 *D* for phenyl azide) [2]. Azido group in aromatic substitution reactions directs to *ortho*- and *para*-positions.

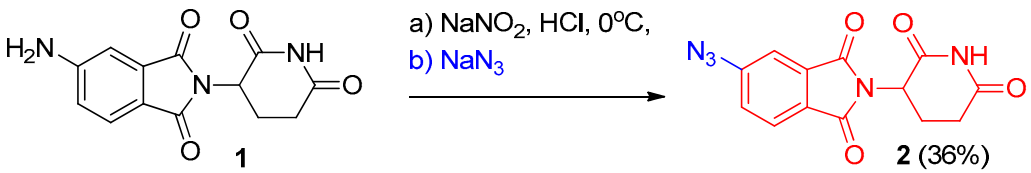
Organic azides engage in useful organic reactions, as the terminal nitrogen is mildly nucleophilic. Generally, nucleophiles attack the azide at the terminal nitrogen N_γ, while electrophiles react at the internal atom N_α [3]. Azides easily extrude diatomic nitrogen, a tendency that is engaged in many reactions, such as the Staudinger ligation or the Curtius rearrangement [4]. Azides can be reduced to amines by hydrogenolysis [5] or with a phosphine (e.g., triphenylphosphine) in the Staudinger reaction [5]. Organic azides can react with phosphines to give iminophosphoranes, which can be hydrolyzed into primary amines (the Staudinger reaction) [6]. They react with carbonyl compounds to give imines (the aza-Wittig reaction) [7,8] or undergo other transformations. Thermal decomposition of azides gives nitrenes, which participate in various reactions; vinyl azides decompose into 2*H*-azirines [9].

Since organic azides are highly reactive and have been long established as versatile building blocks in assembling structurally diverse *N*-containing heterocycles, converting organic azides into high-value compounds, such as heterocycles, would be greatly valued and a subject of enormous current interest. Currently, well over 32,000 total and nearly 1000 in 2021 showed interest in this type of chemistry.

2. Some Synthetic Procedures of Organic Azides

2.1. From Diazonium Salts

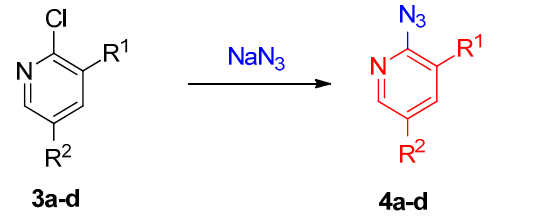
The aryl diazonium salts were decomposed readily on reacting with azide ions (NaN_3 or Me_3SiN_3) to the corresponding aryl azide without a catalyst. As an example, the facile conversion of 5-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (**1**) into 5-azido-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (**2**) via a two-step reaction involving diazotization followed by azidation using sodium azide as a precursor of azide ion [10] (Scheme 1).



Scheme 1. Synthesis of aromatic azide **2** from diazonium salt of **1**.

2.2. Via S_NAr Reactions (Nucleophilic Aromatic Substitution Reactions)

As an example, synthesis of 2-azido-3-nitropyridines (**4**) from 2-chloro-3-nitropyridines (**3**) using NaN_3 as the source of nucleophile (Scheme 2) was established as shown in Scheme 2 [11,12].



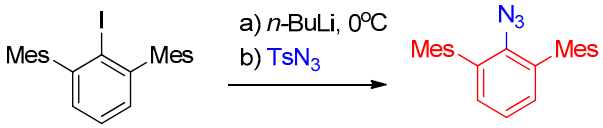
3a-d **4a-d**

3 and **4a-d: a,** $R^1 = R^2 = H$; **b,** $R^1 = NO_2$, $R^2 = H$;
c, $R^1 = H$, $R^2 = NO_2$; **d,** $R^1 = R^2 = NO_2$;

Scheme 2. Synthesis of aryl azides **4a**–**d** via S_NAr reaction.

2.3. From Lithium-Reagent

The reaction of aromatic halides **5** with lithium reagent (*t*-BuLi) followed by the reaction with tosyl azide gave the corresponding aryl azide **6** in 96% yield (Scheme 3) [13].



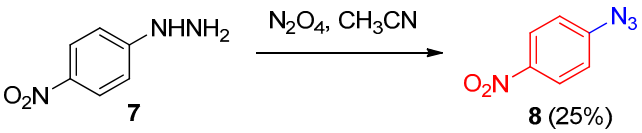
5 **6** (96%)

Mes=mesityl; Ts= *p*-toluenesulfonyl.

Scheme 3. Synthesis of aryl azide **6** using lithium reagent.

2.4. From Aryl Hydrazines

Kim et al. [14] reported the synthesis of aromatic azide **8** from the reaction of arylhydrazine **7** with nitrosyl ion (Scheme 4).



7 **8** (25%)

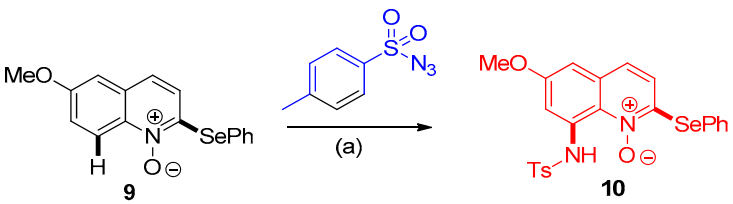
Scheme 4. Formation aryl azide **8** from the corresponding hydrazide **7**.

3. Chemistry of Azides

3.1. Azide as Aminating Group

3.1.1. Synthesis of 8-Aminoquinoline

The biologically active 8-aminoquinoline **10** was obtained through Ir(III)-catalyzed C8-amination of C2-selenylated quinoline *N*-oxide **9** with tosyl azide [15] (Scheme 5).

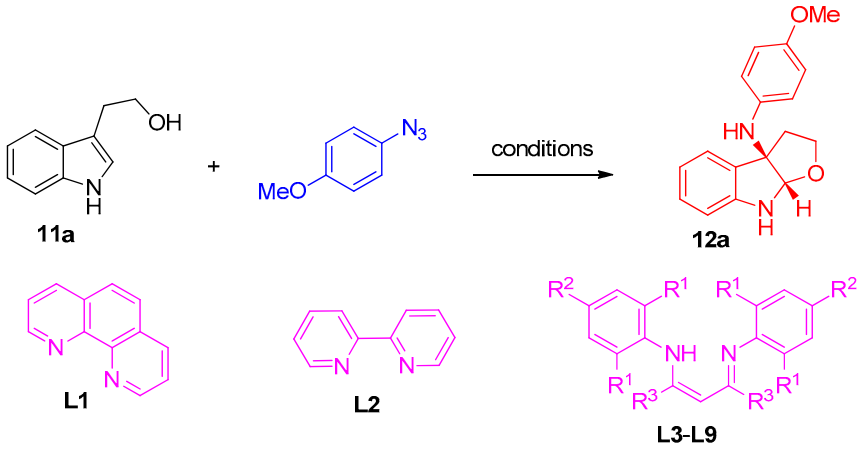


9 **10**

Scheme 5. Formation of biologically active 8-aminoquinoline **10**. *Reagents and conditions*: (a) $[IrCp^*Cl_2]_2$ (2.0 mol%), AcOH, $AgNTf_2$, DCE, room temperature.

3.1.2. Synthesis of Amino Furo/Pyrroloindole Derivatives

Zhang and others [16] reported that tryptophols or tryptamines reacted with aryl azides to produce 3a-nitrogenous furoindolines and pyrroloindolines 3a-nitrogenous indole alkaloids. Using a nitrogen source, the reaction proceeded via nitrene transfer/cyclization under copper-catalyzed conditions. Firstly, the reaction was investigated to stand at the optimal reaction conditions indicated in Scheme 6. Starting with tryptophol (2-(1*H*-indol-3-yl)ethanol) (**11a**) and 1-azido-4-methoxybenzene, the corresponding furoindole **12a** was obtained (Scheme 6). The investigation revealed that the conditions mentioned in entry 14 were chosen to be the optimal reaction conditions for all substrates ($CuBH_4(PPh_3)_2$ + **L7** (12 mol%), DCE 0.5 h).

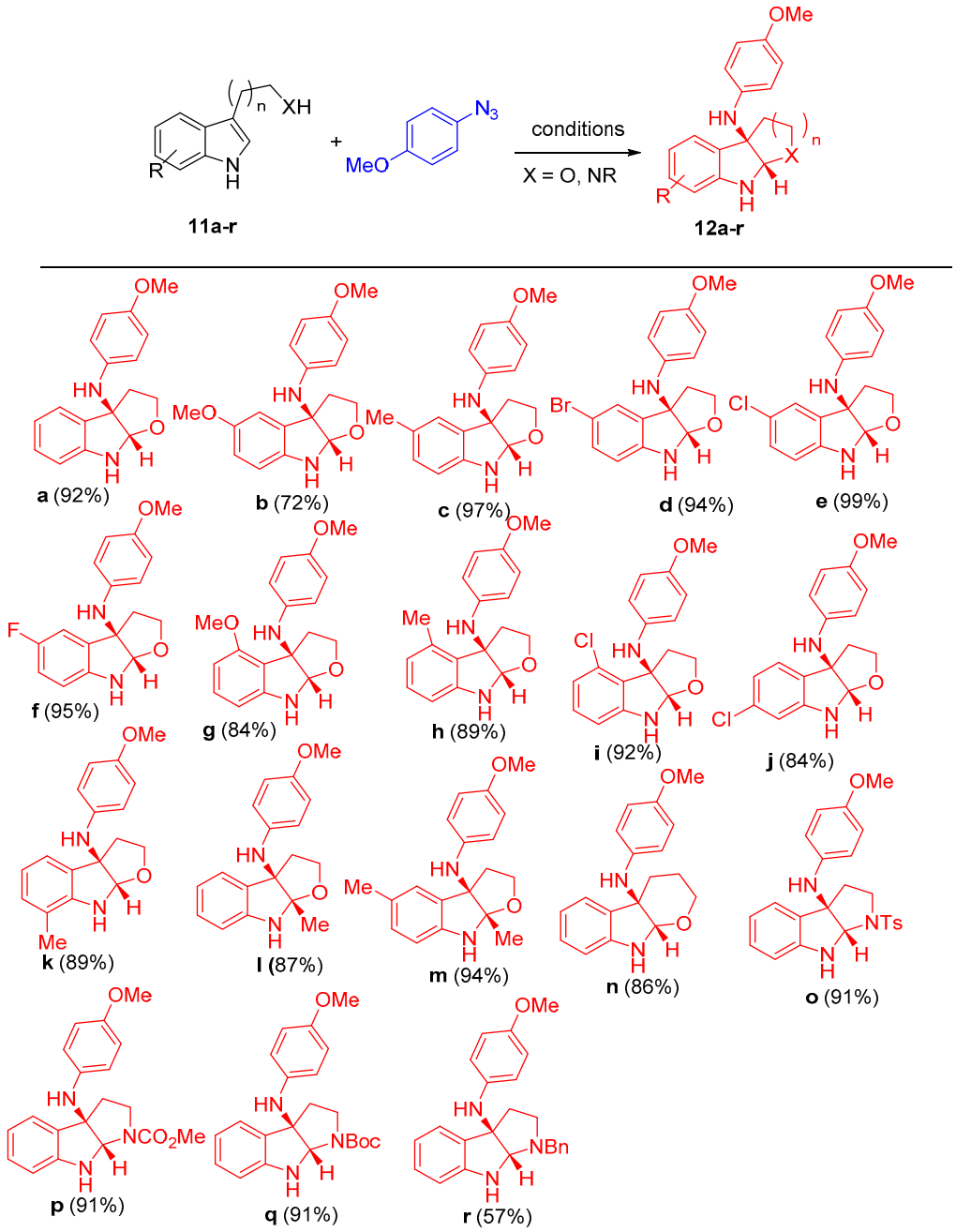


L3-L8: L3, R^1 = Me, R^2 = H, R^3 =Me; **L4**, R^1 = H, R^2 = H, R^3 =Me;
L5, R^1 = H, R^2 = OMe, R^3= Me; **L6**, R^1 = ^{i}Pr, R^2 = H, R^3 =Me;
L7, R^1 = Cl, R^2 = H, R^3 =Me; **L8**, R^1 = F, R^2 = H, R^3 =Me;
L9, R^1 = Me, R^2 = H, R^3 =^{t}Bu.

Entry	[Cu]	Ligand	Solvent	Time (h)	Yield (%)
1	CuCl	**L1**	PhCl	48	27
2	CuCl	**L2**	PhCl	12	13
3	CuCl	**L3**	PhCl	12	17
4	CuCl	**L3**	PhCl	12	45
5	CuOAc	**L3**	PhCl	12	45
6	CuSCN	**L3**	PhCl	12	70
7	$CuBH_4(PPh_3)_2$	**L3**	PhCl	12	88
8	$CuBH_4(PPh_3)_2$	**L4**	PhCl	24	Trace
9	$CuBH_4(PPh_3)_2$	**L5**	PhCl	24	Trace
10	$CuBH_4(PPh_3)_2$	**L6**	PhCl	12	64
11	$CuBH_4(PPh_3)_2$	**L7**	PhCl	0.5	92
12	$CuBH_4(PPh_3)_2$	**L8**	PhCl	24	Trace
13	$CuBH_4(PPh_3)_2$	**L9**	PhCl	24	Trace
14	$CuBH_4(PPh_3)_2$	**L7**	DCE	0.5	95
15	$CuBH_4(PPh_3)_2$	**L7**	MeCN	12	77
16	$CuBH_4(PPh_3)_2$	**L7**	Toluene	12	56
17	$CuBH_4(PPh_3)_2$	**L7**	DCE	2	93
18	$CuBH_4(PPh_3)_2$	**L7**	DCE	2	86

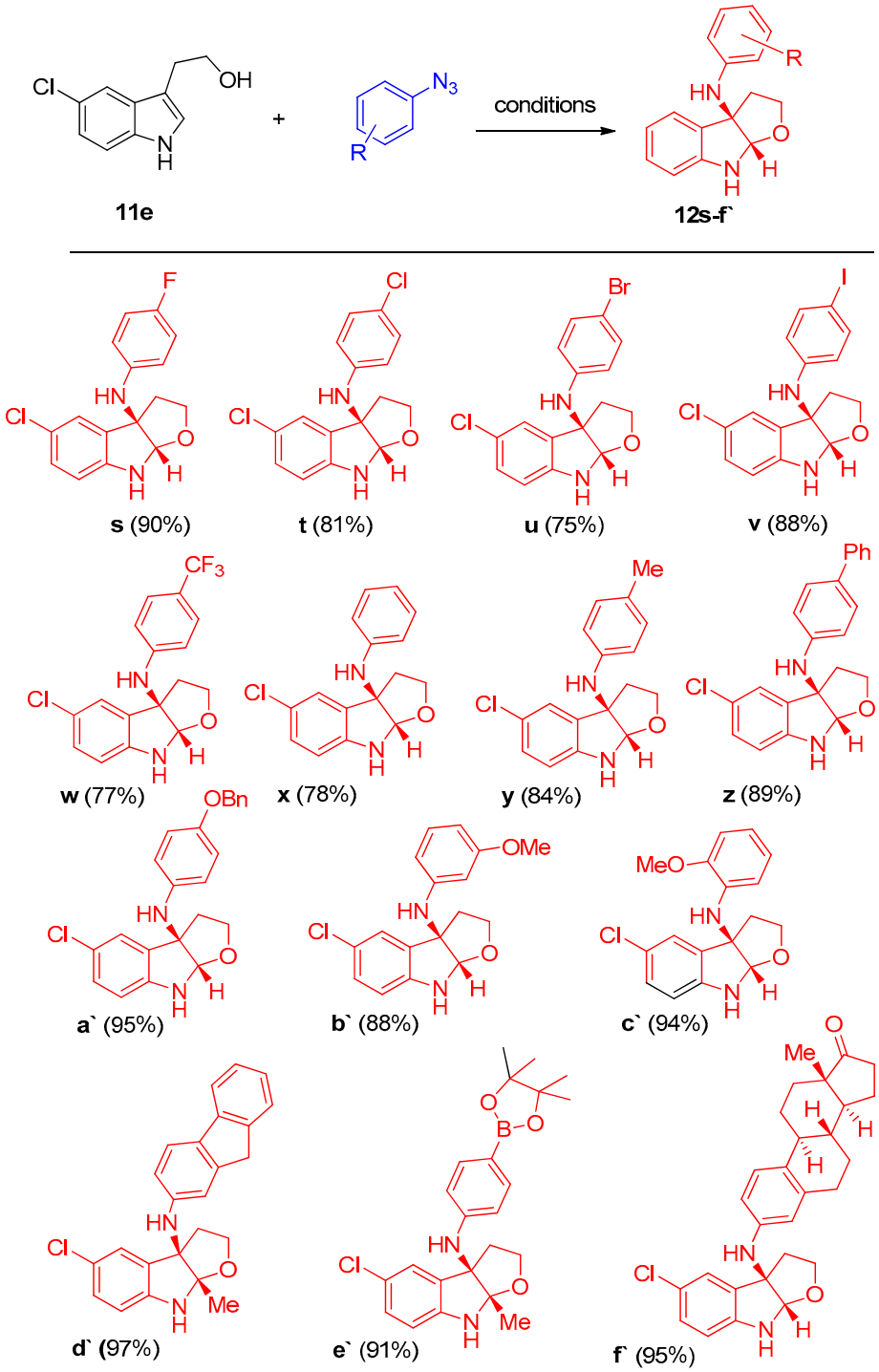
Scheme 6. Synthesis furoindoline **12a**. *Reagents and conditions*: (a) [Cu] (20 mol%), ligand (24 mol%), solvent, 80 °C, N_2.

Utilizing by the aforementioned optimized condition, a variety of tryptophols (**11a–n**) and tryptamine substrates (**11o–r**) were taken to react with 1-azido-4-methoxybenzene, as shown in Scheme 7. According to the electronic nature or positions of the substituents, the reactions proceeded smoothly to give the target products **12a–r** in high yields ranging from 72 to 99%. Moreover, different aryl azides were selected to react with tryptophol (2-(5-chlorobenzofuran-3-yl)ethanol) (**11e**) under the optimized reaction conditions to investigate the effect of substituents on the products' yields.



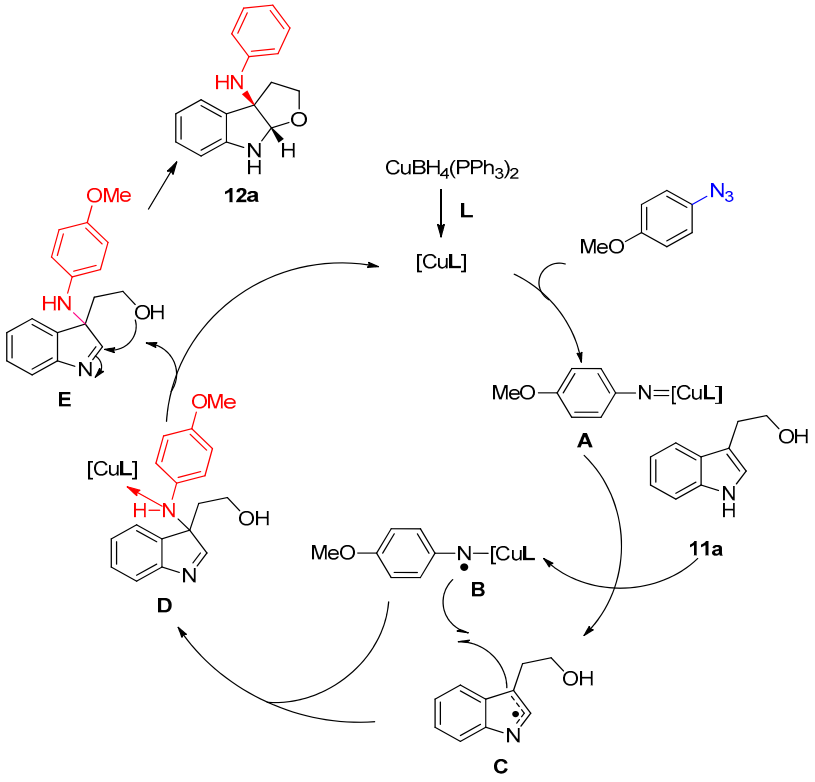
Scheme 7. Synthesis of furoindolines **12a–n** and pyrroloindolines (**120-r**). *Reagents and conditions*: (a) $CuBH_4(PPh_3)_2$ (12 mol%), L7 (14 mol%), DCE, 80 °C, N_2.

Another series of compound **12** was prepared, with azides having electron-donating and -withdrawing groups. The reaction proceeded smoothly to give the corresponding products **12s–f'** in moderate to excellent yields [16] (Scheme 8).



Scheme 8. Synthesis of furoindolines **12s–f'** *Reagents and conditions*: (a) $CuBH_4(PPh_3)_2$ (12 mol%), L7 (14 mol%), DCE, 80 °C, N_2.

The suggested mechanism describes the formation of furroindole **12a**, as shown in Scheme 9 [16]. Firstly, the azide moiety reacted with copper complex to produce copper nitrene complex **A**, which abstracts a hydrogen atom from compound **11a** to form the copper aminyl species **B** and imine radical **C**, which combines to produce the intermediate **D**. The catalyst moiety was then excluded from the intermediate **D** to form the imine species **E**. Finally, **E** was converted to the desired product **12a** via an intramolecular nucleophilic addition [16].

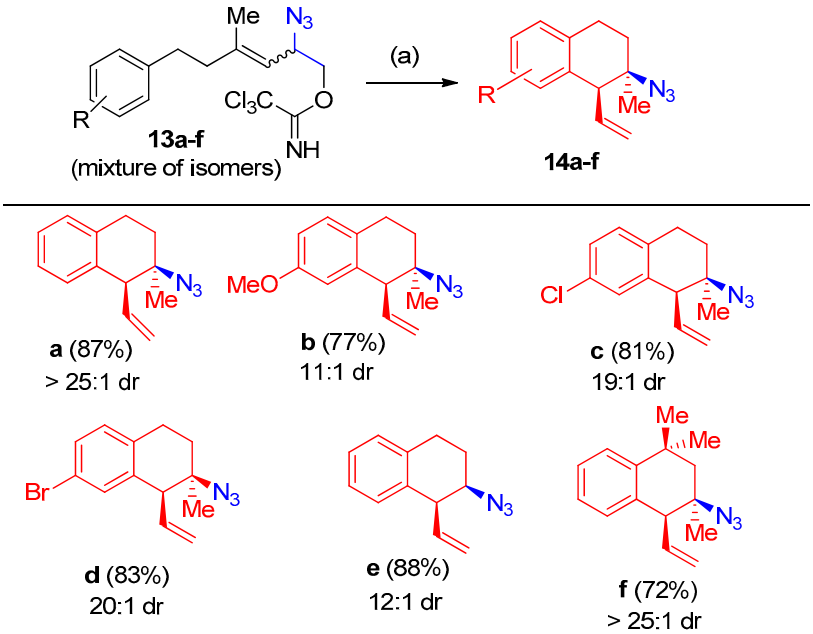


Scheme 9. A plausible mechanism described the formation of compound **12a**.

3.2. Azidation

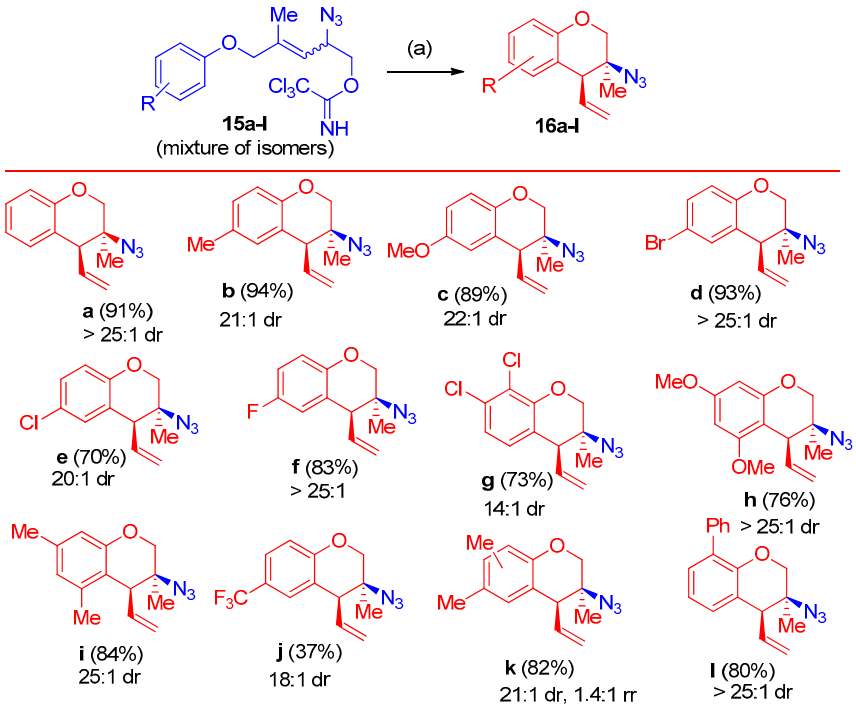
Synthesis of 3-Azido-Tetralins, Chromanes, and -Tetrahydroquinolines

Porter et al. [17] reported the stereoselective synthesis of 3-azido-tetralins, chromanes, and -tetrahydroquinolines via a tandem allylic azide rearrangement/Friedel-Crafts alkylation. The allylic azides **13a–f** were cyclized to the corresponding tetralines **14a–f** in 58–88% (Scheme 10).



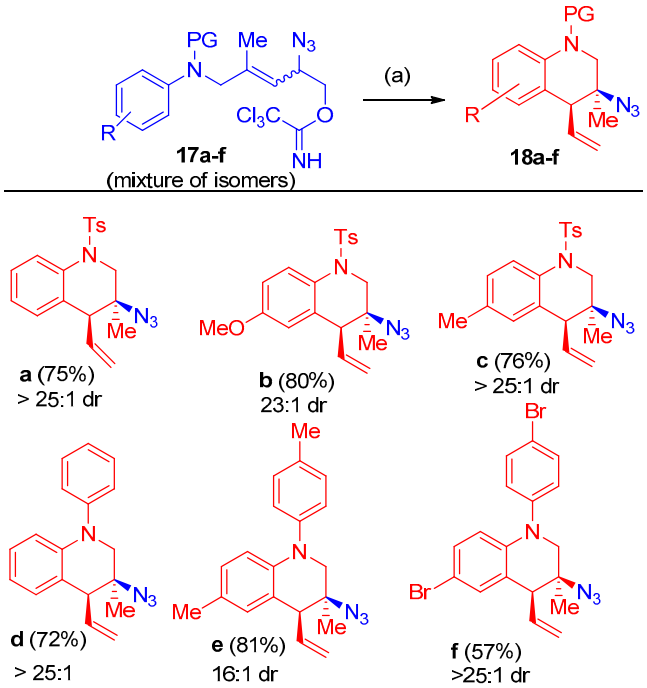
Scheme 10. Azidation by azido group and synthesis of 3-azido-tetralins **14a–f**. *Reagents and conditions*: (a) 10 mol% $AgSbF_6$, $CHCl_3$, 40–60 °C, 24–48 h.

In continuation of the optimized procedure [17], the ethereal allylic azides **15a–i** were converted into chromanes **16a–i** in 34–97% yields (Scheme 11).



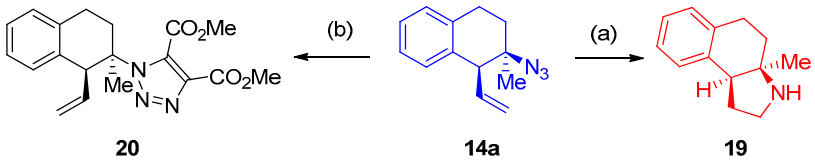
Scheme 11. Azidation by azido group and synthesis of ethereal allylic azides **15a–i**. *Reagents and conditions*: (a) 10 mol% $AgSbF_6$, $CHCl_3$, 40–60 °C, 24–48 h.

On the other hand, aniline-derived allylic azides **17a–f** carrying the *N*-protecting group were also cyclized using the tandem process to tetrahydroquinolines **18a–f** in good yields of 57–81% [17] (Scheme 12).



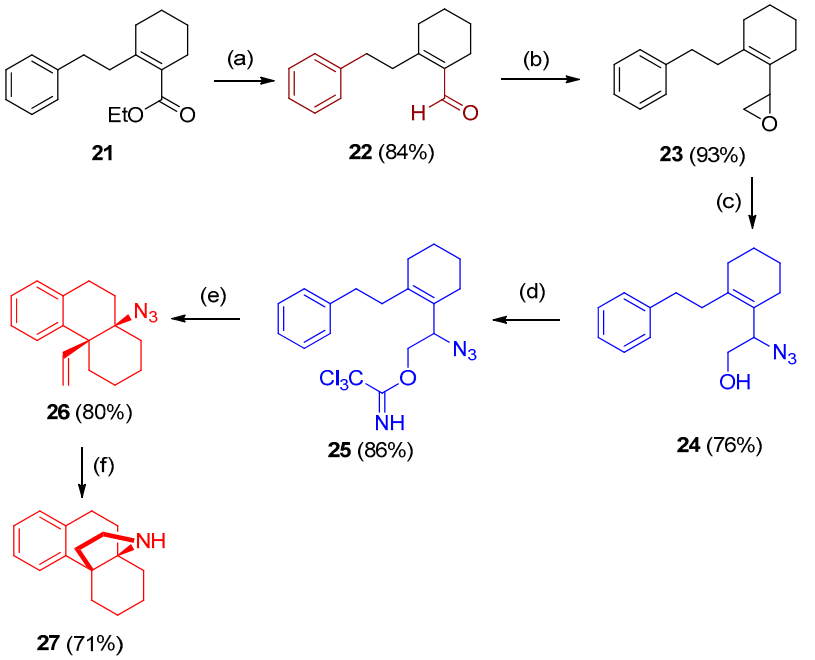
Scheme 12. Azidation and cyclization; Synthesis of compounds **18a–f**. *Reagents and conditions*: (a) 10 mol% $AgSbF_6$, $CHCl_3$, 40–60 °C, 24–48 h.

Finally, the tetraline **14a** was converted into pyrrolidine **19** [17]. At the same time, the cycloaddition reaction of the tetraline **14a** with dimethyl acetylene dicarboxylate gave the triazole **20** (Scheme 13).



Scheme 13. Synthesis of pyrrole **19**. *Reagents and conditions*: (a) $HBCy_2$ (dicyclohexyl borane) (b) DMAD (dimethylacetylene.dicarboxylate).

An interest application of previously reported work, was directed towards synthesizing a large family of botanical natural products group named husbanan [17]. Husbanan was synthesized from ethyl 2-phenethylcyclohex-1-enecarboxylate (**21**), which initially underwent reduction followed by partial re-oxidation to the aldehyde **22** (i.e., from ester to alcohol then aldehyde using tetrapropylammonium perruthenate (TPAP), and *N*-methylmorpholine *N*-oxide (NMO)). Aldehyde **22** was elaborated by Corey-Chaykovsky epoxidation. Epoxide **23** was opened with NaN_3 in acetone/water yielding the allylic azide **24**. Imidate **25** was isolated after activation with trichloroacetonitrile. Finally, reduction of imidate **25** gave **26** on the presence of dicyclohexyl borane ring closer to the hasubanan product **27** [17] (Scheme 14).



Scheme 14. Synthesis of husbanan **27**. *Reagents and conditions*: (a) (i) $LiAlH_4$; (ii) tetrapropylammonium perruthenate (TPAP, NMO); (b) Me_3S^+ $MeOSO_3^-$, NaOH; (c) NaN_3, acetone/H_2O; (d) CCl_3CN, DBU; (e) 10 mol% $AgSbF_6$;(f) $HBCy_2$ (dicyclohexyl borane).

4. Organic Azides in the Synthesis of Heterocycles

Organic azides have synthesized various heterocycles of the five-member ring with one heteroatom, such as pyrroles. They are also involved in synthesizing heterocycles with two heteroatoms, such as pyrazole and isoxazole, oxazole, thiazole, oxazine, and pyrimidine. In addition, heterocycles containing three heteroatoms, such as 1,2,3-triazoles and thiadiazole, are also included. Furthermore, organic azides are used in synthesizing heterocycles of six-membered rings and with one heteroatom, such as pyridine, isoquinoline, and phenanthridine. Heterocycles with four heteroatoms, such as tetrazole, are also discussed.

Synthetic interest applications of organometal heterocycles (i.e., phosphorus-, boron-, and aluminum-containing heterocycles) were also investigated. Figure 2 indicates the contribution of organic azides in heterocyclic synthesis.

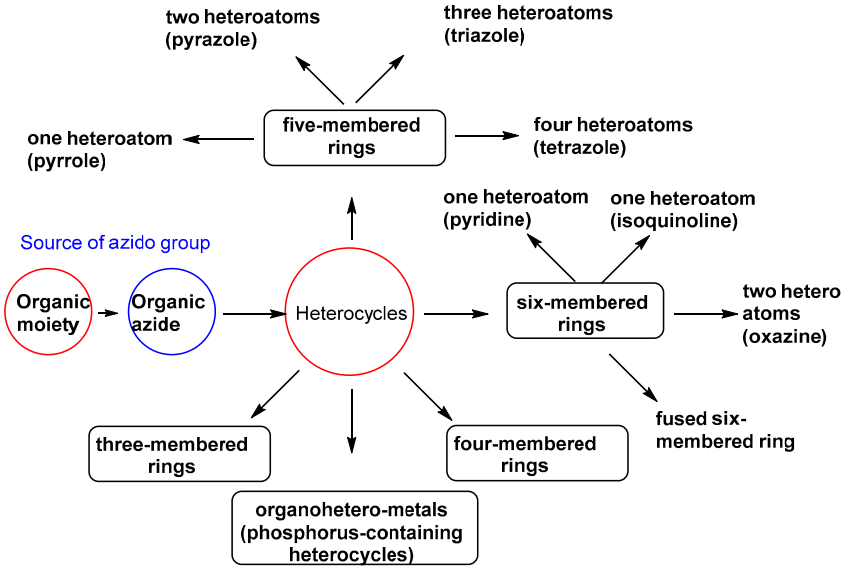
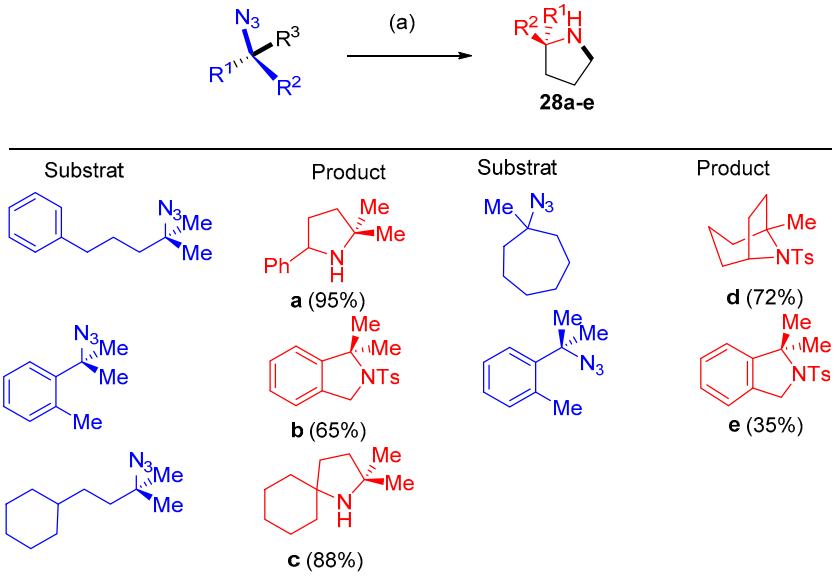


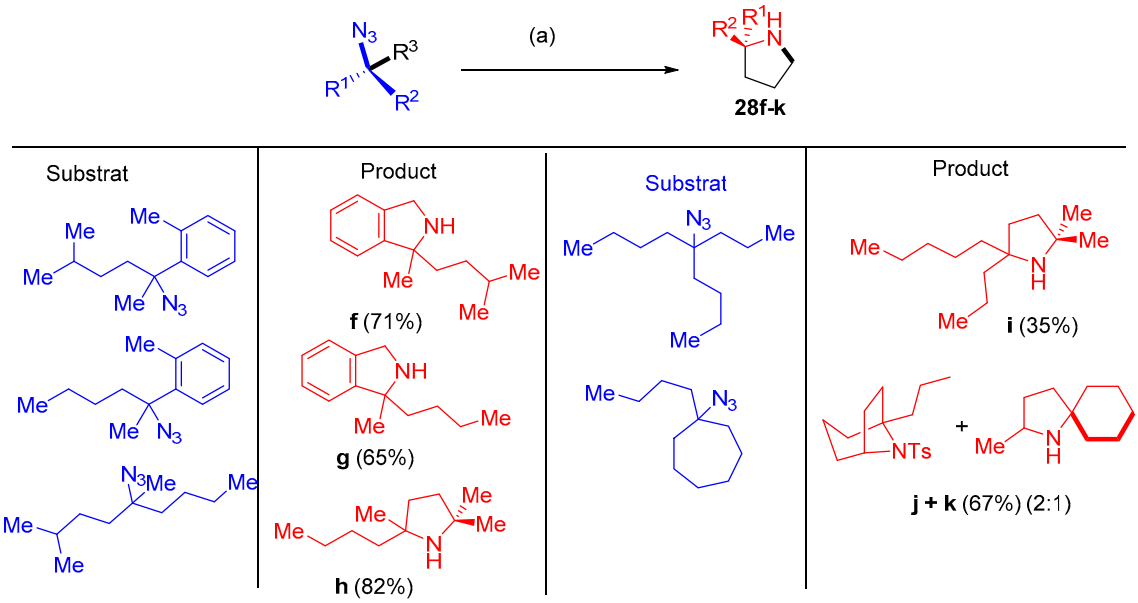
Figure 2. Contribution of organic azides in heterocyclic synthesis, exemplary cases of the heterocycles.

4.1. Synthesis of the Pyrrole Ring

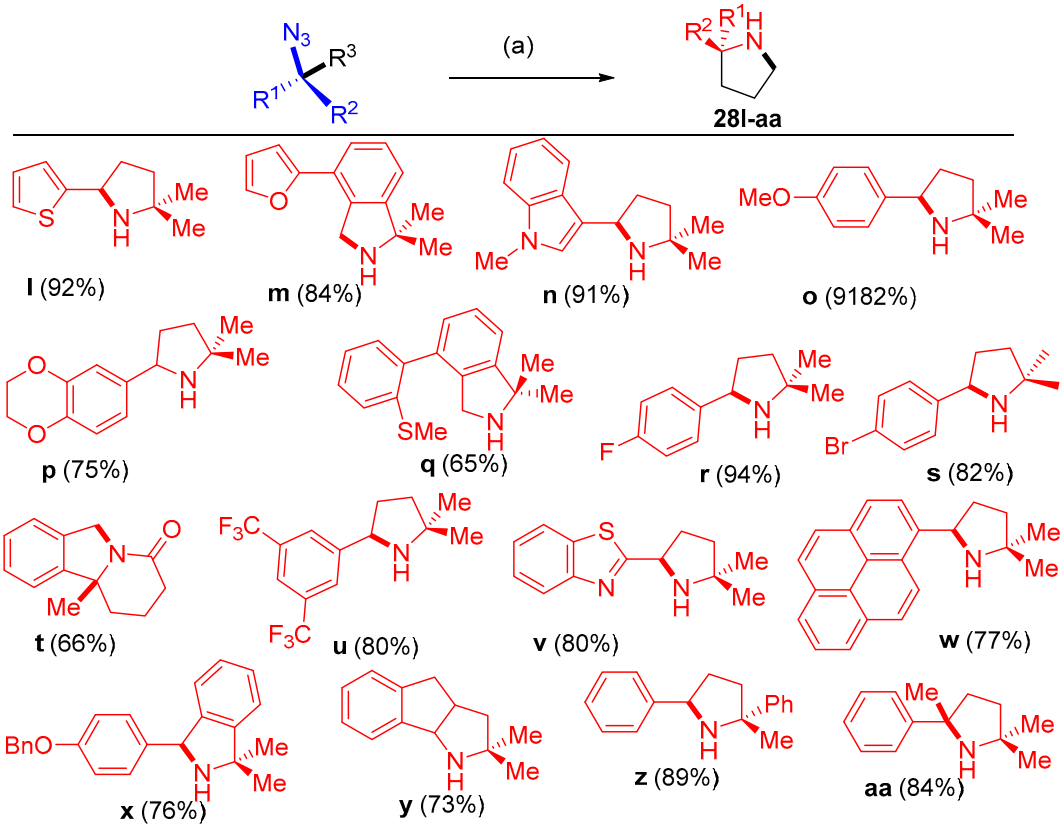
Dong and others [18] reported that dipyrrin-supported nickel catalyst (^{AdF}L)Ni(py) (^{AdF}L: 1,9-di(1-adamantyl)-5-perfluorophenyldipyrrin; py: pyridine) catalyzed the productive intramolecular C−H bond amination to give *N*-heterocyclic products **28a–k** using aliphatic azide substrates. The catalytic amination conditions were mild, requiring 0.1−2 mol% catalyst, and occurred at room temperature. The amination process occurred using different substrates having multiple activatable C−H bonds (Schemes 15 and 16). The selective catalyst showed high chemoselectivity favoring C−H bonds in ethers, halides, thioethers, esters, etc. (Scheme 17). Sequential cyclization of substrates with ester groups was achieved to provide facile preparation of indolizidine derivatives found in various alkaloids [18].



Scheme 15. Synthesis of pyrroles **28a–e**. *Reagents and conditions*: (a) 1 mol% (^{AdF}L)Ni(py) (^{AdF}L), C_6D_6, 25–80 °C.

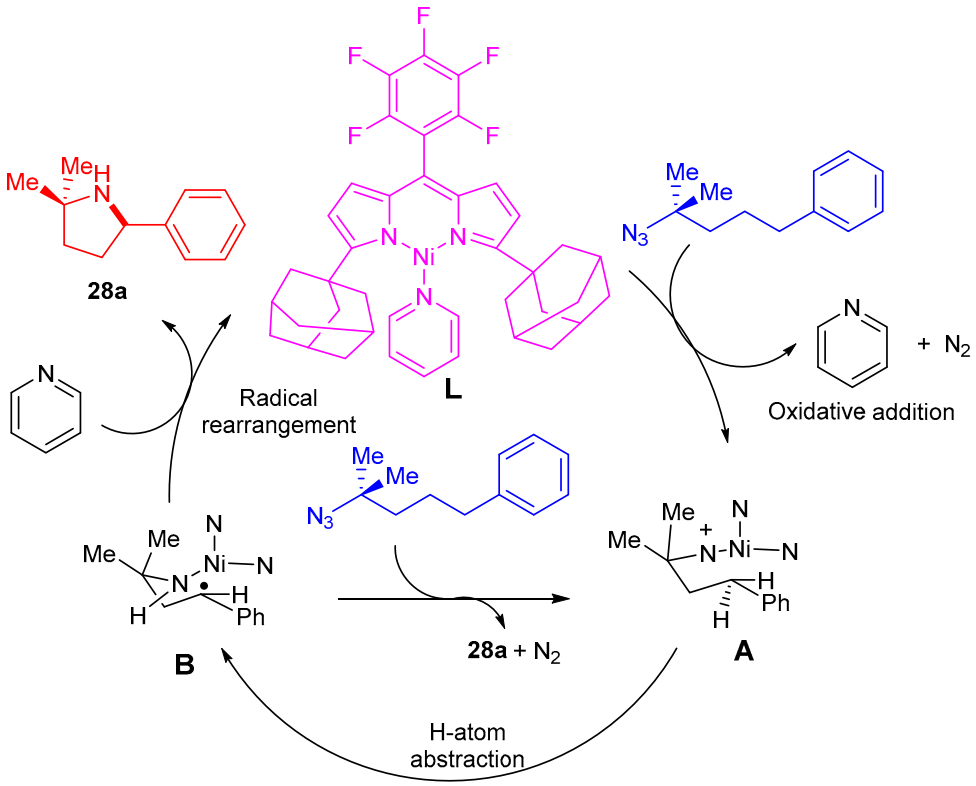


Scheme 16. Synthesis of pyrroles **28f–k**. *Reagents and conditions*: (a) 1 mol% (^{AdF}L)Ni(py) (^{AdF}L), C_6D_6, 60 °C.



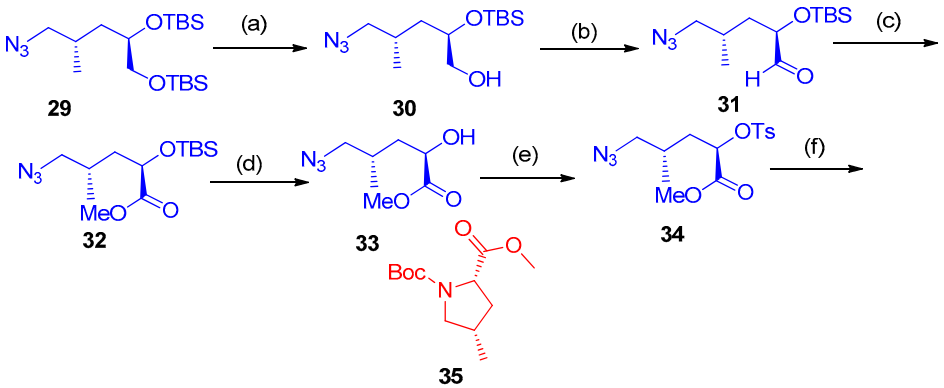
Scheme 17. Synthesis of pyrroles and its fused systems **28l–aa**. *Reagents and conditions*: (a) 1 mol% (^{AdF}L)Ni(py), C_6D_6, 60 °C.

The amination cyclization reaction mechanism is illustrated in Scheme 18. Benzene (4-azido-4-methyl pentyl), as an example, releases pyridine and N_2 from **L** to give the corresponding nickel iminyl species **A**. The next step would be a hydrogen atom abstraction to give radical **B**, followed by radical recombination to give the cyclized product **28a** [18].



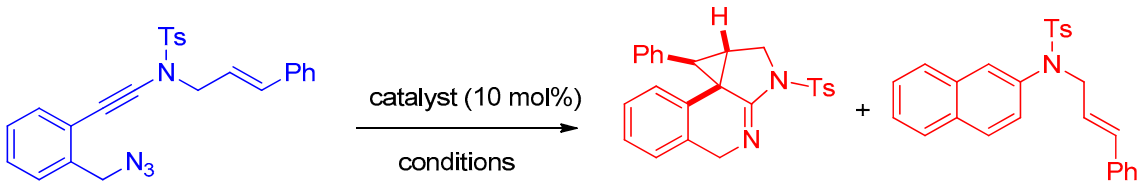
Scheme 18. The postulated reaction mechanism for the formation of pyrroles and C-H amination.

Sun et al. [19] have reported the diastereoselective synthesis of Boc-protected 4-methylproline carboxylates **35**, starting with the reduction of the azido compound **29**. Selective cleavage of the primary TBS-alcohol **30** was performed using NH_4F in MeOH at room temperature for 6 h. Oxidation of the alcohol **30** was achieved using 2-iodoxybenzoic acid (IBX) in DMSO at 30 °C, and the resulting aldehyde **31** was subsequently transformed into the corresponding methyl ester **32** by adding $KOH/I_2/MeOH$. Deprotection of ester **32** with camphorsulfonic acid (CSA) afforded the corresponding alcohol **33**. Tosylation of alcohol **33** with *p*-toluenesulfonyl chloride in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base, gave compound **34** in high yield (90%). Finally, the two-step azide reduction/intramolecular S_N2 cyclization procedure was performed to obtain the desired Boc-protected (2*S*,4*S*)-4-methylproline carboxylate (**35**) in 90% yield (Scheme 19) [19].



Scheme 19. Synthesis of pyrrole **35**. *Reagents and conditions*: (a) NH_4F (50 eq.), MeOH, room temperature., 6 h (75%); (b) IBX, DMSO, room temperature, 2 h; (c) I_2, KOH, MeOH, 0 °C, 1 h (95%); (d) CSA, MeOH, room temperature, 2 h; (e) TsCl, DABCO, CH_2Cl_2, room temperature, 18 h, (90%); (f) 10% $NaHCO_3$, H_2, MeOH, room temperature, 2 h, then $NaHCO_3$, Boc_2O, 12 h (90%).

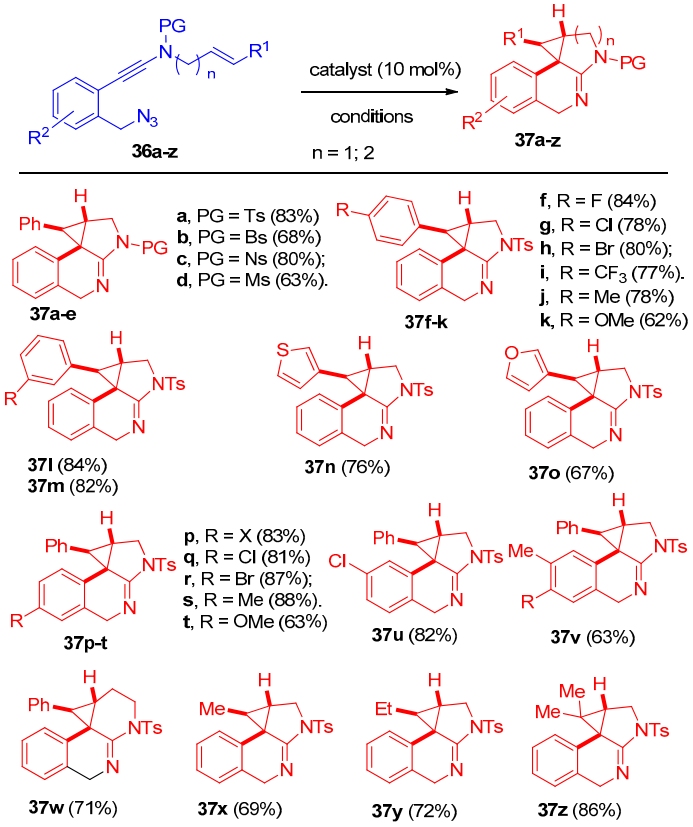
Using chiral bisoxazoline-copper (BOX-Cu) complexes as catalysts, the cyclization process of asymmetric azide-ynamides via α-imino copper carbene intermediates polycyclic *N*-heterocycles with high enantioselectivities (up to 98:2 e.r) was performed [20]. *N*-Styryl benzyl-tethered(azido)ynamide(*N*-((2-(azidomethyl)phenyl)ethynyl)-*N*-cinnamyl-4-methylbenzene sulfonamide) (**36a**) was selected as the model substrate, and $Cu(CH_3CN)_4BF_4$ was used as a catalyst to give ((8b*R*,9*R*,9a*S*)-9-phenyl-2-tosyl-2,4,9,9a-tetrahydro-1*H*-benzo[*e*]cyclopropa[*c*]indole) (**37a**) in 86% yield and *N*-cinnamyl-4-methyl-*N*-(naphthalen-2-yl)benzenesulfonamide (**38**) as a side product (Scheme 20). The reaction was applied to various *N*-(azido)ynamide **36a**–**z**. Firstly, different selected *N*-protecting groups of the ynamides **36a**–**e** were examined, and the reaction proceeded smoothly when Ts-,Bs-, Ns-, SO_2Ph-, and Ms- were used as protecting groups (PG = protecting group, Bs = 4-bromobenzenesulfonyl, Ns = 4-nitrobenzene-sulfonyl)(azido)ynamides) producing the desired tetracyclic heterocycles **37a**–**e** in 63–83% yields. In addition, various aryl-substituted benzyl-tethered (azido)ynamides **36f**–**m,** having either electron-withdrawing and/or electron-donating groups, were also examined, and the corresponding cyclopropanation products **37f**–**m** were obtained in good yields. The reaction was also applied to the thienyl- and furanyl-substituted (azido)ynamides **36n,o** to give **37n** and **37o** in 76% and 67% yields, respectively. Different substituents on the phenyl ring **36p**–**v** (F, Cl, Br, Me, and OMe) were also examined, and products **37p**–**v** were obtained in 63–88% yields. Piperidine fused tetracyclic heterocycle **37w** was also obtained in 71% yield. Moreover, methyl-, ethyl-, and even dimethyl-substituted *N*-allyl (azido)ynamides **36x**–**z** were also suitable substrates for this type of cyclization to give products **37x**–**z** in 69–86% yields (Scheme 21). In addition, the reaction was extended to investigate the copper-catalyzed cyclization for *N*-propargyl benzyl-tethered (azido)-ynamides **39a**–**u** (Scheme 22) to synthesize 3*H*-pyrrolo[2,3-*c*]isoquinolines **40a**–**u** using 10 mol% of $Cu(CH_3CN)_4PF_6$ as the catalyst and 2 equiv. of DDQ (4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile) as oxidant [20].



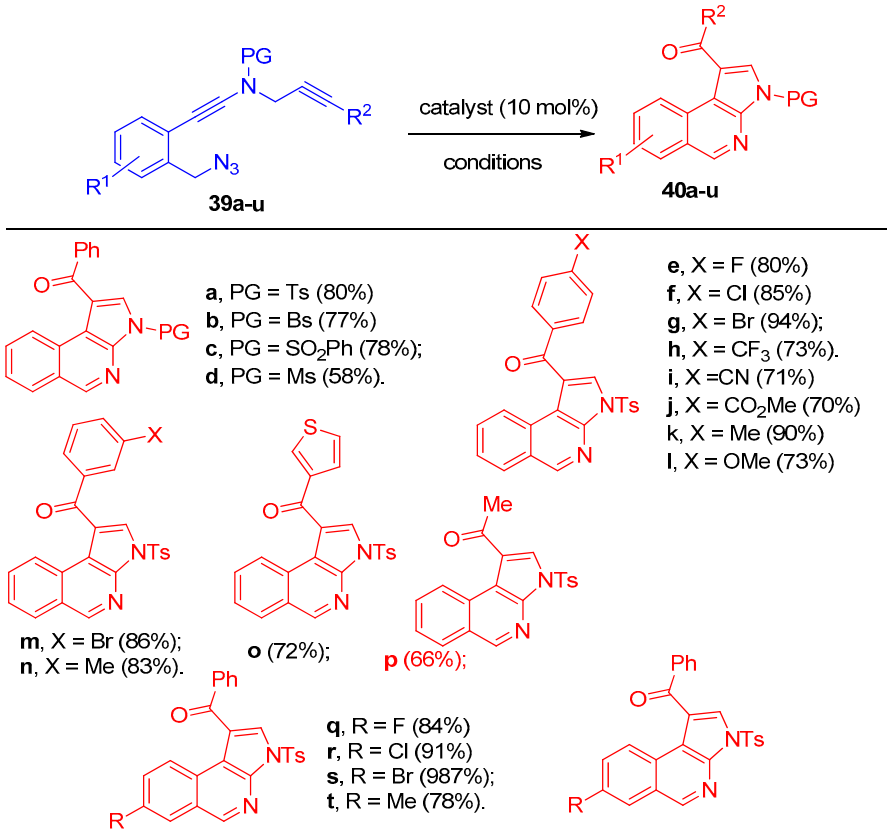
36a **37a** **38**

Entry	Catalyst	Conditions	37a (%)	38 (%)
1	Cu(OTf)	DCE, 80 °C, 4 h	18	54
2	CuI	DCE, 80 °C, 4 h	21	50
3	CuCl	DCE, 80 °C, 4 h	74	8
4	$Cu(CH_3CN)_4PF_6$	DCE, 80 °C, 4 h	82	5
5	$Cu(CH_3CN)_4BF_6$	DCE, 80 °C, 4 h	86	<5
6	$Cu(OTf)_2$	DCE, 80 °C, 16 h	32	30
7	$Zn(OTf)_2$	DCE, 80 °C, 3 h	<1	67
8	$Sc(OTf)_3$	DCE, 80 °C, 3 h	<1	77
9	CF_3CO_2H	DCE, 80 °C, 2 h	<1	55
10	MsOH	DCE, 80 °C, 2 h	10	78
11	$Cu(CH_3CN)_4BF_6$	DCE, 60 °C, 27 h	75	7
12	$Cu(CH_3CN)_4BF_6$	toluene, 80 °C, 6 h	25	35
13	$Cu(CH_3CN)_4BF_6$	PhCl, 80 °C, 5 h	41	24
14	none	DCE, 80 °C, 5 h	<1	62

Scheme 20. Synthesis of pyrrole **37a**. *Reagents and conditions*: **36a** (0.1 mmol), catalyst (0.01 mmol), solvent (2 mL), 60 °C to 80 °C, 2–27 h, in vials.

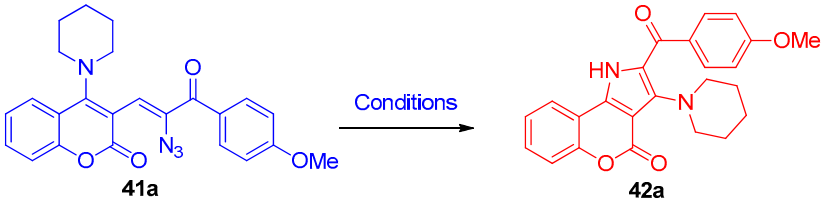


Scheme 21. Synthesis of pyrroles **37a–z**. *Reagents and conditions*: $Cu(CH_3CN)_4BF_4$ (0.02 mmol), DCE (4 mL), 80 °C, 4 h.



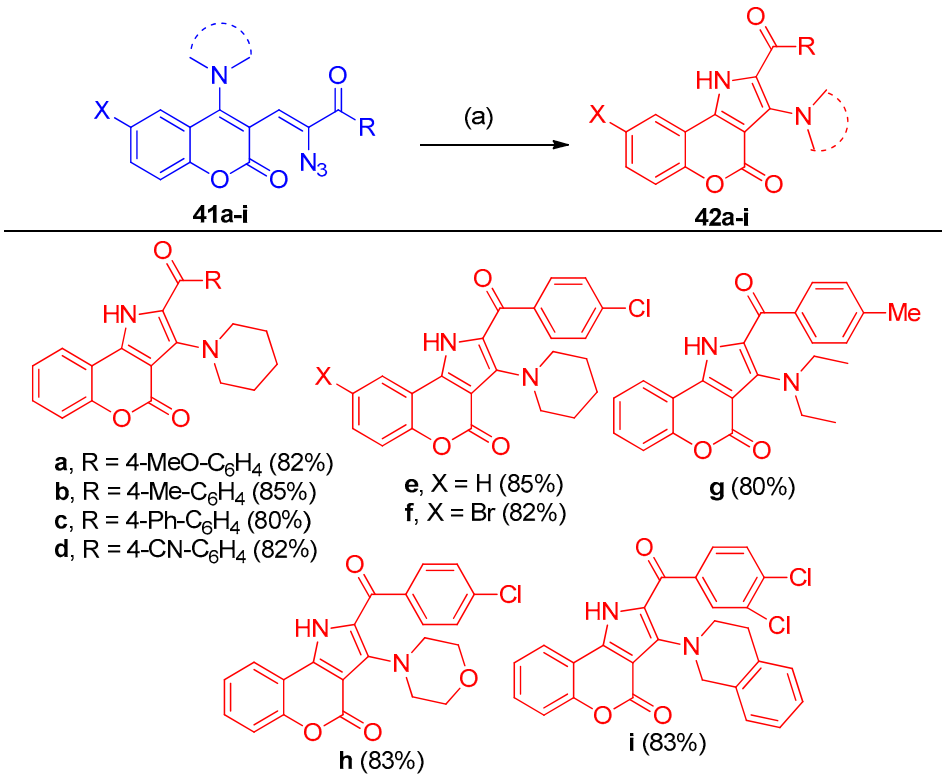
Scheme 22. Synthesis of pyrroles **40a–u**. *Reagents and conditions*: DDQ, Cu-$(CH_3CN)_4PF_6$, DCE, room temperature, 5 h.

Under thermal and UV light exposure, vinyl azides have been known to decompose into nitrenes and/or 2*H*-azirines, and they have been widely utilized to synthesize various *N*-heterocycles [21]. A photocatalyst-free visible light synthesized substituted pyrroles **42a–i** from *α*-keto vinyl azides **41a–i**. The optimized reaction condition was determined by applying the reaction on compound **41a**, and it was observed that the optimal reaction condition was irradiation of 0.1 M solution of **41a** in DCE with a blue LED (7 W) light (Schemes 23 and 24).



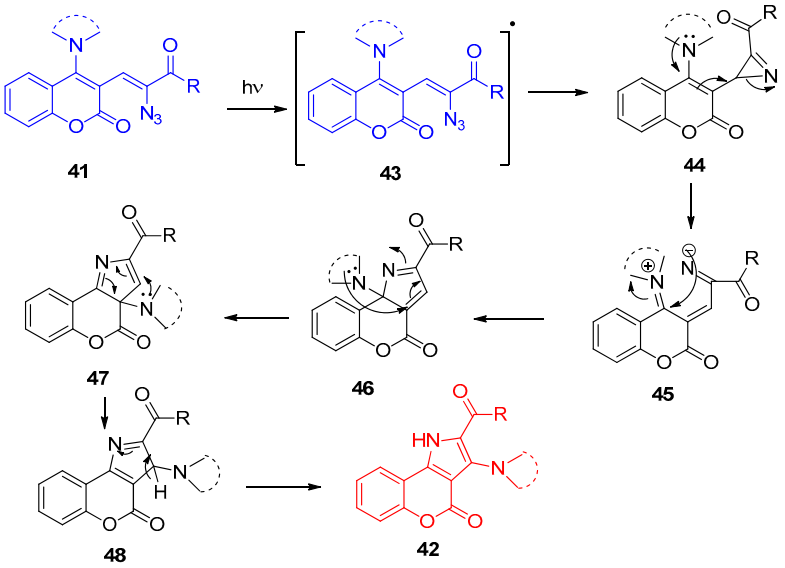
Entry	Energy Source	Solvent	Time (h)	Yield (%)
1	7 W blue LED	DCE	24	85
2	8 W CFL	DCE	24	65
3	Heating (60 °C)	DCE	12	41
4	7 W blue LED	DCE	24	85
5	7 W blue LED	DCM	24	82
6	7 W blue LED	MeOH	24	-
7	7 W blue LED	CH_3CN	24	-

Scheme 23. Optimized reaction condition of the decomposition of vinyl azide **41a**.



Scheme 24. Synthesis of chromenopyrroles **42a–i.** Scope of the photodecomposition of vinyl azides **41** to access substituted pyrroles **42**. *Reagents and conditions*: (a) 7 W blue LED light, DCE, 24 h.

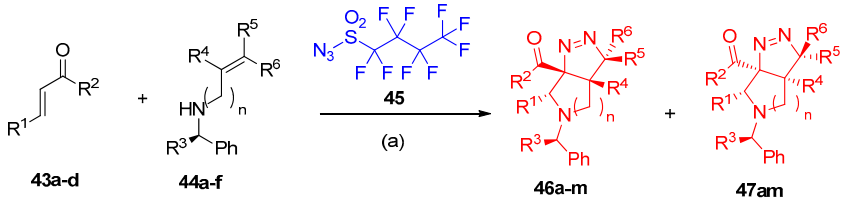
The reaction mechanism was described as a result of the denitrogenative photodecomposition process of *α*-keto vinyl azides, 1,3-amino group migration, and coupling of intermediates **43–48** with secondary amines, as shown in Scheme 25 [22].



Scheme 25. Postulated mechanistic steps for the conversion of vinyl azides **41** into chromenopyrroles **42**.

4.2. Synthesis of the Pyrazole Ring

Quiclet-Sire et al. [23] reported syntheses of tetrahydropyrrolo-pyrazole from hydrazones of pendant alkene using iodine in a basic medium as a catalyst. In contrast, Jahn et al. [24] demonstrated the construction of tetrahedropyrrolo-pyrazole **46**, **47a–m** via Aza-Michael addition/[3+2]cycloaddition between *α*,*β*-unsaturated esters **43a–c** or amide **43d** and allylic amines **44a–f** using nonaflyl azides **45** ($(F_3C(CF_2)_3SO_2N_3$, NfN_3), acting as aza- transfer reagent) in the presence of *n*-BuLi. The reaction proceeded regioselectively with more than 12:1 1,8-*trans*/1,8-*cis* selectivity (Scheme 26) [24].

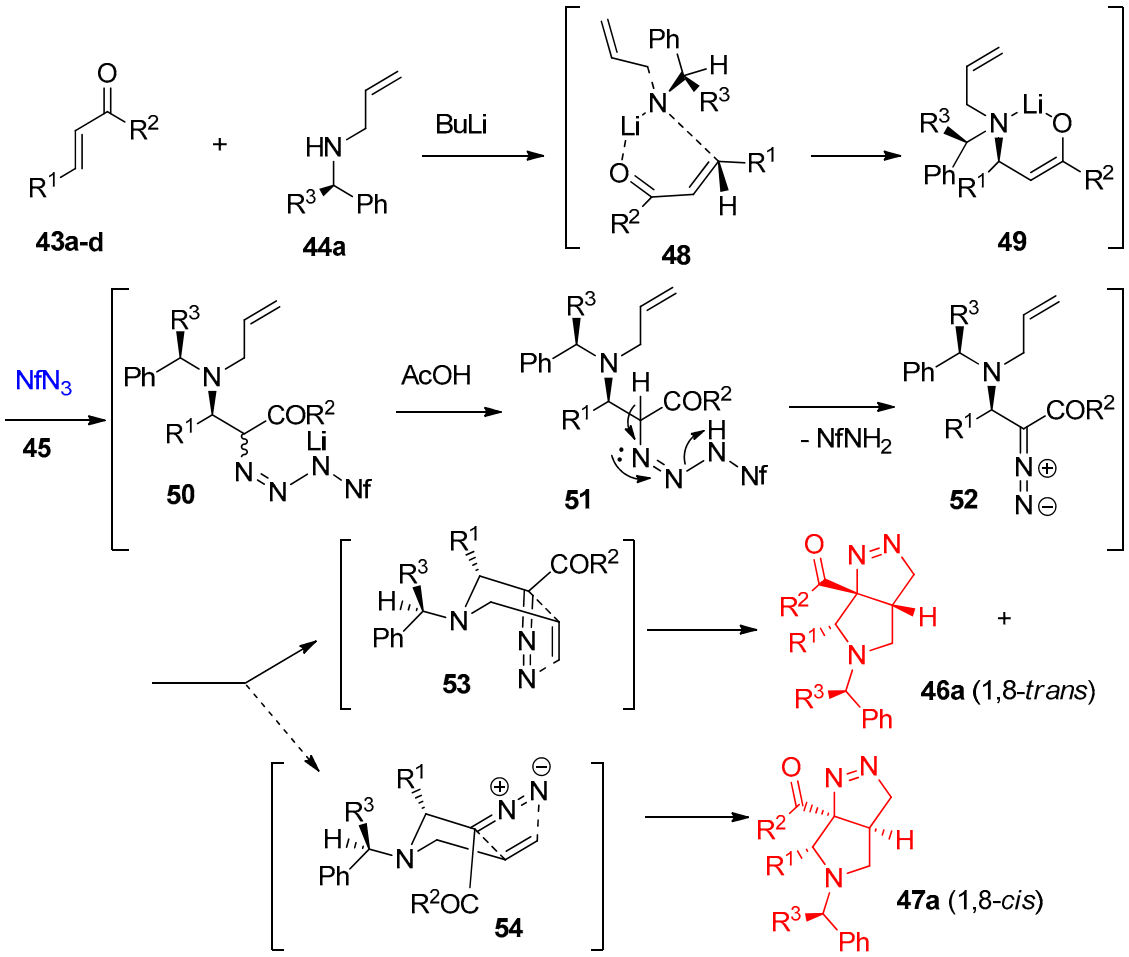


43: **a**, (R^1 = Me, R^2 = O^{t}Bu); **b**, (R^1 = Ph, R^2 = O^{t}Bu); **c**, (R^1 = Me, R^2 = OMe); **d**, (R^1 = Me, R^2 = NMe_2)
44: **a**, (R^3 = R^4 =R^5=R^6= H); **b**, (R^3 = Me, R^4 =R^5=R^6= H); **c**, (R^3 = R^4 = Me, R^5=R^6= H);
d, (R^3 =Me R^4 = H, R^5= Me, R^6= H); **e**, (R^3 =Me R^4 = H, R^5= H, R^6= Me);
f, (R^3 =Me R^4 = H, R^5= Me, R^6= Me)

46/47	R^1	R^2	R^3	R^4	R^5	R^6	*n*	(%)	*Trans*/*cis*
a	Me	O^{t}Bu	H	H	H	H	1	77	12:1
b	Me	OMe	H	H	H	H	1	37	14:1
c	Ph	O^{t}Bu	H	H	H	H	1	72	15:1
d	Me	OMe	Me	H	H	H	1	95	15:1
e	Me	O^{t}Bu	Me	H	H	H	1	91	14:1
f	Me	O^{t}Bu	Me	Me	H	H	1	58	15:1
g	Me	O^{t}Bu	Me	H	Me	H	1	85	12:1
h	Me	O^{t}Bu	Me	H	H	Me	1	70	50:1
i	Me	O^{t}Bu	Me	H	Me	Me	1	62	>20:1
j	Ph	O^{t}Bu	Me	H	H	H	1	90	15:1
k	Me	NMe_2	Me	H	H	H	1	76	>20:1
l	Me	NMe(OMe)	Me	H	H	H	1	71	17:1
m	Me	O^{t}Bu	Me	H	H	H	2	71	>20:1

Scheme 26. Synthesis of pyrrolopyrazoles **46a–m** and **47am**. *Reagents and conditions*: (a) *n*-BuLi, THF. −78 °C, then AcOH, −78–25 °C.

The mechanism for this reaction is illustrated in Scheme 27. Initially, lithiation of the amine **44** gave the lithium amide **48**, which coordinates to the carbonyl group of **43**, followed by transfer of the amide group to the *β*-position via the formation of intermediate **49**. (*Z*)-Enolate then **49** couples with nonaflyl azide (NfN_3) to form the unstable triazenide **50**. Protonation **50** would give the intermediate **51,** followed by the formation of diazo intermediate **52**. Finally, diastereoselective cycloaddition step takes place via transition state **53** and **54** to give the diastereoisomers **46** (1,8-*trans*) and **47** (1,8-*cis*) (Scheme 27) [24].

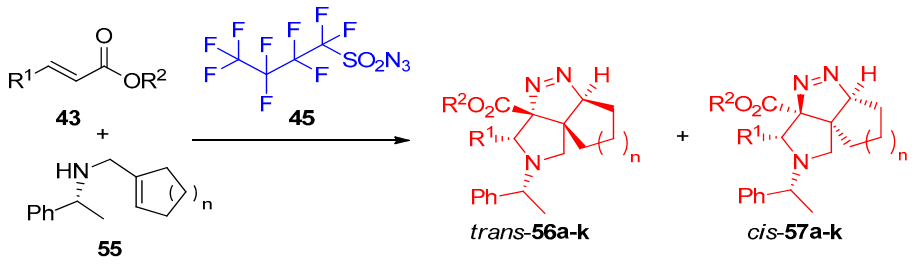


Scheme 27. The proposed mechanism for the formation of pyrrolotriazoles **46** and **47**.

Moreover, Just and others [25] reported the catalytic syntheses of fused tricyclic pyrrolidinopyrazolines via aza-Michael cycloaddition of cyclic amines **55** as well as (*R*)-*N*-benzylcycloalkenyl amines **58** with NfN_3 **45**; the reaction was catalyzed by lithium chloride (LiCl). Diastereoselective products have been obtained in good yields (68–84%) for the tricyclic products (*trans*)-**56a**–**f** and (*cis*)-**57a**–**f**, while in the case of 5,5,5-tricyclic (*trans*)-**59a**–**d** and (*cis*)-**60a**–**d,** the yield ranged from 72 to 85%. Regarding the optimized reaction conditions (Schemes 28 and 29), it was observed that the diastereomers' yields depend on the nature of cycloalkenylmethyl amines having five- or six-membered rings and *α*,*β*-unsaturated esters bearing alkyl or aryl substituents in *β*-position. In Scheme 30, the proposed mechanism for forming the tetrahedral-pyrrolo-pyrazole from the reaction of cycloalkenyl amines and *α*,*β*-unsaturated esters via intermediates **61**–**65** was postulated [25].

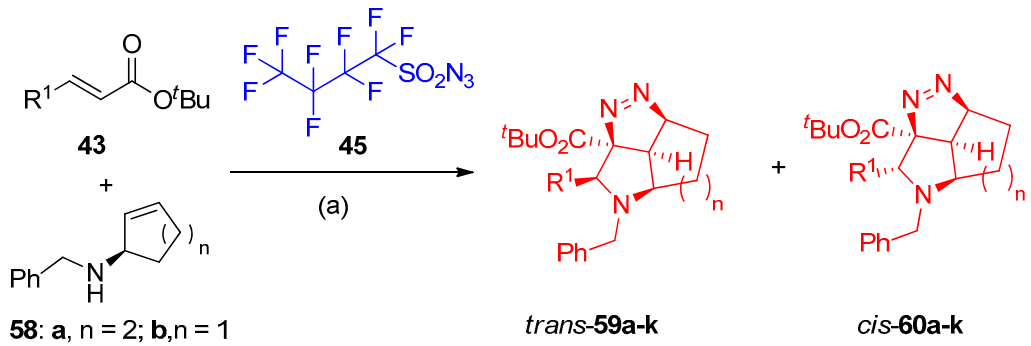
Previously, a cycloaddition reaction was reported between cinnamyl azide and methyl acrylates to obtain the tetrahydro-pyrrole-pyrazole [26,27]. Recently, Carlson et al. [28] developed the previously mentioned procedure via stereoselective interaction between allylic azides and acrylates in high yields. The development includes (i) secondary and tertiary azides, (ii) the use of an enantioenriched azide, (iii) cinnamyl azides substituted at

the α or β-carbon, (iv) derivatization of the products, and (v) additional Michael acceptors. Interestingly, it was found the following sequences: (A) the reaction was not completed during the reaction with cinnamoyl azide **66a**, (B) 1 equivalent of acrylate **43** did not consume the azide at room temperature for three d, and (C) quantitative intermediates **67a–69a** were obtained (Scheme 31). Optimization of acrylates **43** with cinnamoyl azides with aryl group of electrons withdrawing character has been investigated in Scheme 32. Re-optimization of reaction conditions such as (i) solvent, (ii) concentration, (iii) temperature, (iv) equivalents of acrylate, (v) time, and (vi) addition of DIPEA. It was found that the reaction proceeds well with a variety of cinnamoyl azides and the yields were improved. When DIPEA was used as a solvent compound, **70b** was obtained with a 94% yield (Scheme 33). Optimization of the reaction in the scope of the substrate, incorporating methyl or phenyl group adjacent to the azide, for compound **70o** a diastereomer was observed. Furthermore, cyclic azide resulted in the formation of tricyclic compounds **70u–w,** as demonstrated in Scheme 34 [28].



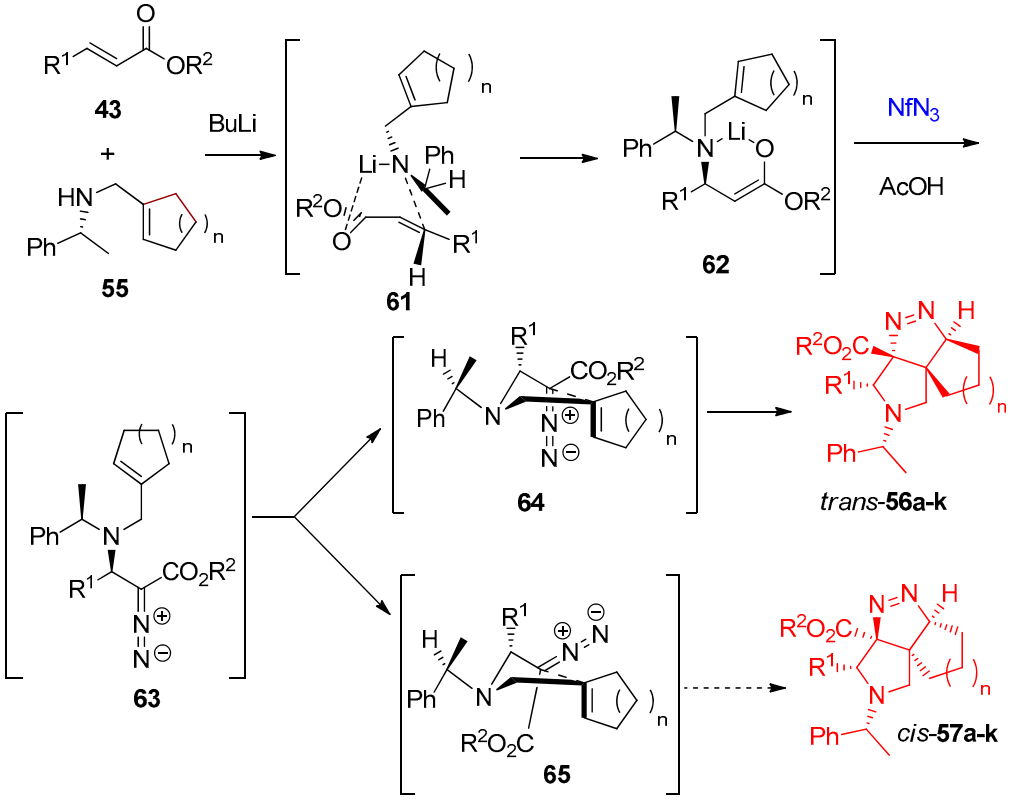
56/57	R¹	R²	56 (%)	56:57	
a (n = 2)	Me	*t*-Bu	31	5:1	Without LiCl
a (n = 2)	Me	*t*-Bu	72	12:1	
b (n = 1)	Me	*t*-Bu	68	12:1	
c (n = 2)	Ph	*t*-Bu	68	12:1	
d (n = 1)	Ph	*t*-Bu	84	12:1	
e (n = 2)	Ph	Me	47	4.5:1	
f (n = 1)	Ph	Me	64	6:1	
g (n = 2)	Me	*i*-Pr	78	15:1	
h (n = 2)	*p*-MeOC$_6$H$_4$	*t*-Bu	60	24:1	
i (n = 1)	*p*-MeOC$_6$H$_4$	*t*-Bu	83	21:1	
j (n = 2)	*p*-FC$_6$H$_4$	*t*-Bu	80	8:1	
k (n = 1)	*p*-FC$_6$H$_4$	*t*-Bu	69	12:1	

Scheme 28. Synthesis of *cis*/*trans*-pyrrolotriazoles **56a–k** and **57a–k**. *Reagents and conditions*: (a) BuLi, THF, 1 mol% LiCl, −78 °C, then AcOH, −78 to 25 °C.

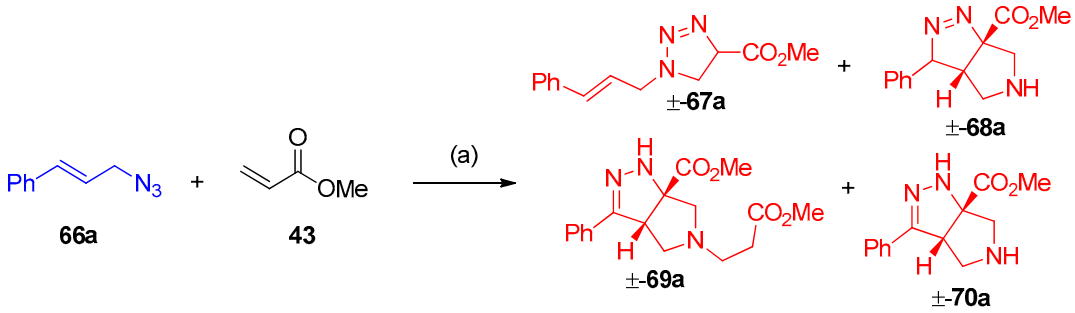


Scheme 29. Synthesis of *cis*/*trans*-pyrrolotriazoles **59a–k** and **60a–k**. *Reagents and conditions*: (a) BuLi, THF, 1 mol% LiCl, −78 °C, then AcOH, −78 to 25 °C.

59/60	R^1	59 + 60 (%)	59:60
a (n = 2)	Me	72	2.6:1
b (n = 2)	Ph	70	3.2:1
c (n = 2)	Me	85	1.4:1
d (n = 2)	Ph	72	1.7:1

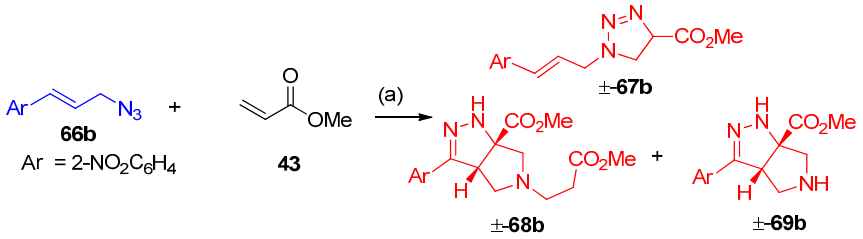


Scheme 30. The suggested stereochemical rationale for the formation of tricyclic compounds **56** and **57a–k**.



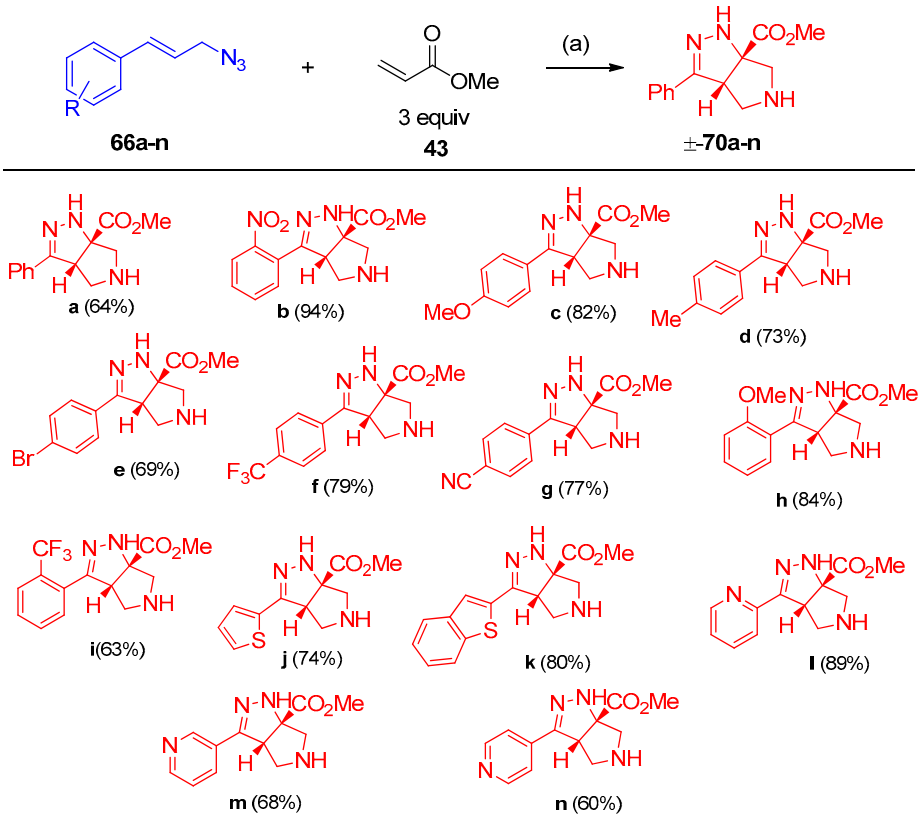
Equiv. 43	66a (%)	67a (%)	68a (%)	69a (%)	70a (%)
1	31	13	8	6	13
2	4	24	13	9	9

Scheme 31. Synthesis of tetrahydro-pyrrole-pyrazoles **67a–70a**. *Reagents and conditions*: (a) THF 5 mL, r.t 3 d.

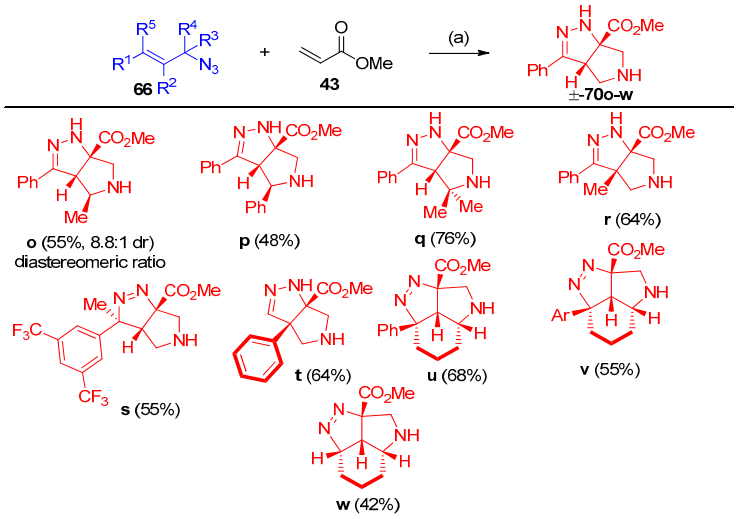


Solvent	Additive	67b (%)	68b (%)	69b (%)
DMSO	-	-	14	77
MeOH	-	-	95	-
Hexane	-	-	54	35
THF	-	34	-	46
benzene	-	37	-	11
benzene	AcOH	-	67	-
benzene	HFIP	-	55	17
benzene	DMAP	-	8	80
benzene	pyridine	5	-	41
benzene	TEA	-	-	85
benzene	DIPEA	-	-	91
toluene	DIPEA	-	-	83
THF	TEA	-	-	72
THF	DIPEA	-	-	78

Scheme 32. Synthesis of tetrahydro-pyrrole-pyrazoles **67b**–**69b**. *Reagent and conditions*: (a) Solvent (0.2 mL), additive (0.5 equiv.), 70 °C, 24 h.



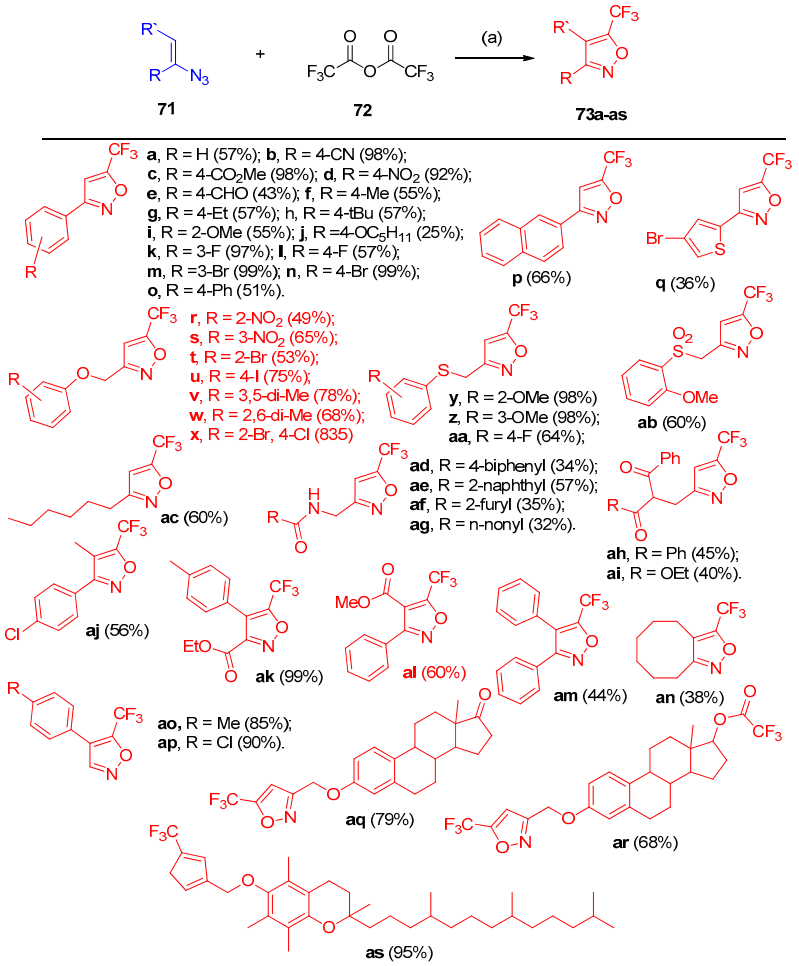
Scheme 33. Synthesis of pyrrole-pyrazoles **70a**–**n**. *Reagent and conditions*: (a) 0.5 equiv. DIPEA, benzene, 70 °C, 24 h.



Scheme 34. Synthesis of pyrrole-pyrazoles **70o**–**w**. *Reagents and conditions*: (a) (i) 3.5 equiv. acrylate, neat; (ii) 0.5 DIPEA, 70 °C.

4.3. Synthesis of Heterocycles Containing Two Heteroatoms

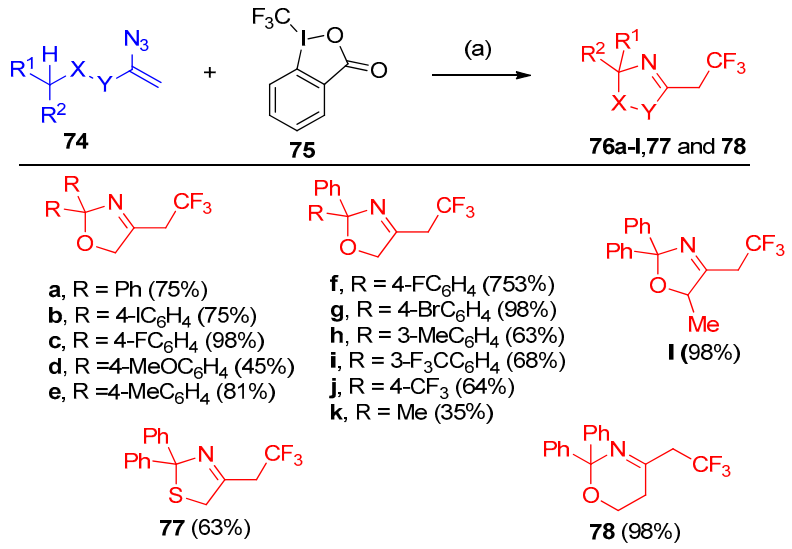
Vinyl azides **71** reacted with trifluoroacetic anhydride **72** in the presence of NEt_3 to give 5-(trifluoromethyl)isoxazoles **73a**–**as** via denitrogenative cyclization processes (Scheme 35) [29].



Scheme 35. Syntheses of 5-trifluoromethyl isoxazoles **73a**–**73as**. *Reagent and conditions*: (a) Et_3N, 1,4-dioxane, under N_2 atmosphere.

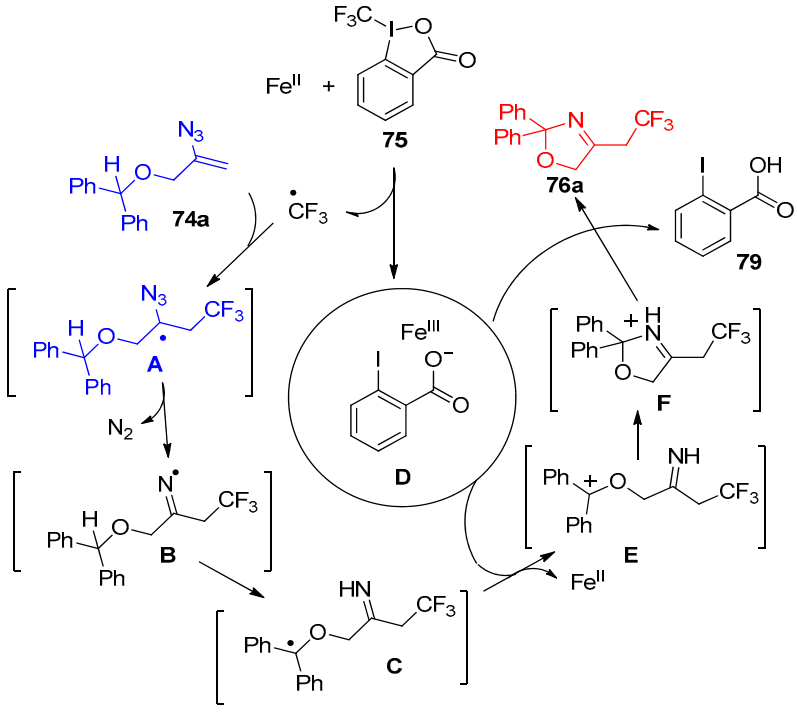
4.4. Synthesis of Oxazole, Thiazole, and Oxazine Derivatives

The reaction of substituted vinyl azides **74** with a combination of substoichiometric amounts of iron(II) chloride and Togni's trifluomethylating reagent **75** resulted in the formation of 2,2,2-trifluoroethyl-substituted 3-oxazolines **76**, 3-thiazolines **77**, and 5,6-dihydro-2*H*-1,3-oxazines **78**. It was found that the optimal reaction conditions clarified that DCM, DCE, DMF, and 1,4-dioxane were solvents of choice, and the temperature varied from 80°C to ambient temperature (Scheme 36) [30].



Scheme 36. Azides in the synthesis of oxazole, thiazole, and oxazine derivatives. *Reagents and conditions*: (a) $FeCl_2$ (20 mol%), DCM, room temperature, 30 min.

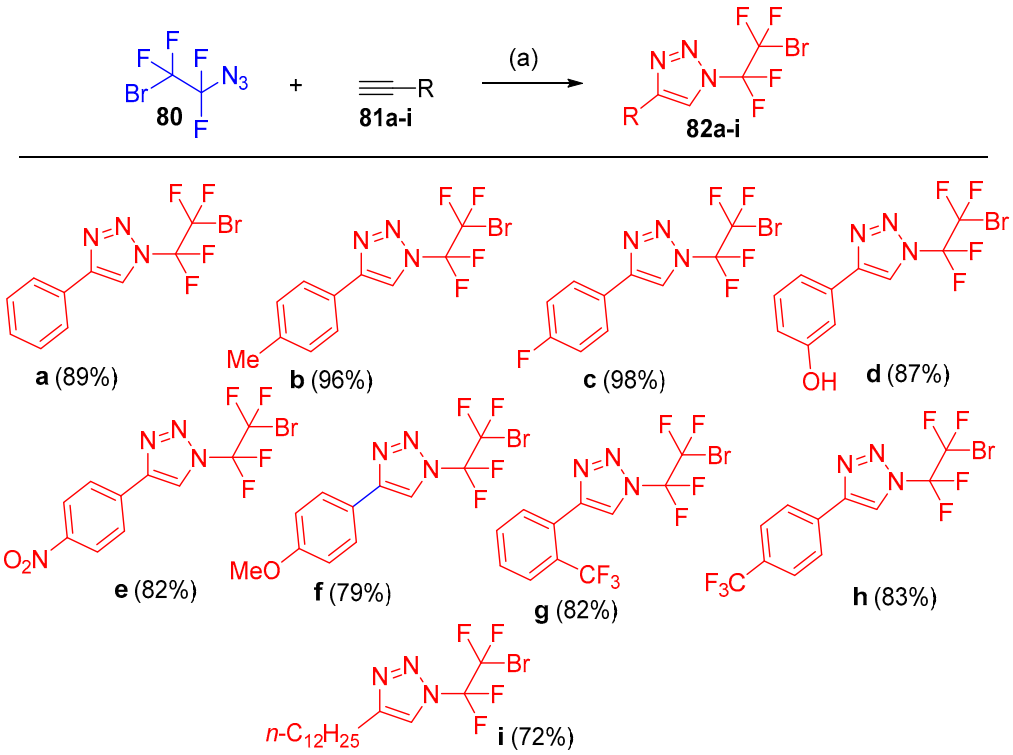
The proposed mechanism described the formation of compound **76a**. It showed the role of Fe^{II} in the reaction steps and its activation of Togni's reagent via the formation of intermediates **A**–**C**; deprotonation was then achieved by the Fe^{III} iodobenzoate complex (**D**) to give compound **76a** and iodobenzoic acid **79** (Scheme 37) [30].



Scheme 37. Plausible Mechanism for the formation of compound **76a**.

4.5. Synthesis of the Triazole Ring

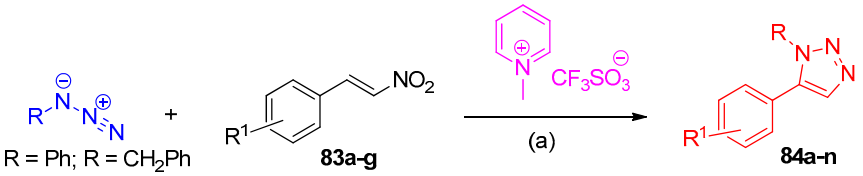
Reactivity of azides **80** in [3 + 2] cycloaddition with aromatic or aliphatic terminal alkynes **81a–i** clarified that 5 mol% of CuMeSal (copper(I) 3-methylsalicylate), with azidotrifluoromethane and other azidoperfluoroalkanes, afforded a range of *N*-bromo tetrafluoroethyl-substituted 1,2,3-triazoles **82a–i** in good to high yields (Scheme 38). Since the reaction gave only one regioisomer, it was described as highly efficient and regiospecific (the reaction exclusively afforded only the 1,4-disubstetuted triazole derivatives) at room temperature [31].



Scheme 38. Synthesis of *N*-bromotetrafluoroethyl-substituted 4-aryl-1,2,3-triazoles **82a–i**. *Reagents and conditions*: (a) THF, CuMeSal (0.05 mmol), r.t. overnight.

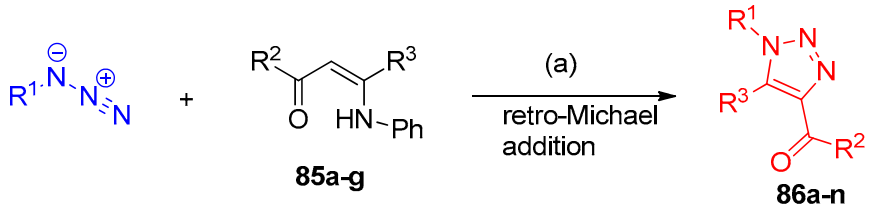
Ionic liquid/iron(III) chloride as a homogeneous catalyst was applied in the synthesis of 1 1,2,3-triazoles **84a–n** from the reaction of substituted azides and substituted styrenes **83a–g** [32] (Scheme 39).

Regioselective synthesis of 1,4,5-trisubstituted-1,2,3-triazoles **86a–p** from the catalyzed reaction between enaminones **85** and aryl azides using 1-methyl pyridinium trifluoromethanesulfonate [mPy]OTf as the ionic liquid in basic medium via 1,3-dipolar cycloaddition (Scheme 40). Herein, the reaction selectively generates only the 1,5-disubstituted triazoles as the only possible product over 1,4-disubstituted triazoles. As illustrated in Scheme 41, the proposed mechanism demonstrated that the formation of triazoles **86a–n** from the reaction of the aryl azides and enaminones **85a–g** was taken via the formation of intermediate **87a–n** [33]. The reaction was described as retro-Michael addition to give two regioisomers. Elimination of aniline from the two regiosomers afforded the corresponding triazoles **86a–n**. Moreover, the reaction took place with complete regioselectivity yielding the regioisomer with the electron-deficient group of the enaminone in position 4 and the alkyl substituent in position 5 as the only product of the reaction.

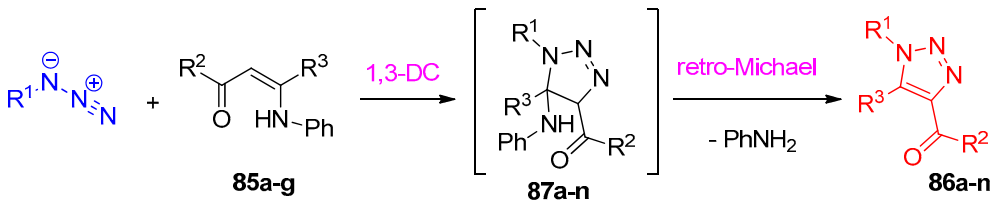


84a–n	R	R¹	Yield (%)
a	Bn	H	95
b	Bn	2-Cl	85
c	Bn	3-Cl	84
d	Bn	4-Cl	86
e	Bn	4-MeO	93
f	Bn	4-Me	92
g	Bn	2-NO_2	81
h	Ph	H	91
i	Ph	2-Cl	87
j	Ph	3-Cl	93
k	Ph	4-Cl	92
l	Ph	4-MeO	92
m	Ph	4-Me	96
n	Ph	2-NO_2	95

Scheme 39. Synthesis of 1,2,3-triazoles **84a–n**. *Reagents and conditions*: (a) $FeCl_3$ (20%), 100 °C.

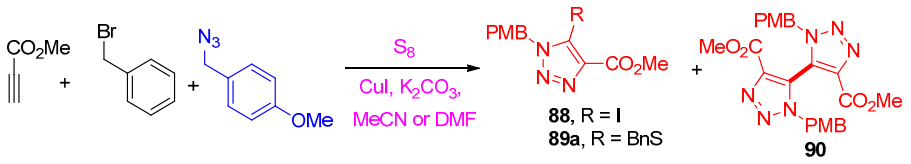


Scheme 40. Synthesis of 1,2,3-triazoles **86a–n**. *Reagents and conditions*: (a) [mPy]OTf/H_2O, Et_3N, 100 °C, 4–10 h.



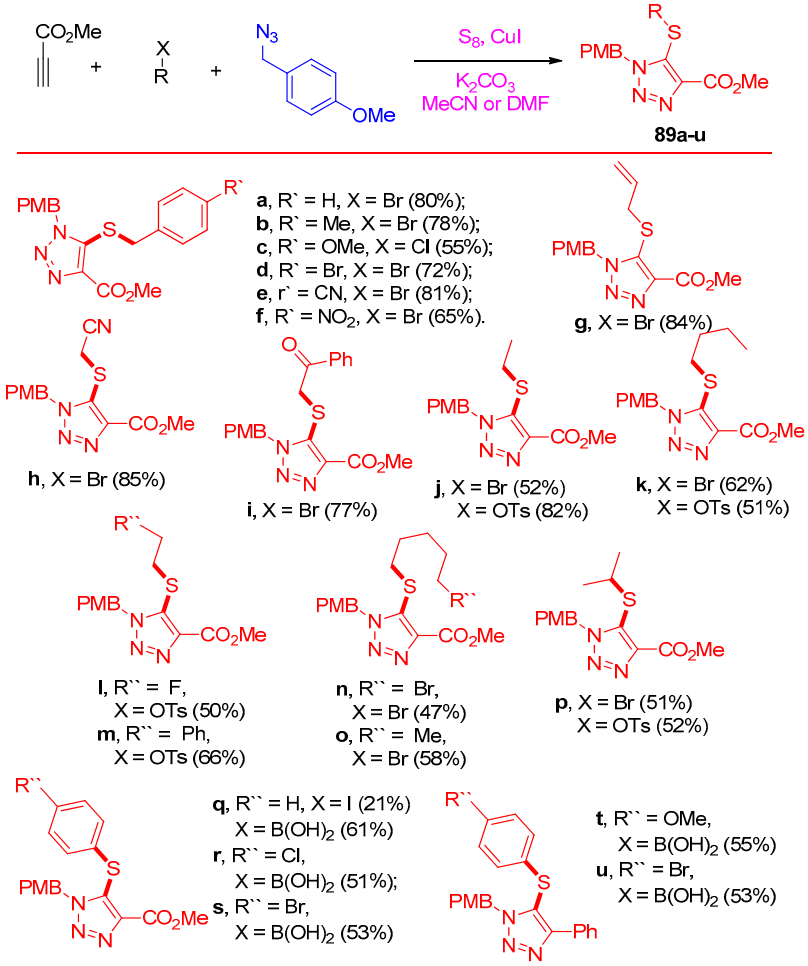
Scheme 41. Reaction mechanism for the reaction between enaminones and azides to form triazoles **86a–n**.

Zhang et al. [34] reporoom temperatureed the one-pot multicomponent reaction for the syntheses of 5-thiotriazoles **89a–u**, **91a–m,** and 5-selenotriazole **92a–l** scaffolds using sulfur and selenium elements. Firstly, the reaction was displayed between methyl propiolate, benzyl bromide, S_8, and 4-methoxybenzyl azide ($PMBN_3$) and was selected to optimize the reaction conditions. It was clear that the optimized condition was achieved for **89a** in the following conditions: CuI (1.3 equiv), K_2CO_3 (2.0 equiv), and S_8 (3.0 equiv) in MeCN (or DMF), first at 0 °C for 1 h and then at 50 °C for 10 h (Scheme 42). The yield was increased with an increasing amount of CuI to 1.3 equivalent and at 50 °C using DMF or MeCN as a solvent. Accordingly, the yields of compounds **89a–u** became good compared with the previous method, as shown in Scheme 43.



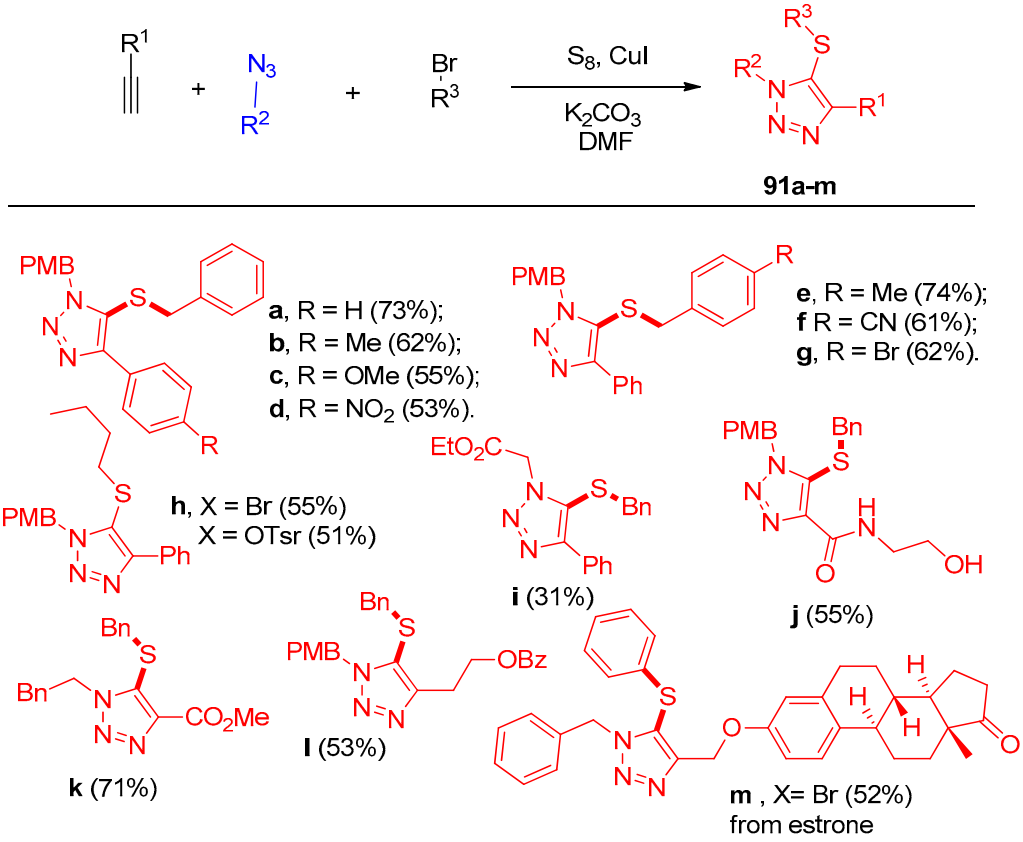
Entry	Additive (2.0 Equiv.)	CuI (Equiv)	Solvent	T (°C)	Yield (%)		
					89a	90	88
1	K_2CO_3	0.5	DMF	0	0	29	40
2	K_2CO_3	0.5	DMF	0-rt	22	34	32
3	K_2CO_3	1.0	DMF	0-rt	55	16	29
4	K_2CO_3	1.3	DMF	0-rt	59	23	0
5	K_2CO_3	1.5	DMF	0-rt	51	12	0
6	K_2CO_3	1.3	DMF	0–50	62	22	0
7	-	1.3	DMF	0-rt	0	0	22
8	K_2CO_3	1.3	DMSO	0–50	0	-	-
9	K_2CO_3	1.3	THF	0–50	41	-	-
10	K_2CO_3	1.3	MeCN	0–50	80	-	0
11	Cs_2CO_3	1.3	MeCN	0–50	36	14	-
12	*t*-BuOK	1.3	MeCN	0–50	34	12	-
13	DIPEA	1.3	MeCN	0–50	20	-	-

Scheme 42. The optimization of the multicomponent reaction for the formation of thiotriazoles **88**, **89a**, and **90**.



Scheme 43. Substrate effect on the formation of 5-thiotriazoles **89a–u** under the optimal conditions.

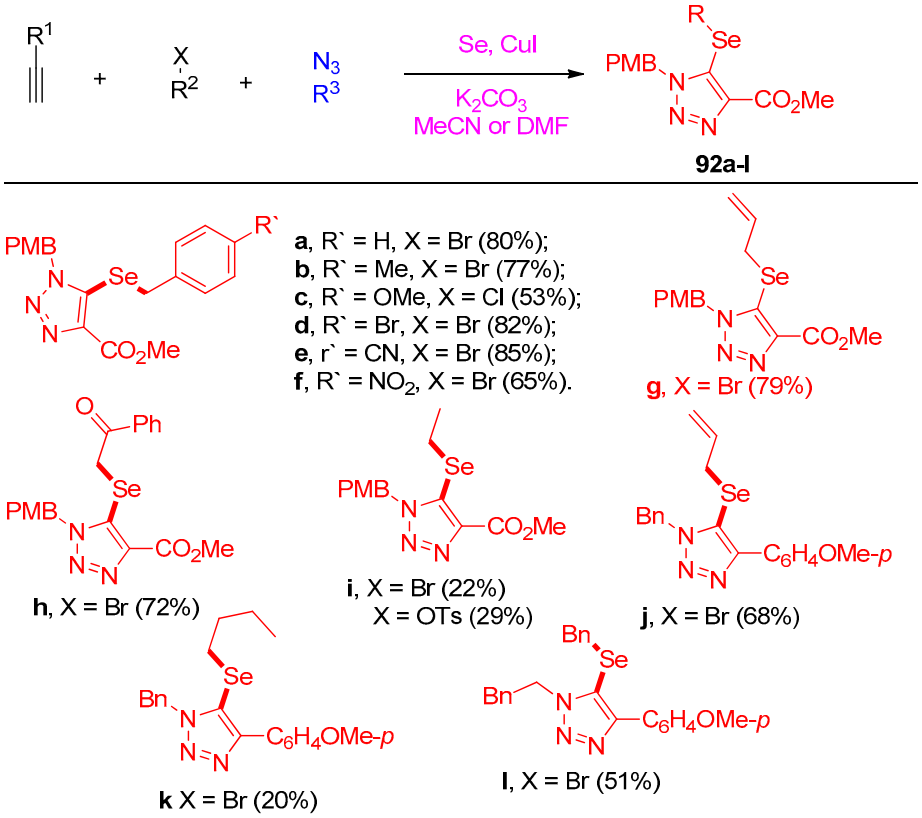
Next, the influence of the alkynes and azides was examined using DMF as the solvent at temperatures ranging from room temperature to 70 °C for the generation of the sulfenylating agent (Scheme 44). Aromatic alkynes with methyl, methoxy, and nitro groups on the benzene ring worked well to produce the corresponding 5-thiotriazoles **91a–i**. The efficiency of acylacetylenes was demonstrated by the generation of **91j** bearing a reactive hydroxyl group. Aliphatic alkynes also proved to be effective for this process **91l**. The excellent availability of this multistep reaction has been well demonstrated by the generation of products **91i** and **91k** from α-azidoacetate and 2-phenylethyl azide, respectively. Under the previous mild sequential copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) and thiolization reaction conditions, the estrone derivative of an alkyne was easily transformed into the corresponding 5-thiotriazole **91m** in 52% yield.



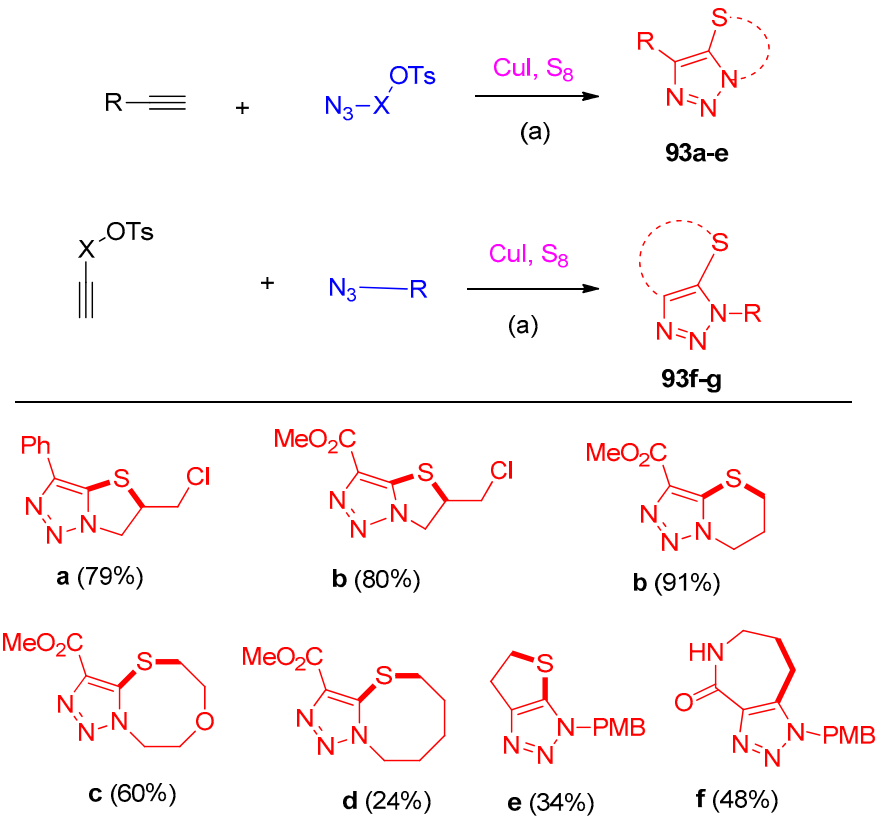
Scheme 44. Substrate effect of alkynes and azides in the synthesis triazolothiols **91a–m**.

5-Selenotriazoles **92a–l** were prepared using selenium as a reagent under the standard conditions in DMF or MeCN, as shown in Scheme 45. The examination was extended to synthesize fused bicyclic 5-thiotriazoles **93a–g** [34] (Scheme 46).

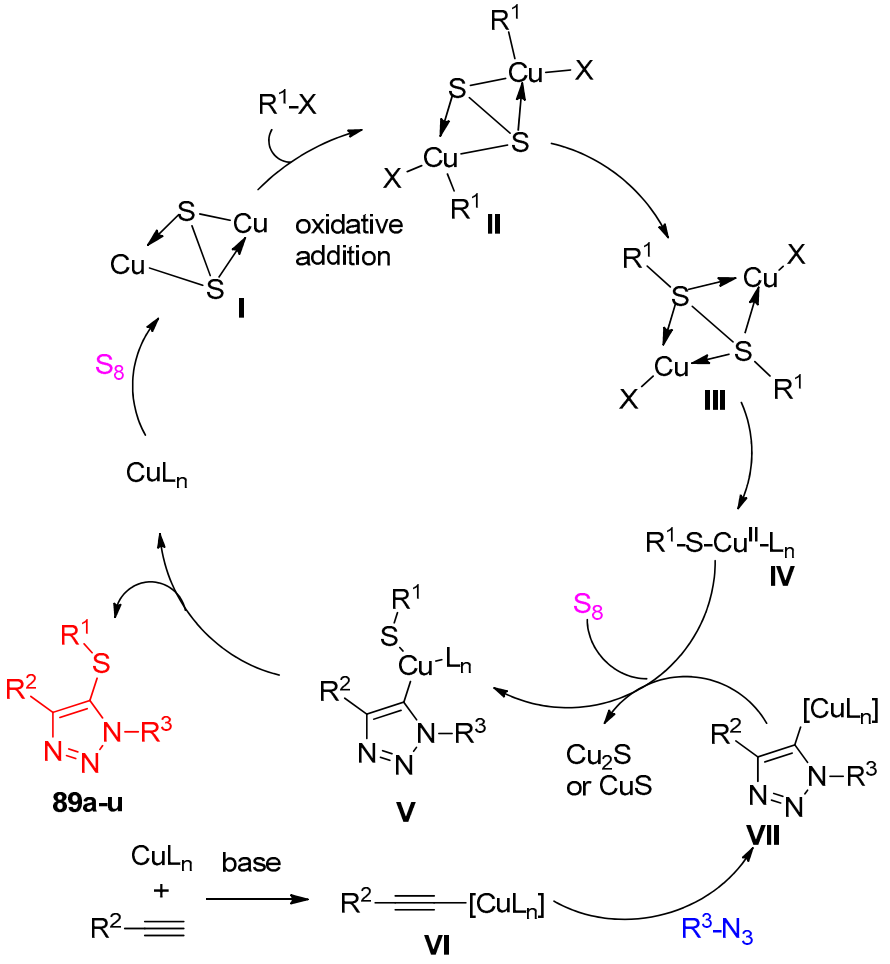
Copper(I) acetylide VI was formed from a terminal alkyne and CuI under basic conditions. The proposed mechanism for this work is shown in Scheme 47. In the beginning, CuI reacted with sulfur to give copper sulfide I. Subsequently, the oxidative addition with a halide forms II, transformed into copper(II) thiolate IV via reductive organic group transfer and oxidation. The cycloaddition of **VI** with the azide produced the copper(I) triazolide intermediate **VI1**. Reaction of copper(II) thiolate **IV** with the copper(I) triazolide would give the intermediate **V**. Finally, reductive elimination of **V** would then lead to the expected 5-thiotriazole **89a**−**u** (Scheme 47) [34].



Scheme 45. Synthesis of selenotriazoles **92a–l**.

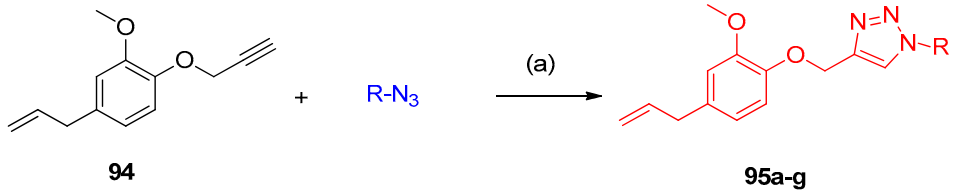


Scheme 46. Synthesis of fused bicyclic 5-thiotriazoles. *Reagents and conditions*: (a) CuI (0.65 mmol), S_8 (1.5 mmol), K_2CO_3 (1.0 mmol), DMF, 0 °C, 30 min, room temperature or 70 °C, 10 h or overnight.



Scheme 47. A plausible mechanism for the formation of thiotriazoles.

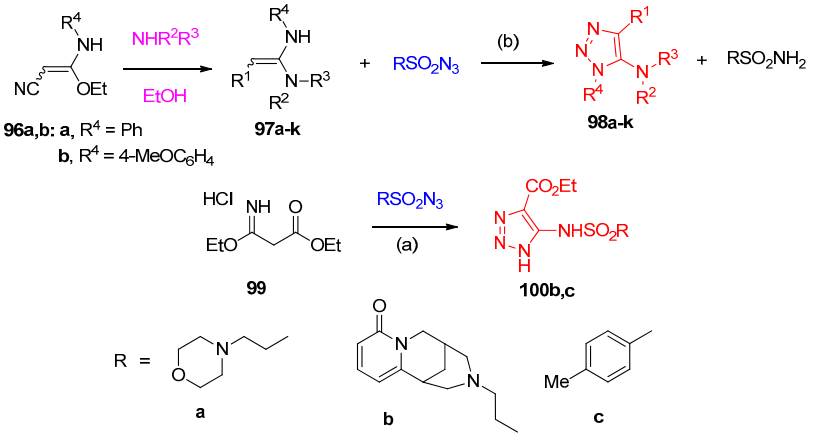
Copper catalyzed 1,3-dipolar cycloaddition between azides and 4-allyl-2-methoxy-1-(prop-2-yn-1yloxy)benzene (**94**) in refluxing acetonitrile afforded the corresponding monocycloadduct **95a–g** with regioselectivity in high yields between 78 and 90% (Scheme 48) [35].



Scheme 48. Synthesis of triazoles **95a–g**. *Reagents and conditions*: (a) CuI, MeCN, room temperature, 2 h.

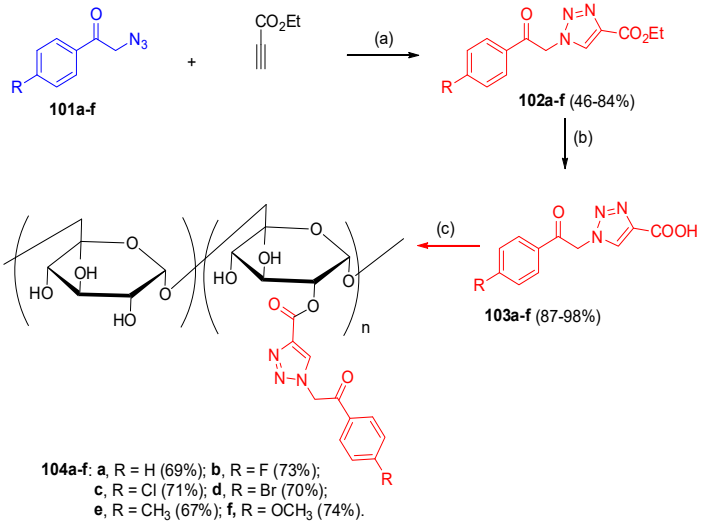
5-Amino-1,2,3-triazoles **98a–k** were prepared from the corresponding amidines **97a**−**k** reacting with tosyl azides in a methanolic basic medium (Scheme 49) [36].

Stanciu et al. [37] reported that *N*, *N*′-carbonyldiimidazole (CDI) synthesized amphiphilic esters based on dextran via a one-pot procedure based on the reaction between the polysaccharide and different substituted 1,2,3-triazoles-4-carboxylates **102a–f**. Firstly, the triazole derivatives **102a–f** were obtained through copper alkyne azide cycloaddition (CuAAC) between azide **101a–f** and ethyl propiolate. Basic hydrolysis of the triazole ester **102a–f** using $KOH_{(aq)}$, $MeOH/H_2O$ gave 1,2,3-triazol-4-carboxylic acid derivatives **103a–f** [37]. Esterification of the dextran (polysaccharide) with the triazole ester activated in situ with 1,1′-carbonyldiimidazole (CDI) to give the dextran esters **104a–f** (Scheme 50).



98	R^1	NR^2R^3	R^4	RSO_2N_3	Et_3N (Equiv.)	Yield (%)
a	CN	Azepane	H	**c**	-	98
a	CN	Azepane	H	**a**	2.0	91
a	CN	Azepane	H	**a**	1.4	81
b	CN	4-benzylpiperidine	H	**c**	-	95
b	CN	4-benzylpiperidine	H	**a**	1.0	98
c	CN	Morpholine	H	**c**	-	93
c	CN	Morpholine	H	**a**	1.0	82
d	CN	Morpholine	Ph	**a**	1.0	91
e	CN	Pyridine	Ph	**a**	1.0	87
f	CN	Pyridine	H	**a**	1.0	85
g	CN	Pyridine	H	**a**	1.0	92
h	CN	NH_2	Bn	**c**	-	84
h	CN	NH_2	Bn	**a**	-	84
i	CN	NH_2	4-$MeOC_6H_4$	**a**	-	89
j	CN	NH_2	4-MeC_6H_4	**a**	1.0	86
k	CO_2Et	NMe_2	H	**c**	2.0	60
k	CO_2Et	NMe_2	H	**a**	2.2	81

Scheme 49. Synthesis of 5-amino-1,2,3-triazoles **98a**–**k**. *Reagents and conditions*: (a) EtOH, reflux; (b) Et_3N, MeOH, room temperature.



Scheme 50. Synthesis of esters of dextran-triazole esters **104a**–**f**. *Reagents and conditions*: (a) $CuSO_4 \cdot 5H_2O$, sodium ascorbate, *t*-BuOH/MeOH/H_2O; (b) KOH (aq), MeOH/H_2O; (c) (i) CDI (DMSO, room temperature, 24h); (ii) Dex40 (DMSO, 80 °C, 24 h).

N-Heterocyclic carbene-copper (NHC-Cu) complexes were known as organometallic catalysts that could differentiate the reactivities of simple terminal alkynes and azides through amplified steric discrimination, allowing efficient sequential ligations of a diyne with two different azides under conditions of premixing all of the reaction partners in solution [38,39]. The interlocked NHC-CuI complexes were found as 1-TFPB and 2-TFPB (TFPB: tetrakis[3,5-bis(trifluoromethyl)phenyl] borate) (Figure 3). The rotaxane 1-TFPB catalyzed a competition reaction involving two pairs of individual alkynes and azides. Therefore, a heating mixture of the non-bulky alkyne **105**, the bulky alkyne **106**, the non-bulky azide **107**, and the bulky azide **108** in THF at 323 K for 48 h in the presence of rotaxane 1-TFPB (15 mol%), four possible triazole products were formed **109**–**112** with good selectivity. The triazole **109** was predominant, with the ratio of the triazoles **109**–**112** being 14:1:0:0 (Scheme 51) [40].

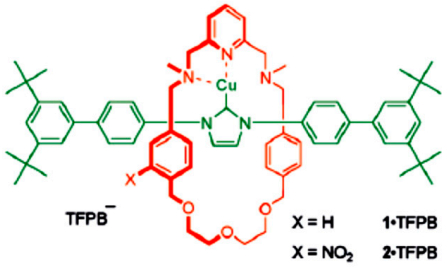
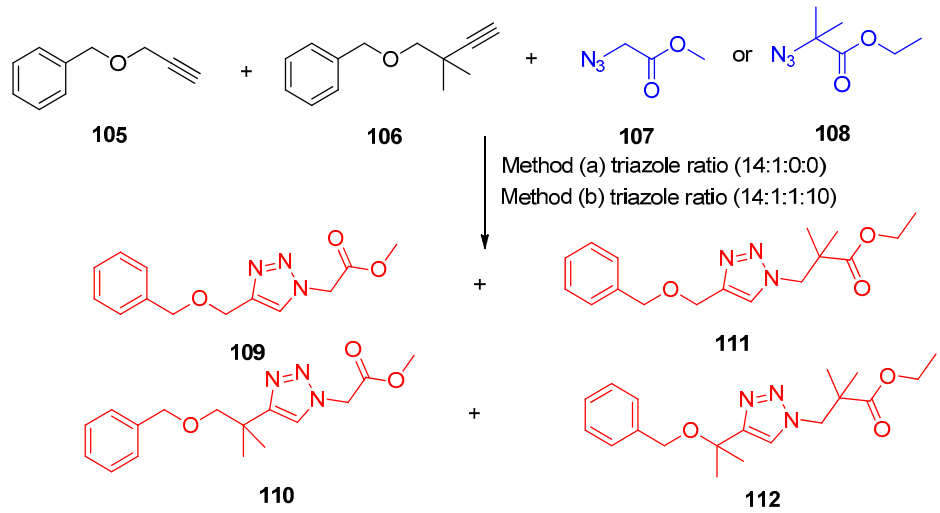
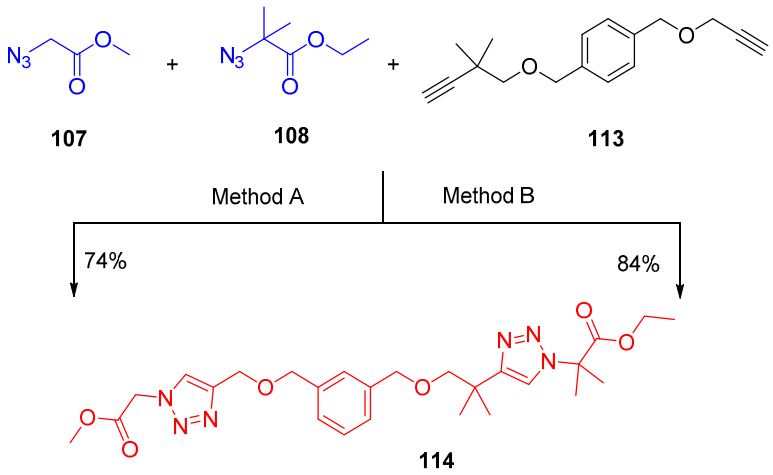


Figure 3. Structure of the interlocked NHC-Cu^{I} complexes 1-TFPB and 2-TFPB [40].



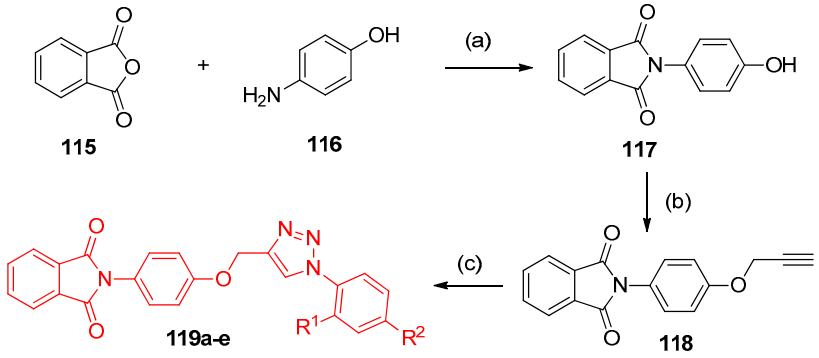
Scheme 51. Synthesis of triazoles **109**–**112**. Reagents and conditions: Method (a) 1-TFPB (15 mol%), THF-d6, 50 °C, 48 h; Method (b) (i)1-TFPB (15 mol%), THF, 50 °C, 48 h; (ii) $Cu(MeCN)_4PF_6$/2,6-lutidine.

Moreover, when azides **107** and **108** were reacted with diyne **113**, under the same conditions in the presence of rotaxane 1-TFPB (15 mol%) and then adding $[Cu(MeCN)_4]PF_6$ and 2,6-lutidine to the intermediate mixture bis-triazole, **114** was isolated in 74% yield (Method A) (Scheme 52). When the last reaction was performed in the presence of 2-TFPB (15 mol%) under the same conditions in the dark for 48 h, the less bulky alkyne and azide had disappeared, while those of the bulky alkyne and azide remained, exhibiting good chemoselectivity toward the coupling of the less bulky parts. Irradiation of this intermediate mixture with light (350 nm, 5 min) cleaved approximately half of the macrocyclic components formed. Heating the resulting mixture (323 K, 12 h) led to the coupling of the bulky pair of alkyne/azide partners and the formation of triazole product **114** in 84% yield (Scheme 52) [40].



Scheme 52. Synthesis of ethyl 2-(4-(1-((3-(((1-(2-methoxy-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methoxy) methyl)benzyl)oxy)-2-methylpropan-2-yl)-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoate (**114**). *Reagents and conditions*: Method A (i)1-TFPB (15 mol%), THF-d_6, 50 °C, 48 h; (ii) $Cu(MeCN)_4PF_6$/2,6-lutidine. Method B (i) 2-TFPB (15 mol%), THF-d_6, 50 °C, 48 h, dark; (ii) hν, (350 nm), 5 min, room temperature; (iii) hν, 15 min, room temperature, then 50 °C, 12 h.

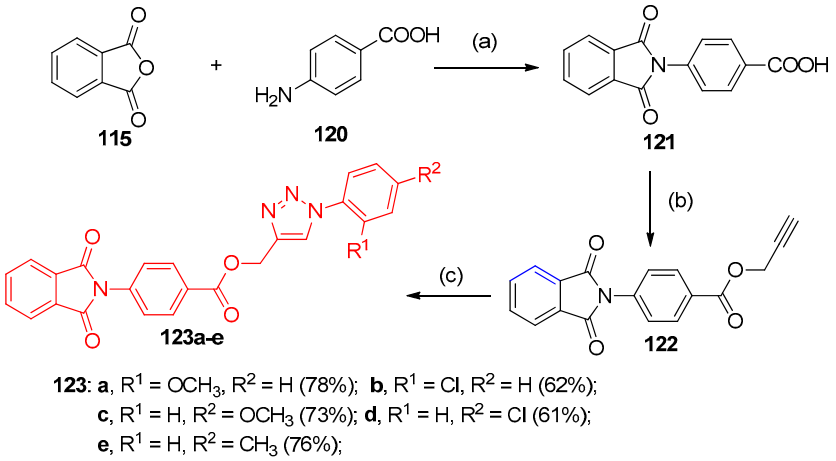
Syntheses of 2-(4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)isoindoline-1,3-dione derivatives **119a–f** were involved in three steps. 4-Aminophenol **116** reacted with phthalic anhydride (**115**) in acetic acid at 100 °C to give compound **117** (Scheme 53). Propargylation of **117** afforded the corresponding 2-(4-(prop-2-yn-1-yloxy)phenyl)isoindoline-1,3-dione (**118**), which in the presence of potassium carbonate and subsequently treated with various azides via 1,3-dipolar cycloaddition (click reaction) during treatment with 10 mol% of sodium ascorbate and 10 mol% of copper sulfate. Consequently, the reaction afforded 1,2,3-triazolyisoindoline-1,3-dione derivatives **119a–e** in excellent 70% to 81% yield, as shown in Scheme 53 [41].



119: **a**, R^1 = H, R^2 = H (81%); **b**, R^1 = OCH_3, R^2 = H (79%);
c, R^1 = H, R^2 = OCH_3 (80%); **d**, R^1 = Cl, R^2 = H (73%);
e, R^1 = H, R^2 = Cl (70%);

Scheme 53. Synthesis of 1,2,3-triazolyisoindoline-1,3-dione derivatives **119a–f**. *Reagents and conditions*: (a) Acetic acid, 100 °C, 3 h; (b) K_2CO_3, Propargyl bromide, DMF, room temperature, 3 h; (c) Azides, 10 mol% of sodium ascorbate, 10 mol% of $CuSO_4 \cdot H_2O$, DMF: Water (1:1), room temperature, 10 to 12 h.

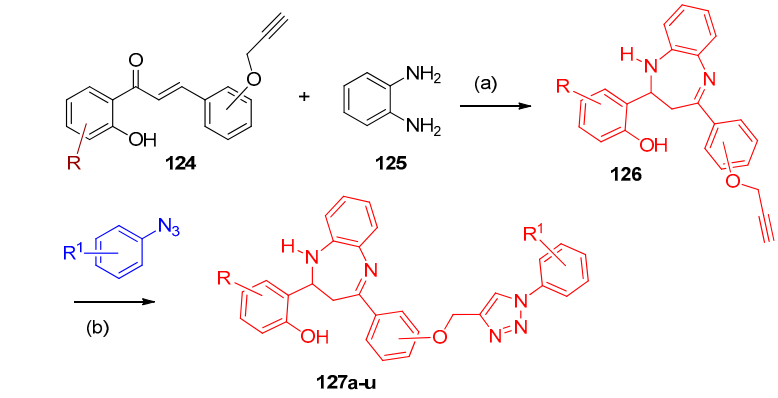
Applying the same procedure mentioned, the synthesis of triazoles **123a–e** was also established in the same three steps. Compound **122** was obtained, which in the presence of potassium carbonate and subsequently treated with various azides and 10 mol% of sodium ascorbate and 10 mol% of copper sulfate, afforded the final compounds **123a–e** via 1,3-dipolar cycloaddition (Click reaction) (Scheme 54) [41].

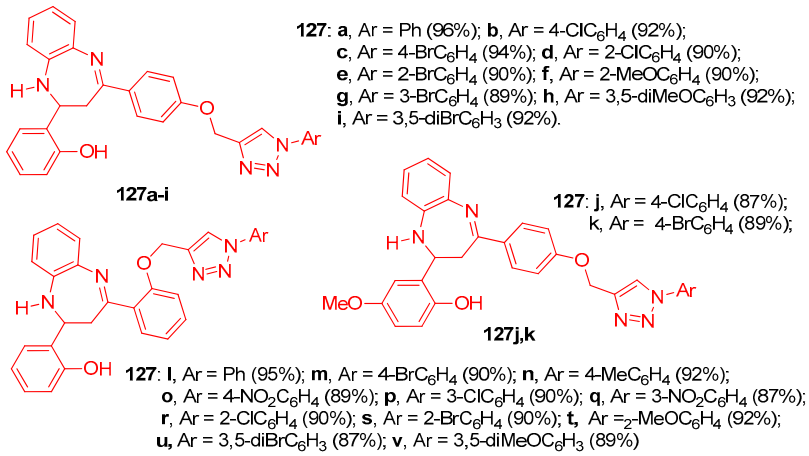


123: **a**, R^1 = OCH_3, R^2 = H (78%); **b**, R^1 = Cl, R^2 = H (62%);
c, R^1 = H, R^2 = OCH_3 (73%); **d**, R^1 = H, R^2 = Cl (61%);
e, R^1 = H, R^2 = CH_3 (76%);

Scheme 54. Synthesis of triazoles **123a–e**. *Reagents and Conditions*: (a) acetic acid, 100 °C, 3 h; (b) K_2CO_3, propargyl bromide, DMF, room temperature, 3 h; (c) Azides, 10 mol% of sodium ascorbate, 10 mol% of $CuSO_4 \cdot 5H_2O$, DMF:H_2O (1:1), room temperature, 10 to 12 h.

$CuFe_2O_4$@MIL-101(Cr) was used as a catalyst in synthesizing benzodiazepine triazole derivatives during the reaction of chalcones containing the acetylene group in the *o* or *p* positions **124a–c** with substituted azides containing both electron-withdrawing groups and electron-donating groups (Scheme 55). Firstly, the chalcones **124** reacted with *o*-phenylene diamine **125** to furnish the corresponding diazepine acetylene derivatives **126**, which on click reaction underwent cyclization to give the triazole derivatives **127a–u** [42].





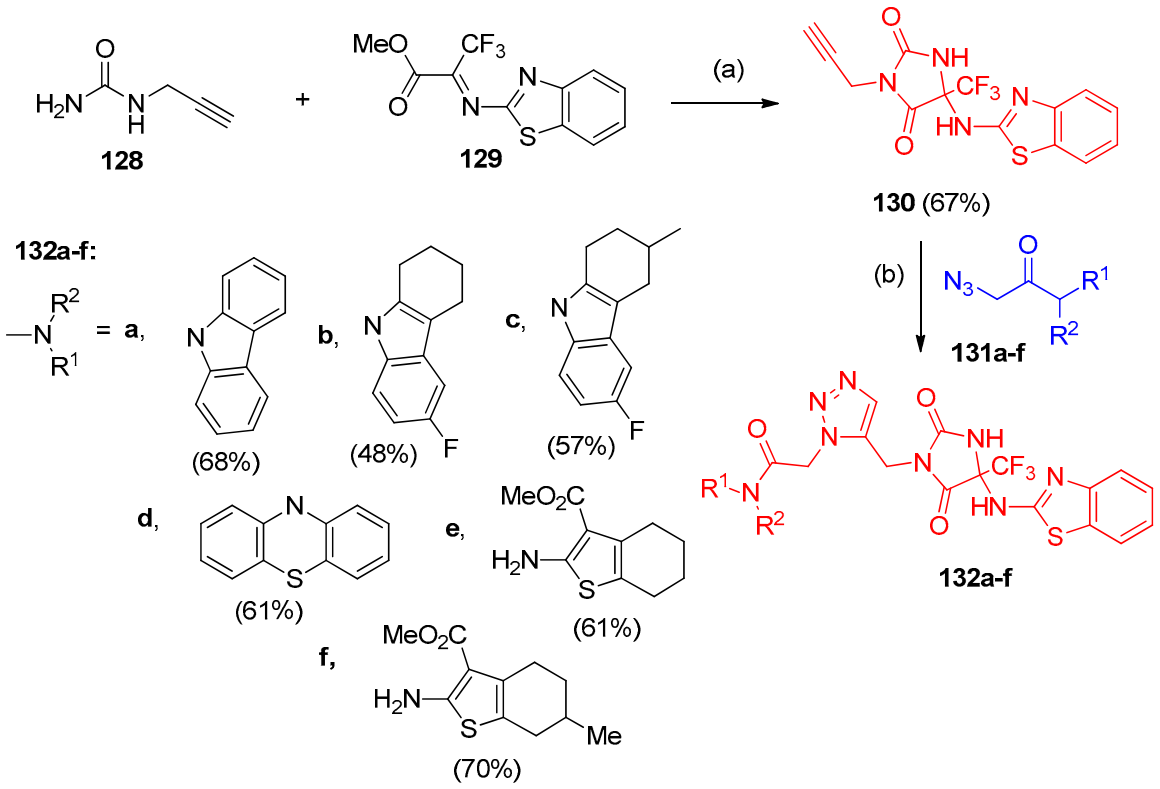
127: **a**, Ar = Ph (96%); **b**, Ar = 4-ClC_6H_4 (92%);
c, Ar = 4-BrC_6H_4 (94%); **d**, Ar = 2-ClC_6H_4 (90%);
e, Ar = 2-BrC_6H_4 (90%); **f**, Ar = 2-$MeOC_6H_4$ (90%);
g, Ar = 3-BrC_6H_4 (89%); **h**, Ar = 3,5-di$MeOC_6H_3$ (92%);
i, Ar = 3,5-diBrC_6H_3 (92%).

127: **j**, Ar = 4-ClC_6H_4 (87%);
k, Ar = 4-BrC_6H_4 (89%);

127: **l**, Ar = Ph (95%); **m**, Ar = 4-BrC_6H_4 (90%); **n**, Ar = 4-MeC_6H_4 (92%);
o, Ar = 4-$NO_2C_6H_4$ (89%); **p**, Ar = 3-ClC_6H_4 (90%); **q**, Ar = 3-$NO_2C_6H_4$ (87%);
r, Ar = 2-ClC_6H_4 (90%); **s**, Ar = 2-BrC_6H_4 (90%); **t**, Ar =$_2$-$MeOC_6H_4$ (92%);
u, Ar = 3,5-diBrC_6H_3 (87%); **v**, Ar = 3,5-di$MeOC_6H_3$ (89%)

Scheme 55. Synthesis of triazoles **127a–v**. *Reagents and conditions*: (a) $CuFe_2O_4$@MIL-101(Cr), water reflux; (b) H_2O, reflux.

Propargylurea (**128**) underwent cyclocondensation with methyl trifluoropyruvate benzothiazolylimine (**129**) in the presence of Et_3N to give 5-alkynyl-substituted trifluoromethyl hydantoin **130** in 67% yield. The alkyne **130** was subjected to CuAAC reaction with 2-azidoacetamides **131** to give the corresponding 1,4-substituted 1,2,3-triazoles **132a–f** (Scheme 56) [43].

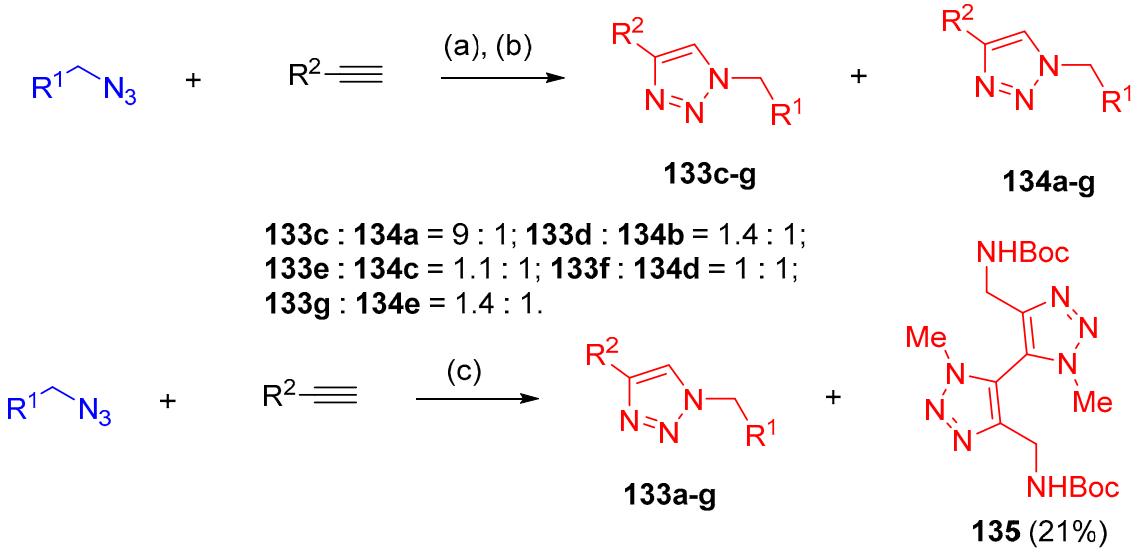


Scheme 56. Synthesis of 1,2,3-triazoles **132a–f**. *Reagent and conditions*: (a) (i) DMF, 20 °C, stirring then at 90 °C for 1 h; (ii) E_3N, 90 °C, 2 h; (b) CH_2Cl_2, $CuSO_4$ (0.05 mmol), sodium ascorbate (0.05 mmol), stirring 3 h, 40 °C.

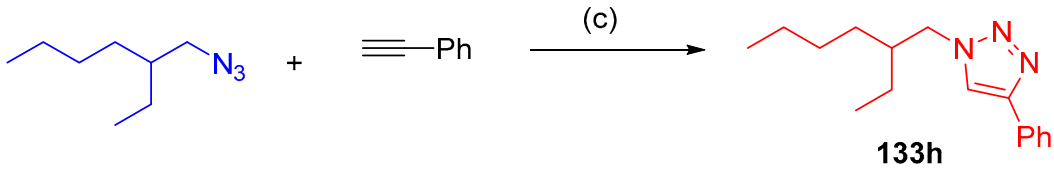
Azides reacted regioselectivity with alkynes via CuAAC 1,3-dipolar cycloaddition using CuI to form triazoles **133a–g** as a major product and triazoles **134a–g** as minor products. An exception was the reaction of methyl azide with tert-butyl prop-2-yn-1-ylcarbamate, which resulted in a mixture of triazole **133a** and 5,5′-bitriazole **135** at a ratio of 2.4:1. Under similar conditions, the longer aliphatic chain azide (3-(azidomethyl)heptane) reacted with phenylacetylene to give triazole **133h** in low yield by using copper(I) iodide as a catalyst in combination with a catalytic amount of benzoic acid furnished **133h** in a high yield (90%) (Scheme 57). Bis-triazoles **137** and **139** were obtained in high yields with a faster rate of reaction via click reaction of 1,3-diazidopropane (**136**) and diazide **138** with ethyl propiolate and phenylacetylene, respectively (Scheme 58). Furthermore, azide **140** (1-(2-azidoethyl)-5,6-dimethyl-1*H*-benzo[*d*][1,2,3]triazole) was reacted with diethyl acetylenedicarboxylate and methyl propiolate afforded triazole **141** (97%) and triazole **142** (94%) yields, respectively (Scheme 59). Azide **143** was reacted even with a reactive dipolarophile, such as acetylenecarboxylate in *t*-BuOH in the presence of a basic cocatalyst gave triazole **144** (74%) (Scheme 59) [44].

N-Propargylated cinnolinones **145a–c** reacted with benzyl azide to afford the corresponding triazole derivatives **146a–c** via CuAAC in $CHCl_3$. It was noted that the complexes of the [(IPr)CuX] series (X = Cl, Br, I) did not exhibit catalytic activity. However, [(IMes)CuX] complexes (X = Cl, Br, I) containing a less sterically hindered ligand showed higher activity under the same reaction conditions; this was attributed to the electronic

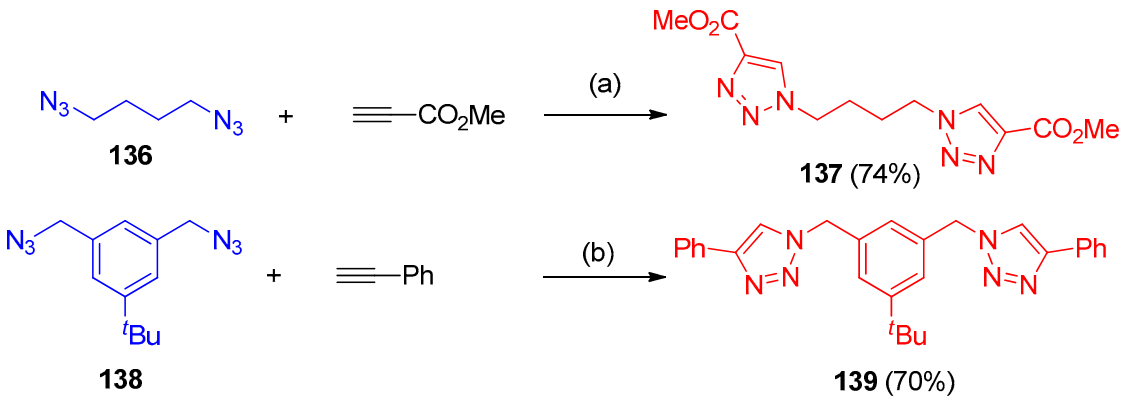
nature of the halides, and the catalytic reactivity increased in the order of $Cl^- < Br^- \approx I^-$, (Scheme 60) [45].



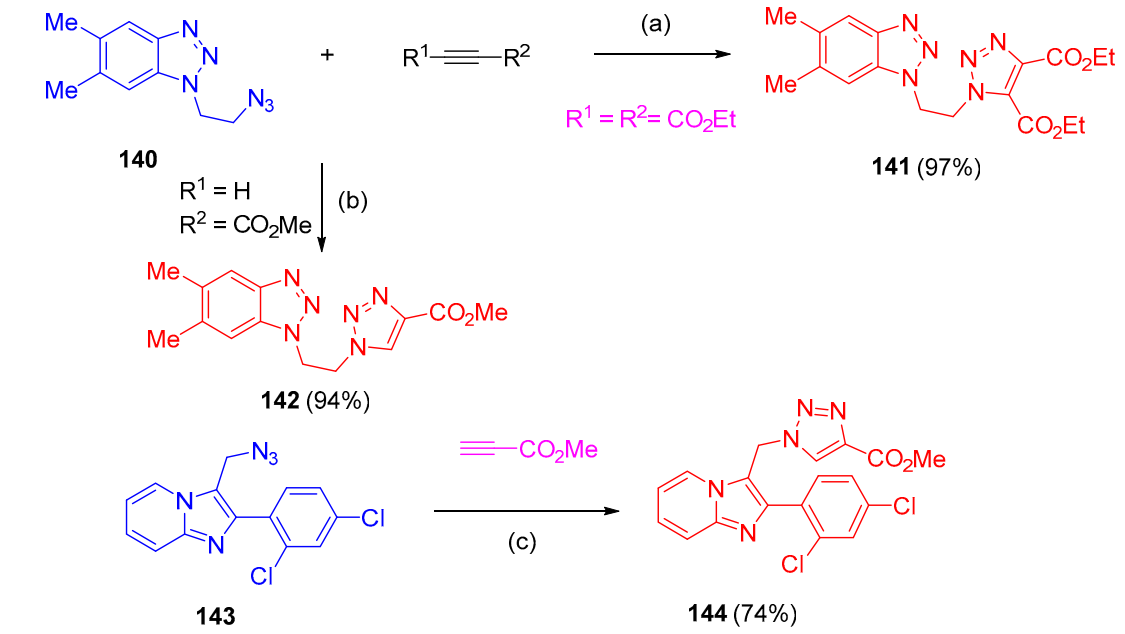
133a-g: R^1 = H, R^2 = (**a**, CH_2NHBoc (49%), **b**, CH_2OH (94%), **c**, COOMe (97%));
d, $R^1 = CH_2OH$, $R^2 = CH_2NHBoc$ (52%); **e**, R^1 = CN, $R^2 = CH_2NHBoc$ (40%);
f, R^1 = COOEt, $R^2 = CH_2OH$ (47%); **g**, $R^1 = CONH_2$, $R^2 = CH_2NHBoc$ (55%).
134a-e: **a**, R^1 = H, R^2 = COOMe (9.5%); **b**, $R^1 = CH_2OH$, $R^2 = CH_2NHBoc$ (37%);
c, R^1 = CN, $R^2 = CH_2NHBoc$ (36%); **d**, R^1 = COOEt, $R^2 = CH_2OH$ (47%);
e, $R^1 = CONH_2$, $R^2 = CH_2NHBoc$ (40%).



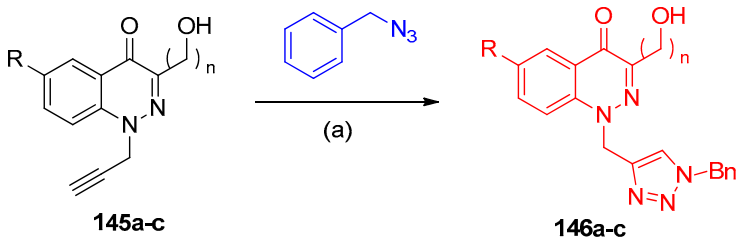
Scheme 57. Synthesis of various regioisomers of triazoles **133**–**135**. *Reagent and conditions*: (a): R^1 = H, $R^2 = CO_2Me$, PhH, 20 °C to room temperature, 12 h; (b): R1 ≠ H, PhMe, 80–90 °C, 24 h; (c) CuI, PhCOOH, *i*-PrOH–H_2O.



Scheme 58. Synthesis of bis-triazoles **137** and **139**. *Reagent and conditions*: (a) CuI (1 mol%), Et_3N, THF; (b) $CuSO_4 \cdot 5\ H_2O$, NaAsc, DMSO–H_2O.



Scheme 59. Synthesis of bis-triazole carboxylate derivatives **141**, **142** and **144**. *Reagents and conditions:* (a) PhMe; (b) CuI (1 mol%), THF; (c) CuI (10 mol%), Et_3N, THF.



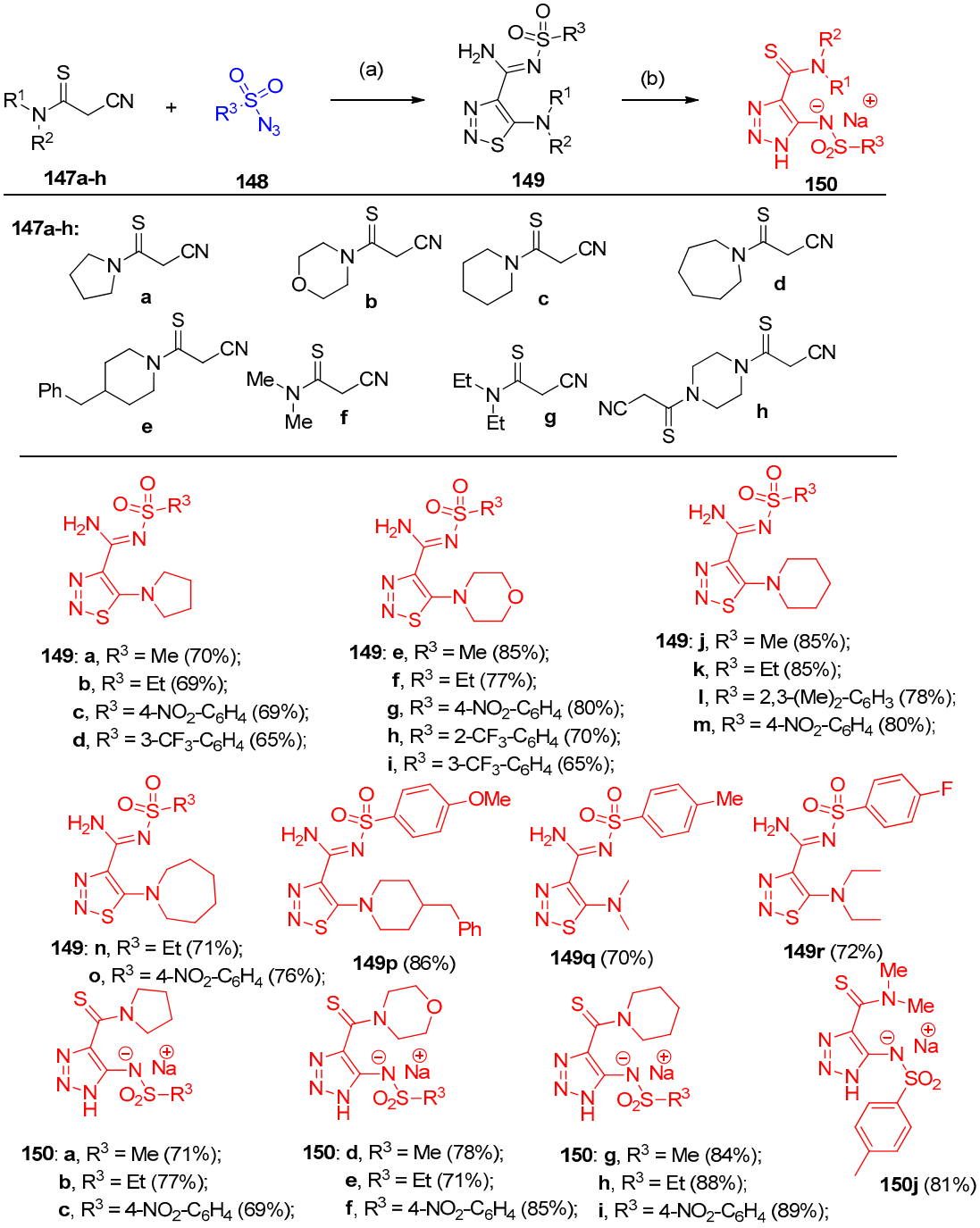
146a-c: **a**, R = CO_2Et, n = 1; **b**, R = Br, n = 1; **c**, R = Br, n = 2;

Compound 146	[(NHC)CuX]	Solvent	Conversion of Compounds 8a–c According to ^1H NMR Spectrum, %
a	[(IPr)CuX] X = Cl, Br, I	$CDCl_3$	traces
a	[(IMes)CuCl]	$CDCl_3$	10
a	[(IMes)CuBr]	$CDCl_3$	75
a	[(IMes)CuI]	$CDCl_3$	82 (75 isolated yield)
a	CuI	$CDCl_3$	0
b	[(IMes)CuI]	$CHCl_3$	62 (55 isolated yield)
c	[(IMes)CuI]	$CHCl_3$	50
c	[(IMes)CuI]	THF	87
c	[(IMes)CuI]	Me_2CO	92
c	[(IMes)CuI]	MeCN	99 (94 isolated yield)

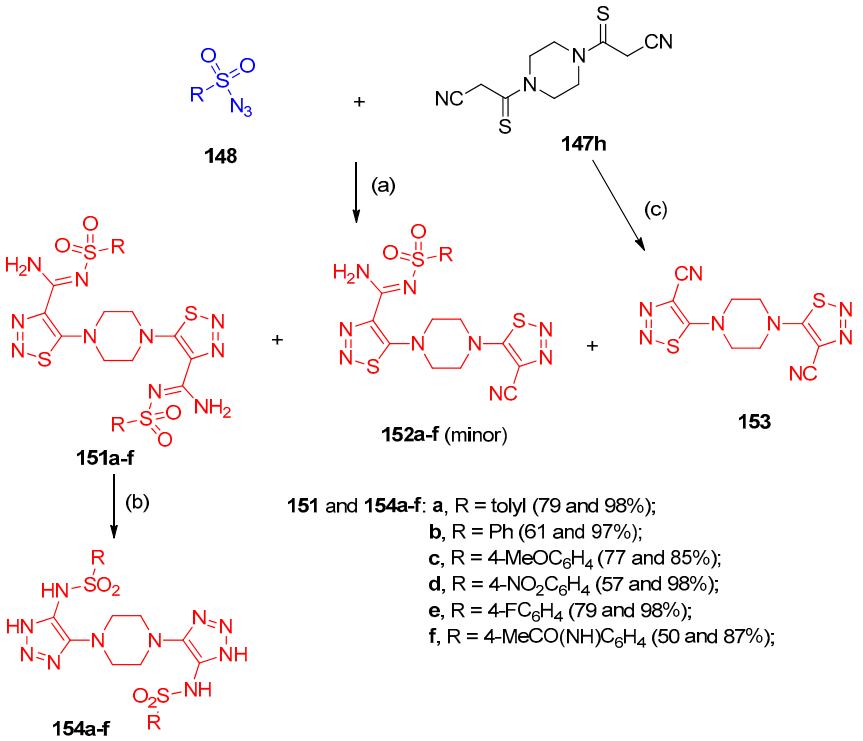
Scheme 60. Synthesis of 1,2,3-triazoles **146a–c**. *Reagents and conditions*: (a) [(NHC)CuX] (2 mol%), solvent, room temperature, 18 h.

Filimonov et al. [46] reported a one-step, eco-friendly method for synthesizing 1,2,3-thiadiazol-4-carbimidamides **149a–r** and 1,2,3-triazole-4-carbothioamides **150a–j**, during the reactions of 2-cyanothioacetamides **147a–g** with various types of azides **148** in water in the presence of alkali (Scheme 61). Furthermore, *N*,*N*′-bis-(2-cyanothiocarbonyl)-pyrazine

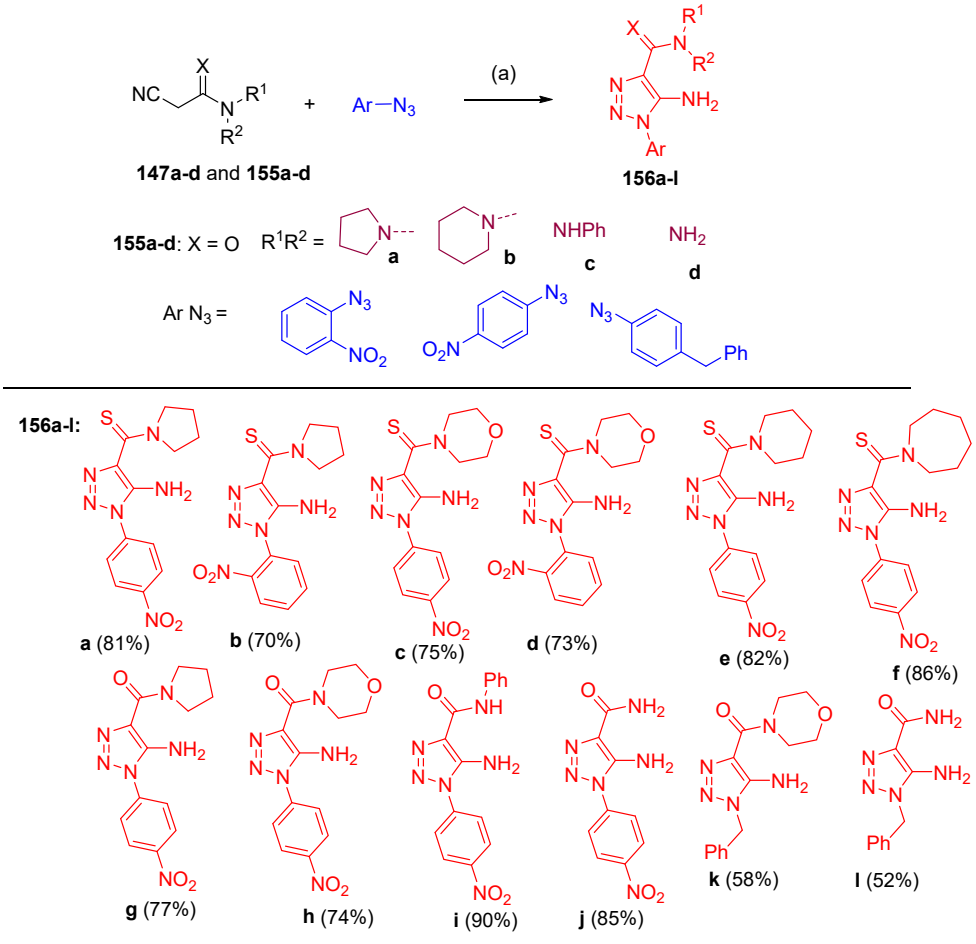
147h was reacted with sulfonyl azides **148** to give the bicyclic 1,2,3-thiadiazoles **151–153,** and 1,2,3-triazoles **154a–f** connected via a 1,1′-piperazinyl linker (Scheme 62). On the other hand, 2-cyanothioacetamides **155** reacted with aromatic azides in water in the presence of alkali to afford 1-aryl-5-amino-1,2,3-triazole-4-carbothioamides **156a–l** (Scheme 63). In contrast to aromatic azides and sulfonyl azides, 6-azidopyrimidine-2,4-diones **157a–c** reacted with cyanothioacetamides **147a–e** to give *N*-pyrimidine-6-yl-5-dialkylamino-1,2,3-thiadiazole-4-*N*-l-carbimidamides **158a–i**. Additionally, compounds **158a–i** were obtained in two step-reaction starting with 6-chloro-1,3-disubstituted-pyrimidine-2,4-dione **159** (Scheme 64).



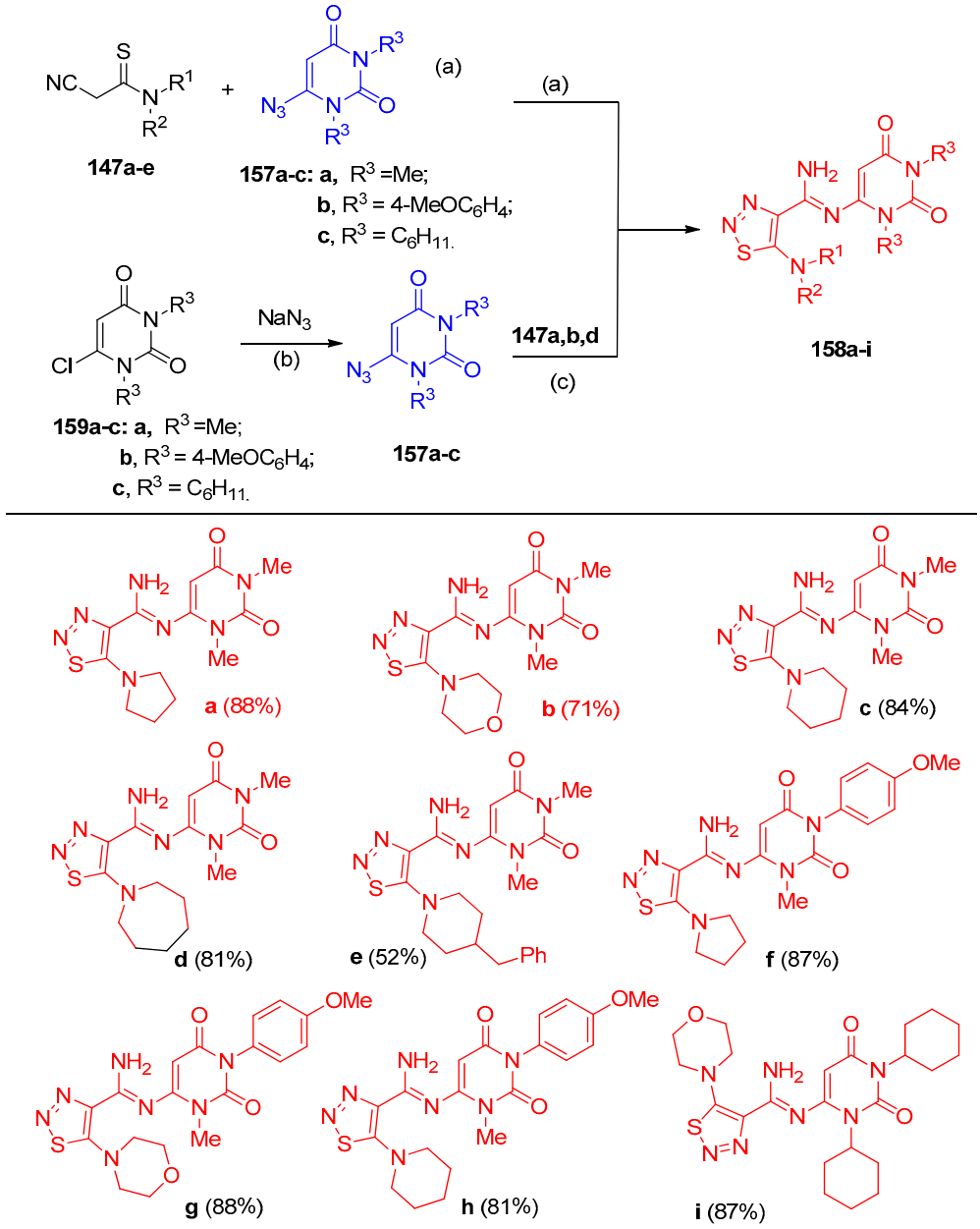
Scheme 61. Synthesis of triazoles **147–150**. *Reagents and conditions*: (a) NaOH, H_2O, 0 °C; (b) EtONa, EtOH, 23 °C, 1 h.



Scheme 62. Synthesis of bis-triazoles **154a–f**. *Reagents and conditions*: (a) H_2O, NaOH; (b) NaOMe, MeOH; (c) TsN_3, pyridine.

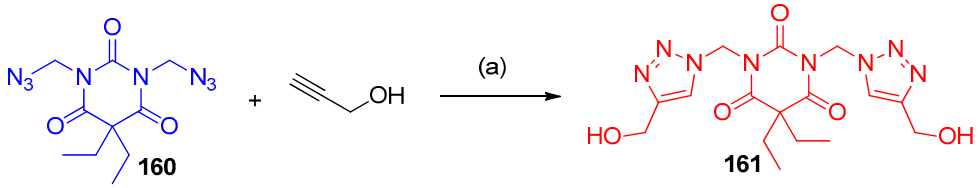


Scheme 63. Synthesis of triazoles **156a–l**. *Reagents and conditions*: (a) NaOH, H_2O, 50–60 °C.



Scheme 64. Synthesis of *N*-pyrimidin-6-yl-5-dialkylamino-1,2,3-thiadiazole-4-*N*-l-carbimidamides **158a–i**. *Reagents and conditions*: (a) H_2O, NaOH, 0 °C; (b) NaN_3, H_2O, r.t., 24 h; (c) H_2O, 0 °C, 24 h.

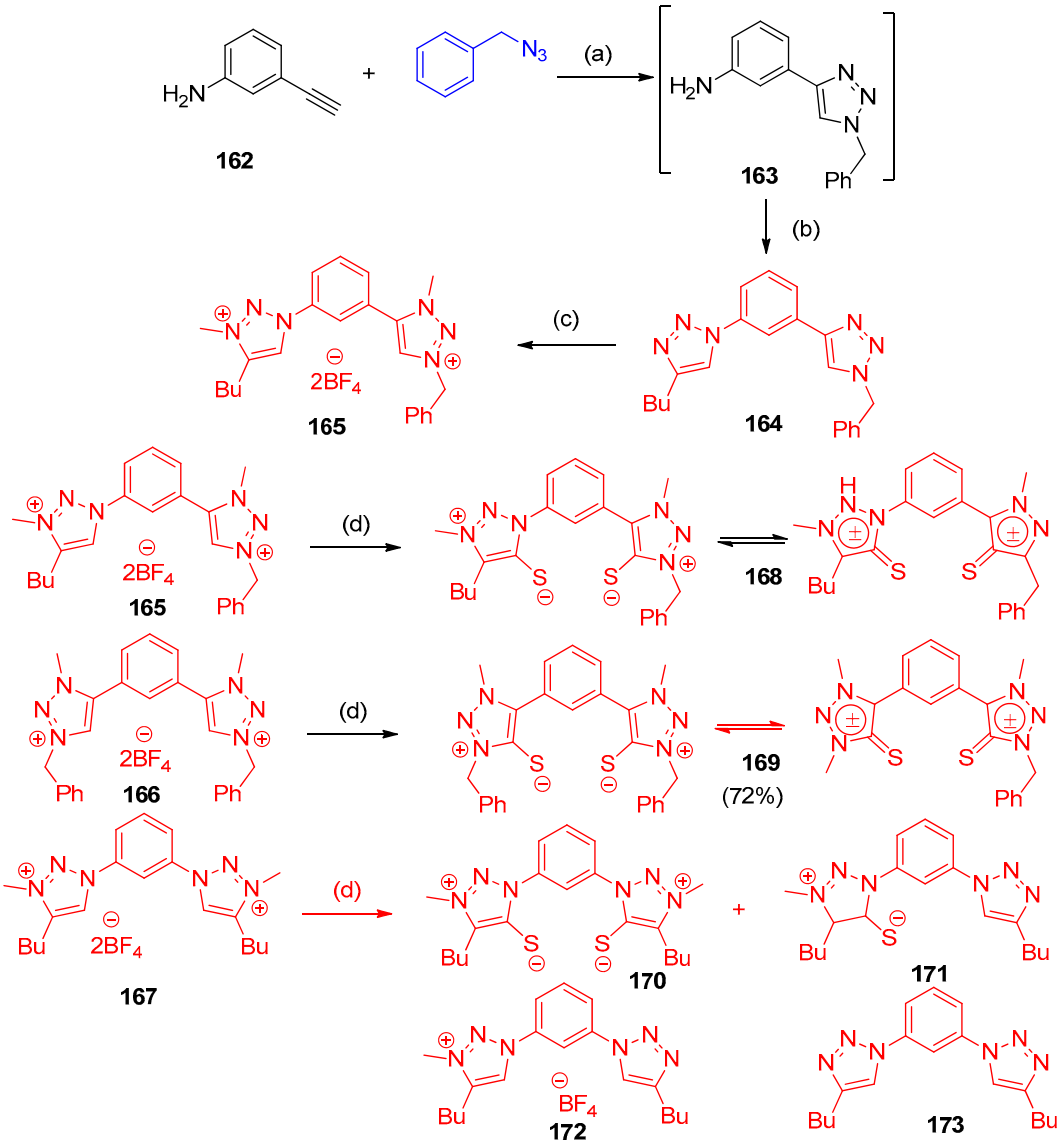
Bis(azidomethyl)-5,5-diethylpyrimidinetrione (**160**) underwent CuAAC 1,3-dipolar cycloaddition with alkyne (prop-2-yn-1-ol) to afford bis((4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)methyl)pyrimidinetrione (**161**) (Scheme 65) [46].



Scheme 65. Synthesis of bistriazolylpyrimidinetrione **161**. *Reagents and conditions*: (a) $CuSO_4 \cdot 5H_2O$, NaAsc, DMF, 50 °C, stirring 15–50 h.

The copper-mediated click reaction using 3-aminophenyl-acetylene (**162**) and benzyl azide as the starting materials gave the monotriazole **163** using a well-defined copper

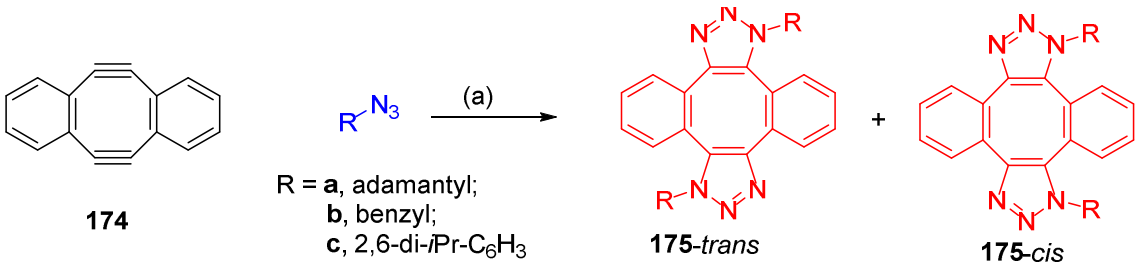
carbene complex [CuCl (IPr)] (IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazolin-2-ylidene) as a catalyst. Compound **163** underwent diazotization and azidation followed by [3 + 2] click reaction to afford the non-symmetrical bis(triazoles) **164**. Alkylation of **164** using Meerwein's salt $(CH_3)_3OBF_4$ gave the dicationic pro-ligand salt **165**. The non-symmetrical triazolium salt **165** and symmetrical 1,2,3-triazolium salts [47–50] **166** and **167** were utilized to synthesize mesoionic carbene-sulfur adducts **168a**, **169b,** and **170c**. Firstly, the triazolium salts **165**/**166** were reacted with elemental sulfur in a base (KO^tBu and K_2CO_3) non-symmetrical mesoionic bis (NHT) compound **168** the symmetrical analog **169** in good yields, 76% and 72%, respectively. Complexes **170**–**173** were formed with the treatment of **167** with elemental sulfur in the presence of K_2CO_3 as a base (Scheme 66) [51].



Scheme 66. Synthesis of cationic-anionic triazoles. *Reagents and conditions*: (a) [CuCl(IPr)], $EtOH/H_2O$; (b): $NaNO_2$, HCl, and then NaN_3, and then 1-hexyne, [CuCl (IPr)], $EtOH/H_2O$, 82% (two-step combined yield); (c): $(CH_3)_3OBF_4$, dichloroethane (DCE), 56%; (d) K_2CO_3, S8, MeCN, 90 °C, 24 h.

Yoshida et al. [52] reported that the double-click reaction between aryl azides and the diyne (**183**) afforded a regioisomeric mixture of bicyclo-adduct **184** (*trans*/*cis*) in an excellent yield. It was observed that 1-adamantyl azide was bulky, caused retention to the cycloaddition and gave the bis-cyclo-adduct with 18% for 4 h. The 2,6-diisopropylphenyl

azide gave the bis-cyclo-adduct in quantitative yields, while the unhindered benzyl azide gave the bis-cyclo-adduct in 83% yields for 1 h. The studies were prolonged to cover the effect of the substituent in the aryl azide to clarify that the bulkiness groups enhanced the reaction rate, and the electronic nature of substituted groups in both *o*- and *p*-positions showed a limited effect on the reaction rate. In contrast, 2,6-disubstituted phenyl azides had accelerated reaction rates as the size of substituents became bulkier (the lower click ability of adamantyl azide than that of diisopropylphenyl azide was attributed to the stabilization of the azido group by hyper-conjugation with C-H bonds, which decreases the distort ability of the azido group) (Scheme 67) [52]. The click ability of the alkyl and alkenyl azides with Sondheimer diyne (**174**) afforded the regioisomeric bicyclo adducts **176** (*trans*/*cis*). The studies showed that the reaction rate was faster in the case of alkyl azides than in the alkenyl azides, indicating that resonance retarded the reaction rate and that both the inductive effect and hyper-conjugation increased the reaction rate (Scheme 67) [52,53].



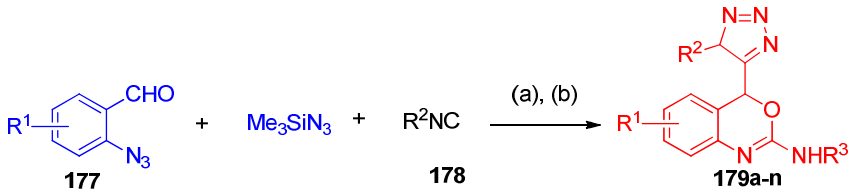
175a-j:**a**, R = adamantyl (18%), **b**, R = benzyl (83% (62/28%)),
c, R = 2,6-di-*i*Pr-C_6H_3 (95%(96/4%)); **d**, R = C_6H_5(94% (43/57%);
e, R = *p*-OMe-C_6H_4 (89%(36/64%); **f**, R = *p*-CF_3-C_6H_4 (97%(50/50);
g, R = *o*-Me-C_6H_4(98%(52/48%)); **h**, R = *o*-*i*Pr-C_6H_4 (95%(60/40));
i, R = 2,6-di-Me-C_6H_3 (92%(64/36%));
j, R = 2,6-di-Et-C_6H_3 (93%(73/2755)

Compound 176	R	Yield (%)	*Trans*/*cis*	K ($M^{-1}s^{-1}$)
a	$PhCH_2CH_2$…	99	57/43	9.6×10^{-2}
b	PhCH=CH…	98	53/47	4.1×10^{-2}
c	MePhCH…	98	Not determined	2.1×10^{-2}
d	CH_2=CHPh	98	49/51	3.9×10^{-3}
e	CH_2=CCH_2CH_2Ph	97	54/46	6.1×10^{-3}
f	PhCH=CPh	Quant.	75/52	8.9×10^{-2}

Scheme 67. Cycloaddition of Sondheimer diyne **174** with aryl azides. *Reagents and conditions*: (a) 2.4 equiv. of azide, MeOH room temperature.

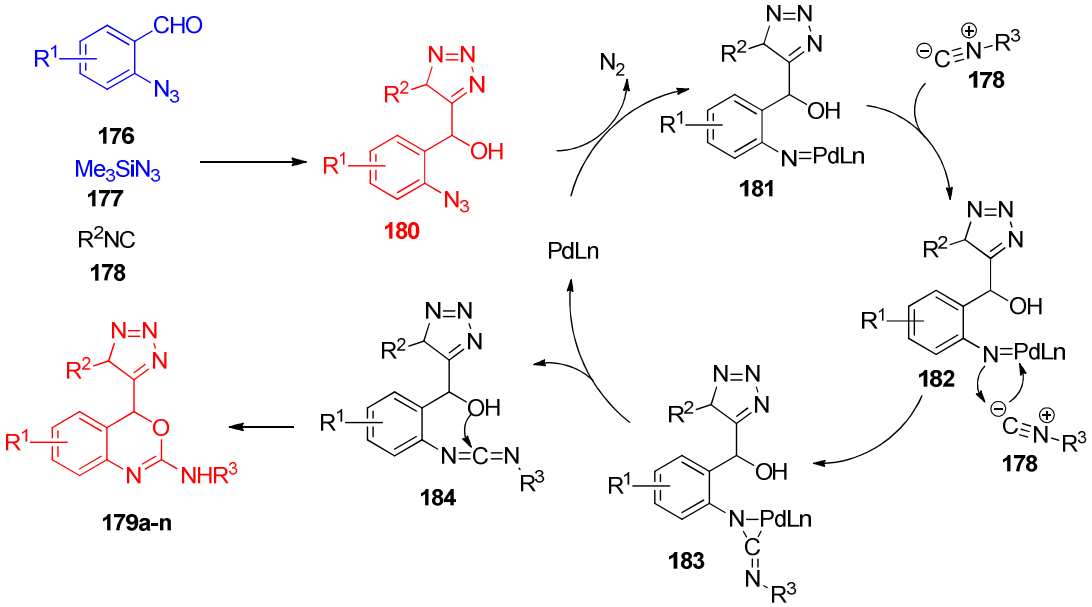
The synthesis of triazolyl benzoxazine derivatives **179a-n** via one-pot reaction (e.g., Ugi reaction [54]) using the so-called Passerini-azide reactions (a method to prepare tetrazoles by substituting hydrazoic acid generated in situ from NaN_3 or TMS-N_3 (**177**), has been reported [54–56]. The reaction of 2-azidobenzaldehydes **176**, **177,** and isocyanides **178** gave 4*H*-3,1-benzoxazine derivatives by the in-situ formation of azide intermediate (Scheme 68) [56].

The proposed mechanism for the formation of compounds **179a–n** was started from the Passerini-azide adduct **180,** which reacted with the palladium reagent to form the palladium–nitrogen intermediate **181** with the elimination of the nitrogen molecule. Insertion of isocyanide **178** to the formed intermediate **181** gave the three-membered ring intermediate **182**. The carbodiimide intermediate **183** was formed via reductive elimination of intermediate **182**. Finally, intermolecular cyclization of intermediate **184** resulted in the formation of the benzoxazine derivatives **179a–n,** as illustrated in Scheme 69 [56].



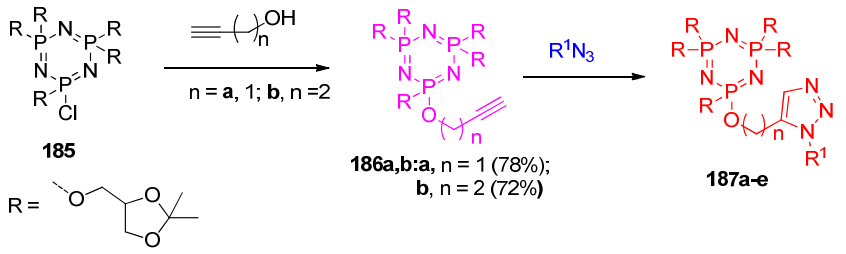
Compound 179	R^1	R^2	R^3	Yield (%)
a	H	*t*-Bu	*t*-Bu	84
b	5-Me	*t*-Bu	*t*-Bu	81
c	4-Cl	*t*-Bu	*c*-C_6H_{11}	80
d	H	*t*-Bu	Ph	70
e	H	*t*-Bu	4-MeC_6H_4	78
f	4-Cl	*t*-Bu	Ph	69
g	H	*t*-Bu	4-BrC_6H_4	62
h	5-Me	*t*-Bu	*c*-C_6H_{11}	82
i	H	*t*-Bu	$PhCH_2$	78
j	4-Cl	*t*-Bu	*t*-Bu	77
k	H	$PhCH_2$	*t*-Bu	78
l	4-Cl	*t*-Bu	1-adamantyl	75
m	H	Ph	*t*-Bu	59
n	H	*t*-Bu	2-IC_6H_4	0

Scheme 68. Synthesis of 4-triazolylbenzoxazoline derivatives. *Reagents and conditions*: (a) CH_2Cl_2; (b) R^3NC **178**, $Pd(PPh_3)_4$, THF, 60 °C.



Scheme 69. A plausible mechanism for the formation of oxazine derivatives **179a–n**.

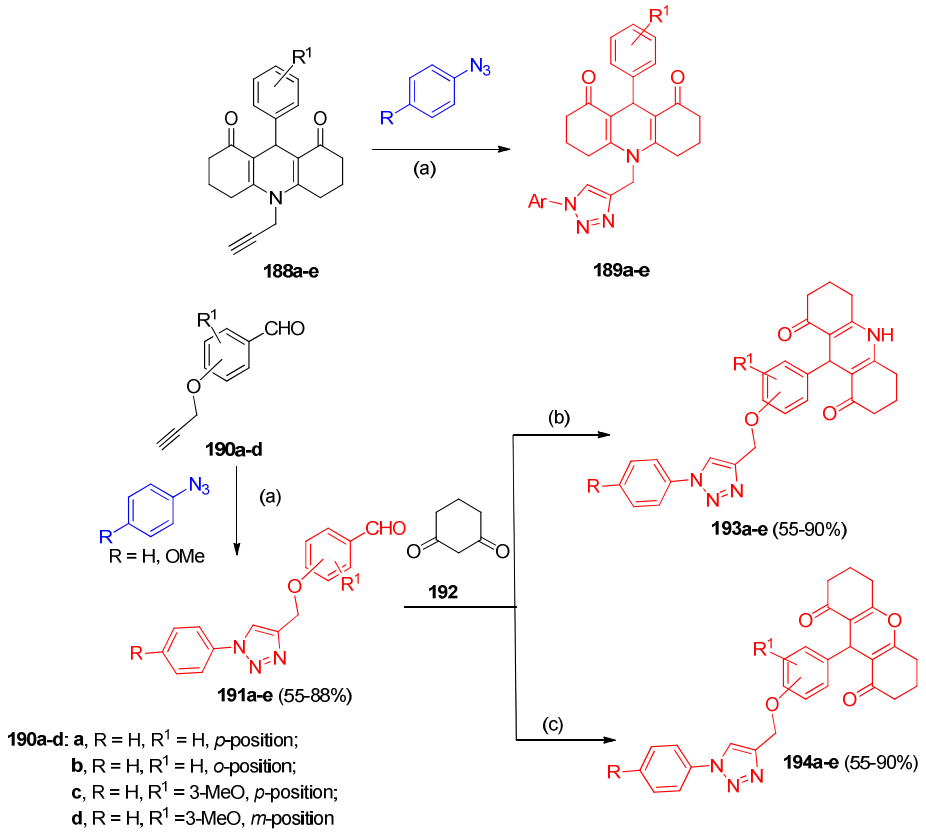
Regioselective syntheses of functionalized cyclotriphosphazenes linked via 1,2,3-triazole **187a–e**. Firstly, 1,3,3,5,5-penta[1-(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]-1-chlorocyclotri phosphazene (**185**) reacted with 2-propyn-1-ol and 3-butyn-1-ol in the presence of NaH to give the alkynyl derivatives **186a,b**. That was followed by the cycloaddition click reaction with phenyl azide, azido acetic acid *tert*-butyl ester or diethyl (4-azidobutyl) phosphonate at 20 °C in the presence of Cu(I) (Scheme 70) [57].



187a-e: **a**, R^1 = Ph, n= 1 (64%); **b**, R^1 =$CH_2CO_2Bu^t$, n = 1 (58%);
c, R^1 = $(CH_2)_4PO(OEt)$ (38%); **d**, R^1 =$CH_2CO_2Bu^t$, n = 2 (51%);
e, n = 2, R^1 = $(CH_2)_4PO(OEt)$ (47%).

Scheme 70. Synthesis of 1,2,3-triazoles **187a**–**e**. *Reagents and conditions*: (i) THF, NaH, 0 °C stirring, then 20 °C, 1 h; (ii) $CuSO_4{\cdot}5H_2O$ (0.06 mmol, 20 mol%) of sodium ascorbate (0.12 mmol, 20 mol%).

Another regioselective 1,3-dipolar cycloaddition reaction was established between *N*-propargyl-substituted-1,8-dioxodecahydroacridines **188a**–**d** with aromatic azides in the presence of $CuSO_4.5H_2O$/ascorbic acid as catalyst (Click reaction) in a 2:1 mixture of CH_2Cl_2:H_2O at room temperature gave 1,2,3-triazole-dioxodecahydroacridine hybrids **189a**–**e** in high yields (70–86%). Furthermore, the click reaction was subjected to propargyloxy-benzaldehydes **190a**–**d** to give 1,4-disubstituted 1,2,3-triazolealdehydes **191a**–**e** in 55–88% yields (Scheme 71). The application of the Hantzsch route on the corresponding 1,2,3-triazolealdehydes **191a**–**e** with 1,3-cyclohexanedione **192** produced 1,4-disubstituted 1,2,3-triazole-*O*-acridinedione **193a**–**e** (55–90% yields). Treatment of 1,2,3-triazolealdehydes **191a**–**e** with two molecules of 1,3-cyclohexanedione in triethylamine and acetic acid gave the corresponding 1,2,3-triazole-*O*-xanthenediones **194a**–**e** in 67–91% yields (Scheme 71) [58].



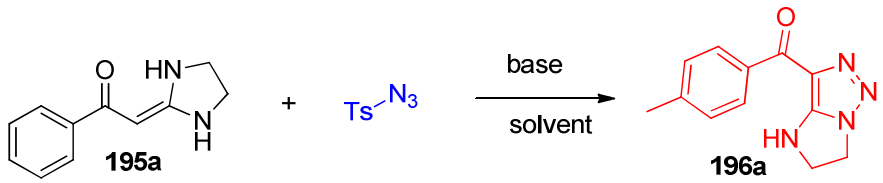
190a-d: **a**, R = H, R^1 = H, *p*-position;
b, R = H, R^1 = H, *o*-position;
c, R = H, R^1 = 3-MeO, *p*-position;
d, R = H, R^1 =3-MeO, *m*-position

Scheme 71. Regioselective synthesis of 1,2,3-triazoles **193a**–**e** and **194a**–**e**. *Reagents and conditions*: (a) $CuSO_4{\cdot}5H_2O$, sodium ascorbate, DCM:H_2O (1:1), 12 h; (b) $AcONH_4$, Et_3N, EtOH, 12 h; (c) Et_3N, AcOH, 12 h.

Annulation reactions between *gem*-diamino enaminones **195** and **197** (ketene aminals) and tosyl azide furnished *N*-heterocycle fused **196a–q** and 5-amino side-chain **198a–g** functionalized 1,2,3-triazoles under transition metal-free conditions, using $NaHCO_3$ as a catalyst to promote the reaction (Schemes 72–74). The reaction was screened to optimize the reaction conditions. Firstly, the reaction was performed using different solvents, such as water, DMSO, DMF, toluene, and MeCN; it was observed that DMSO is the solvent of choice. Additionally, the reaction was performed under different basic conditions using NaOH, ^{t}BuONa, $NaHCO_3$, and DBACO; it was found that using $NaHCO_3$ is favorable for obtaining high yields (Scheme 72) [58].

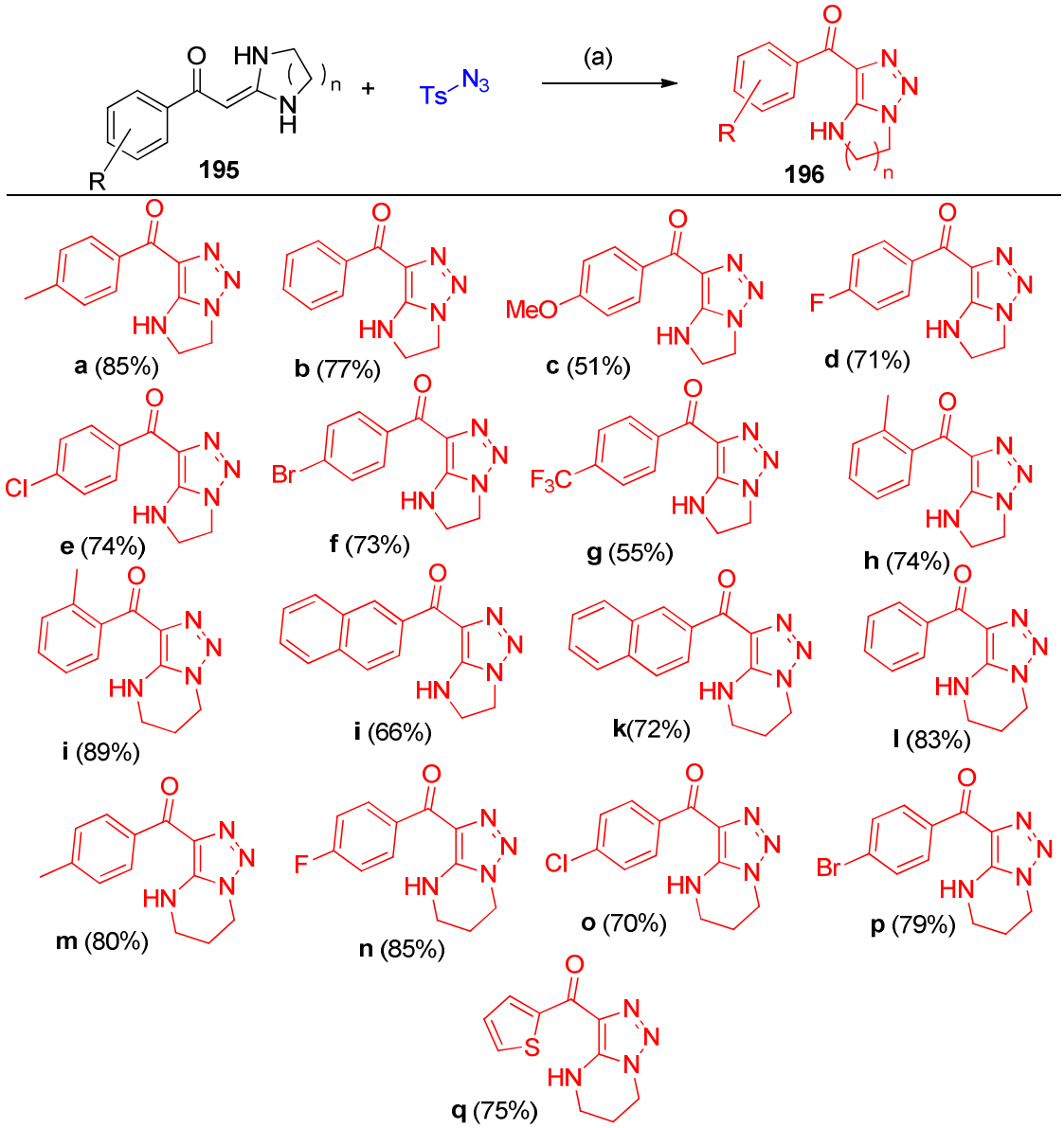
1,2-Diacetylenic benzenes **199** were cyclized with sodium azide (NaN_3) furnished the corresponding [1,2,3]triazolo[5,1-*a*]isoquinolines **201**, but with low regioselectivity for substrates bearing two different alkyne substituents ($R^1 \neq R^2$) [59–61]. Additionally, the same triazoloisoquinolines **201** were obtained via annulation of acetylenes with (2-halo)phenyl-1,2,3-triazoles **200** under transition-metal catalyzed conditions [62–65]. On the other hand, the annulation of 2-azido-3-(2-iodophenyl)acrylates **202** to the corresponding triazolo-isoquinolines **203** was achieved using copper chloride as a transition metal catalyst in these heterocyclization [66,67] (Scheme 75).

Recently, Wu et al. [68] reported that $AlCl_3$ syntheses of triazoloisoquinolines via three-component Henry reaction–triazole formation–intramolecular 6-*endo*-dig cyclization were successfully achieved. Upon reacting 2-(phenylethynyl)-benzaldehyde **204a**, nitromethane, and sodium azide in the presence of Lewis acid in DMF at 100 °C, a mixture of [1,2,3]triazolo[5,1-*a*]isoquinoline **205a** and isoquinoline **206** was obtained. However, triazole **207** was obtained when an excess of $AlCl_3$ was used. Among these studies, it was found that $Sc(CF_3SO_3)_3$ and $AlCl_3$ were the preferable Lewis acids to promote the formation of triazoloisoquinolones, as shown in Scheme 76.

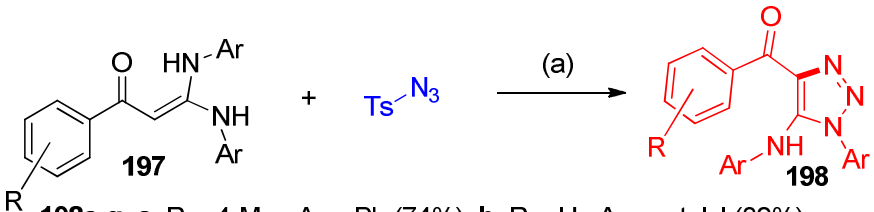


Entry	Base	Solvent	T (°C)	Yield (%)
1	TMEDA	H_2O	reflux	38
2	TMEDA	DMF	120	42
3	TMEDA	DMSO	120	44
4	TMEDA	MeCN	Reflux	39
5	TMEDA	Toluene	reflux	20
6	NaOH	DMSO	120	41
7	^{t}BuONa	DMSO	120	63
8	$NaHCO_3$	DMSO	120	74
9	DABCO	DMSO	120	55
10	$NaHCO_3$	DMSO	120	77
11	$NaHCO_3$	DMSO	120	59
12	$NaHCO_3$	DMSO	120	85
13	$NaHCO_3$	DMSO	120	66
14	$NaHCO_3$	DMSO	130	78
15	$NaHCO_3$	DMSO	110	71
16	$NaHCO_3$	DMSO	100	66

Scheme 72. Screening of the optimized reaction conditions for the reaction of enaminones and tosyl azide.

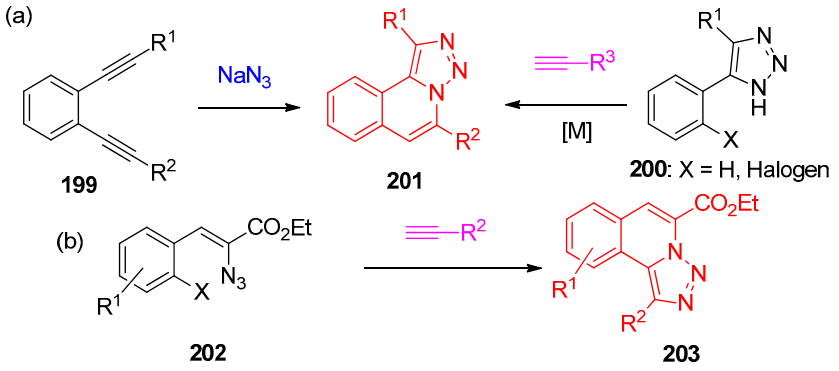


Scheme 73. Syntheses of fused imidazotriazoles **197a–q**. *Reagent and conditions*: (a) $NaHCO_3$, DMSO, 120 °C, 12 h.



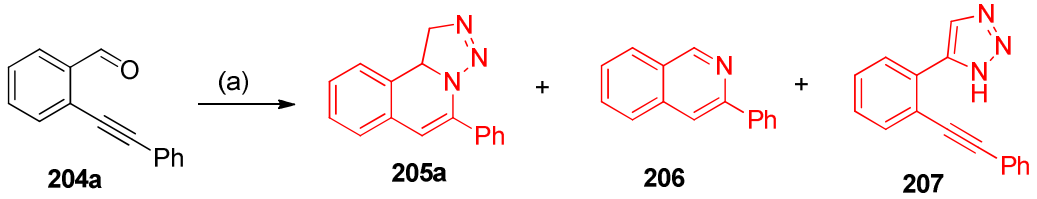
198a-g: **a**, R = 4-Me , Ar = Ph (74%); **b**, R = H , Ar = *p*-tolyl (80%);
c, R = H, Ar = 3-MeC_6H_4 (62%); **d**, R = h, Ar = 4-$MeOC_6H_4$ (69%);
e, R = H, Ar = 4-ClC_6H_4 (75%); **f**, R = , Ar = 4-BrC_6H_4 (66%);
g, R = 4-Me, Ar = 4-$NO_2C_6H_4$ (45%).

Scheme 74. Syntheses of 5-amino-1,2,3-triazoles **198a–g**. *Reagent and conditions*: (a) $NaHCO_3$, DMSO, 120 °C.



203a-t: X = **I**, R^1 = H, (**a**, R^2 = Ph (75%); **b**, R^2 = 4-$MeOC_6H_4$ (60%);
c, R^2 = 4-MeC_6H_4 (42%); **d**, R^2 = 4-BrC_6H_4 (32%); **e**, R^2 = 4-ClC_6H_4 (29%);
f, R^2 = 4-$MeCOC_6H_4$ (59%); **g**, R^2 = ^{n}Pr (68%); **h**, R^2 = ^{n}Pn (42%);
i, R^2 = $HOCH_2$ (63%); **j**, R^2 = $HO(CH_3)CH$ (71%);
k, R^2 = $HO(CH_3)_2C$ (75%); **l**, R^2 = $THPOCH_2$ (65%);
m, R^2 = HO(Ph)CH (93%)).
n, X = Br, R^1 = H, R^2 = HO(Ph)CH (28%).
X = **I**, R^1 = Me, (**o**, R^2 = Ph (58%); **p**, R^2 = $THPOCH_2$ (57%); **q**, R^2 = HO(Ph)CH (90%).
X = **I**, R^1 = 5-MeO, (**r**, R^2 = Ph (16%); **s**, R^2 = $THPOCH_2$ (33%); **t**, R^2 = HO(Ph)CH (61%).

Scheme 75. Synthesis of triazoloisquinolines **203**.

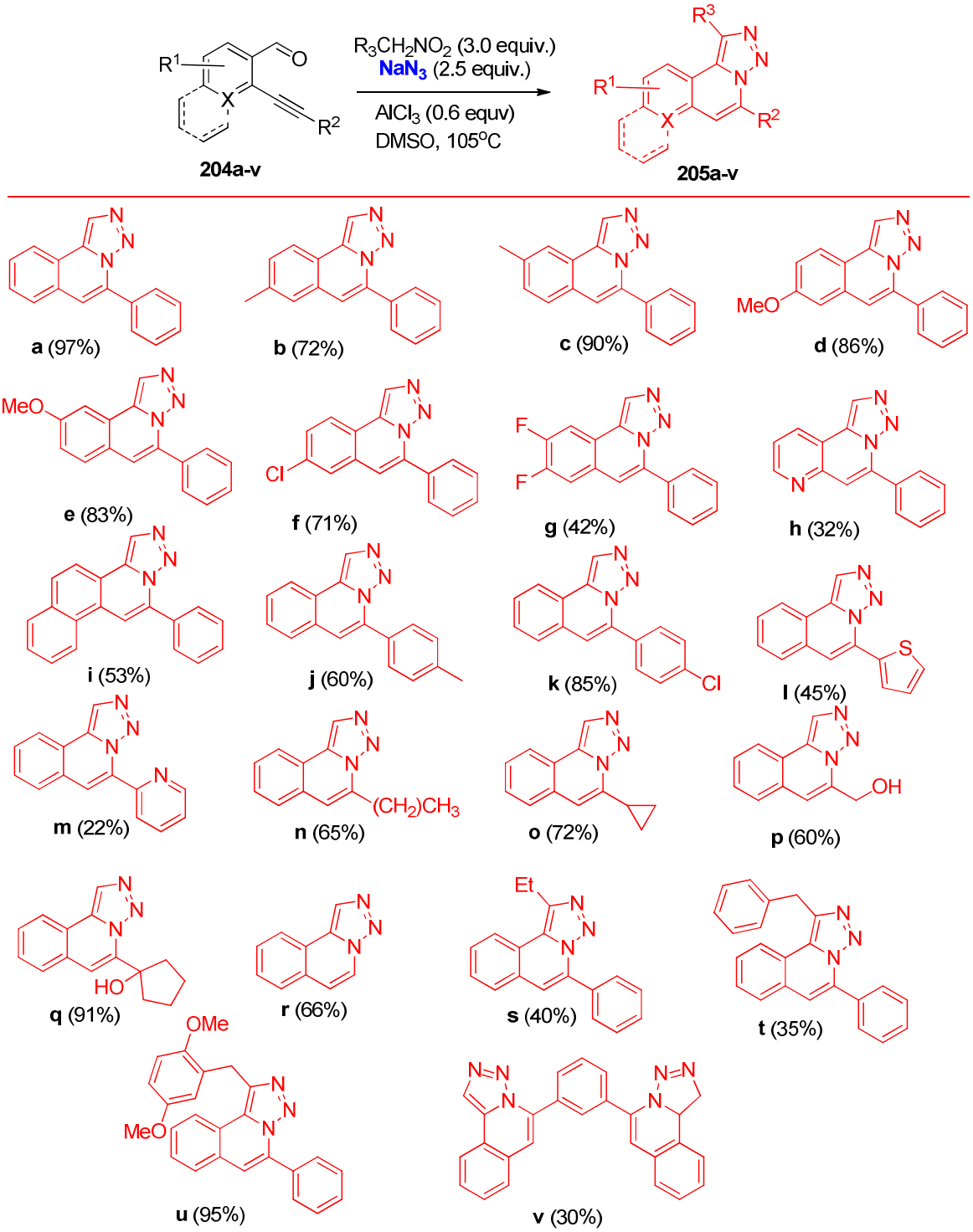


Entry	LA (Equiv.)	Solvent	Temp. (°C)	205a (Yield%)	206 (Yield%)	207 (Yield%)
1	$FeCl_3$ (0.1)	DMF	100	87	13	0
2	$Sc(CF_3SO_3)_3$ (0.1)	DMF	100	90	10	0
3	$ZnCl_2$ (0.1)	DMF	100	83	17	0
4	$Cu(OAc)_2$ (0.1)	DMF	100	87	13	0
5	$AlCl_3$ (0.1)	DMF	100	91	9	0
6	$AlCl_3$ (0.05)	DMF	100	87	13	0
7	$AlCl_3$ (0.2)	DMF	100	92	8	0
8	$AlCl_3$ (0.5)	DMF	100	94	6	0
9	$AlCl_3$ (0.6)	DMF	100	95	5	0
10	$AlCl_3$ (0.8)	DMF	100	42	5	53
11	$AlCl_3$ (1.0)	DMF	100	3	6	91
12	$AlCl_3$ (0.6)	DMSO	100	90	-	-
13	$AlCl_3$ (0.6)	toluene	100	-	-	-
14	$AlCl_3$ (0.6)	1,4-dioxane	100	-	-	-
15	$AlCl_3$ (0.6)	$HO(CH_2)_2OH$	100	-	-	-
16	$AlCl_3$ (0.6)	DMSO	90	87	-	-
17	$AlCl_3$ (0.6)	DMSO	105	97	-	-
18	$AlCl_3$ (0.6)	DMSO	110	86	-	-

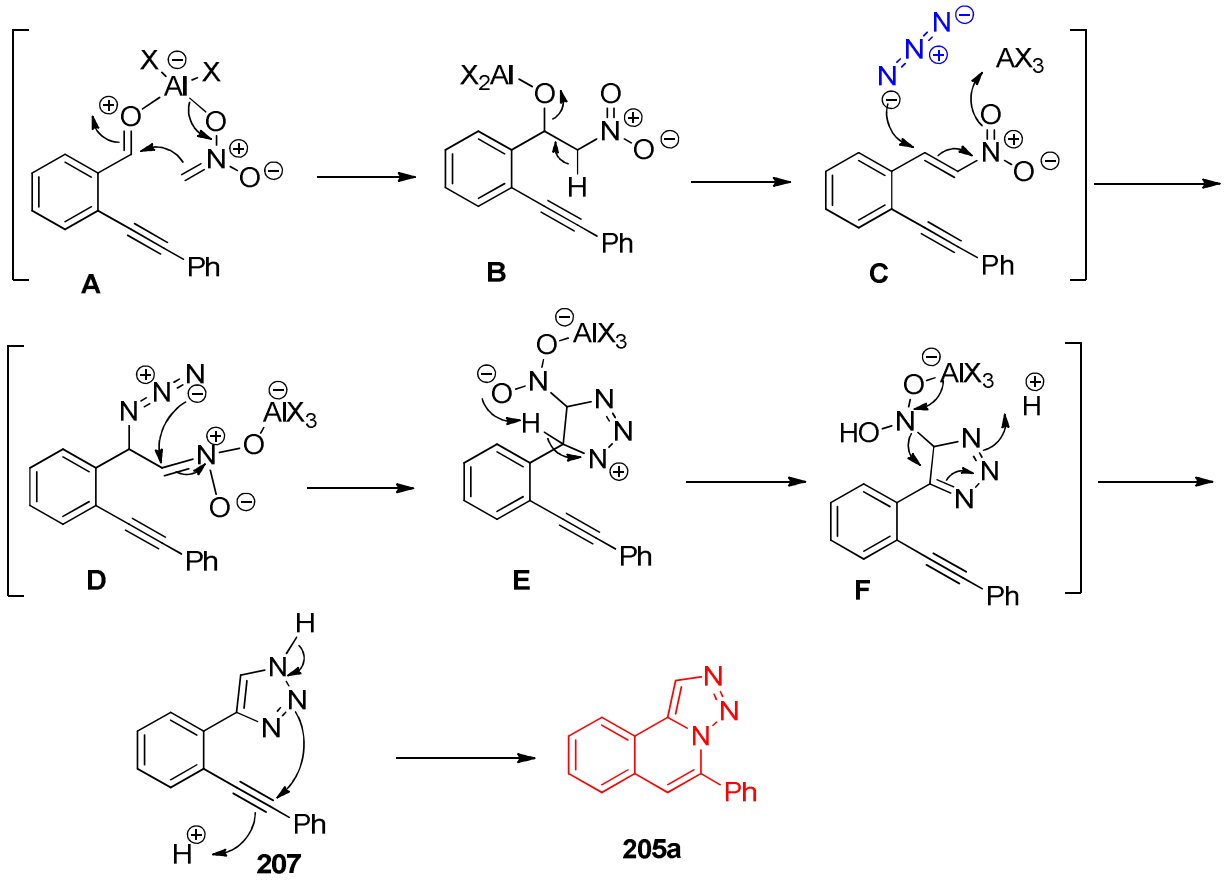
Scheme 76. Synthesis of triazoloisoquinoline **205a**. *Reagent and conditions*: (a) CH_3NO_2 (3.0 equiv.), NaN_3 (2.5 equiv.), Lewis acid.

The type of solvent and Lewis acid affected the yield and the regioselectivity of the product, as in **205a**. Additionally, the substituted group affected the yield of the target product in which the presence of electron-donating groups gave higher yields than electron-withdrawing groups. On replacing the phenyl ring with pyridine ring (an electron-

deficient) and naphthalene (π-electron delocalized group), the triazoloisoquinolones **205h** and **205i** were synthesized in moderate yields of 32 and 53%, respectively, as shown in Scheme 77 [68].



Scheme 77. Substituent affected the yields of the synthesized triazoloquinolines **205a–v**. The plausible mechanism for the formation of compound **205a** is illustrated in Scheme 78 [68].

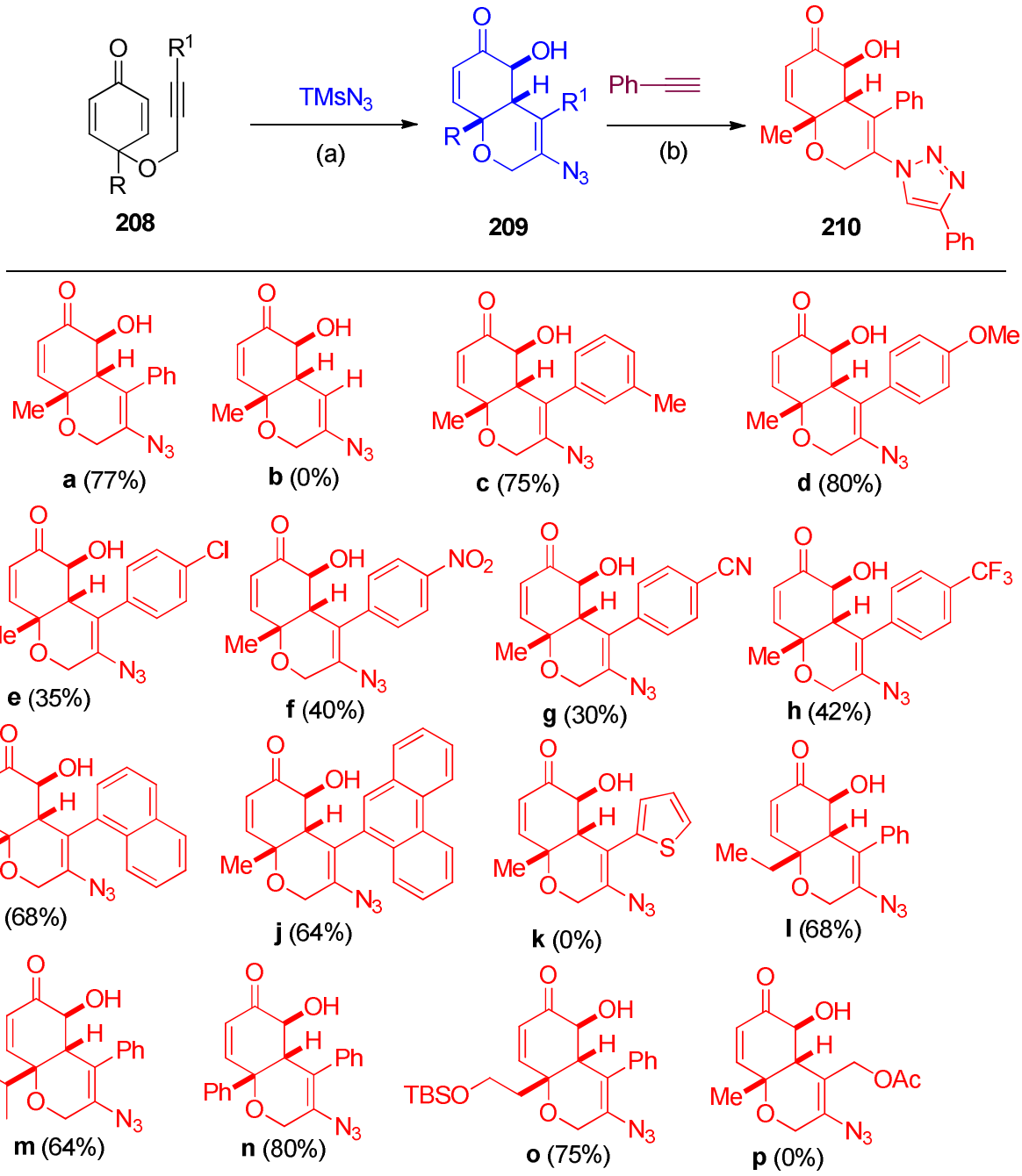


Scheme 78. Mechanistic equations for the formation of 5-phenyl-[1,2,3]triazolo[5,1-*a*]isoquinoline **205a**.

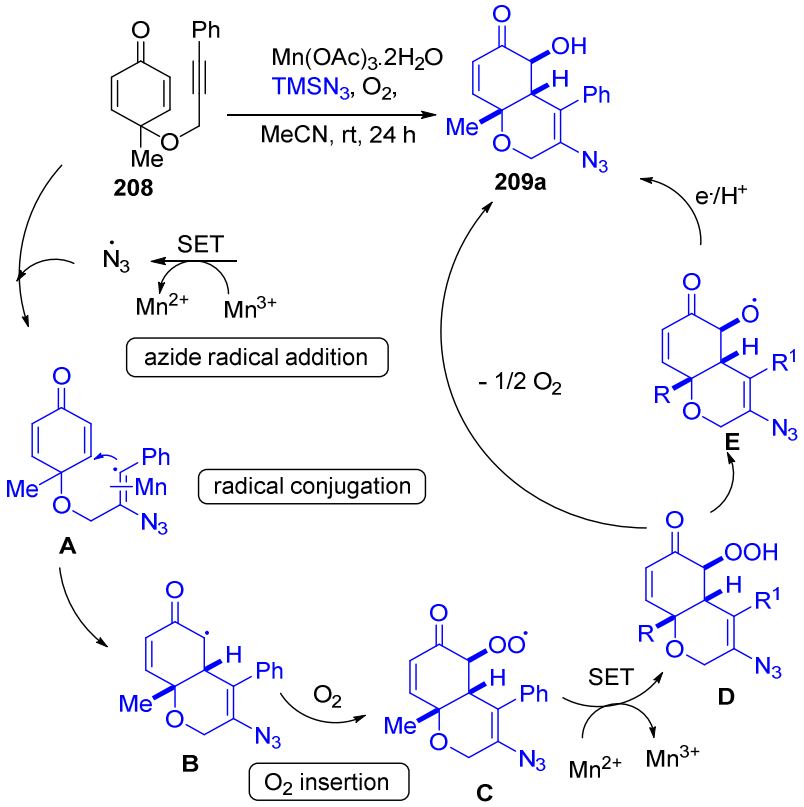
$Mn(OAc)_3 \cdot 2H_2O$ were used as catalysts in the syntheses of bicyclic azido alcohol **208** via azide radical addition/cyclization/oxygen insertion reaction of alkyne-tethered cyclohexadienones **208** with $TMSN_3$ under mild conditions. The azido alcohol **209a** was led to react with phenylacetylene via Cu-catalyzed click reaction 1,2,3-triazole **210** was obtained in 84% yield (Scheme 79) [69]. The plausible mechanism for forming the azido alcohol **209a** is shown in Scheme 80. It was described due to azide radical addition, then radical conjugation, and lastly, oxygen insertion process through the formation of the intermediates **A**–**E** [69].

Intramolecular azide–alkene cycloaddition of *N*-bromoalkyl indole and pyrrole derivatives **211a**–**v** resulted in the formation of polycyclic fused 1,2,3-triazoles **212a**–**v** [70]. As a model example, the reaction progress was investigated to determine the optimized conditions via the reaction of **211a** (0.5 mmol) with sodium azide (0.6 mmol) in ethanol at room temperature for 20 h and under catalyst-free conditions. The reaction proceeded smoothly to give (6,7-dihydro-5H-[1,2,3]triazolo[5′,1′:3,4][1,4]diazepino[1,2-*a*]indol-1-yl)(phenyl)-methanone **212a** in 64% yield (Scheme 81). When the reaction was first applied to the seven-membered ring annulated indole by varying substituents (R^1) on the benzoyl group. It was observed that electron-donating groups, such as amine, methoxy, hydroxyl, and isobutyl, under the optimal reaction conditions, gave the desired products in 65–91% yields (Scheme 82). Similarly, halogen substituents were also produced the appropriate products (**212b**–**d**, **212i**, and **212m**) in good to high yields (73–81%). However, highly electron-poor substituents, such as CF_3, showed lower efficiency (**212k**, 69% yield), and the reaction of 3,5-ditrifluoromethyl acetophenone failed to give the corresponding product. Additionally, the investigation was extended to prepare six-membered ring annulated indoles by using *N*-bromoethyl substituent on the indole under the optimized conditions. It was shown that electron-donating and electron-withdrawing groups produced the corresponding fused polycyclic *N*-heterocycles (**212o**–**t**) in slightly lower yields (72–81%). Alkyl groups on the

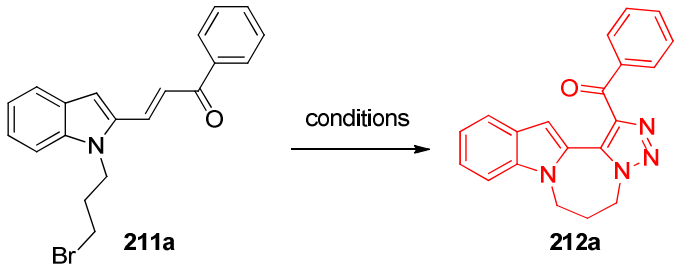
ketone derivatives led to the desired products **212u** and **212v** in good yields (77% and 72%, respectively) [70].



Scheme 79. Synthesis of 1,2,3-triazoles **210a–p**. *Reagents and conditions*: (a) $Mn(OAc)_3 \cdot 2H_2O$ (50 mol%), $TMSN_3$ (2.1 mmol, 5 eq.), CH_3CN (2 mL), O_2 balloon, room temperature, 6–24 h. (b) $CuSO_4 \cdot H_2O$, Sodium ascorbate, ^tBuOH:H_2O (1:1), room temperature, 24 h.

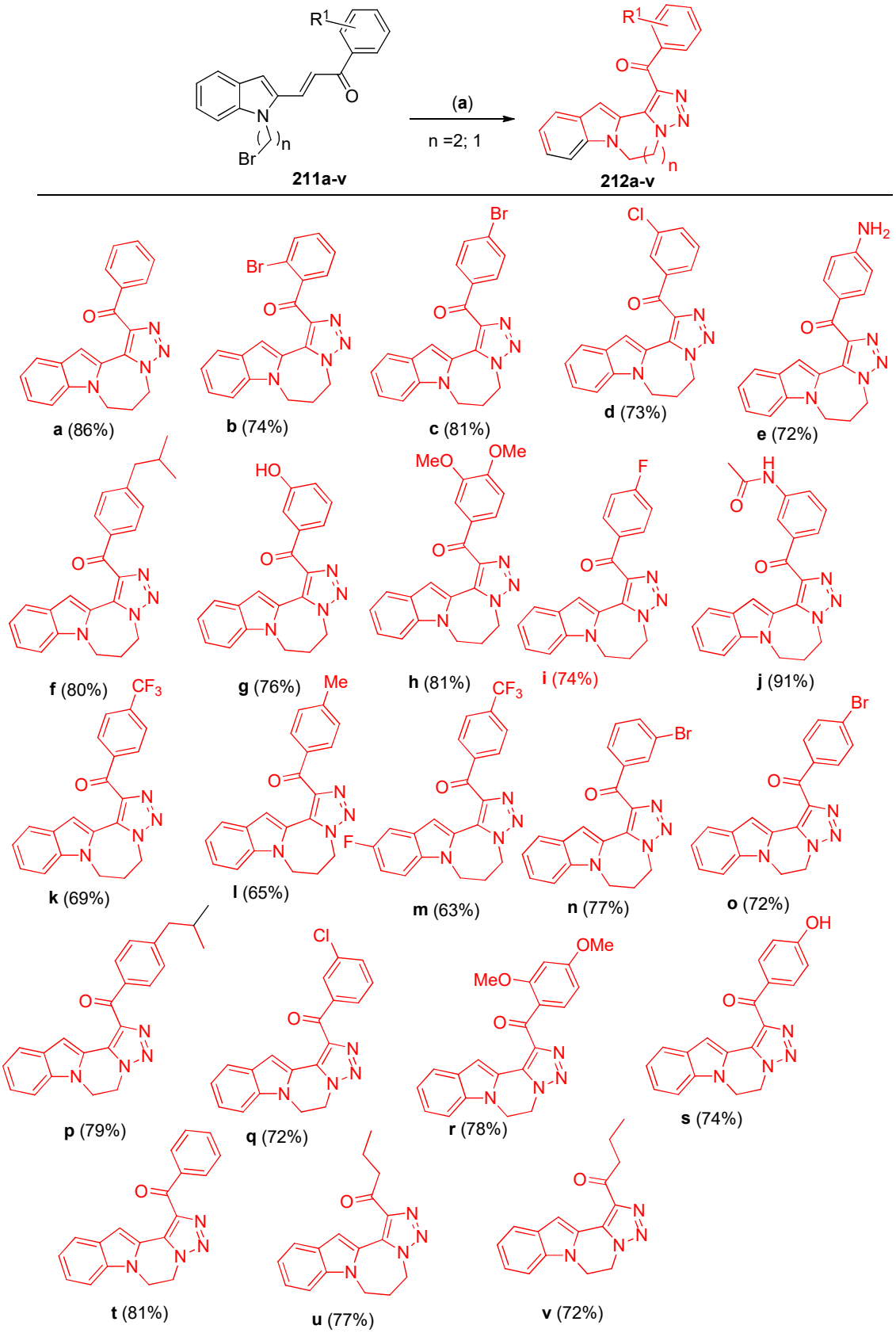


Scheme 80. Proposed mechanism for the formation of the azido alcohol **188a**.



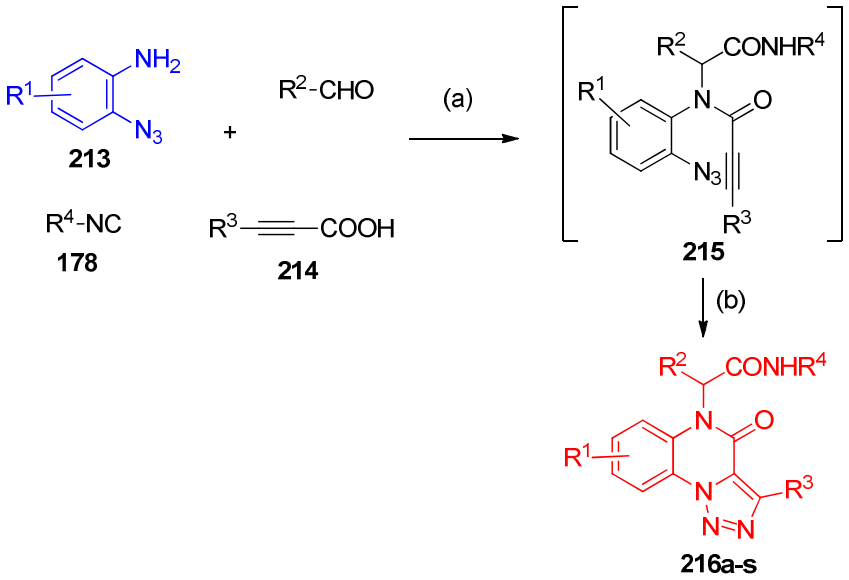
Entry	Catalyst	Solvent	Yield (%)
1	None	Ethanol	64
2	None	DMF	71
3	Cu(OTf)$_2$ (5 mol%)	DMF	76
4	Sc(OTf)3 (5 mol%)	DMF	78
5	AgOAc (5 mol%)	DMF	48
6	CuI (5 mol%)	DMF	0
7	KO-*t*-Bu (50 mol%)	DMF	0
8	None	Water	Trace
9	None	ACN	-
10	None	DCM	-
11	None	Water:Acetone (1:1)	86
12	None	Water:Acetone	32
13	None	Water:Acetone	15

Scheme 81. Optimization of reaction conditions in the synthesis of 1,2,3-triazolo-diazapine **134a**.



Scheme 82. Synthesis 1,2,3-triazolo-diazapines **212a**–**j** and 1,2,3-triazolopyrazines **212k**–**v**. *Reagents and conditions*: (a) NaN_3 (0.6 mmol), solvent (5 mL), room temperature 18–20 h.

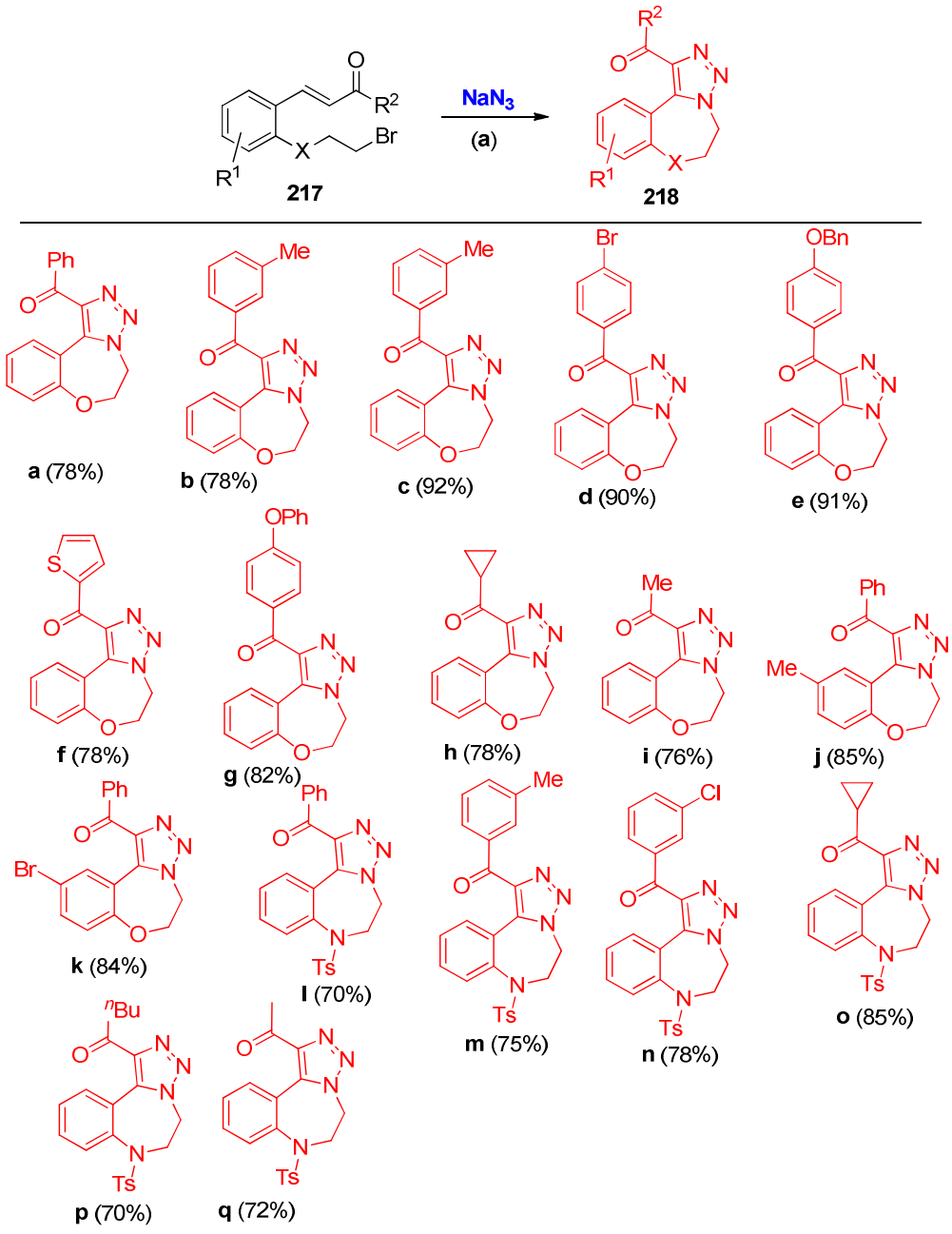
Ugi four-component reaction/alkyne–azide cycloaddition reaction was applied to synthesize triazoloquinoxalines. Reacting 2-azidobenzenamines **213**, isocyanide **178**, aldehydes, and propiolic acids **214** afforded [1,2,3]triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones **216a–s** via the formation of Ugi adducts **215**. The cyclization occurs via an alkyne–azide cycloaddition reaction (Scheme 83) [71].



Entry	Compd. 216	R¹	R²	R³	R⁴	Yield (%)
1	**a**	H	4-ClC$_6$H$_4$	Ph	*t*-Bu	85
2	**b**	H	Ph	Ph	*c*-C$_6$H$_{11}$	75
3	**c**	H	2-ClC$_6$H$_4$	Ph	*t*-Bu	70
4	**d**	H	4-MeC$_6$H$_4$	Ph	*t*-Bu	72
5	**e**	H	4-O$_2$NC$_6$H$_4$	Ph	*t*-Bu	0
6	**f**	H	4-ClC$_6$H$_4$	Ph	*c*-C$_6$H$_{11}$	83
7	**g**	H	4-ClC$_6$H$_4$	Me	*t*-Bu	92
8	**h**	H	*n*-Pr	Ph	*t*-Bu	0
9	**i**	H	4-MeC$_6$H$_4$	Ph	*c*-C$_6$H$_{11}$	73
10	**j**	4-Me	4-ClC$_6$H$_4$	Ph	*t*-Bu	90
11	**k**	4-Cl	4-ClC$_6$H$_4$	Ph	*t*-Bu	77
12	**l**	4-Me	4-MeC$_6$H$_4$	Me	*c*-C$_6$H$_{11}$	78
13	**m**	4-Cl	2-ClC$_6$H$_4$	Me	*c*-C$_6$H$_{11}$	72
14	**n**	4-Br	4-ClC$_6$H$_4$	Ph	*t*-Bu	75
15	**o**	4-Br	4-MeC$_6$H$_4$	Me	*t*-Bu	75
16	**p**	4,6-Me$_2$	4-MeC$_6$H$_4$	Ph	*t*-Bu	50
17	**q**	4-Cl	2-ClC$_6$H$_4$	Ph	*t*-Bu	68
18	**r**	4-Br	2-furyl	Ph	*t*-Bu	71
19	**s**	4-Br	2-thiophenyl	Ph	*t*-Bu	72

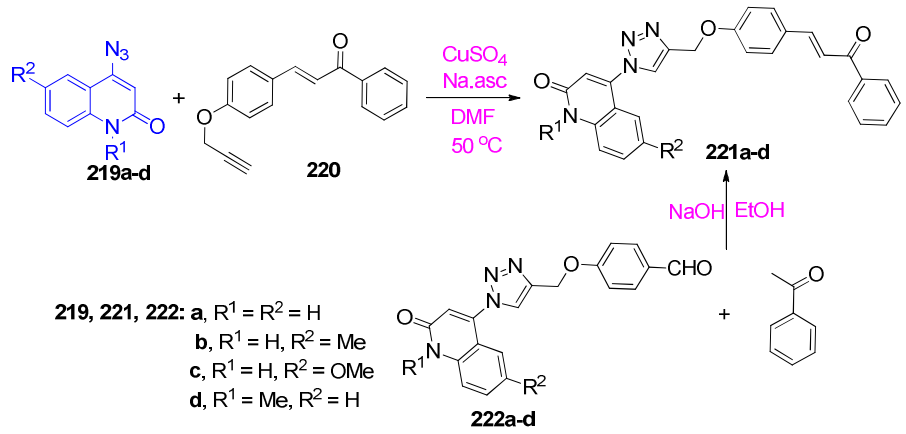
Scheme 83. Synthesis of triazoloisoquinoxalines **216a–s**. *Reagents and conditions*: (a) MeOH, r.t., 12–24 h; (b) DMF, 90 °C.

Gangaprasad et al. [72] reported the syntheses of 1,2,3-triazole fused benzooxazepine and benzodiazepine analogs **218a–q** via one-pot azide substitution and intramolecular azide-olefin **217** oxidative cycloaddition sequence under metal-free conditions (Scheme 84) [72].



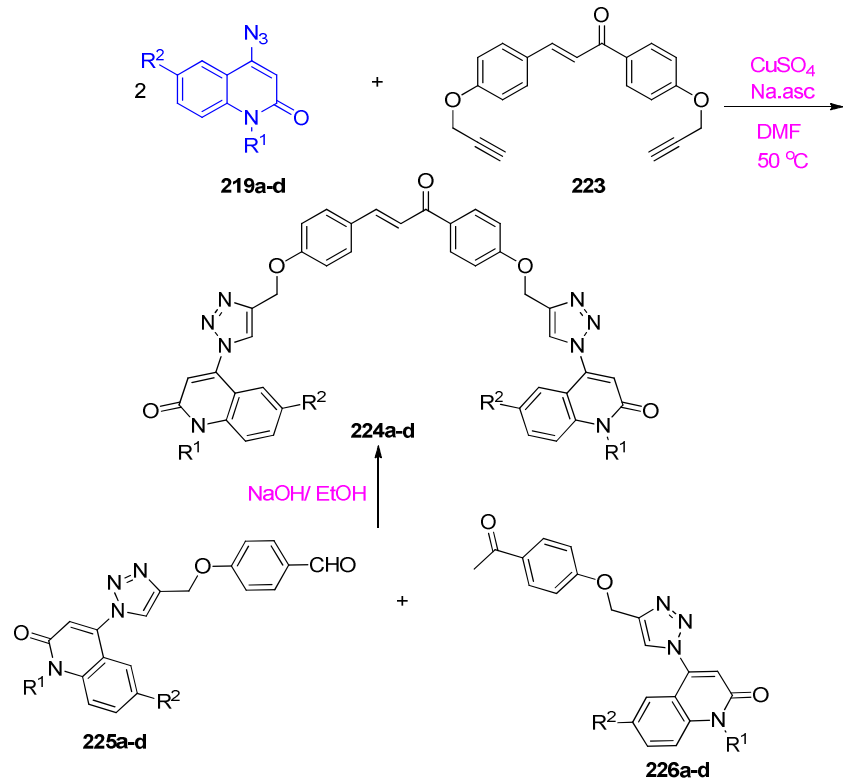
Scheme 84. Synthesis of 1,2,3-triazole fused benzooxazepine and benzodiazepines analogs **218a–q**. *Reagents and conditions*: (a) DMF, 90 °C, 6 h.

Aly et al. [73] reported that copper(I)-catalyzed azide-alkyne [3+2] dipolar cycloaddition reaction (CuAAC) between **219a–d** and **220** to afford the target hybrids **221a–d**, in good to excellent yields depending on the concentration of catalyst (Scheme 85). Additionally, the target compounds **221a–d** were synthesized, in very good yields, via the reaction of 4-{[1-(2-oxo-1,2-dihydroquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl]methoxy}benzaldehydes **222a–d** [73] with acetophenone (Scheme 85).



Scheme 85. Reaction of 4-azido-2-quinolinones **219a–d** with chalcone **220**.

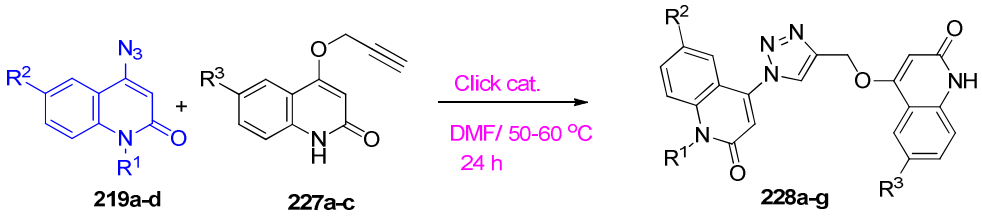
Similarly, doubly derivatized chalcones were prepared by the interaction between (*E*)-1,3-bis[4-(prop-2-yn-1-yloxy)phenyl]prop-2-en-1-one (**223**) and 4-azidoquinolin-2(1*H*)-ones **219a–d** in the presence of CuAAC to obtain 1,2,3-triazoles **224a–d** [73]. The 1,2,3-triazoles **224a–d** were also synthesized by the reactions of aldehydes **225a–d** with 4-{4-[(4-acetylphenoxy)-methyl]-1*H*-1,2,3-triazol-1-yl}-quinolin-2(1*H*)-ones **226a–d** in basic medium, as shown in Scheme 86.



Scheme 86. Synthesis of compounds **224a–d**.

Aly et al. [74] also reported that the synthesis of hybrids **228a–g** through click chemistry which is a powerful tool for a quick, highly selective, and reliable access to a reaction product with high yields. The [3+2] cycloadditions of 4-azidoquinolin-2(1*H*)-ones **219a–d** with 4-(prop-2-yn-1-yloxy)quinolin-2(1*H*)-ones **227a–c**, gave the corresponding 4-((1-(2-oxo-1,2-dihydroquinolin-4-yl)-1*H*-1,2,3-triazol-4-yl)methoxy)quinolin-2(1*H*)-ones **228a–g** (Scheme 87). Compounds **228a–c** were found to be the most active antiapoptotic hy-

brids with significant measurements for the antioxidant parameters (malondialdehyde (MDA), total antioxidant capacity (TAC), and the apoptotic biomarkers (testicular testosterone, tumor necrosis factor (TNFα) and caspase-3) in comparison to the reference. A preliminary mechanistic study was performed in order to improve the antiapoptotic activity through caspase-3 inhibition. A compound assigned as 6-methoxy-4-(4-(((2-oxo-1,2-dihydroquinolin-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)quinolin-2(1*H*)-one (**228c**) was selected as a representative of the most active hybrids in comparison to *N*-acetyl cysteine (NAC). Assay of cytochrome *C* for **228c** revealed a down expression of cytochrome *C* level by about 3.54 fold, comparable to NAC (4.13 fold). In caspases-3,8,9 assays, **228c** was found to exhibit more potency and selectivity toward caspase-3 than other caspases. Testicular histopathological investigation was carried out on all targeted compounds **228a–g,** indicating a significant improvement in spermatogenesis process for compounds **228a–c** if compare with the reference relative to the control [74].

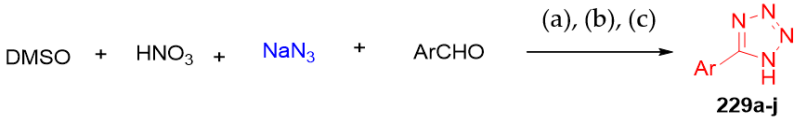


219: a, $R_1 = R_2 = H$; **b,** $R_1 = H$, $R_2 = Me$; **c,** $R_1 = H$, $R_2 = OMe$; **d,** $R_1 = Me$, $R_2 = H$
227: a, $R_3 = H$; **b,** $R_3 = Me$; **c,** $R_3 = OMe$
228: a, $R_1 = R_2 = R_3 = H$; **b,** $R_1 = R_3 = H$, $R_2 = Me$; **c,** $R_1 = R_3 = H$, $R_2 = OMe$; **d,** $R_1 = Me$, $R_2 = R_3 = H$; **e,** $R_1 = R_2 = H$, $R_3 = Me$; **f,** $R_1 = H$, $R_2 = R_3 = Me$; **g,** $R_1 = R_2 = H$, $R_3 = OMe$

Scheme 87. Click reactions between 4-azido-quinolin-2(1*H*)-ones **219a–d** and alkynes **227a–c**.

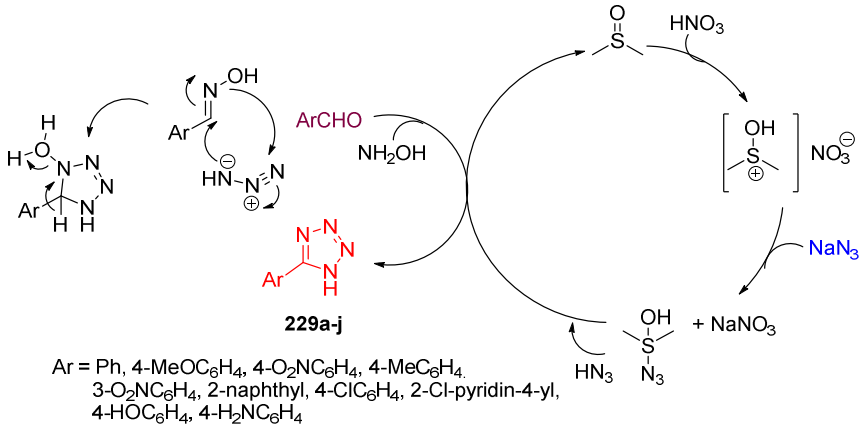
4.6. Synthesis of Tetrazole Ring

One-pot syntheses of 5-substituted 1*H*-tetrazole derivatives **229a–j** [75] were achieved using a dimethyl sulfoxide–nitric acid combination in an aldehyde, hydroxylamine combination hydrochloride, and sodium azide under mild conditions (Scheme 88). The proposed mechanism is illustrated in Scheme 89 [75].



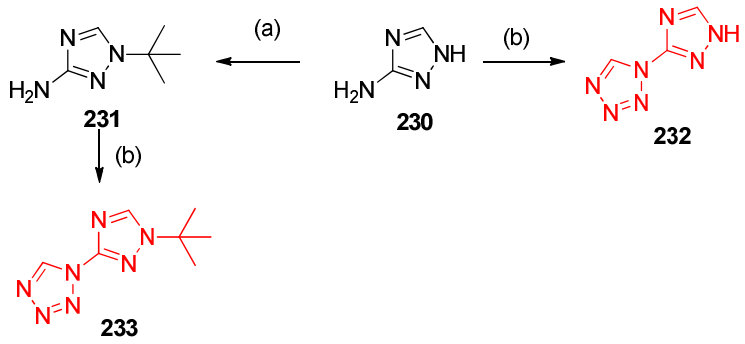
Entry	Ar	Time (h)	Product	Yield (%)
1	Ph	4.5	**a**	94
2	4MeOC$_6$H$_4$	4	**b**	97
3	4-O$_2$NC$_6$H$_4$	3	**c**	95
4	4-MeC$_6$H$_4$	5	**d**	79
5	3-O$_2$NC$_6$H$_4$	3.5	**e**	95
6	2-naphthyl	6	**f**	85
7	4-ClC$_6$H$_4$	3	**g**	95
8	2-Cl-pyridin-4-yl	3	**h**	95
9	4-HOC$_6$H$_4$	4	**i**	89
10	4-H$_2$NC$_6$H$_4$	3.5	**j**	92

Scheme 88. 5-substituted 1*H*-tetrazole derivatives **229a–j**. *Reagents and conditions*: (a) 20 min, 40 °C; (b) NaN_3(10 mmol), 20 min, H_2O, 40 °C; (c) ArCHO (0.05 mmol), $NH_2OH{\cdot}HCl$ (0.05 mmol), DMSO, 40 °C, 3–6 h.



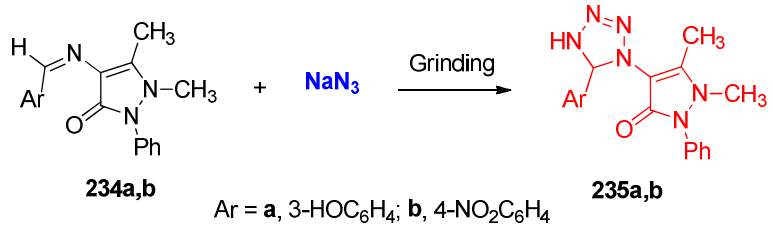
Scheme 89. The proposed mechanism for the formation of tetrazoles **229a–j**.

Heterocyclization of 1,2,4-triazol-3-amine **230** and 3-amino-1-*tert*-butyl-1,2,4-triazole **231** was established via alkylation of 3-amino-1,2,4-triazole **230** using *t*-BuOH-$HClO_4$ with triethyl orthoformate and sodium azide in absolute ethanol. The reaction gave 1-(1,2,4-triazol-3-yl)-1*H*-tetrazole **232** and 1-(1-*tert*-butyl-1,2,4-triazol-3-yl)-1*H*-tetrazole **233**, respectively, as depicted in Scheme 90 [76].



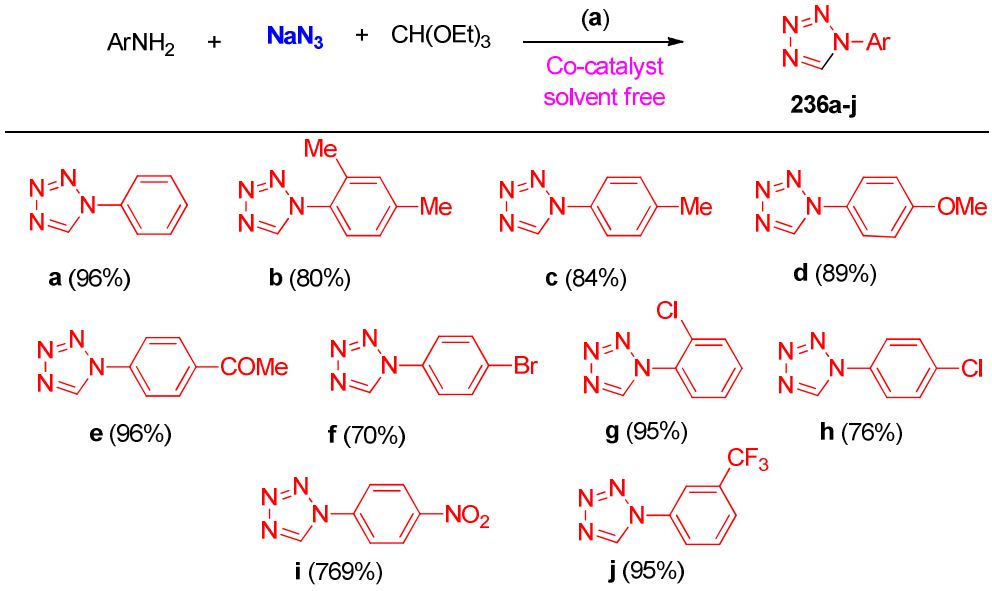
Scheme 90. Formation of 1-(1,2,4-triazol-3-yl)-1*H*-tetrazole **232** and 1-(1-*tert*-butyl-1,2,4-triazol-3-yl)-1*H*-tetrazole **233**. *Reagents and conditions*: (a) *t*-BuOH, $HClO_4$; (b) $HC(OEt)_3$, NaN_3, AcOH.

Grinding a mixture of Schiff bases: 4-(3-hydroxybenzylideneamino)antipyrine and 4-(4-nitrobenzylideneamino)antipyrine **234a,b** with sodium azide (NaN_3) gave the corresponding tetrazoles **235a,b** (Scheme 91) [77].

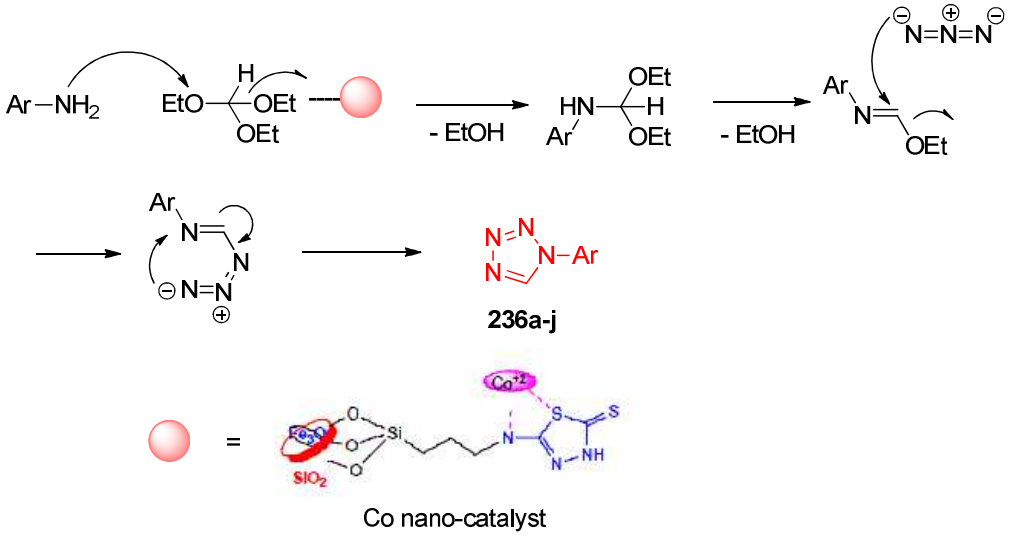


Scheme 91. Synthesis of tetrazoles **235a,b**.

Cobalt nano-particles, a heterogeneous catalyst, catalyzed the synthesis of tetrazoles **236a–j** from a multicomponent reaction of amines, sodium azide, and triethyl orthoformate under solvent-free conditions at 100 °C (Scheme 92). The reaction was screened for the effects of the amount of both catalyst and solvent; it was found that carrying the reaction using 50 mg of the catalyst under solvent-free conditions gave the tetrazole **236a** a 96% yield. The proposed mechanism is illustrated in Scheme 93, which involved condensation between the amine and ethyl orthoformate followed by cycloaddition ([1,3]-dipolar cycloaddition) of azide and imine to give the tetrazole product [78].

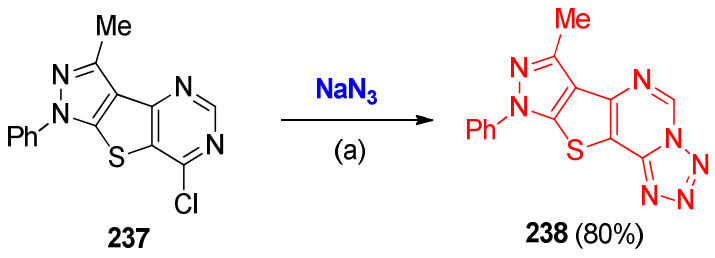


Scheme 92. Cobalt nano-particles, a heterogeneous catalyst, catalyzed the synthesis of tetrazoles **236a**–**j**. *Reagents and conditions*: (a) Co-nano-catalyst, Solvent-free.



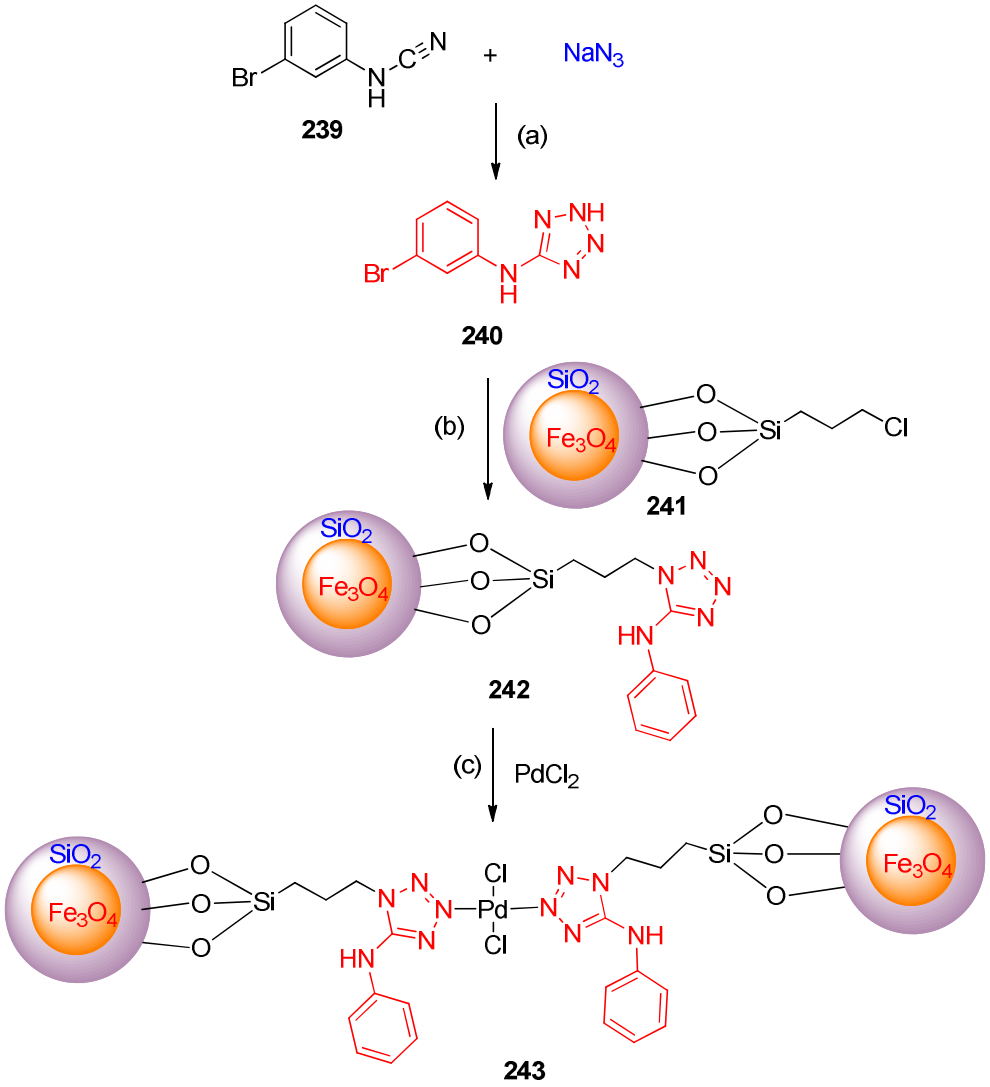
Scheme 93. Proposed mechanism for the formation of tetrazoles **236a**–**j**.

Reaction of the chloropyrimidine (7-chloro-3-methyl-1-phenyl-1*H*-pyrazolo [4′,3′:4,5] thieno[3,2-*d*]pyrimidine) (**237**) with sodium azide in DMF in presence of NH_4Cl gave the tetrazole derivative **238**, which was identified as (7-methyl-9-phenyl-9*H*-pyrazolo-[4′,3′:4,5]thieno[2,3-*e*]tetrazolo[1,5-*c*]pyrimidine) (Scheme 94) [79].



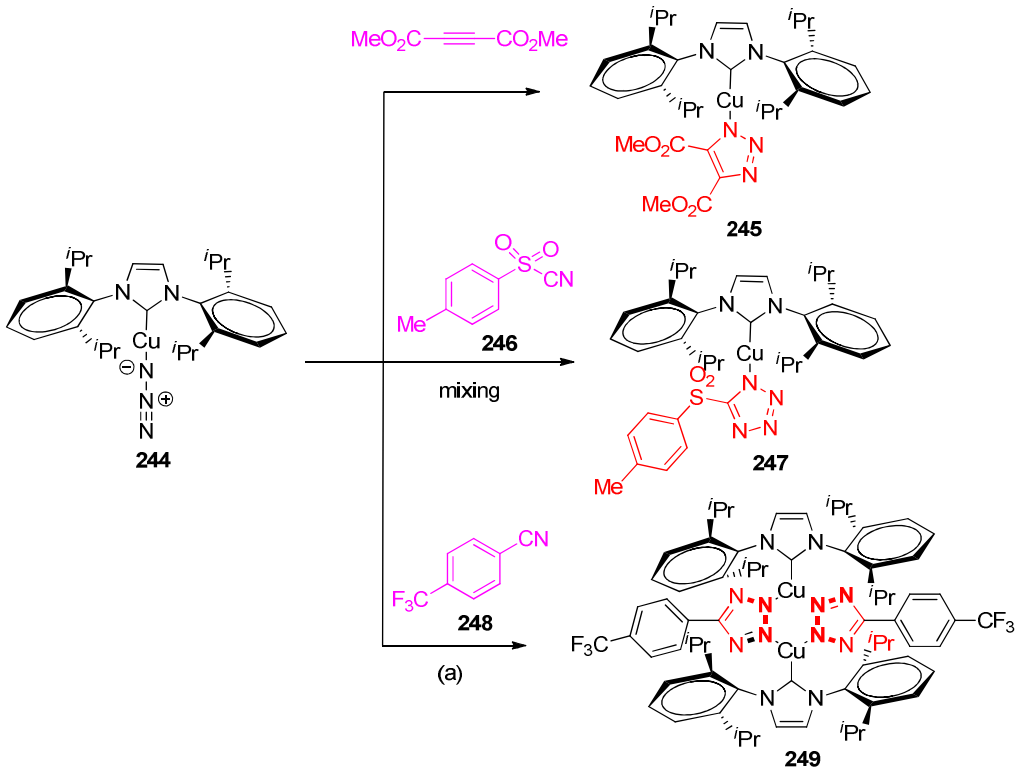
Scheme 94. Synthesis of tetrazole derivative **238**. *Reagents and conditions*: (a) NH_4Cl, DMF.

Ag/Fe_3O_4 nanocomposite catalyzed the synthesis of 5-(3-bromophenyl)amino-1*H*-tetrazole**240** from 3-bromophenyl cyanamide **239** and sodium azide in DMF at 110 °C [78]. Aminotetrazole–palladium (II) complex **243** was prepared via the nucleophilic substitution between 5-(3-bromophenyl)amino-1*H*-tetrazole **240** and Fe_3O_4@SiO_2@$(CH_2)_3$-Cl (**241**), followed by incorporation of the Pd-ions using $PdCl_2.2H_2O$ in EtOH under reflux for 24 h [80] (Scheme 95).



Scheme 95. Synthesis of tetrazole **243**. *Reagents and conditions*: (a) Ag/Fe_3O_4 nanocomposite, DMF, 110 °C; (b) DMF, K_2CO_3; (c) EtOH, reflux, 24 h.

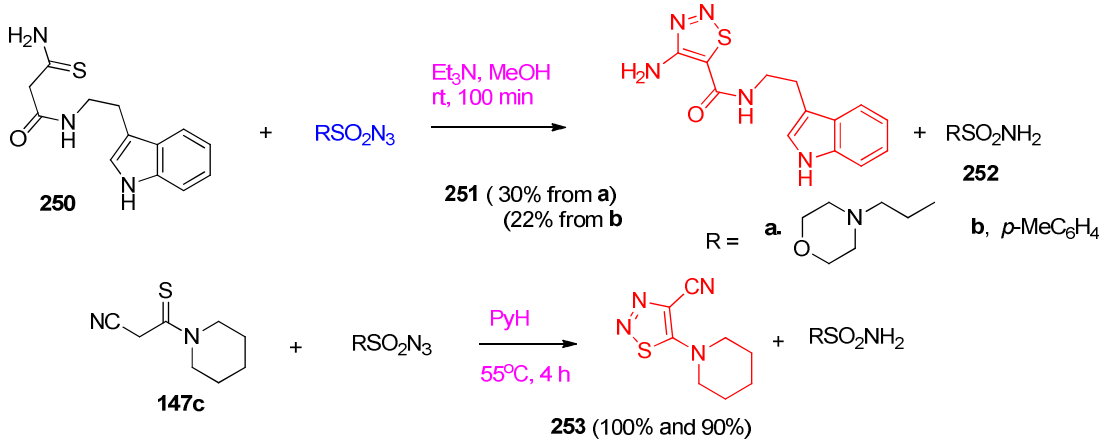
Trose et al. [79] have reported that the reaction of *N*-Heterocyclic carbene (NHC)-based copper azide complex [Cu(N_3)(IPr)] (**244**) (IPr = *N*,*N*'-bis[(2,6-(di-isopropyl)phenyl)]-imidazole-2-ylidene) with dimethyl acetylenedicarboxylate (as an activated alkyne), produced triazolate copper complex **245** (Scheme 96). However, complex **244** was found that it was reacted with the activated *p*-toluenesulfonyl cyanide (**246**) to give the tetrazole complex **247** in quantitative yield upon mixing (98%). In contrast, the reaction of complex **244** with the less activated 4-(trifluoromethyl)benzonitrile (**248**) needed heating and longer reaction times (50 °C, 16 h) to form the bis tetrazole complex **249** in high yield (93%) (Scheme 96) [81].



Scheme 96. Syntheses of triazolate and tetrazolate copper complexes **245**, **247,** and **249**, *Reagents and conditions*: (a) heating 50 °C, 16 h.

4.7. Synthesis of Thiadiazole

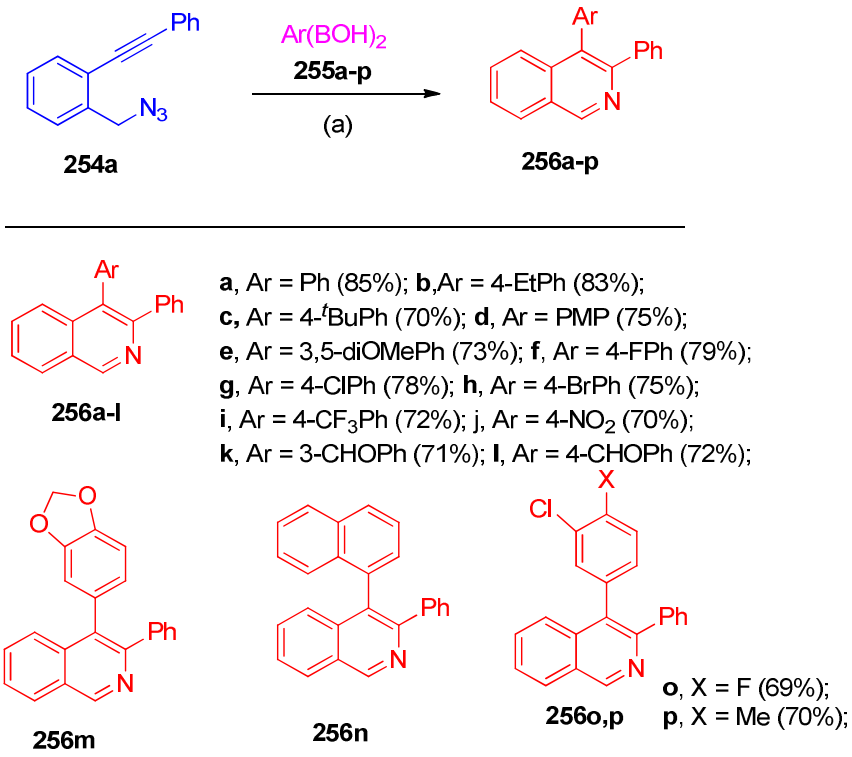
The more reactive thioamide **250** was reacted with tosyl azide in the presence of Et_3N at room temperature to afford 1,2,3-thiadiazole **251** (30 and 22% yield) together with compounds **252**. At the same time, the thioamide **147c** reacted with tosyl azide (R = *p*-Me-C_6H_4) to produce thiadiazole **253** (100 and 90% yield) (Scheme 97) [36].



Scheme 97. Synthesis of thiadiazole **253**. *Reagents and conditions*: (a) Et_3N, MeOH, room temperature, 100 min; (b) PyH, 55 °C, 4 h.

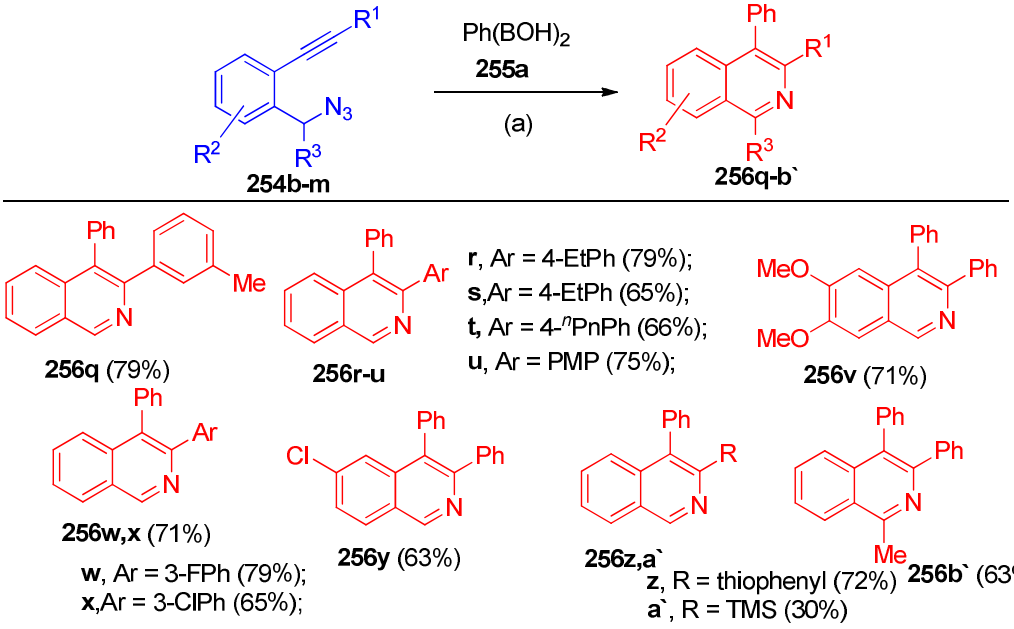
4.8. Synthesis of Pyridine and Isoquinoline Derivatives

Singam et al. [82] reported the regioselective arylnicalation of *ortho* functional di-aryl acetylene **254a** with $Ar(BOH)_2$ **255a–p** to synthesize substituted di-aryl isoquinolines **256a–p** (Scheme 98).



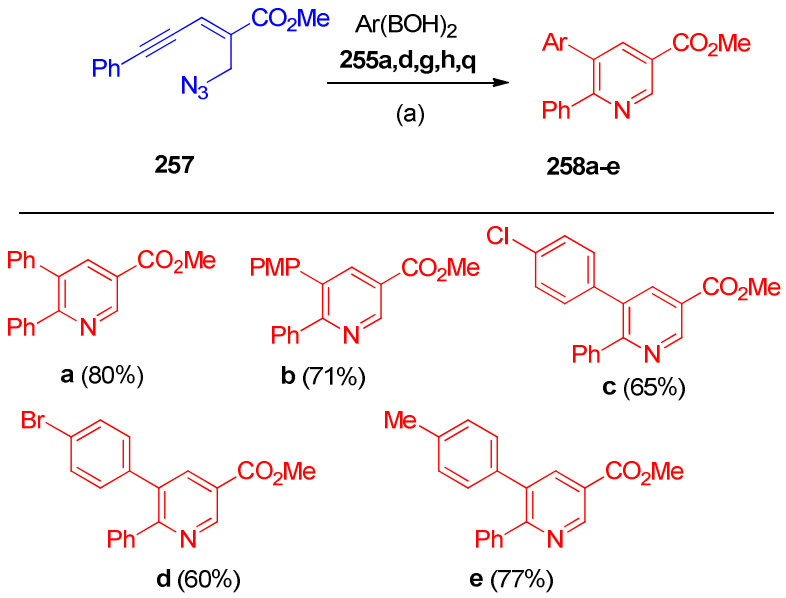
Scheme 98. Synthesis of isoquinoline derivatives **256a**–**p.** *Reagents and conditions*: (a) $Ni(acac)_2$ (10 mol%), PPh_3 (10 mol%), Cs_2CO_3 (20 mol%), dioxane, 90 °C.

Additionally, *ortho* diarylacetylene derivatives **254b**–**m** were investigated under the same reaction conditions, which on reacting with $Ph(BOH)_2$ **255a** gave the desired product **256q**–**b'** in high yields, as depicted in Scheme 99.



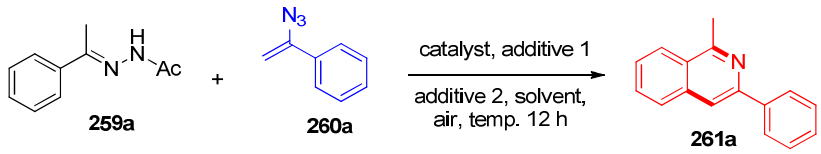
Scheme 99. Synthesis of isoquinoline derivatives **256q**–**b'**. *Reagents and conditions*: (a) $Ni(acac)_2$ (10 mol%), PPh_3 (10 mol%), Cs_2CO_3 (20 mol%), dioxane, 90 °C.

The 5,6-diarylnicotinates **258a**–**e** were performed from enynyl azides **257** with **255a,d,g,h,q** under the same standard conditions (Scheme 100) [82].



Scheme 100. Synthesis of 5,6-diarylnicotinates **258**. *Reagents and conditions*: (a) $Ni(acac)_2$ (10 mol%), PPh_3 (10 mol%), Cs_2CO_3 (20 mol%), dioxane, 90 °C.

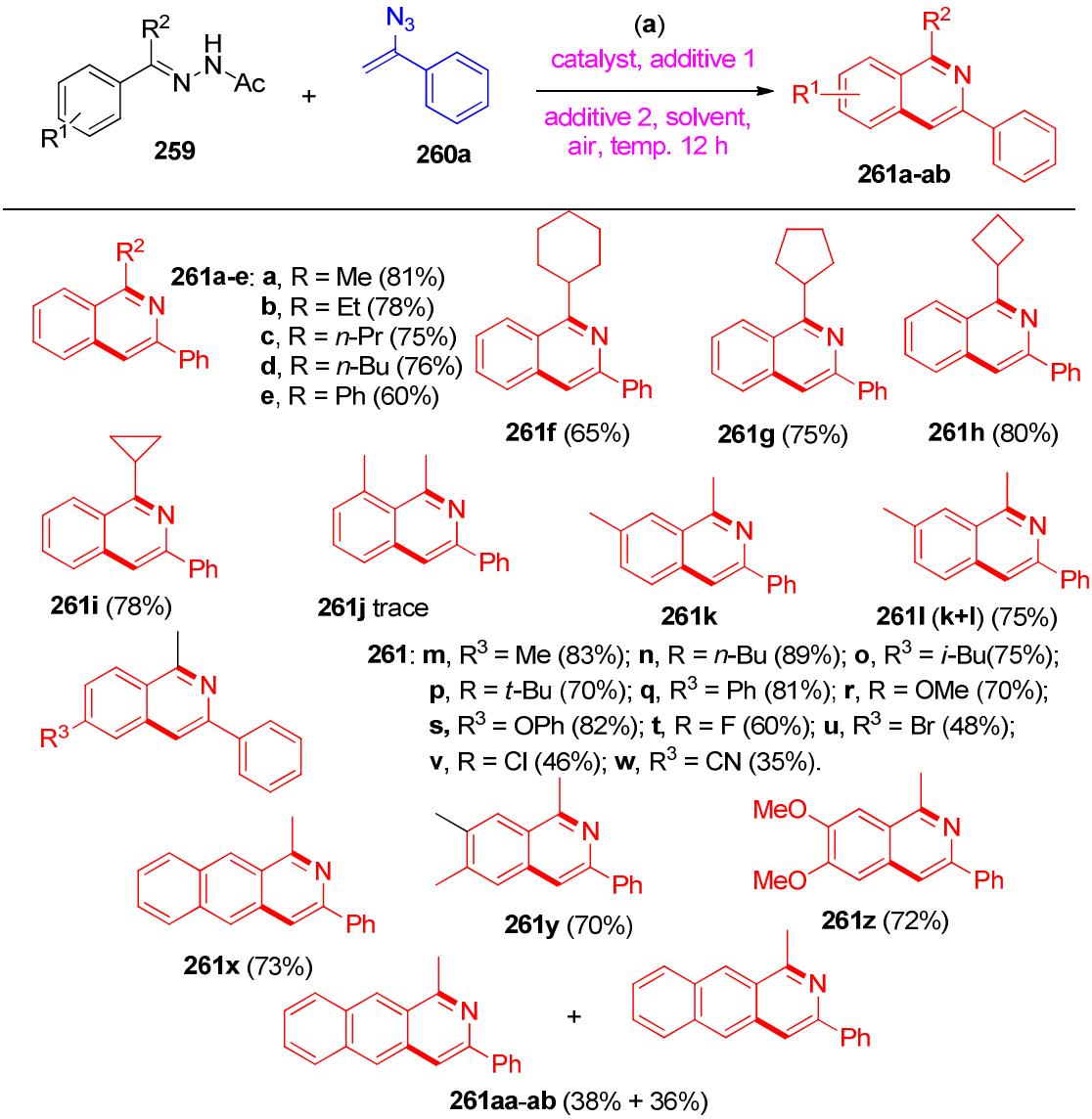
Pd-PEPPSI-IPr was used as a catalyst to reach the optimal reaction conditions during the reaction of acetophenone-*N*-acetylhydrazone (**259a**) and (1-azidovinyl) benzene (**260a**) (Scheme 101) [83]. It was concluded that toluene was the best solvent of choice, and heating to 100 °C gave 81% yield of **261a** (Scheme 101)



Entry	Catalyst	Additive 1	Additive 1	Solvent	Temp (°C)	Yields (%)
1	$Pd(OAc)_2$	NaOAc	Cu_2O	Toluene	80	30
2	$Pd(TFA)_2$	NaOAc	Cu_2O	Toluene	80	41
3	$Pd(OPiv)_2$	NaOAc	Cu_2O	Toluene	80	27
4	Pd-PEPPSI-IPr	NaOAc	Cu_2O	Toluene	80	56
5	Pd-PEPPSI-IPr	KOAc	Cu_2O	Toluene	80	45
6	Pd-PEPPSI-IPr	AgOAc	Cu_2O	Toluene	80	50
7	Pd-PEPPSI-IPr	CsOAc	Cu_2O	Toluene	80	34
8	Pd-PEPPSI-IPr	NaOAc	Cu_2O	Toluene	90	66
9	Pd-PEPPSI-IPr	NaOAr	Cu_2O	Toluene	100	81
10	Pd-PEPPSI-IPr	NaOAc	BQ	Toluene	100	50
11	Pd-PEPPSI-IPr	NaOAc	$K_2S_2O_8$	Toluene	100	41
12	Pd-PEPPSI-IPr	NaOAc	DDQ	Toluene	100	-
13	Pd-PEPPSI-IPr	NaOAc	Cu_2O	THF	100	35
14	Pd-PEPPSI-IPr	NaOAc	Cu_2O	CH3CN	100	trace
15	Pd-PEPPSI-IPr	NaOAc	Cu_2O	DMSO	100	trace
16	Pd-PEPPSI-IPr	NaOAc	Cu_2O	DMF	100	trace
17	Pd-PEPPSI-IPr	NaOAc	Cu_2O	Dioxane	100	37
18	-	NaOAc	Cu_2O	Toluene	100	-
19	Pd-PEPPSI-IPr	NaOAc	-	Toluene	100	Trace

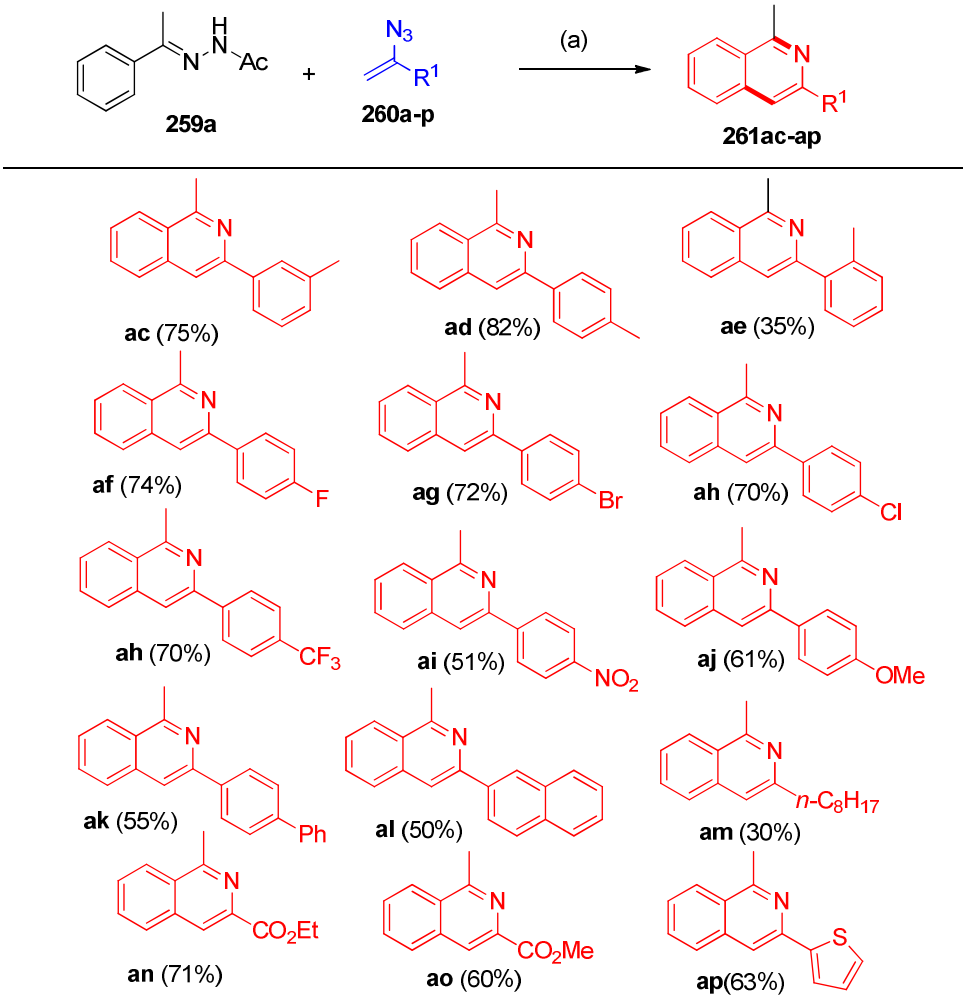
Scheme 101. Optimization of reaction conditions described the formation of **261a**.

The procedure showed that *N*-acetyl hydrazones **259** were screened to react with (1-azidovinyl)benzene (**260a**), as shown in Scheme 102. Variation from alkyl aryl ketones to benzophenone and cycloalkyl aryl ketones hydrazones reacted smoothly with **260a** to afford isoquinolines **261a–ab** in 60–81% yields (Scheme 102) [83]. The C-H functionalization occurred regioselectively at the less hindered site for *meta*-substituted substrate (Me, **259k**), yielding a mixture of two isomers, **261k** (major) and **261l** [83]. Either electron-donating (Me, Bu, Ph, OMe, OPh) or electron-withdrawing (F, Br, Cl, CN) group on the *para*-position of the phenyl ring of acetophenone *N*-acetylhydrazones were transformed to the desired products in moderate yields.



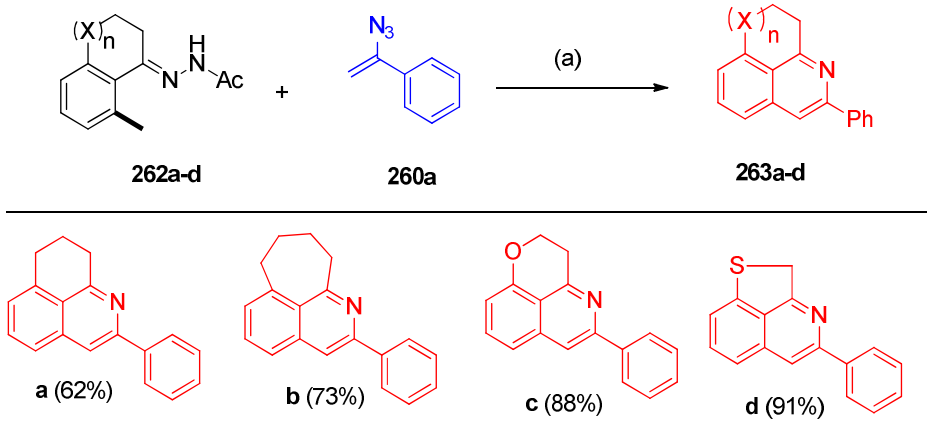
Scheme 102. Synthesis of isoquinolines **261a–ab**. Reagents *and conditions*: (a) Pd-PFPPSI-IPr (10 mol%), Cu_2O (2.0 equiv.), NaOAc (1.0 equiv), toluene, 100 °C, 12 h.

The reaction of various vinyl azides **260a–p** with *N*-acetyl hydrazone **259a** under the standard reaction conditions was examined (Scheme 103). Fused isoquinolines **261ac–ap** were obtained via the same previous procedure [83].



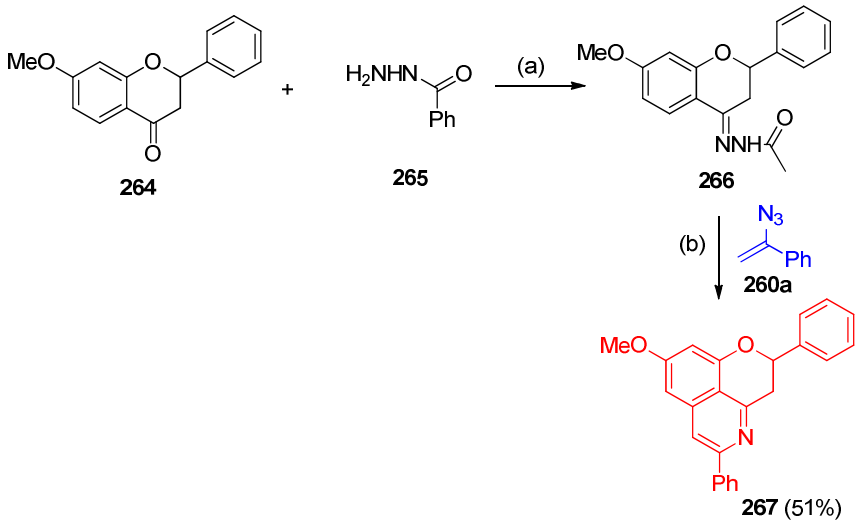
Scheme 103. Syntheses of isoquinolines **261ac–ap**. *Reagents and conditions*: (a) Pd-PFPPSI-IPr (10 mol%), Cu_2O (2.0 equiv.), NaOAc (1.0 equiv), toluene, 100 °C, 12 h.

The transformations of 1-tetralone, 1-benzosuberone hydrazones **262a–d** proceeded smoothly to give the desired polycyclic product **263a,b** in moderate yields. Moreover, chroman-4-one and thiochroman-4-one-hydrazone substrates were converted to polyheterocyclic products **263c,d** in 88% and 91% yields (Scheme 104).



Scheme 104. Synthesis of fused isoquinolines **263a–d**. *Reagents and conditions*: (a) Pd-PFPPSI-IPr (10 mol%), Cu_2O (2.0 equiv.), NaOAc (1.0 equiv), toluene, 100 °C, 12 h.

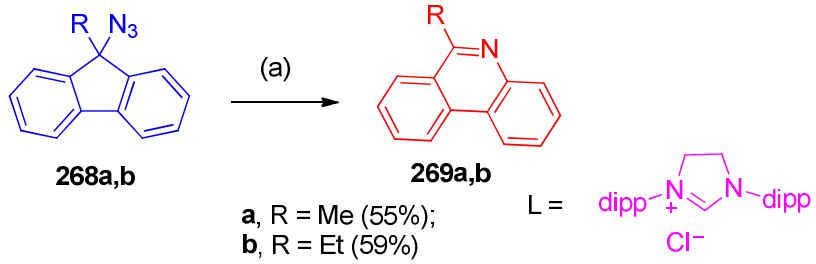
7-Methoxyflavanone **264** was reacted with acetohydrazide **265** to hydrazone **266**, which, when treated with vinyl azide **260a**, provided the isoquinoline product **267** in 51% yield (Scheme 105) [83].



Scheme 105. Formation of isoquinoline product **267**. *Reagents and conditions*: (a) EtOH, reflux; (b) Pd-PFPPSI-IPr (10 mol%), Cu_2O (2.0 equiv.), NaOAc (1.0 equiv), toluene, 100 °C, 12 h.

4.9. Synthesis of Phenanthridine

Phenanthridines **269a,b** were synthesized using the catalytic system of $FeCl_2$/*N*-heterocyclic carbene (NHC) SIPr-HCl (1,3-bis-(2,6-diisopropylphenyl)imidazolinium chloride) from 9-azidofluorenes **268,b** via 1,2-aryl migration (Scheme 106) [84].

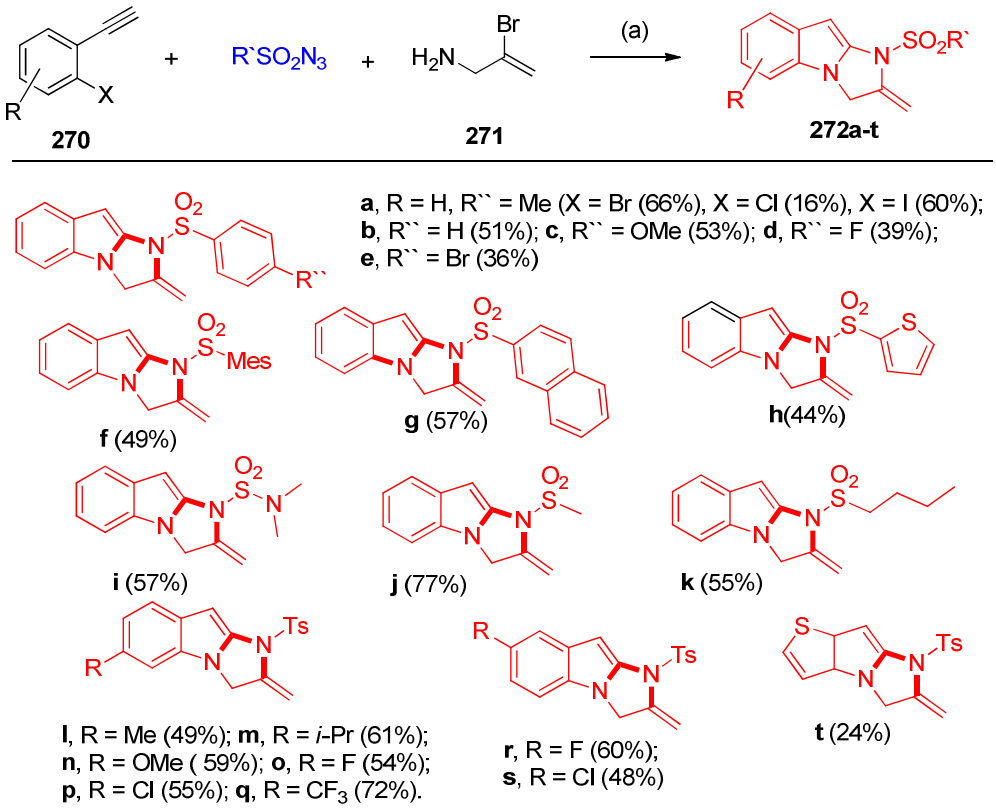


Scheme 106. Formation of phenanthridines **269a,b**. *Reagents and conditions*: (a) $FeCl_2$ (10 mol%), ligand (10 mol%), PhCl, Ar, 80 °C.

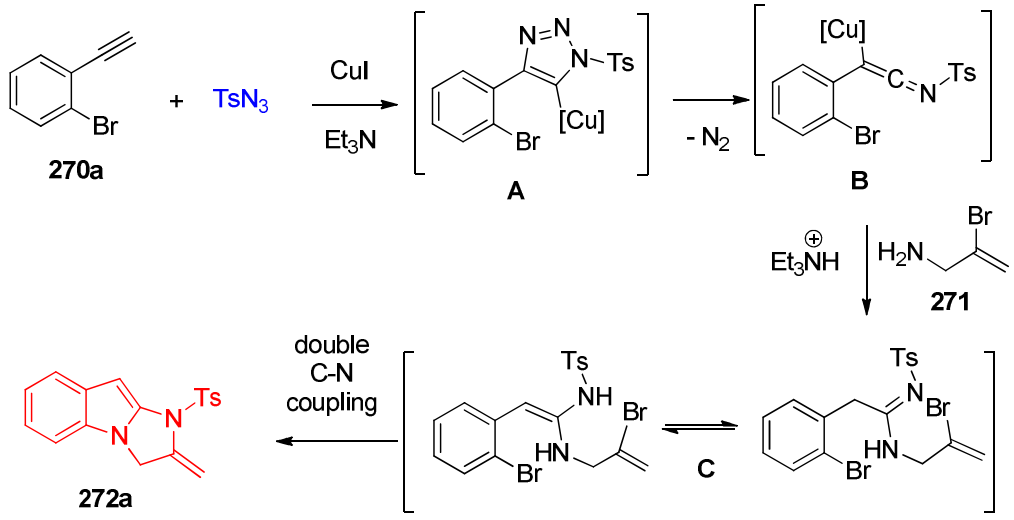
4.10. Synthesis of Imidazoindoles

Jin and others [85] reported that the multicomponent reaction of sulfonyl azides, alkynes **270**, and allylamines **271** was catalyzed by copper iodide in the presence of triethylamine in DMSO/K_2CO_3 and dimethyl ethylenediamine as a ligand (**L**), affording 2,3-dihydro-1*H*-imidazo[1,2-*a*]indoles **272a–t** (Scheme 107). Four C–N bonds were formed by way of azide-alkyne cycloaddition (CuAAC) and double Ullmann-type coupling reactions in a one-pot process, as illustrated in the reaction mechanism (Scheme 107) [85].

The proposed mechanistic steps were proposed, as shown in Scheme 108. First, a copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) takes place to generate intermediate **A**, which then transforms to ketenimine **B** by the extrusion of N_2. Nucleophilic addition of 2-bromoprop-2-en-1-amine (**270a**) to intermediate **B** affords carboxamidine **C** and/or its tautomer. Finally, a consecutive coppercatalyzed C–N coupling reactions proceeds to provide 2,3-dihydro-1*H*-imidazo[1,2-*a*]indole **272a** (Scheme 108) [85].



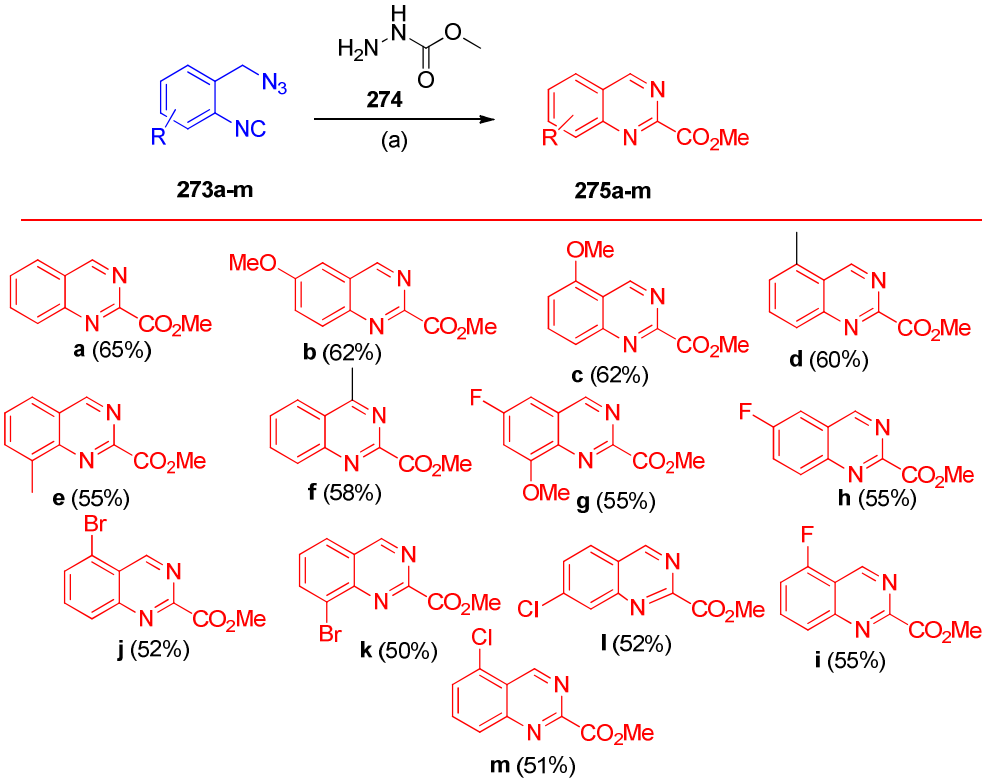
Scheme 107. Synthesis of 2,3-dihydro-1*H*-imidazo[1,2-*a*]indoles **272a–t**. Substrate scope of azides and alkynes. *Reagents and conditions*: (a) CuI (10 mol%), Et_3N (1.0 equiv), **270** (0.5 mmol), azide (0.6 mmol), **271a** (0.5 mmol), DMSO (3 mL) at r.t. for 1 h; 2) CuI (20 mol%),**L** (0.3 mmol), K_2CO_3 (2 equiv) at 80 °C for 6 h. Mes = 2,4,6-Trimethylphenyl.



Scheme 108. Proposed mechanism for the formation of imidazoindoles **272a**.

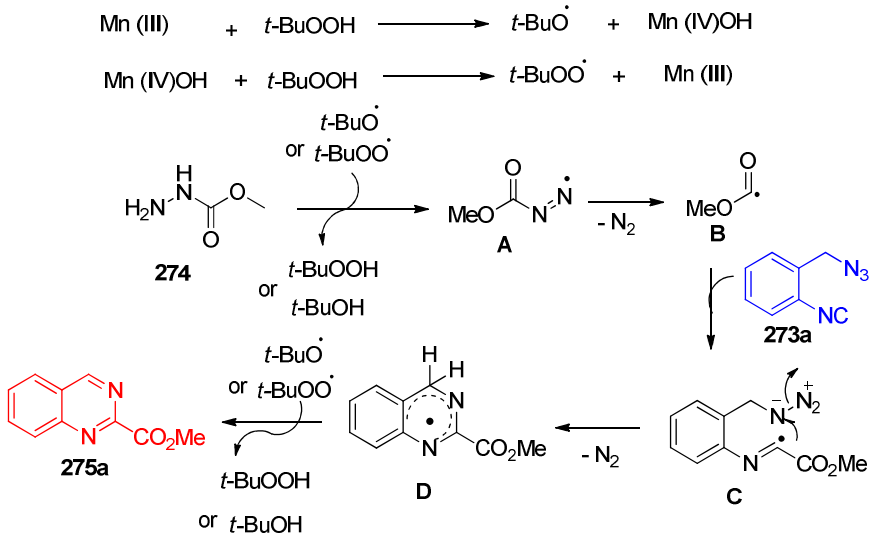
4.11. Synthesis of Quinazoline Derivatives

Kumar et al. [86] reported the tandem synthesis of 2-quinazoline carboxylates **275a–m** using 2-(azidomethyl)phenyl isocyanides **273a–m** along with carbazates **274** in the presence of $Mn(OAc)_3 \cdot 2H_2O$ (Scheme 109).



Scheme 109. Synthesis of quinazoline derivatives **275a–m**. *Reagents and conditions*: (a) $Mn(OAc)_3 \cdot 2H_2O$ (0.63 mmol), TBHP (1.89 mmol, 5 M in decan), and EtOAc, 12 h at 80 °C.

The postulated mechanism is illustrated in Scheme 110. Initially, the $Mn(OAc)_3 \cdot 2H_2O$-assisted homolysis of *tert*-butyl hydroperoxide (TBHP) generates the *tert*-butoxy and the *tert*-butyl peroxy radicals. Bond cleavage of the C-N in methyl carbazate **274** forms the alkoxycarbonyl radical (**B**), which loses molecular N_2. Radical (**B**) then attacks the R–NC bond of 2-(azidomethyl)phenyl isocyanide (**273a**) to form an imidoyl radical intermediate (**C**). The intermediate **C** then undergoes intermolecular cyclization with the azido group to give a cyclized aminyl radical (**D**) by nitrogen loss. Finally, a hydrogen abstraction of the radical intermediate (**D**) leads to the desired product (**275a**) (Scheme 110) [86].

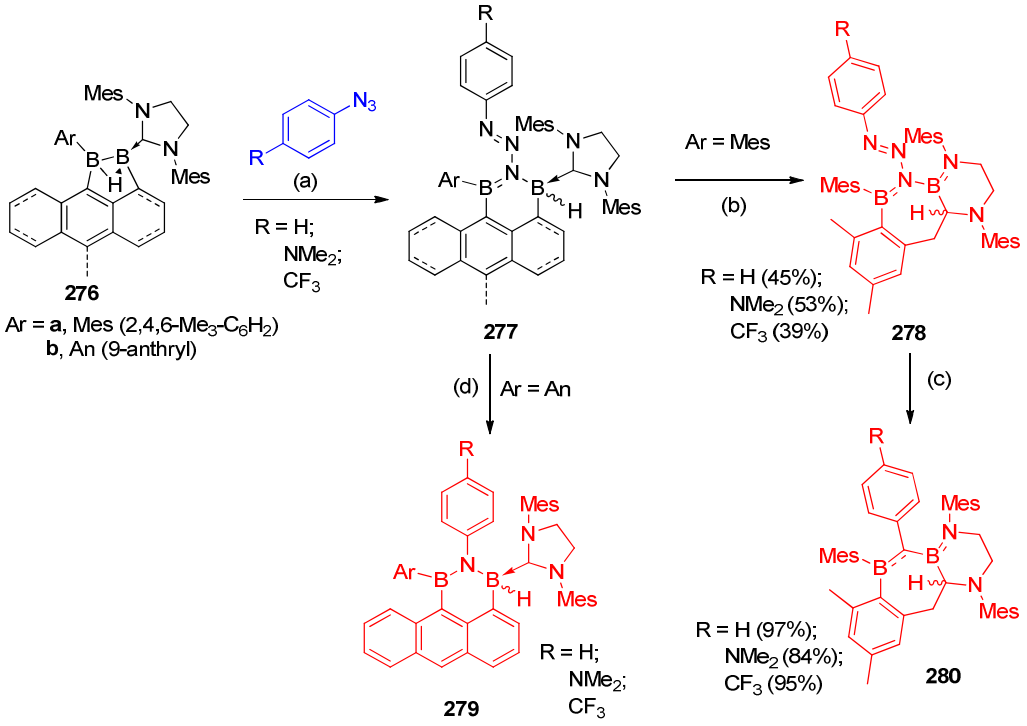


Scheme 110. Proposed mechanism for the formation of quinazoline **275a** via the radical pathway.

4.12. Synthesis of Borane Containing Heterocycles

4.12.1. Synthesis of Diborylaniline and Diboryl-Fused Pyrimidine

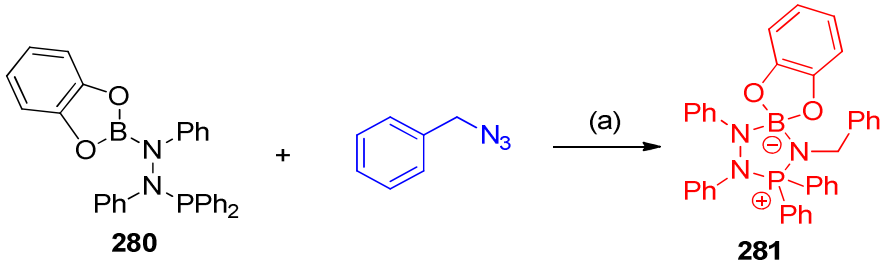
Prieschl et al. [87] reported that the c-nitrogen insertion of aryl azides into the B–B bond of electron-rich cyclic l-hydridodiboranes **276** was stabilized by one *N*-heterocyclic carbene (NHC) ligand leads to the expansion of the central C_3B_2 ring, yielding unsymmetrical polyheterocyclic 1,1-diboryltriazenes **278** and **279** via the intermediate **277**. The 2-benzyl-bridged analogs undergo further NHC ring expansion and thermally-induced loss of N_2 to give polyheterocyclic diborylanilines **280** (Scheme 111) [87].



Scheme 111. Syntheses of diborylfused pyrimidines **279** and diborykanilines **280**. *Reagents and conditions*: (a) benzene, 60 °C; (b) benzene 80 °C; (c) benzene, 80–100 °C, 12–15 d; (d) benzene, room temperature.

4.12.2. Synthesis of Triazaphosphaborolidine

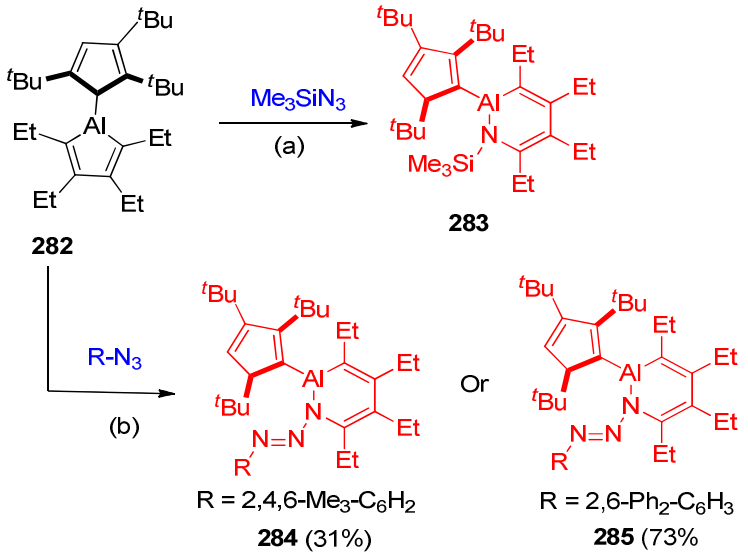
1-(Benzo[*d*][1,3,2]dioxaborol-2-yl)-2-(diphenylphosphino)-1,2-diphenylhydrazine (280) showed frustrated Lewis pairs (FLPs) reacted with benzyl azide, forming 4′-benzyl-1′,2′,3′,3′-tetraphenylspiro[benzo[*d*][1,3,2]dioxaborole-2,5′-[1,2,4,3,5]triazaphosphaborolidin]-3′-ium-12-uide (**281**) in 73% yield (Scheme 112) [88].



Scheme 112. Formation of 4′-benzyl-1′,2′,3′,3′-tetraphenylspiro[benzo[*d*][1,3,2]dioxaborole-2,5′-[1,2,4,3,5]triazaphosphaborolidin]-3′-ium-12-uide (**281**). *Reagents and conditions*: (a) CH_2Cl_2, room temperature, 24 h stirring.

4.13. Synthesis of Aluminum-Containing Heterocyclic

Drescher and others [89] reported the ring expansion of alumina cyclopentadienes (alumoles) on treatment with organic azides. Treatment of alumole **282** and trimethylsilyl azide in benzene at 60 °C gave cycloadduct **283** in 61% yield, while mesityl (Mes = 2,4,6-$Me_3C_6H_2$) or 2,6-diphenylphenyl azide forming the aza-cycloadducts **284** (31%) or **285** (73%), respectively (Scheme 113) [89].

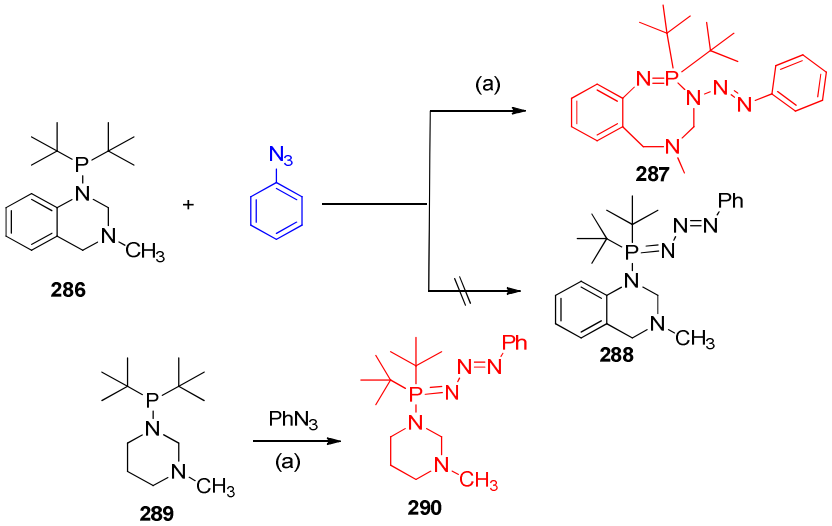


Scheme 113. Synthesis of aluminum heterocycles **283**–**285**. *Reagents and conditions*: (a) benzene, 60 °C. (b) room temperature.

4.14. Synthesis of Phosphorus-Containing Heterocycles

4.14.1. Synthesis of Triazphosphocine

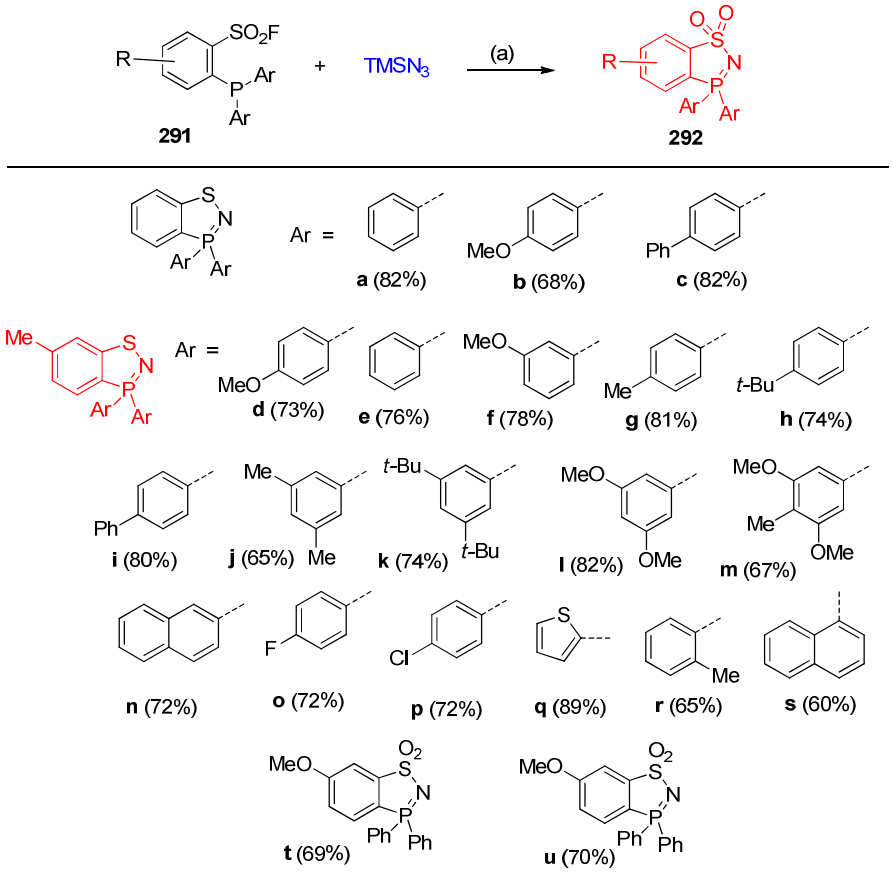
Treatment of 1-(di-tert-butylphosphino)-3-methyl-1,2,3,4-tetrahydroquin azoline (**286**) with phenyl azide gave benzo[*g*][1,3,5,2]triazaphosphocine (**287**) instead of phosphazide derivative ((*E*)-1-(di-tert-butyl(phenyltriaz-2-en-1-ylidene)phosphoranyl)-3-methyl-1,2,3,4-tetrahydroquinazoline) (**288**). The reaction of compound **286** with phenyl azide takes place on P(III) of compound **286** was believed to give P(V) product phosphazide **288**, which underwent ring enlargement to give benzotriazaphosphocine **287**. Derivative **289** reacted readily with phenyl azide to give compound **290** in a high yield (Scheme 114) [90].



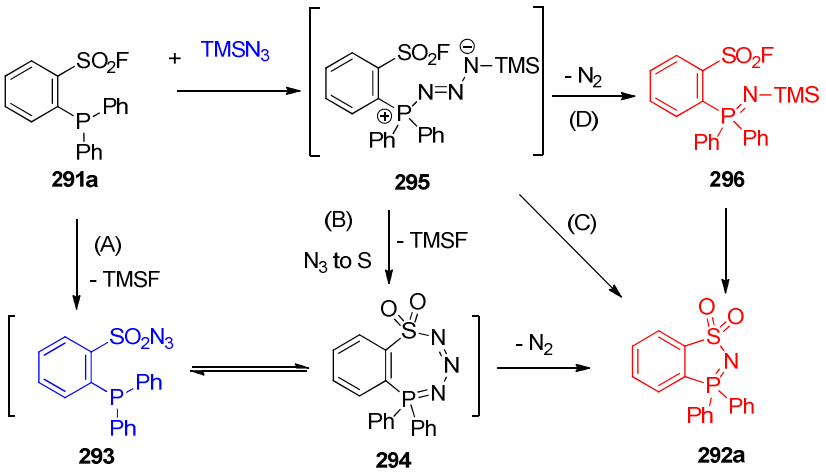
Scheme 114. Synthesis of triazphosphocine **287**. *Reagents and conditions*: (a) Benzene, r.t., 3 h.

4.14.2. Synthesis of Benzothiazaphosphole

The reaction of *ortho*-phosphinoarenesulfonyl fluorides **291** with trimethylsilyl azide resulted in benzo-1,2,3-thiazaphosphole **292** [91]. To optimize the reaction condition, it was found that a mixture of acetonitrile and 10 equivalents of trimethylsilyl azide at 60 °C was the optimal reaction chosen condition (Scheme 115) [92]. The three possible mechanistic pathways (A), (B) and (C) for forming the benzo-thiazaphosphole **292a** are illustrated in Scheme 116 [91].



Scheme 115. Syntheses of benzo-1,2,3-thiazaphospholes **292a**–**u**. *Reagents and conditions*: (a) MeCN, 10 equiv. Azide, 60 °C, 12 h.



Scheme 116. Mechanistic pathways for the formation of compound **292a**.

5. Conclusions

In summary, the azido group in organic substrates are effectively served in the synthesis of various heterocycles through different mechanistic steps, such as one-pot reactions, nucleophilic additions (such as Aza-Michael addition), cycloaddition reactions (such as [3+2] cycloaddition), mixed addition/cyclization/oxygen, and insertion reactions of C-H amination. The selectivity of the chosen catalyst plays an important role in the chemoselectivity favoring C−H and C-N bonds, as it can be seen that organic azides have been used in the synthesis of various types of natural products producing good to excellent yields. Most indicative is the utility of organic azides in the synthetic procedures of fused heterocycles, such as quinazoline derivatives along with organo-metal heterocycles (i.e., phosphorus-, boron-, and aluminum-containing heterocycles). This review focused on synthesizing various heterocycles using azide chemistry and mechanistic aspects.

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Abbreviations

TMS: trimethylsilyl: pmp: pentamethylpiperidines; DCE dichloroethane; Tf: trifluorosulfonyl; Nf: nonafluorbutanesulfonyl; Py: pyridinyl; Ms: mesyl; Bs: brosyl; Ts: tosyl; Ns: nosyl; CuMeSal: copper 3-methylsalicylate; NHC: N-heterocyclic carbene; Boc: ter-butyloxycarbonyl; IBX: 2-Iodoxybenzoic acid; DABCO: diazobicyclooctane; BOX: bisoxazoline; CSA: camphorsulfonic acid; TBS: tribuylsilyl; IMes. 1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene; TFPB: tetrakis[3,5-bis(trifluoromethyl)phenyl] borate.

Hazardous Information: A qualified scientist with appropriate safety precautions should be mandatory for using azides. The website azide.org should be consulted [92].

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