RSC Advances

ROYAL SOCIETY OF CHEMISTRY

REVIEW

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Cite this: *RSC Adv.*, 2024, **14**, 278

Recent advances in the application of alkynes in multicomponent reactions

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Received 9th November 2023
Accepted 2nd December 2023

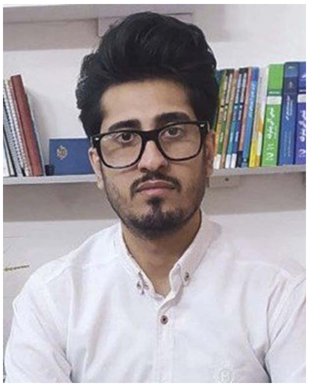
DOI: 10.1039/d3ra07670a

rsc.li/rsc-advances

Alkynes have two active positions to carry out chemical reactions: C≡C and C–H. These two positions are involved and activated in different reactions using different reagents. In this study, we investigated the reactions of alkynes that are involved in multi-component reactions through the C–C and C–H positions and examined the progress and gaps of each reaction by carefully studying the mechanism of the reactions. Firstly, we investigated and analyzed the reactions involving the C≡C position of alkynes, including the reactions between derivatives of alkynes with RN_3, sulfur compounds (RSO_2R', DMSO, S_8, $DABCO(SO_2)_2$ and DABSO), barbituric acids, aldehydes and amines, COOH, α-diazoesters or ketones, and isocyanides. Then, we examined and analyzed the important reactions involving the C–H position of alkynes and the progress and gaps in these reactions, including the reaction between alkyne derivatives with amines and aldehydes for the synthesis of propargylamines, the reaction between alkynes with CO_2 and the reaction between alkynes with CO.

1 Introduction

Alkynes are versatile molecules that can be widely applied for transformations in organic synthesis.[1] Also, alkynes and their derivatives are among the most valuable chemical motifs owing to their versatile reactivities and abundance.[2] These basic chemicals can serve as molecular building blocks for the



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Seyedmohammad Hosseininezhad was born in 1997 in Zanjan, Iran. He received his B.Sc in Pure Chemistry from Payam Noor University (PNU) in 2020 as a first-ranked student. Then, he received his M.Sc in Organic Chemistry with a GPA of 4 out of 4 from Babol Noshirvani University of Technology (BNUT) in 2023. During this period, he worked on intramolecular hydrogen bonding, multicomponent reactions, and synthesis of shift bases. After graduating with the M.Sc. Degree, he immediately joined Prof. Ramazani's group at the University of Zanjan (ZNU) as a research assistant to increase his knowledge in the fields of organic chemistry, medicinal chemistry, and synthesis of heterocyclic and organic compounds with modern methods.

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development of new organic reactions and the construction of functional materials.[3] Alkynes have at least one C–C triple bond in which the carbon atoms are sp hybridized. The C atoms are connected by one σ bond and two π bonds, in which the two p orbitals in the C atoms overlap.[4] In recent years, several novel organic transformations involving alkynes have been explored for the construction of valuable molecular scaffolds.[5–13] However, because sp-hybridized carbon atoms are less reactive, activating the C≡C bonds in alkynes is key to their synthetic transformation. In addition, C≡C bond substituents in alkynes can be selectively activated by either both π- and σ-activation (terminal alkynes) or π-activation (internal alkynes) alone.[14] Alternatively, alkynes play a significant role as a coupling agent in transition metal-catalysed directed C–H activation reactions (Fig. 1). Also, because of the linear geometry and low steric requirements of alkynes, they can be effectively coordinated with metal d-orbitals. All these applications make alkynes useful coupling partners in terms of their numerous beneficial transformations.[15]

Creating molecular complexity and molecular diversity from available and simple compounds is considered one of the basic challenges in organic synthesis. Therefore, the use of methods that use simple compounds to form complex molecules while creating several links in chemical processes in a single process is progressing. In this regard, multicomponent reactions provide these conditions.[16] The applications of multicomponent reactions include the synthesis of natural products,[17] polymer chemistry,[18] agrochemistry,[19] medicinal chemistry, and drug discovery.[20] In addition, through multicomponent reactions, it is possible to synthesize different and important molecular skeletons, such as γ-lactams, quinoxalinones, benzodiazepinedione, benzimidazoles, and thiazoles.[21,22] These molecular skeletons have been demonstrated to possess medicinal properties, for example, thiazole scaffolds have anticancer, anti-inflammatory, and antibacterial properties.[23] Among the advantages of multi-component reactions, the most notable are the purification and separation of products at low cost, the formation of low tracer waste, high atom economy, and high efficiency of products.[24] However, many practical features of these methods and the role of multicomponent reactions in solving delicate chemical problems still have to be demonstrated.[25] Alternatively, the mechanism of multi-component reactions is often complex, and thus most of the processes in these reactions have reversible equilibrium, whereas the last stage is irreversible.[26]

In this review, we focus on some C–H and C≡C activation reactions of alkynes. In the case of the activation of C–C alkynes, we review the gaps, developments, and mechanisms of reactions of alkynes with carboxylic acids, RN_3, sulfur-containing compounds, barbituric acids, aldehydes, amines, alpha-diazo esters or ketones, and isocyanides. Then, for the activation of C–CH alkynes, we investigate the gaps, advances and reaction mechanisms of alkynes with amines and aldehydes for the synthesis of propargylamines, reaction between alkynes with CO_2, and reaction between alkynes with CO.

2 C≡C activation

2.1 Reaction of RN_3

Click chemistry was discovered by Sharpless *et al.*[27] These reactions refer to reactions that are easy to perform, generate products with high efficiency and little or no side products, are not affected by the nature of different groups, and perform well under different conditions.[28] The features of click reactions have are presented in Fig. 2.

Among the known reactions, a small number has the characteristics of click reactions, including the azide–alkyne cycloaddition (AAC) reaction, which produces 1,2,3-triazoles (**T**) (Fig. 3). This is one of the most important click reactions.[28] It should be noted that 1,2,3-triazoles have wide biological activities such as anti-fungal and anti-bacterial, anti-virus, anti-tuberculosis, anti-cancer.[29] The AAC reaction has the following characteristics: (1) high chemical potential energy of azides and alkynes, (2) slow reaction rate (long-term heating for inactive alkynes), (3) in the presence of solvent, electrophiles and nucleophiles are stable (azide and alkyne groups) and (4) they are accelerated by catalysts such as Cu(I) (CuAAC).[28] One of the most widely used click reactions is the CuAAC reaction; however, despite its widespread use, it has disadvantages because copper is cytotoxic and the excessive consumption of copper can cause Alzheimer's, neurological disorders, and hepatitis.[30]

Click chemistry is used in drug discovery, organic synthesis, pharmaceutical industry, and polymer chemistry, materials

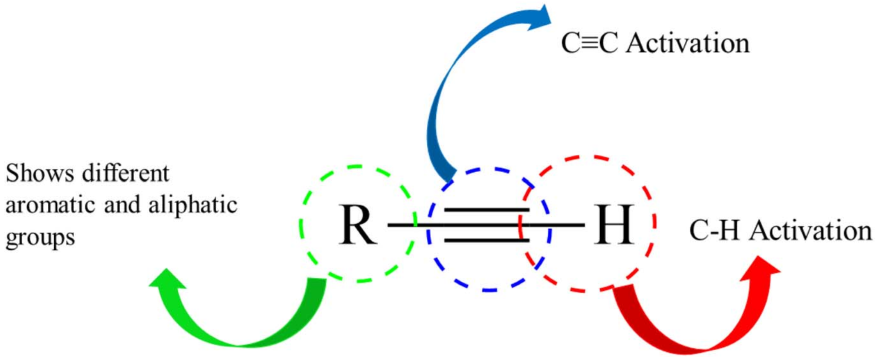


Fig. 1 Structure of an alkyne showing its two active positions: C–H and C≡C.

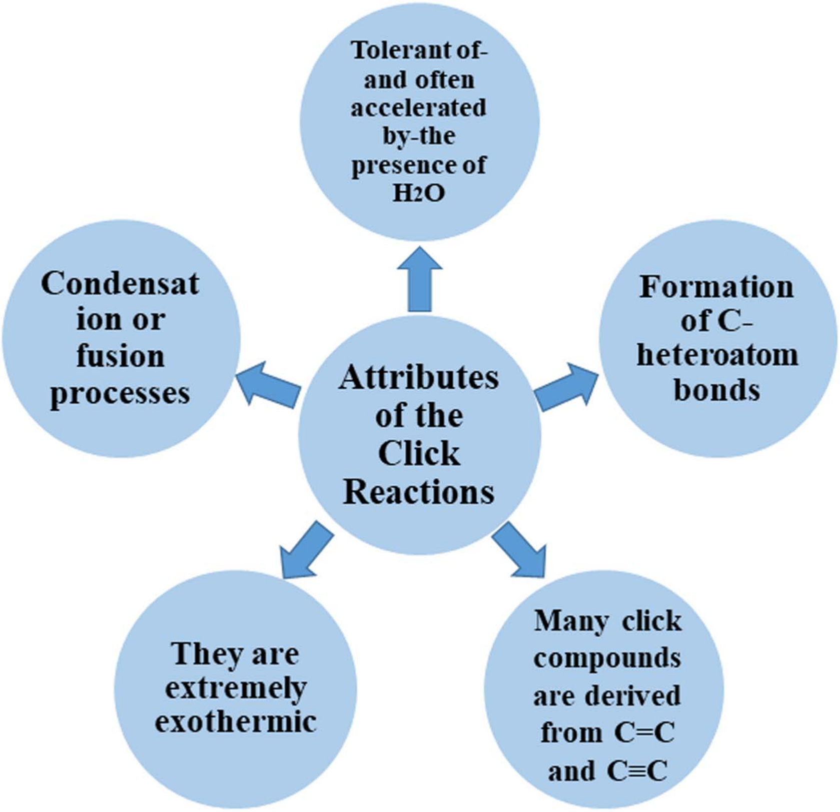
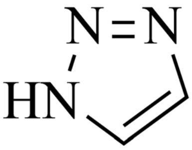


Fig. 2 General attributes of click reactions.



1,2,3-triazoles

T

Fig. 3 Structure of 1,2,3-triazoles.

science, and bioconjugation.[29] Meanwhile, drug discovery based on click chemistry classified as shown in Fig. 4.

A series of N^1- and N^2-oxyalkylated 1,2,3-triazole derivatives **4** and **5** was synthesized *via* the reaction of ethers **3**, alkynes **1**, and $TMSN_3$ **2** in the presence of CuI and TBHP (as an oxidant) at 80 °C for 16 h by Bao and co-workers (Scheme 1).[31]

In the first stage for the formation of **4**, the radical species t-$BuO^{\bullet}$ and t-$BuOO^{\bullet}$ are produced through the Cu-catalyzed homolytic decomposition of TBHP. This process causes **A** to convert to **B.** Next, **B** is oxidized, producing α-alkoxyalkyl cation

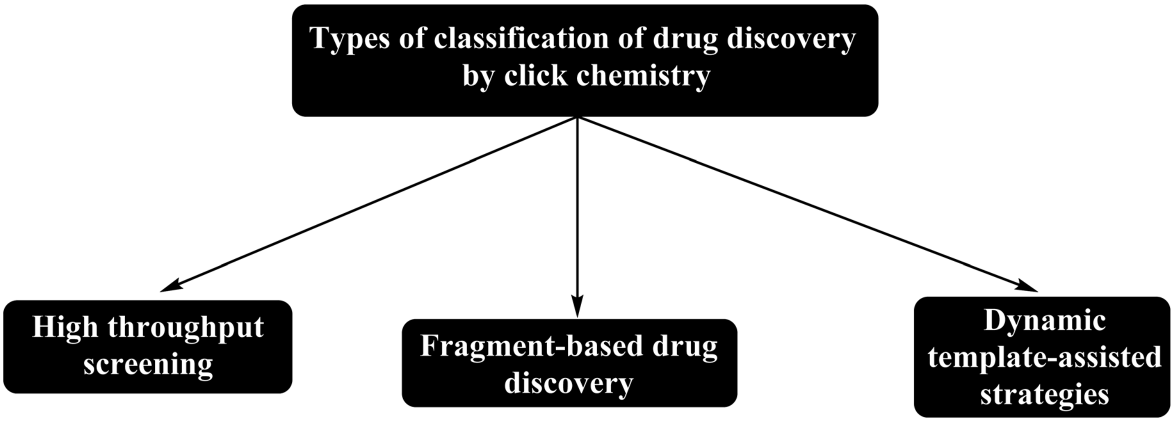
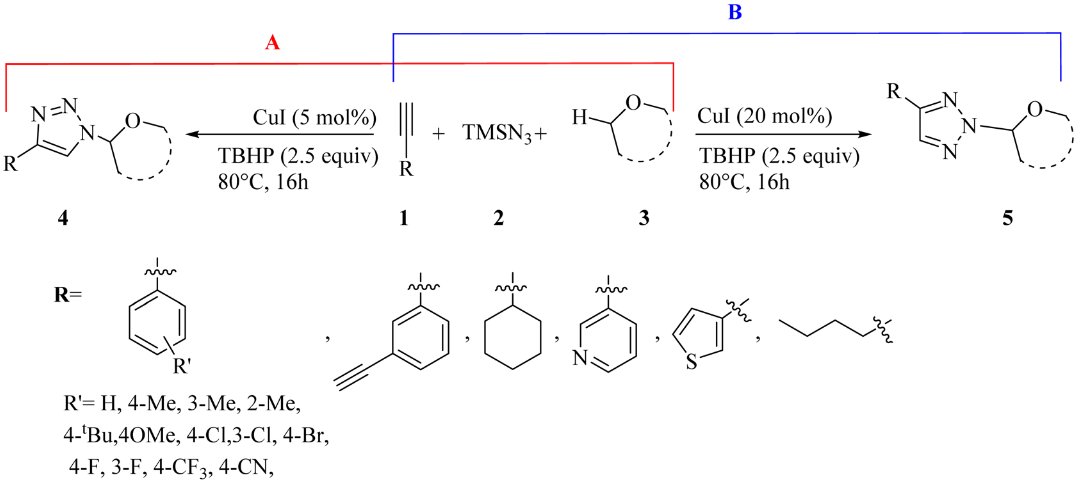


Fig. 4 Classification of drug discovery based on click chemistry.



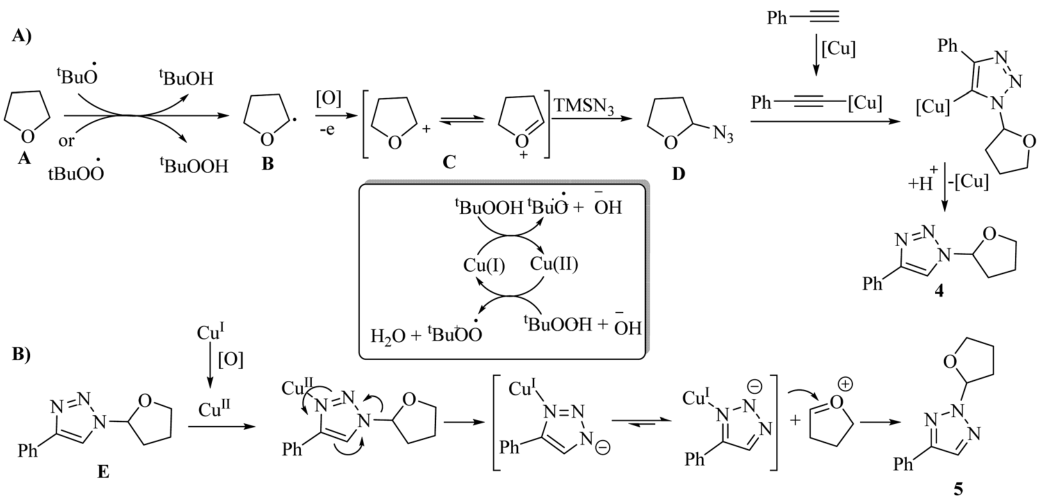
Scheme 1 (A) Synthesis of N^1-oxyalkylated triazoles **4** and (B) synthesis of N^2-oxyalkylated triazoles **5**.[31]

C. Then, **C** undergoes nucleophilic attack by $TMSN_3$ to produce oxyalkylated azide **D**, which in the presence of phenylacetylene, undergoes the click reaction and produces **4** (Scheme 2A). **E** produces **5** *via* the copper-promoted 1,2-shift of the ether group. This process leads to a sequential electronic transfer process (Scheme 2B).

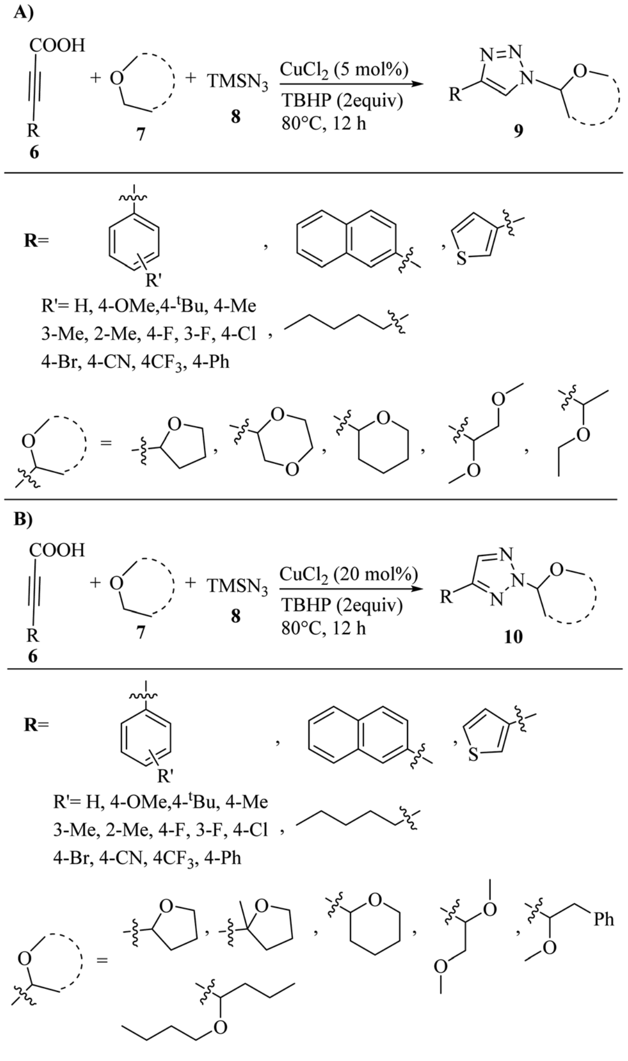
In the case of **4** (Scheme 1A), the Me group at different positions of the benzene ring (*ortho*, *meta*, and *para*) in aromatic alkynes produced the desired triazole derivatives in 70%, 75%, and 66% yield, respectively. ^{t}Bu and OMe groups at the *para* position of phenylacetylene produced the desired products in 76% and 66% yield, respectively. Also, phenylacetylene with CF_3, Cl, Br, and F substituents gave the corresponding triazole derivatives in 57–71% yield. Notably, aliphatic alkynes (hex-1-yne and ethynylcyclohexane) and heterocyclic aromatic alkynes (3-ethynylpyridine and 3-ethynylthiophene) produced the corresponding triazole derivatives in 65% and 60% yield and 67% and 72%, respectively. In the case of **5** (Scheme 1B), aromatic alkyne derivatives with various substituents produced the corresponding triazole derivatives in 64–80% yield. In addition, aliphatic and heterocyclic aromatic alkynes (3-ethynylthiophene) produced the corresponding triazole derivatives in 66–78% yield.

In another study, Bao and co-workers[32] synthesized a selective assembly of N^1- and N^2-alkylated 1,2,3-triazole derivatives **9** and **10** *via* the reaction between ether **7**, alkynyl carboxylic acid derivatives **6**, and azidotrimethylsilane ($TMSN_3$) **8** in the presence of $CuCl_2$ in TBHP at 80 °C for 12 h (Scheme 3).

Two pathways were proposed for the formation of **9**. In the first pathway, t-BuO$^•$ and t-BuOO$^•$ abstract the α-H atom from **A**, producing alkoxyalkyl radical **B**. Then, **B** is oxidized to produce **C**. Next, **B** undergoes nucleophilic attack by $TMSN_3$, generating **D**. Subsequently, an alkynyl copper intermediate is produced *via* the reaction between the alkynyl carboxylic acid and Cu salt and *via* the reaction with one molecule of HCl, releasing CO_2. The alkynyl copper intermediate reacts with **D** and generates **E** *via* a click reaction. Finally, **D** is quenched by a proton to give **9** (Scheme 4A). In the second pathway, propiolic acids **6** react with



Scheme 2 Possible reaction mechanism for the synthesis of (A) N^1-oxyalkylated triazoles and (B) N^2-oxyalkylated triazoles.[31]



Scheme 3 (A) Synthesis of N^1-alkylated 1,2,3-triazoles **9** *via* $CuCl_2$ and (B) synthesis of N^2-alkylated 1,2,3-triazoles **10** *via* $CuCl_2$.[32]

8 *via* the copper-catalyzed decarboxylative cycloaddition, which generates **F**. Next, **F** undergoes alkylation to generate **9** (Scheme 4A). Then, the copper-mediated 1,2-shift of the ether group in **9** generates **10** (Scheme 4B).

The above-mentioned method is a selective and efficient approach for the synthesis of the desired triazole derivatives in 40–92% yield. In the case of **9** (Scheme 3A), arylpropiolic acids with electron-poor or -rich aryl rings react well and the desired triazole derivatives were obtained in 57–92% yield. Also, 2-naphthalenyl propiolic acid, 3-(thiophen-3-yl)propiolic acid and biphenyl propiolic acid produced the corresponding triazole derivatives in 61%, 75%, and 57% yield, respectively. In addition, alkylpropiolic acid (oct-2-ynoic acid) also reacted and produced the desired 1,2,3-triazole derivative in 60% yield. Furthermore, the tolerance of ether derivatives was examined in the above-mentioned method, and besides THF, other cyclic ether derivatives such as tetrahydro-2*H*-pyran and 1,4-dioxane produced the corresponding triazole derivatives in 60% and 40% yield, respectively. Also, acyclic ethers (1,2-dimethoxyethane and methylphenylethyl ether) produced the desired triazole derivatives in 40% and 71% yield, respectively. In the case of **10** (Scheme 3B), similar to the preparation of N^1-alkylated 1,2,3- triazoles, substituted arylpropiolic acid derivatives containing electron-withdrawing and -donating groups produced the corresponding triazole derivatives in 70–85% yield. Specifically, 3-(thiophen-3-yl)propiolic acid produced the desired product in 73% yield, while oct-2-ynoic acid also produced the desired 1,2,3-triazole derivatives in 70% yield. Furthermore, cyclic and acyclic ether derivatives produced the corresponding triazole derivatives in 40–68% yield.

He and co-workers[33] synthesized 3-triazolylcoumarin derivatives **14** *via* a one-pot, copper-catalyzed multicomponent reaction. The desired product was produced from the reaction of arylacetylenes **13**, salicylaldehydes **11**, ethyl 2-azidoacetate **12**, and CuI in EtOH and K_3PO_4 at 50 °C for 5 h (Scheme 5).

Initially, **12** and **13** generates **A** *via* the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction. Then, **A** reacts with an aldehyde group of **11** in the presence of K_3PO_4 *via* Knoevenagel condensation, generating intermediate **B**. Next, in the presence of K_3PO_4 the intermediate **C** is generated. Subsequently, **14** is generated *via* the intramolecular nucleophilic addition of **C**, followed by transesterification (Scheme 6).

The above-mentioned method has advantages such as eco-friendly nature, convenience and production of substituted 3-trizolylcoumarin derivatives in moderate to excellent yields. According to this study, halide substituents in arylacetylenes were compatible to produce the desired triazolylcoumarin derivatives in good yield in the range of 67% to 82%. Also, ferrocenylacetylene **15** was investigated *via* the one-pot optimized condition, which produced the desired products **16** in a good yield (R = H, 85% and R = Cl, 87%).

Saikia and co-workers[34] synthesized 1,4-disubstituted 1,2,3-triazole derivatives **20** *via* the reaction of benzyl bromide derivatives **19**, NaN_3 **18**, and alkyne derivatives **17** in the presence of Cu(II) precatalyst in MeOH at 65 °C for 8–10 min under microwave irradiation (Scheme 7).

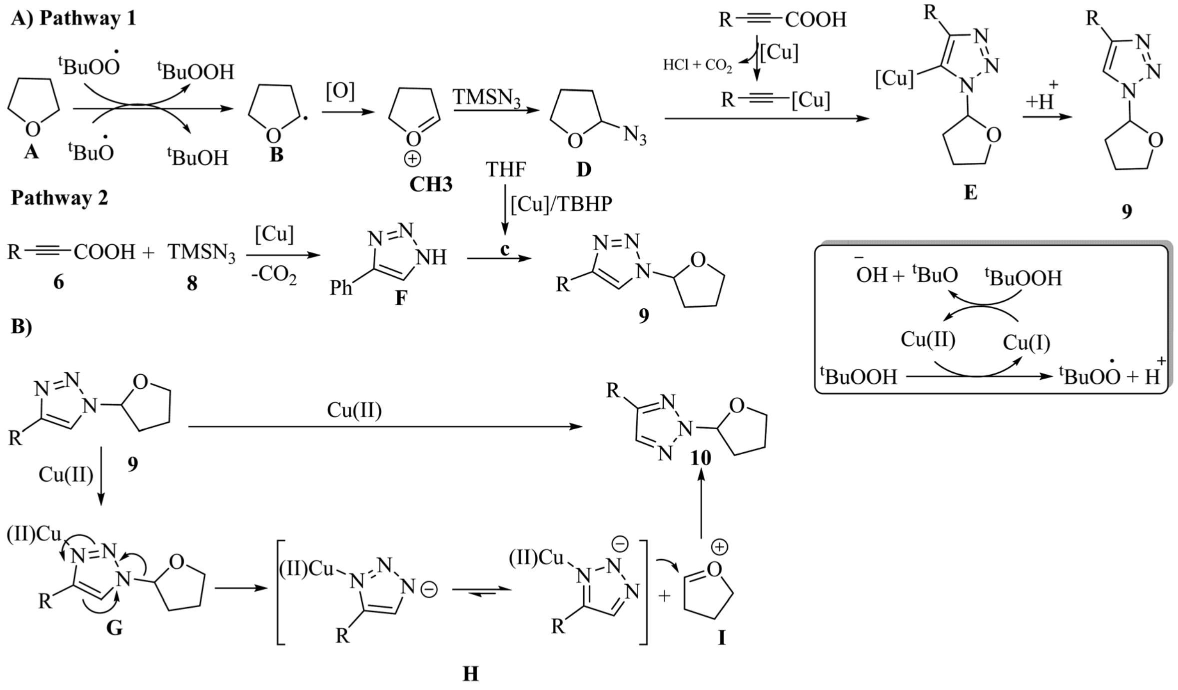
In the first stage, the reaction between **18** and organic halides in MeOH forms azides. Then, the Cu(II) catalyst is added and reduced by MeOH to Cu(I) species. Subsequently, **17** is added and forms **T**. Finally, **20** is generated *via* the protonolysis of **T** (Scheme 8).

Different types of benzyl bromide and alkyne derivatives were investigated, and results showed that the corresponding products were produced in 85–95% yield. Also, aromatic alkyne derivatives bearing an electron-withdrawing substitute such as F did not have an effect on the reaction result.

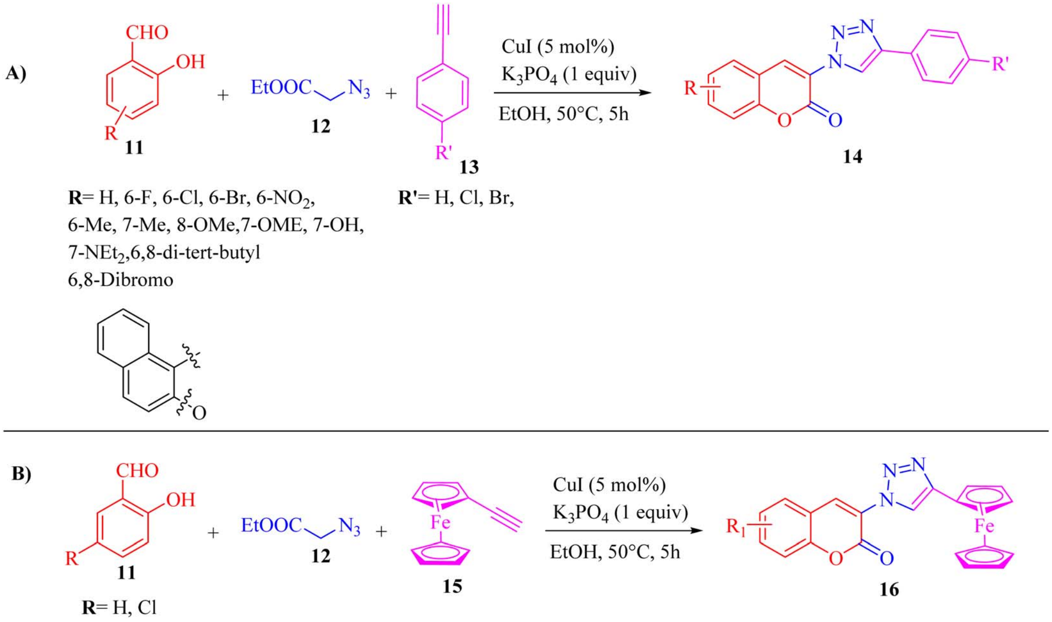
Zhang and co-workers[35] synthesized 5-trifluoromethylthio-1,2,3-triazole derivatives **23** using S_8, alkynes **21**, (trifluoromethyl)trimethylsilane ($TMSCF_3$), and 4-methoxybenzyl azide ($PMBN_3$) **22** (Scheme 9).

The desired products were obtained in two steps. In the first step, $PMBN_3$, alkynes, CuI, and KF in DMF were mixed at 0 °C for 3 h. In step 2, S_8, Ag_2CO_3 as a silver salt, 1,10-phen as a ligand, and $TMSCF_3$ were mixed at room temperature for 12 h.

S_8 and $TMSCF_3$ convert to $[(phen)Cu(SCF_3)]_2$ in the presence of CuI, 1,10-phen, and KF, which reacts with intermediate **S** and



Scheme 4 Possible reaction mechanism for the synthesis of (A) N^1-alkylated 1,2,3-triazoles and (B) N^2-alkylated 1,2,3-triazoles.[32]

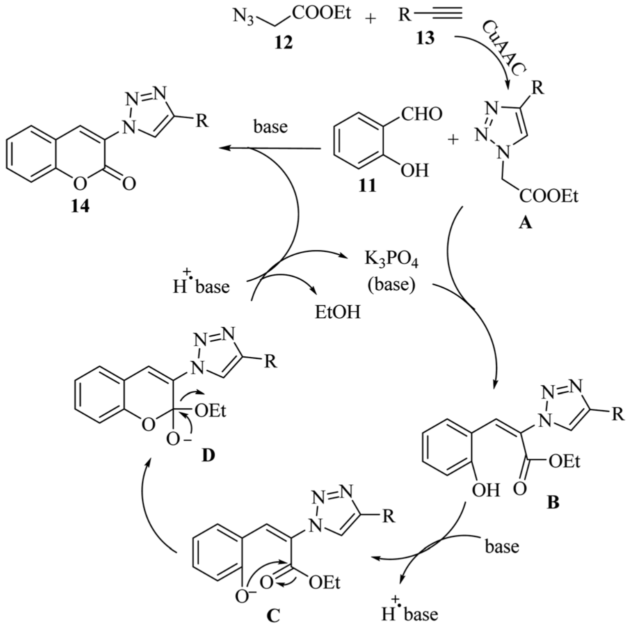


Scheme 5 (A) Synthesis of 3-triazolylcoumarin derivatives **14** and (B) synthesis of 3-(4-ferrocenyl)-trizaolycoumarins **16**.[33]

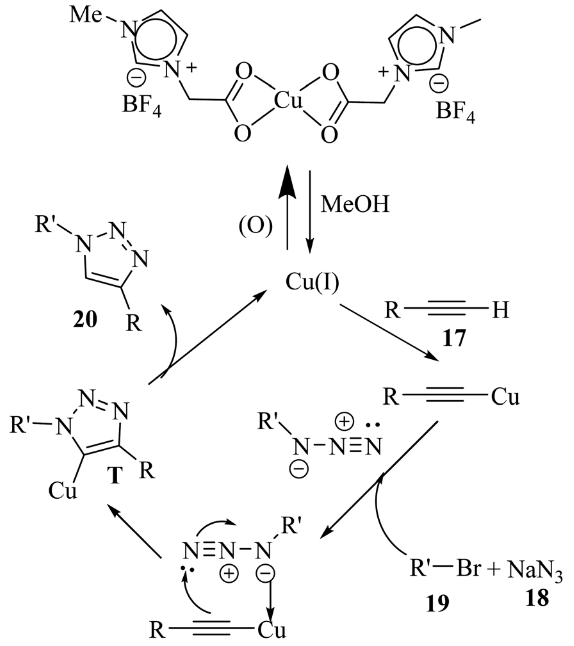
generates key intermediate **K**. Finally, **23** is prepared *via* the reductive elimination of **K** (Scheme 10).

Alkyne derivatives with electron-donating substituents on the aryl gave the desired products in 74–75% yield, whereas electron-withdrawing groups led to lower yields with an isolated yield of 30–48%. Also, alkyl alkynes produced the corresponding triazole derivatives in moderate yields in the range of 36–56%.

Khandar *et al.*[36] synthesized 1,4-disubstituted 1,2,3-triazoles **28** *via* the reaction of $R'N_3$ **26**, alkyne derivatives **27** and benzyl halide derivatives (**24** and **25**) using a novel binuclear copper(II)–oxalate complex as the catalyst in H_2O at 70 °C (Scheme 11). Various benzyl chloride derivatives **24** with both electron-donating and -withdrawing groups (H, 2-Me, and 4-NO_2) were reacted with phenylacetylene and produced the corresponding triazole derivatives in 99%, 77%, and 87% yields, respectively. It



Scheme 6 Possible reaction mechanism for the synthesis of 3-triazolylcoumarin derivatives.[33]



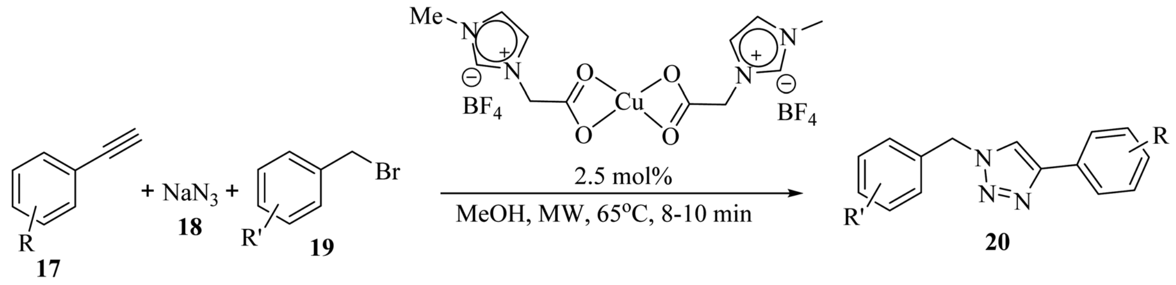
Scheme 8 Possible reaction mechanism for the synthesis of 1,4-disubstituted 1,2,3-triazole derivatives.[34]

seems that 2-Me substituted benzyl chloride resulted in a much lower yield due to the steric hindrance effect. Also, substituting phenylacetylene with dimethyl propargyl alcohol and propargyl alcohol decreased the reaction yield (34% and 64%, respectively). In addition, the reaction of benzyl bromide **25** with dimethyl propargyl alcohol and propargyl alcohol led to the production of the corresponding products in 73% and 74% yield, respectively.

Liu and co-workers[37] synthesized sulfuryl-substituted *N*-vinyl-1,2,3-triazole derivatives **32** *via* the reaction of vinyl azide surrogate **30**, S- and O-nucleophiles **31** and alkynes **29** in the presence of CuI/Pd(PPh$_3$)$_4$, and Et$_3$N in DMSO at 60 °C for 2 h (Scheme 12).

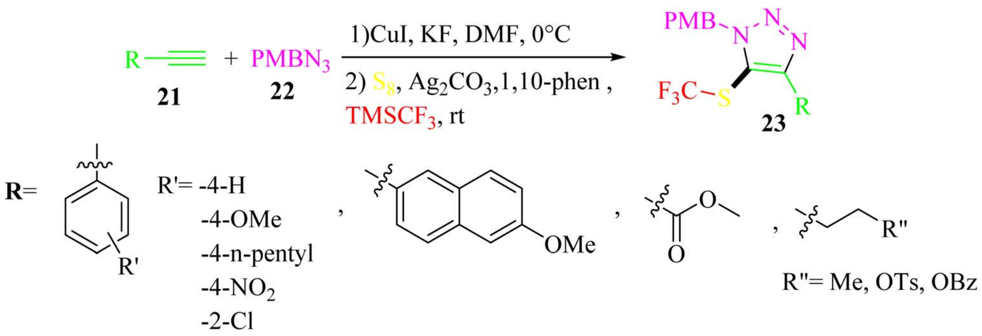
Active palladium species **Q** was prepared *via* the dissociation of Pd(PPh$_3$)$_4$ catalyst, which underwent oxidative addition with **30** to generate complex **R**. Then, intermediate **R** reacted with **31** and generated functionalized vinyl azide **S**. Next, activated acetylide **T** and intermediate **S** reacted *via* a click reaction and produced Cu(I) triazoles **U**. Finally, **32** was generated *via* the protolysis of **U** by trace H$_2$O in solvent or air (Scheme 13).

In the case of **29**, *para*-substituted aromatic alkyne derivatives bearing various groups gave the desired triazole derivatives in 82% to 88% yield. Also, substrates with *meta*-substituents such as halogen, Me, and amino gave the desired triazole derivatives in 78% to 88% yield. In addition, *ortho*-substituents on the benzene ring of the alkyne derivatives were reacted and produced the desired triazole derivatives in 80% to 83% yield. Also, S-containing aromatic alkynes in the reaction were tolerated and the corresponding triazole derivatives obtained in 75–77% yield. Furthermore, alkenyl and aliphatic alkynes were tested and the corresponding triazole derivatives obtained in 72% to 82% yield. A variety of aliphatic alkynes with heteroatoms was reacted and produced the corresponding triazole derivatives in 74% to 79% yield. Various sulfinates were reacted with phenylacetylene and the results showed that aryl sulfinates

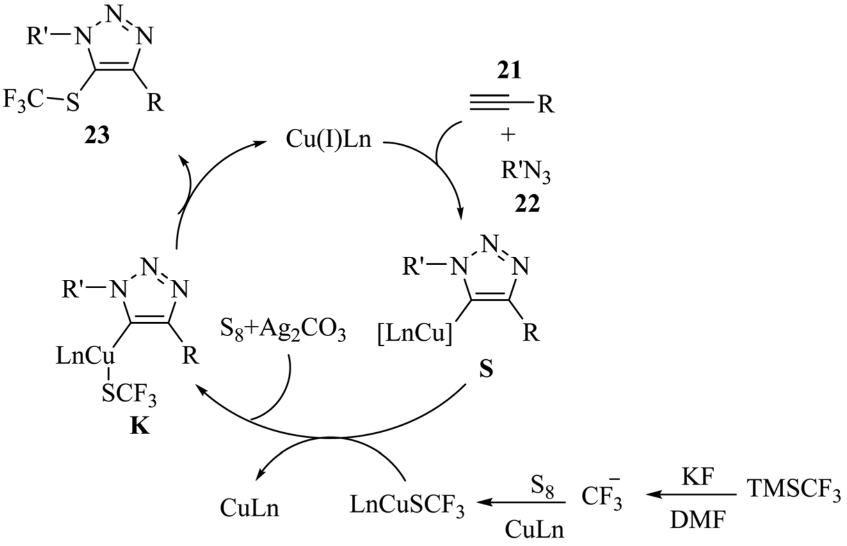


R=H, 4-Me, 4-F, 4-hexane
R'=H, 4-NO2, 4-CN, 3-Me

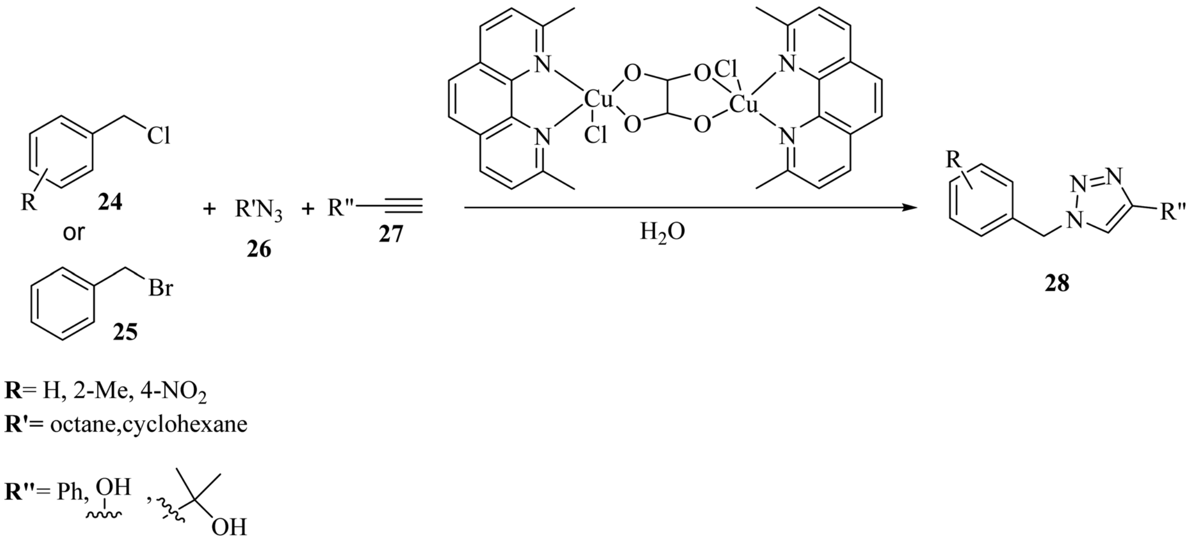
Scheme 7 Synthesis of 1,4-disubstituted 1,2,3-triazole derivatives **20** using a ionic liquid-supported Cu(II) catalyst.[34]



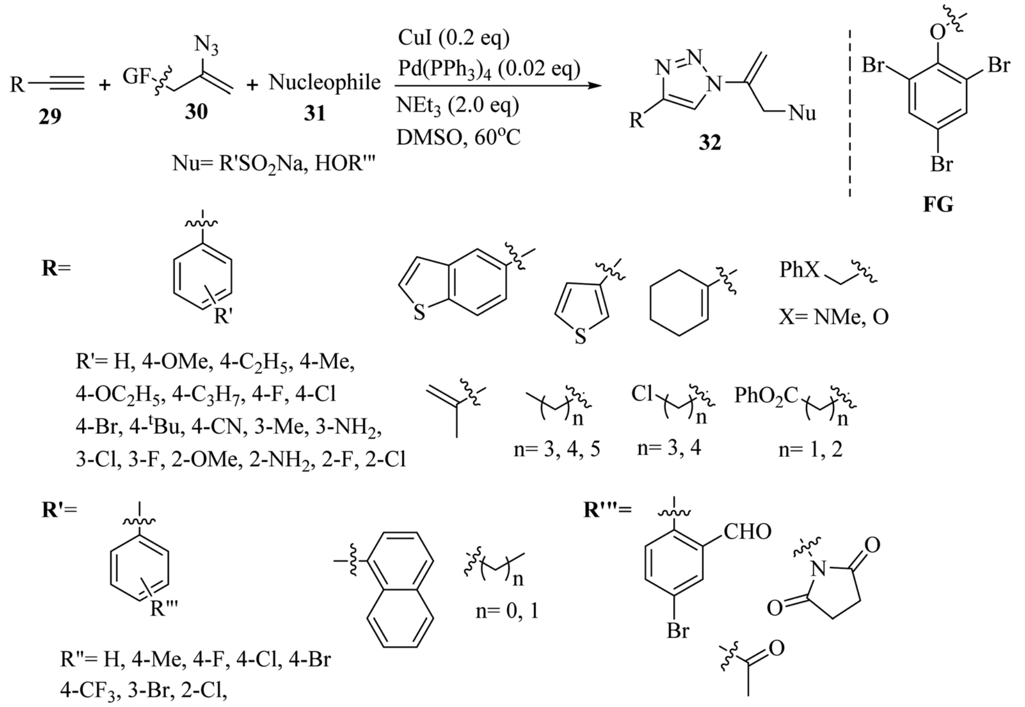
Scheme 9 Synthesis of 5-trifluoromethylthio-1,2,3-triazole derivatives **23**.[35]



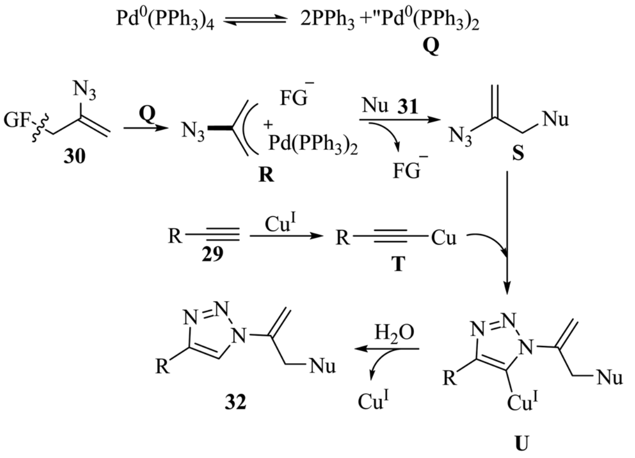
Scheme 10 Possible reaction mechanism for the synthesis of 5-trifluoromethylthio-1,2,3-triazole derivatives **23**.[35]



Scheme 11 Synthesis of 1,4-disubstituted 1,2,3-triazoles **28** *via* the binuclear copper(II)–oxalate complex containing 2,9-dimethyl-1,10-phenanthroline.[36]



Scheme 12 Synthesis of *N*-vinyl-1,2,3-triazoles **32** *via* CuI.[37]



Scheme 13 Possible reaction mechanism for the synthesis of sulfuryl-substituted *N*-vinyl-1,2,3-triazole derivatives **32**.[37]

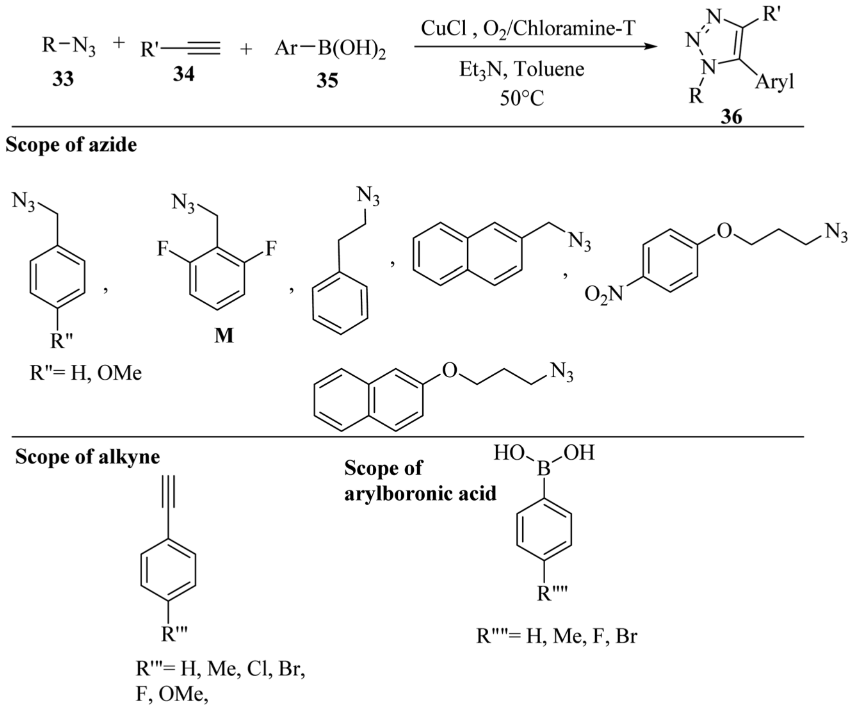
with *para*-substituents produced the corresponding triazole derivatives in 78% to 89% yield. *Ortho*- and *meta*-substituted aryl sulfinates were also reacted and produced the desired triazole derivatives in 83% to 82% yield, respectively. In addition, 2-naphthyl sulfinate produced the corresponding product in 85% yield. Alkyl-substituted sulfonate derivatives were also evaluated in the above-mentioned method and produced the corresponding triazole derivatives in 74% to 77% yield. Finally, a variety of O-nucleophiles **31** was reacted and the corresponding triazole derivatives obtained in 69% to 83% yield.

Wang and co-workers[38] synthesized 5-aryl-1,4-disubstituted 1,2,3-triazole derivatives **36** *via* one-pot *in situ* oxidative-coupling. The compounds were prepared using arylboronic acid derivatives **35**, organic azide derivatives **33** and alkyne derivatives **34** in the presence of O_2/chloramine-T as an oxidant, CuCl as a catalyst, and TEA in toluene at 50 °C (Scheme 14).

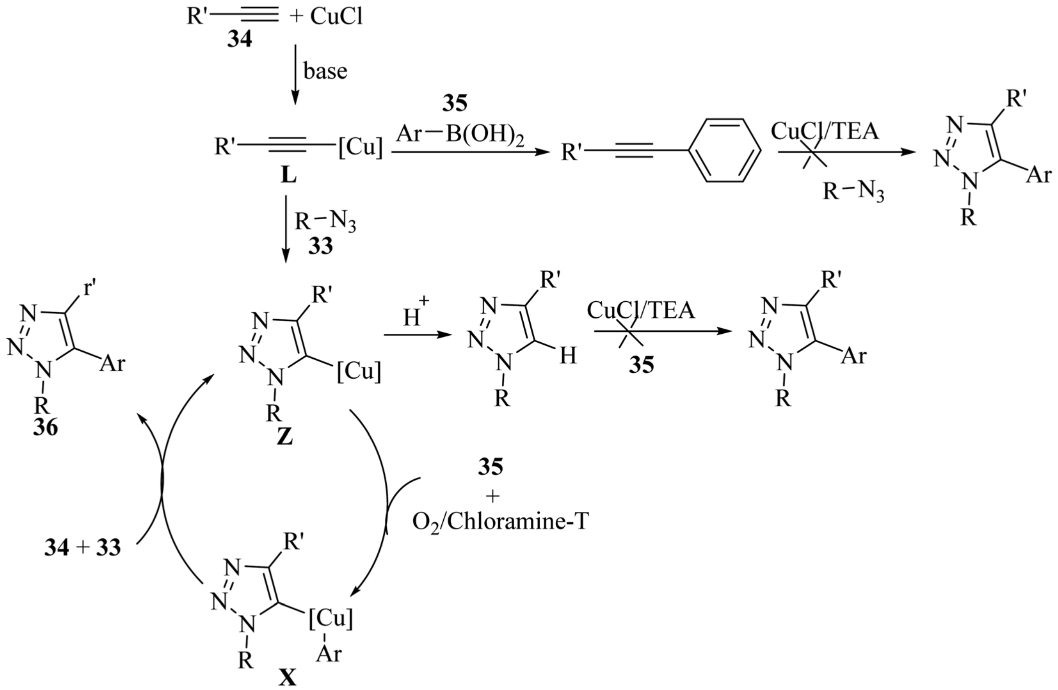
Intermediate **L** was produced *via* the reaction between **34** and CuCl in the presence of TEA. Then, intermediate **L** reacted with **33** *via* the CuAAC reaction and generated triazolide copper **Z**. Next, **Z** reacted with **35** under oxidative conditions and generated **X.** It should be noted that transmetalation must take place, and then the protonation of **Z** (Scheme 15).

The benefits of this method include the use of a low reaction temperature, low-cost catalyst, and less-toxic additive. The reaction among aryl alkynes with various substituents, arylboronic acids, and benzyl azides produced 5-aryl-1,2,3-triazoles in 80–90% yield. The reaction among various alkyl azides with different substituted groups, benzyl azides, and arylboronic acids produced triazole derivatives in moderate to good yield (68–80%). Azide **M** with 2,5-difluorobenzyl motifs that exist in the clinic drug rufinamide reacted with arylboronic acids and terminal alkynes and produced triazole derivatives, showing that this method has potential applications for drug screening.

Camberlein and co-workers[39] synthesized 1,5-disubstituted 1,2,3-triazole derivatives **40** *via* the reaction between NaN_3 **39**, alkyne derivatives **38**, and bromides **37** in the presence of Cp_2Ni (precatalyst), Cs_2CO_3, and xantphos ligand in DMF under microwave irradiation at 50 °C for 4 h (Scheme 16). Various alkynes (aromatic and aliphatic) **38** were evaluated, and the desired triazole derivatives were obtained in 27% to 84% yield. According to the regioselectivity of *para*-NO_2 phenylacetylene (ratio 66 : 34) with respect to phenylacetylene (ratio 89 : 11), and then *para*-F phenylacetylene (ratio 91 : 9) and *para*-OMe

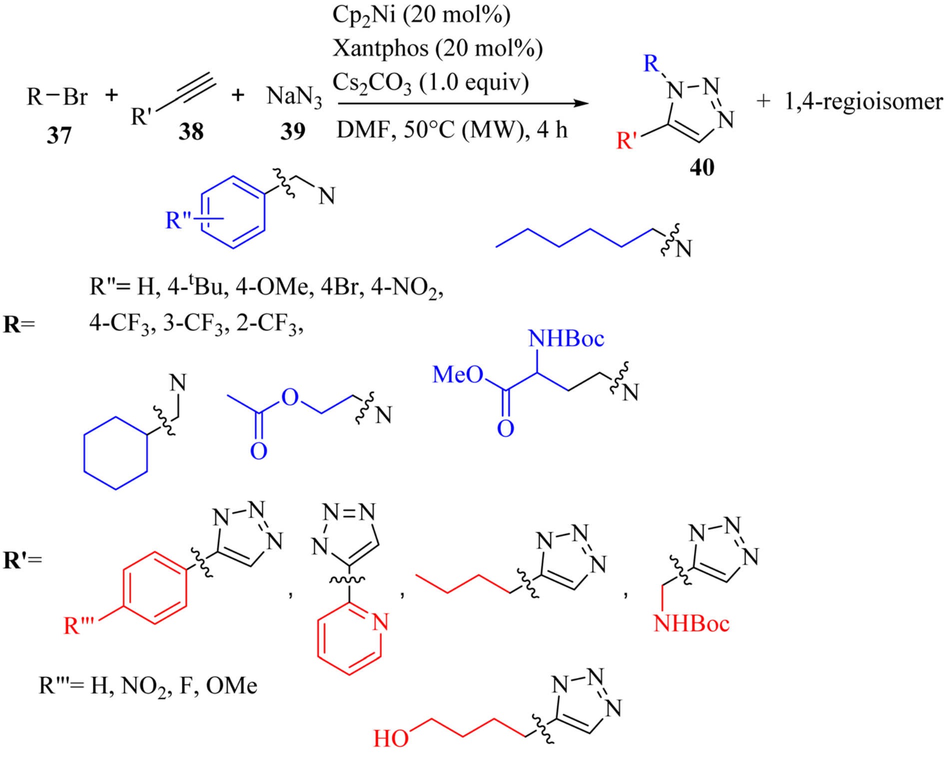


Scheme 14 Synthesis of 1,2,3-triazole derivatives **36** using CuCl.[38]



Scheme 15 Possible reaction mechanism for the synthesis of 5-aryl-1,4-disubstituted 1,2,3-triazole derivatives **36**.[38]

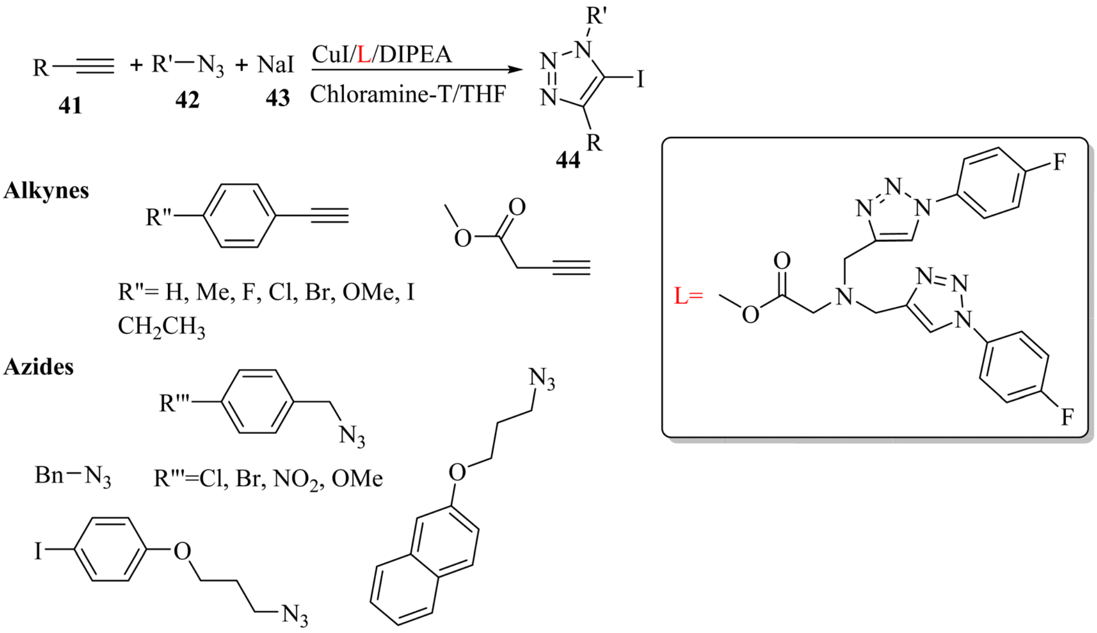
phenylacetylene, it had a positive mesomeric effect on the phenyl ring, but did not affect the yield. Interestingly, heteroaryl and alkyl chains can be employed in the above-mentioned reaction. In the case of the scope of bromide derivatives **37**, aromatic benzyl bromides bearing electron-donating or electron-withdrawing groups after flash chromatography purification (64–79%) and semi-preparative SFC (31–84%) purification produced the corresponding 1,5-regioisomers in high yields. The ortho isomer in this series was obtained in the lowest yield due to the steric effect. The regioisomerism of the



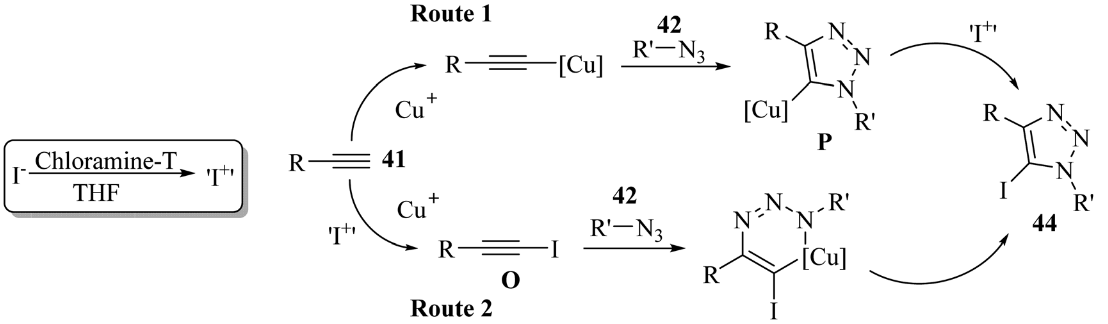
Scheme 16 Synthesis of 1,2,3-triazole derivatives using the nickelocene (Cp_2Ni) precatalyst.[39]

phenyl substitution did not influence the regioselectivity (ratio = 85 : 15 to 97 : 3) and only had a minor effect on the yield. Also, functional groups (ester and carbamate-protected amine) were tolerated in the reaction and produced the corresponding triazole derivatives in 34% and 90% yield, respectively.

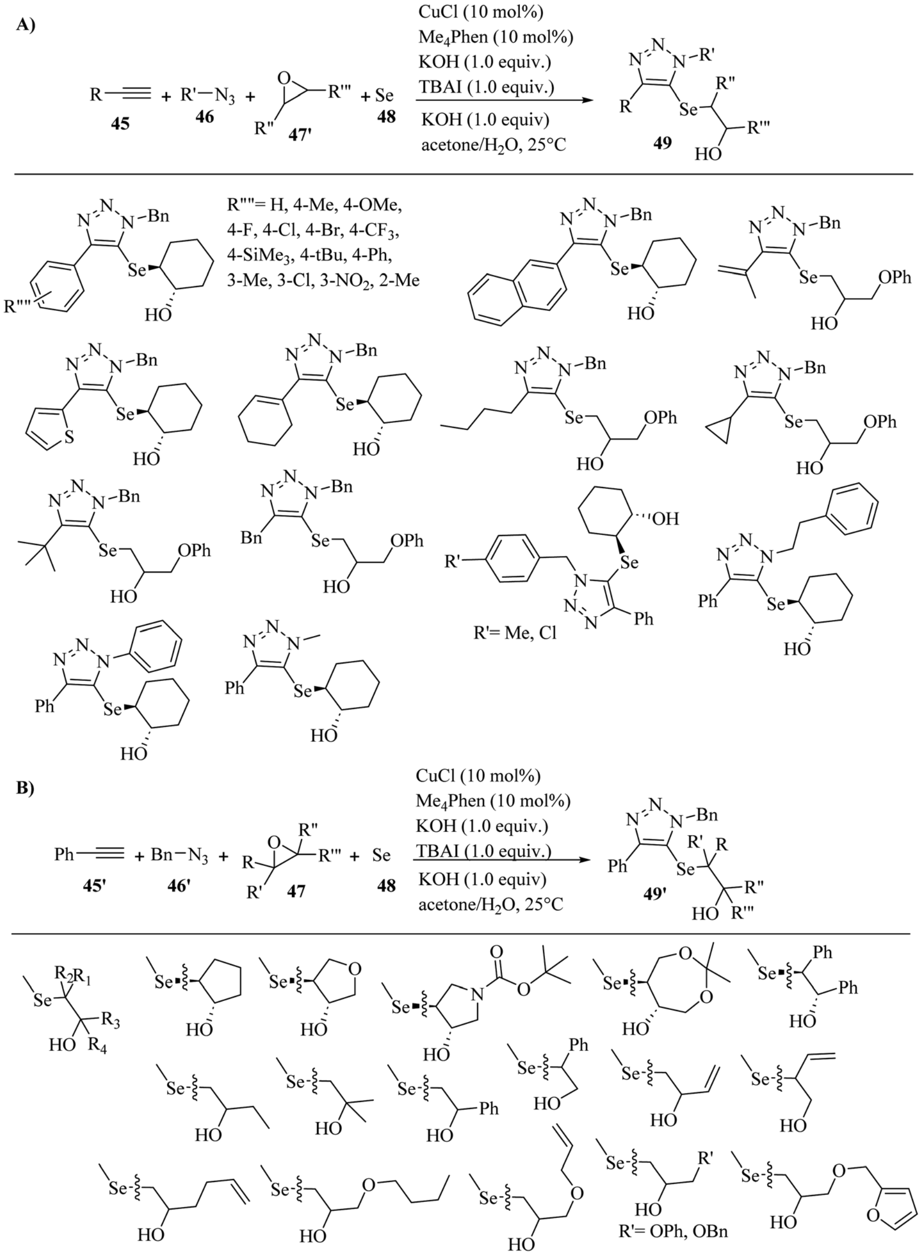
Yuan *et al.*[40] synthesized 5-iodo-1,4-substituted 1,2,3-triazoles **44** *via* the reaction among terminal alkyne derivatives **41**, organic azide derivatives **42**, and NaI **43** in the presence of CuI, DIPEA as a base, chloramine-T as an oxidant, and L as a ligand in THF under an N_2 atmosphere at 50 °C (Scheme 17).



Scheme 17 Synthesis of 5-iodo-1,4-substituted 1,2,3-triazoles **44** by CuI.[40]



Scheme 18 Possible reaction mechanism for the synthesis of 5-iodo-1,4-substituted 1,2,3-triazoles **44**.[40]



Scheme 19 Synthesis of triazole derivatives using CuCl catalyst. (A) Substrate scope of alkyne derivatives and azide derivatives. (B) Substrate scope of epoxide derivatives.[41]

Two reaction pathways were proposed by the authors. It should be noted that **43** was oxidized to electrophilic "I^+" by chloramine-T. In pathway B, iodoalkyne(III) **O** may be generated *via* iodination directly on **41**, whereas in pathway A, iodination may occur on intermediate copper triazolide(II) **P** (Scheme 18).

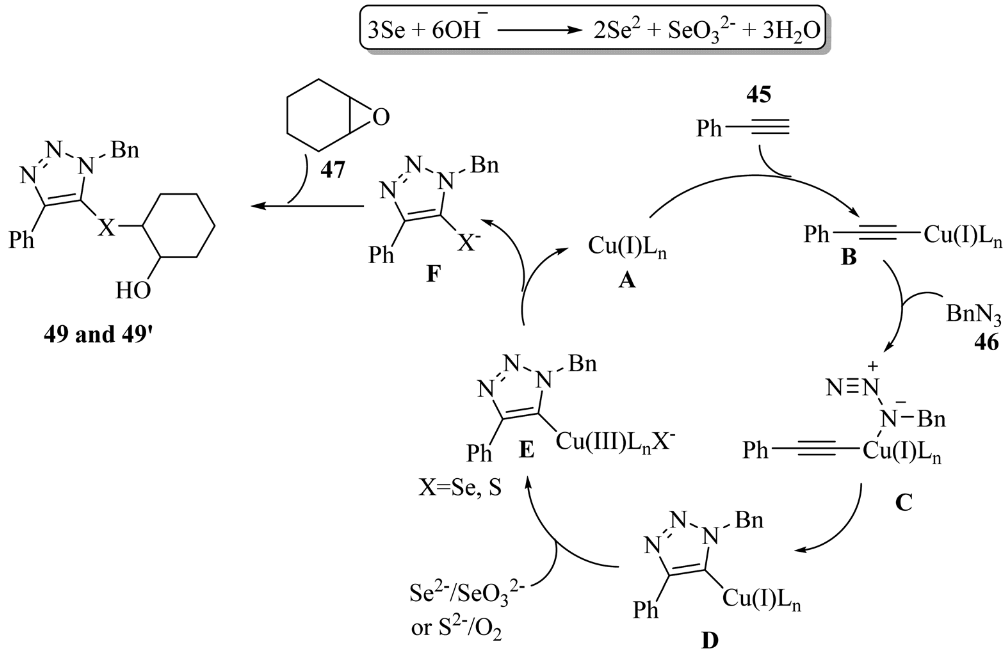
Also, **41** and **42** were investigated. Phenylacetylenes bearing various groups were reacted and produced the desired triazole derivatives in 71% to 78% yield. Also, benzyl azides with electron-withdrawing and -donating substituents were tested and the desired triazole derivatives obtained in 67% to 84% yield. In addition, alkyl azides were tolerated in the reaction and the desired triazole derivatives obtained in 73% to 74% yield.

In 2021, Wang and co-workers[41] synthesized triazoles bearing β-hydroxy chalcogenides (**49** and **49′**) *via* the reaction among terminal alkyne derivatives **45**, azide derivatives **46**, epoxide derivatives (**47** and **47′**), and Se/K_2S **48** in the presence of CuCl, Me_4Phen as a ligand, KOH as a base, and TBAI as an additive in acetone/H_2O [1/1(v/v)] at 25 °C for 6 h under an air atmosphere (Scheme 19).

Initially, Se^{2-} and SeO_3^{2-} were produced *via* the disproportionation reaction of Se in the presence of KOH. Then, **45** reacted with copper salt **A** and generated copper(I) acetylide **B**. Subsequently, **B** reacted with **46** and produced triazolyl-copper **D** by [3 + 2] cycloaddition. In this stage, cycloaddition included the coordination of **46** with **B** to afford a six-membered ring intermediate, and then generated 5-cuprated triazole *via* reductive elimination. Next, copper(III) species **E** was generated *via* the ligand exchange of **D** with Se^{2-}/S^{2-} and oxidation by SeO_3^{2-}/O_2. In the next step, **E** generated triazolylchalcogenide anion **F** *via* reductive elimination together with the release of the copper(I) catalyst. Finally, **49** or **49′** was produced by nucleophilic attack of **F** to **47** (Scheme 20).

In the case of **45** (Scheme 11a), phenylacetylenes with both electron-withdrawing and -donating groups (Me, OMe, F, Cl, Br, CF_3, Me_3Si, ^{t}Bu, Ph, and NO_2) on the benzene ring were reacted and produced the desired triazole derivatives in 39% to 81% yield and >20 : 1 dr. Importantly, the electronic effect of phenylacetylenes affected the yield. Phenylacetylene derivatives containing CF_3 and NO_2 gave the products in low yields (45% and 39%, respectively). In addition, thienylacetylene and naphthylacetylene reacted well and produced the corresponding products in 82% and 65% yield, respectively. Also, alkenyl-substituted alkyne derivatives showed high reactivity under the above-mentioned conditions and produced the corresponding products in 64–65% yield. Moreover, alkyl-substituted alkyne derivatives containing 3,3-dimethylbut-1-yne, ethynylcyclopropane, prop-2-yn-1-ylbenzene, and hex-1-yne were reacted with elemental selenium, epoxide, and azide and produced the corresponding products in 70%, 66%, 72%, and 70% yield, respectively. In the case of **46** (Scheme 19A), Cl- and Me-substituted benzyl azides were tested and produced the corresponding triazole derivatives in 68% and 76% yield, respectively. Also, phenethyl azide was tested and produced the corresponding triazole in 68% yield. In addition, phenyl azide was tested and produced the desired triazole in 40% yield. Especially, (trimethylsilyl)methyl azide also reacted well and produced the 1-Me substituted 1,2,3-triazole in 54% yield and >20 : 1 dr. In the case of the scope of **47** (Scheme 19B), epoxide derivatives containing linear, aromatic, aliphatic, and cyclic epoxides reacted with elemental selenium **48**, phenylacetylene **45′**, and benzyl azide **46′** and produced the corresponding 5-selenotriazoles **49′** in 47% to 79% yield.

In 2023, Sun *et al.*[42] synthesized ditriazolyl diselenides (**53** and **53′**) *via* the reaction among azides (**51** and **51′**), terminal alkyne derivatives **50**, and elemental selenium **52** in the

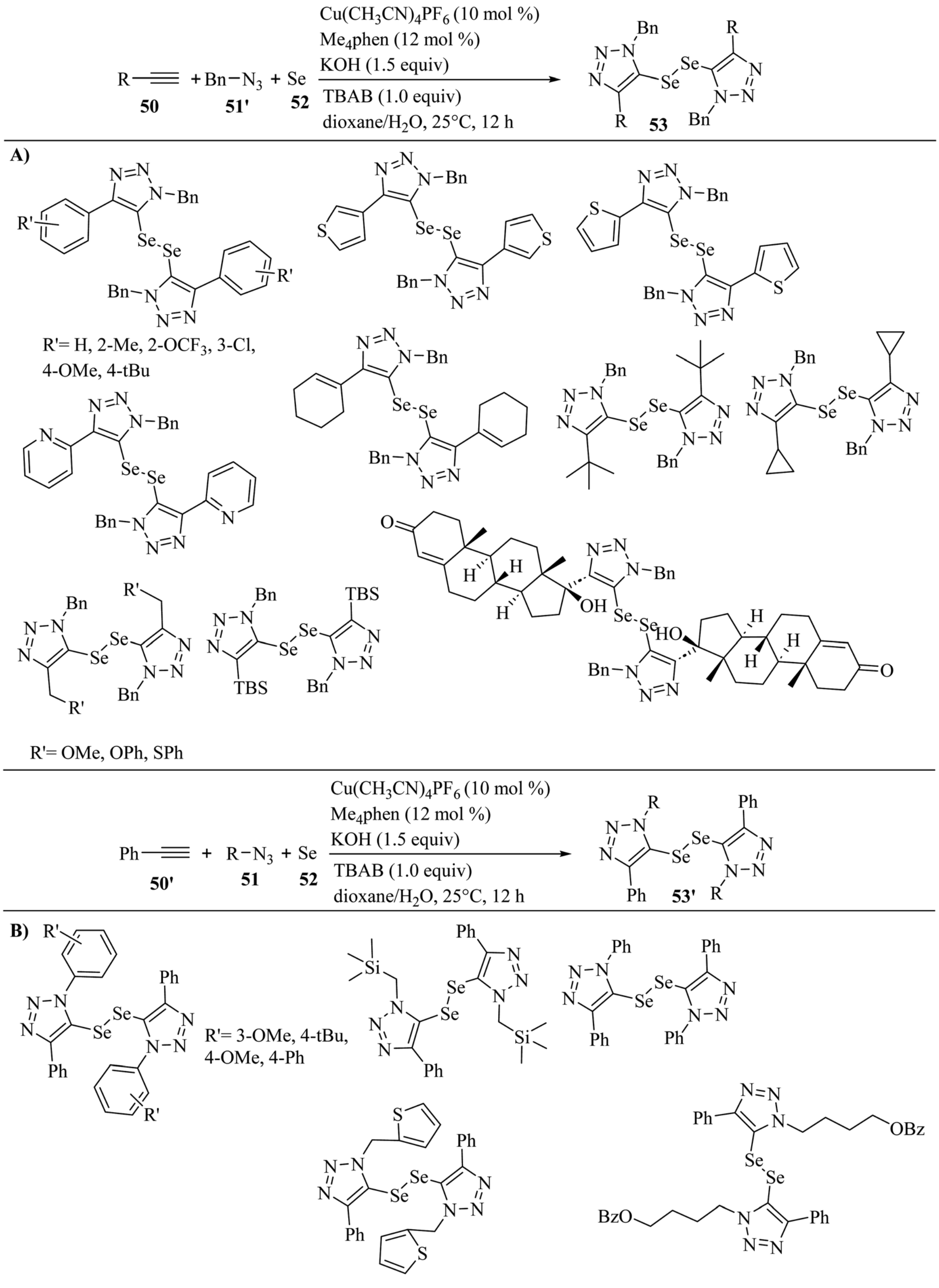


Scheme 20 Possible reaction mechanism for the synthesis of triazoles bearing β-hydroxy chalcogenides.[41]

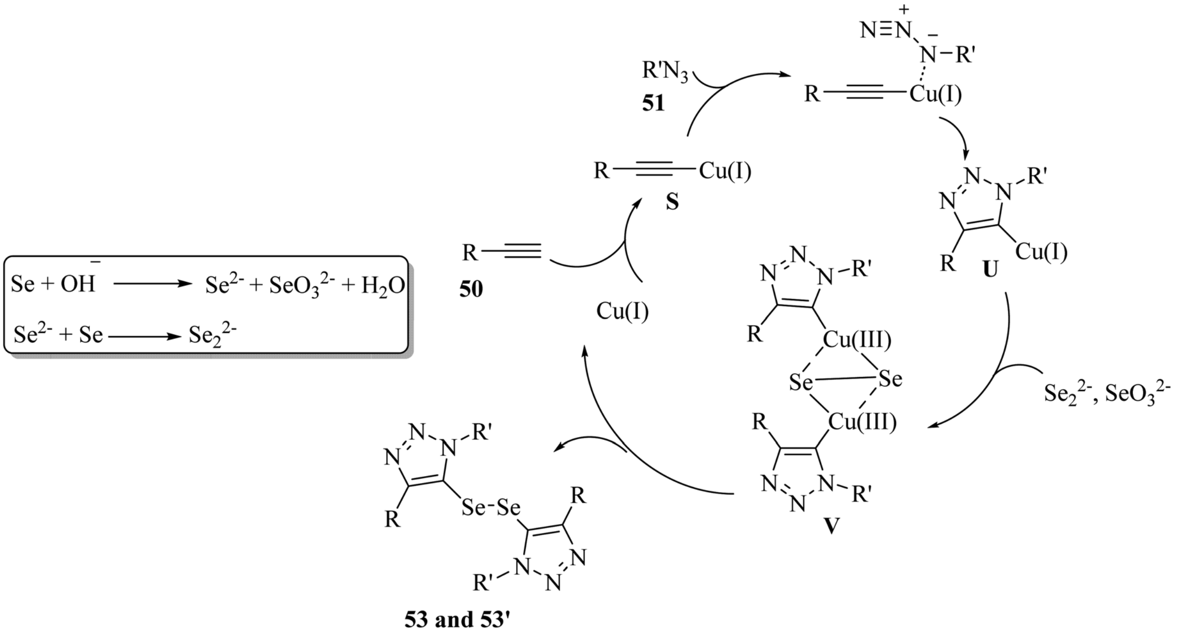
presence of $Cu(CH_3CN)_4PF_6$, Me_4phen, KOH, and tetrabutylammonium bromide in dioxane/H_2O at 25 °C for 12 h (Scheme 21).

SeO_3^{2-} and Se^{2-} were produced *via* the disproportionation of **52** in the presence of KOH. Then, Cu(I) reacted with **50** and generated alkynyl copper **S**. Next, **S** in the presence of **51** underwent cycloaddition and generated 5-cuprated triazole **U**. After that, copper(III) species **V** was produced *via* the exchange of **U** with Se_2^{2-} and oxidation by SeO_3^{2-}. Finally, intermediate **V** generated **53** or **53′** and Cu(I) *via* reductive elimination (Scheme 22).

The above-mentioned reaction produced the corresponding products with high atom-economy. In the case of **50** (Scheme 21A), phenylacetylenes containing Me, ^{t}Bu, OMe, OCF_3, and Cl on the phenyl ring were tested and produced the corresponding products in 40–75% yield. Also, ethynylthiophenes showed high reactivity and produced the corresponding ditriazolyl



Scheme 21 Synthesis of ditriazolyl diselenides in the presence of $Cu(CH_3CN)_4PF_6$. (A) Substrate scope of alkynes and (B) substrate scope of azides.[42]



Scheme 22 Possible reaction mechanism for the synthesis of ditriazolyl diselenides.[42]

diselenides in 53–57% yield. Unfortunately, 2-ethynylpyridine did not produce the corresponding product. Alkenyl-substituted alkyne in the above-mentioned reaction was tested and produced the corresponding ditriazolyl diselenide in 62% yield. Also, alkyl-substituted alkynes in the above-mentioned method were tolerated in the present transformation. Moreover, phenoxy-, phenylthio-, and methoxy-incorporated alkyl alkynes reacted well and the corresponding ditriazolyl diselenides obtained in 51–73% yield. Also, butyldimethylsilyl (TBS)-substituted alkyne was compatible and gave the desired product in 55% yield. It should be noted that ethisterone-derived alkyne demonstrated high reactivity and afforded the desired diselenide in 51% yield. In the case of **51** (Scheme 21B), tBu-, OMe-, and phenyl-substituted benzyl azide derivatives **51** reacted with **50′** and **52** and produced the corresponding ditriazolyl diselenides **53′** in 47–59% yield. Also, 2-(azidomethyl)-thiophene reacted smoothly in the above-mentioned reaction and afforded the desired ditriazolyl diselenide in 73% yield. Subsequently, (trimethylsilyl)-methyl azide reacted well with elemental selenium and phenylacetylene to obtain the desired ditriazolyl diselenide in 48% yield. 4-Azidobutyl benzoate was suitable in the above-mentioned reaction and produced the desired ditriazolyl diselenide in 57% yield. Unfortunately, phenyl azide failed to give the corresponding product in this method.

A summary of the reaction of alkyne derivatives with various RN_3 derivatives, and also the limitation of some reactions are presented in Table 1.

2.2 Reaction of sulfur-containing compounds

Ansari *et al.*[49] synthesized (*Z*)-β-phenoxy vinylsulfones **57** *via* the reaction between phenols **56**, 1-phenyl-1-propyne **54**, and sodium sulfonate derivatives **55** in the presence of I_2 and K_2CO_3 in EtOH at 60 °C (Scheme 23).

Initially, sulfonyl radical **Q** was generated *via* the reaction between I_2 and **55**. Subsequently, radical **Q** reacted with **54** and produced vinyl sulfone radicals **X**. After that, the vinyl sulfone radical was attacked by $R'SO_2I$, I_2, or $I^{\bullet}$ and generated β-iodovinylsulfone intermediate **Y**. Next, intermediate **Z** was generated *via* the nucleophilic addition of PhO^- to intermediate **Y**. Finally, intermediate **Z** produced the desired product *via* the elimination of iodide (Scheme 24).

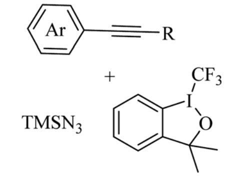
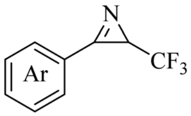
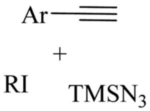
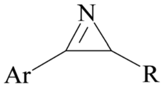
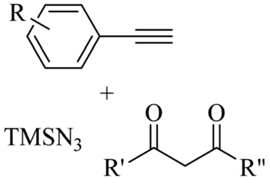
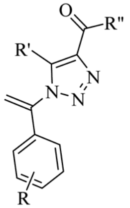
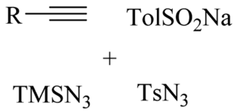
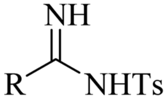
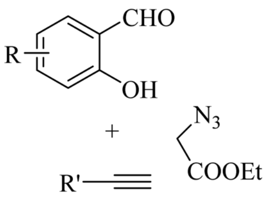
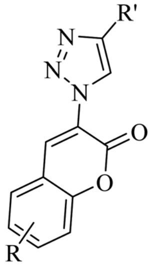
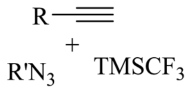
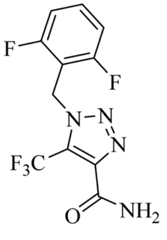
The desired products were obtained in 73% to 87% yield. According to the results, the electron-deficient groups (Cl and CF_3) on the phenyl ring gave lower reactivity than electron-rich groups (Me and *t*-Bu). In addition, the internal alkynes and aliphatic terminal alkynes produced **57** in 72–77% yield.

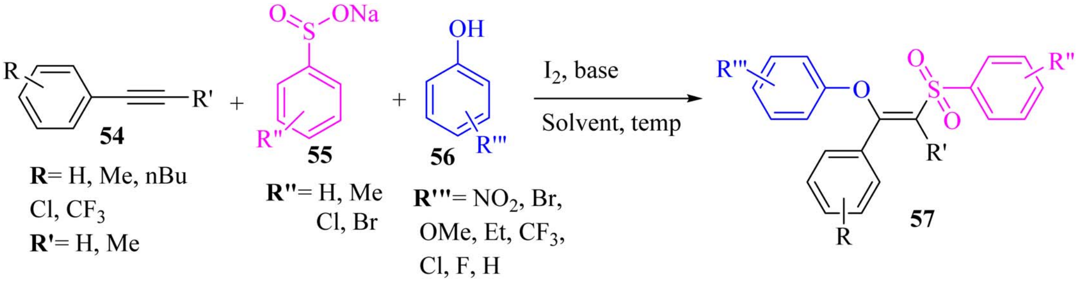
Chen *et al.*[50] constructed C–S and C–Se bonds and produced unexpected β-sulfonylvinylselane structures **60** *via* the reaction among alkyne derivatives **58**, SO_2, and diselenides **59** in high selectivity for the E configuration (Scheme 25).

Initially, **59** under blue light irradiation generated selenium radical **O**. Then, **58** reacted with **O** and produced vinylic radical intermediate **P**, which after being captured by SO_2, produced sulfonyl radical intermediate **Q**. After that, vinylic radical intermediate **R** was generated *via* the attack of radical intermediate **Q** to **59** and trapped by **59**. Finally, **60** was obtained (Scheme 26).

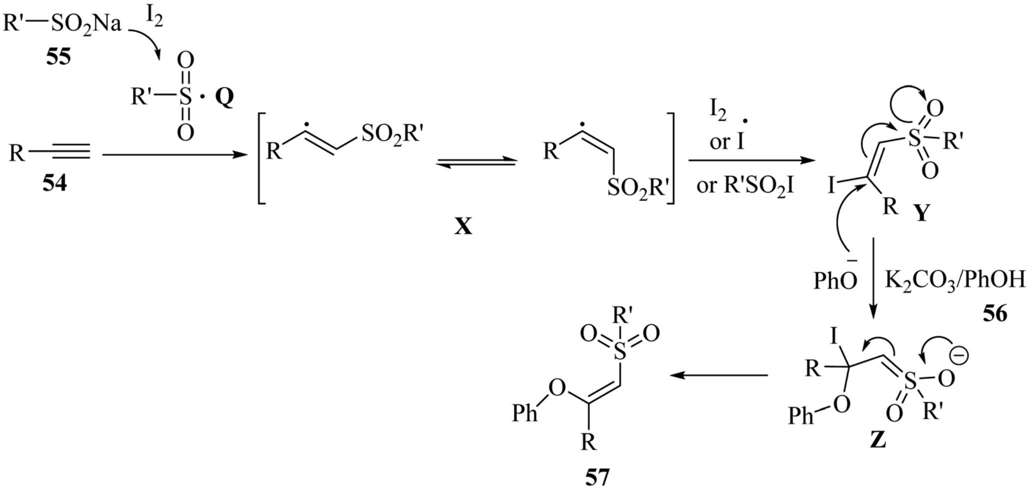
The starting materials were mixed in CH_3CN under blue LEDs. The unexpected β-sulfonylvinylselanes were produced in good yield (up to 71%). According to the results, when various substrate alkynes **58** on the phenyl ring were used, the desired unexpected β-sulfonylvinylselanes were produced in 35–71% yield and when 4-ethynyl-1,1′-biphenyl was used, the unexpected β-sulfonylvinylselane was obtained in 54% yield. Also, 3-ethynylpyridine and its isomer were investigated and the corresponding unexpected β-sulfonylvinylselanes were obtained in moderate to low yield (42% and 3%, respectively). In contrast,

Table 1 A summary of the reaction of alkynes with various RN_3 and the limitations of the reactions

Reactants	Product	Catalyst	Solvent	Method employed	Reaction time	Yield	Limitations	Ref.
		CuBr	(1) MeOH (2) Toluene	(1) RT, N_2 (2) *hν*	(1) 8 h (2) 2–6 h	23–70%	Alkyl-substituted alkynes had poor reactivity and produced trace amount of corresponding product	Wang *et al.*[43]
		$Fe(OTf)_3$	(1) DME (2) Toluene	(1) TBPB, RT (2) 120 °C	(1) 5–20 min (2) 10 min	30–78%	Reaction of ethynylbenzene and 1-iododecane did not produce the desired product	Xiong *et al.*[44]
		Ag_2SO_4	DMF	K_2CO_3, H_2O, 70 °C	8 h	17–86%	Alkyne containing electron-donating group produced the products in lower yields than those with an electron-withdrawing group	Chen *et al.*[45]
		Ag_3PO_4	DMSO	H_2O, 70 °C	4–10 h	52–85%	(1) C≡C triple bond cleavage (2) High product yield (3) High efficiency (4) An unprecedented 4-component reaction (5) Good functional group tolerance	Liu *et al.*[46]
		CuI	EtOH	K_3PO_4, 50 °C	5 h	Trace-90%	(1) Four new bonds formation (2) Large-scale synthesis (3) Eco-friendly (4) Mild conditions	He *et al.*[47]
		CuI	DMF	Phen, Ag_2CO_3, Et_3N, Ar, RT	15 h	Up to 87%	– 2 equiv. $AgNO_3$ as the oxidant – Only CF_3- substitution – Only alkyl azides as valid reactants	Cheung *et al.*[48]



Scheme 23 Synthesis of (*Z*) β-phenoxy vinylsulfone derivatives **57**.[49]



Scheme 24 Possible reaction mechanism for the synthesis of (*Z*)-β-phenoxy vinylsulfones **57**.[49]

alkyl acetylene was unsuitable and the corresponding product not obtained. In the case of alkyl diselenides, the tandem reactions of 1,2-dimethyldiselane with 3- ethynylthiophene, 4-methylphenylacetylene, phenylacetylene, and 4-bromophenylacetylene produced the corresponding unexpected β-sulfonylvinylselanes in good yield of 47% to 64%.

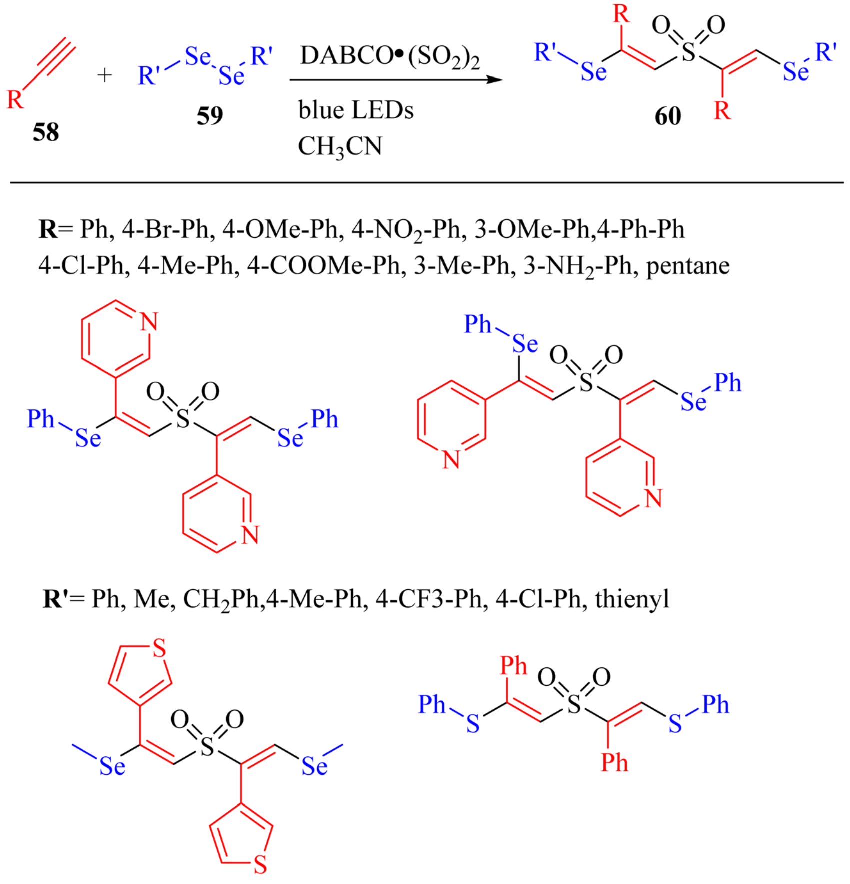
Zhu and co-workers[51] synthesized stereo-defined olefins **64** *via* single electron/triplet energy transfer and nickel catalysis. This strategy is a good method for producing tri-substituted alkenes. The reaction proceeded *via* the reaction among aryl halide derivatives **61**, alkyne derivatives **62**, and sodium sulfonate **63** in the presence of an Ru photocatalyst, $NiCl_2\cdot$dme, and 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine as a ligand in DMF at room temperature for 24 h under blue LED irradiation (7.4 W) (Scheme 27).

Initially, the Ru^{II} or Ir^{III} complex absorbed visible light in the photocatalytic cycle and generated $^*Ir^{III}$ or $^*Ru^{II}$ triplet excited state. Then, the radical precursor was oxidized to the corresponding radical and formed Ru^{I} and Ir^{II} reductants. The desired radical was added to a Ni^{I} complex and entered the Ni catalytic cycle. Subsequently, it underwent reduction and 1,2 migratory insertion of alkyne, producing **A**. Then, intermediate **B** was produced by intermediate **A** under Ni-assisted *anti*/*syn* isomerization. Next, intermediate **C** was produced by intermediate **B** *via* the oxidative addition of the aryl halide. Subsequently, **64** was generated from intermediate **C** *via* reductive elimination (Scheme 28).

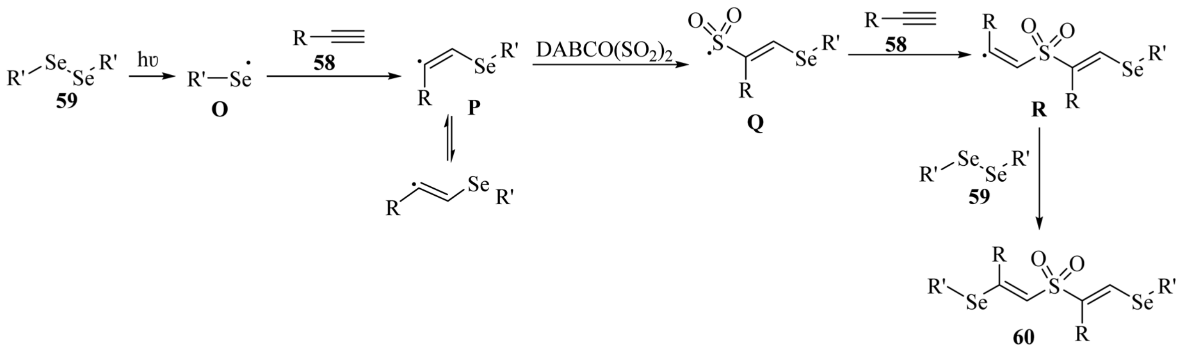
According to the results, various alkynes with various functional groups were used (boronic ester, acetal, amine, bromide, ester, fluoride, chloride, alkyl, methoxy, and methylthio groups) and produced the desired olefins in 29–99% yields. Furthermore, 3-ethynylthiophene produced the corresponding olefin in 76% yield and cyclohexenyl alkyne and internal alkyne derivatives were suitable substrates for producing the desired products (29–60%).

Yi *et al.*[52] synthesized arylamidines **69** *via* the four-component reaction of sulfonyl azide derivatives **65**, terminal alkyne derivatives **66**, water **67**, and oxime halide **68** by [3 + 2] cycloaddition in the presence of triethylamine and Cu(I) in DCM at room temperature for 12 h under open air (Scheme 29).

Initially, ketenimine intermediate **F** was generated *via* the reaction between **66** and TsN_3 in the presence of Et_3N and CuI. Then, oxime halide **68** generated nitrile oxide **G** under Et_3N. Subsequently, **G** reacted with intermediate **F** and produced intermediate **H** *via* the formal [3 + 2] cycloaddition reaction. Next, intermediate **I** was generated *via* the electronic ring opening of intermediate **H** with the help of OH^- or H_2O. Intermediate **I** reacted with OH^- or H_2O and produced intermediate **J**, accompanied by the formation of **66**. Finally, **69** was obtained from intermediate **J** in the presence of OH^- or H_2O,



Scheme 25 Synthesis of β-sulfonylvinylselane **60** *via* the visible-light-mediated multicomponent reaction.[50]



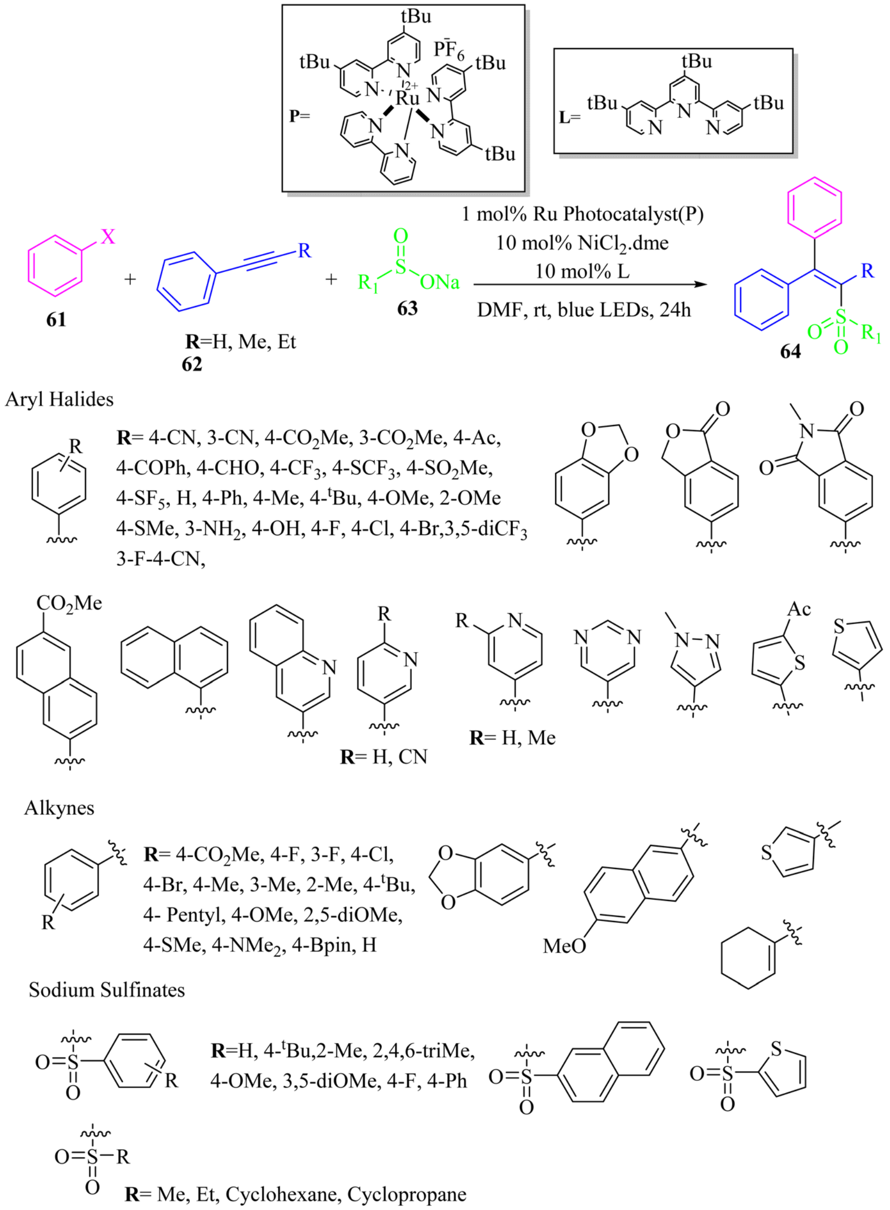
Scheme 26 Possible reaction mechanism for the synthesis of unexpected β-sulfonylvinylselanes **60**.[50]

accompanied by the release of O_2. It should be noted that the role of H_2O in the reaction is important, which provides the OH^- anion and the source of proton, and also may promote the cleavage of the N–O and C–O bonds (Scheme 30).

According to the results, arylamidines were produced in 68–92% yield. Importantly, oxime chloride derivatives **68** as the carbon source and water **67** played a critical role in the reaction. In addition, terminal alkyne derivatives, which can lead to high yields of corresponding products using lower amounts of reactant, may play a catalytic role.

Hazarika *et al.*[53] synthesized 2-[(*ortho*-methylthio)aryloxy] substituted dialkyl maleates **73** *via* the reaction among alkyne derivatives **70**, DMSO **72**, and aryne derivatives **71** in the presence of KF at 50 °C (Scheme 31).

Initially, four-membered ring intermediate **E** was formed *via* the reaction between benzyne, which was produced *in situ*, and DMSO. Then, intermediate **E** underwent ring opening due to the ring strain, and *o*-quinone intermediate **F** was generated. Zwitterion **G** was the resonance form of **F**. **G** underwent nucleophilic attack to form the activated alkyne, and also

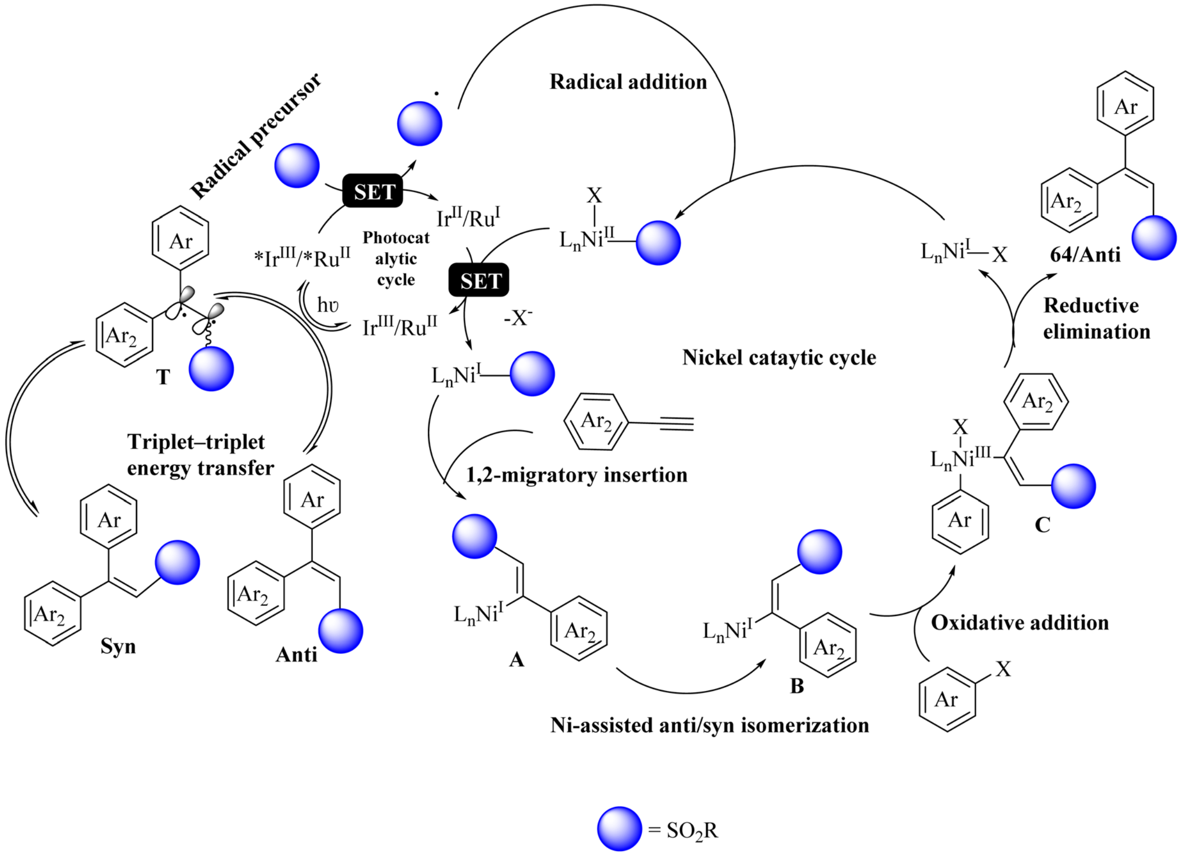


Scheme 27 Synthesis of tri-substituted alkenes *via* nickel catalysis.[51]

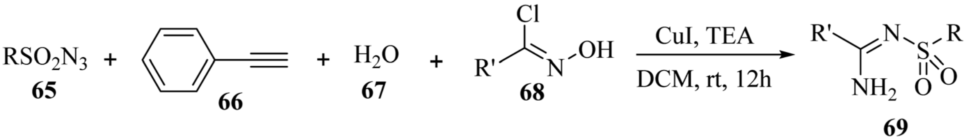
demethylation, which led to the generation of anion **H**. Finally, anion **H** produced **73** in the presence of H_2O (Scheme 32).

This strategy produces trisubstituted vinyl ethers with remarkable stereospecificity. According to the results, different types of activated alkyne derivatives treated with *o*-silyl aryl triflate produced the corresponding products in 63–81% yield. Notably, bulky alkyl group-substituted activated alkyne derivatives as a comparison to small alkyl group-substituted activated alkyne derivatives showed lower yields. Investigation of symmetrical aryne precursors showed that the desired products were produced in 59–77% yield. Interestingly, the symmetrical aryne precursors 3-(trimethylsilyl)-2-naphthyl trifluoromethanesulfonate, and 4,5-dimethoxy-2-(trimethylsilyl) phenyl trifluoromethanesulfonate produced a small amount of the corresponding products, which could be due to steric hindrance. Also, unsymmetrical aryne precursors such as 4-methoxy-2-(trimethylsilyl)phenyltrifluoromethanesulfonate and 2-methyl-6-(trimethylsilyl)phenyltrifluoromethanesulfonate were evaluated and produced the desired products in 66–69% yield. When the unsymmetrical aryne precursor 4-methyl-2-(trimethylsilyl)phenyltrifluoromethanesulfonate was treated with activated alkyne derivatives such as dimethylacetylenedicarboxylate and diethylacetylenedicarboxylate, regioisomer mixtures, they gave 69% and 63% yield, respectively.

In 2019, indolizine thione derivatives **76** were synthesized *via* the formation of C–N, C–C and C–S bonds *via* the reaction among ynals **75**, elemental sulfur, and 2-alkylpyridines **74** was reported by Chen and co-workers (Scheme 34).[54] Two conditions



Scheme 28 Possible reaction mechanism for the synthesis of stereo-defined olefins.[47]



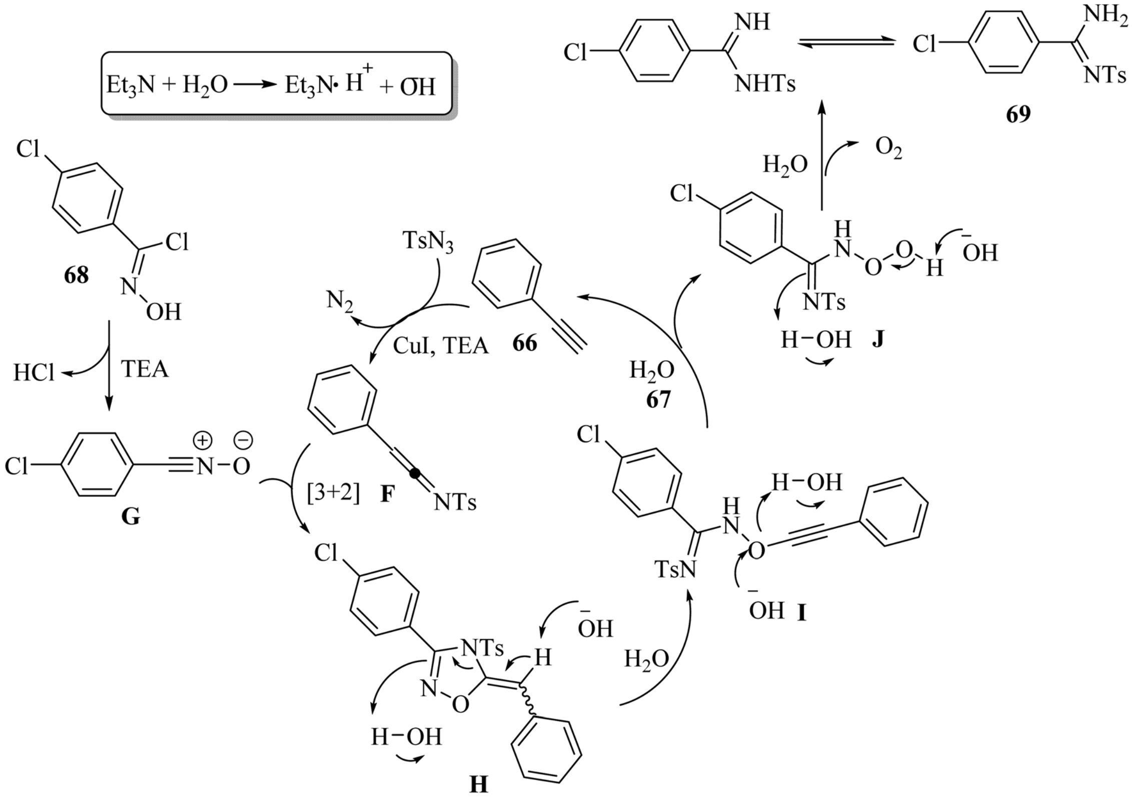
R= Me, Ph, 4-ClPh, 4-MePh, 4-NO$_2$Ph
R'= Ph, 2,4-diClPh, 4-MePh,3-MePh, 4-MeOPh,4-ClPh
4-BrPh, 3ClPh, 3-BrPh

Scheme 29 Synthesis of arylamidines **69** from oxime chlorides.[52]

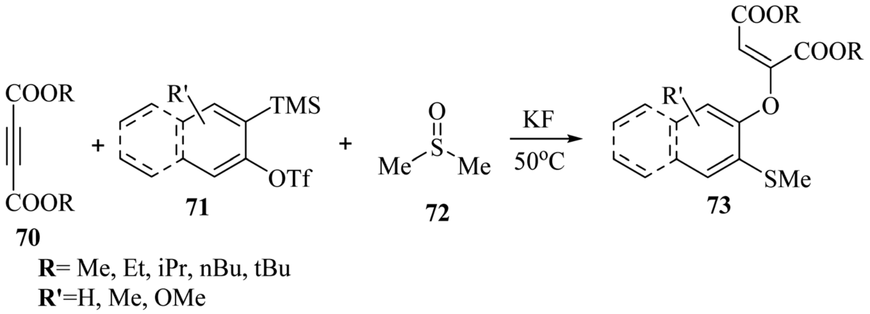
were investigated for the synthesis of indolizine thione derivatives **76**.

Firstly, **74** and **75** reacted and generated enyne intermediate **U** *via* Knoevenagel condensation. Intermediate **V** was produced from intermediate **U** *via* the intramolecular nucleophilic attack and activation of **S**. Then, the cleavage of the disulfide bond produced **76** (Scheme 33a). Also, **W** generated intermediate **Z** *via* the elimination process and electrophilic addition. Next, intermediate **Z** produced **76** *via* aminothiation with elemental sulfur (Scheme 33b).

The desired products were synthesized once in 50–88% yield in DMF under argon at 80 °C for 1 h, and again the reaction process for the synthesis of the corresponding products was carried out in the presence of iodine as a catalyst and under the same conditions for 4 h and products were obtained in 52–93% yield. According to the results without the catalyst, ynals **75** with different groups (electron-donating and -withdrawing) produced the corresponding indolizine thiones in 50–86% yield. Me or OMe at the *o*-position of the benzene ring had a low impact on the efficiency of the reaction. In addition, the disubstituted substrates (3,5-(Me)$_2$ and 3,5-(F)$_2$) produced the desired indolizine thiones in 70% and 52% yield, respectively. Ynals with strong and weak electron-poor substitutes reacted smoothly. In contrast, aliphatic ynal did not produce the corresponding indolizine thione. According to the results from the I_2-catalyzed aminothiation of 2-alkylpyridines, the ynal bearing a naphthalene moiety produced the desired indolizine thione in 93% yield. Interestingly, the heterocycle ynal produced the desired indolizine thione in 53% yield.



Scheme 30 Possible reaction mechanism for the synthesis of arylamidines **69**.[52]



Scheme 31 Synthesis of dialkyl maleates **3** from activated alkyne.[53]

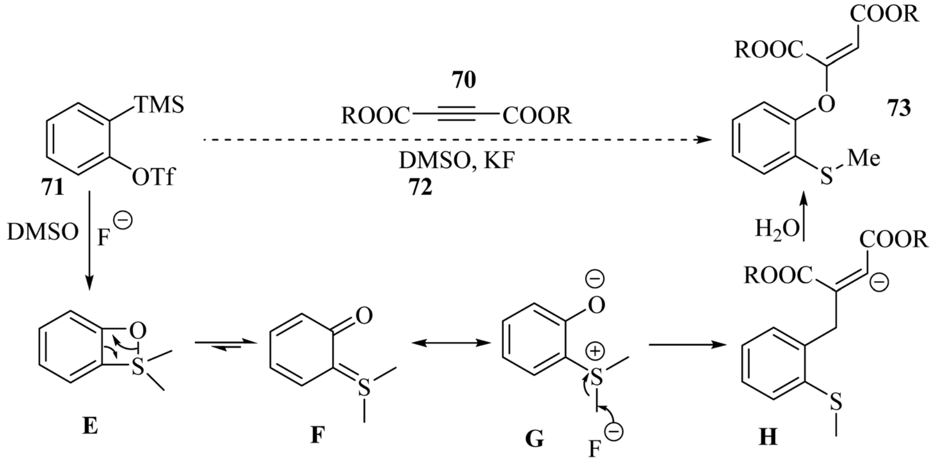
Jin and co-workers[55] synthesized 2,3-dihydro-1*H*-imidazo[1,2-*a*]indole derivatives **80** *via* the reaction among allylamine derivatives **79**, sulfonyl azide derivatives **78**, and alkyne derivatives **77** (Scheme 35). In the first step, triethylamine (Et_3N) as a base and CuI as a catalyst were added to the mixture in DMSO at room temperature for 1 h. After that, L1, K_2CO_3, and CuI were added to the mixture and heated at the temperature of 80 °C for 6 h.

Initially, **77** and **78** generated intermediate **G** *via* a Cu-catalyzed azide–alkyne cycloaddition reaction. Then, intermediate **G** produced ketenimine **H** by the extrusion of N_2, and carboxamidine **I** and/or its tautomer **I′** was generated *via* the nucleophilic addition of **79** to intermediate **H**. After that, **80** was produced *via* the Cu-catalyzed C–N coupling reaction (Scheme 36).

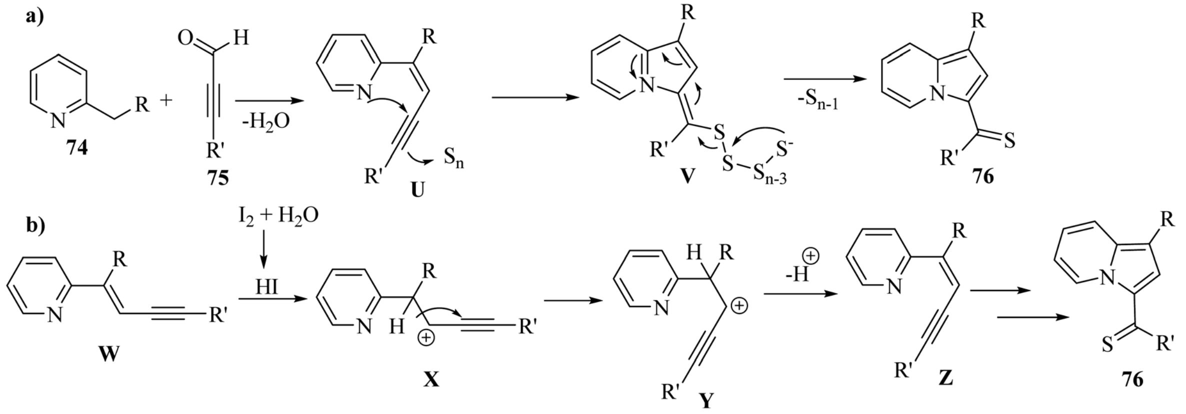
The corresponding products were produced with in isolated yield of 16–77%. According to the results, 1-bromo-2-ethnylbenzene demonstrated higher reactivity compared to the iodo- and chloro-substituted substrates. In addition, aromatic alkyne derivatives with different groups reacted with *para*-toluenesulfonyl azide.

Xu *et al.*[56] synthesized α,α-bis-sulfonyl arylketone derivatives **84** *via* the reaction among H_2O **83**, bromoalkyne derivatives **81**, and sulfinic acid derivatives **82** at room temperature under visible-light irradiation in DMSO solvent and N_2 atmosphere for 12 h (Scheme 37).

Initially, sulfinyl sulfones **B** were produced *via* the condensation of **A**, which decomposed to radical **C**. Then, radical **C** was added to **81** and generated intermediate **D**, which removed the



Scheme 32 Possible reaction mechanism for the synthesis of 2-[(*o*-methylthio)aryloxy]-substituted dialkyl maleate.[53]

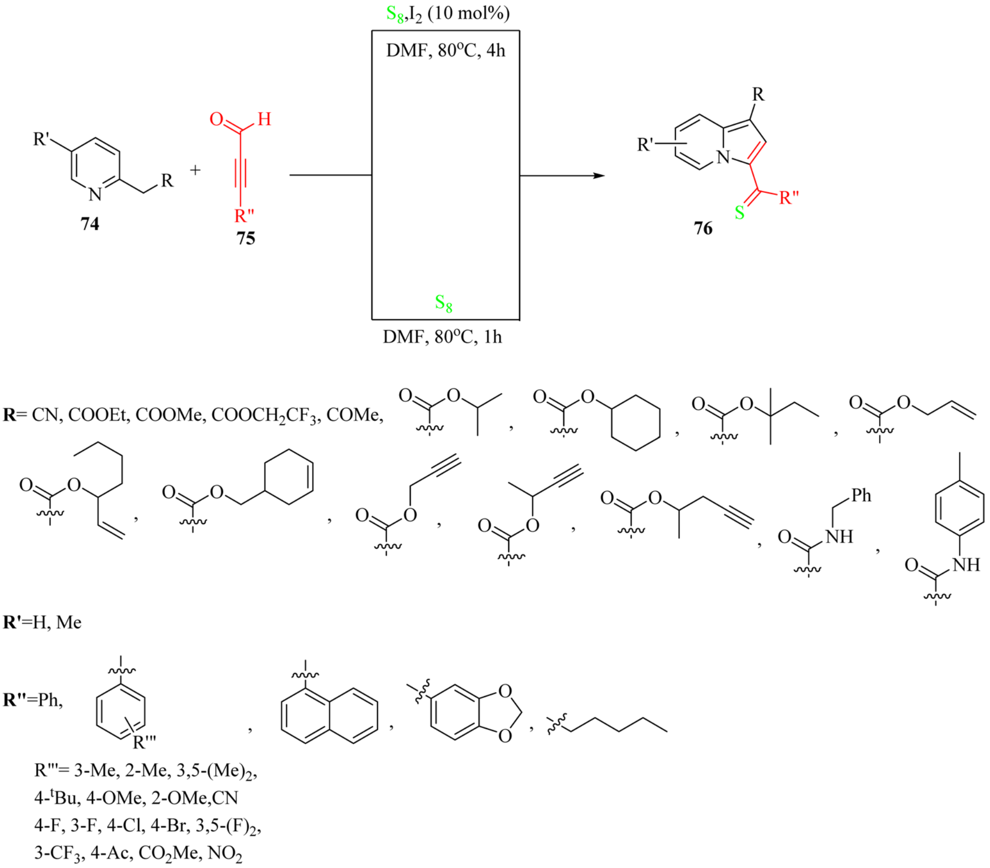


Scheme 33 Possible reaction mechanism for the synthesis of (a) indolizine thione derivatives without I_2 and (b) indolizine thione derivatives with I_2.[54]

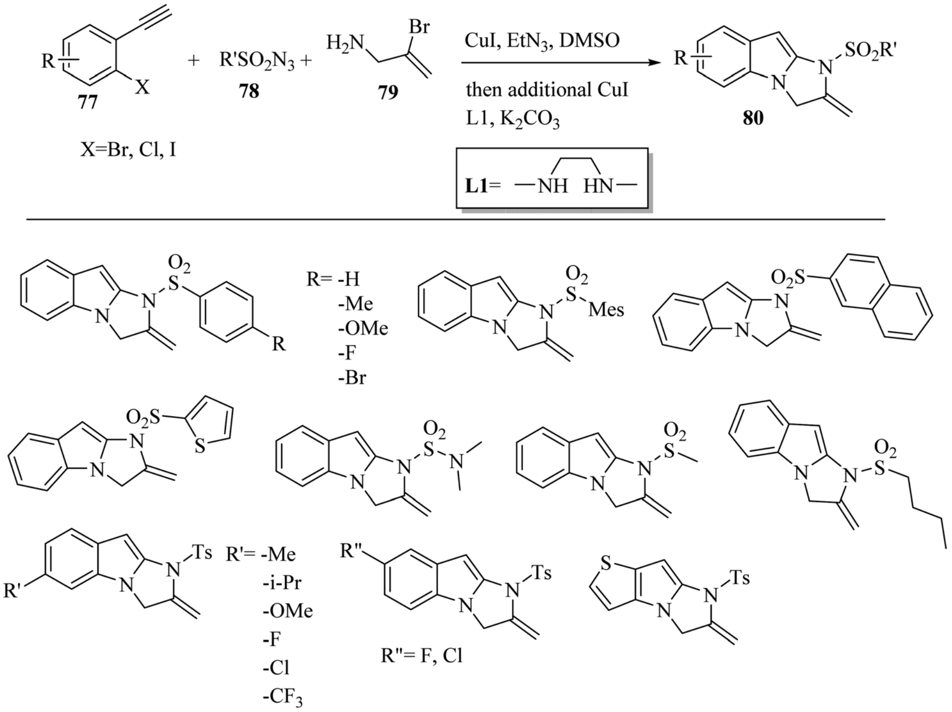
bromide radical (Br˙). After that, surplus sulfonyl **C** reacted with **E** to afford intermediate **F** *via* conjugate addition. Next, the hydroxyl radical (˙OH) coupled with intermediate **F** and produced intermediate **G**, which was tautomerized to **84**. It should be noted that ˙OH may be generated *via* the reaction between H_2O and possible radical intermediates (Scheme 38a). Also, **E** was afforded *via* a similar procedure, except intermediate **H** was produced *via* the 1,4-addition reaction of **E** and extra **A′**, and also an initial hydrolysis. In addition, Br˙ and alkynyl radical were generated *via* the homolytic cleavage of **81**. Next, intermediate **I** was produced *via* the coupling of intermediate **H** with an alkynyl radical. The important point about intermediate **I** was that it can be unstable. Finally, $R'SO_3H$ reacted with intermediate **I** *via* electrophilic addition and generated **86** (Scheme 38b).

In the case of **81**, aromatic bromoalkynes bearing *para*-Me, *meta*-Me, *para*-Et, *para*-Pr, and *para*-^{t}Bu were reacted with benzenesulfonic acid and produced the corresponding arylketone derivatives in 76% to 89% yield. A phenyl substituent at the para-position on the benzene ring of bromoalkyne produced the corresponding arylketone in 94% yield. Bromoalkyne derivatives with a halogen-substituent at the *meta*- and *para*-position were tested and produced the corresponding arylketone derivatives in 72% to 82% yield. In contrast, substrates with Cl at the *o*-position did not react with benzenesulfonic acid to obtain the corresponding product. CF_3 and thiophene substituents on the alkynyl bromide were also reacted and produced the corresponding arylketone derivatives in 68% and 53% yield, respectively. Importantly, the aliphatic bromoalkyne of 1-bromohex-1-yne was not transformed in this reaction, and no desired product was produced. Toluenesulfonic acid was tested and produced the corresponding arylketone in 60% yield. In contrast, when *o*-toluenesulfonic acid was employed, no reaction occurred. Furthermore, sulfonic acid derivatives with halogen substituents on the benzene ring produced the desired arylketone derivatives in 64% to 84% yield. An CF_3 group on the benzene ring was reacted and produced the desired product in 57% yield. In addition, benzenesulfonic acid with disubstituted groups of Me and F produced the corresponding product in 43% yield. Also, ethanesulfonic and methylsulfonic acid were tolerated and the desired arylketone derivatives obtained in 85% and 81% yield, respectively.

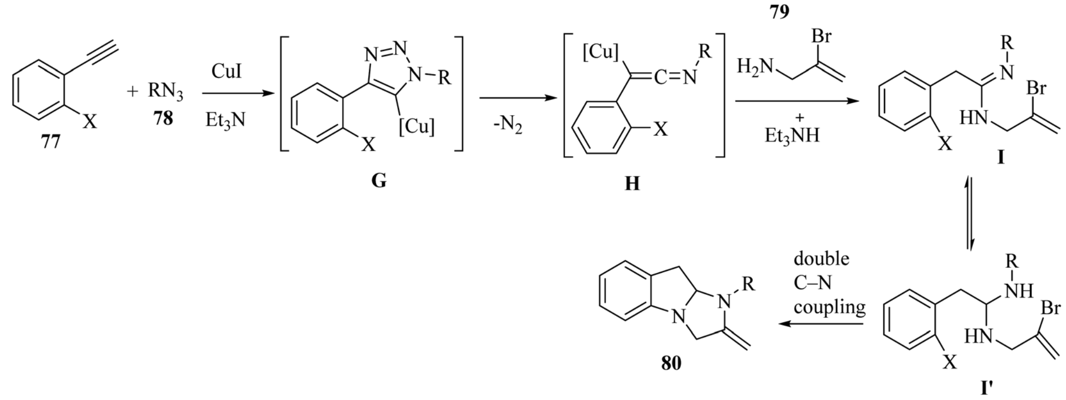
Bhat and Lee[57] synthesized 3-arylsulfonylated thioflavones **90** *via* the three-component reaction of aryl diazonium salts **88**,



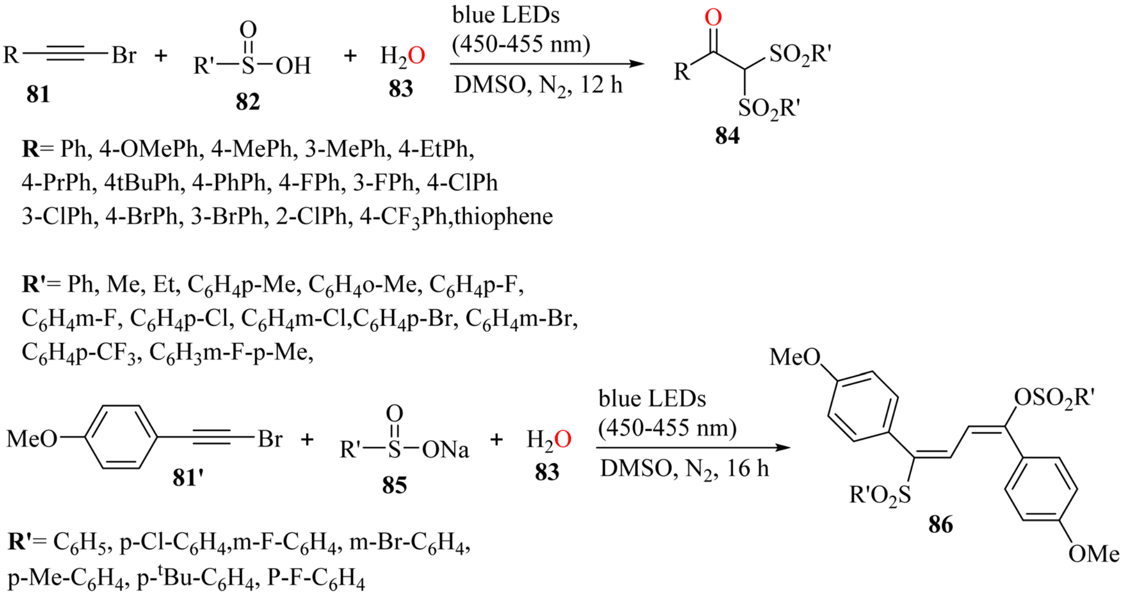
Scheme 34 Synthesis of indolizine thiones **76** from ynals.[54]



Scheme 35 Synthesis of 2,3-dihydro-1*H*-imidazo[1,2-*a*]indole derivatives **80**.[55]



Scheme 36 Possible reaction mechanism for the synthesis of 2,3-dihydro-1*H*-imidazo[1,2-*a*]indole derivatives **80**.[55]

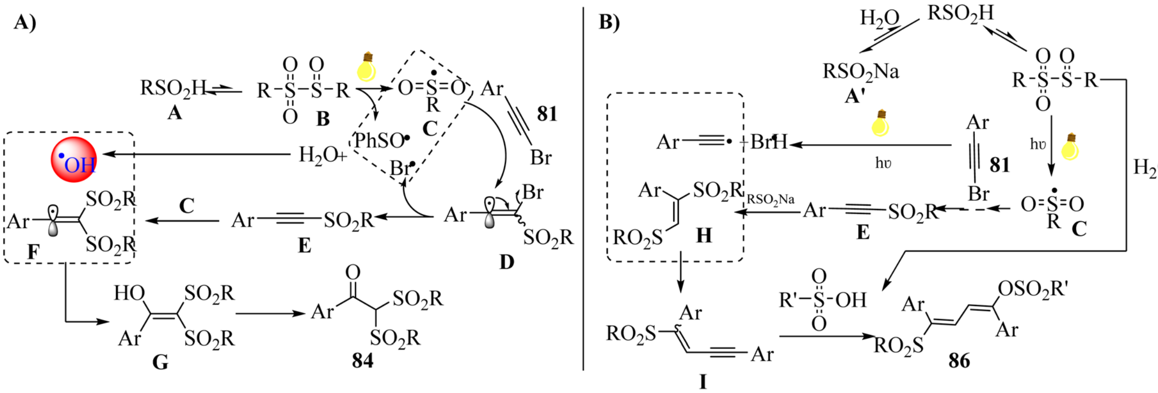


R= Ph, 4-OMePh, 4-MePh, 3-MePh, 4-EtPh, 4-PrPh, 4tBuPh, 4-PhPh, 4-FPh, 3-FPh, 4-ClPh 3-ClPh, 4-BrPh, 3-BrPh, 2-ClPh, 4-CF_3Ph,thiophene

R'= Ph, Me, Et, C_6H_4p-Me, C_6H_4o-Me, C_6H_4p-F, C_6H_4m-F, C_6H_4p-Cl, C_6H_4m-Cl,C_6H_4p-Br, C_6H_4m-Br, C_6H_4p-CF_3, C_6H_3m-F-p-Me,

R'= C_6H_5, p-Cl-C_6H_4,m-F-C_6H_4, m-Br-C_6H_4, p-Me-C_6H_4, p-^{t}Bu-C_6H_4, P-F-C_6H_4

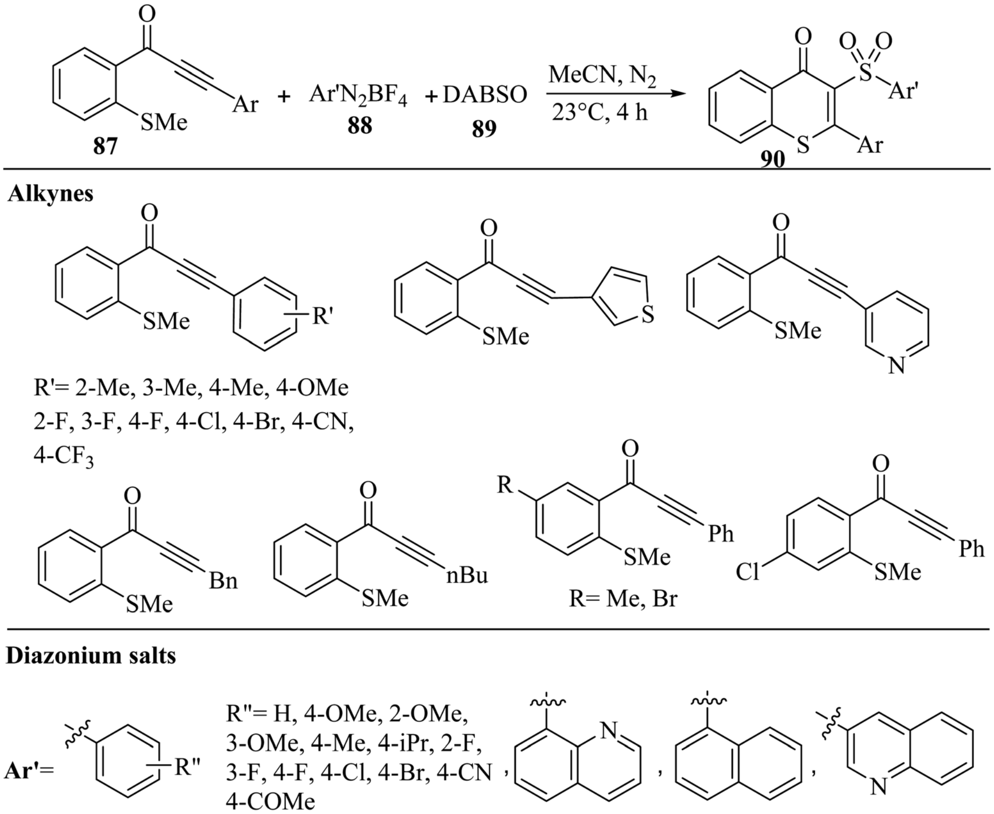
Scheme 37 Synthesis of α,α-bis-sulfonyl arylketones under visible-light irradiation.[56]



Scheme 38 Possible reaction mechanism for the synthesis of α,α-bis-sulfonyl arylketones.[56]

DABSO **89**, and alkyl-substituted alkynones **87** in CH_3CN under N_2 at 23 °C for 4 h (Scheme 39).

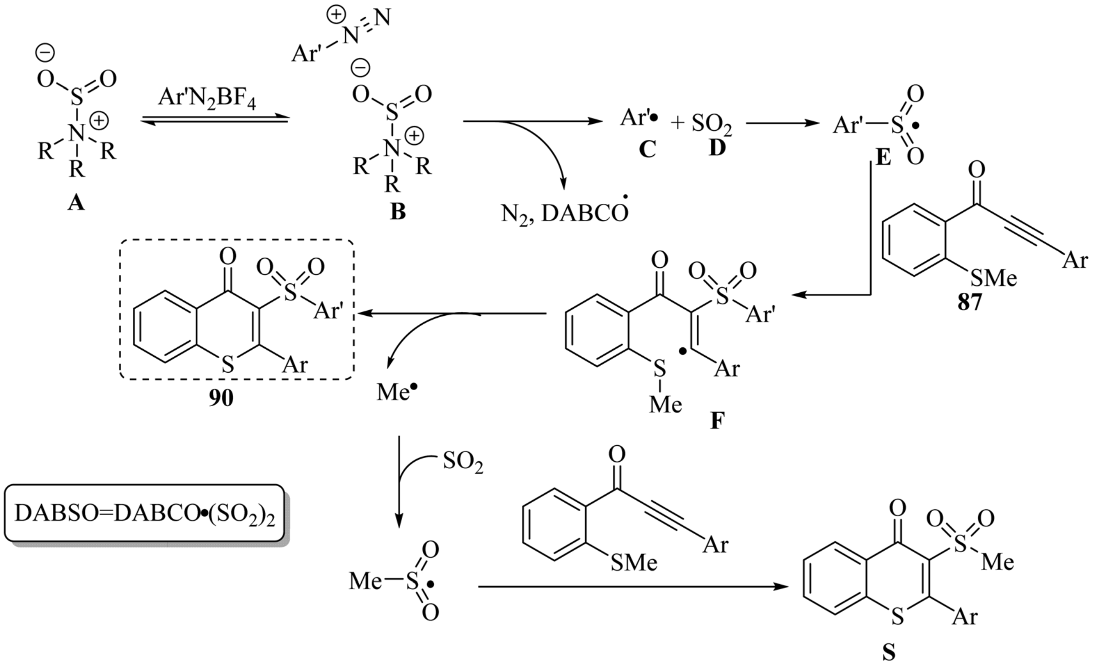
Initially, complex **B** was produced *via* the electrostatic interaction between **A** and DABSO. Then, complex **B** produced **C** and **D** *via* homolytic cleavage of the N–S bond and concomitant single-electron transfer. After that, a radical intermediate was generated *via* the reaction between **E** and **87**. Finally, *via* intramolecular radical cyclization, **90** was produced. It should be



Scheme 39 Synthesis of 3-arylsulfonylated thioflavone derivatives **90** by alkyl-substituted alkynone derivatives.[57]

noted that by-product **S** was observed in this reaction, which was produced *via* the reaction between **87** and the methylsulfonyl radical (Scheme 40).

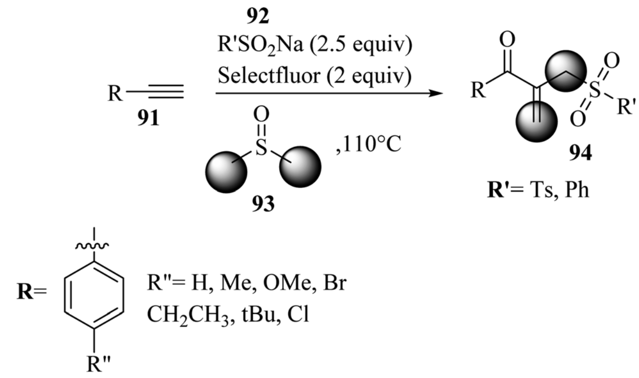
In the case of **88,** the corresponding products in the presence of different substituents produced in 40–97% yield. No obvious electronic effects of these substituents were observed.



Scheme 40 Possible reaction mechanism for the synthesis of 3-arylsulfonylated thioflavones.[57]

Moreover, the *p*-, *m*-, and *o*-substituted aryl diazonium salt derivatives produced the desired -arylsulfonylated thioflavones in 87–97% yield. Heteroaromatic and naphthyl substituents were tested, although lower yields were shown with quinoline-substituted diazonium salt derivatives. In the case of **87**, alkyne derivatives with electron-donating and -withdrawing substituents produced the corresponding 3-arylsulfonylated thioflavones in 52–91% yield. No significant differences in reactivity were observed for the *ortho*, *meta*, and *para* substituents. Also, thienyl or pyridyl groups produced the corresponding 3-arylsulfonylated thioflavones in 57–96% yield. Unfortunately, the use of 1-(2-(methylthio)phenyl)hept-2-yn-1-one or 1-(2-(methylthio)phenyl)-4-phenylbut-2-yn-1-one as the alkyl-substituted alkynone was not successful and did not produce the corresponding products.

In 2022, Kalari and co-workers[58] synthesized β-acyl allyl sulfone **94** *via* the reaction among alkynes **91**, DMSO **93**, and sodium sulfinate derivatives **92** in the presence of Selectfluor at 110 °C for 12 h (Scheme 41).



Scheme 41 Synthesis of β-acyl allyl sulfone **94** by Selectfluor.[58]

Initially, **93** was activated by Selectfluor to afford **E** (radical cation). Then, **E** reacted with F^- and generated key intermediate **F**. Intermediate **G** was produced *via* the reaction between **91** and intermediate **F**, which reacted with additional **F** to afford intermediate **H**. After that, **I** was generated *via* the demethylthiolation of intermediate **H**. Finally, **94** was obtained *via* the reaction between **92** and **I** (Scheme 42).

In the above-mentioned reaction, DMSO acts as a dual-carbon synthon. Phenyl acetylene without substrates and phenyl acetylenes bearing Me-, OMe-, *t*Bu-, ethyl-, Br-, and Cl- afforded the desired products in 41–66% yield. It should be noted that the investigation of aliphatic alkyne ethynylcyclohexane or 1-ethynylcyclohex-1-ene showed that no desired product was synthesized.

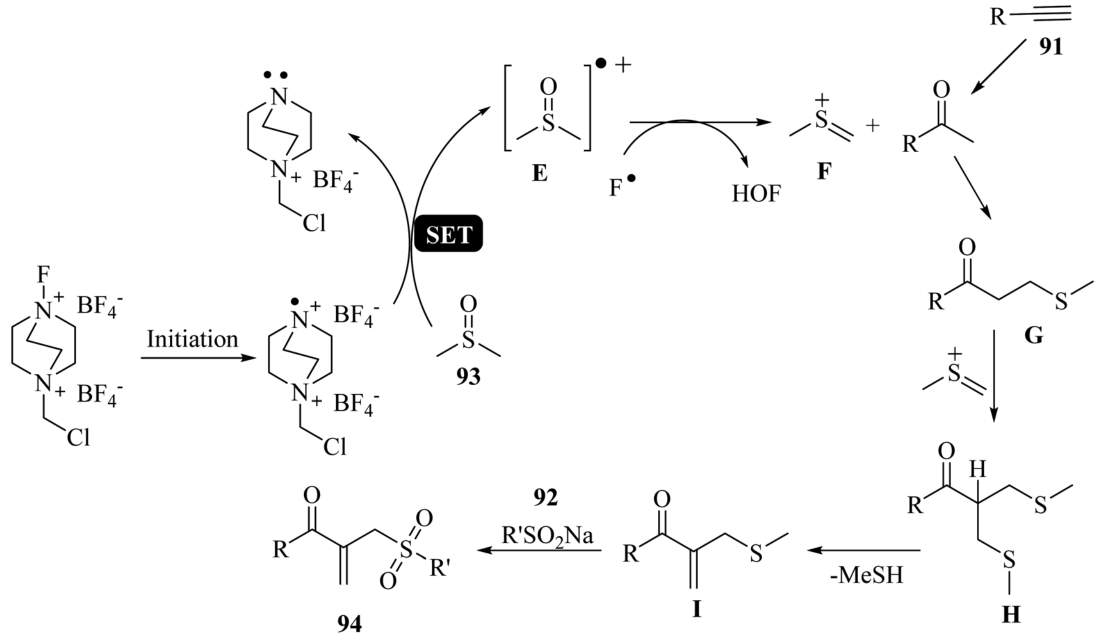
A summary of the reaction of alkynes with some of sulfur-containing structures, and also the limitations and progress of reactions are presented in Table 2.

2.3 Reaction of acids

2.3.1 Reaction of barbituric acids.

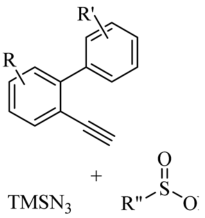
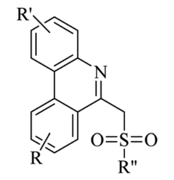
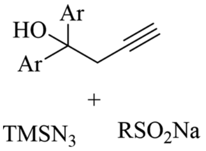
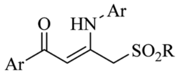
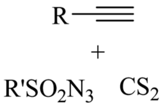
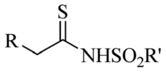
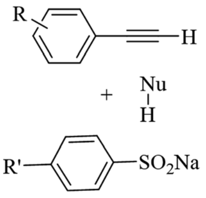
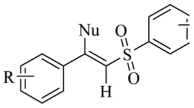
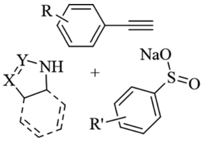
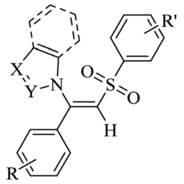
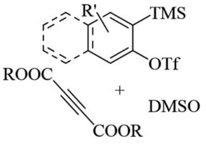
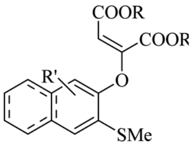
Jana and co-workers[65] synthesized 2-arylbenzo[*d*]imidazo[2,1-*b*]thiazole derivatives **98** *via* the I_2/DMSO-mediated reaction among arylacetylene **95**, 2-aminobenzothiazole **96**, and barbituric acid derivatives **97** at 110 °C for 12 h (Scheme 43).

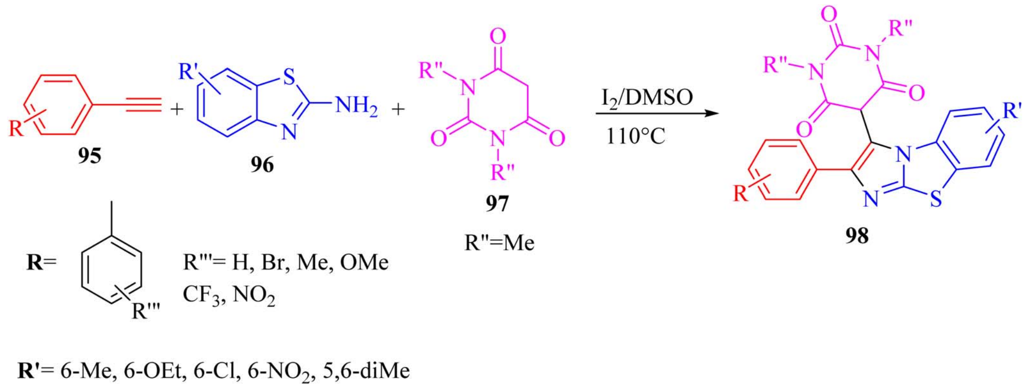
Initially, **95** reacted with I_2 in DMSO and generated **B** *via* intermediate **A**. Then, electron-deficient alkene **C** was produced *via* Knoevenagel condensation between **B** and **97**. After that, **D** was produced *via* the aza-Michael addition of **96** to **C**. Finally, **98** was prepared *via* the intramolecular cyclization of **D** under acidic conditions together with H_2O removal (Scheme 44).



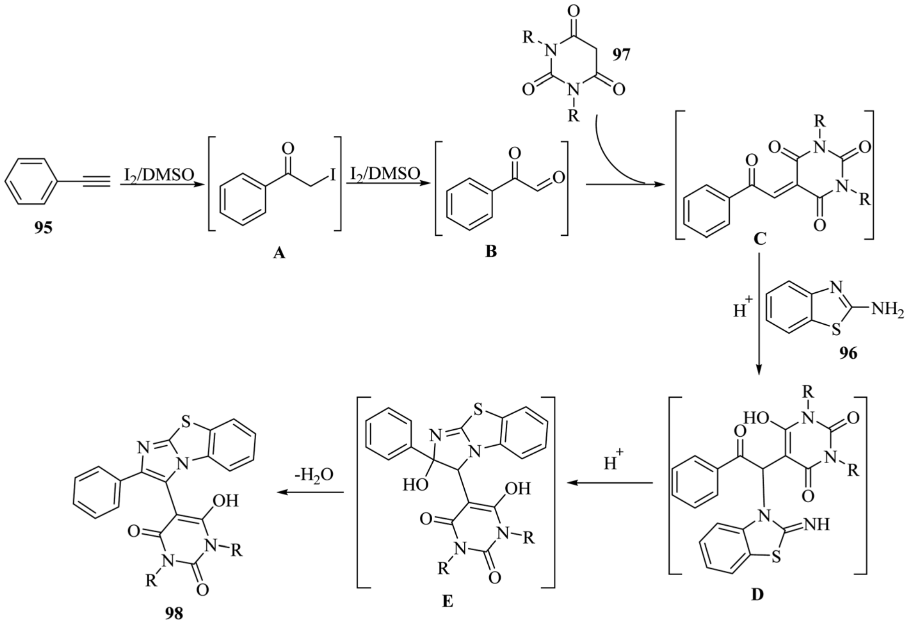
Scheme 42 Possible reaction mechanism for the synthesis of β-acyl allyl sulfones **94**.[58]

Table 2 Summary of the reaction of alkynes with sulfur-containing structures and limitations or progress of the reactions

Reactants	Product	Catalyst	Solvent	Method employed	Reaction time	Yield	Limitations or progress	Ref.
		Ag_3PO_4	DMSO	H_2O, 70 °C	6 h	Up to 74%	(1) New transformation of alkynes (2) C–C, C–N, and C–S bonds formed. (3) Excellent FG tolerance	Tang *et al.*[59]
		Ag_3PO_4	DMSO	H_2O, 70 °C	4 h	Up to 75%	Efficient C to N aryl migration of homopropargylic alcohol	Ning *et al.*[60]
		$CuBr\cdot SMe_2$	Toluene	BDU, 100 °C	22 h	53–97%	Electronic and steric variations had not remarkable effect on the reaction	Khalaj *et al.*[61]
		Eosin Y	EtOH	I_2, K_2CO_3, visible light, RT	48 h	52–80%	(1) Exclusive Z-selectivity (2) C–S and C–O bond formation	Sahoo *et al.*[62]
		—	DMF	I_2, K_2CO_3, 70 °C	5 h	Up to 85%	(1) C–S and C–N bond formation (2) Excellent stereoselectivity (3) Mild operation	Ansari *et al.*[63]
		—	—	KF, 50 °C	5 h	Up to 81%	(1) Stereoselective (2) Transition-metal-free (3) Multiple bond cleavage and bond formation	Hazarika *et al.*[64]



Scheme 43 Synthesis of 2-arylbenzo[*d*]imidazo[2,1-*b*]thiazole derivatives **98**.[65]



Scheme 44 Possible reaction mechanism for the synthesis of 2-arylbenzo[*d*]imidazo[2,1-*b*]thiazole derivatives **98**.[65]

According to the results, 2-aminobenzothiazoles **96** with a variety of groups such as 6-NO_2, 6-Me, 5,6-dimethyl, 6-OEt and 6-Cl produced the desired products in 74%,78%, 80%, 83%, and 76% yield, respectively. Moreover, phenyl acetylene derivatives **95** with either electron-donating or -withdrawing groups (Br, Me, OMe, CF_3, and NO_2) produced the desired products in 79%, 85%, 70%, 85%, and 84% yield, respectively.

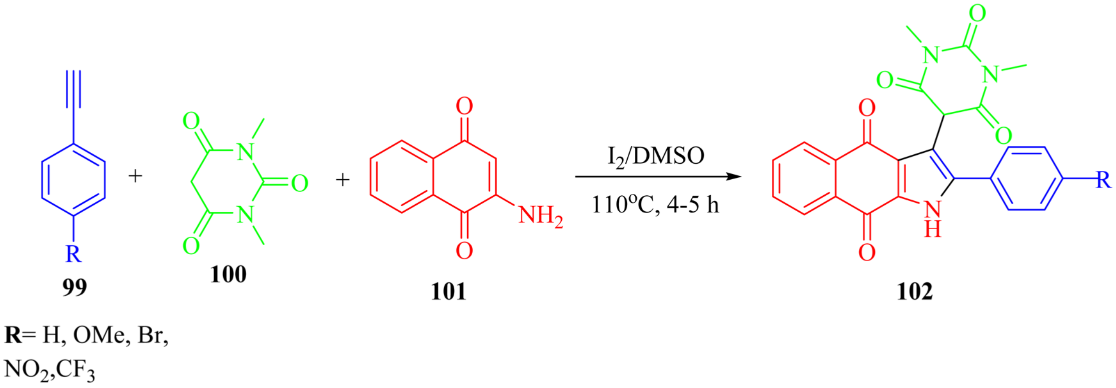
Panday *et al.*[66] synthesized pyrimidine-linked naphthoquinone-fused pyrrole derivatives **102** *via* iodine-mediated one-pot multicomponent reactions (Scheme 45). The desired product was obtained *via* the reaction among 2-amino-1,4-naphthoquinone **101**, barbituric acid derivatives **100**, and terminal aryl alkynes **99** in DMSO and molecular iodine at 110 °C for 4–5 h.

2-Iodoacetophenone **C** was generated *via* the reaction between **99** and I_2. Next, **C** oxidized to phenylglyoxal **T** in the presence of DMSO. Then, alkene compound **U** was produced *via* the reaction between **T** and **100.** After that, trisubstituted methane intermediate **V** was obtained *via* the 1,4 addition of reaction between **U** and **101.** Finally, **102** was obtained *via* intramolecular cyclization together with H_2O removal (Scheme 46).

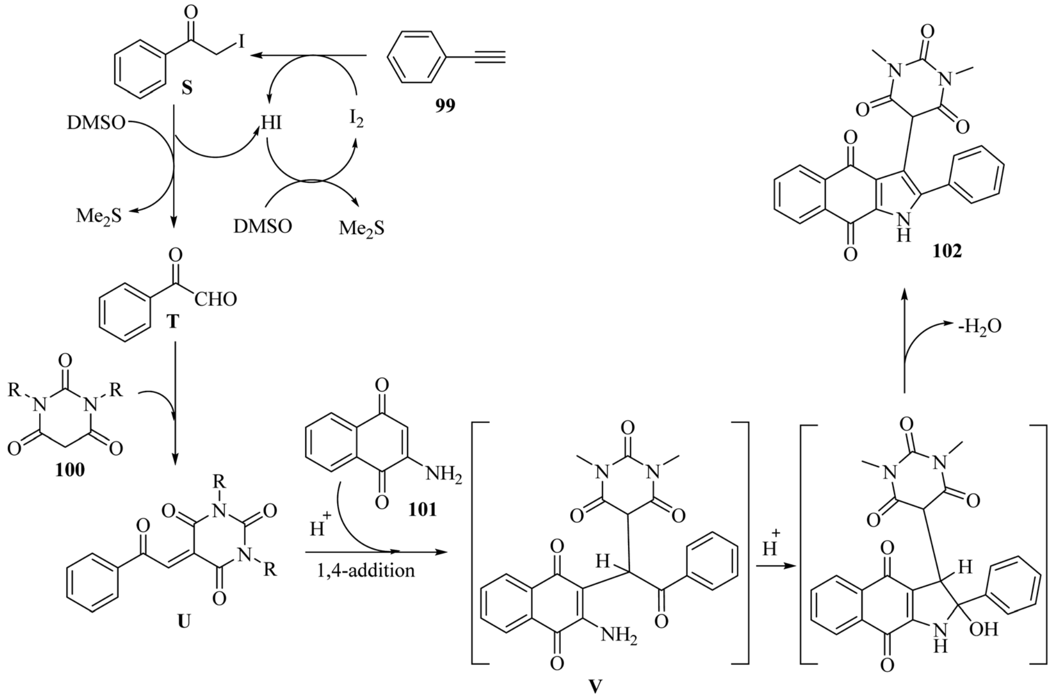
Various alkynes (4-OMe, 4-Br, 4-NO_2, and 4-CF_3 phenyl acetylenes) produced the desired products with an isolated yield of 60% to 78%.

In 2022, Bhuyan *et al.*[67] synthesized pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-dione derivatives **106** *via* the reaction among aromatic aldehydes **104**, *N*,*N*-dimethyl barbituric acid **103**, and terminal alkyne derivatives **105** in the presence of $ZnCl_2$ in HFIP under ultrasonic irradiation at 50 °C for 1 h (Scheme 47).

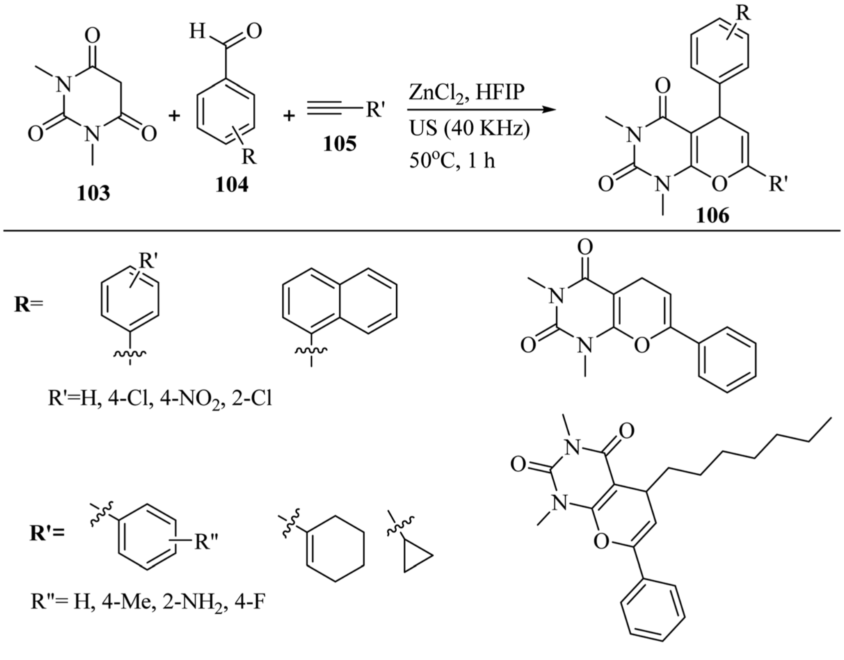
Firstly, **103** reacted with **104** *via* Knoevenagel condensation and generated **G.** Simultaneously, $ZnCl_2$ reacted with **105** and produced zinc(II) alkynilide **H.** After that, **H** underwent conjugative alkynylation with **G** and produced the intermediate **I.**



Scheme 45 Synthesis of naphthoquinone-fused pyrroles **102**.[66]



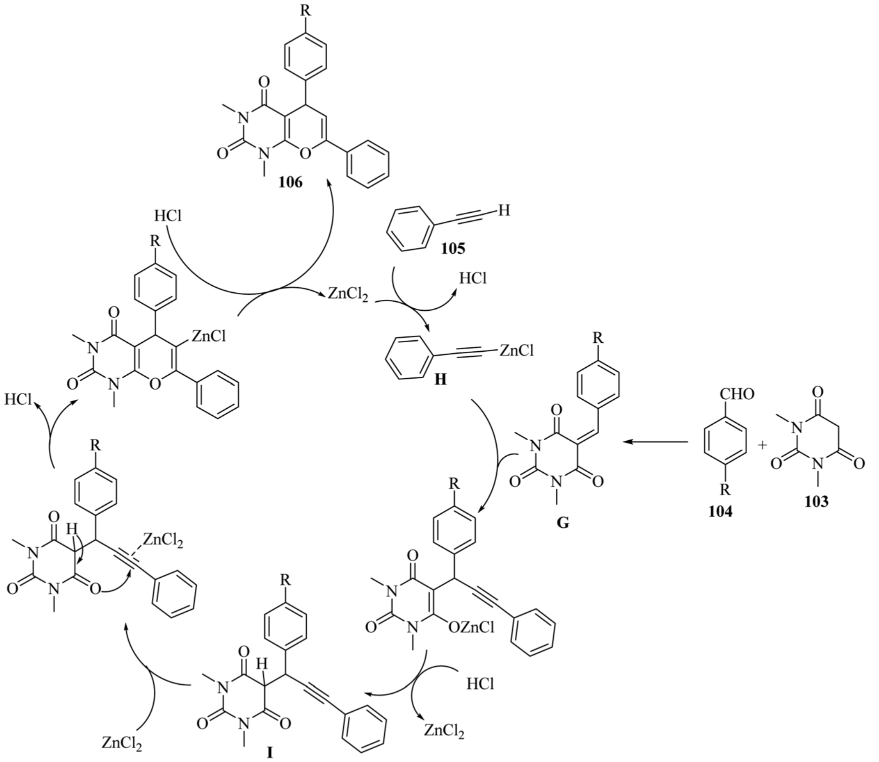
Scheme 46 Possible reaction mechanism for the synthesis of pyrimidine-linked naphthoquinone-fused pyrrole derivatives **102**.[66]



Scheme 47 $ZnCl_2$-catalyzed synthesis of pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-dione derivatives **106**.[67]

Finally, the alkynylated product **106** was produced through 6-*endo-dig* cyclization (Scheme 48).

Various electronic functional groups such as –F, $-NO_2$, $-NH_2$, –Me, and –Cl present on both aldehyde derivatives **104** and alkyne derivatives **105** were shown to tolerate the reaction conditions. However, although all terminal alkynes performed well, aromatic alkynes (yield: 79–95%) gave higher yields than aliphatic alkynes (yield: 68–73%). Electronic factors play a role among aromatic alkynes, given that those with electron-donating groups such as $-NH_2$ and CH_3 were observed to produce slightly lower products than their unsubstituted counterparts. Also, the electron-withdrawing –F group has little impact on the product yield. Among the various groups on the aromatic ring of aldehydes, the electron-withdrawing groups -Cl



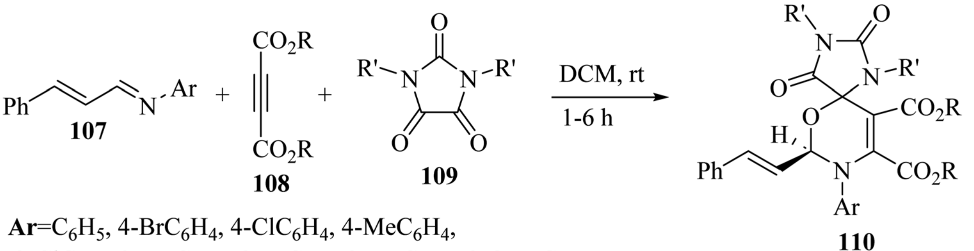
Scheme 48 Possible reaction mechanism for the synthesis of pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-dione derivatives **106**.[67]

and –NO_2 in the *para* position were found to support the reactions when aromatic alkyne derivatives were used as one of the reaction partners. However, when using aliphatic alkynes, this trend was not observed, but the effect was minimal. Interestingly, the –Cl group placed in the *ortho* position in aromatic aldehydes had the opposite effect, with lower yields being obtained in these cases. The aromatic bicyclic aldehyde also reacted well and gave a good yield of product (70%). *n*-Octanal provided the desired product in trace amounts, as identified by HRMS. All other aliphatic aldehydes did not give suitable products under the reaction conditions.

Asghari and co-workers[68] synthesized spiro 1,3-oxazines **110** *via* the reaction among *N*,*N*′-disubstituted parabanic acid derivatives **109**, imine derivatives **107**, and dialkyl acetylenedicarboxylate derivatives (DAAD) **108** in dry dichloromethane without catalyst at room temperature for 1–6 h (Scheme 49).

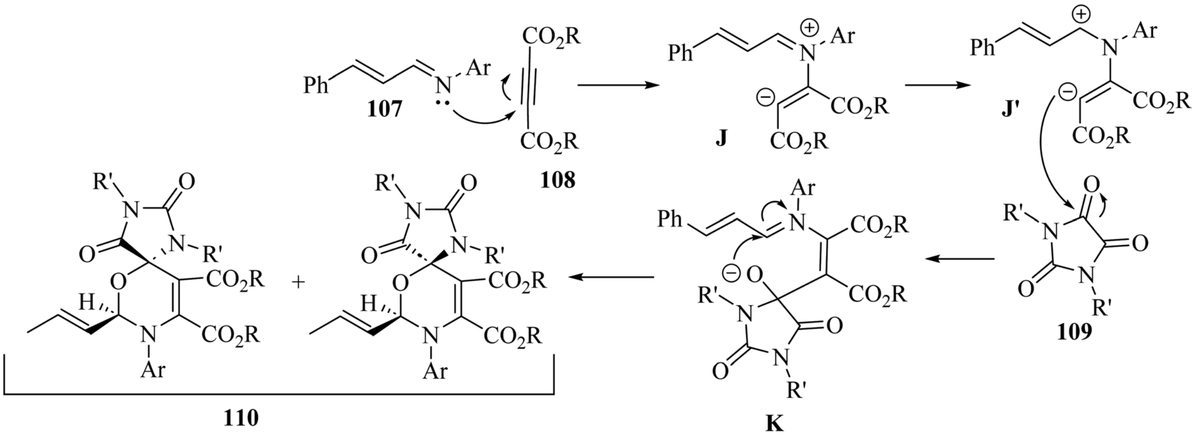
Initially, **107** reacted with **108** and produced 1,4-dipolar intermediate **J**. After that, zwitterionic intermediate **K** was generated *via* attack of **J** to the carbonyl group of **109**. Finally, **110** was obtained *via* the intramolecular reaction between iminium and alkoxide group of intermediate **K** (Scheme 50).

The desired products in the above-mentioned method were produced in 44–98% yield. According to the results, the different groups (withdrawing and donating) at the *para* position of the *N*-arylaldimine derivatives as nucleophiles were effective and the desired 1,3-oxazines obtained in 84–98% yield. The reaction yields decreased when using electron-withdrawing



Ar=C_6H_5, 4-BrC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4,
3-ClC_6H_4,3-MeC_6H_4, 2-BrC_6H_4,2-MeC_6H_4, 2-$OMeC_6H_4$
R= Me, Et,
R'= Me, Et, Ph,

Scheme 49 Synthesis of spiro 1,3-oxazine derivatives **110**.[68]



Scheme 50 Possible reaction mechanism for the synthesis of spiro 1,3-oxazines **110**.[68]

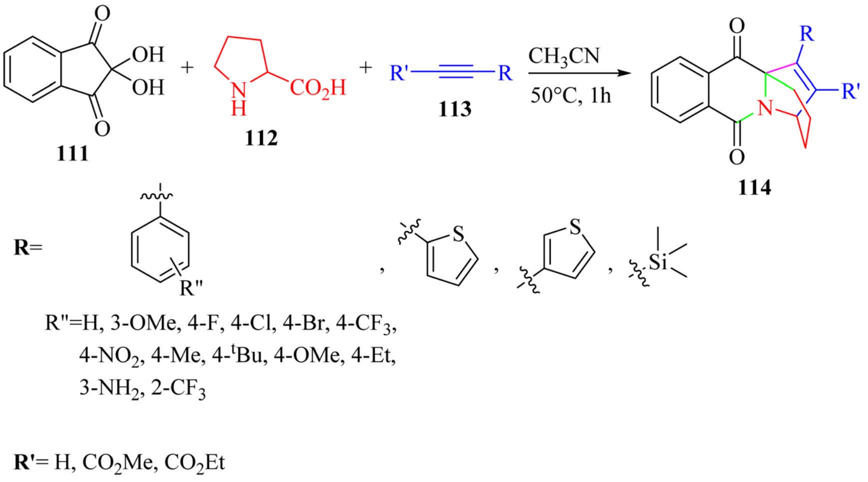
groups at the *meta* position in the *N*-arylaldimine derivatives (65–84%) but the yield of the reaction in the presence of a methyl group increased, which could be due to the inductive effect at the *meta* position (96%). In addition, when 2-substituted *N*-arylaldimines were tested, the reaction yields decreased, which could be because of the hindrance effect at the *ortho* position (44–76%).

2.3.2 Reaction of RCOOH. Shinde *et al.*[69] reported a novel method for the synthesis of ethanopyrido[1,2-*b*]isoquinolines **114** *via* the reaction among ninhydrin **111**, proline **112**, and alkynes **113** in CH$_3$CN at 50 °C for 1 h (Scheme 51).

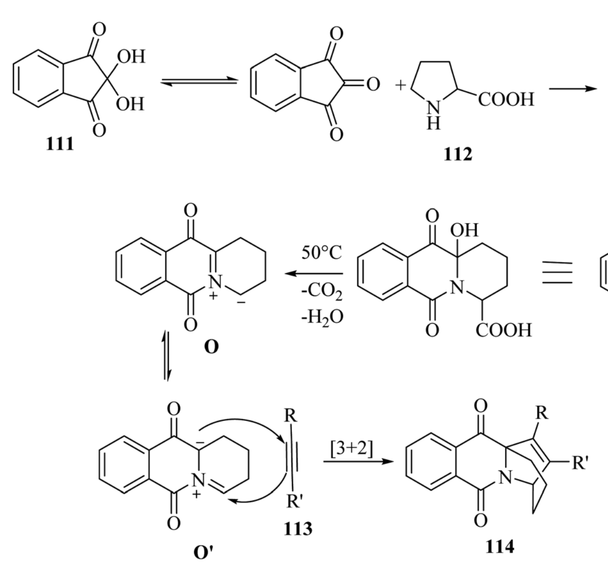
Initially, intermediate **K** was generated *via* the reaction between ninhydrin and **112**. After that, aziridinium cation intermediate **L** was produced *via* the attack of amine on the ninhydrin carbonyl carbon. Next, intermediate **L** underwent ring expansion and produced intermediate **M**. After that, intermediate **N** was obtained *via* the nucleophilic attack of the enol carbon on the proline carbon. It should be noted that the authors could not isolate intermediate **N**. In the next step, intermediate **O** was produced from intermediate **N** by the loss of H$_2$O, followed by decarboxylation. Next, intermediate **O** was converted into isoquinolinium ylide **O′**, probably. Finally, **114** was produced *via* the reaction between **O′** and **113** by [3 + 2]-cycloaddition reaction (Scheme 52).

According to the results, various aromatic alkyne derivatives containing different types of groups at different positions on the aromatic ring produced the desired of ethanopyrido derivatives in 67–90% yield. Heteroaryl alkyne (thiophene) also produced the desired ethanopyrido derivatives in 75–80% yield. The above-mentioned method was extended with ethyl phenylpropiolate derivatives and produced the corresponding ethanopyrido derivatives in 70–90% yield. Furthermore, unactivated terminal alkynes produced the desired products in 70–88% yield. Importantly, terminal aromatic alkynes containing free amine group also produced the corresponding of ethanopyrido [1,2-*b*]isoquinoline in 88% yield. Moreover, TMS acetylene was also treated with isoquinolinium ylide and produced the corresponding ethanopyrido[1,2-*b*]isoquinoline in 73% yield. However, the reaction did not proceed with 1-butyne and cyclohexylacetylene.

Thakur *et al.*[70] synthesized 3-substituted 2-quinolone derivatives **118** *via* the reaction among terminal alkynes **116**, 2-



Scheme 51 Synthesis of pyrido [1,2-*b*] isoquinoline derivatives **114**.[69]

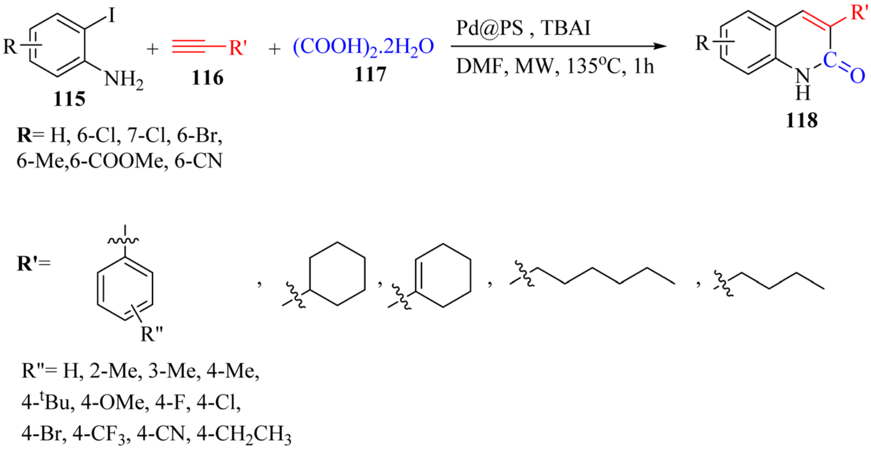


Scheme 52 Possible reaction mechanism for the synthesis of ethanopyrido[1,2-*b*]isoquinolines **114**.[69]

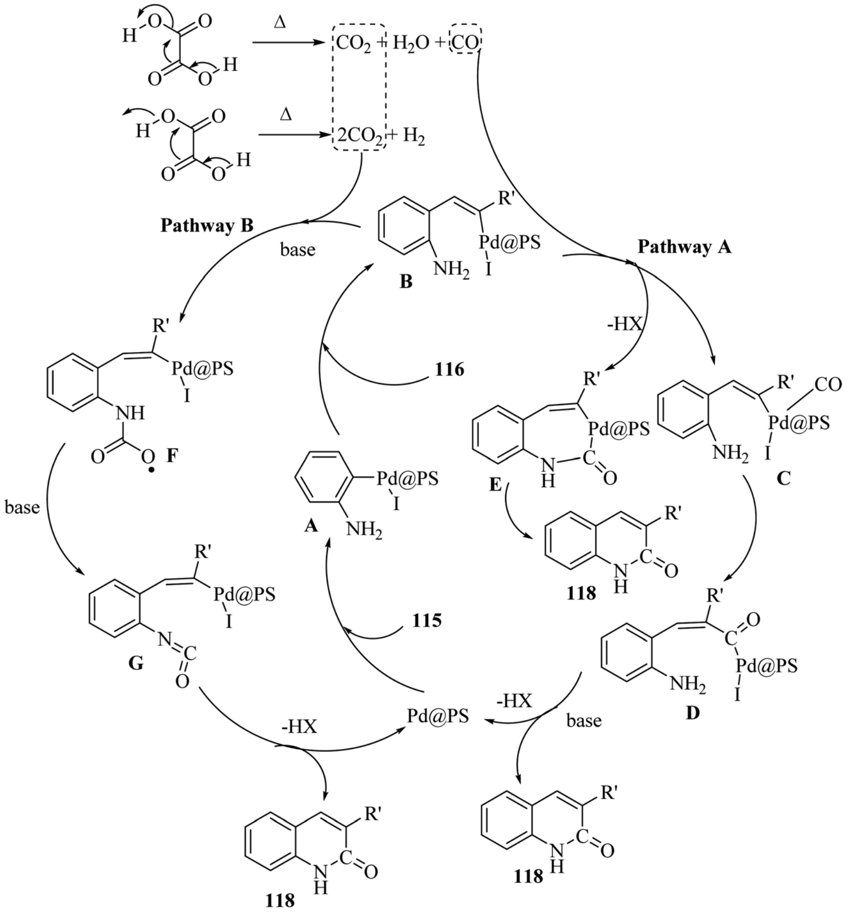
iodoaniline derivatives **115**, and oxalic acid **117** as the C1 source in the presence of polystyrene-supported palladium (Pd@PS) nanoparticle catalyst, and TBAI as a base in DMF at 135 °C under MW irradiations for 1 h (Scheme 53).

Initially, **115** and Pd@PS reacted and generated arylpalladium intermediate **A** *via* oxidative addition. Then, vinylpalladium intermediate **B** was obtained *via* the insertion of **116** in intermediate **A.** When intermediate **B** is produced, two pathways (A or B) may be followed. In the case of pathway A, intermediate **C** was produced *via* the interaction of CO with Pd metal. Next, acylpalladium intermediate **D** was obtained *via* the insertion reaction. After that, **118** was generated *via* the nucleophilic attack of the amine group on the carbonyl of intermediate **D.** In this pathway for synthesis of the **118**, another minor pathway exists, where intermediate **E** was obtained *via* the formylation of intermediate **B.** Then, intermediate **E** formed **118.** In the case of pathway B, intermediate **F** was produced *via* the reaction between CO_2 and the amine group of intermediate **B.** Next, intermediate **F** produced intermediate **G** in the presence of base. Finally, intermediate **G** generated **118** *via* the nucleophilic attack of the vinyl group at the carbon of the isocyanate group together with the regeneration of Pd@PS (Scheme 54).

All the 4-CH_3, 4-$COOCH_3$, 4-CN, 4-Cl, 5-Cl, 4-Br, and 4-F substituted 2-iodoanilines reacted well with 4-ethynyltoluene and phenylacetylene to produce the desired 2-quinolone derivatives in 43–75% yield. The relatively lower yield of 2-ethynyltoluene compared to 3-ethynyltoluene could be due to the steric hindrance at the *ortho* position of the alkyne. The reaction of 2-iodoaniline with 4-*tert*-butylphenylacetylene led to the formation of the corresponding 3-substituted 2-quinolone in 64% yield. Moreover, the C_2H_5/4-OCH_3-substituted alkynes produced the desired 2-quinolone derivatives in 56% and 58% yield, respectively. The halogen-substituted aromatic alkynes also produced the corresponding products in 43–55%. The aromatic alkyne



Scheme 53 Synthesis of 3-substituted 2-quinolone derivatives **118** by oxalic acid.[70]



Scheme 54 Possible reaction mechanism for the synthesis of 3-substituted 2-quinolone derivatives **118**.[70]

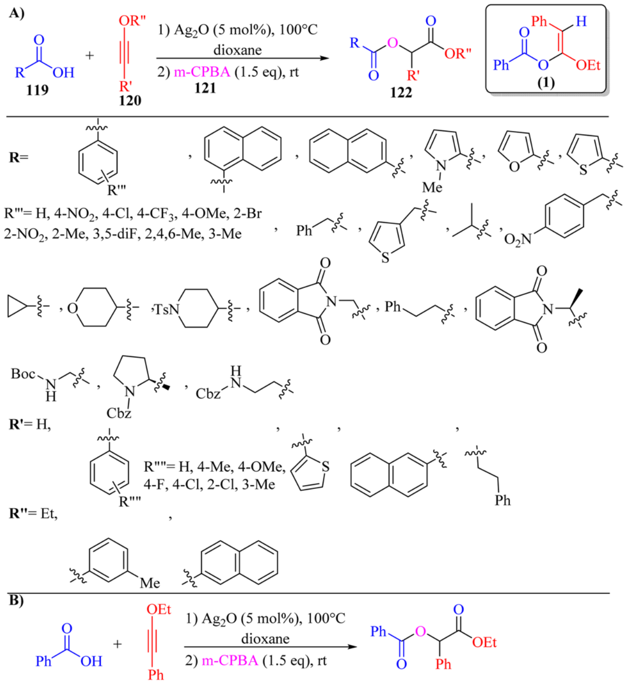
derivatives containing electron-withdrawing groups (–CF_3 and –CN) produced the desired 2-quinolone derivatives in 42% and 55% yield, respectively. In addition, alicyclic alkynes (1-ethynylcyclohexene and 1-ethynylcyclohexane) also produced the desired 2-quinolone derivatives in 52% and 49% yield, respectively. The aliphatic alkynes were tested and produced the desired 2-quinolone derivatives in 54–57% yield.

Zeng and co-workers[71] synthesized α-carbonyloxy ester derivatives **122** *via* a two-stage process. In the first stage, carboxylic acids **119**, and ynol ethers **120** reacted in the presence of Ag_2O in dioxane at 100 °C for 5 h and produced alpha-alkoxy enol ester intermediate (**1**), and then 3-chloroperoxybenzoic acid **121** added to the mixture and stirred at room temperature for 12 h (Scheme 55).

Firstly, **119** and **120** reacted and produced α-alkoxy enol ester **K** under catalytic Ag_2O promotion. After the synthesis of **K**, two pathways may exist. In pathway A, intermediate **L** was generated *via* the reaction between **121** and the carbonyl group of **K**. Next, **122** was produced from intermediate **L** *via* fragment cascade and Baeyer–Villiger-type reaction. In pathway B, intermediate **M** was generated *via* the epoxidation of **K** by **121**. Finally, **122** was obtained from **M** (Scheme 56).

When various carboxylic acid derivatives **119** and ynol ether derivatives **120** were evaluated, the desired α-carbonyloxy ester derivatives were produced in 45–91% yields. In the case of **119**, various groups produced the corresponding products in 69–83% yield. Also, heterocyclic carboxylic acid derivatives (thiophene, pyrrole, and furan) and naphthyl carboxylic acids produced the corresponding product in 91%, 57%, 53%, 86% and 70% yield, respectively. Moreover, aliphatic carboxylic acids also produced the corresponding products in 49–79% yield. Also, *N*-protected amino acid derivatives produced the corresponding products in 72–81% yield. Importantly, the products generated from L-proline and L-alanine showed dr values of 54 : 46 and 53 : 47, respectively. In the case of **120**, various substituted groups in the benzene ring such as *para*-methoxy, *para*-fluoro, *para*-chloro, *ortho*-chloro, *meta*-methyl, and *para*-methyl produced the corresponding products in 49–83% yield. In addition, the aliphatic and terminal ynol ether in the above-mentioned method engaged and produced the desired α-carbonyloxy ester derivatives in 45% and 49% yield, respectively.

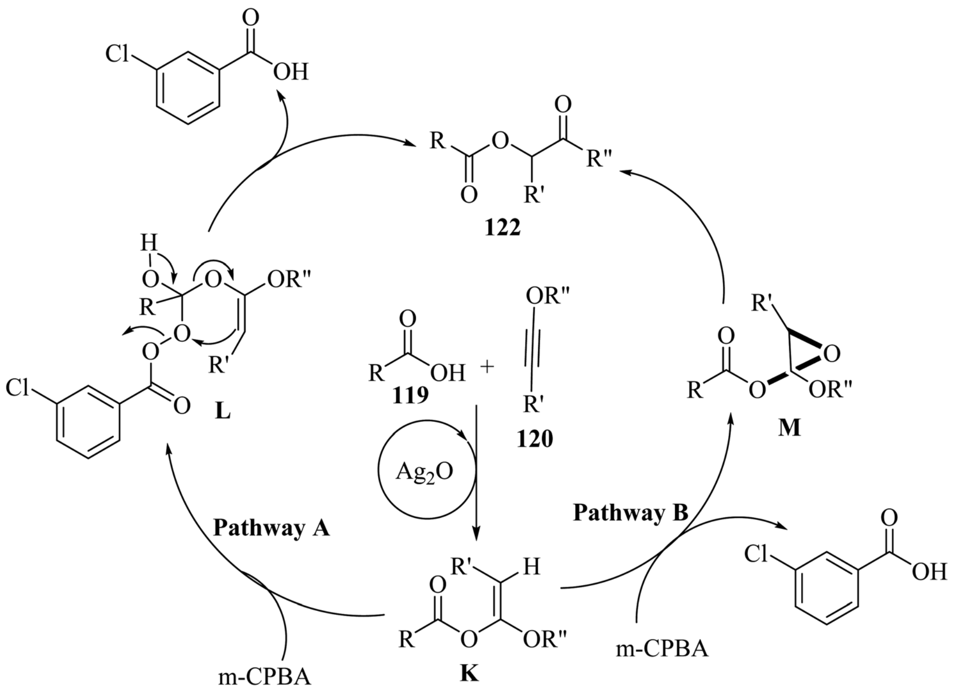
Wang *et al.*[72] synthesized β-amino amides **127** with high diastereoselectivity *via* the four-component reaction of triazenyl alkynes **123**, carboxylic acids **125**, aldehydes **124** and anilines **126** in the presence of $Sc(OTf)_3$ and 4 Å MS in DCE at 80 °C (Scheme 57). In the above-mentioned method, the alkyne scaffold serves as a C2 fragment, which can lead to high diastereoselectivity.



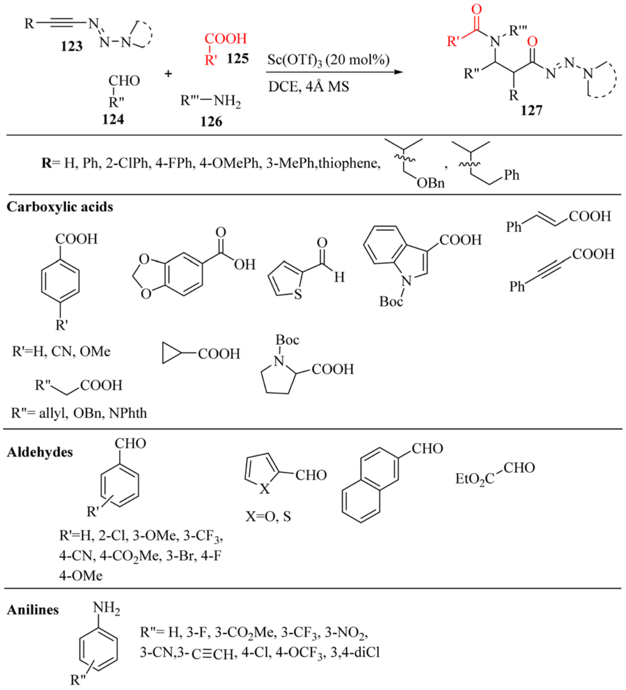
Scheme 55 (A) Ag_2O catalyzed synthesis of α-carbonyloxy esters **122**. (B) Gram-scale reaction for the synthesis of α-carbonyloxy ester; 1: α-alkoxy enol ester intermediate synthesized *via* the reaction between benzoic acid and ynol ether.[71]

Initially, **124** and **126** reacted and produced imine **R**, probably, and also probably **123** reacted with **125** and generated *E*-enol ether **Q**. After that, a Zimmerman–Traxler chair-like transition state was formed. It should be noted that $Sc(OTf)_3$ could be coordinated with the nitrogen atom of the imine and triazene group. Next, intermediate **T** was obtained *via* intramolecular addition of the enol ether to **R**. Finally, **127** was produced *via* the Mumm rearrangement together with the regeneration of the catalyst. The important point about this reaction was that **123** acted as a bifunctional building block (Scheme 58).

In the case of **123**, various substitutions in the aromatic ring such as F, Cl, Me, and OMe were tolerated and produced the corresponding products in 81–87% yield with excellent diastereoselectivity (d.r = up to >20 : 1). It should be noted that the substitution position did not have a remarkable effect on the reaction yields. The thiophene-2-yl-substituted triazenyl alkyne also produced the corresponding β-amino amide in 90% yield (d.r = >20 : 1). The alkyl-substituted triazenyl alkyne derivatives such as benzyloxymethyl and phenylethyl produced the corresponding β-amino amides in 87% and 86% yield (d.r = 5 : 3 and >20 : 1), respectively. The benzyloxymethyl-substituted triazenyl alkyne produced the corresponding beta-amino amide with moderated d.r, which may be due to the O atom of the benzyloxymethyl group coordinating with $Sc(OTf)_3$. In addition, the trimethylsilyl-substituted triazenyl alkyne produced the desilylation beta-amino amide product in 70% yield, and when piperidine-substituted triazenyl alkyne was tested, the desired β-amino amide could be formed in 76% yield (d.r = >20 : 1). In the case of **125**, aldehydes, and anilines, various substituted benzoic acids such as methoxy, [1,3]dioxole, and cyano were tested in the reaction and produced the corresponding β-amino amides in 89%, 90%, and 80% yield, respectively with excellent d.r (d.r = >20 : 1). The heterocyclic carboxylic acids bearing indole and thiophene produced the corresponding β-amino



Scheme 56 Possible reaction mechanism for the synthesis of α-carbonyloxy ester derivatives **122**.[71]



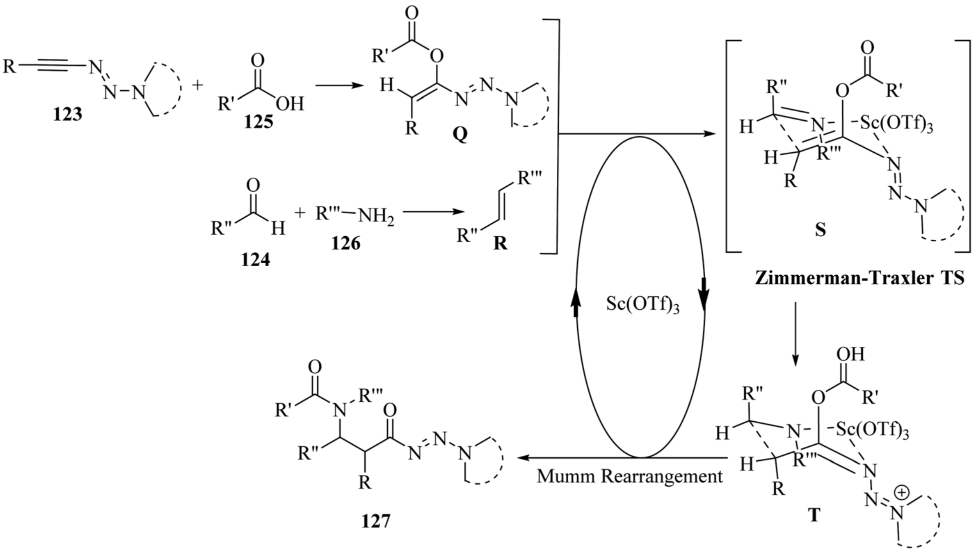
Scheme 57 Synthesis of β-amino amide derivatives **127** using Sc(OTf)$_3$.[72]

amides in 82% and 90% yield, respectively. Unsaturated carboxylic acids such as 3-phenylpropiolic acid and cinnamic acid also produced the corresponding beta-amino amides in 80% and 90% yield, respectively. Aliphatic carboxylic acids (allyl, protected alcohol, amino, and cyclopropyl) were well engaged in the reaction and produced the corresponding β-amino amide derivatives in 92%, 90%, 90%, and 87% yield, respectively. Also, *N*-Boc L-proline produced the desired product in 80% yield. Next, a variety of benzaldehydes with the substitution of OMe, Cl, F, Br, CF$_3$, CN, and CO$_2$Me was tolerated and produced the corresponding beta-amino amide derivatives in 80% to 95% yield. In addition, anisaldehyde produced the desired product in 63% yield. The heterocyclic aldehyde derivatives were tested and the desired beta-amino amide derivatives obtained in 62% to 73% yield. Ethyl oxoacetate also produced the desired β-amino amide in 70% yield. Finally, various aniline derivatives **126** were tested and anilines with differential substituted positions and functionalities (F, Cl, CF$_3$, CO$_2$Me, NO$_2$, CN, ethyne, and OCF$_3$) were tolerated and the desired β-amino amide derivatives obtained in 71–89% yield. Importantly, aliphatic aldehydes and alkylamines failed in the reaction and did not produce the desired β-amino amides.

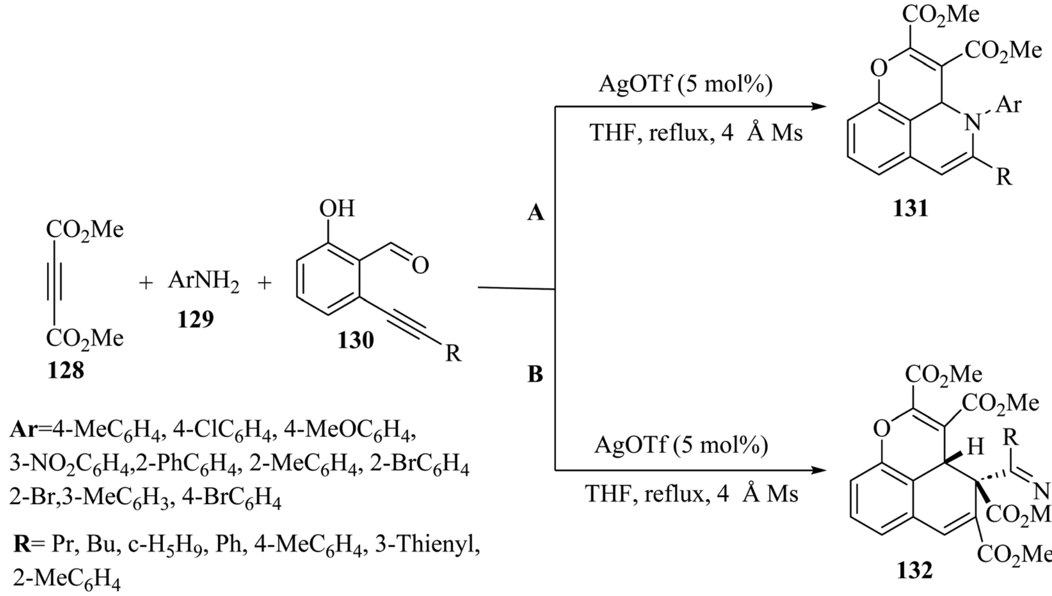
2.4 Synthesis of heterocyclic structures *via* the reaction among alkynes, aldehydes and amines

Fernández and co-workers[73] synthesized pyrano[2,3,4-*ij*]isoquinoline derivatives **131** (**132** was generated in a molar ratio of 2.5 : 1 : 1) *via* the reaction among dimethyl acetylenedicarboxylate **133**, *ortho*-alkynylsalicylaldehydes **135** and anilines **134** (molar ratio: 1 : 1 : 1) in the presence of AgOTf in THF under reflux (Scheme 59).

Initially, intermediate **L** was generated *via* the coordination of AgOTf to the triple bond of **K**, which was prepared by the reaction between **129** and **130**. After that, intermediate **M** was obtained *via* the intramolecular addition of the nitrogen of the imine to the alkyne. Subsequently, 8-isoquinolinones **N** was produced *via* the intramolecular protodemetalation reaction together with the regeneration of the silver catalyst. Next, intermediate **N** *via* [4 + 2] cycloaddition reactions with **128** generated the first desired product **131**. In addition, when an excess of **128** was used, derivatives **131** reacted with it and produced cyclobutenes **O** *via* [2 + 2] cycloaddition reactions. After that, the cyclobutene underwent electrocyclic ring opening and produced novel tricyclic intermediates **P**. Then, **P** may produce the bicyclic intermediates **Q** *via* another ring-opening



Scheme 58 Possible reaction mechanism for the synthesis of β-amino amides **127**.[72]



Scheme 59 (A) Synthesis of pyrano[2,3,4-*ij*]isoquinoline derivatives (molar ratio = 1 : 1 : 1) and (B) synthesis of benzo[*de*]chromene derivatives (molar ratio = 2.5 : 1 : 1).[73]

process. Finally, **132** was obtained *via* the electrocyclic ring-closing process of intermediates **Q** (Scheme 60).

The desired products were produced in moderate yields. According to the results, when an excess of dimethyl acetylenedicarboxylate (molar ratio: 2.5) was used under the same condition, benzo[*de*]chromene derivatives **137** were synthesized instead of pyrano[2,3,4-*ij*]isoquinoline derivatives **136**. The corresponding products were obtained in moderate yield (40–48%).

Das *et al.*[74] synthesized 1,3-disubstituted tetrahydroisoquinolines **141** and isoindolines **142** *via* the reaction among aldehyde derivatives **138**, aniline derivatives **140** and alkyne derivatives **139** with high yield (up to 92%), diastereoselectivity (up to 9 : 1), and enantioselectivity (up to 99%) (Scheme 61). Imination–alkynylation occurred at room temperature in $C_6H_5CH_3$, but the desired products were produced in the presence of an equimolar solution of lithium hexamethyldisilyl amide in THF at 0 °C. According to the results, due to higher yield and enantioselectivity using 4-methoxyaniline, the above-mentioned reaction was extended to various terminal alkyne derivatives with this amine. When different substituents were used on the aromatic ring of the alkyne, no remarkable changes in selectivities and yields were shown and the corresponding products obtained in high yields (up to 86%), and ee (up to 96%). Trimethylsilyl acetylene in this reaction was unable to produce the desired product. In addition, aliphatic terminal alkynes were investigated and produced the corresponding products with enantioselectivities of 87–93% and high yields of 84–86%.

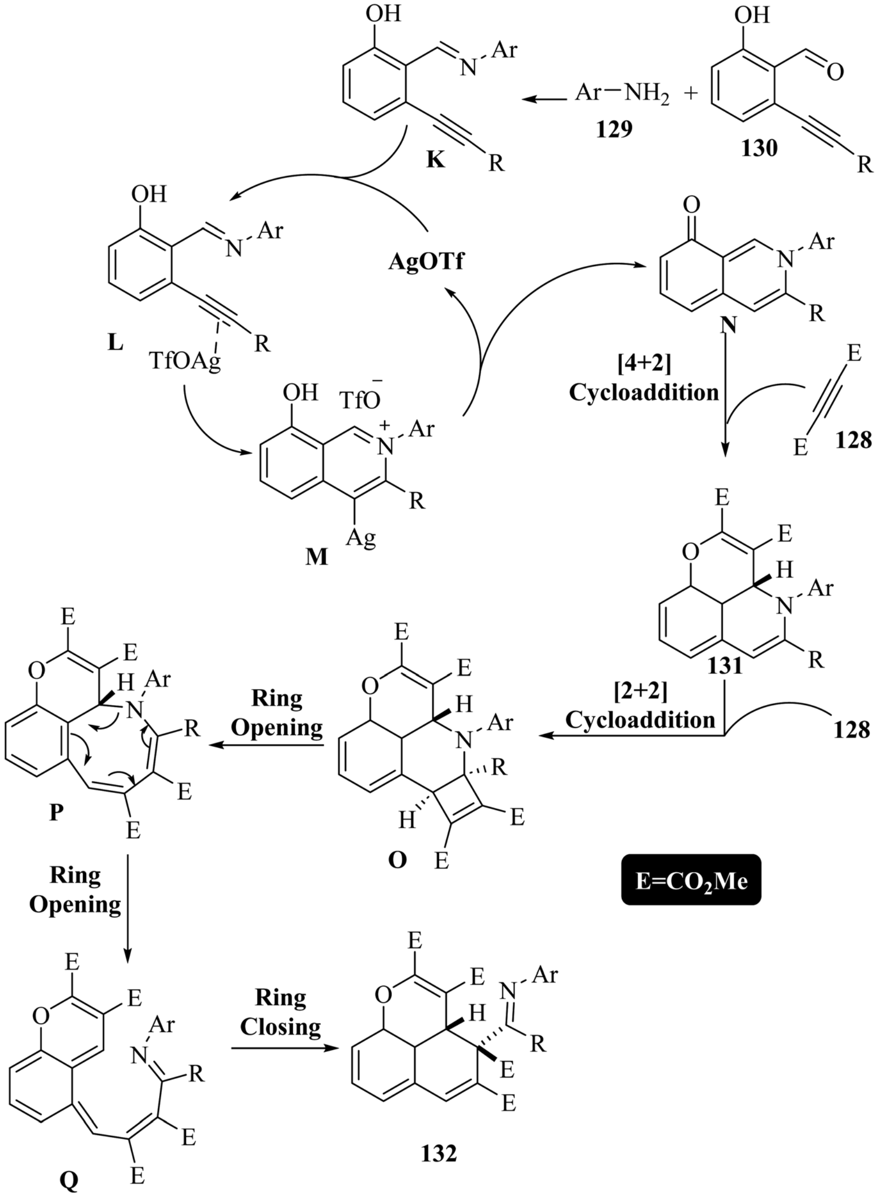
Chandra *et al.*[75] synthesized 4-arylated quinolines **146** *via* the reaction among paraformaldehyde **145**, anilines **143**, and alkynes **144** through [4 + 2] cycloaddition of alkyne derivatives and imine in the presence of (±) camphor-10-sulfonic acid (CSA) in TFE under microwave irradiation at 90 °C for 20 to 30 min (Scheme 62).

Initially, the reaction between **145** and **143** may *in situ* produce intermediate **A**. After that, intermediate **D** was generated from [4 + 2] cycloaddition of **142** with intermediate **B** *via* a Povarov-type multicomponent reaction. Finally, **146** was produced *via* the spontaneous oxidation of intermediate **D** (Scheme 63).

According to the results, the corresponding products with different paraformaldehyde, aniline, and alkyne derivatives were produced in excellent yields (up to 90%). In the case of **144**, various alkyne derivatives were reacted with *ortho*-toluidine and different *para*-substituted phenyl acetylenes produced the corresponding quinolines in 31–76% yield. Interestingly, polyaromatic alkyne was tolerated and the desired quinoline was produced in 68% yield. In addition, 3-ethynylthiophene produced the desired quinoline in 48% yield. In contrast, internal alkyne did not react.

In 2019, 2,4-disubstituted quinolones **150** were synthesized *via* the reaction among alkynes **148**, aldehydes **147**, and amines **149** in toluene at 110 °C (Scheme 64). When different alkynes **148**, aldehydes **147**, and amine derivatives **149** were used, the desired quinolines were produced in 46–92% yield. Also, 3-thienylacetlyene, 1-hexyne, and 1-ethynylcyclohexene produced the desired quinolone derivatives in 91%, 55%, and 86% yield, respectively.[76]

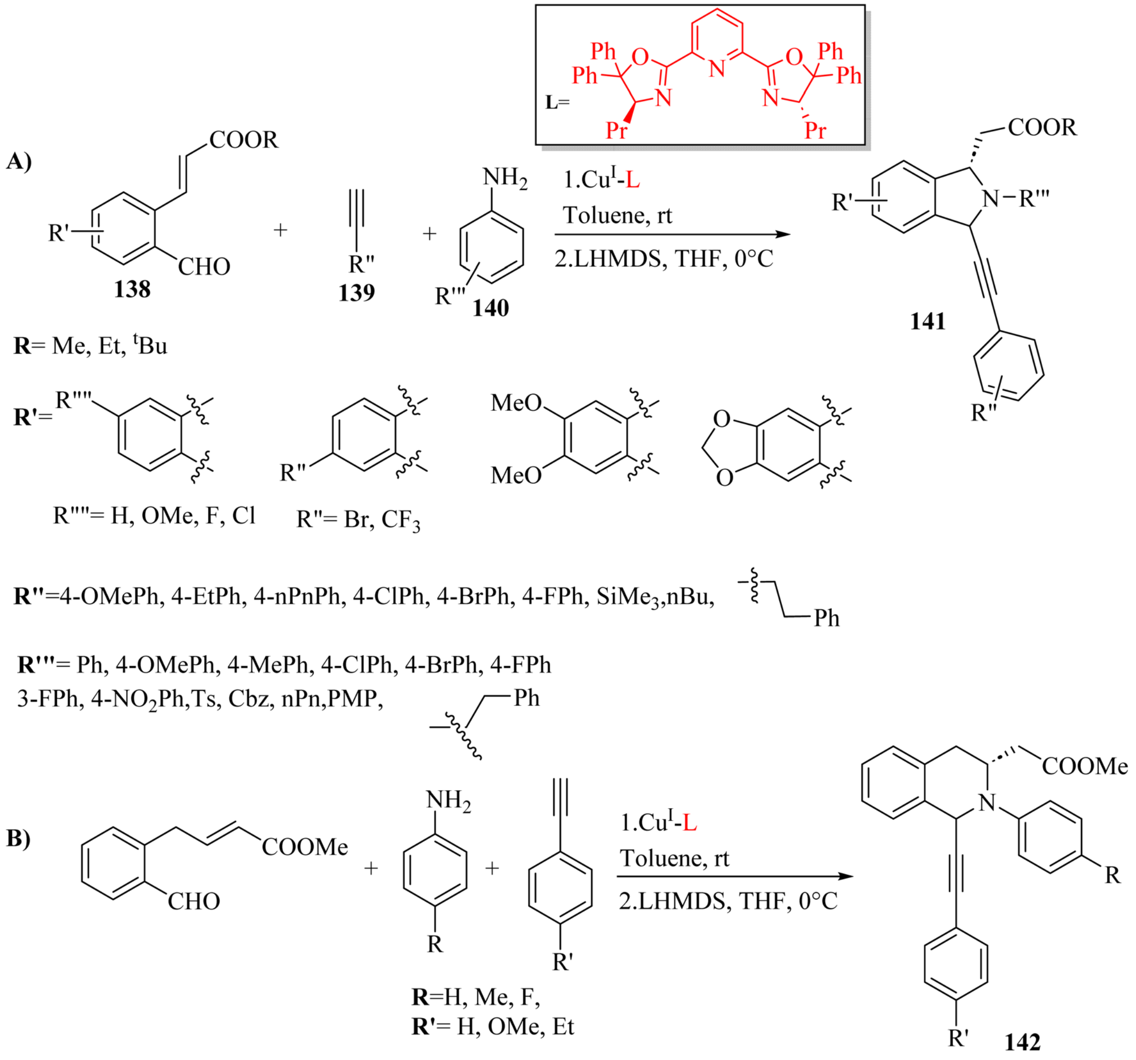
Yu and co-workers[77] synthesized spirofuran-hydropyrimidinone derivatives **154** *via* the three-component Biginelli-like tandem reaction of alkynol **153** as an enolizable carbonyl equivalent, aromatic aldehydes **151**, and (thio)urea **152** in the presence of co-catalyst of palladium chloride (transition metal) and trifluoroacetic acid (Brønsted acid) in dioxane at 50 °C for 12 h (Scheme 65).



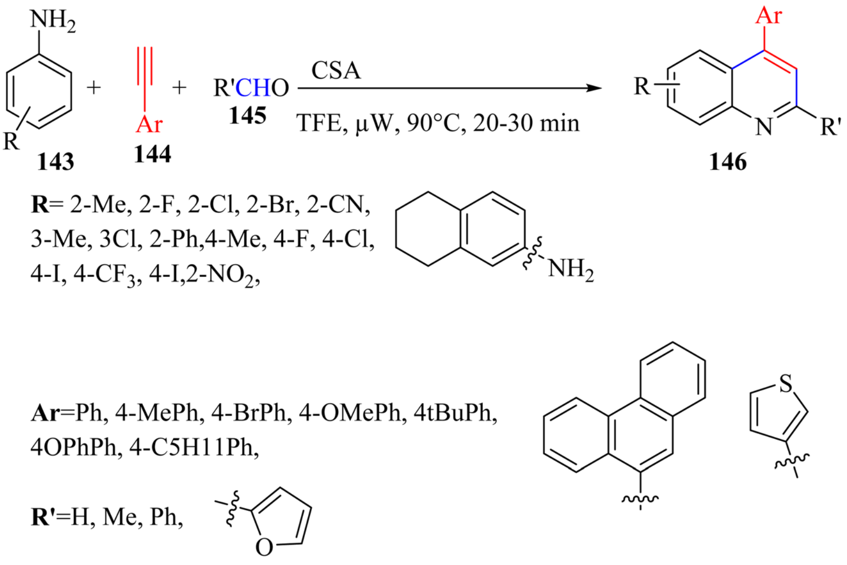
Scheme 60 Possible reaction mechanism for the synthesis of benzo[*de*]chromenes and pyrano[2,3,4-*ij*]isoquinolines.[73]

Initially, *N*-acyliminium intermediate **G** was generated *via* the condensation of **151** and **152** in the TFA. After that, vinyl-palladium species **H** was obtained *via* intramolecular addition of the OH group to the electron-deficient alkyne, where it should be mentioned that the coordination of $PdCl_2$ with **153** increased the electrophilicity of the triple bond. Next, intermediate **I** was produced *via* the attack of **H** to intermediate **G**. Then, endocyclic enol ether **J** was generated *via* the isomerization of the exocyclic double bond in the presence of the Pd catalyst. Next, oxonium intermediate **K** was obtained *via* the nucleophilic attack of the enol ether to a second aldehyde. Finally, the catalyst was regenerated and **154** was obtained *via* intramolecular cyclization (Scheme 66).

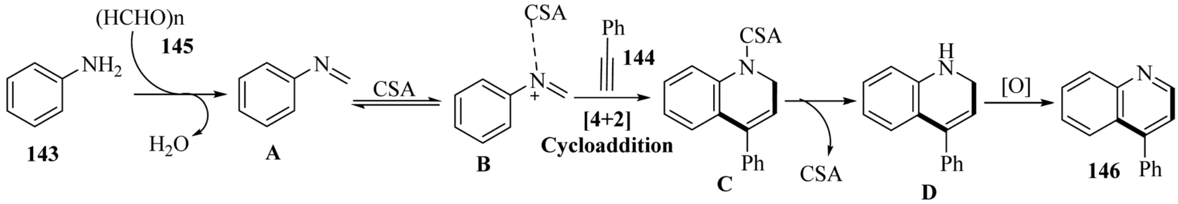
The desired spirofuran-hydropyrimidinone derivatives were produced in 45–87% yield and diastereoselectivity. In the case of **151**, some groups such as ester, carbonyl, nitro, halide, and hydroxyl were amenable in this catalytic system. Generally, benzaldehyde with electron-withdrawing substituents produced the corresponding spirofuran-hydropyrimidinone derivatives in worse yields compared to that with donating groups (71–78% and 80–87% yield). Notably, the reaction of benzaldehyde with a substituent at the *meta* position proceeded worse than that at the *para* position. Also, di- and tri-substituted benzaldehydes produced the corresponding spirofuran-hydropyrimidinone derivatives in 77–85% yield. Other aldehydes such as furfural and 1-naphthaldehyde produced the corresponding spirofuran-hydropyrimidinone derivatives in 73% and 81% yield, respectively but no desired product could be produced with 2-pyridine formaldehyde. When urea was replaced with thiourea, the corresponding spirofuran-hydropyrimidinone derivatives were



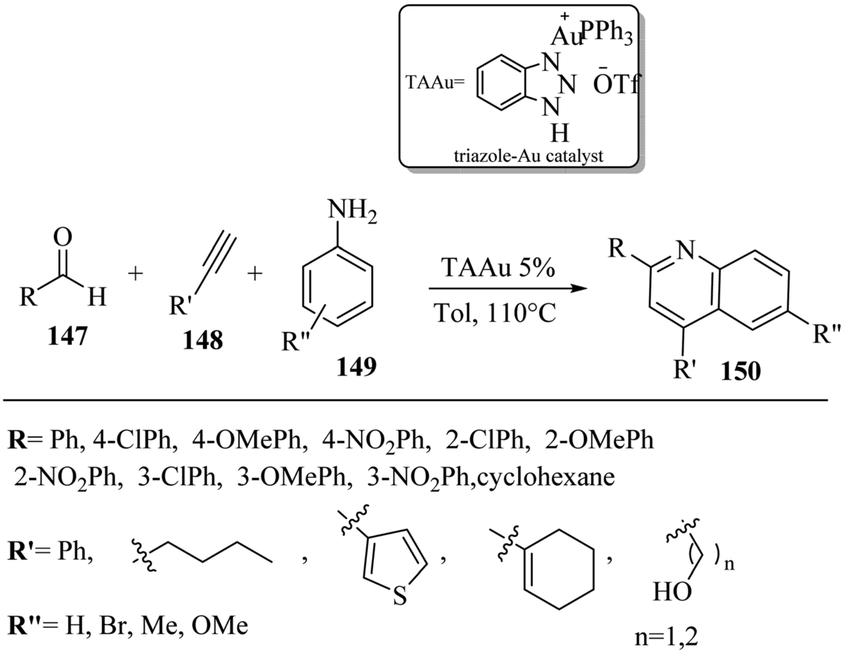
Scheme 61 (A) Synthesis of 1,3-disubstituted tetrahydroisoquinolines and (B) isoindolines.[74]



Scheme 62 Synthesis of 4-arylated quinoline derivatives **146**.[75]



Scheme 63 Possible reaction mechanism for the synthesis of 4-arylated quinolones **146**.[75]



Scheme 64 Synthesis of 2,4-disubstituted quinoline derivatives **150** *via* the triazole–gold catalyst.[76]

produced in 45–57% yield. The scope of **153** also was investigated and the desired products were produced in 62–77% yield.

Purohit and co-workers[78] *via* the reaction among aldehyde derivatives **156**, aminopyridines **155** and alkynes **157** synthesized substituted imidazopyridines **158** in the presence of PW-CIS500 nano-catalyst at 100 °C under neat condition (Scheme 67). The reaction proceeded smoothly when used various alkynes **157**, aldehydes **156**, and amines **155**. According to the study, the desired imidazopyridines were produced with an isolated yield of 82–95%. Also, various aryl-alkynes/aldehydes with electron-donating and electron-withdrawing groups produced the desired imidazopyridines with an isolated yield of 82% to 95%.

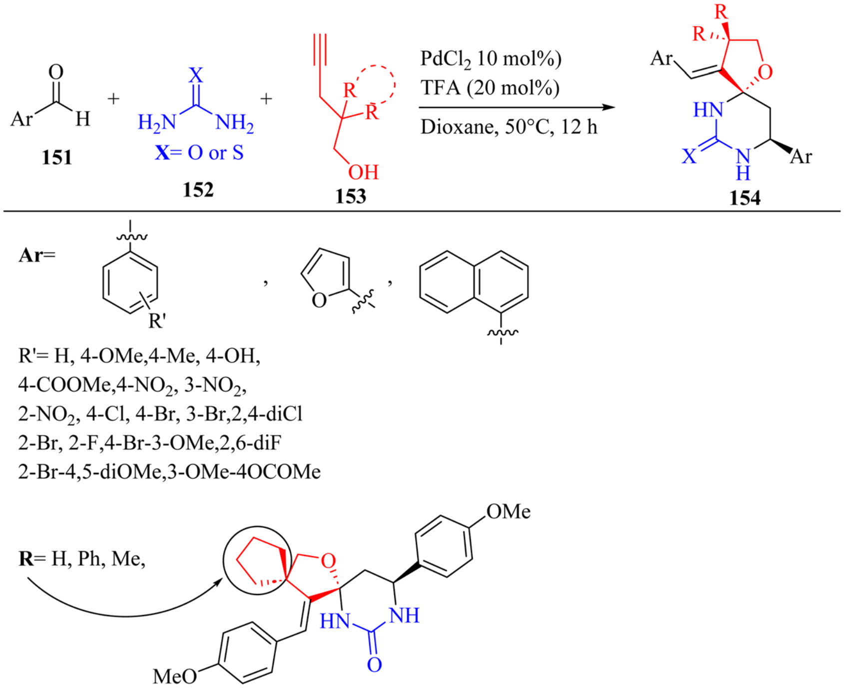
Xian *et al.*[79] synthesized 2,4-diphenylpyrimido[1,2-*b*]indazole derivatives **162** *via* the reaction among alkyne derivatives **161**, 1*H*-indazol-3-amine **159**, and aldehydes **160** under solvent-free conditions in the presence of $FeCl_3$ at 110 °C (Scheme 68).

Initially, the condensation reaction between **159** and **160** led to the formation of imine **A**, which released an H_2O molecule through the reaction. Then, iron complex intermediate **B** was obtained *via* the attack of iron acetylide complex to **A**, which isomerized to intermediate **C**. After that, intermediate **D** was obtained after regioselective attack of the intramolecular N–H bond activated the triple bond through 6-*endo-dig*-cyclization. Finally, **162** was generated *via* the autoxidation and demetalation of intermediate **D** (Scheme 69).

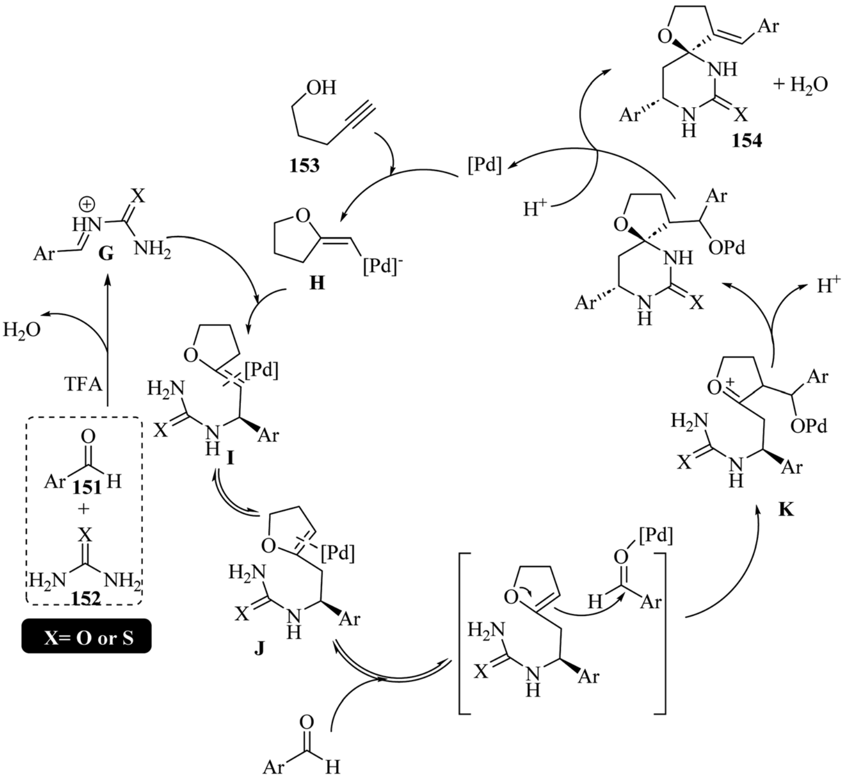
The desired indazole derivatives were produced in 69% to 93% yield. Alkynes with different groups gave the desired indazole derivatives in 83–85% yield. Under the same conditions, substituted aromatic alkynes and substituted aromatic aldehydes were evaluated and produced the corresponding products with an isolate yield of 73% to 79%. This method has advantages such as the use of available materials and an environmentally friendly catalyst. Also, the above-mentioned method is a good way to produce pyrimidine derivatives.

Yuan *et al.*[80] synthesized γ-carbonyl-α-amino acids **166** *via* the reaction among amines **165**, α-carbonyl aldehyde derivatives **163**, and propargylic alcohols **164** in the presence of $AgNO_3$ in CH_2Cl_2 at room temperature for 24 h (Scheme 70).

Initially, the reaction among **164**, **165**, and glyoxylate in the presence Ag catalyst generated product **A** *via* a Mannich-type reaction with intermediate **B**. In this section, intermediate **B** acted as a nucleophile (cycle Z). Subsequently,



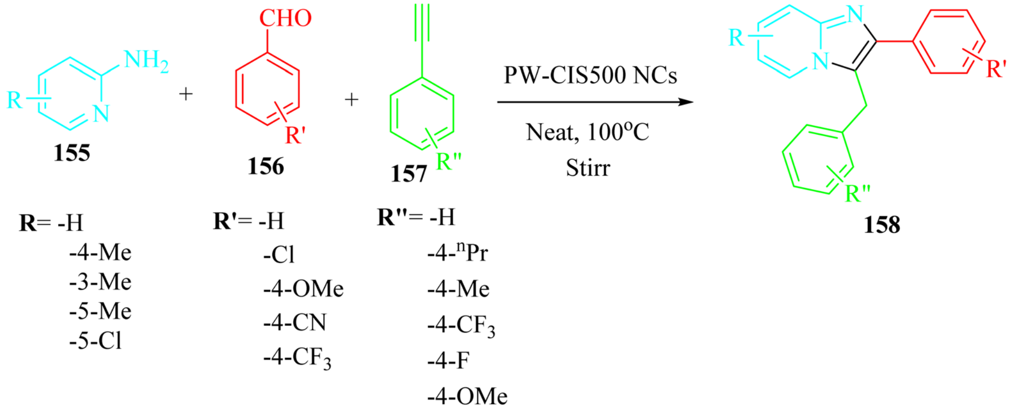
Scheme 65 Synthesis of spirofuran-hydropyrimidinones **154** through a Biginelli-like tandem reaction with co-catalyst of $PdCl_2$ and TFA.[77]



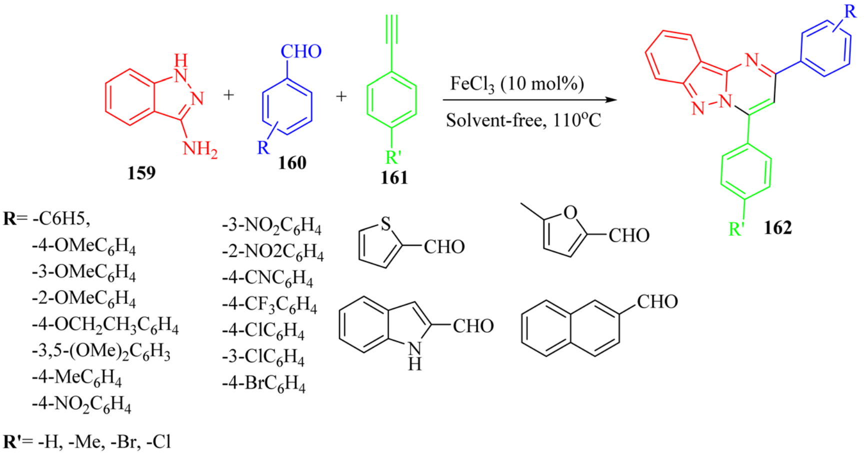
Scheme 66 Possible reaction mechanism for the synthesis of spirofuran-hydropyrimidinone derivatives **154**.[77]

intermediate silver–alkyne complex **C** was produced *via* the coordination of intermediate **A** with Ag^+. Next, intermediate **D** was obtained *via* the reaction between intermediate **C** and H_2O. In the last step, enol **E** was generated *via* the protonation of intermediate **D**, and then **E** was tautomerized to **166** (cycle X) (Scheme 71).

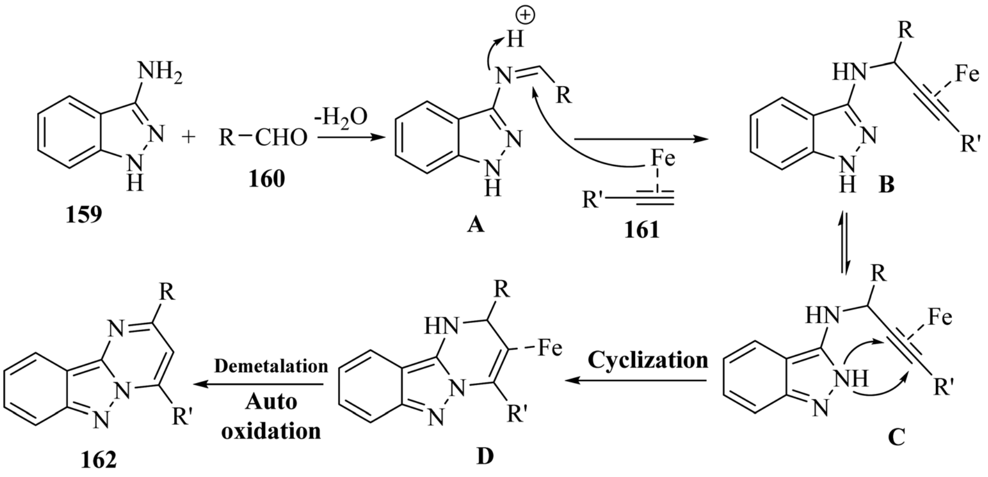
According to the results, γ-carbonyl-α-amino acids were produced in 71% to 91% yield. Aromatic amine derivatives



Scheme 67 Synthesis of imidazopyridine derivatives **158**.[78]

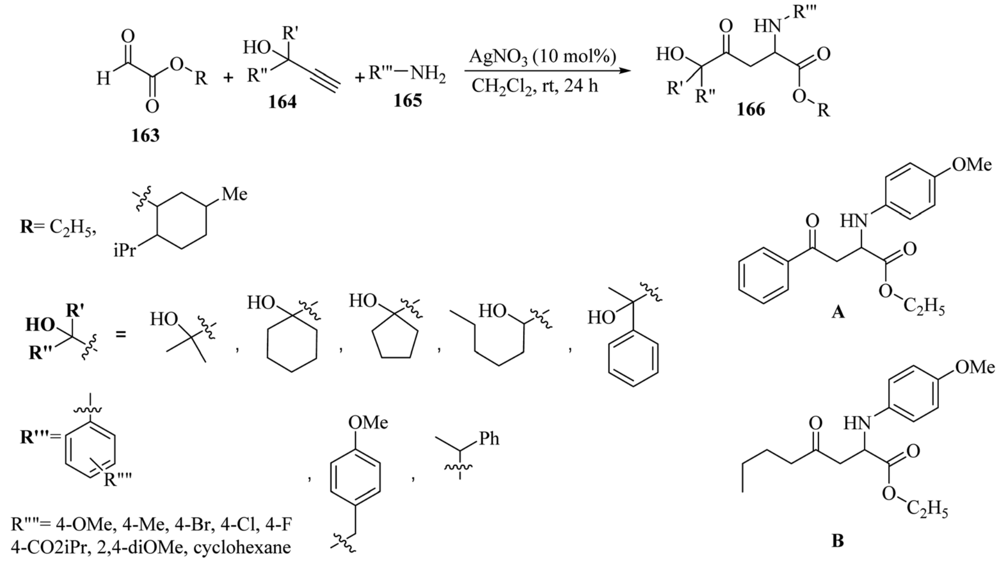


Scheme 68 Synthesis of 2,4-diphenylpyrimido[1,2-*b*]indazole derivatives **162** under solvent-free conditions.[79]

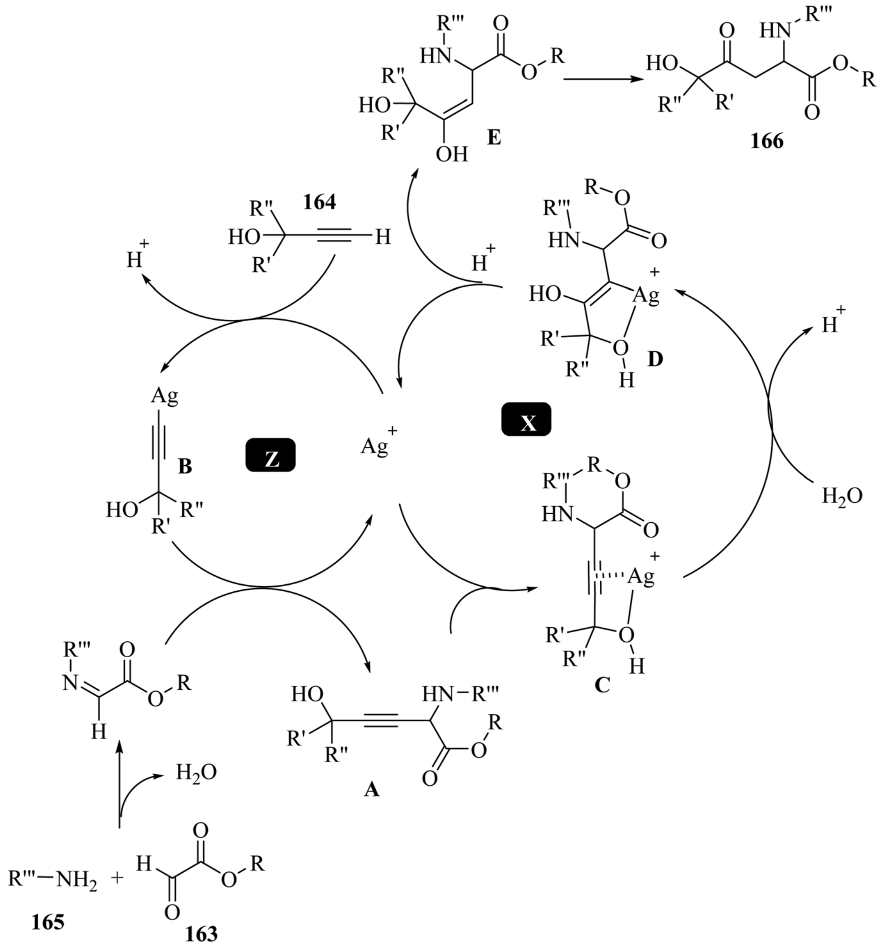


Scheme 69 Possible reaction mechanism for the synthesis of 2,4-diphenylpyrimido[1,2-*b*]indazole derivatives **162**.[79]

containing either electron-withdrawing or -donating groups on the aromatic ring produced the corresponding γ-carbonyl-α-amino acids in 78–90% yield. Aliphatic amine derivatives were also compatible and produced the corresponding γ-carbonyl-α-amino acids in 71–87% yield. In the above-mentioned method, when morpholine was used, none of the desired γ-carbonyl-α-amino acids were detected. In addition, a variety of secondary and tertiary propargyl alcohol derivatives including acyclic and



Scheme 70 $AgNO_3$-catalyzed synthesis of γ-carbonyl-α-amino acid derivatives **166**.[80]

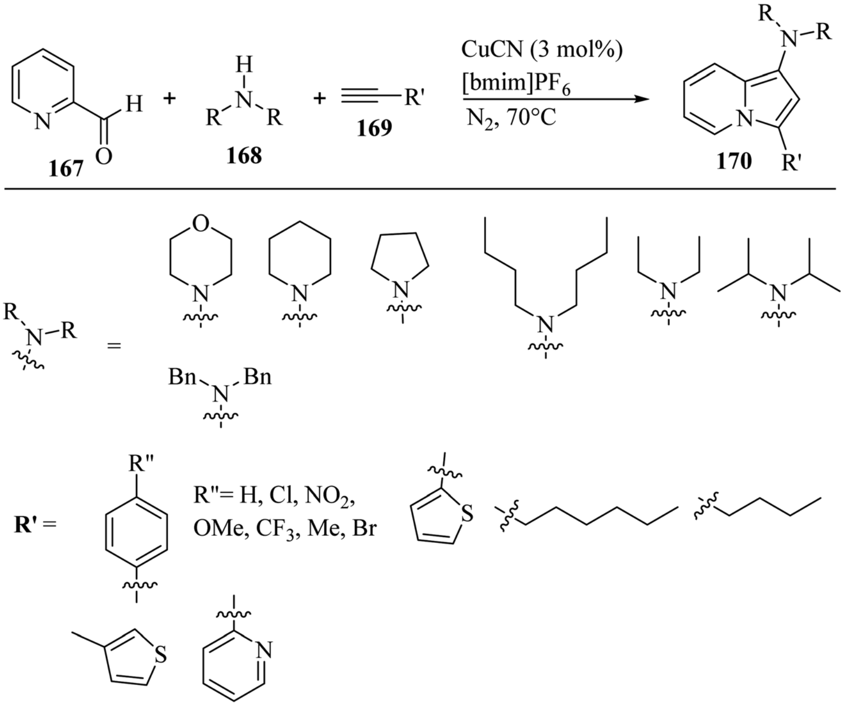


Scheme 71 Possible reaction mechanism for the synthesis of γ-carbonyl-α-amino acids **166**.[80]

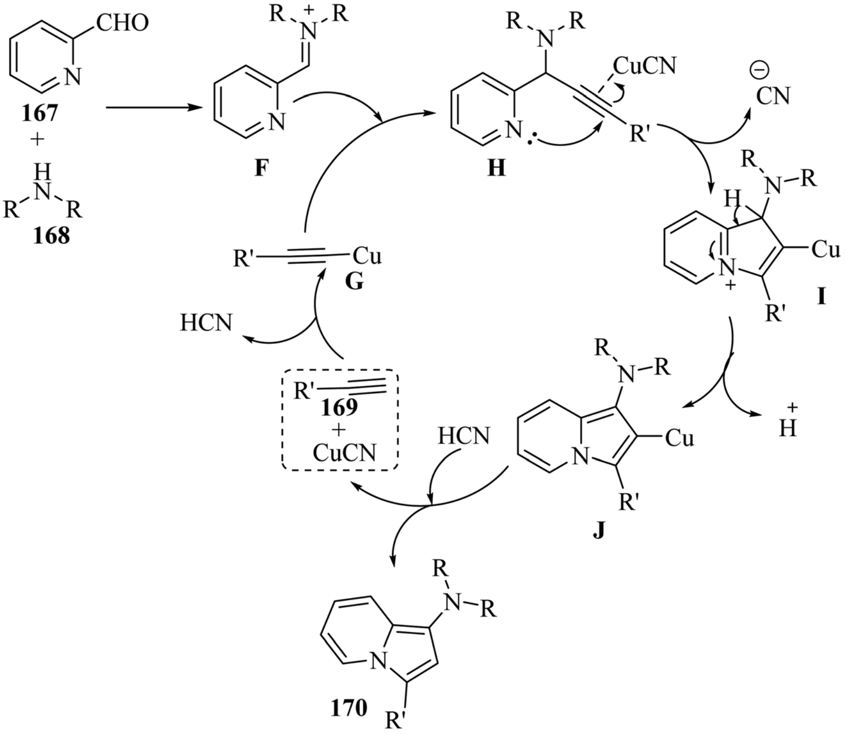
cyclic substituted propargyl alcohol derivatives produced the desired products. However, general aliphatic and aromatic alkynes such as 1-hexyne and phenylacetylene were used, and none of the corresponding products were detected (B and A, respectively). In this transformation, the alcohol OH group of propargylic alcohol played an essential role.

Mohammod and co-workers[81] synthesized 3-aminoindolysines **170** *via* the reaction among pyridine-2-carbaldehyde **167**, secondary amine derivatives **168**, and terminal alkyne derivatives **169** in the presence of the CuCN/[bmim][PF$_6$] system under an N$_2$ atmosphere at 70 °C (Scheme 72).

Firstly, Cu-acetylide intermediate **G** was generated *via* the activation of **169** by CuCN. Then, *N*-propargylamine amine intermediate **H** was obtained *via* the reaction between intermediate **G** and iminium ion **F.** In this stage, the electrophilicity of the internal alkyne increased because the triple bond of **169**



Scheme 72 Synthesis of 3-aminoindolysines **170** in the presence of the CuCN/[bmim][PF$_6$] system.[81]



Scheme 73 Possible reaction mechanism for the synthesis of 3-aminoindolysines **170**.[81]

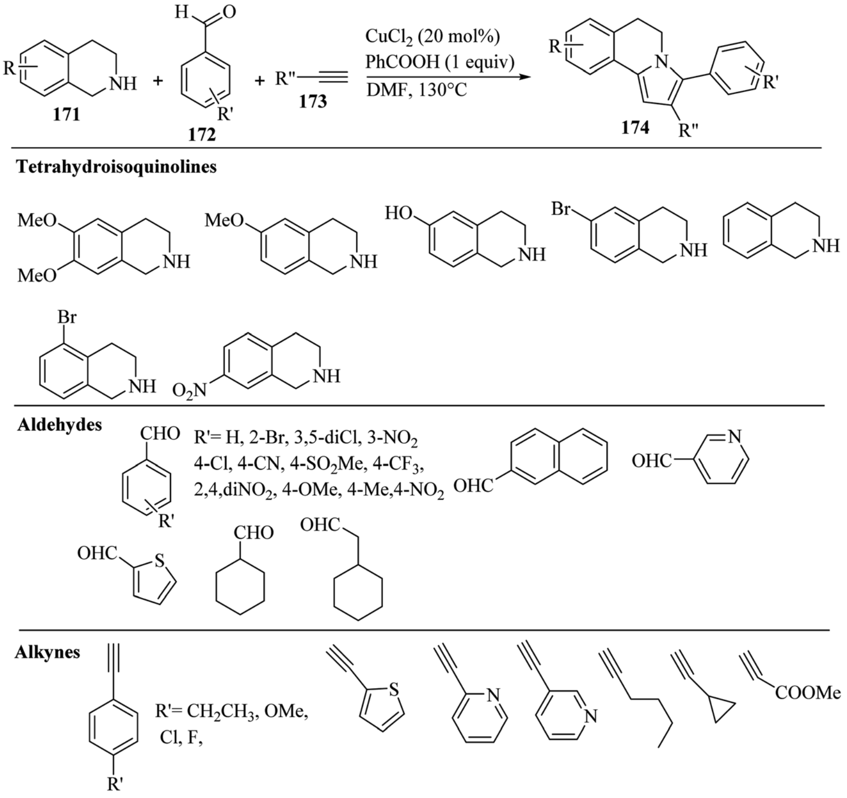
was coordinated with CuCN. After that, cationic heterocyclic intermediate **I** was produced *via* the nucleophilic attack of the N lone pair to the activated triple bond of alkyne, which proceeded *via* intramolecular cyclization. Next, intermediate **J** was generated through the deprotonation of intermediate **I**. Finally, the desired product **170** was produced together with the regeneration of catalyst *via* the protonation and demetallation of intermediate **J** (Scheme 73).

It should be noted that the CuCN/[bmim][PF_6] system was reused six times with no noticeable change in its performance. In the case of **169**, phenylacetylene and phenylacetylene derivatives with various substituents such as 4-Me, 4-OMe, 4-CF_3, 4-Br, 4-Cl, and 4-NO_2 provided the corresponding 3-aminoindolizines in 67–89% yield. However, only modest yields of the corresponding 3-aminoindolysines were isolated with aliphatic alkynes (70–71%), which is possibly due to the instability of the products, where they rapidly degraded during column chromatography. In addition, the use of heteroaryl alkynes was effective to obtain the corresponding 3-aminoindolizines in 82–84% yield. In the case of **168**, moderate yields of the resulting 3-aminoindolizine derivatives were obtained with aliphatic acyclic amine derivatives (67–72%).

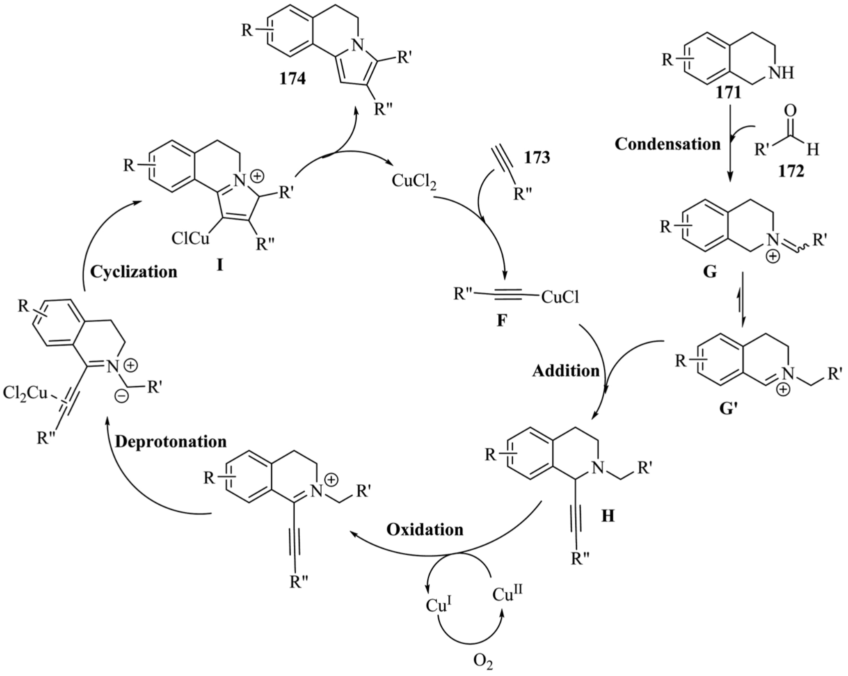
Cui *et al.*[82] synthesized pyrrolo[2,1-*a*]isoquinolines **174** *via* the reaction among terminal alkyne derivatives **173**, aldehydes **172**, and tetrahydroisoquinolines **171** in the presence of $CuCl_2$ and PhCOOH (condensation promoter) in DMF at 130 °C (Scheme 74).

Initially, the Cu catalyst reacted with **173** and produced **F**. Meanwhile, two imine ions **G** and **G′** were generated *via* the reaction between **171** and **172**. Then, amine **H** was obtained *via* the Mannich-type addition of activated alkyne **F** to ion **G′**, which is more stable than the other ion. After that, **H** underwent oxidation in the presence of the Cu catalyst, and then its product was deprotonated to produce azomethine ylide. After that, intermediate **I** was generated *via* the 5-*endo-dig* cyclization of azomethine ylide. Lastly, **174** was obtained *via* the final proton transfer together with the release of the Cu catalyst (Scheme 75). It should be noted that the Cu catalyst may have played three roles in the reaction, as follows: (1) activation of **173** for Mannich-type addition, (2) producing an iminium ion *via* the oxidation of the tertiary amine, and (3) 5-*endo-dig* cyclization *via* the activation of propargyl amine.

According to the results, the corresponding isoquinoline derivatives were produced in 17–69% yield *via* a condensation/Mannich-type addition/oxidation/cyclization cascade sequence. In the case of **171**, with the exception of the NO_2 group, the usual electron-withdrawing and -donating groups can be compatible under the optimal conditions at the tetrahydroisoquinoline moiety such as MeO, OH, Br, and Cl (28−66% yield). The NO_2 group dramatically deactivated tetrahydroisoquinoline and did not produce the corresponding product. In the case of **172**, various substituted benzaldehydes were tested in the above-mentioned reaction and produced the desired isoquinoline derivatives in 17–69% yield. In general, aldehyde derivatives with electron-withdrawing groups

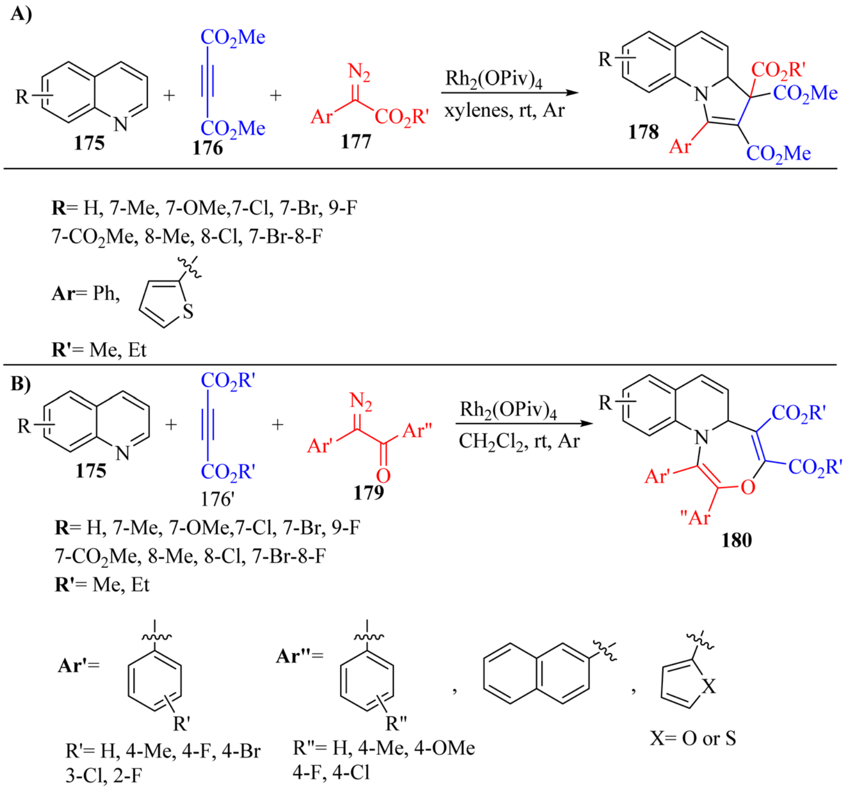


Scheme 74 $CuCl_2$-catalyzed synthesis of pyrrolo[2,1-*a*]isoquinolines **174**.[82]



Scheme 75 Possible reaction mechanism for the synthesis of pyrrolo[2,1-*a*]isoquinolines **174**.[82]

performed better in terms of reaction yield, which is likely due to the easier condensation and better stability of the intermediates generated *in situ*. Also, when using 2,4-dinitrobenzaldehyde, no corresponding product was detected, which is probably due to steric hindrance. All pyridyl, thienyl, and naphthyl substituents could be incorporated in the pyrrole



Scheme 76 (A) Synthesis of five-membered indolizine (scope for [3 + 2] cycloaddition) and (B) synthesis of seven-membered 1,4-oxazepine (scope for [5 + 2] cycloaddition).[83]

[2,1-*a*]isoquinoline backbone in reasonable yields (31–33%). Moreover, a trace amount of the corresponding isoquinoline derivative was detected when using aliphatic aldehyde and the corresponding intermediate (37%). In the case of **173**, the electron-rich and -deficient terminal alkynes were compatible in the present reaction (53–66%). Heterocyclic alkynes such as 2-pyridyl, 3-pyridyl, and 2-thienyl also were tolerated and produced the corresponding isoquinoline derivatives in 31%, 46%, and 51% yield, respectively. In addition, alkyl-substituted terminal alkynes were tested and produced the corresponding products in 19–35% yield. Unfortunately, ethyl propiolate did not give the corresponding product, which may be related to the high reactivity of this alkyne.

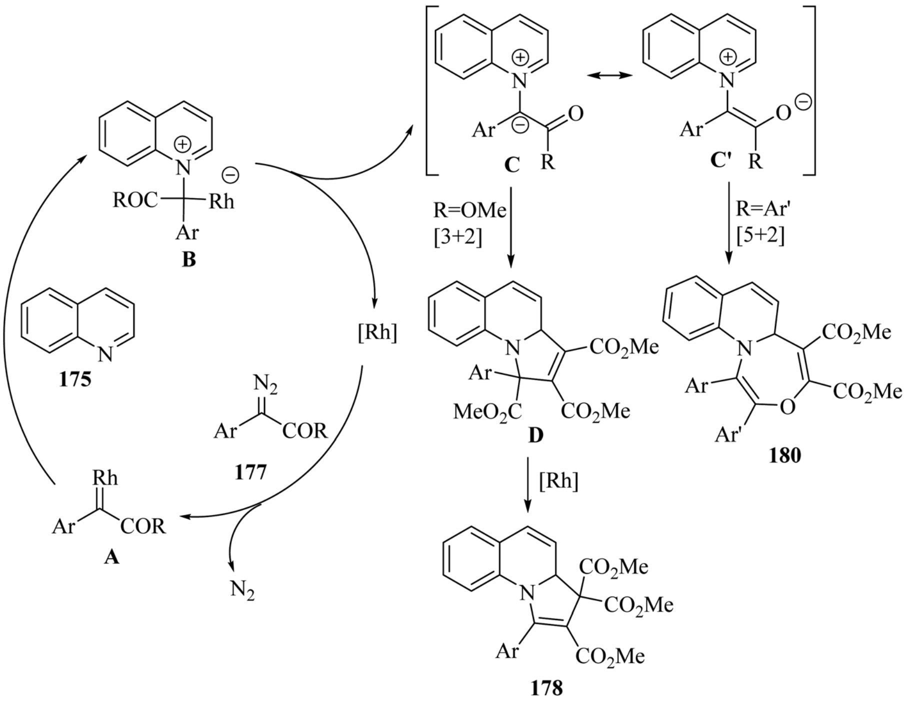
2.5 Reaction of α-diazoesters or ketones

He *et al.*[83] synthesized seven-membered 1,4-oxazepine structures **180** and five-membered indolizine derivatives **178** in 34–93% yield *via* the rhodium-catalyzed regiodivergent [5 + 2] and [3 + 2] cycloaddition of quinolinium ylide derivatives **175** with alkyne derivatives (**176** or **176′**), respectively, in CH_2Cl_2 for [5 + 2] cycloaddition and xylenes for [3 + 2] cycloaddition at room temperature (Scheme 76).

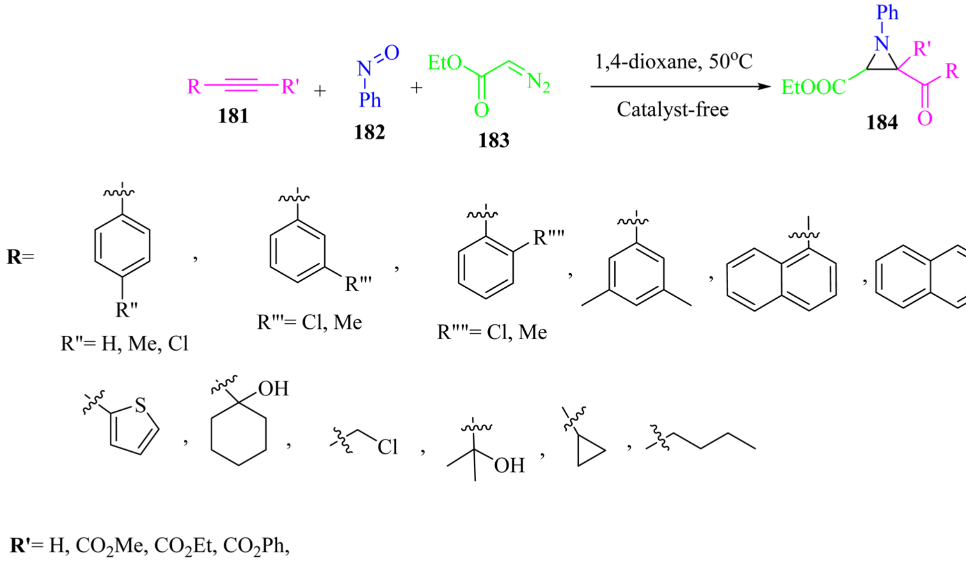
Initially, rhodium carbene **A** was produced *via* the reaction between diazo compound **177** and Rh complex together with $\mathbf{N_2}$ removal. Then, intermediate **B** was generated *via* the nucleophilic addition of **175** to **A**. After that, intermediates **C** and **C′** were produced *via* the dissociation of the rhodium salt. Next, intermediate **D** was obtained *via* the reaction between an alkyne and intermediate **C**, and this reaction was processed *via* 1,3-dipolar [3 + 2] cycloaddition. Subsequently, **178** was produced *via* a metal-assisted 1,3-ester migration process. In addition, the reaction between an alkyne and intermediate **C′** led to **180**, which proceeded *via* 1,5-dipolar [5 + 2] cycloaddition (Scheme 77).

In the case of **180**, various α-diazoketone derivatives were investigated and produced the desired oxazepines in 51% to 96% yield. The types of groups (electron-donating and -withdrawing) on both aryl rings of the α-diazoketone derivatives produced the desired oxazepines in 51–96% yield. In addition, diazoketone derivatives containing a bulky 2-naphthyl group, thiophene, and furan gave the desired products in 61%, 56%, and 68%, yield, respectively. Diethyl acetylenedicarboxylate also produced the corresponding oxazepine in 87% yield. A variety of quinoline derivatives was evaluated, and the desired oxazepines were obtained in 34–93% yield, except for 8-fluoroquinoline, which could not produce the corresponding product. In the case of **178**, various aryl diazoacetates were tested and produced the corresponding indolizines in 71–87% yield. Moreover, a diazo compound with thiophene was compatible in the transformation and produced the corresponding indolizine in 38% yield. Next, a variety of quinolines was tested and quinolone derivatives with various 6- and 7-substituents produced the corresponding indolizines in 58% to 92% yield. Notably, 6-Br-7-fluoroquinoline produced the corresponding indolizine in 68% yield, but 8-fluoroquinoline did not produce the corresponding product in the above-mentioned method.

Li *et al.*[84] synthesized multi-substituted 1-arylaziridine-2-carboxylates *via* the reaction among alkyne derivatives **181**, α-diazoester derivatives **183** and nitrosoarenes **182** and the mixture was stirred in 1,4-dioxane at 50 °C for 24 h under catalyst-free conditions (Scheme 78).



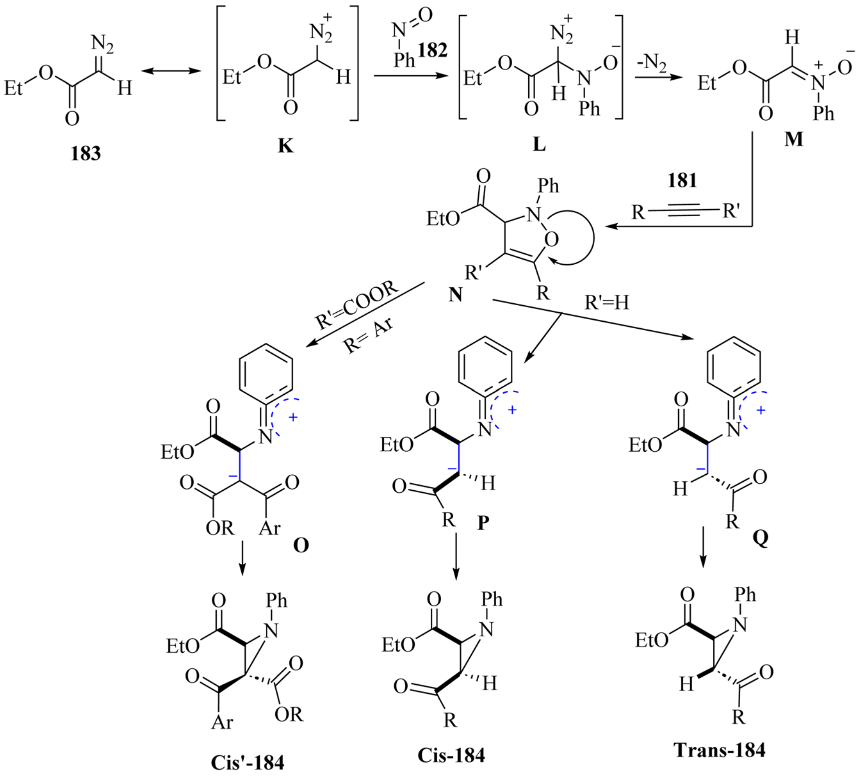
Scheme 77 Possible reaction mechanism for the synthesis of seven-membered 1,4-oxazepines **180** and five-membered indolizines **178**.[83]



Scheme 78 Synthesis of 1-arylaziridine-2-carboxylates **184**.[84]

Firstly, intermediate **K** was formed from **183.** Then, intermediate **L** was generated *via* the reaction between **182** and intermediate **K.** After that, intermediate **M** was produced *via* the removal of N_2 from intermediate **L.** Next, isoxazoline **N** was prepared from the reaction between **M** and **181** *via* [3 + 2] cycloaddition. Finally, the desired product ***cis*-184** or ***trans*-184** was generated *via* a Baldwin rearrangement. The important point about this reaction is that the use of an ester group instead of R′ and an aryl group instead of R led to the production of ***cis*′-184** due to steric hindrance in transition state **O.** Also, when using an H atom instead of R′, two transition states (**P** and **Q**) were formed, where the *cis* form was dominant (Scheme 79).

The above-mentioned method provides mild conditions for the synthesis of different types of multi-functionalized



Scheme 79 Possible reaction mechanism for the synthesis of multi-substituted 1-arylaziridine-2-carboxylates **184**.[84]

aziridine derivatives in up to 91% yield. Also, this method has advantages such as the use of catalyst-free strategy and readily accessible and cheap starting materials. According to the screened internal and terminal alkynes, they all produced the desired products in 56–91% yield. Internal alkynes produced the corresponding products (as single diastereomeric) exclusively in 71–91% yield. The evaluation of ester moieties of phenylpropiolic acid ester (Me, Et, and Ph) demonstrated that steric hindrance affected the yield, where sterically hindered aryl group provided relatively lower yields (89%, 87%, and 73%, respectively). Also, ethyl 3-phenylpropiolate derivatives with an electron-donating group (Me at *ortho*, *meta*, and *para* position) resulted in higher yields than that having an electron-withdrawing group such as Cl (84–91% and 71–80% yield). In addition, the structure with two substituents (3,5-dimethyl) on the phenyl ring gave the corresponding product produced in 75% yield, which showed that steric hindrance affected the yield. Furthermore, internal alkyne derivatives with a naphthyl group gave the corresponding products in 83% to 91% yield. Moreover, aliphatic terminal alkyne derivatives were evaluated and produced the corresponding *cis* isomers as the major products (56–82% yield) with moderate diastereoselectivity (up to 71 : 29 *cis*/*trans*). Unfortunately, ethynylcyclopropane and 2-ethynylthiophene gave the corresponding products in 78% and 83% yield with very low diastereoselectivity (50 : 50 *cis*/*trans* and 52 : 48 *cis*/*trans*), respectively.

Zhou *et al.*[85] synthesized tetrasubstituted pyrrole **188** *via* the reaction among alkynes **187**, 1-substituted benzimidazoles **186**, diazoacetates **185**, and [Fe(TPP)Cl] in 1,4-dioxane for 12 h under an Ar atmosphere at room temperature (Scheme 80).

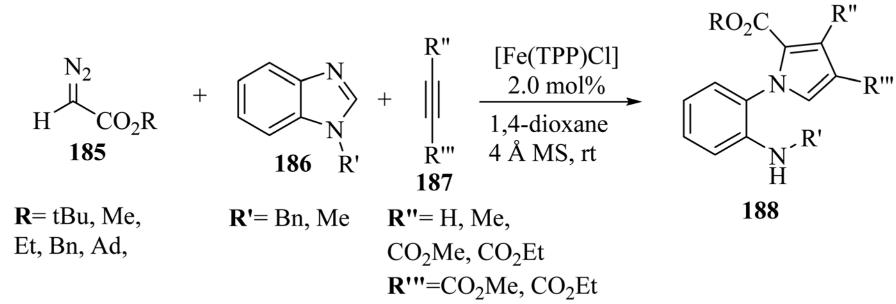
Initially, the reaction between **185** and **186** produced benzimidazolium *N*-ylide intermediate **A** in the presence of an iron catalyst. Then, intermediate **B** was produced *via* the reaction between **187** and intermediate. Finally, **188** was generated *via* fast isomerization of intermediate **B**, which was a thermodynamically favorable ring-opening aromatization process (Scheme 81).

The desired products were produced with an isolated yield of 70–90%. The above-mentioned method has advantages such as the use of mild reaction conditions, available starting materials, operational simplicity, and inexpensive catalyst.

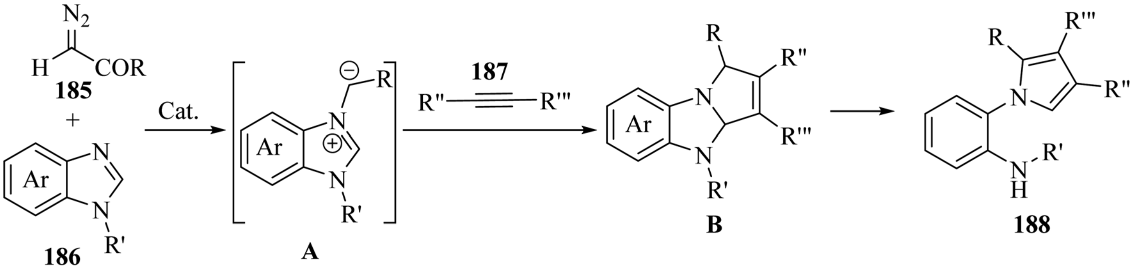
Lv and co-workers[86] synthesized (*E*)-beta-monofluoroalkyl-β,γ-unsaturated esters (**192** and **195**) *via* the reaction among 1,1-alkylmonofluoroalkylation of terminal alkyne derivatives **189**, 2-fluoro-1,3-dicarbonyl compounds (**191** and **194**), and diazo compounds (**190** and **193**) in the presence of CuI and K_2CO_3 in acetone at 80 °C for 2 h (Scheme 82).

Initially, Cu acetylide was produced *via* the reaction between **189** and CuI in the presence of K_2CO_3. Then, copper carbene **K** was generated *via* the reaction between **190** and Cu acetylide. Next, intermediate **L** was obtained from the migratory insertion of the alkynyl group into the **K**, followed by protonation of intermediate **L** to produce intermediate **M**. After that, intermediate **N** was produced by the rearrangement of intermediate **M**. Finally, the desired product **192** was produced *via* the reaction between intermediate **N** and dimethyl 2-fluoromalonate in the presence of K_2CO_3. It should be noted that the nucleophilic attack of the monofluoroalkyl group to the Ph from the opposite side was preferred to avoid steric interactions (Scheme 83).

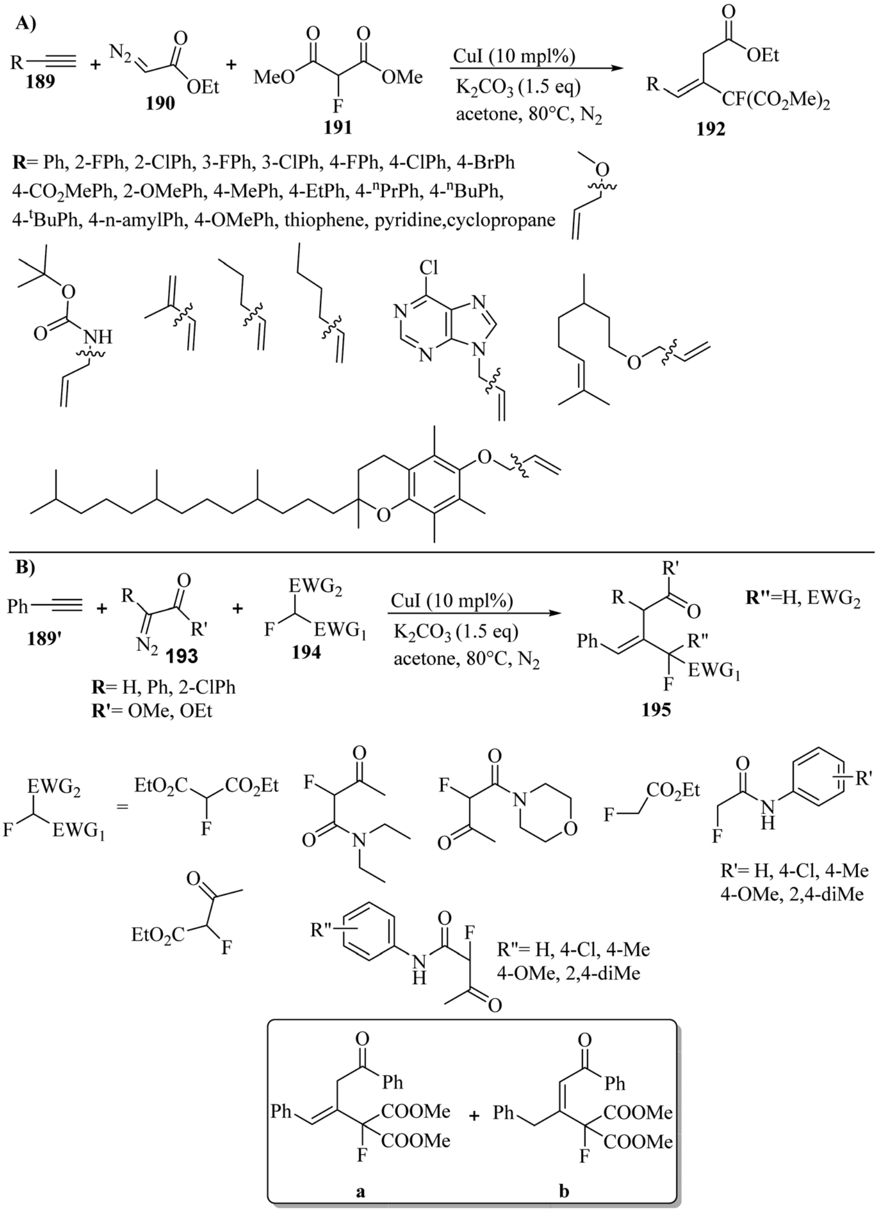
In the case of **189**, the reaction of dimethyl 2-fluoromalonate, 2-diazoacetate, and various terminal alkynes gave the



Scheme 80 Synthesis of multi-substituted pyrroles 188.[85]

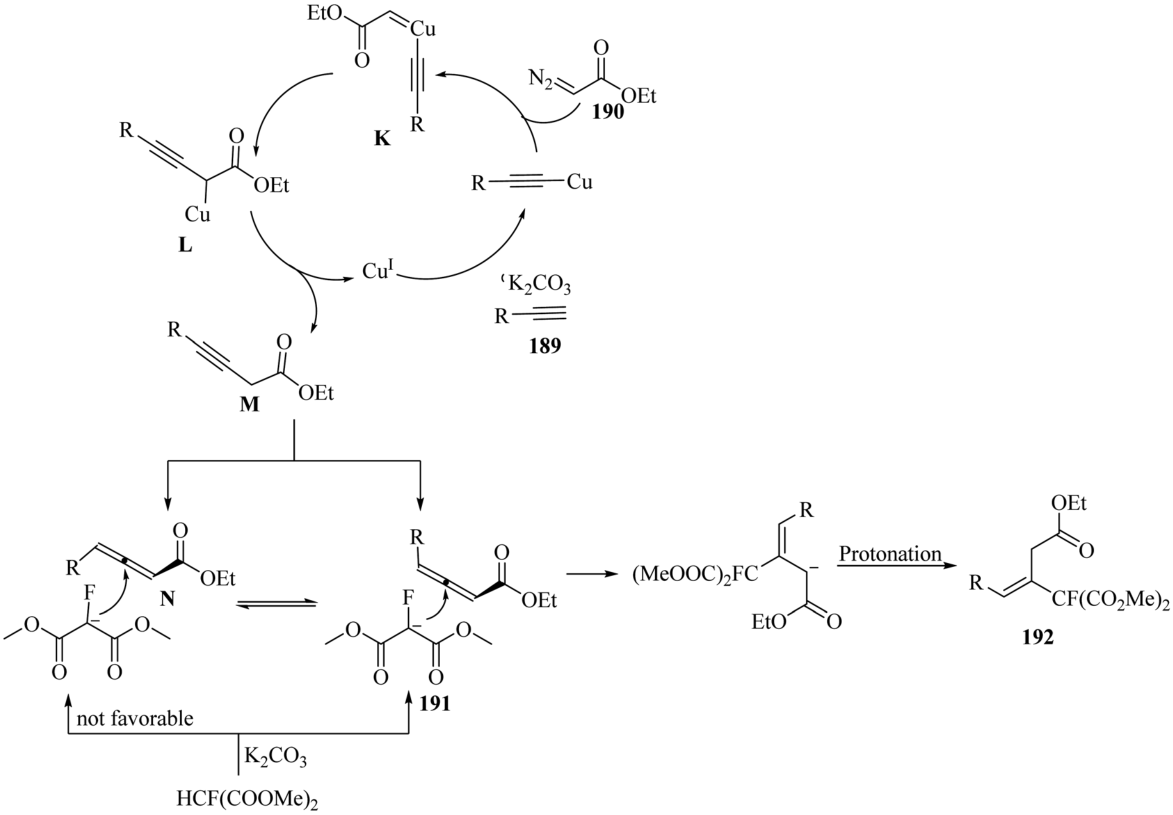


Scheme 81 Possible reaction mechanism for the synthesis of tetra-substituted pyrrole 188.[85]



Scheme 82 CuI-catalyzed synthesis of (*E*)-β-monofluoroalkyl-β,γ-unsaturated esters or ketones: (A) scope of alkynes in the 1,1-alkylmonofluoroalkylation and (B) scope of diazo compounds and monofluoroalkylation reagents in 1,1-alkylmonofluoroalkylation.[86]

corresponding β,γ-unsaturated products in 35–91% yield. Also, para, ortho, and *meta*-fluoro, chloro ethynylbenzenes under the 1,1-alkylmonofluoroalkylation reaction produced the desired products in the same yields, which showed that steric hindrance had no effect. 4-Br and 4-COOMe ethynylbenzenes were reacted and produced the corresponding products in 76% and 70% yield, respectively. In addition, alkyne derivatives with electron-donating groups on the aromatic rings gave the corresponding β,γ-unsaturated products in 70% to 85% yield. Alkynes with a pyridine or thiophene moiety gave the desired β,γ-unsaturated in 45–77% yield. *N*-propargyl amides, conjugated enynes, and alkyl propargyl ethers gave the desired products in 70–75% yield. Moreover, the non-activated aliphatic alkynes produced the corresponding β,γ-unsaturated products in 35% to 40% yield. Further, the citronellol-based alkyne derivative, D,L-α-tocopherol-based alkyne derivative, and purine-based alkyne derivative produced the desired β,γ-unsaturated products in 85%, 70%, and 81% yield, respectively. Diethyl 2-fluoromalonate produced the desired product in 78% yield. Also, 2-F-1-morpholinobutane-1,3-dione and *N*,*N*-diethyl-2-F-3-oxobutanamide were tested and produced the desired products in 70% and 56% yield, respectively. Interestingly, ethyl 2-fluoro-3-oxobutanoate reacted with ethynylbenzene and ethyl 2-diazoacetate and produced the desired β,γ-unsaturated product in 70% yield. In addition, 2-F-acetoacetamides with different groups on the aromatic rings were converted to the desired β,γ-unsaturated products in 68% to 81% yield. Importantly, when K_2CO_3 was replaced with K_3PO_4, the corresponding products



Scheme 83 Possible reaction mechanism for the synthesis of (*E*)-beta-monofluoroalkyl-β,γ-unsaturated esters.[86]

were produced in 52% to 78% yield. The reaction of ethyl 2-diazoacetate compared to 2-diazo-1-phenylethanone and methyl aryldiazoacetates was higher under identical conditions. When acetone was replaced with THF, methyl aryldiazoacetates were suitable substrates and produced the desired β,γ-unsaturated products in 39–40% yield. Finally, 2-diazo-1-phenylethanone was transformed into the 1,1-alkylmonofluoroalkylation products (Scheme 82B(a) and (b)) in 1,4-dioxane with a total yield of 35%.

2.6 Reaction of isocyanides

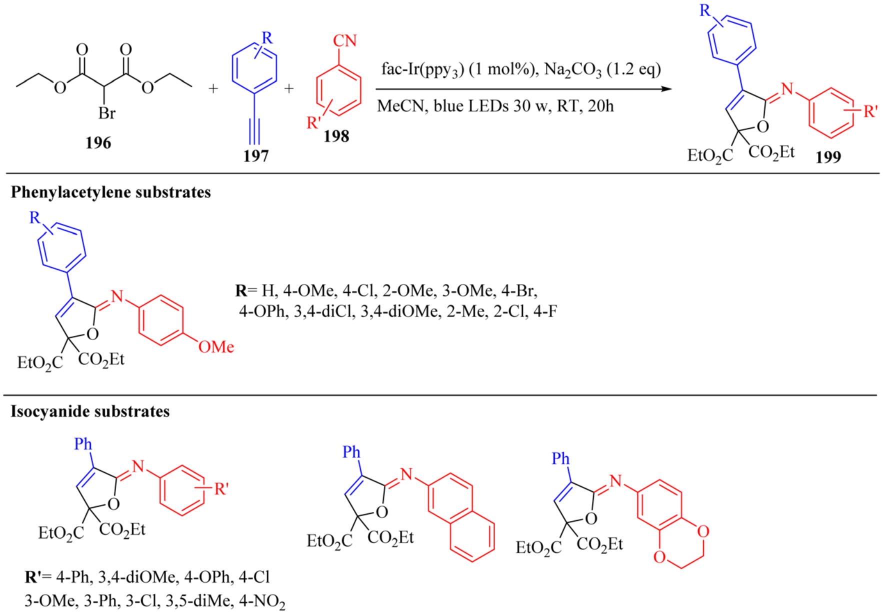
Pelliccia *et al.*[87] synthesized iminofurans **199** *via* an isocyanide-based three-component reaction with the reactants of diethyl bromomalonate **196** and phenylacetylene derivatives **197** in the presence of *fac*-Ir(ppy)$_3$ as the photoredox catalyst and Na_2CO_3 as the base in MeCN under irradiation with a 30 W blue LED at room temperature for 20 h (Scheme 84).

Initially, the Ir^{3+*} photocatalyst was generated from *fac*-Ir(ppy)$_3$, which underwent metal-to-ligand charge transfer under visible-light irradiation. Then, alkyl radical **A** was formed *via* single-electron transfer (SET) between Ir^{3+*} and **196**. Next, vinyl radical **B** was generated *via* the reaction between **A** and **197**, followed by the reaction of **198** with **B**, which led to the formation of imidoyl radical intermediate **C**. After that, Ir^{4+} oxidized this key species to nitrilium ion **D**. Next, amide **E** was prepared from **D** in the presence of H_20. In the following step, **199** was generated from **E**, which underwent oxidative cyclization (Scheme 85).

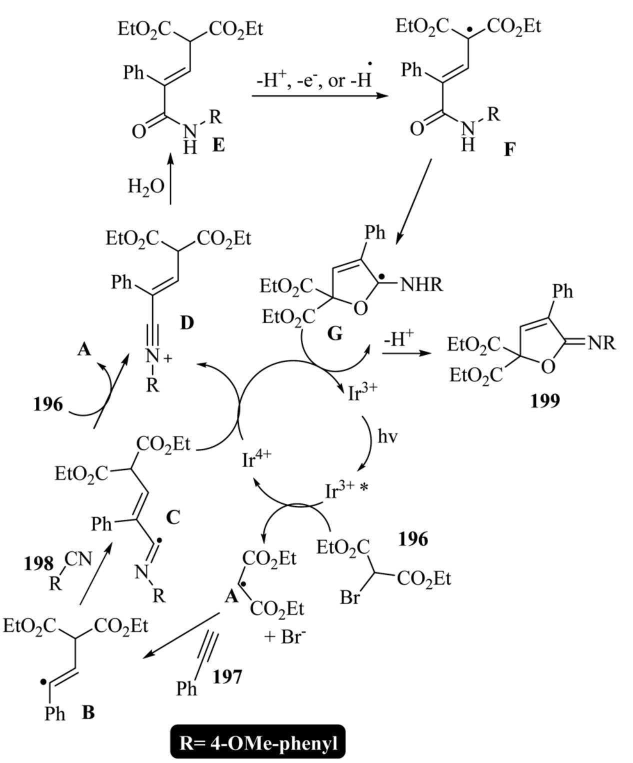
Investigation of isocyanides in the above-mentioned reaction demonstrated that a variety of groups on the phenyl ring could produce the corresponding products in 35–54% yield. In contrast, aliphatic isocyanides such as cyclohexylisocyanide and *tert*-butylisocyanide did not produce the corresponding products. Moreover, the evaluation of phenylacetylene derivatives showed that neither the position of the aromatic ring substituents nor their electronic nature significantly affected the reaction yield (23–60%) except when bromo phenylacetylene was tested, where the reaction yield dramatically decreased (23%). In the case of aliphatic derivatives of alkynes, the use of these derivatives was not possible due to them not being reactive at all.

Gao and co-workers[88] synthesized captodative olefins (**203** or **207**) *via* the palladium-catalyzed (Pd(OAc)$_2$) three-component reaction of alkynes (**200** or **204**), carboxylic acids (**206** or **202**), and isocyanides (**201** or **205**) in the presence of Ag_2O as a silver salt, and P(*o*-tol)$_3$ as a ligand in PhCl under N_2 at 30–50 °C for 5 h (or 70 °C for 5–15.5 h) (Scheme 86).

Initially, the reaction among **200**, **206**, and Ag_2O produced silver acetylide **K** together with the formation of silver carboxylate. Then, complex **L** was obtained *via* the attack of the carboxylic anion on **K**, which subsequently caused the transmetalation process with Pd(II). Then, imidoyl palladium(II) intermediate **N** was generated *via* the isocyanide migratory insertion reaction to vinyl palladium complexes **M**. Finally, *via* the successive reductive elimination process and treatment with H_2O **270** or **203** was produced (Scheme 87).



Scheme 84 *Fac*-Ir(ppy)$_3$-catalyzed synthesis of iminofuran derivatives **199**.[87]

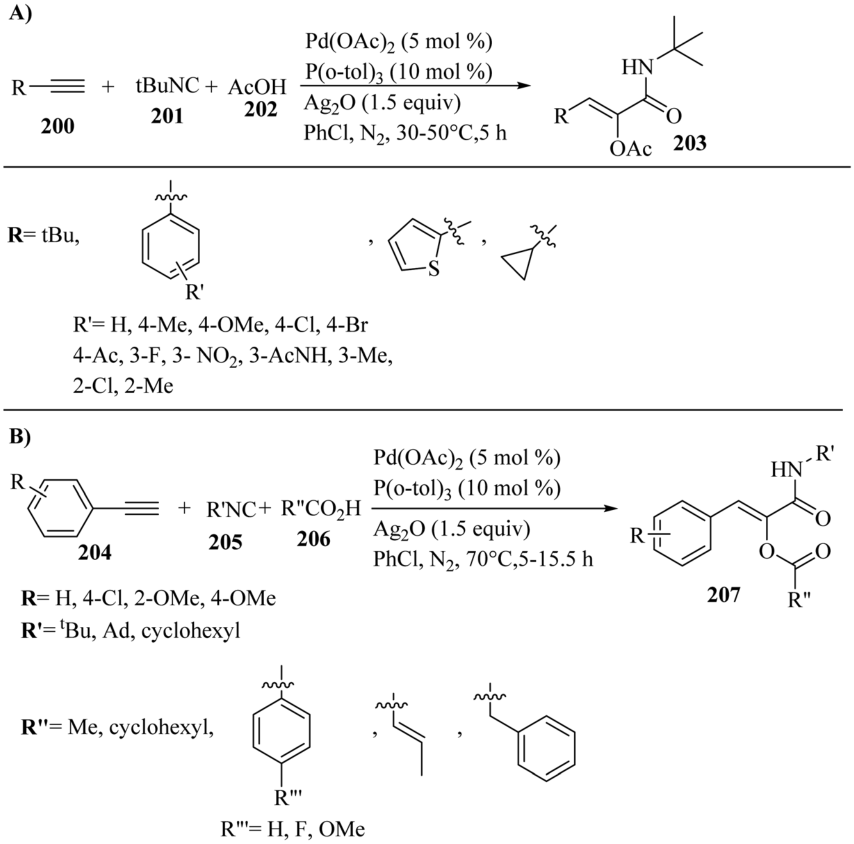


Scheme 85 Possible reaction mechanism for the synthesis of iminofurans **199**.[87]

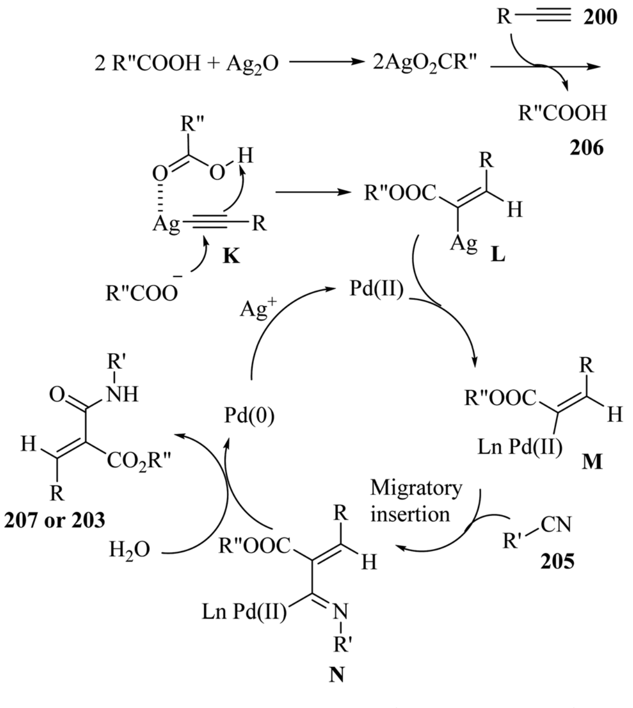
A variety of alkyne, carboxylic acid, and isocyanide derivatives was investigated. According to the results, aryl acetylenes bearing different substitutions (alkyl, alkoxy, halides, acyl, nitro, and amide) produced the corresponding olefins in 48% to 90% yield. Interestingly, when phenylpropiolic acid was used instead of phenylacetylene, the corresponding olefin was produced in 87% yield. In addition, thienyl alkyne gave the corresponding olefin in 44% yield, and the enyne substrate also could be transformed into the corresponding olefin in 57% yield. Also, alkyl acetylenes (^{t}Bu and cyclopropane) produced the corresponding olefins in 70% and 67% yields, respectively (Scheme 86A). A variety of acids and isocyanides was tested in the above-mentioned reaction. It was found that for other carboxylic acids, higher temperature was more favorable and produced the corresponding olefins in 47% to 86% yield (Scheme 86B). Moreover, 1-adamantyl and cyclohexyl isocyanide were tested and produced the corresponding olefins in 44% to 79% yield, respectively. Interestingly, when α-acidic isocyanides such as isocyanoacetates were used, no desired products could be observed.

Singh and co-workers[89] reported a novel method for the synthesis of tetrahydroquinoline-fused tetracyclic derivatives **2a**. This method was performed in two steps. In the first step, aniline derivatives **209**, benzaldehyde derivatives **208**, propiolic acid derivatives **211**, and isocyanide derivatives **210** were stirred in MeOH at room temperature and produced derivatives **1a**. Then derivatives **1a** were reacted with molecular iodine (electrophile) and produced the corresponding derivatives **2a** (Scheme 88).

Initially, intermediate **A** was generated *via* the activation of a triple bond of alkyne (π activation) by the iodonium (I^+) ion. After that, the regioselective spirocyclic carbocation intermediate **B** was obtained *via* the ipso nucleophilic attack of the aniline to the activated triple bond. In this step, it should be noted that this process was done *via* a 5-*endo-dig* method. Finally, **2a** was produced *via* the immediate trapping of the carbocation by the intramolecular nucleophile. In this step, it should be noted that this process was done through the Friedel–Crafts-type cyclization (Scheme 89).



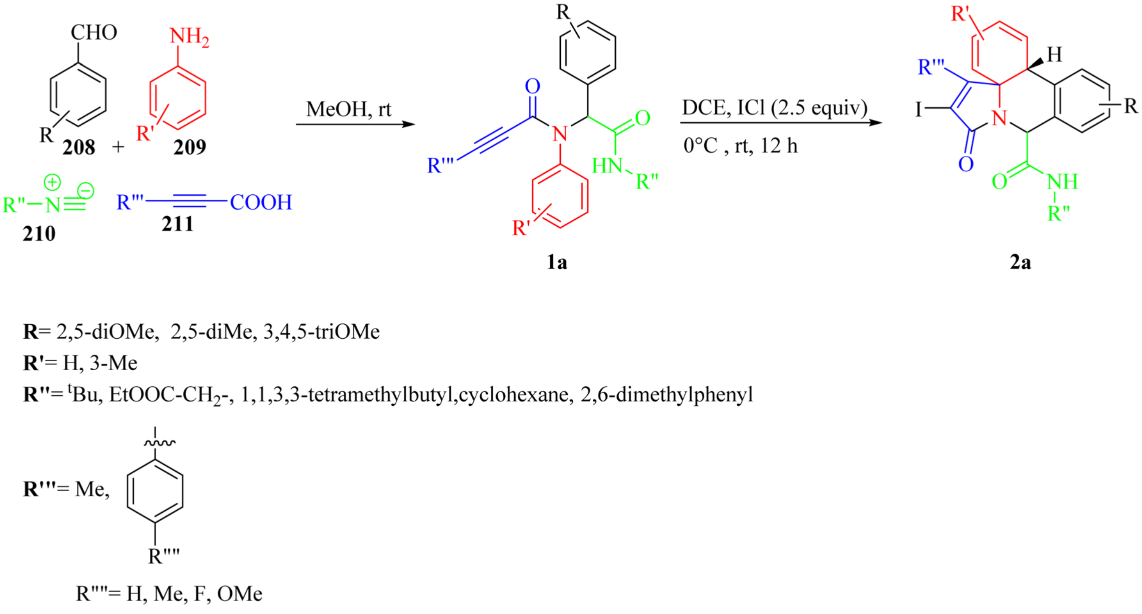
Scheme 86 Synthesis of captodative olefins: (A) substrate scope of alkyne derivatives and (B) substrate scope of isocyanides, alkynes, and carboxylic acids.[88]



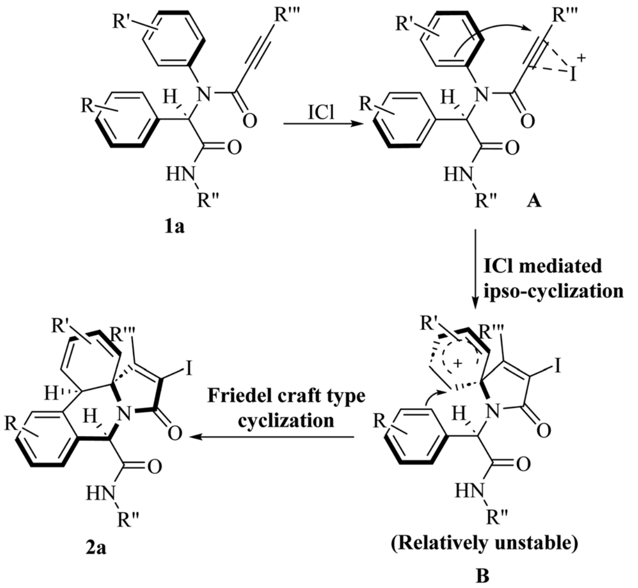
Scheme 87 Possible reaction mechanism for the synthesis of captodative olefins.[88]

The Ugi adducts were produced in 67–91% yield and were compatible with substituted phenyl propiolic acid derivatives, which transformed to the corresponding tetrahydroquinolines in 64% to 87% yield. Also, in this transformation, substituent electronic factors had an influence on the phenyl propiolic acid. The presence of an electron-donating group on phenyl propiolic acid produced the required products in better yields (71–87%) compared to fluorine-substituted adducts (58–64%). The Ugi adducts derived from 2,5-dimethoxy and 3,4,5-trimethoxy aldehyde reacted with the various isocyanide derivatives and produced the corresponding products in 71% to 76% yield. Furthermore, functionalized phenyl propiolic acid, aldehyde and cyclohexylisocyanide-derived Ugi adduct produced the corresponding products in 58% to 77% yield. It should be noted that the aliphatic acid derivatives having Ugi adducts transformed the corresponding products in 69% to 71% yield. In addition, a variety of aromatic and aliphatic substituted isocyanides was tested and produced the corresponding cyclized products in 52% to 83% yield. Among the aliphatic isocyanide derivatives, only *n*-pentyl isonitrile showed the minimum yield. Moreover, the aromatic isonitrile-based Ugi adduct produced the corresponding products in 56% and 62% yield.

Yang and co-workers[90] synthesized perfluoroalkyl-containing pyrano[3,4-*c*]pyrroles **215** *via* the reaction among methyl perfluoroalk-2-ynoate derivatives **214**, 3-aroyl (or heteroyl)



Scheme 88 Synthesis of tetrahydroquinoline-fused tetracyclic heterocycles **2a**.[89]



Scheme 89 Possible reaction mechanism for the synthesis of tetrahydroquinoline-fused tetracyclic derivatives **2a**.[89]

acrylic acid derivatives **212**, and isocyanide derivatives **213** in MeCN at room temperature for 12 h (Scheme 90).

Initially, zwitterion **J** was obtained *via* the Michael addition of **213** to **214**. Then, **J** was protonated by **212** to give aminium **K** and carboxyl anion **L**. After that, isoimide **M** was generated from the reaction between intermediate **K** and **L** *via* a Passerini-type reaction. Next, **M** produced conformers **N** and **N′** *via* the Mumm rearrangement. Finally, the exo isomer was generated conformer **N** as the major diastereoisomer *via* the intramolecular oxo-Diels–Alder reaction. It should be noted that the endo isomer was obtained as the minor product due to the steric hindrance between CO_2Me and the R group in conformer **N′** (Scheme 91).

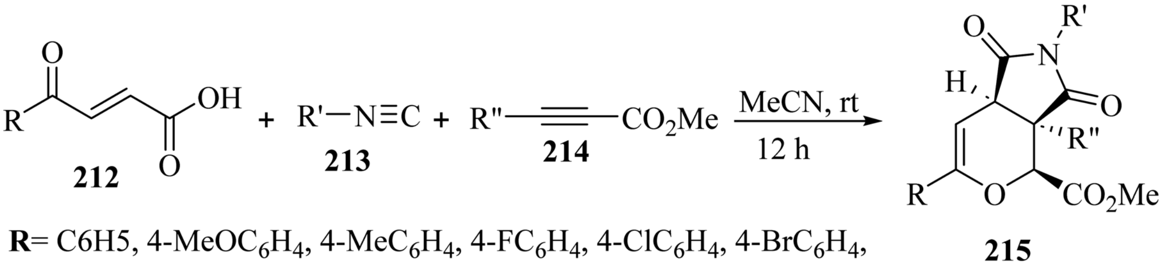
Various R-substituted acrylic acid derivatives were evaluated and acrylic acid derivatives with different types of heteroaryl or aryl groups at the terminal position produced the desired perfluoroalkyls in 45% to 97% yield with high diastereoselectivity (up to >99 : 1 dr). Generally, an electron-withdrawing group on the acrylic acid phenyl ring afforded the corresponding perfluoroalkyls in higher yields compared to an electron-donating substituent at the same position. Substrates with n-C_3F_7, CF_2H, and C_2F_5 were tested and produced the corresponding perfluoroalkyls in 45% to 93% yield, which showed little detrimental effect on the yields and had no adverse influence on the diastereoselectivity. Next, various isocyanides were investigated and the corresponding perfluoroalkyls produced in 32% to 98% yield (up to >92 : 1 dr). A summary of the reaction of alkynes with isocyanide derivatives, and also the limitations and progress of the reactions are presented in Table 3.

The reaction among isocyanides, alkynes and fullerenes was reviewed by Li *et al.*[91–93] Investigating the types of alkynes in this type of multicomponent reaction requires a more detailed investigation to discover a way to carry out the reaction of alkynes that are not involved in the reaction. Even checking the position of C–H alkynes and activating this part to be involved in the reaction need to be investigated. The yield of the obtained products is also low, which is a limitation in this field and requires more extensive research in this type of reaction. Some recent developments in this field are shown in Table 4.

3 C–H activation

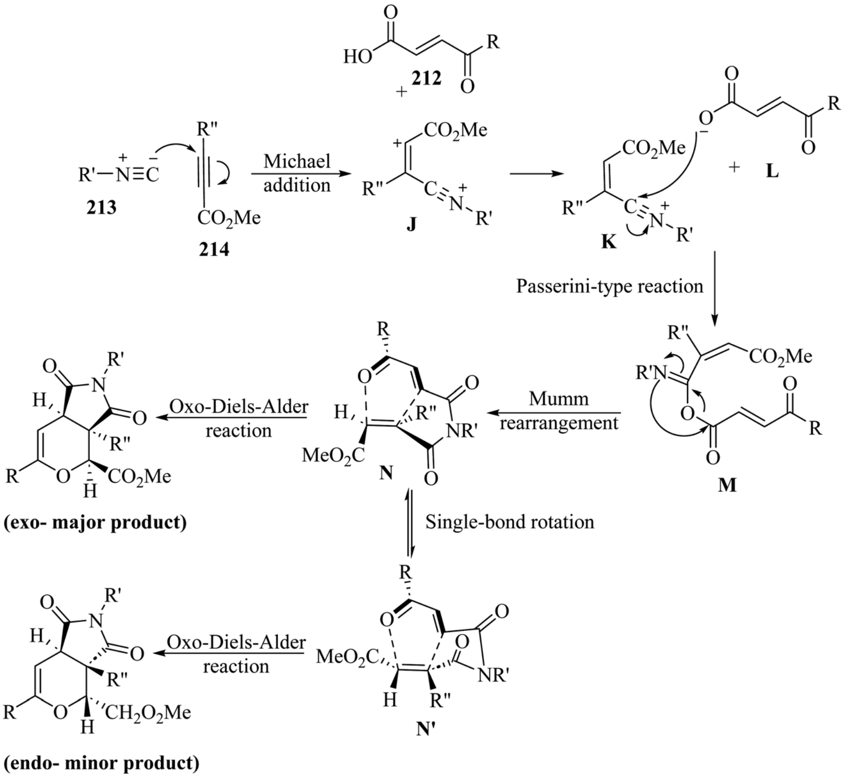
3.1 Synthesis of propargylamines

Yan and co-workers[96] reported a green method for the synthesis of propargylamine derivatives **219** *via* the reaction among alkynes **218**, aldehyde derivatives or ketone derivatives **216**, and amines **217** in the presence of PS–PEG-BPy–$CuBr_2$ as a catalyst



R= C6H5, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-MeC$_6$H$_4$, 3-CF$_3$C$_6$H$_4$, 2-BrC$_6$H$_4$, 2-Thienyl, 2-puryl,
R'= t-Butyl, Cyclohexyl, 4-NO$_2$C$_6$H$_4$, 4-MeOC$_6$H$_4$, 2,6-dimethylC$_6$H$_4$
R"=CF$_3$, CF$_2$H, C$_2$F$_5$,n-C$_3$F$_7$

Scheme 90 Synthesis of perfluoroalkyl derivatives **215** without a catalyst.[90]



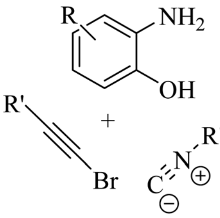
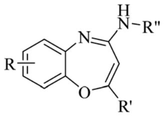
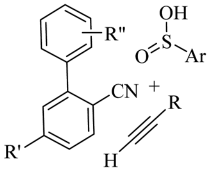
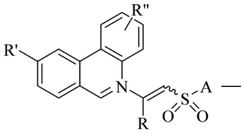
Scheme 91 Possible reaction mechanism for the synthesis of perfluoroalkyl-containing pyrano[3,4-*c*]pyrroles.[90]

and N$_2$ at 110 °C under solvent-free conditions (Scheme 92). The desired propargylamines were produced in 66–97% yield. Several alkynes were investigated and the results showed that aromatic alkynes with *p*-trifluoromethyl or *p*-methyl substituents produced the corresponding products in 99% and 98% yield, respectively. When the aromatic alkyne has a methyl substitution on the *ortho* position, it gave the corresponding product in 94% yield. Furthermore, aliphatic acetylenes were used and the desired propargylamines were produced in yields of 79% and 74%.

Propargylamines **223** were synthesized by Dhanasekaran and co-workers[97] *via* the reaction among 2-ethynyl anilines **222**, amines **221**, and substituted benzaldehydes **220** in the presence of a Cu$^{\text{I}}$-$^{\text{i}}$PrpyboxdiPh complex and *N*-Boc-(L)-proline as the catalyst system in DCE at room temperature (Scheme 93). According to the results, *N*-substituted 2-ethynyl aniline derivatives gave the desired propargylamines in high yields (up to 87%). *N*-Tosyl-2-ethynyl aniline produced the products in low enantioselectivities with respect to *N*-substituted 2-ethynylaniline derivatives. Also, 2-ethynyl anilines with various substituents on the aromatic ring produced the desired products with high levels of enantioselectivities (up to 95% ee) in good yields (up to 87%).

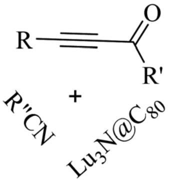
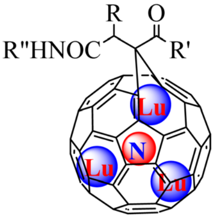
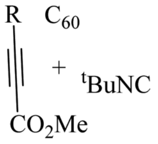
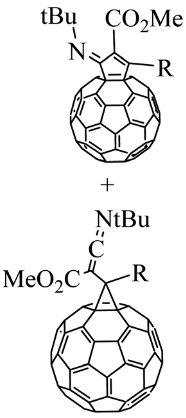
Milen *et al.*[98] synthesized propargylamines **227** *via* the reaction among acetylenes **225**, aldehydes **224**, and secondary amines **226**, where they studied twelve readily available copper-containing mineral derivatives. It should be noted that the

Table 3 Summary of the reaction of alkynes with isocyanides and limitations or progress of the reactions

Reactants	Product	Catalyst	Solvent	Method employed	Reaction time	Yield	Limitations or progress	Ref.
		$Pd(PPh_3)_2Cl_2$	1,4-Dioxane	PPh_3, Cs_2CO_3, 80 °C	2 h	47–94%	2-Amino-3-pyridinol and 2-aminothiophenol did not react	Liu *et al.*[94]
		—	DMSO/H_2O	Method 1: pyridine, LED, O_2[a], RT Method 2: pyridine, UV, O_2[a], RT	Method 1: 16 h Method 2: 24 h	Up to 73%	(1) High selectivity (2) Made new EDA complexes from arylsulfinate anions	Li *et al.*[95]

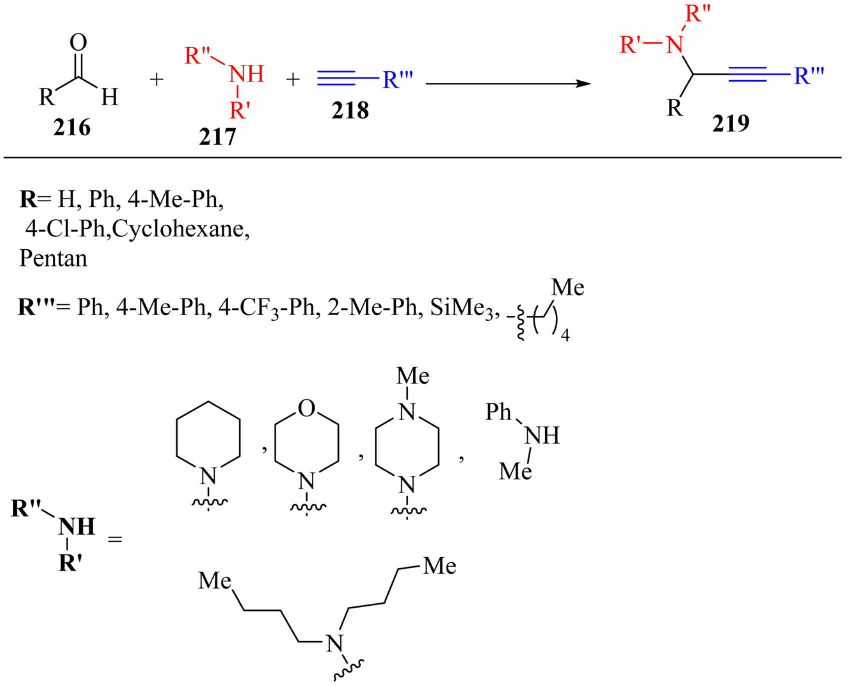
[a] Investigation of scope of arylacetylenes under N_2 (UV and LED method = 24 h).

Table 4 A summary of the reaction of alkynes with isocyanides and fullerene and limitations or progress of the reactions

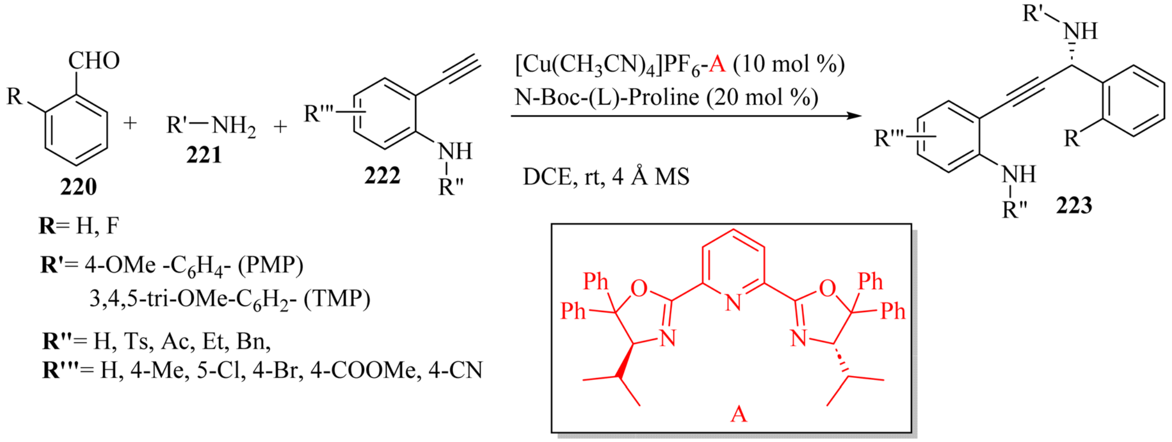
Reactants	Product	Catalyst	Solvent	Method employed	Reaction time	Yield	Limitations or progress	Ref.
			*o*-Dichlorobenzene	Air, 120 °C	1 h	27–30%	(1) One-step reaction for synthesis of a static solid-state cluster in an NCF (2) This research proposed a vision about potential regioselectivity in further reactions and advances in quantum information materials	Li *et al.*[91]
		—	*o*-Dichlorobenzene	N_2, 80 °C[a] or 120 °C[b]	1 h	4–36%	(1) Alkynes containing a substituent and an ester group on one side provided resonance and inductive effects on the other side of the triple bond (ester group has key role) (2) The 4-NO_2-Ph substituent at both ends of the C≡C triple bond of did not show similar results	Li *et al.*[92]

[a] Used in the reaction between fullerenes, alkyl isocyanides, and DMAD. [b] Used in the reaction between fullerenes, alkyl isocyanides, and unsymmetric alkyne substrates.

reaction was performed in the presence of chrysocolla, brochantite, azurite, and malachite in PhMe under reflux for 20 h and the corresponding propargylamines were obtained in 36% to 96% yield (Scheme 94). Firstly, various benzaldehyde derivatives with phenylacetylene and morpholine were tested and the results showed that aldehydes with either electron-donating or -withdrawing groups on the phenyl ring produced the desired propargylamine derivatives in 21% to 92% yield. Also, the reaction of 9*H*-fluorene-2-carbaldehyde and naphthalene-2-carbaldehyde produced the desired propargylamines in 87% and 91% yield, respectively. Furthermore, heteroaromatic carbaldehyde derivatives with a furanyl, thiazolyl, pyridinyl or thiophenyl moiety produced the corresponding propargylamines in 78% to 94% yield. When 1-methylpyrrol-2-carboxaldehyde and 5-



Scheme 92 Green synthesis of propargylamine derivatives **219** *via* A3 coupling reactions.[96]

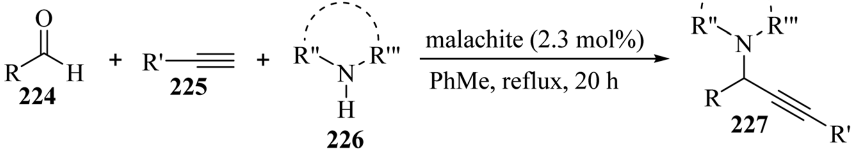


Scheme 93 Synthesis of propargylamines **223** *via* a chiral CuI–box complex with 2-ethynyl anilines.[97]

fluoro-1-benzothiophene-2-carbaldehyde were used as the starting materials, lower yields were obtained (36% and 51%, respectively). In addition, aliphatic aldehyde heptanal produced the corresponding propargylamine in 88% yield. Subsequently, the reaction of benzaldehyde and morpholine with 4-substituted phenylacetylenes was evaluated. 4-Methylphenylacetylene showed good reactivity and produced the corresponding propargylamine in 93% yield. However, 4-nitrophenylacetylene gave the corresponding product in 47% yield. Furthermore, the reaction could be performed with aliphatic acetylene derivatives (dec-1-yne and oct-1-yne) and produced the corresponding propargylamines in 77% and 83% yield, respectively. Next, secondary amine derivatives were also investigated and produced the corresponding propargylamines in 59% to 96% yield. Dibutylamine was also reacted with phenylacetylene and benzaldehyde to produce the corresponding propargylamine in 71% yield. Importantly, an attempted extension of the reaction to aniline, with phenylacetylene and benzaldehyde, led to the formation of a Schiff base.

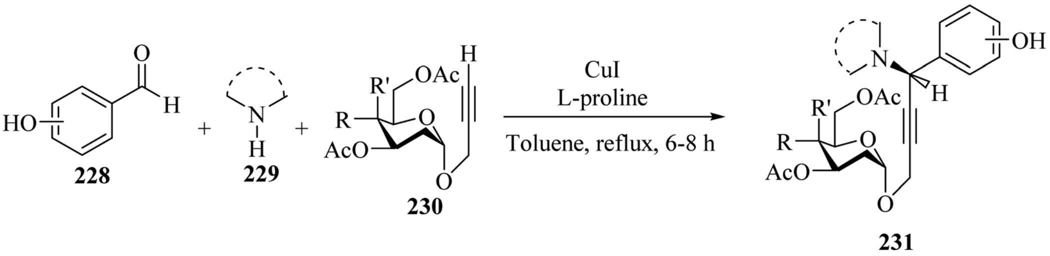
Thakur and Khare[99] synthesized stereoselective chiral propargylamines **231** *via* the reaction among heterocyclic amine derivatives **229**, aromatic aldehyde derivatives **228**, deoxy sugar based alkyne **230** in the presence of CuI, and L-proline (**L**) in $CH_3C_6H_5$ under reflux (Scheme 95).

Initially, complex **A** was generated *via* the reaction between CuI and **230**. Then, **228** and **229** reacted and produced intermediate aminal **B** *via* the Aldol-type condensation. Next, **A** and **B** reacted together and produced the complex **C**. Then, the



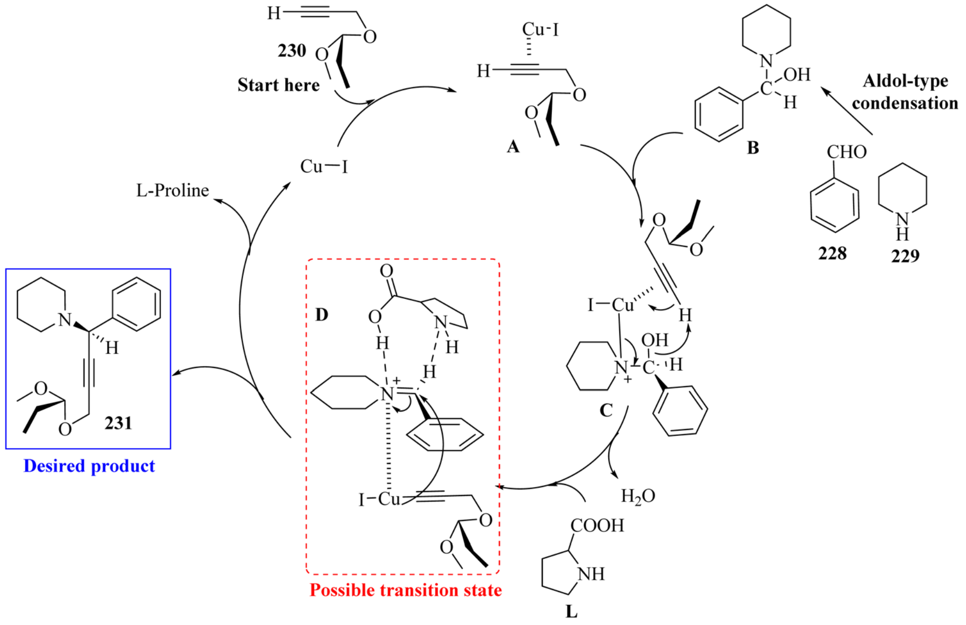
R= Ph, 2-$F_3CC_6H_4$, 3-BrC_6H_4, 4-$F_3CC_6H_4$, 4-NCC_6H_4
4-i-PrC_6H_4, 4-$MeOC_6H_4$, 4-$PhOC_6H_4$, 2,3-diF-C_6H_3
naphthalen-2-yl, 9H-fluoren-2-yl, thiophen-2-yl, 5-methylfuran-2-yl
1,3-thiazol-4-yl, pyridin-3-yl, 5-F-benzothiophen-3-yl,
1-Me-1H-pyrrol-2-yl, hexyl
R'=Ph, 4-MeC_6H_4, 4-$O_2NC_6H_4$, hexyl, octyl,
R"R'"= -$(CH_2)_2O(CH_2)_2$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$(CH_2)_2NMe(CH_2)_2$-,
Buf

Scheme 94 Synthesis of propargylamine derivatives *via* Cu-containing minerals.[98]



R= H, OAc
R'= H, OAc
228= 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-hydroxybenzaldehyde
229= Morpholine, Pyrrolidine, Piperidine

Scheme 95 CuI-catalyzed synthesis of deoxy sugar-based chiral propargylamine derivatives.[99]



Scheme 96 Possible reaction mechanism for the synthesis of stereoselective chiral propargylamines.[99]

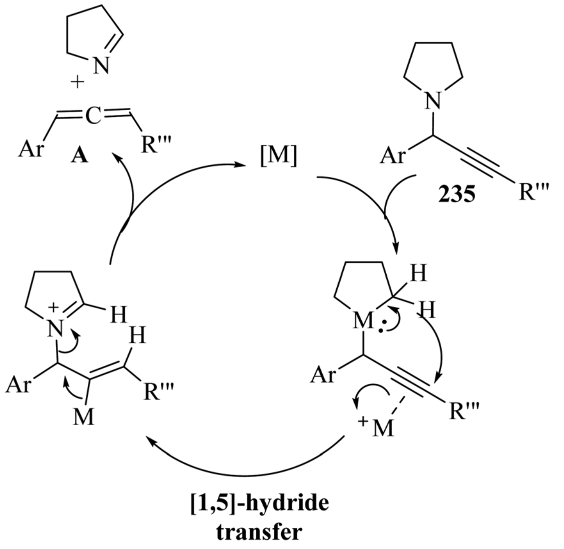
coordinated alkyne in the complex **C** was deprotonated together with the removal of H_2O. After that, complex **D** was produced *via* the ligation of L-proline (**L**) with complex **C**, which gave Cu-acetylide with a coordinated iminium ion at the end. Finally, **231** was generated *via* the addition of Cu-acetylide with a coordinated iminium ion together with the regeneration of the catalyst and **L** (Scheme 96).

According to the results, when *ortho*/*meta*-substituted benzaldehyde derivatives reacted with 3,4,6-tri-*O*-acetyl-2-deoxy propargyl-*O*-α-D-glucopyranoside/3,4,6-tri-*O*-acetyl-2-deoxy propargyl-*O*-α-D-galactopyranoside and piperidine/morpholine/pyrrolidine the desired propargylamine derivatives were produced in 68% to 86% yield. Under similar conditions, 4-hydroxy benzaldehyde compounds decreased the percentage yield of the corresponding products in comparison with other synthesized compounds (30–65%).

Martinez-Amezaga[100] synthesized 1-substituted propargylic tertiary amines **235** *via* the three-component reaction of alkynes **234**, amines **233**, and aldehydes or 2-oxoacid derivatives **232** in the presence of $Cu(OTf)_2$ in toluene at 120 °C for 6 h (Scheme 97). When the reaction condition for the synthesis of **235** was done under microwave heating for 1 h, a mixture of **235** and 1,3-disubstituted allene **A** was observed (Scheme 97).

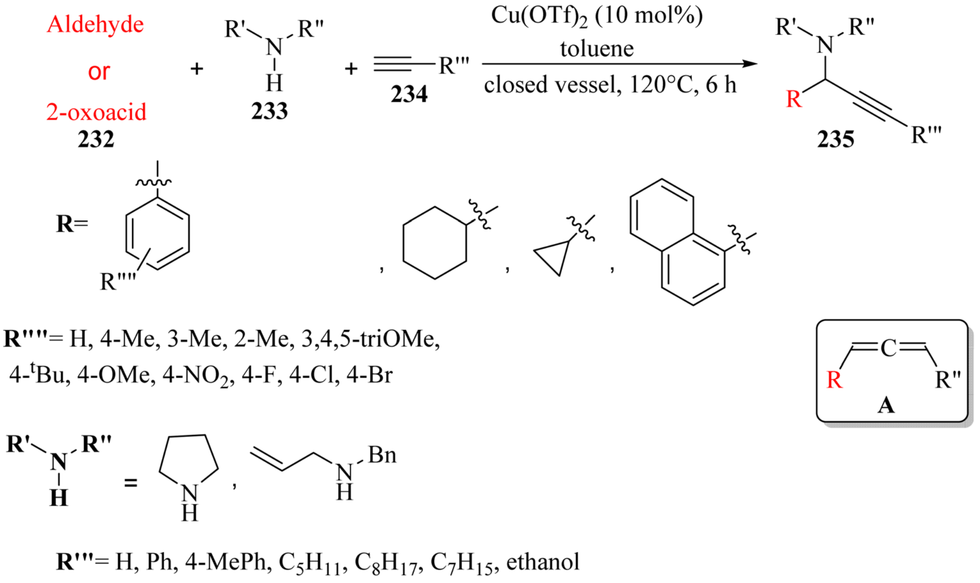
The synthesis mechanism of **A** could have occurred as follows: initially, **235** was generated, followed by the coordination of Cu to the triple bond. After that, this process caused 1,5-hydride transfer and β-elimination, which led to the synthesis of **A** (Scheme 98).

According to the study, propargylamines were obtained in 9% to 99% yield. In addition, propargylamines were obtained in 50% to 65% yield using phenylglyoxylic acid. Also, ethynyltrimethylsilane as the alkyne component in the above-mentioned method gave the corresponding propargylamine in 49% yield. Also, Sonogashira coupling was performed using tetrakis(triphenylphosphine)palladium(0) as the catalyst and aryl iodide, giving the corresponding product in 79% yield.

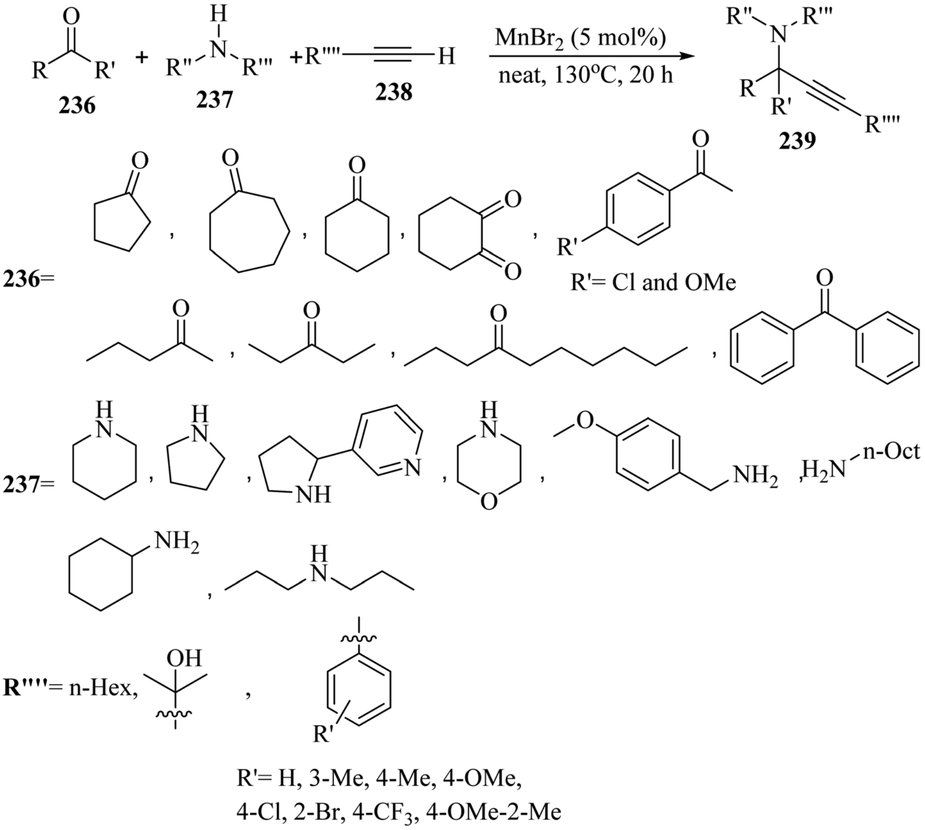


Scheme 98 Possible reaction mechanism for the synthesis of 1-substituted propargylic tertiary amines.[100]

Neofotistos and co-workers[101] synthesized tetrasubstituted propargylamines **239** *via* the reaction among amine derivatives **237**, alkyne derivatives **238**, and ketone derivatives **236** in the presence of $MnBr_2$ as a metal source under neat conditions at 130 for 20 h (Scheme 99). In the case of **236**, the mixture of cyclopentanone, piperidine, and phenylacetylene produced the corresponding propargylamine in 67% yield. Cycloheptanone produced the corresponding product in 73% yield. In addition, when cyclohexanone or cyclopentanone was reacted with pyrrolidine produced, the desired propargylamines were obtained in 91% and 75% yield, respectively. In contrast, when

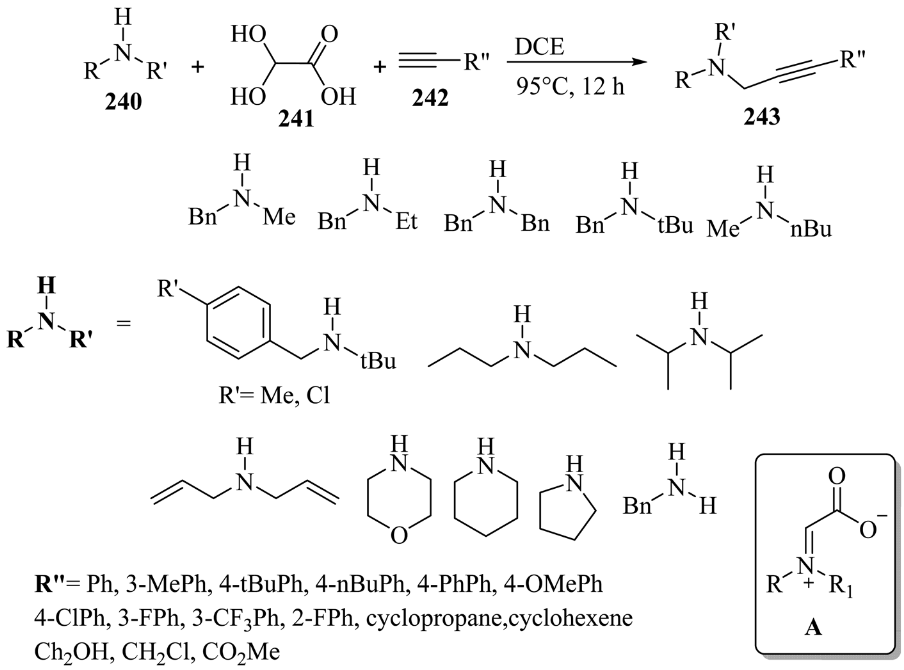


Scheme 97 $Cu(OTf)_2$-catalyzed synthesis of propargylamine derivatives.[100]



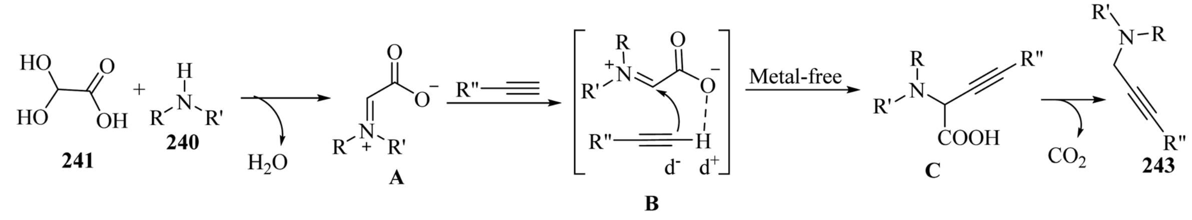
Scheme 99 MnBr$_2$-catalyzed synthesis of propargylamine derivatives.[101]

cyclohexane-1,2-dione was used, the corresponding propargylamine was not obtained. Linear ketones such as 3-pentanone, 2-pentanone, and 4-decanone decreased the yields (48%, 38%, and 68%, respectively). Also, 4-methoxy-acetophenone and 4-chloro-acetetophenone produced the corresponding propargylamines in 34% and 42% yield, respectively. When



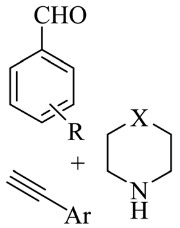
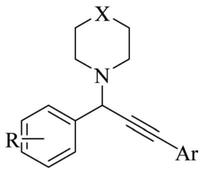
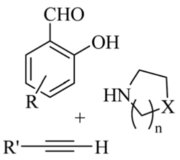
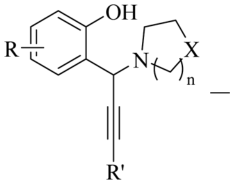
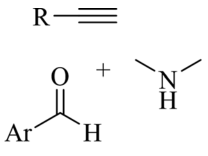
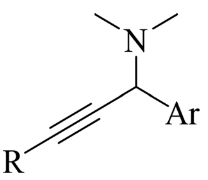
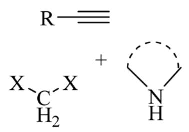
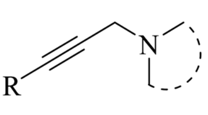
Scheme 100 Synthesis of propargylamine derivatives using glyoxylic acid monohydrate.[102]

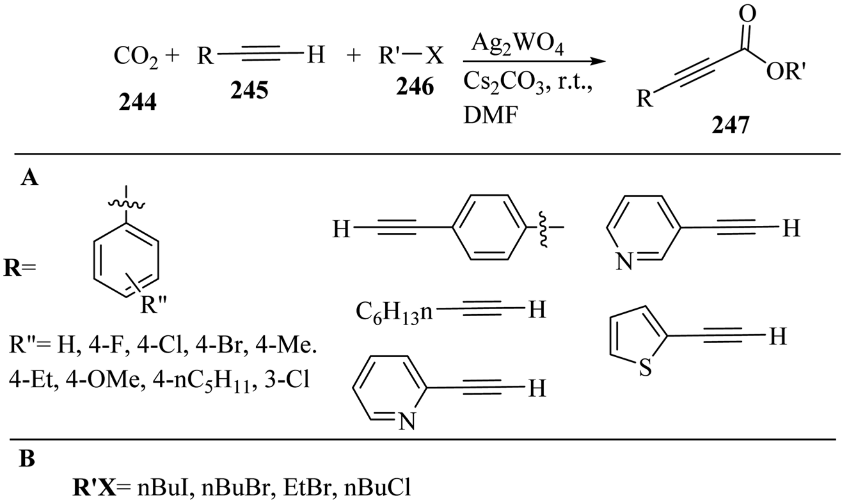
benzophenone was used, the corresponding propargylamine was not observed, which may be due to the increased steric hindrance imparted from the two phenyl moieties in the alpha-position of the carbonyl group. In the case of **238**, cyclohexanone with pyrrolidine or piperidine was coupled with a variety of terminal alkyne derivatives and the corresponding propargylamines obtained in 57% to 89% yield. 3-Ethynyl-toluene was coupled with piperidine and cyclohexanone and produced the corresponding propargylamine in 81% yield. *p*-Methoxyphenylacetylene reacted was with piperidine and cyclohexanone and produced the corresponding propargylamine in 87% yield. Interestingly, the reaction and nornicotine, 2-methylbut-3-yn-2-ol, and cyclohexanone gave the corresponding product in 81% yield, which was produced as a single diastereoisomer. In addition, 4-chloro-ethynylbenzene was reacted with cyclohexanone and pyrrolidine and produced the corresponding propargylamine in 77% yield, and when piperidine replaced pyrrolidine, the corresponding product was



Scheme 101 Possible reaction mechanism for the synthesis of propargylamines.[102]

Table 5 Summary of the synthesis of propargylamine derivatives under metal-free conditions

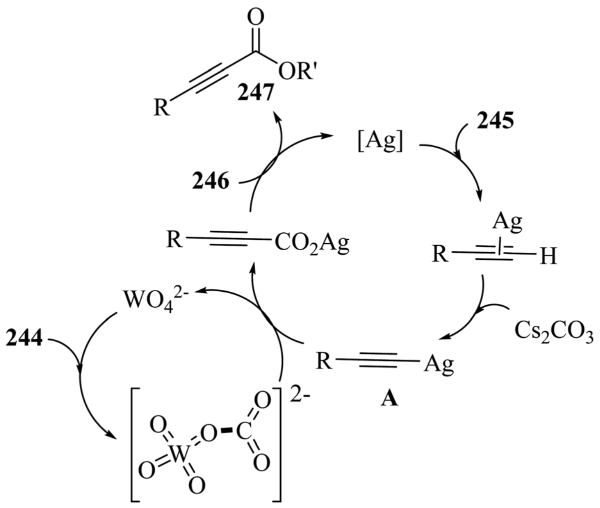
Reactants	Product	Catalyst	Solvent	Method employed	Reaction time	Yield	Limitations or progress	Ref.
		Nano-colloidal silica@APTPOSS	Toluene	Microwave irradiation, 50 °C	20–25 min	Up to 96%	(1) Efficient catalyst (2) Recoverability of the catalyst. (3) Low catalyst loading (4) Short reaction times. (5) A simple procedure (6) High atom economy	Safaei-Ghomi *et al.*[103]
		—	Solvent-free	80–90 °C	4–8 h	82–90%	(1) Metal-catalyst-free (2) Solvent-free conditions	Ghosh *et al.*[104]
		—	Magnetized water	MW, 60 °C	110–160 min	65–90%	(1) Simplicity (2) Low cost (3) Short reaction time (4) High reaction yield (5) Easy work-up (6) Absence of hazardous organic solvents	Bakherad *et al.*[105]
 X=Cl, Br, I		—	DCM (play solvent and reactant role)	70 °C	12 h		(1) Simplicity of operation (2) Mild conditions (3) High functional group tolerance	Rawat *et al.*[106]



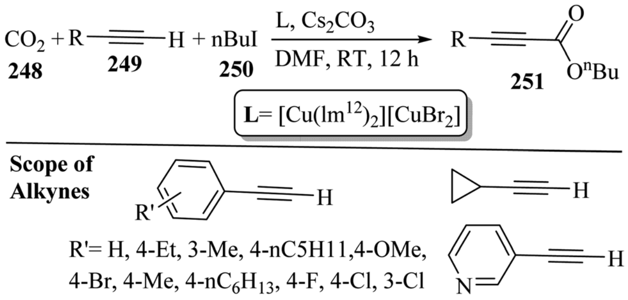
Scheme 102 Synthesis of alkyl 2-alkynoates by Ag_2WO_4: (A) scope of alkynes and (B) scope of alkyl halides.[107]

produced in 64% yield. 2-Br-phenylacetylene was coupled with piperidine and cyclohexanone and produced the corresponding propargylamine in 57% yield. Furthermore, when *p*-trifluomethyl-phenylacetylene was used, the corresponding product was obtained in low yield. Finally, 1-octyne reacted well with piperidine and cyclohexanone and produced the corresponding propargylamine in 70% yield. In the case of **237**, various amine derivatives were reacted with cyclohexanone and phenylacetylene. When morpholine was used, the corresponding product was obtained in 94% yield. Also, benzylamine produced the corresponding propargylamine in 46% yield. In addition, when *p*-methoxybenzylamine was used, it gave the corresponding propargylamine in 43% yield. Aliphatic amines were also investigated. *N*-Octylamine reacted with phenylacetylene and cyclohexanone and produced the desired propargylamine in 67% yield. Also, cyclohexylamine gave the corresponding propargylamine in 58% yield. In addition, secondary amine di-*n*-propylamine produced the desired propargylamine in 61% yield. Finally, the corresponding product of *p*-methoxy-aniline decomposed when exposed to light.

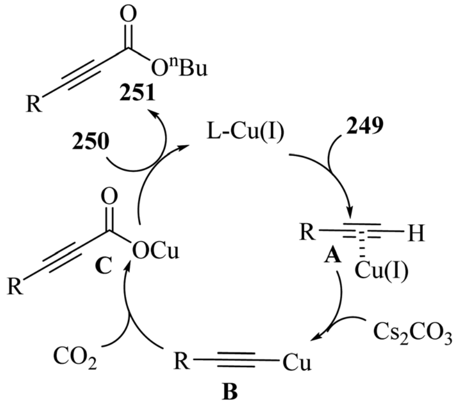
Huang *et al.*[102] synthesized propargylamines **243** *via* the reaction among alkyne derivatives **242**, glyoxylic acid monohydrate **241**, and secondary amine derivatives **240** in DCE at 95 °C for 12 h (Scheme 100).



Scheme 103 Possible reaction mechanism for the synthesis of alkyl 2-alkynoates.[107]



Scheme 104 Synthesis of alkynoates.[108]



Scheme 105 Possible reaction mechanism for the synthesis of alkynoates.[108]

Initially, iminium salt species **A** was generated *via* the reaction between **240** and **241** together with H_2O removal. Then, the sp carbon of alkyne was activated by the carboxyl group of intermediate **A** and produced the coupled product **C** *via* the subsequent Michael addition. Finally, **243** was produced *via* the further conversion of **C** (Scheme 101).

In the case of **240** and **242**, the yield increased when the steric bulk on the amine substrate increased, which may be due to intermediate **A**. All *N*-alkyl substituted benzylamine derivatives were tested and produced the desired propargylamines in 78–93% yield except for the product $NH(Bn)_2$ (21%). *N*-*tert*-Butyl benzylamines containing various groups on the phenyl moiety were reacted and produced the corresponding propargylamines in 78% and 93% yield, respectively. Moreover, secondary aliphatic amine derivatives were also reacted and produced the corresponding propargylamines in 54–79% yield. When the primary and cyclic amine derivatives were tested, only morpholine gave a low yield of the corresponding propargylamine (13%). Next, phenylacetylenes bearing electron-neutral groups such as phenyl and electron-donating substituents such as Me, *t*Bu, and OMe produced the corresponding propargylamines in 89%, 72%, 78%, and 82% yield, respectively. Also, phenylacetylene derivatives with electron-withdrawing groups such as CF_3, Cl, and F produced the corresponding propargylamines in 65–69% yield. In addition, aliphatic alkyne derivatives were investigated and produced the corresponding propargylamines in 72% to 83% yield. Importantly, methyl propiolate and prop-2-yn-1-ol, 3-chloroprop-1-yne were tested, but no desired products were produced.

A summary of the synthesis of propargylamine derivatives under metal-free conditions, and also the limitations and progress of the reactions are presented in Table 5.

3.2 Reaction of CO_2

Guo *et al.*[107] synthesized alkyl 2-alkynoates **247** (24–96%) *via* the reaction among terminal alkyne derivatives **245**, CO_2 **244**, and alkyl halides **246** in the presence of Ag_2WO_4 (cat.) and Cs_2CO_3 (base) in DMF at room temperature for 24 h (Scheme 102).

Initially, Ag-acetylide **A** was generated *via* the coordination of Ag and **245** in the presence of the base. Then, simultaneously WO_4^{2-}-CO_2 adduct **B** was obtained *via* CO_2 activation by tungstate. After that, Ag-phenylpropiolate **C** was produced *via* the insertion of **B** into the sp-hybridized Ag–C bond together with the release of WO_4^{2-}. Finally, **247** was generated from **C** using *n*-BuI (Scheme 103). It should be noted that the type of solvent in this transformation played an important role, where DMF showed the best result among the solvents.

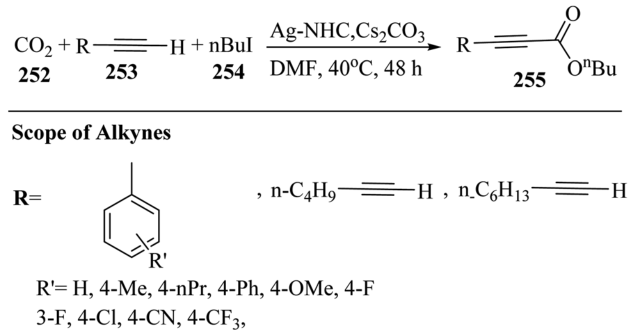
Phenylacetylenes containing electron-withdrawing and electron-donating groups were carboxylated and produced the desired alkyl 2-alkynoate derivatives in 75–91% yield. 1,4-Diethynylbenzene generated the biscarboxylative and monocarboxylative products. Between them, the biscarboxylative product was the major product and the monocarboxylative product was the minor product (64% and 24% yield, respectively). In this transformation, heteroaromatic acetylenes and aliphatic alkyne derivatives also were tolerated and produced the desired alkyl 2-alkynoate derivatives. This method has advantages such as use of a halogen-free catalyst and simple preparation of the catalyst.

Xie *et al.*[108] synthesized alkynoates **251** *via* the reaction among terminal alkyne derivatives **249**, CO_2 **248**, and *n*-BuI **250** in the presence of L (cat.) and Cs_2CO_3 in DMF at room temperature for 12 h (Scheme 104).

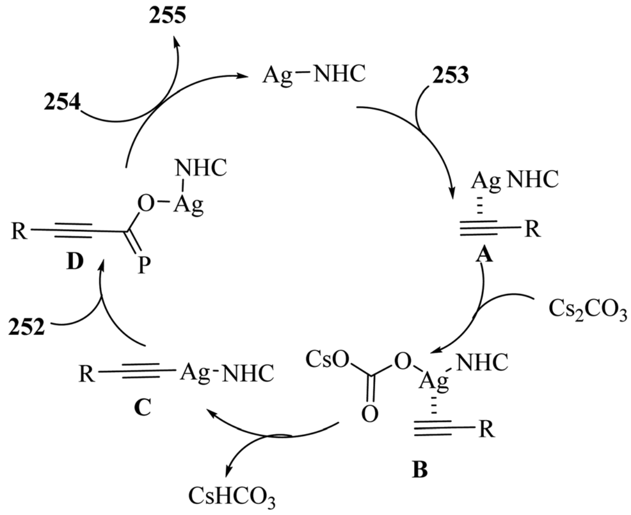
Initially, Cu-acetylide **B** was generated from activated alkyne **A**, in the presence of Cs_2CO_3. Then, propynoate intermediate **C** was produced from **B** *via* the insertion of CO_2 into the sp-hybridized Cu–C. Finally, **251** was obtained from intermediate **C** in the presence of **250**. According to this report, the ligand causes the reaction to proceed under mild conditions, and also advances the efficiency of the catalyst (Scheme 105).

Phenylacetylene derivatives **249** containing electro-rich groups at the *para* or *meta* positions generated the desired **251** in 88–96% yield. Also, the substrate with Br produced the desired **251** in 85% yield. In addition, aliphatic alkynes generated the desired **251** in up to 97% yield. Generally, the yield of the reaction decreased when using a strong electron-withdrawing group.

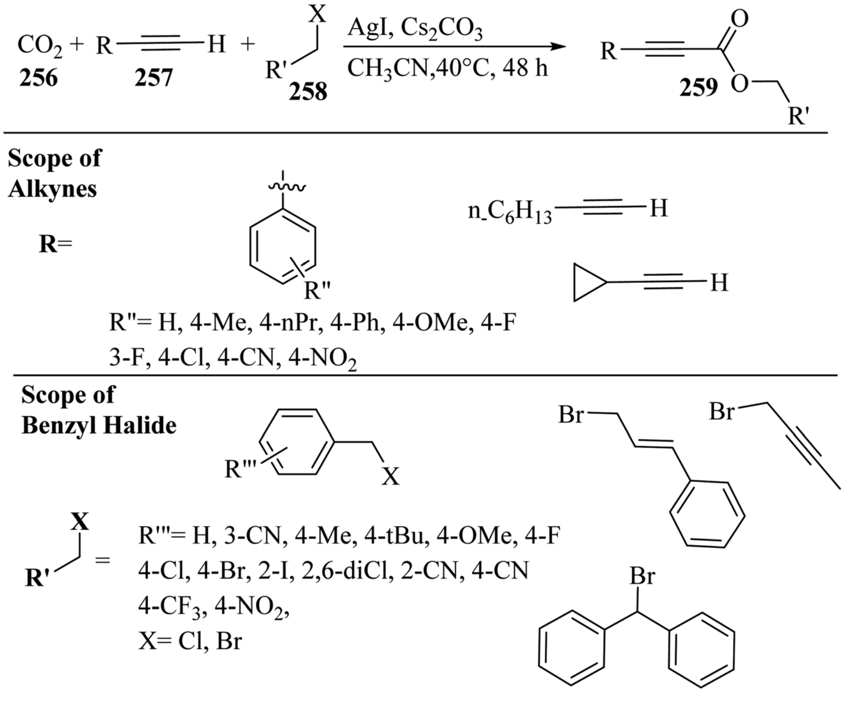
Zhang *et al.*[109] synthesized 2-alkynoate derivatives **255** *via* the reaction among CO_2 **252**, *n*BuI **254**, and terminal alkyne



Scheme 106 Synthesis of 2-alkynoate derivatives.[109]



Scheme 107 Possible reaction mechanism for the synthesis of 2-alkynoate derivatives.[109]

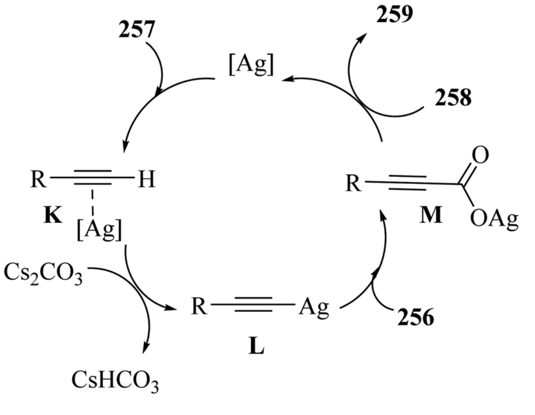


Scheme 108 Synthesis of benzyl 2-alkynoate derivatives.[110]

derivatives **253** in the presence of Ag–NHC and Cs_2CO_3 in DMF at 40 °C for 48 h (Scheme 106).

Initially, **253** coordinated with Ag–NHC and produced intermediate **A**. Then, intermediate **B** was produced from intermediate **A** in the presence of Cs_2CO_3. After that, Ag-acetylide **C** was obtained from intermediate **B** together with the elimination of $CsHCO_3$. Next, Ag-propiolate intermediate **D** was produced *via* the insertion of CO_2 into the Ag–C bond of intermediate **C**. Finally, **255** was generated *via* the reaction between *n*BuI and intermediate **D** together with the regeneration the catalyst (Scheme 107).

Derivatives of **253** containing electron-donating groups gave the desired 2-alkynoate derivatives **255** in 77–94% yield. In addition, halo derivatives of **253** generated the desired 2-alkynoate derivatives **255** in 82–86% yield. Derivatives of **253** containing a CN or CF_3 group produced the desired 2-alkynoate derivatives **255** in 84% and 81% yield, respectively. Furthermore, linear alkyl terminal alkyne derivatives **253** were tolerated and produced the desired 2-alkynoate derivatives **255** in 80–82% yield. It should be noted that the selectivity of the reaction was good due to the production of only one isolated product.

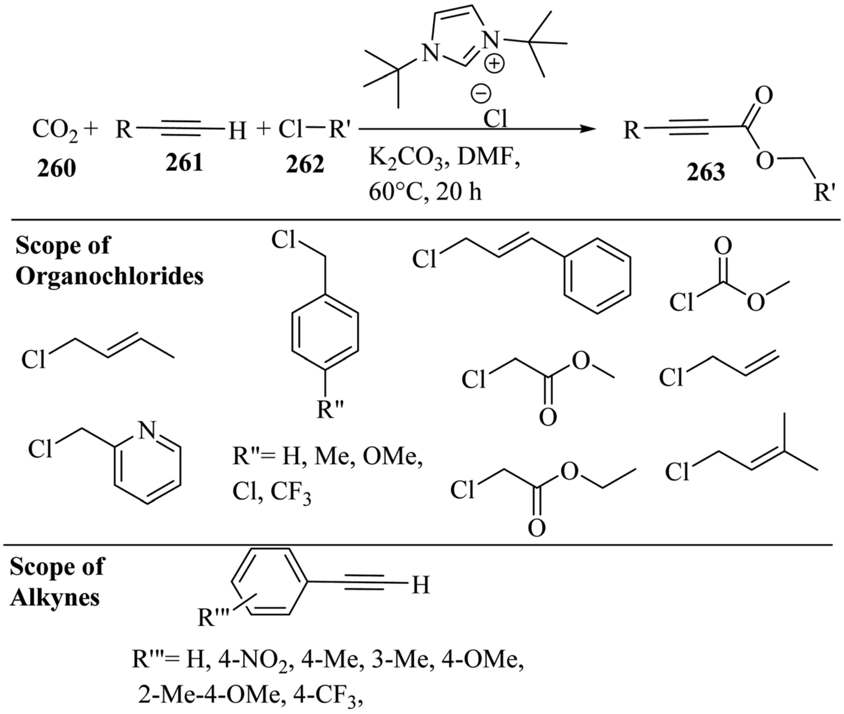


Scheme 109 Possible reaction mechanism for the synthesis of benzyl 2-alkynoate derivatives.[110]

Guo *et al.*[110] synthesized benzyl 2-alkynoate derivatives **259** *via* the reaction among CO_2 **256**, aryl/alkyl terminal alkyne derivatives **257**, and benzyl halide derivatives **258** in the presence of Cs_2CO_3 and AgI in CH_3CN under ligand-free conditions at 40 °C for 48 h (Scheme 108).

Initially, intermediate **K** was obtained *via* the coordination of **257** and Ag(I). Then, Ag(I)-acetylide **L** was generated *via* the deprotonation of **K** by Cs_2CO_3 together with the release of $CsHCO_3$. After that, Ag-propiolate intermediate **M** was produced *via* the insertion of CO_2 in the C–Ag bond. Finally, **259** was obtained *via* the reaction between **M** and **258** together with the release of Ag(I) (Scheme 109).

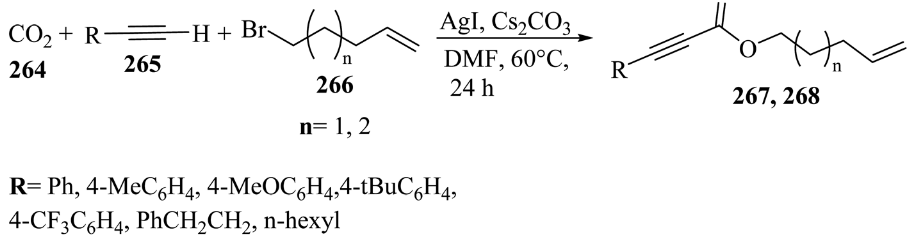
The electronic effect of the groups on the phenyl ring of aryl alkyne derivatives were demonstrated to have an important effect on the reactivity. In the case of **257**, derivatives of **257** containing electron-donating groups produced the desired **259** in 66–73% yield. Also, derivatives of **257** containing F and Cl groups were produced the desired **259** in 65–75% yield. In contrast, aryl alkyne derivatives containing CN or NO_2 group produced the desired **259** in 45% and 33% yield, respectively. Also, aliphatic alkyne derivatives **257** generated desired 2-alkynoate derivatives **259** in 38–50% yield. The low product yields by aliphatic alkynes may be due to the low activity of the activation of their sp C–H bond. In the case of the benzyl halide derivatives **258**, aryl chlorides or bromides **258**



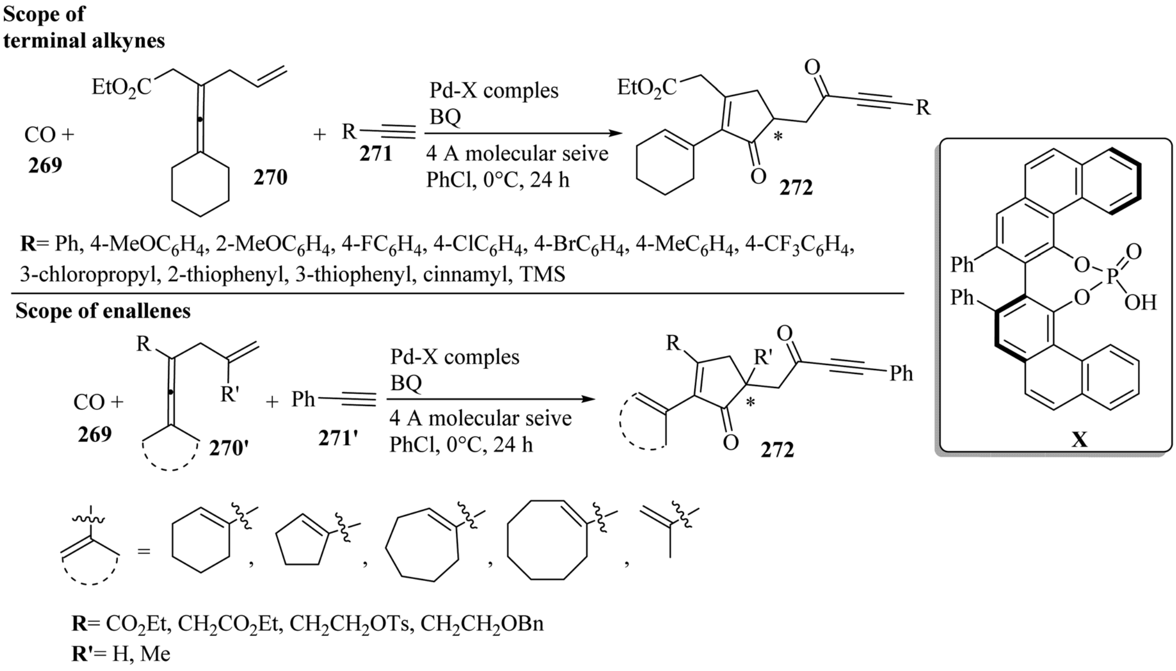
Scheme 110 Synthesis of propargylic esters.[111]

containing electron-donating groups generated the desired 2-alkynoate derivatives **259** in 71–85% yield. Also, halo derivatives of **258** gave the desired 2-alkynoate derivatives **259** in 62–91% yield. Aryl halide derivatives containing CF_3, NO_2, and CN gave the desired 2-alkynoate derivatives **259** in 63–87% yield. In addition, allylic/propargylic halide derivatives produced the desired 2-alkynoate derivatives **259** in 42–47% yield. It should be noted that secondary benzyl halide-(bromomethylene) dibenzene was tested and produced the desired 2-alkynoate **259** in 8% yield.

Papastavrou *et al.*[111] synthesized propargylic esters **263** *via* the reaction among organochlorides **262**, CO_2 **260**, and terminal alkyne derivatives **261** in the presence of K_2CO_3 and NHC in DMF at 60 °C for 20 h (Scheme 110). In the case of **262**, 2-chloroacetate esters generated the desired **263** in 25–28% yield. Organochlorides containing a Cl atom on the carbonyl carbon did not give the desired **263**. In contrast, allylic chlorides showed good activity and produced the desired **263** in 42–97%. The low yield of chloropropene and chlorobutene may be related to their low boiling points, which were lower than the reaction temperature. Similarly, the yield of crotyl chloride was high, which has a boiling point of 85 °C. In addition, benzyl chloride derivatives produced the desired ester **263** in 59–84% yields. In contrast, picolyl chloride did not generate the desired ester **263**, which may be due to the presence of a pyridine moiety in its structure. It should be noted that organobromide derivatives did not give the desired esters **263**. Furthermore, benzyl chlorides containing electron-poor and electron-rich groups produced the desired esters **263** in 59–84% yield. In the case of **261**, alkyl-substituted terminal alkyne derivatives and a hydroxyl-bearing alkyne did not generate the desired esters **263**. Phenyl acetylene bearing p-NO_2 and p-CF_3 produced the desired esters in trace and 91% yield, respectively. The result showed that electron-poor groups could produce the desired esters **263** but the NO_2 group was not very consistent. Phenylacetylene derivatives containing an Me or OMe group on



Scheme 111 Synthesis of 4-pentenyl 2-alkynoate derivatives.[112]



Scheme 112 Synthesis of a-chirality ketones **272**.[113]

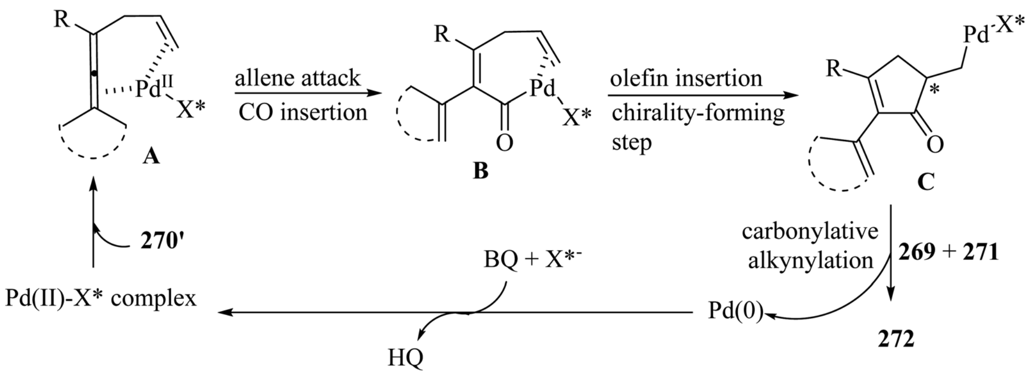
the aromatic ring, and also containing no aromatic substituents produced the desired esters **263** in 64–97% yield.

Zhang *et al.*[112] synthesized 4-pentenyl 2-alkynoate derivatives **267** and 5-hexenyl 2-alkynoate derivatives **268** *via* the reaction among CO_2 **264**, terminal alkyne derivatives **265**, and 5-bromopentene or 6-bromohexene derivatives **266** in the presence of AgI and Cs_2CO_3 in DMF at 60 °C for 24 h (Scheme 111). The selectivity of the reaction was high and no direct coupling by-products were observed. Alkyne derivatives containing electron-withdrawing and -donating groups on the phenyl ring produced the desired carboxylative products (**267** and **268**) in 69–91% yield. Alkyl-substituted terminal alkynes in comparison to aryl-substituted substrates showed low yields (59–66%). These results may be due to the higher stability of the aryl-substituted Ag(I) acetylide with respect to the alkyl-substituted Ag(I) acetylide intermediate.

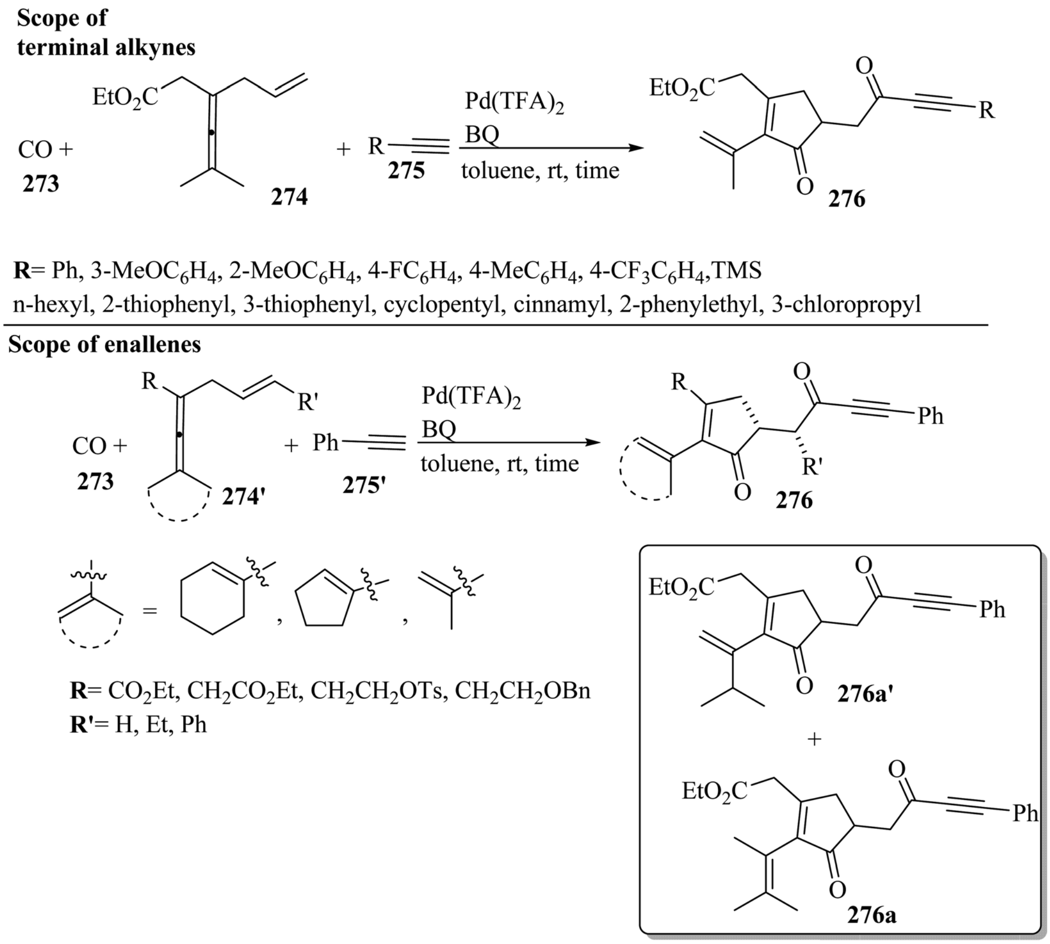
3.3 Reaction of CO

Yang *et al.*[113] synthesized a-chirality ketones **272** *via* the reaction among terminal alkyne derivatives (**271** and **271′**), CO **269**, and enallene derivatives (**270** and **270′**) in the presence of BQ, $Pd(OAc)_2$, and chiral phosphoric acid (CPA) **X** in PhCl at 0 °C for 24 h (Scheme 112).

Initially, intermediate **A** was generated *via* the coordination of **270′** to Pd^{II}. Then, carbonyl Pd^{II} intermediate **B** was obtained *via* the insertion of CO and the subsequent attack of **270** on intermediate **A.** After that, olefin inserted into the C–Pd bond *via* enantioselective migration and produced intermediate **C**, which caused chirality at the alpha-position of the ketone. Lastly, **272** was generated *via* the carbonylative alkynylation of intermediate **C** together with the release of Pd^0. To close the catalytic cycle, BQ reoxidized the released Pd^0 to Pd^{II} (Scheme 113).



Scheme 113 Possible reaction mechanism for the synthesis of a-chirality ketones **272**.[113]



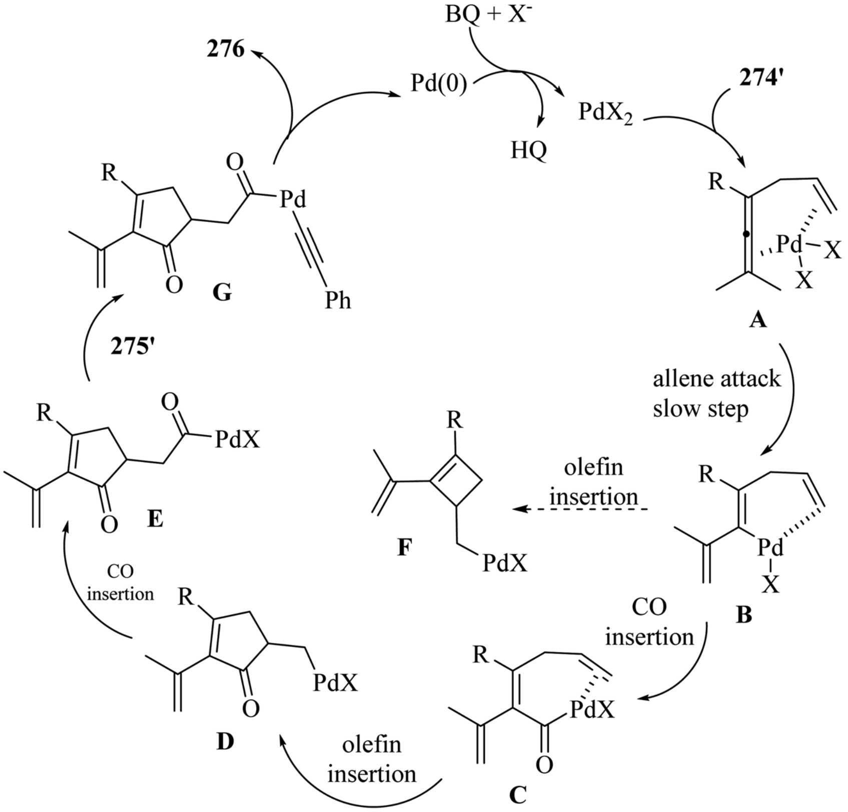
Scheme 114 Synthesis of ynone derivatives **276**.[114]

In the case of **271**, phenylacetylenes containing electron-donating and -withdrawing groups generated the desired **272** in 48–81% yield and high er (up to 95.5 : 4.5). Aliphatic acetylene derivatives, as well as heteroaryl acetylene derivatives, were tolerated and produced the desired **272** in 64–73% yield. Importantly, alkyne containing TMS generated the desired **270** in 5% yield and poor er (56.5 : 43.5), and the reaction time for the preparation of this desired compound was 60 h. Poor enantioselectivity of the desired **272** was obtained when slow alkyne-quenching of the key Pd species existed. In the case of **270′**, when two Me were replaced with a terminal cycloalkyl group, the desired **272** was generated with a slight decrease in the enantiomeric ratio. The size of the ring was tested and the results showed that all rings could generate the desired **272** but had slightly lower er values compared to the six-membered rings. When an internal Me group on the olefin moiety was used, the desired **272** was generated in a lower er. Substituents on the allene moiety had a remarkable effect on the reactivity, as well as enantioselectivity. 2,3-Allenoate had lower er and yield with respect to 3,4-allenoate. Functional groups of sulfonyl ester and ether were suitable in the reaction and produced the desired **272** in 66% and 70% yield (93.5 : 6.5 and 95 : 5 er), respectively.

Zhu *et al.*[114] synthesized ynone derivatives **276** *via* the reaction among CO **273**, terminal alkyne derivatives **275**, and enallene derivatives **274** in the presence of Pd(TFA)$_2$ and BQ in CH$_3$Ph at room temperature (Scheme 114).

Initially, intermediate **A** was produced *via* the coordination of **247′** to Pd(II). Then, intermediate **B** was generated from intermediate **A** *via* allene attack, where the additional coordination of the olefin to Pd(II) was vital. After that, intermediate **C** was obtained *via* the selective insertion of CO in the C–Pd bond of intermediate **B.** In this step, olefin insertion could occur, which led to the formation of intermediate **F**. Next, intermediate C produced intermediate **E** *via* olefin and carbon monoxide insertion reactions. Lastly, intermediate **G** was generated *via* the reaction between **275′** and Pd in intermediate **E**, which after reductive elimination, gave the desired product together with the release of Pd(0). The released product was reoxidized to Pd(II) by *p*-benzoquinone (Scheme 115).

In the case of **275**, phenylacetylene derivatives containing electron-withdrawing and -donating groups generated the desired **276** in 70–81% yield. Also, heteroaryl acetylenes produced the desired **276** in 66–75% yield. It should be noted that aliphatic cyclic and acyclic terminal alkynes were tolerated well and produced the desired **276** in 74–83% yield. In addition,



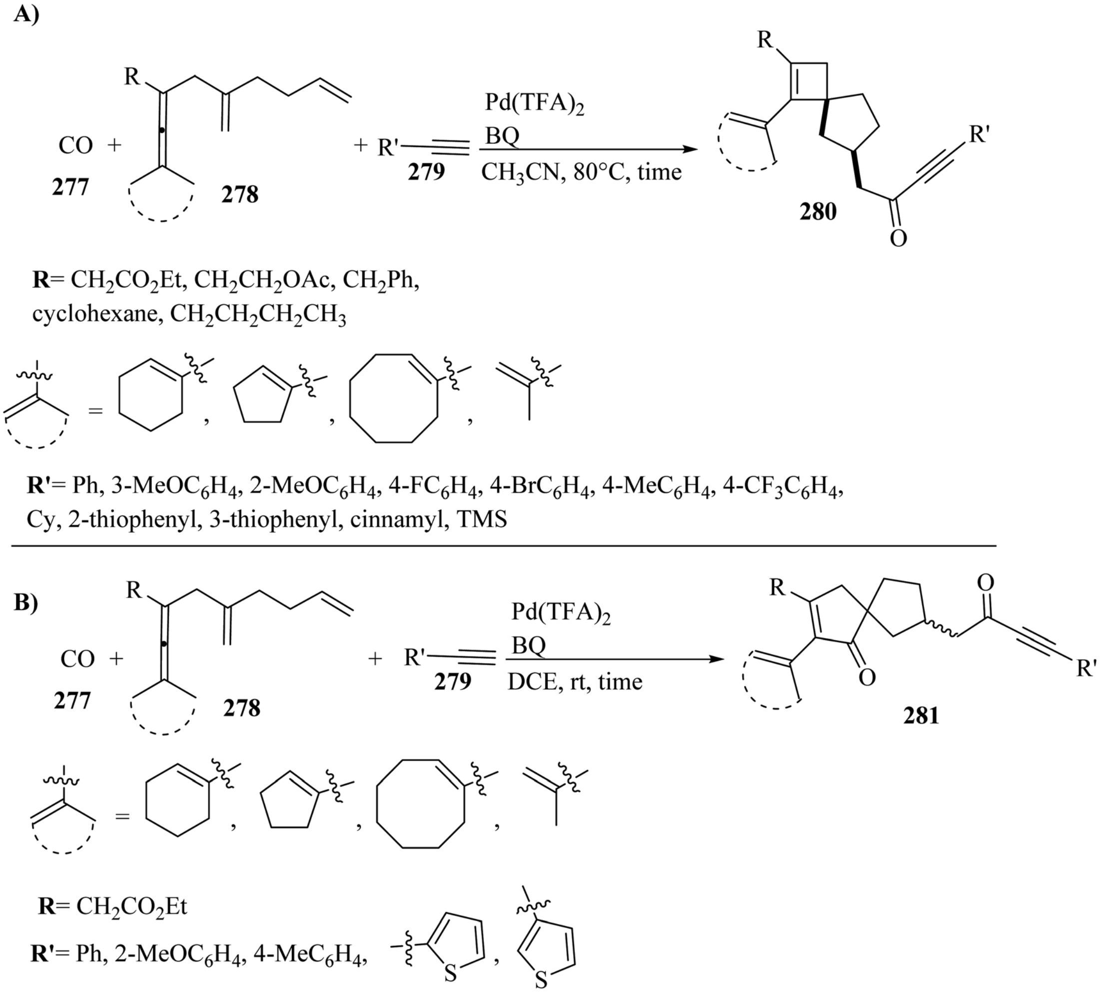
Scheme 115 Possible reaction mechanism for the synthesis of ynone derivatives **276**.[114]

functional groups of TMS and Cl were tested and produced the desired **276** in 73% and 72% yield, respectively. In the case of **274′**, cyclohexylidene enallene produced the desired **276** in 73% yield but cyclopentylidene enallene gave the desired **276** in a lower yield (58% yield). Tosyl and benzyl 3,4-dienol were tested and produced the desired **276** in 76% and 75% yield, respectively. It should be noted that the use of Ph or Et substituent rather than R″ substituent on the olefin had a great effect on the reaction (41% and 40% yield, respectively). Also, the dissymmetric allene containing i-Pr and Me gave the desired **276a** and **276a′** in 40% and 30% yield, respectively. It should be noted that selective allenic C–H cleavage gave **276a** and **276a′**.

Qiu *et al.*[115] synthesized spiro[3.4]octene derivatives **280** and spiro[4.4]nonene derivatives **281** *via* the reaction among dienallene derivatives **278**, CO **277**, and alkyne derivatives **279** in the presence of $Pd(TFA)_2$ and BQ. For the preparation of **280**, CH_3CN was used as the solvent at 80 °C, whereas DCE was used as the solvent for the preparation of **281** at room temperature (Scheme 116).

Initially, intermediate **A** was generated from the reaction between $Pd(TFA)_2$ and **278** *via* allene attack involving allenic C–H bond cleavage. Then, intermediate **B** was produced from intermediate **A** *via* olefin insertion. After that, intermediate **D** was obtained from intermediate **C** *via* olefin and CO insertions. Lastly, intermediate **E** was generated *via* the reaction between intermediate **D** and **279**, which gave the desired **280** after reductive elimination. Alternatively, intermediate **F** was obtained from intermediate **A** *via* carbonylation. Then, intermediate **I** was generated from intermediate **G** and **H** *via* olefin–olefin–CO insertion. Finally, the desired **281** was generated from the reaction between intermediate **I** and **279** *via* intermediate **J** (Scheme 117). It should be noted that CH_3CN choose the pathway that was favorable for the production of intermediate **B** instead of intermediate **F**. This solvent suppressed CO coordination, and hence insertion.

In the case of **279** for the formation of **280**, arylalkyne derivatives with electron-donating and -withdrawing groups generated the desired **280** in 64–79% yield. Also, heteroaryl acetylene derivatives were tolerated well and produced the desired **280** in 71–83% yield. Aliphatic terminal alkyne derivatives were tested and produced the desired **280** in 66–70% yield. Importantly, the TMS group reacted well and generated the desired **280** in 79% yield, which could be utilized for further functionalization after desilylation. In the case of **278** for the formation of **280**, cyclooctylidene, cyclopentylidene, and cyclohexylidene produced the desired **280** in 80%, 71%, and 66% yield, respectively. In addition, the unsymmetric allene containing methyl and phenyl groups generated the desired **280** in 62% yield. It should be noted that when using *n*-butyl, cyclohexyl, and benzyl groups instead of R, the desired **280** was obtained in 55%, 60%, and 63% yield, respectively. In the case of the formation of **281**, substrates of Me, cyclopentylidene, cyclohexylidene, or cyclooctylidene on the dienallene moiety were tolerated well and generated the desired **281** in 90%, 82%,



Scheme 116 Synthesis of (A) spiro[3.4]octene derivatives **280** and (B) spiro[4.4]nonene derivatives **281**.[115]

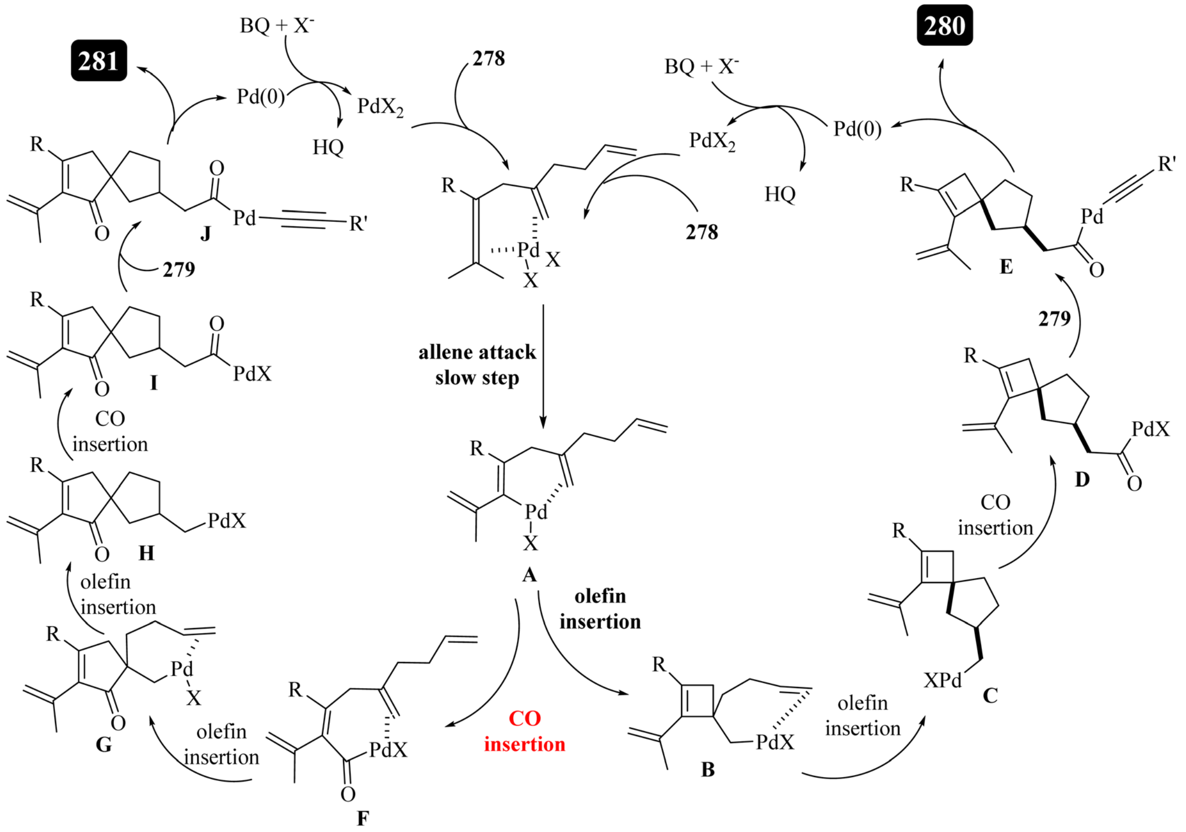
93%, and 89% yield, respectively. Arylacetylenes containing *o*-MeO and *p*-Me groups produced the desired product in 80% and 87% yield, respectively. Furthermore, heteroaryl acetylene derivatives were tested and the desired **281** obtained in 72–78% yield.

Volla and Backvall[116] reported an oxidative carbocyclization–carbonylation–alkynylation reaction for the synthesis of ynone derivatives **285** *via* the reaction among alkyne derivatives **283**, CO **282**, and enallene derivatives **284** in the presence of Pd(TFA)$_2$ and 1,4-BQ in ClCH$_2$CH$_2$Cl at room temperature for 12 h (Scheme 118).

Initially, π-complex **A** was generated with alkene and allene units by Pd. Then, intermediate **B** was obtained from intermediate **A** *via* the attack of the allene moiety on Pd(II), which was followed by the production of intermediate **C** *via* carbocyclization. After that, acylpalladium(II) species **D** was obtained from intermediate **C** *via* the insertion of CO in the Pd–C bond of intermediate **C**. Next, intermediate **E** was generated *via* the subsequent transfer of an alkynyl moiety. Finally, **285** was produced from **E** *via* reductive elimination together with the release of Pd(0), and Pd(0) was converted to Pd(II) *via* oxidization (Scheme 119).

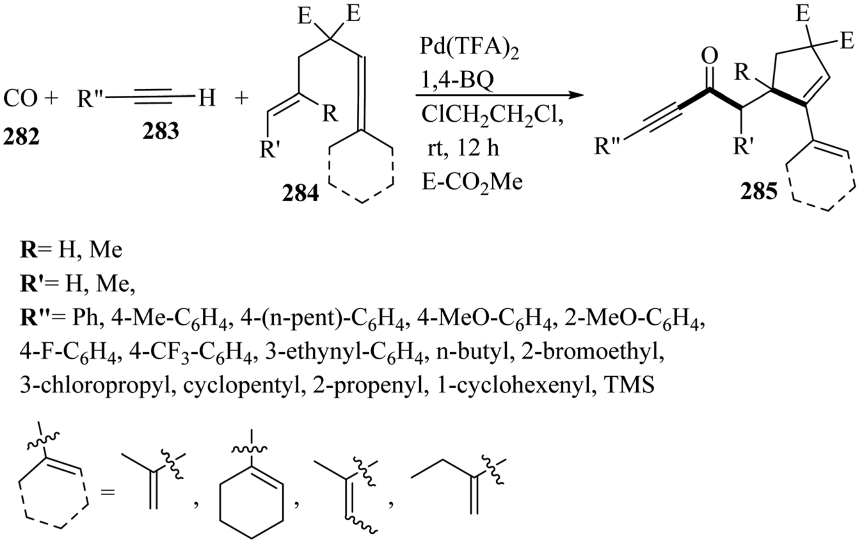
In the case of **283**, phenylacetylene derivatives possessing electron-donating and -withdrawing groups produced the desired **285** in 72–87% yield. It should be noted that steric and electronic factors on the aromatic ring did not show sensitivity. 1,3-Diethynylbenzene, which has two terminal alkyne units, produced monoalkynylation **285** without reaction of the second alkyne group during the reaction. Also, aliphatic cyclic and acyclic terminal alkyne derivatives generated the desired **285** in 54–94% yield. Importantly, TMS was tolerated well in the reaction and produced the desired TMS-product **285** in 81% yield, which could be utilized for further functionalization after desilylation. In the case of **284,** when the dimethyl groups of the allene unit were replaced with methylethyl or pentamethylene units, the temperature was increased to 40 °C, and the desired **285** was produced in 88% and 76% yield, respectively. In addition, enallene, which contains a methyl group on the olefin unit, gave the desired **285** with an all-carbon quaternary center *via* the cascade carbocyclization–carbonylation–alkynylation in 73% yield at 80 °C. It should be noted that 1,6-enallene **X** did not generate the desired **258** even at high temperatures.

Chandrasekhar *et al.*[117] synthesized 3-aryl-4-(arylethynyl)-2*H*-chromen-2-one derivatives **289** *via* the reaction among CO



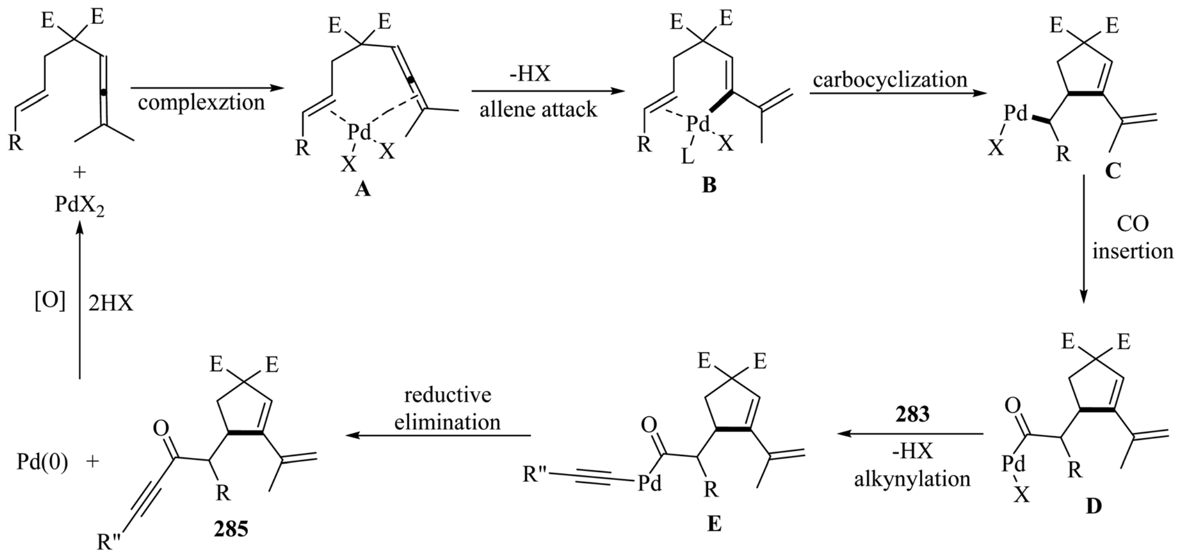
Scheme 117 Possible reaction mechanism for the synthesis of spiro[3.4]octene derivatives **280** and spiro[4.4]nonene derivatives **281**.[115]

286, terminal alkyne derivatives **287**, and 2-iodoaryl 2-arylacetate derivatives **288** in the presence of $Pd(PPh_3)_2(Cl)_2$ and Et_3N in toluene at 80 °C for 3–10 h (Scheme 120A). According to the results, various substituents were evaluated on the three aryl rings, and all groups such as Cl, NO_2, Br, Me, OMe, and *t*Bu were tolerated well in the reaction and produced the desired **289** in 70–95% yield (Scheme 120a). In addition, trimethylsilylacetylene **291** generated the desired **292** in 78% yield, and the reaction time for the preparation was increased to 12 h (Scheme 120B). For more evaluations, 2-iodo-3,5-dimethylphenyl 2-phenylacetate **293** was investigated under the standard reaction conditions and produced just

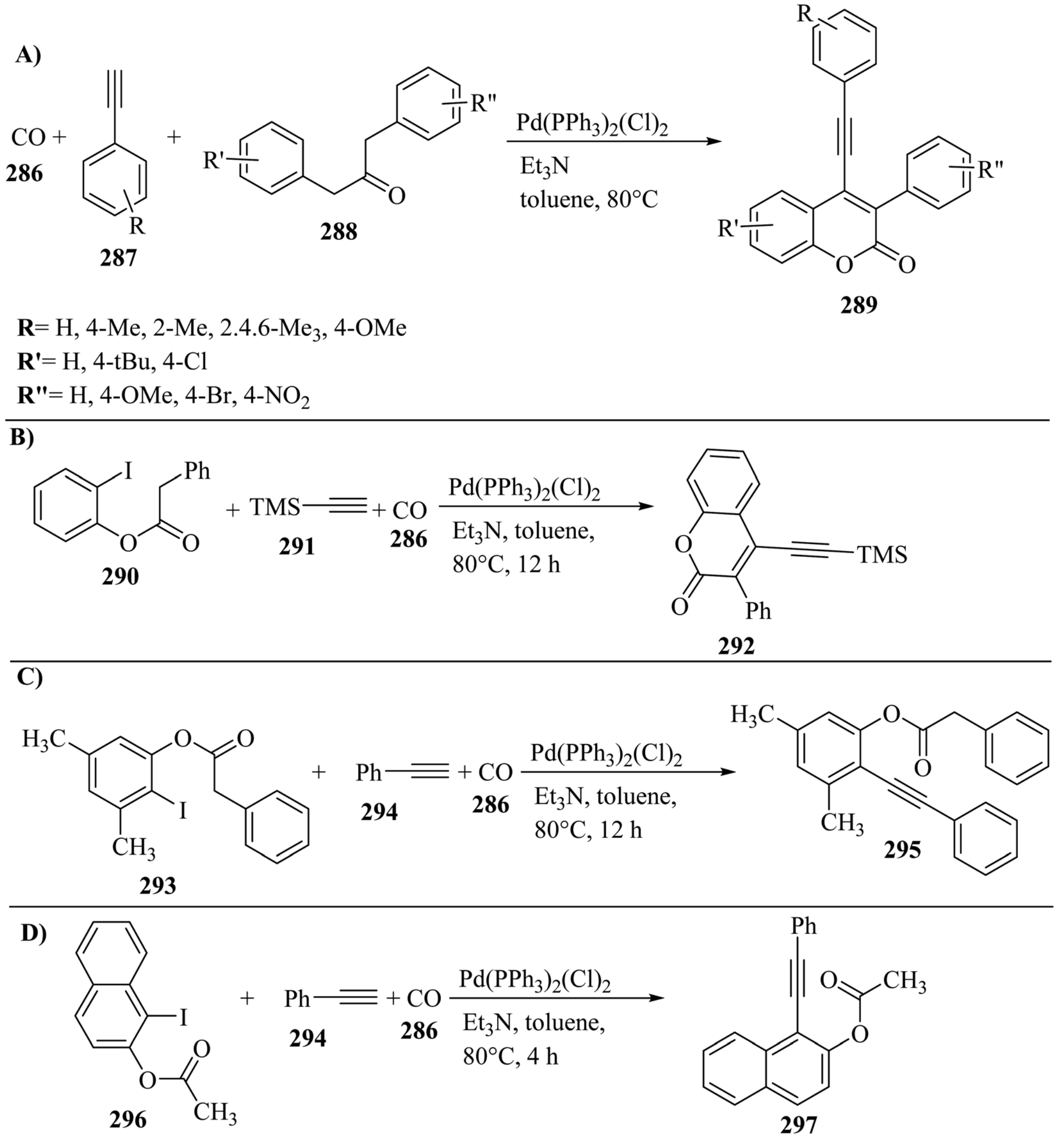


R= H, Me
R'= H, Me,
R''= Ph, 4-Me-C_6H_4, 4-(n-pent)-C_6H_4, 4-MeO-C_6H_4, 2-MeO-C_6H_4, 4-F-C_6H_4, 4-CF_3-C_6H_4, 3-ethynyl-C_6H_4, n-butyl, 2-bromoethyl, 3-chloropropyl, cyclopentyl, 2-propenyl, 1-cyclohexenyl, TMS

Scheme 118 Synthesis of ynone derivatives **285**.[116]



Scheme 119 Possible reaction mechanism for the synthesis of ynone derivatives **285**.[116]



Scheme 120 (A) Synthesis of 3-aryl-4-(arylethynyl)-2*H*-chromen-2-one derivatives **289**, (B) 3-phenyl-4-((trimethylsilyl)ethynyl)-2*H*-chromen-2-one **292**, (C) 3,5-dimethyl-2-(phenylethynyl)phenyl 2-phenylacetate **295**, (D) 1-(phenylethynyl)naphthalen-2-yl acetate **297**.[117]

Table 6 Summary of the reaction of alkynes with CO and limitations or progress of the reactions

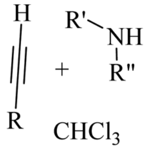
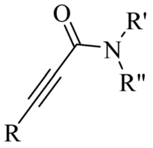
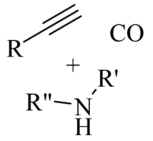
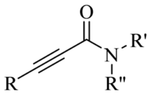
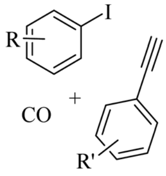
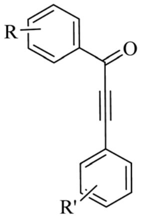
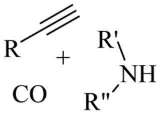
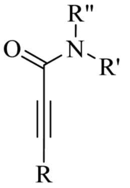
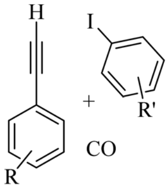
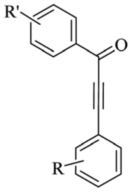
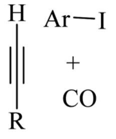
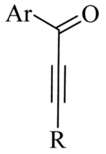
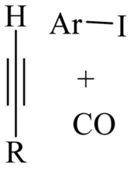
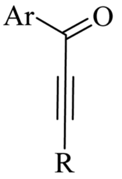
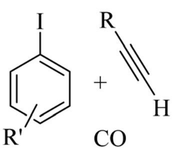
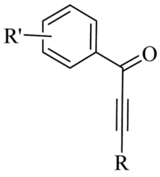
Reactants	Product	Catalyst	Solvent	Method employed	Reaction time	Yield	Limitations or progress	Ref.
		$PdCl_2(PPh_3)_2$–cataCXium A	1,4-Dioxane	$CsOH\cdot H_2O$, 80 °C, microwave	50 min	35–70%	(1) $CHCl_3$ as *in situ* CO surrogate (2) Short reaction time (3) No prefunctionlization needed (4) Bioactive alk-2-ynamides (5) Catalytic system was new (6) Substrate scope was broad (7) 2-Ethynylpyridine could not produce the desired product (8) Trace amount of product was produced by trimethylsilylacetylene (9) Di-*n*-propylamine did not produce the desired product	Rathod and Jain[118]
		IPr-Pd-Peppsi-Cl_2	Dioxane	KI, K_3PO_4, 100 °C	18 h	50–95%	(1) Mild conditions (2) High atom efficiency (3) Alkyl and aryl of the alkynes could be efficiently	Zhang *et al.*[119]
		$NiCl_2\cdot 6H_2O$	DMF	dppb, K_2CO_3 130 °C	7–12 h	20–76%	(1) First time $(CO_2H)_2$ was used as *in situ* CO surrogate, bench stable, *ex situ* solid, and easy to handle (2) First report for carbonylative Sonogashira coupling by using CO-surrogate under Ni catalyst	Shaifali *et al.*[120]
		$Pd(OAc)_2$	EtOAc	$[NBu_4]I$, 80 °C, O_2 in N_2	6 h	52–92%	(1) The method avoids the use of dangerous 1,4-Dioxane (2) Used O_2 as the terminal oxidant (3) Does not require the use of ligands (4) Develop synthesis of 2-ynamides through oxidative carbonylation (5) A variety of alkynes and amines can be used	Hughes *et al.*[121]
		Pd(II) APTES@K10	DME	NEt_3 80 °C	7 h	60–92%	(1) Method gave easy and simple access toward dibenzoylmethane (2) The electron withdrawing aryl halides can be efficiently used as an electrophile (3) Recovery of catalyst by simple filtration	Chavan *et al.*[122]
		Pd/C	Toluene	Et_3N, 130 °C	4 h	63–97%	(1) Mild conditions (2) No need to add toxic phosphine ligands (3) Easy catalyst recycling	Liu *et al.*[123]
		P(DVB-IL)-Pd	H_2O	Et_3N, 130 °C	6 h	27–95%	(1) The catalyst is easily separated from the products. (2) Reuse of catalyst without activity loss (3) Environmental synthesis of α, β-alkynyl ketones *via* the heterogeneous carbonylation reaction (4) The method avoids the use of toxic phosphine ligands	Wang *et al.*[124]

Table 6 (*Contd.*)

Reactants	Product	Catalyst	Solvent	Method employed	Reaction time	Yield	Limitations or progress	Ref.
		Pd/Fe_3O_4	Toluene	Et_3N, 130 °C	4 h	50–95%	(1) Highly efficient catalyst for the carbonylative Sonogashira coupling reaction (2) Catalyst can be reused with sustained selectivity and activity (3) Recoverability of catalyst (4) Catalyst could be reused seven times without remarkable loss in activity and selectivity	Liu *et al.*[125]

Sonogashira coupling product **295** in 8% yield after 12 h and did not produce the desired **289** (Scheme 120C). Also, 1-iodo-2-naphthyl acetate **296** under the standard reaction conditions generated just Sonogashira coupling product **297** in 98% after 4 h and did not produce the desired **289** or other products (Scheme 120D). A summary of the recent reaction of alkynes with CO and also limitations and progress of the reactions have been shown in Table 6.

4 Conclusion

The need to improve the reaction conditions in the synthesis of heterocyclic compounds is an important and constant issue, and thus researchers are devoting their efforts to finding optimal and better methods and trying to design methods that solve the related problems. Among them, alkynes, which are a very important and widely use groups in chemistry, are used in important multi-component reactions given that they possess two active sites to carry out the reaction. Due to this characteristic of alkynes, it is challenging for researchers to design and activate a specific position. Meanwhile, researchers use ligands, catalysts, solvents, and even different methods such as microwave heating, which is a priority to perform the desired reactions using environmentally friendly conditions because both the reaction time is short and a low temperature is required, and also non-toxic materials are used, which help to improve the reaction conditions. We present our vision for improving the C≡C and C–H activation of alkynes in the various reactions that lead to a variety of important structures.

The amount of catalyst used in the investigated reactions showed that the amount of catalyst was very effective in the reactions and the alkyne used acted selectively. Furthermore, the presence of electron-withdrawing groups in alkynes (most of the reactions) reduces the efficiency of the reactions, and also aromatic alkynes participate in reactions better than aliphatic alkynes and have higher efficiency, although it should be noted that in some reactions aliphatic alkynes did not react at all. Also, the type of solvent is decisive in the reactions and plays a key role, especially in the reaction of alkynes with CO_2 or CO. In addition, the used molar ratios of alkynes are effective in the synthesis of compounds and different products are created by using different molar ratios.

This article highlighted some applications of the C≡C and C–H positions of alkynes in reactions with other important compounds in multicomponent reactions for the synthesis of important compounds and heterocycles and focused on recent advances in the use of alkynes. Also, the articles highlighted in this review are impressive and extensive and provide valuable insight into the activation of C≡C and C–H alkynes.

We hope that this review will encourage researchers to do more research in this field and cover the gaps in previous research, as well as offer insight into the design of new reactions and new chemical transformations of alkynes to prepare important structures.

4.1 Future remarks

In the selectivity of alkynes, the use of a suitable catalyst is very important, and thus we suggest the use of efficient catalysts in this field, such as nanocatalysts, photocatalysts as well as enzymes. Also, in this case, the used ligands are very effective, and the use of a suitable ligand and catalyst combination helps to optimize the reactions, the selectivity of alkynes and also helps to carry out the reaction of all types of alkynes. Therefore, we suggest using or synthesizing ligands and catalysts that can activate the C≡C or C–H position with the highest selectivity.

Conflicts of interest

There are no conflicts to declare.

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