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Synthesis of N-, O-, and S-heterocycles from aryl/alkyl alkynyl aldehydes

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In the field of heterocyclic synthesis, alkynyl aldehydes serve as privileged reagents for cyclization reactions with other organic compounds to construct a broad spectrum of N-, O-, and S-heterocycles. Due to the immense application of heterocyclic molecules in pharmaceuticals, natural products, and material chemistry, the synthesis of such scaffolds has received wide attention. The transformations occurred under metal-catalyzed, metal-free-promoted, and visible-light-mediated systems. The present review article highlights the progress made in this field over the past two decades.

1. Introduction

The alkynyl group is found in various natural products, bioactive molecules, and pharmaceutical agents¹ and also, regards as a versatile and valuable building block for the organic transformations and manipulations in organic chemistry.² If there is a carbonyl functionality in conjugation with a C–C triple bond, it can expand the application and synthetic significance of the compound. In this regard, a substituted alkynyl aldehyde as an end-product or an intermediate is widely used in organic synthesis, including 1,4-addition, or cyclization reactions which result in the preparation of imidazoles, imidazo[1,2-*a*]pyridines, oxazoles, thiazoles, triazoles, indolizines, pyrimidines, thiophenes, pyrroles, pyridines, pyranones, furans, quinolines, thiopyranes, *etc.* Due to the immense presence of N-, O-, and S-heterocyclic molecules in medicinal, and material science, the synthesis of such compounds has attracted extensive attention from chemists.³ A variety of drugs, drug candidates, and natural products consist of one N-, O-, and S-heterocycle ring or two bound, linked, spaced, or fused heterocycles. Some of these biologically heterocyclic compounds are depicted in Scheme 1. These structural motifs have emerged as novel targets in modern organic chemistry because of their hybrid features and improved potential applications in comparison with their discrete components in many areas.

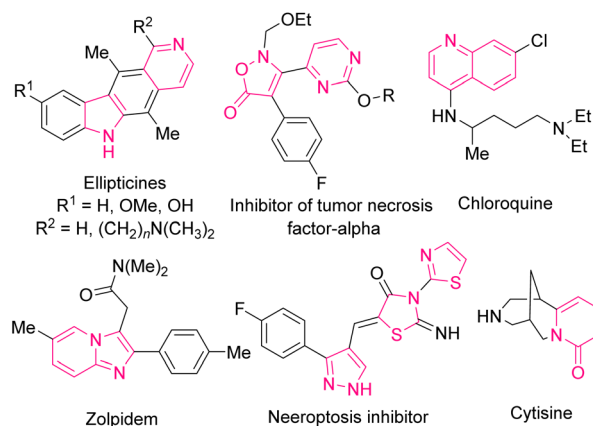
Over the years, many approaches have been described for the preparation of heterocycles from alkynyl moieties and different kinds of chemical compounds.

This review covers the developments in the last two decades in the construction of valuable N-, O-, and S-heterocyclic compounds from aryl/alkyl/heteroaryl alkynyl aldehydes, and other organic compounds, including amidines, amines, alcohols, oximes, hydrazines, ylides, isonitriles, aryl nitrones, nitrosobenzenes, isatins, 1,3-dicarbonyl compounds, *etc.* *via* transition metal-catalyzed, metal-free or visible light-promoted the transformations. In addition, several challenging mechanistic studies and the scope of some substrate ranges have been described.

2. Synthesis of N-heterocyclic compounds

2.1. Synthesis of triazoles

Triazoles are interesting compounds for many years in terms of biological properties.⁴ In 2001, Journet and co-workers synthesized 5-substituted-4-carbaldehyde-1,2,3-triazoles **1b** through



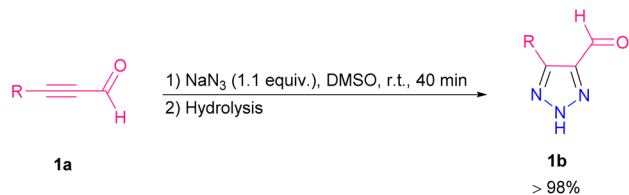
Scheme 1 Some biologically heterocyclic compounds.

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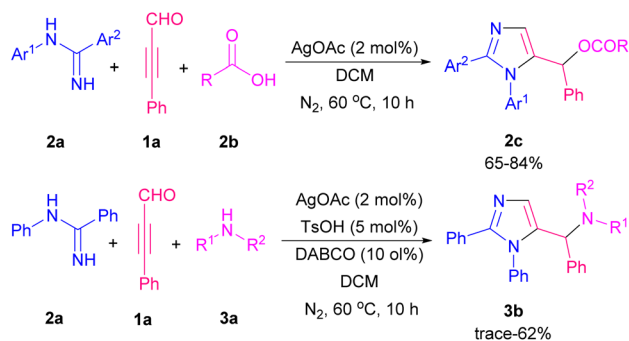
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Scheme 2 Synthesis of 5-substituted-4-carbaldehyde-1,2,3-triazoles.



Scheme 3 Synthesis of imidazoles using acids and amines as a nucleophile.

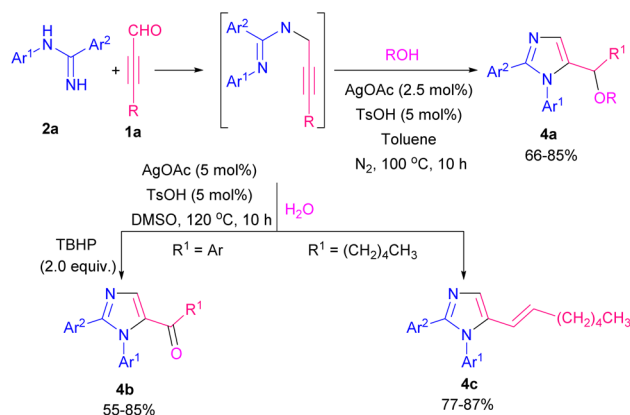
the reaction of α,β -acetylenic aldehydes **1a** with sodium azide (NaN_3) (Scheme 2).⁵ It is essential to keep the reaction alkaline to prevent the generation of hazardous HN_3 .

2.2. Synthesis of imidazoles

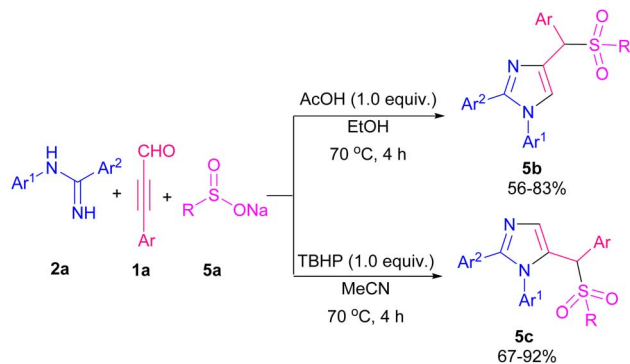
Imidazole and its derivatives are highly polar five-membered aromatic heterocycles present in various natural products, applied pharmaceuticals, and biologically active molecules.⁶ In 2017, a three-component reaction of amidines **2a**, aryl alkynyl aldehydes **1a**, and carboxylic acids **2b** or amines **3a** was accomplished by Li and Cao *et al.* (Scheme 3).⁷ For the synthesis of imidazole products **2c**, and **3b**, various Ag salts such as AgOAc , AgOTf , Ag_2O , AgSbF_6 , AgNO_3 , AgBF_4 , and AgCl , as the metal catalysts were examined, in which the best reaction yield was obtained in the presence of AgOAc . In this ionic pathway, carboxylic acids and amines acted as nucleophiles to regenerate $\text{Ag}(i)$ from the Ag complex. After a while, the same group achieved imidazole-5-carbaldehydes in the presence of amidines and aryl alkynyl aldehydes using AgOTf as the optimized catalyst. The [3 + 2] domino reaction proceeded under O_2 as a green oxidant.⁸ Cao and co-workers by controlling the substrates, could achieve diversely functionalized imidazoles from the reaction of amidines **2a**, propargyl aldehydes **1a**, and phenols, alcohols, or water (Scheme 4).⁹ When propargyl aldehydes **1a** reacted with aliphatic and aromatic alcohols in the presence of a silver catalyst, imidazole products **4a** were obtained. When alkynyl **1a** ($\text{R} = \text{aryl}$) reacted with H_2O in the presence of TBHP, arylimidazoles **4b** were detected, while the reaction of alkynyl **1a** ($\text{R} = \text{alkyl}$) with H_2O without using any peroxide resulted in vinylimidazoles **4c**.

Cao's research group designed two transition metal-free reactions for the construction of imidazole derivatives. In one

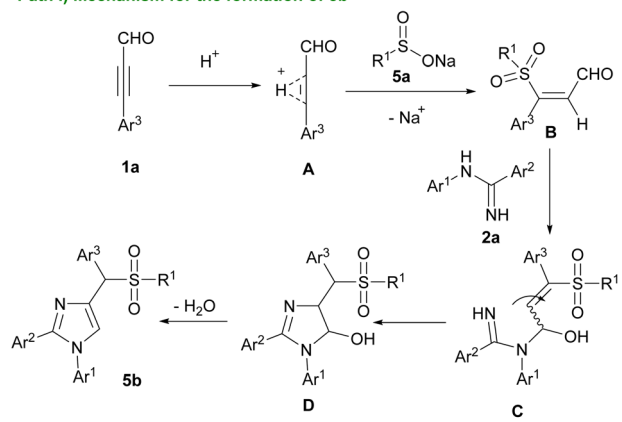
work, they used amidines **2a**, aryl alkynyl aldehydes **1a**, and sodium sulfonates **5a** to provide 4- or 5-sulfonylated imidazoles by additive control (Scheme 5).¹⁰ Two possible pathways suggested for the reaction in the presence of AcOH or TBHP as the additives (Scheme 6). In path I, cation **A** generated by acid, which was subjected to nucleophilic addition of **5a** to afford intermediate **B**. Subsequently, nucleophilic attack of **2a** to **B** gave **C** that underwent intramolecular cyclization formed **D**. Product **5b** produced by dehydration of **D**. In path II, oxidation of **5a** by TBHP furnished sulfonyl radical **E**. Intermolecular dehydration of **1a** and **2a** resulted in imine intermediate **F**. Intramolecular annulation and protonation of **F** created **G**. Adding sulfonyl radical **E** to **G** and aromatization led to the production of product **5c**. The same group, in a similar transformation, used boronic acids **6a** with amidines **2a**, and aryl alkynyl aldehydes **1a** where pivalic acid acted as a catalyst for the synthesis of imidazole-containing triarylmethanes **6b** (Scheme 7).¹¹ In continuation of previous works, Cao *et al.* reported the preparation of 4- and 5-hydroxyalkyl-substituted imidazoles using amidines, aryl alkynyl aldehydes, and H_2O in a controllable regioselective route.¹² When they employed $\text{TsOH}/\text{NaSO}_2\text{CF}_3$ catalytic system, 4-hydroxyalkyl-substituted imidazoles were obtained while they achieved 5-hydroxyalkyl-substituted imidazoles in the presence of CuI .



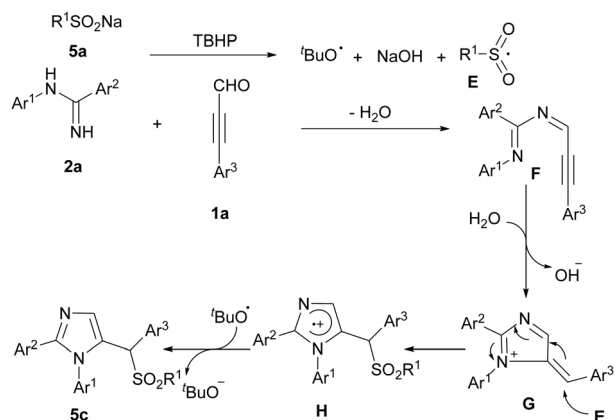
Scheme 4 Reaction of amidines, propargyl aldehydes, and phenols, alcohols, or water.

Scheme 5 Synthesis of 4- or 5-sulfonylated imidazoles using AcOH or TBHP as the additive.

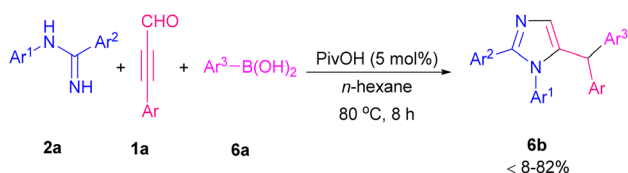
Path I) Mechanism for the formation of 5b



Path II) Mechanism for the formation of 5c



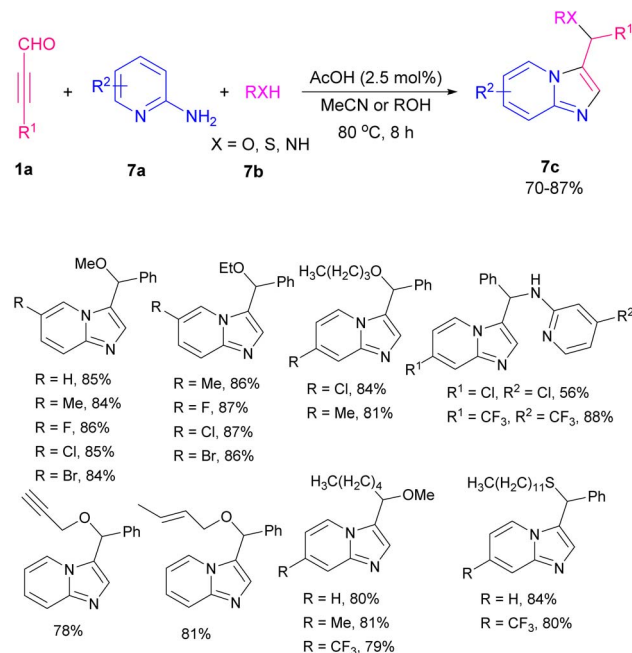
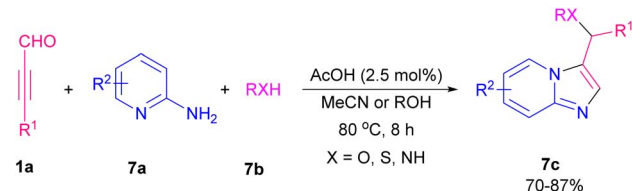
Scheme 6 Two mechanistic pathways for the synthesis of 4- or 5-sulfonated imidazoles using AcOH or TBHP as the additive.



Scheme 7 Synthesis of imidazole-containing triarylmethanes promoted by pivalic acid.

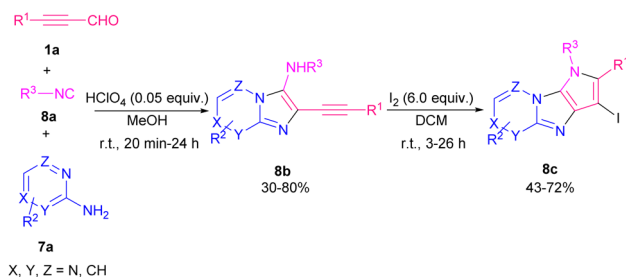
2.3. Synthesis of imidazo[1,2-*a*]pyridines

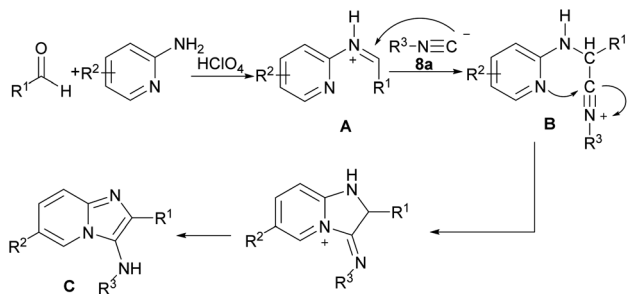
Imidazo[1,2-*a*]pyridine scaffolds are recognized as an important structural motif in the field of organochemistry due to divergent bioactivity features.¹³ In 2014, an efficient metal-free approach was developed by Cao *et al.* for the construction of imidazo[1,2-*a*]pyridine derivatives **7c**, 2-amino pyridine **7a**, aryl alkynyl aldehydes **1a**, and alcohols, thiols or amines **7b** as starting materials contributed in the one-pot C–N, C–O, or C–S bond formation process. The reaction worked well for both alcohols, thiols, and amines (Scheme 8).¹⁴ Subsequently, the formation of functionalized imidazo[1,2-*a*]pyridine aldehydes/ketones and 3-vinyl imidazo[1,2-*a*]pyridines *via* the reaction of aryl alkynyl aldehydes and 2-amino pyridines in the presence of Pd(II) and

Scheme 8 Metal-free synthesis of imidazo[1,2-*a*]pyridines.Scheme 9 F₃CCO₂H-promoted formation of sulfoether-decorated imidazo[1,2-*a*]pyridines.

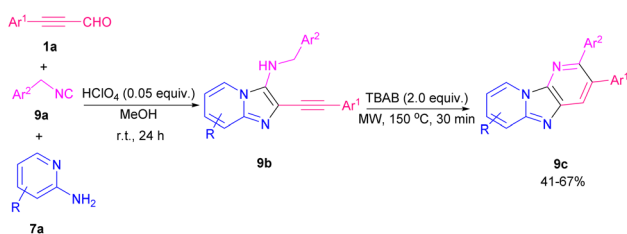
Cu(I) catalysts was developed by the previous group.¹⁵ After a while, they could synthesize sulfoether-decorated imidazo[1,2-*a*]pyridines **7c** by utilizing aryl alkynyl aldehydes **1a**, 2-amino pyridines **7a**, and aliphatic thiols **7b**. F₃CCO₂H catalyzed C–N and C–S bond formation under microwave 500 W in 30 minutes (Scheme 9).¹⁶

I₂-promoted electrophilic cyclization strategy for the preparation of 3-iodo-1*H*-pyrrolo[3',2':4,5]imidazo[1,2-*a*]pyridines **8b** and [1,2-*b*]pyridazines **8c** from aryl alkynyl aldehydes **1a**, 2-

Scheme 10 I₂-promoted synthesis of 3-iodo-1*H*-pyrrolo[3',2':4,5]imidazo[1,2-*a*]pyridines.



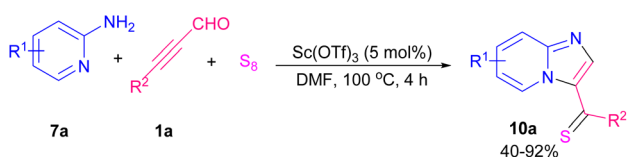
Scheme 11 Groebke–Blackburn–Bienaymé MCR reaction toward 3-aminoimidazo[1,2-*a*]pyridine.



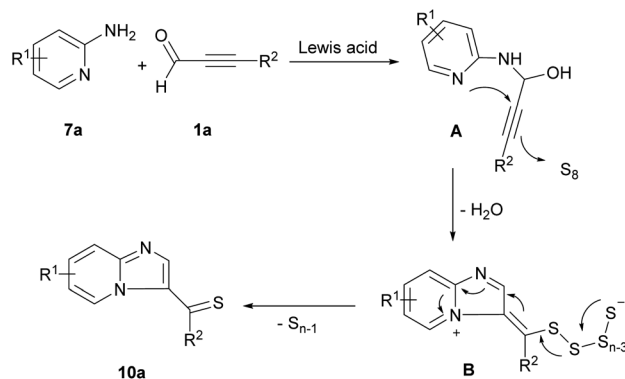
Scheme 12 TBAB-mediated synthesis of imidazo-dipyridines.

amino pyridines **7a** and isonitriles **8a** was developed (Scheme 10).¹⁷ Generally, in a Groebke–Blackburn–Bienaymé MCR reaction, the intermediate imine **A** underwent the nucleophilic addition of an isonitrile to afford the nitrilium ion **B**, followed by intramolecular cyclization and dehydration to achieve 3-aminoimidazo[1,2-*a*]pyridine **C**. In the next step, by the addition of molecular iodine, subsequent cyclization took place (Scheme 11). The reaction of 2-alkynyl aldehydes with 2-aminopyridines in the presence of FeCl_3 (5 mol%) as a Lewis acid catalyst in toluene as a solvent at 60 °C led to a series of 3-arylimidazo[1,2-*a*]pyridines in moderate to good yields (41–85%).¹⁸ In 2019, a novel approach to diverse imidazo-dipyridines in a similar manner was introduced in two steps. In first step, the reaction between aryl alkynyl aldehydes **1a**, 2-amino pyridines **7a**, and isonitriles **9a** resulted in product **9b**, which by tetrabutylammonium bromide (TBAB), second cyclization occurred to achieve imidazo-dipyridine product **9c** (Scheme 12).¹⁹ Anti-cancer activity of products against human prostate cancer also were determined by biological evaluation.

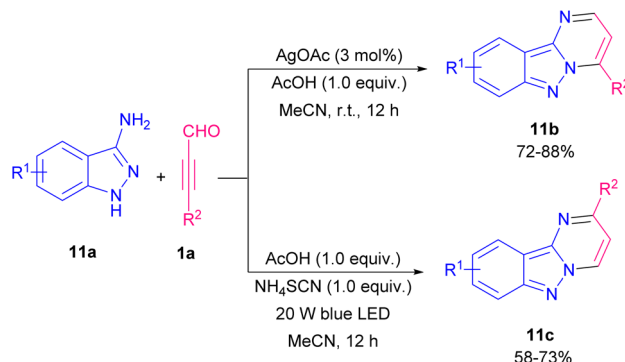
Chen and co-workers investigated Lewis acid-catalyzed synthesis of imidazo[1,2-*a*]pyridine thiones in moderate to excellent yields through the reaction of 2-amino pyridines **7a**, aryl alkynyl aldehydes **1a**, and sulfur element (Scheme 13).²⁰ The



Scheme 13 Lewis acid-catalyzed synthesis of imidazo[1,2-*a*]pyridine thiones.



Scheme 14 Proposed mechanism for synthesis of imidazo[1,2-*a*]pyridine thiones.



Scheme 15 Controllable site-selective synthesis of 2- and 4-substituted pyrimido[1,2-*b*]indazoles.

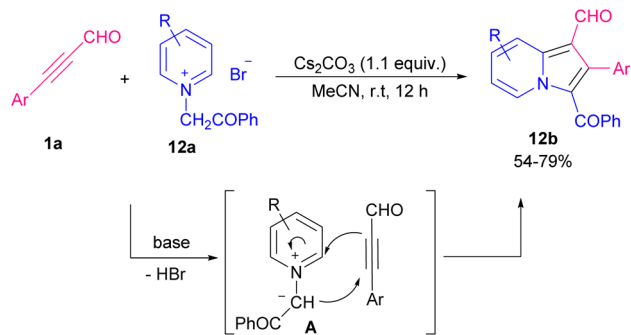
reaction began with Lewis acid-promoted the generation of intermediate **A** through nucleophilic addition of **7a** to **1a**. Nucleophilic attack of the nitrogen to the $\text{C}\equiv\text{C}$ and activation of S_8 by dehydration afforded intermediate **B**. Elimination process of **B** led to imidazo[1,2-*a*]pyridine thione **10a** (Scheme 14). Cao *et al.* extended a strategy for the preparation of imidazo[1,2-*a*]pyridine by gold-catalyzed coupling reaction of propargyl aldehydes and 2-aminopyridines and a series of 3-acylimidazo[1,2-*a*]pyridines were obtained in reasonable yields.²¹ In 2021, the first example of providing 2- and 4-substituted pyrimido[1,2-*b*]indazole **11b**, and **11c** in a controllable site-selective manner from 3-aminoindazoles **11a** and aryl alkynyl aldehydes **1a** was introduced by He and Cao *et al.* (Scheme 15).²² In this strategy, when AgOAc and AcOH were used as a catalytic system, 2-substituted pyrimido[1,2-*b*]indazoles were obtained, whereas if metal-free conditions containing AcOH and NH_4SCN under blue LED irradiation were examined, a series of 4-substituted pyrimido[1,2-*b*]indazole products were detected.

2.4. Synthesis of indolizines

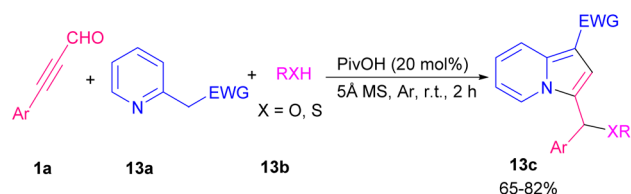
In 2016, Sun and Xing *et al.* described an easy practical strategy for providing indolizine-1-carbaldehydes *via* the reaction between aryl alkynyl aldehydes and pyridinium ylides (Scheme 16).²³ Removal of HBr from pyridinium ylide **12a** by a base



Review



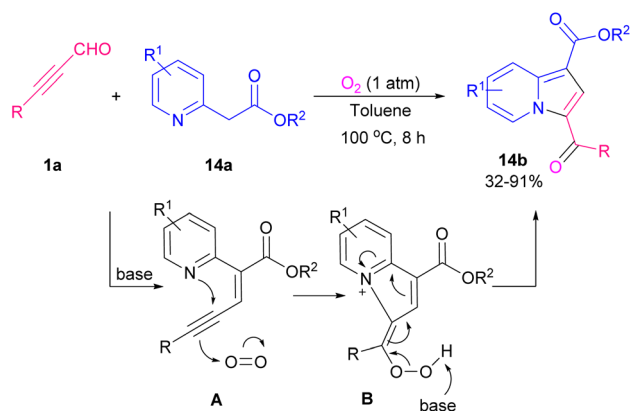
Scheme 16 Base-mediated the reaction between aryl alkynyl aldehydes with pyridinium ylides.



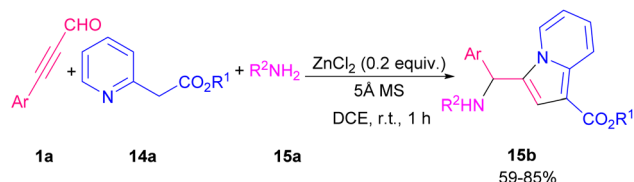
Scheme 17 Acid-promoted the synthesis of indolizines.

resulted in nonstabilized pyridinium ylide **A**, which underwent 1,3-dipolar cycloaddition with alkynyl **1a** to produce **12b**. Synthesis of indolizines also can be assisted by an acid catalyst. 2-(pyridin-2-yl)acetates **13a**, aryl alkynyl aldehydes **1a**, and alcohols or thiols **13b** participated in a multi-component reaction to construct a wide range of functionalized indolizines **13c** in the presence of pivalic acid (Scheme 17).²⁴ Molecular oxygen as a green oxidant employed in the cyclization of 2-pyridylacetates **14a** and aryl/alkyl alkynyl aldehydes **1a** to form 3-acylated indolizines **14b**. Using radical scavenger for mechanism study revealed that the reaction proceeded under an ionic process involving Knoevenagel condensation of **1a** with **14a**, nucleophilic attack, the addition of O₂, and elimination of OH group (Scheme 18).²⁵

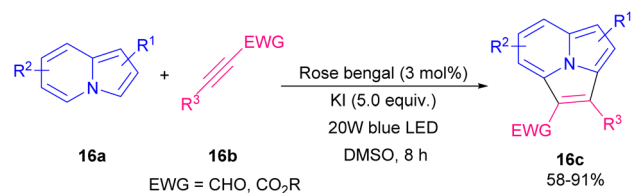
In 2020, aryl alkynyl aldehydes were also employed by Zhu and Cao's research team to furnish aminoalkyl indolizine



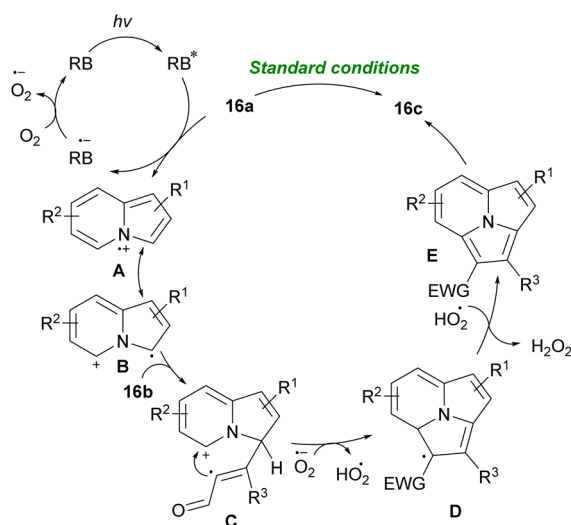
Scheme 18 Metal-free formation of 3-acylated indolizines.



Scheme 19 Metal-free formation of 3-acylated indolizines.

Scheme 20 Zn-catalyzed synthesis of pyrrolo[2,1,5-*cd*]indolizine.

derivatives (Scheme 19).²⁶ Thus, the reaction of 2-(pyridin-2-yl)acetates **14a**, aryl alkynyl aldehydes **1a**, and amines **15a** in the presence of 0.2 equivalent of zinc(II) chloride afforded the desired aminoalkyl indolizine products **15b** in good yields. Their transformation had the advantages of an inexpensive catalyst, short reaction time, mild conditions, and easy product separation. Related work by the same group demonstrated that the use of rose bengal (RB) as a photocatalyst under visible-light irradiation could catalyze constructing pyrrolo[2,1,5-*cd*]indolizine rings **16c** in good to high yields (Scheme 20).²⁷ Intermolecular [3 + 2] annulation of indolizines with internal alkynes under 20 W LED irradiation as an energy source using various photocatalysts such as RB, eosin Y, eosin B, rhodamine 6G, and fluorescein was carried out. The best results were obtained in the presence of RB. Mechanistically, the reaction is proposed to proceed *via* the conversion of ground state RB to excited state RB* under visible-light irradiation, which reacts with **16a** to



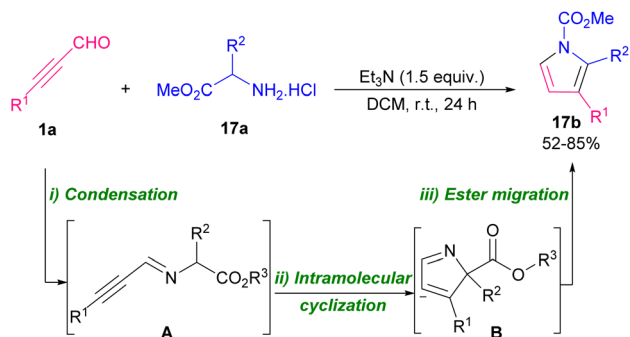
Scheme 21 Visible-light-induced intermolecular [3 + 2] cycloaddition of indolizines.



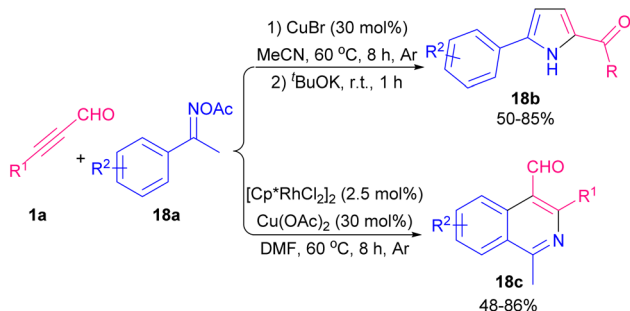
form the radical intermediate **A**. Next, the intermolecular addition of intermediate **B** to alkyne **16b** led to intermediate **C** that underwent sequential dehydrogenation oxidation *via* $O_2^{\cdot-}$ generated **D** and **E**. Finally, aromatization of **E** produced **16c** (Scheme 21).

2.5. Synthesis of pyrroles

Pyrroles are recognized as valuable simple five-membered heterocycles, due to their existence in numerous pharmaceutical agents,²⁸ molecular optics,²⁹ conducting polymers,³⁰ electronics,³¹ gas sensors for organic molecules,³² and also scaffolds in diverse physiologically natural products.³³ In 2020, Wang and co-workers demonstrated the use of triethyl amine in the reaction of α -amino acid esters hydrochloride **17a** and alkynyl aldehydes **1a** for the formation of 1,2,3-trisubstituted pyrroles **17b**. The authors suggested that the reaction proceeded *via* the cascade condensation/intramolecular cyclization reaction followed by a C–N ester migration (Scheme 22).³⁴ In related work, Chen *et al.* by using transition metal catalysts like copper and rhodium complex could synthesize pyrrole **18b** and isoquinoline **18c** scaffolds (Scheme 23).³⁵ From [3 + 2] annulation of ketoxime acetates **18a** and propargyl aldehydes **1a** in the presence of Cu(I) salt and a base, pyrrole derivatives **18b** were obtained. At the same time, Rh(III) and Cu(II) as co-catalysts triggered the [4 + 2] annulation of substrates to afford isoquinoline derivatives **18c**. Two plausible mechanisms are suggested for synthesizing pyrroles and isoquinolines. Sequential

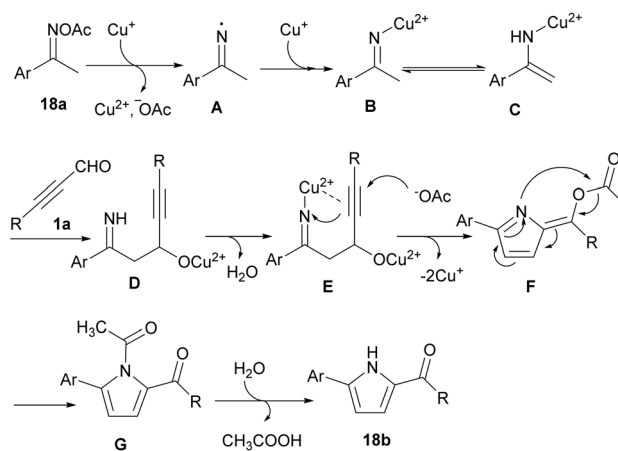


Scheme 22 Metal-free-cascade reaction of α -amino esters and alkynes.

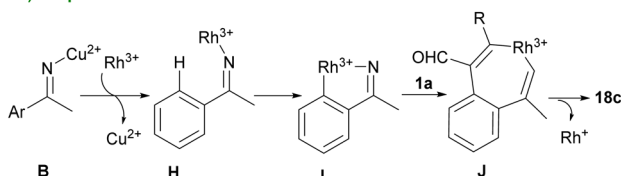


Scheme 23 Transition metal-catalyzed synthesis of pyrrole and isoquinoline scaffolds.

1) Pyrrole formation

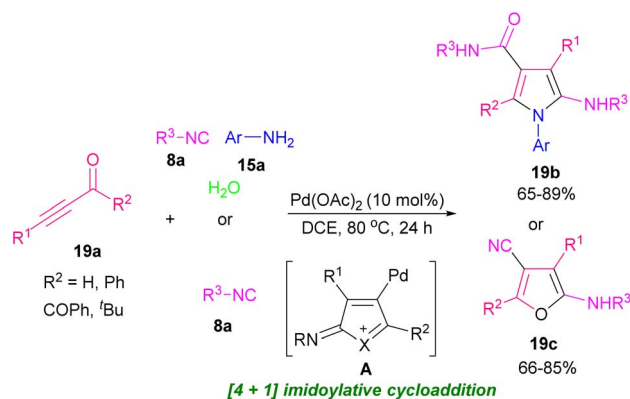


2) Isoquinoline formation



Scheme 24 Proposed mechanisms for transition metal-catalyzed synthesis of pyrrole and isoquinoline scaffolds.

single-electron reduction can form intermediate **C** that involves tautomerization from oxime acetate **18a**. In the next step, nucleophilic addition of **C** to aldehyde **1a** produced intermediate **D**, and H_2O elimination of **D** created intermediate **E**. Consequently, pyrrole **G** was generated *via* a nucleophilic attack and cyclization perused by a rearrangement process. Eventually, product **18b** formed *via* the *N*-acetylation step (Scheme 24, part 1). For achievement to isoquinolines, iminyl-Cu(II) **B** with Rh(III) gave rhodacyclic intermediate **G** through an iminyl rhodium intermediate **I**. Intercalation of aldehyde **1a** afforded intermediate **K**, which was transformed into product **18c**. Rh(III) and Cu(I) are released through the redox reaction between Rh(I) and Cu(II) (Scheme 24, part 2). Internal alkynes

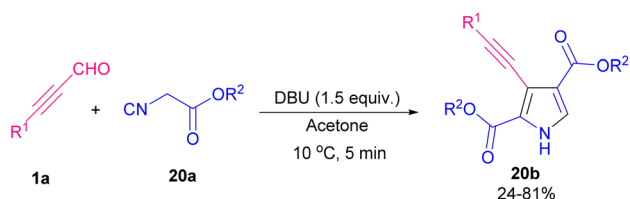


Scheme 25 Pd-catalyzed [4 + 1] cyclization of prop-2-yn-1-ones and isocyanides.

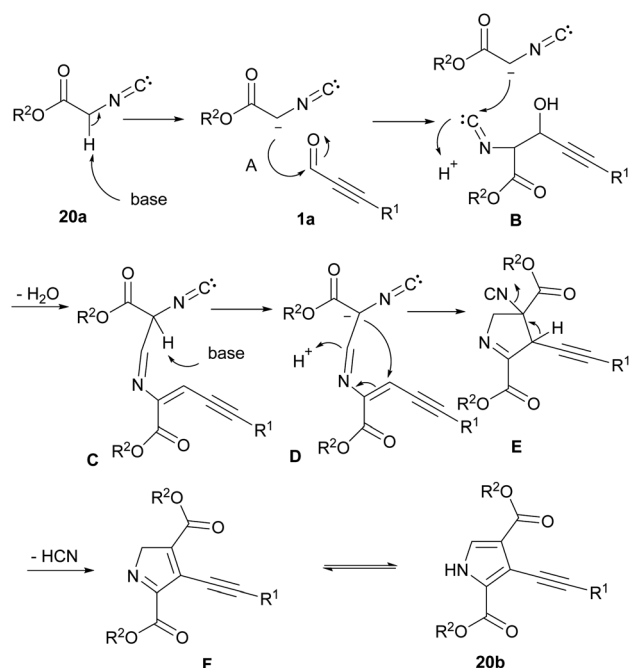


were also employed by Chen *et al.* to form 2-amino-4-amidylpyrroles **17e** and 2-amino-4-cyanofurans **17c** through an [1 + 4] imidolative cycloaddition process (Scheme 25).³⁶ Thus, the reaction of aryl/alkyl/heteroaryl prop-2-yn-1-ones **19a** with isocyanides **8a**, aryl amines **15a**, and H₂O in the presence of catalytic amount of palladium acetate furnished pyrrole rings **19b**. Interestingly, under these conditions, prop-2-yn-1-ones **19a** were reacted with isocyanides **8a** to afford the desired furan rings **19c**.

A convenient transition metal-free approach for constructing 3-alkynylpyrrole-2, 4-dicarboxylates **20b** from alkynyl aldehydes **1a**, and methylene isocyanides **20a** was introduced by Shao's laboratory in 2021 (Scheme 26).³⁷ A tentative mechanism was proposed for the system. As shown in Scheme 27, firstly, isocyanide **20a** was deprotonated by DBU to form **A**. Nucleophilic attack **A** to **1a** generated the intermediate **B** that underwent further attack by the second molecule **20a** to afford **C**. Next, deprotonation of **C** followed by intra-molecular cyclization produced **E**. Removal of HCN created intermediate **F**, which upon interconversion furnished the target product **20b**. Meantime, another procedure for the synthesis of acylpyrrole



Scheme 26 Constructing 3-alkynylpyrrole-2,4-dicarboxylates from methylene isocyanides and alkynyl aldehydes.

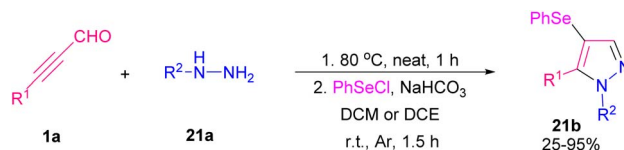


Scheme 27 Plausible mechanism for constructing 3-alkynylpyrrole-2,4-dicarboxylates.

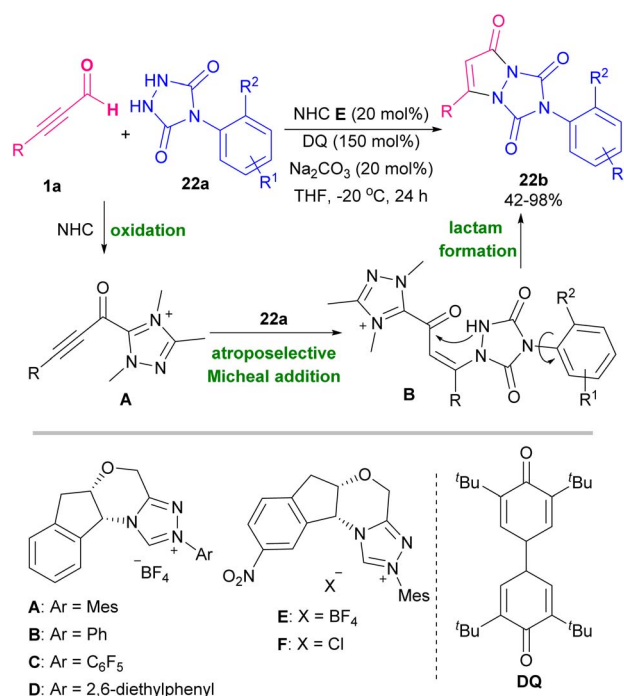
derivatives through the cyclization of ketoxime acetates and alkynyl aldehydes was performed by Huang *et al.*³⁸ The reaction moved upon using 15 mol% of CuBr as the inexpensive metal catalyst to promote synthesizing 2,5-disubstituted and 1,2,5-trisubstituted pyrroles. Both electron-rich and electron-deficient aromatic rings were tolerated under these conditions and gave desired products in moderate yields.

2.6. Synthesis of pyrazoles

Pyrazoles are well-known five-membered nitrogen-containing heterocycles that contain characteristic structural motifs exist in numerous natural products and pharmaceuticals.³⁹ A general synthetic methodology to make 4-(phenylselenanyl)-substituted pyrazoles **21b** was described. The reaction started with the reaction of alkynyl aldehydes **1a** with hydrazines **21a** to generate *in situ* α,β -alkynyl hydrazones followed by the cyclization reaction with phenylselenenyl chloride to produce 4-(phenylselenanyl) pyrazoles **21b** (Scheme 28).⁴⁰ An annulation between alkynyl aldehydes **1a** and urazoles **22a** catalyzed by a chiral N-heterocyclic carbene (NHC) organocatalyst *via* atroposelective [3 + 2] Micheal addition and lactam ring formation was described by Chi research group in 2021. A broad range of

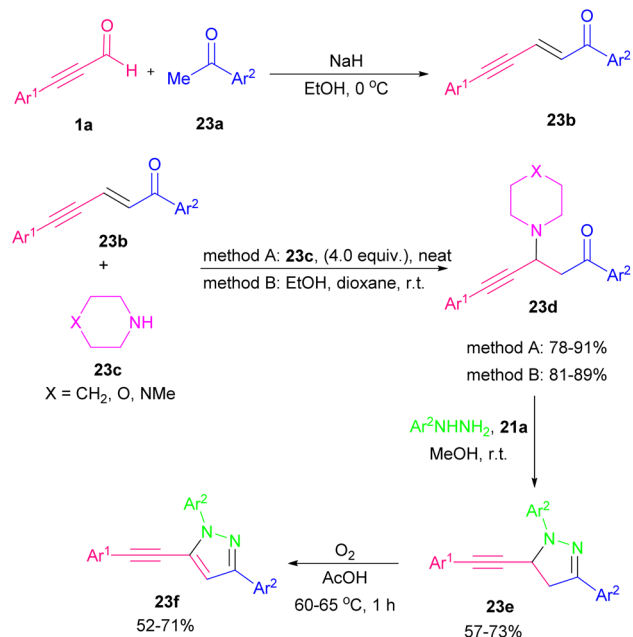


Scheme 28 Synthesis of 4-(phenylselenanyl)-substituted pyrazoles.



Scheme 29 NHC-catalyzed annulation of alkynyl aldehydes and urazoles.



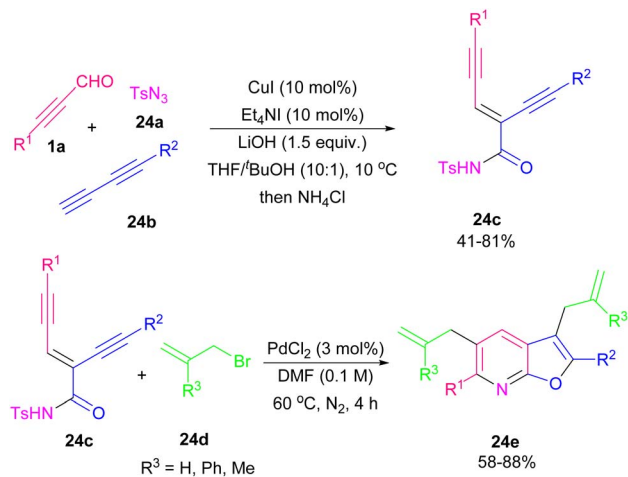


Scheme 30 Synthesis of acetylenic 2-pyrazolines and pyrazoles.

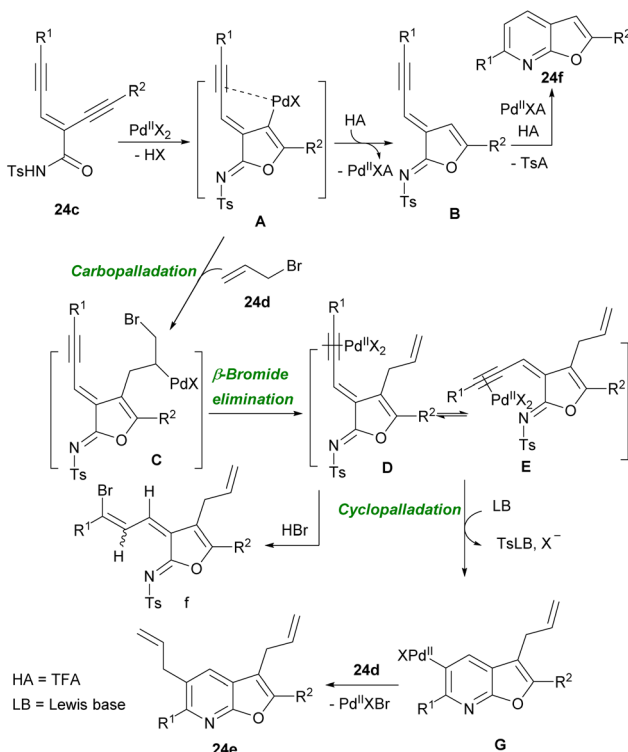
axially chiral/heteroatom-rich pyrazolo[1,2-*a*]triazoles **22b** with good enantioselectivities were achieved by this method. The reaction in the presence of chiral NHCs **A**, **B**, **D**, and **E** showed high chemical yields (Scheme 29).⁴¹ In 2022, Golovanov *et al.* investigated the formation of acetylenic 2-pyrazolines **23e** and pyrazoles **23f** from propargyl aldehyde **1a** as starting material (Scheme 30).⁴² Propargyl aldehyde **1a** in the reaction with arylmethyl ketone **23a** led to 2,4,1-enynone **23b**, which in the next step reacted with morpholine to generate propargylamine **23d**. Finally, cyclocondensation of **23d** in the presence of arylhydrazine **21a** delivered pyrazoline **23e**, which underwent further oxidative dehydrogenation to give pyrazole product **23f**. The author found that the presence of cyclic amine was necessary for the cyclization reaction between **23d** with arylhydrazine **21a**. The N-heterocycle products demonstrated good fluorescent abilities.

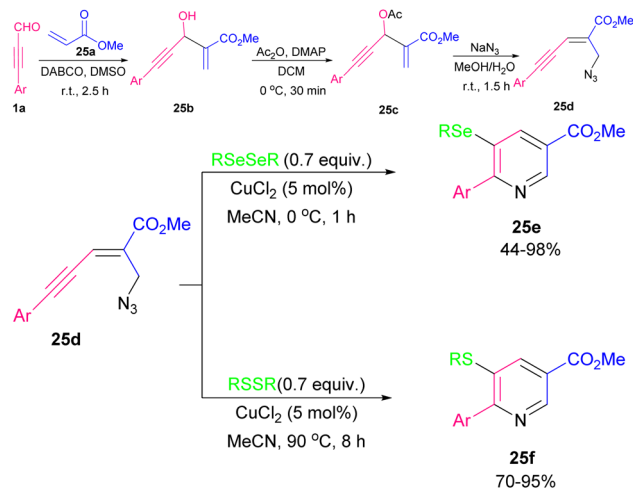
2.7. Synthesis of pyridines

In 2014, Ma's research group successfully synthesized 3,5-dialkylfuro[2,3-*b*]pyridine and 2,6-disubstituted furo[2,3-*b*]pyridines **24e** employing *N*-tosyl carboxamide moiety **24c** as the *N,O*-bisnucleophile in the presence of palladium metal catalyst (Scheme 31).⁴³ The authors proposed a mechanism for this cyclization system involving Pd-promoted *trans*-oxypalladation via 5-*endo*-dig to create the vinyl-palladium species **A**. Under acidic conditions, protonolysis of **A** formed imidate **B**, which underwent cycloisomerization to form product **24f** with the removal of the tosyl groups. On the other hand, **A** coupled with **24d** led to intermediate **D** through olefin insertion and β -bromide elimination. Next, olefin *E/Z* isomerization, and *N*-nucleophilic cyclopalladation of intermediate **D**, gave another palladium species **G**. Finally, **G** coupled with **24d** to produce **24e** (Scheme 32). Reddy and co-workers utilized enynyl azide **22e** to construct

Scheme 31 Pd-catalyzed cyclization of enediyne-imides toward furo[2,3-*b*]pyridines.

substituted pyridines and 5-aminonicotinate derivatives in the presence of Ag(I) and Cu(I) catalysts, respectively.⁴⁴ For the preparation of this substrated they performed a Morita–Baylis–Hillman (MBH) reaction using alkynyl aldehyde **1a** and methyl acrylate **25a** to obtain **25b**. Then, **25b** underwent *O*-acylation followed by allylic substitution with NaN₃ to form enynyl azide **25d**. In the next step, enynyl azide **25d** was subjected to an intramolecular chalcogenoamination with diselenides and disulfides using Cu(II) catalyst to produce 5-selenyl/sulfenyl

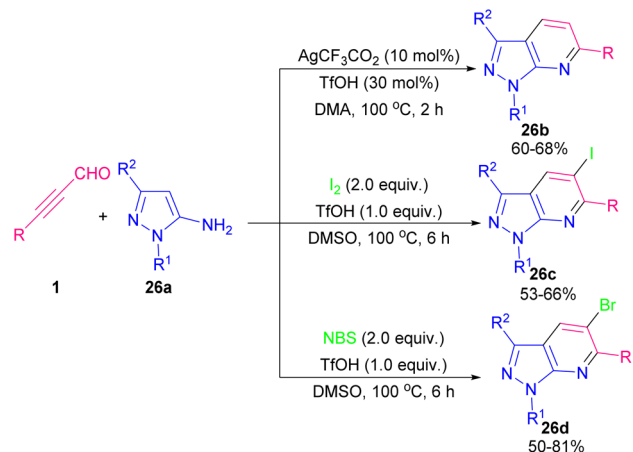
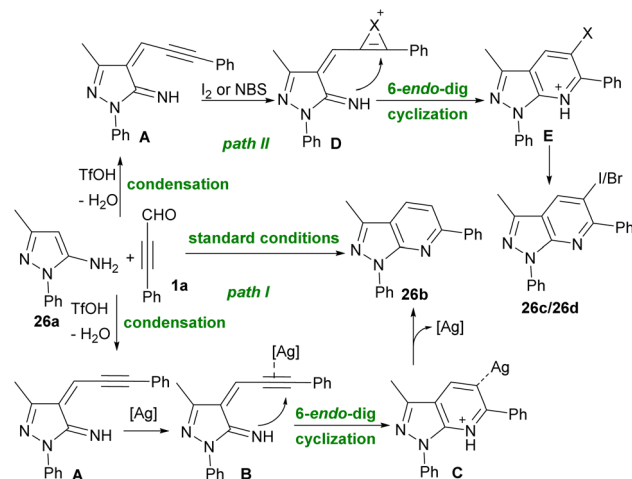
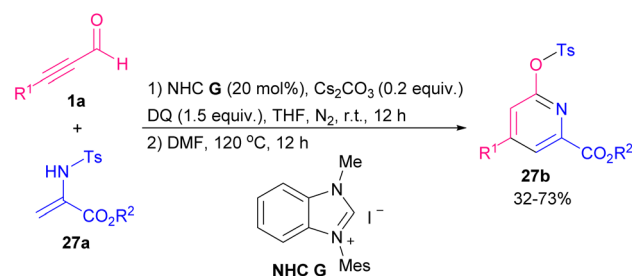
Scheme 32 Proposed mechanism for Pd-catalyzed cyclization of enediyne-imides toward furo[2,3-*b*]pyridines.



Scheme 33 Cu-promoted synthesis of 5-selenyl/sulfenyl nicotines.

nicotines **25e**, and **25f** in moderate to excellent chemical yields (Scheme 33).⁴⁵ This is the first example of the one-pot C–Se, C–S and C–N bond formation approach toward biologically important substituted 5-chalcogenyl nicotines.

The synthesis of pyridine derivatives from alkynyl aldehydes **1a** and 5-aminopyrazoles **26a** was reported by Zhu *et al.* in 2022 (Scheme 34).⁴⁶ In this method, Ag, I₂ and NBS were used to activate the C≡C bond of alkynyl aldehydes **1a**. A wide variety of halogen and non-halogen-functionalized pyrazolo[3,4-*b*]pyridine compounds **26b**, **26c**, and **26d** were achieved in moderate to good chemical yields. Two possible pathways are depicted in Scheme 35. In path I, the condensation of amine **2** with alkynyl aldehyde **1a** generated intermediate **A**. The coordination of Ag salt into alkyne **1a** formed intermediate **B**, which underwent 6-*endo-dig* cyclization to produce **C**. Finally, the demetallation of **B** delivered product **26b**. In path II, the addition of I₂ or NBS into a C≡C bond of alkyne **A** led to intermediate **D**, which underwent 6-*endo-dig* cyclization to create **E**. Elimination of a proton from **E** resulted in **26c** or **26d**.

Scheme 34 Synthesis of pyrazolo[3,4-*b*]pyridine frameworks from 5-aminopyrazoles and propargyl aldehydes.Scheme 35 Proposed mechanism for synthesis of pyrazolo[3,4-*b*]pyridine frameworks from 5-aminopyrazoles and propargyl aldehydes.

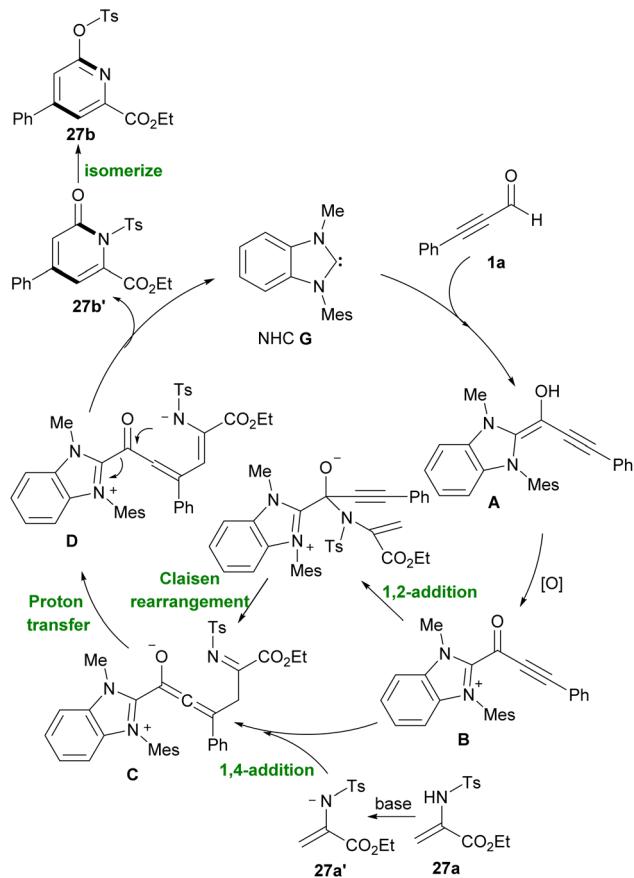
Scheme 36 NHC-catalyzed construction of functional pyridines.

In 2019 Duan and Qi *et al.* proposed a way to synthesize functional pyridines by which the reaction of NHC-bounded alkynyl acyl azolium with N-Ts-protected 2-aminoacrylate **27a** led to final product **27b** (Scheme 36).⁴⁷ In these products, ester functional groups were directly attached to the pyridines. The synthesis of chiral pyridine ligands was another advantage of their work. Plausible mechanism of this report is depicted in Scheme 37. The addition of the NHC **G** to alkynyl aldehyde **1a** produced the alkynyl intermediate **A**. Oxidative reaction of **A** gave NHC-bounded alkynyl acyl azolium **B**. Then nucleophilic 1,4-addition or 1,2-addition/Claisen rearrangement of deprotonated N-Ts 2-aminoacrylate **27a'** with **B** gave intermediate **C**, which in continue during a proton transfer process, produced intermediate **D**. Eventually, through an *N*-acylation reaction NHC catalyst released and the lactam product **27b** formed.

2.8. Synthesis of pyrimidines

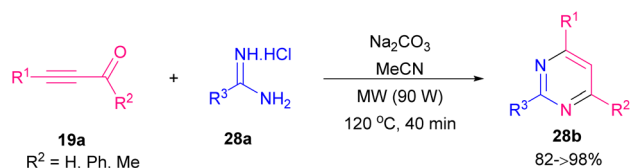
Amongst all heterocycles, pyrimidine shows a broad spectrum of biological activities.⁴⁸ The core of pyrimidine is found in vitamin B1 and barbiturates. Pyrimidines are also used as hypnotics, like vernal. The bioactive structure pyrimidine has a vast therapeutic sketch as it is an essential component of natural composites, and chemotherapeutic drugs. This structure has been applied excellently against bacterial, malarial,



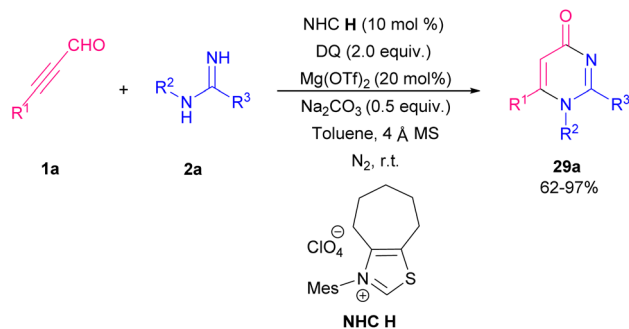


Scheme 37 Plausible mechanism for NHC-catalyzed construction of functional pyridines.

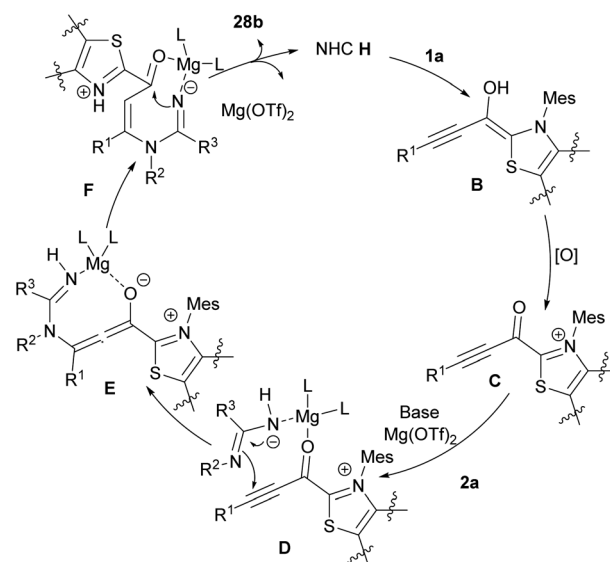
viral, fungal, and cancerous contagions.⁴⁹ In 2003, Bagley *et al.* proposed an effective microwave-assisted method for synthesizing pyrimidines **28b**. In this new procedure, they used a variety of readily accessible alkynones **19a**, and an excess of hydrochloride salt of either acetamidine, benzamidine, or guanidine **28a**. These starting materials were stirred at 120 °C for 40 min in MeCN in the presence of Na₂CO₃ utilizing microwave irradiation at 90 W in a self-tunable microwave synthesizer (Scheme 38).⁵⁰ NHCs are effective organocatalysts that promote a wide variety of Umpolung transformations of various aldehydes.⁵¹ Wang *et al.* developed a mild synthetic method *via* the NHC-catalyzed condensation of alkyne aldehydes **1a**, and amidines **2a** (Scheme 39).⁵² In comparison with previous methods, this synthesis showed remarkable regioselectivity and a vast substrate scope and high functional group tolerance. An assumed mechanism is portrayed in Scheme 40.



Scheme 38 Cyclization reaction between alkynones and guanidine.

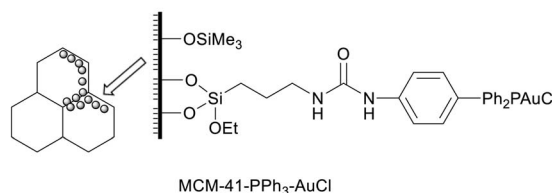
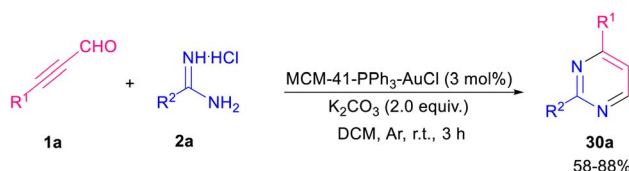


Scheme 39 NHC-catalyzed reaction of alkyne aldehydes and amidines.



Scheme 40 Proposed mechanism for NHC-catalyzed reaction of alkyne aldehydes and amidines.

Alkyne aldehydes **1a** reacted with the NHC catalyst **H** to yield the intermediate **B**, then its oxidation produced the alkyne acylazolium intermediate **C**. Then, both *N*-substituted amidine **2a** and alkyne acylazolium **C** activated by coordination to magnesium(II). Michael addition and following proton transfer



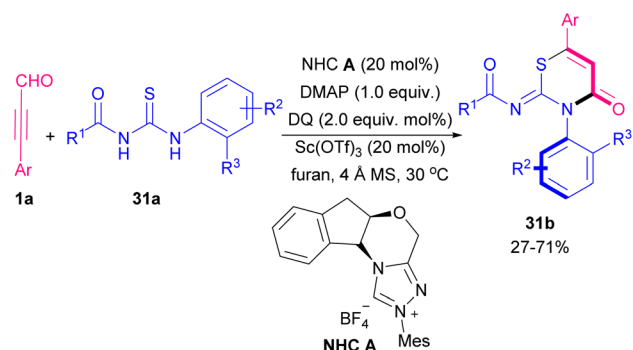
Scheme 41 Synthesis of 2,4-disubstituted pyrimidines.



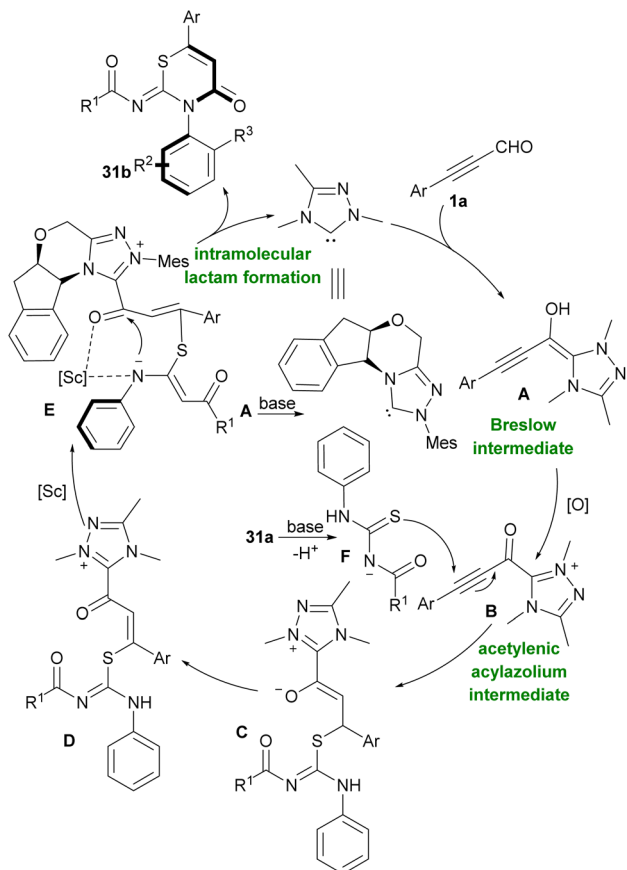
Review

results in intermediate **F**. Eventually, an intramolecular cycloaddition of **F** delivered the final product **28b**. In 2019, Cai and Jiang reported the cyclization of 3-aryl/alkyl propiolaldehyde **1a** and amidines **2a** by using MCM-41-PPh₃-AuCl as an effective recyclable catalyst. The reaction took place under mild conditions and resulted in 2,4-disubstituted pyrimidines **30a** in moderate to high yields. The presence of heterogeneous gold(I) complex was essential for the reaction process (Scheme 41).⁵³

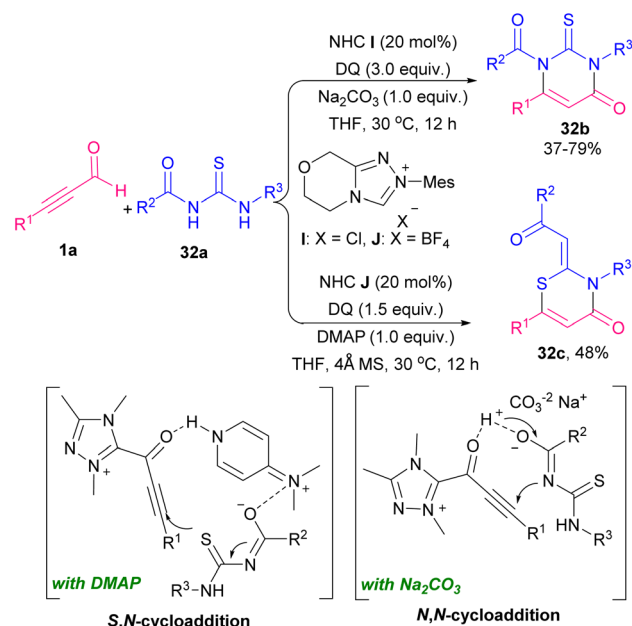
In 2021 Jin *et al.* explained the first example of a chiral NHC catalyst in the reaction of thioureas **31a** and alkynyl aldehydes



Scheme 42 NHC-catalyzed synthesis of axially chiral thiazine derivatives.



Scheme 43 Proposed cyclic route for NHC-catalyzed synthesis of axially chiral thiazine derivatives.

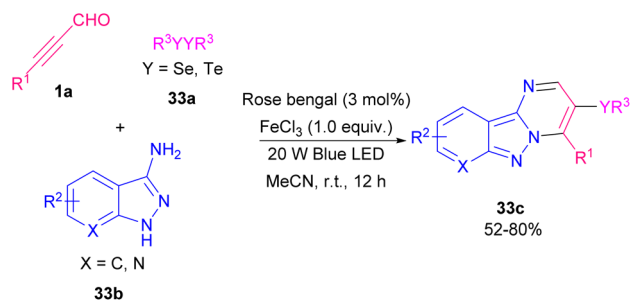


Scheme 44 NHC-catalyzed synthesis of pyrimidinethione derivatives.

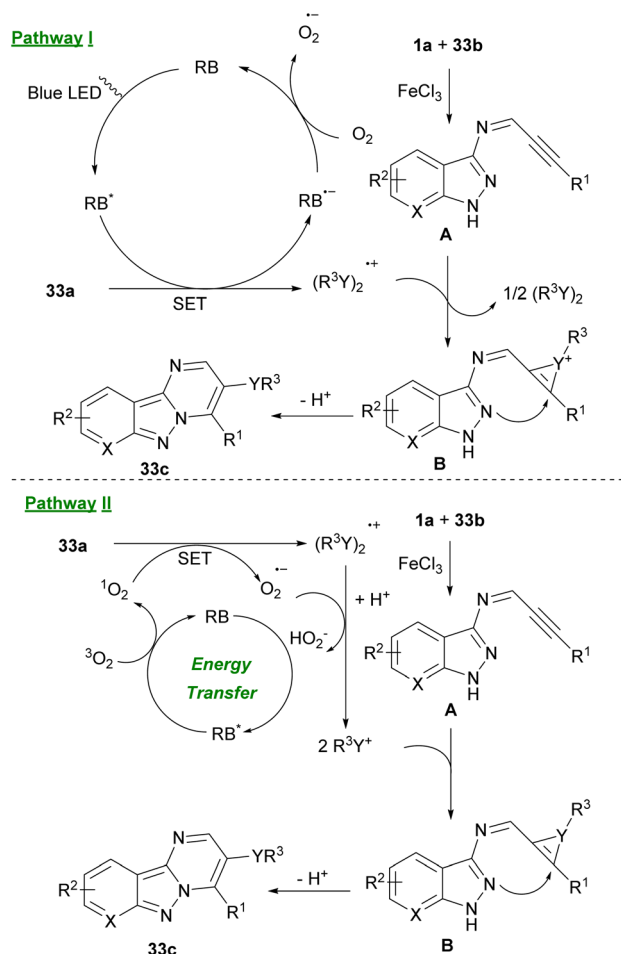
1a to achieve axially chiral thiazine derivatives **31b** with high optical purities (Scheme 42).⁵⁴ The authors proposed a cyclic route for this atroposelective heteroatom cycloaddition involving a base promoted the formation of NHC catalyst **A**. Then, NHC **A** reacted with the alkynyl aldehyde **1a** to afford the Breslow intermediate **A**. Acetylenic acylazolium intermediate **B** was created by the oxidation of **A**. Next, **B** reacted with **F** via a thio-Michael addition to rendering the adduct **C**, which led to the acylazolium intermediate **D** by a proton transfer. Interaction between the 2-isopropylbenzyl group in the substrate **31a** and chiral NHC catalyst, triggered intermediate **D** under a selective intramolecular lactam generation to deliver thiazine **31b** (Scheme 43). A similar transformation was reported by this research team in the application of thioureas **32a** for [3 + 3] cycloaddition reaction with alkynyl aldehydes **1a** using the NHC catalysts (Scheme 44).⁵⁵ NHC-bound acetylenic acylazolium intermediate acted as an electrophilic agent in this reaction. This work provided pyrimidinethione derivatives **32b** with various substitutions. In addition, the authors showed two different pathways for cyclization by varying bases. *N,N*-Cycloaddition was observed in the presence of Na₂CO₃ while a *S,N*-cycloaddition product **32c** was detected by changing the base into DMAP.

Liu and Cao *et al.* reported a green method for synthesizing selenium/tellurium-substituted pyrimido[1,2-*b*]-indazoles **33c** from 3-amino indazoles **33b**, alkynyl aldehydes **1a** and chalcogenes **33a** through a visible-light-promoted three-component reaction (Scheme 45).⁵⁶ Two possible pathways for this synthesis are depicted in Scheme 33. In pathway I, **RB** was transformed to excited **RB*** via visible-light irradiation. Afterward, **33a** underwent a SET process with **RB*** to create the (PhSe)₂^{•+} radical cation and the **RB**^{•-} radical anion. Then, oxygen oxidized **RB**^{•-} to the ground state, completing the





Scheme 45 Blue LED-induced reaction between 3-amino indazoles, alkynyl aldehydes and chalcogenes.



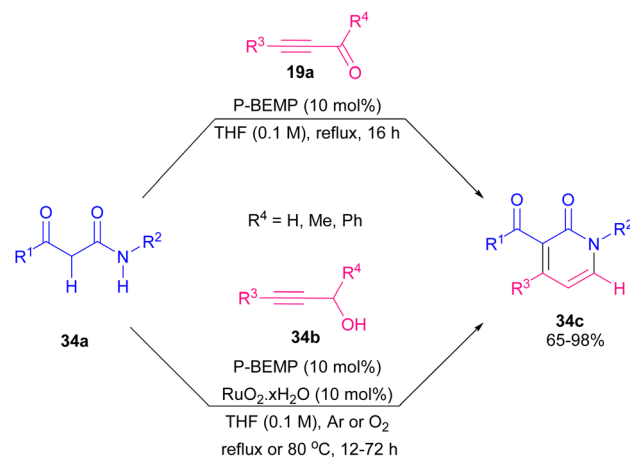
Scheme 46 Two possible pathway for blue LED-induced reaction of 3-amino indazoles, alkynyl aldehydes and chalcogenes.

photoredox cycle. On the other hand, FeCl_3 promoted intermolecular condensation of **1a** and **33b** to form intermediate **A**. Intermediate **A** captured the $(\text{PhSe})_2^{++}$ radical cation, resulting in cation **B**. Finally, intramolecular nucleophilic cyclization of cation **B** gave **33c**. In pathway II, an energy-transfer process is likely involved in the reaction. RB converted to excited RB^* under visible-light irradiation. Then, energy transfer between ground-state oxygen atom and RB^* occurred to generate singlet oxygen, which underwent a SET reaction with diselenide **33a** to

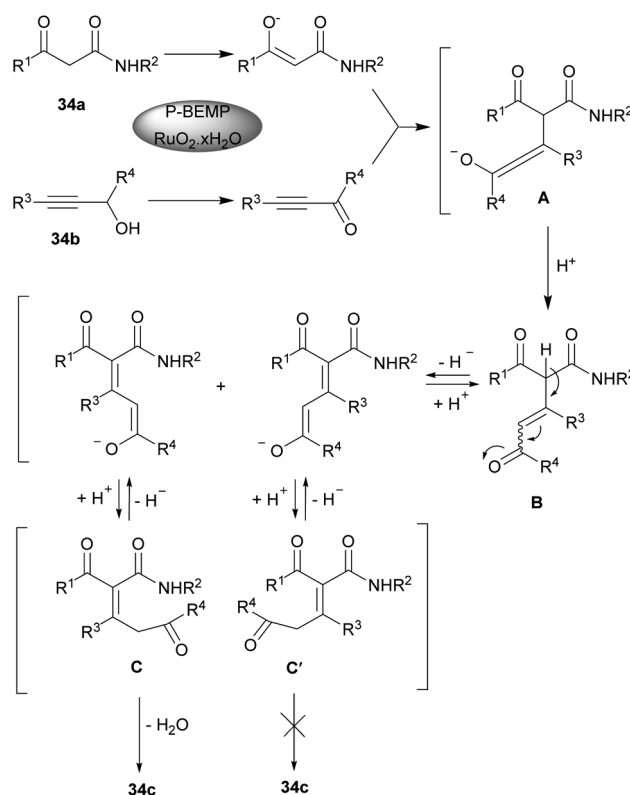
form $(\text{PhSe})_2^{++}$ radical cation. Radical cation $(\text{PhSe})_2^{++}$ can be converted to intermediate PhSe^+ . At last, target product **33c** was furnished *via* an electrophilic cyclization of **A** and PhSe^+ (Scheme 46).

2.9. Synthesis of pyridones

2-Pyridone scaffold is one of the essential structures found in various biological and natural compounds and its potent pharmaceutical and agrochemical activities provoke

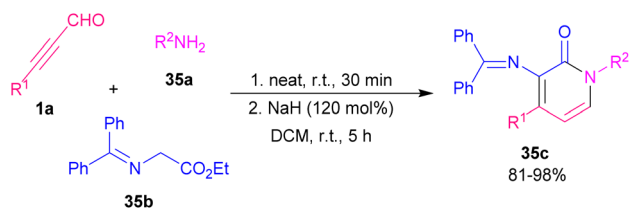


Scheme 47 Synthesis of 2-pyridones from alkynyl aldehydes or alkynyl alcohols and β -keto amides.



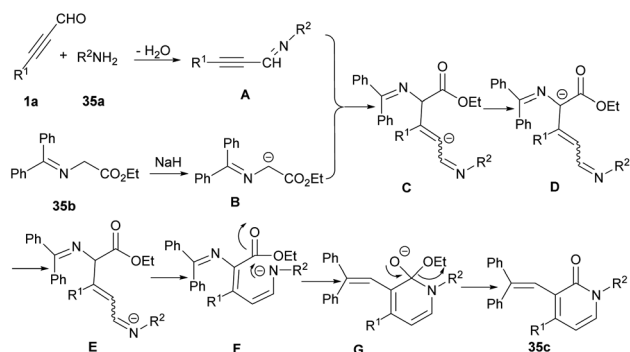
Scheme 48 Suggested mechanism for synthesis of 2-pyridones.





Scheme 49 Three-component reaction of alkynyl aldehydes, amines and ethyl 2-(diphenylmethylene)amino acetate.

researchers to study it.⁵⁷ Additionally, pyridone core is found in heterocycles which are important intermediates in the construction of alkaloid derivatives.⁵⁸ Consequently, many methodologies have been developed for constructing 2-pyridones. In 2012 Rodriguez and Constantieux *et al.* succeeded in using alkynyl aldehydes **19a** with β -keto amides **34a** for constructing 2-pyridones **34c**. Afterward, they can extend the substrate scope to alkynyl alcohols **34b** instead related aldehydes (Scheme 47).⁵⁹ β -keto amide **34a** underwent the reaction with alkynyl alcohol **34b** in refluxing THF for 12 hours using 10 mol% of P-BEMP (phosphazene-supported organocatalyst and $\text{RuO}_2 \cdot x\text{H}_2\text{O}$ as an oxidizing catalyst. A possible mechanism is shown in Scheme 48. Apparently, the mixture $\text{RuO}_2 \cdot x\text{H}_2\text{O}$ /P-BEMP sets off a domino reaction, allowing both *in situ* oxidation of the alkynyl alcohol **34b** for construction of the transient amino enolate to generate the intermediate **B** by an intramolecular Micheal addition. At this level, proton transferred will drive the reaction by the selective cyclodehydration of diastereomer **C**. Lu *et al.* also developed a similar strategy for preparing 1,4-disubstituted 3-amino pyridone derivatives **35c** through the three-component reaction of ynals **1a** and amines **35a** with ethyl 2-(diphenylmethylene)amino acetate **35b** (Scheme 49).⁶⁰ Sodium hydride deprotonated the active methylene proton of the 2-(diphenylmethylene)amino acetate **35b** to produce intermediate **B**. Then, this intermediate was added to alkynyl imine **A**, which was formed by the reaction of **1a**, and **35a** to give **C** followed by proton transfer to afford compound **D**. Intermediate **D** underwent double bond migration and the consequent intramolecular aza-cyclization reaction of **F** led to the final product **35c** (Scheme 50). Chen and Ye presented

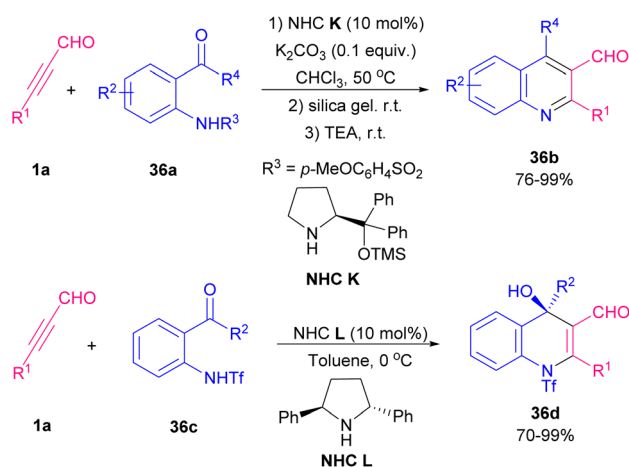


Scheme 50 Plausible mechanism for the reaction of alkynyl aldehydes, amines and ethyl 2-(diphenylmethylene)amino acetate.

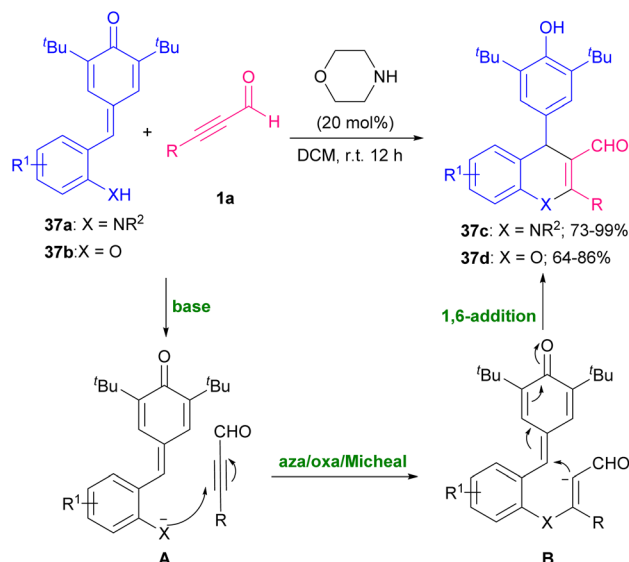
a simple procedure toward 2-pyridones from β -keto amides and alkynyl aldehydes through Micheal addition and intramolecular dehydration process under metal-catalyzed conditions.⁶¹ The reaction conditions were evaluated by varying solvent, base, and temperature. The best results were achieved by utilizing 30 mol% of K_2CO_3 , which led to the highest yield.

2.10. Synthesis of quinolines

Quinoline is one of the most widespread heterocyclic compounds with potent industrial and medicinal applications. It is an essential moiety of both natural and synthetic compounds. This compound is used mainly as a central component for the synthesis of many drugs.⁶² For the synthesis of this sublime compound and its derivatives, numerous synthetic techniques have been reported. In 2012 Yu and Wang *et al.* investigated the reaction of *N*-tosyl-2-aminobenzaldehyde



Scheme 51 Reaction of *N*-tosyl-2-aminobenzaldehyde with alkynyl aldehyde.

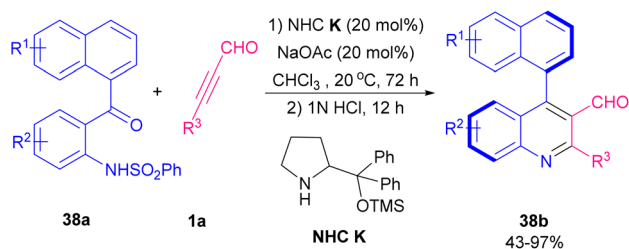


Scheme 52 Synthesis of 1,4-dihydroquinolines and 4H-chromenes.

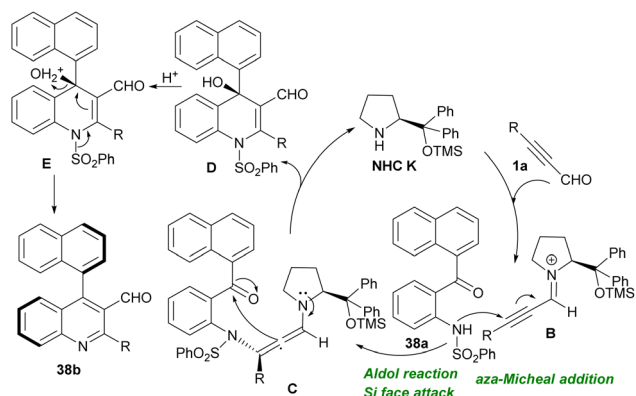


36a with alkynyl aldehyde **1a** by using diphenylprolinol TMS ether **K** (30 mol%) in CHCl_3 at ambient temperature (Scheme 51).⁶³ The tosyl(Ts) group was selected as a protecting group for the nitrogen atom, since its potent electron-withdrawing nature increased the acidity of the NH functionality, so facilitating ionization that generate a more nucleophilic nitrogen anion for primary Michael addition. Another use of organocatalysts in the construction of quinoline rings was proposed by Wang, Zhao and Hu *et al.* in 2020 (Scheme 52).⁶⁴ In this regard, various organocatalysts, including pyrrolidine, piperidine, morpholine, triethylamine, *N,N*-diisopropylethylamine (DIPEA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and also inorganic bases, such as NaOH, Cs_2CO_3 , and K_2CO_3 were examined. Among them, morpholine showed better results in [4 + 2] annulation reaction between *o*-tosylaminophenyl-*p*-QMs **37a** and alkynyl aldehydes **1a**. A series of 1,4-dihydroquinolines **37c** were provided through aza/oxa-Michael/1,6-addition reactions. Moreover, *o*-hydroxyphenylsubstituted *p*-QMs **37b** also exhibited good compatibility with this procedure and led to 4-aryl-4*H*-chromene products **57d**.

In 2021, Wang *et al.* revealed a NHC-catalyzed cascade aza-Michael/Aldol reaction of alkynyl aldehydes **1a** with *N*-(2-(1-naphthoyl) phenyl)benzenesulfonamides **38a** (Scheme 53).⁶⁵ diverse axially chiral 4-naphthylquinoline-3-carbaldehyde structures **38b** were acquired up to 97% chemical yield with high enantioselectivities (up to 96%). Besides, target chiral products could be transformed into chiral 4-naphthylquinolines with preserved enantioselectivities. Intrinsically, the



Scheme 53 Aza-Michael/Aldol reaction of alkynyl aldehydes with *N*-(2-(1-naphthoyl) phenyl)benzenesulfonamides.



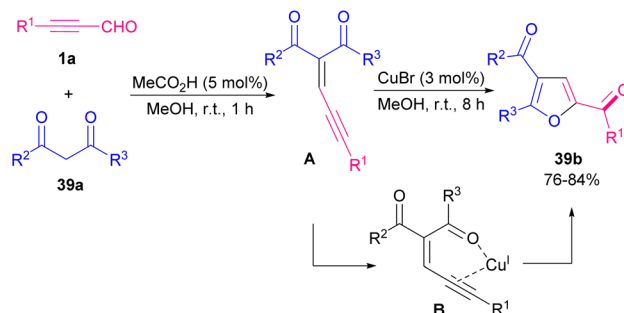
Scheme 54 Suggested mechanism for aza-Michael/Aldol reaction of alkynyl aldehydes with *N*-(2-(1-naphthoyl) phenyl) benzenesulfonamides.

alternative protocol to the preparation of chiral 4-naphthylquinolines can be anticipated. A possible reaction mechanism is depicted in Scheme 54. The reaction started *via* the nucleophilic addition of amine catalyst **K** to alkynyl aldehydes **1a**, to form active iminium intermediate **B**. The aza-Michael addition of *N*-(2-(1-naphthoyl)phenyl)benzenesulfonamide **38a** to iminium intermediate **B** gave the chiral intermediate **C**. After that, the nucleophilic attack of **C** onto ketone from *Si* face afforded a chiral dihydroquinoline intermediate **D** and regenerated catalyst **K**. Eventually, the protonation of **D** converted the OH group into OH_2^+ as a good leaving group. By a central-to-axial chirality conversion, the dehydration-deprotection of intermediate **E** delivered the axially chiral product **38b**.

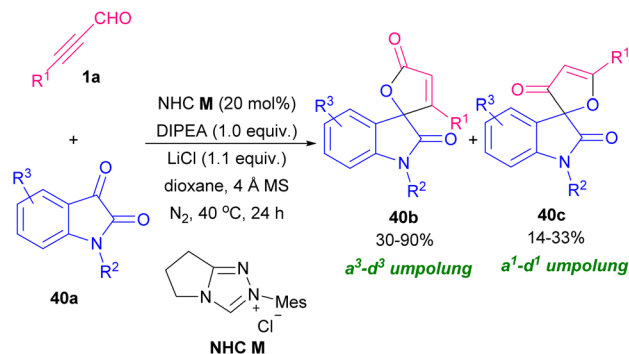
3. Synthesis of *O*-heterocyclic compounds

3.1. Synthesis of furans

In 2013, Cao, Jiang and co-workers constructed tri-substituted furan derivatives **39b** using a copper catalyst in a one-pot manner, which opened the door for constructing different useful α -carbonyl furans using air as an external oxidant (Scheme 55).⁶⁶ The reaction proceeded through the formation of intermediate **A** in the reaction mixture, followed by coordination with Cu(I) **B**, an intramolecular 5-exodig cyclization, and carbene oxidation by air oxygen. A cooperative NHC/Lewis acid-

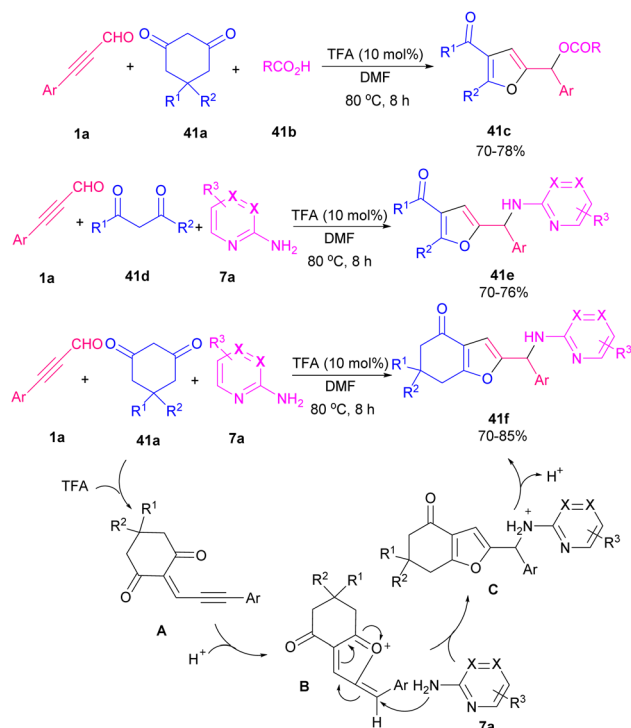


Scheme 55 Visible-light-induced intermolecular [3 + 2] cycloaddition of indolizines.



Scheme 56 NHC/Lewis acid-mediated regioselective [3 + 2] annulation of alkynyl aldehydes with isatins.

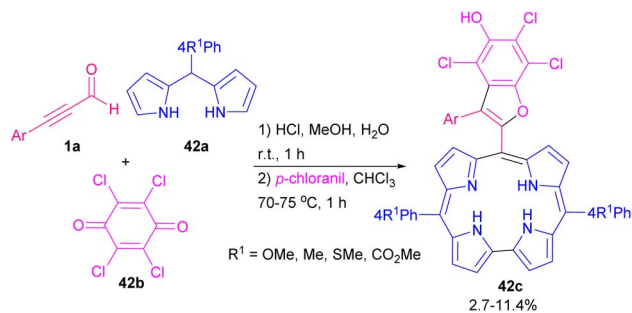




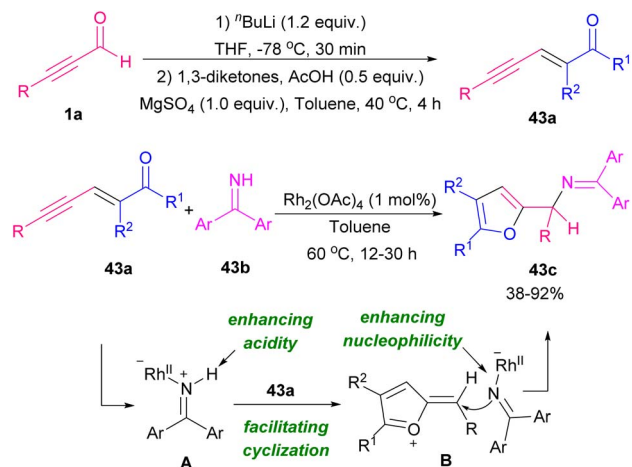
Scheme 57 Synthesis of furans from aryl alkynyl aldehydes, 1,3-dicarbonyl compounds and aromatic amines or aliphatic acids.

promoted regioselective [3 + 2] annulation of *N*-substituted isatins **40a** with aryl alkynyl aldehydes **1a** was performed toward oxindole core with furan-2-(5*H*)-one motif. The reaction proceeded in the presence of NHC **M** as an organocatalyst, LiCl as a Lewis acid, and *N,N*-diisopropylethylamine (DIPEA) as a base. By control of the reaction conditions, a^3-d^3 Umpolung products **40b** were obtained, whereas in a few cases, a decrease in the reaction temperature resulted in a^1-d^1 Umpolung products **40c** (Scheme 56).⁶⁷ Synthesis of furan derivatives from readily available aryl alkynyl aldehydes **1a**, 1,3-dicarbonyl compounds **41a** and aromatic amines (pyridin-2-amine, pyrazin-2-amine, pyrimidin-2-amine) **7a** or aliphatic acids **41b** using trifluoroacetic acid (TFA) was reported by Cao *et al.* in 2016 (Scheme 57).⁶⁸ The reaction began with Knoevenagel condensation of **1a** and **41a** toward intermediate **A**. Intermediate **B** was created by an intramolecular nucleophilic attack of the carbonyl oxygen under acidic conditions. By conjugate addition of **7a** to **B**, and a dehydration process, target product **41f** was obtained. In related work, the preparation of substituted furans was achieved through a three-component coupling of 1,3-dicarbonyl compounds, aryl/alkyl alkynyl aldehydes, and alkenes in the presence of 2 mol% ZnCl₂.⁶⁹

The corrole macrocycles showed good fluorescence features, which makes them potent candidate for cancer-targeting imaging and treatment.⁷⁰ Aryl alkynyl aldehyde **1a** can react with dipyrans **42a**, and *p*-chloranil **42b** to form the corrole macrocycle bearing substituted benzofuran-2-yl **42c** (Scheme 58).⁷¹ The presence of *p*-chloranil was essential in this three-segment reaction. Evaluating other oxidants, such as 2,3-



Scheme 58 Synthesis of persubstituted benzofurans.



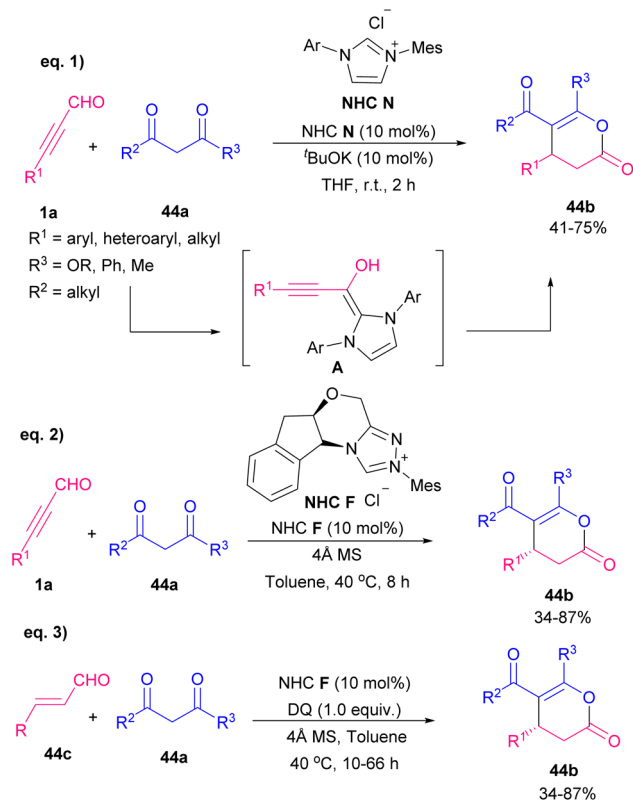
Scheme 59 Rh-catalyzed synthesis of furan derivatives.

dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), *p*-benzoquinone, and bis(acetoxy)iodobenzene (BAIB) resulted in no product. Afterward, resulting products were investigated for UV-vis and fluorescence absorption. Recently, an atom-economical approach to the synthesis of furan derivatives starting from aryl alkynyl aldehyde was disclosed by Kim *et al.* (Scheme 59).⁷² In the procedure, at first, coordination of rhodium(II) with nitrogen atom of diarylimine **43b** occurred that enhanced *N*-H acidity. After the annulation of **43a** to form cyclized intermediate **B**, the authors proposed a nucleophilic addition of Rh(II)-iminyl complex **A** into **B** resulting in target product **43c**.

3.2. Synthesis of pyranones

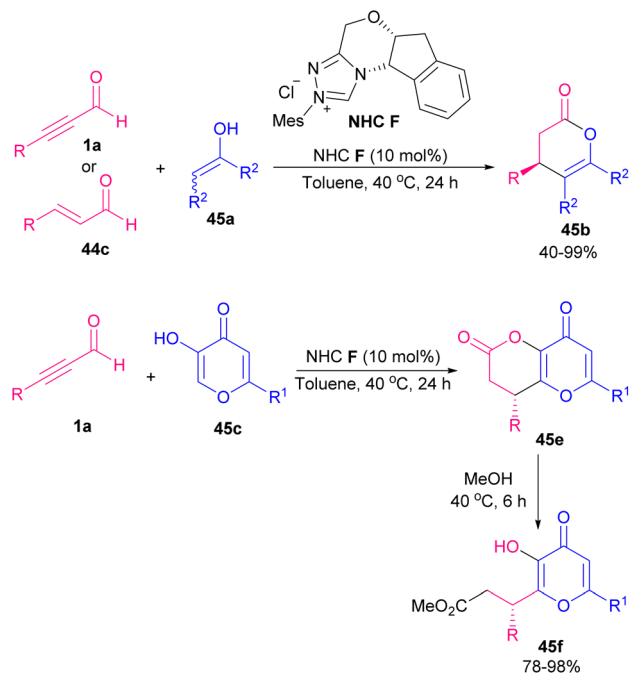
Xiao and co-workers developed two similar NHC-catalyzed protocols for the synthesis of highly functionalized dihydropyranones (Scheme 60).⁷³ In one work, alkynyl aldehydes **1a** reacted with 1,3-diketones **44a** or 1,3-keto esters through the formation of Breslow intermediate **A** alkynyl aldehydes **1a** with catalyst NHC **B** (Scheme 60, eqn (1)). The reaction in the absence of base did not proceed. In other work, they use chiral NHC **C** to catalyze annulation between 1,3-dicarbonyls with alkynyl aldehydes **1a** or alkenyl aldehydes **44c** (Scheme 60, eqn (2) and eqn (3)). The reaction in the presence of molecular sieves showed higher yield and better stereoselectivity. In the case of alkenyl aldehydes **44c**, the addition of quinone oxidant **D**



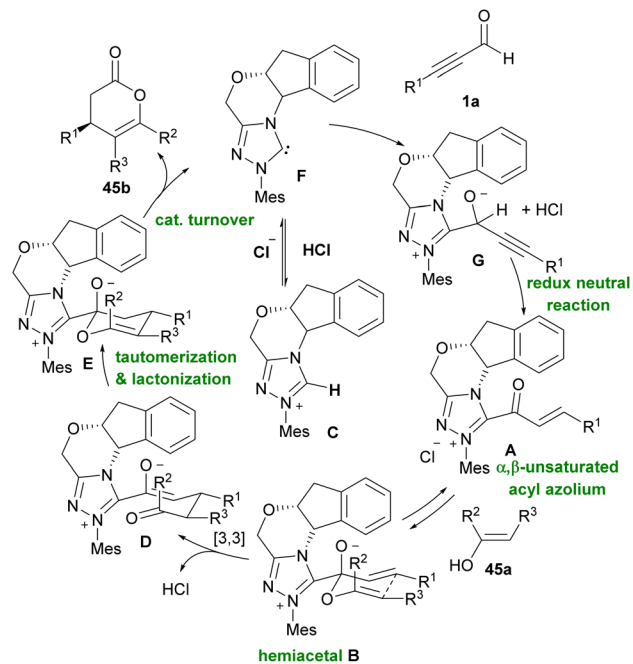


Scheme 60 NHC-catalyzed synthesis of functionalized dihydropyranones.

modified the efficiency of the transformation. In 2012, Bode *et al.* prepared dihydropyranone scaffolds by using the chiral NHC F through an enantioselective Coates–Claisen



Scheme 61 NHC-catalyzed annulation of ynals and enals with stable enols.



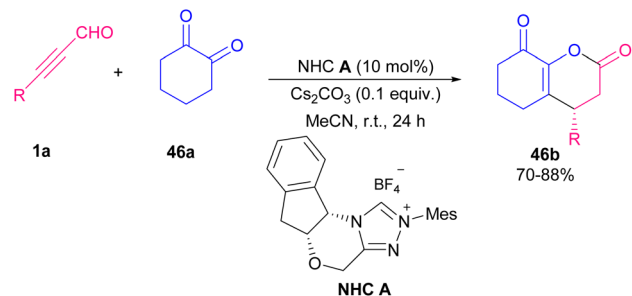
Scheme 62 Proposed mechanism for NHC-catalyzed tandem Michael addition/lactonization.

rearrangement. For this purpose, they used ynals **1a** and enals **44c** and enols **45a** as starting materials (Scheme 61).⁷⁴ The key step in the reaction was most likely the formation of hemiacetal intermediate **A**. Mechanistic studies indicated that Claisen rearrangement on this intermediate was stereochemically determining step, which led to annulation reaction in competition with esterification. So, a cyclic pathway was proposed for this transformation. The deprotonation of triazolium salt pre-catalyst **A** by a base produced active NHC **F**, which added to ynals **1a** to generate an adduct that underwent the proton transfer and the internal redox reaction to create α,β -unsaturated acyl azolium **C**. The species **C** and the enol **3** are in equilibrium with hemiacetal **D**, which underwent a [3,3]-sigmatropic rearrangement to produce adduct **E**. This was followed by tautomerization and lactonization to regenerate the catalyst and render dihydropyranone **45b** (Scheme 62). In 2013, Du and Lu *et al.* in a related process provided 3,4-dihydropyrano [3,2-*b*]indol-2-ones. For this purpose, they employed 15 mol% of NHC catalyst, 1.1 equivalent of quinone oxidant, 4 Å MS, and a base for the annulation of alkynyl or alkenyl aldehydes with indolin-3-ones.⁷⁵

Ren and Yuan *et al.* disclosed an approach toward chiral fused dihydropyranones **46b** via NHC-catalyzed Michael addition/lactonization sequence of alkynyl aldehydes **1a** with 1,2-diones **46a** (Scheme 63).⁷⁶ Among different kinds of organic bases (NMM, TBD/DIPEA, DMAP, TEA) and inorganic bases (K_2CO_3 , Cs_2CO_3 , KOH, KO^tBu), inorganic ones exhibited notable increase in chemical yield. After a while, Wang and co-workers reported a variant of the same cyclization reaction between aryl alkynyl aldehydes **1a** with *N*-quinolinium, *N*-pyridinium, and *N*-imidazolium ylides **47a** to construct biologically active 4,6-disubstituted α -pyrones **47b** (Scheme 64).⁷⁷

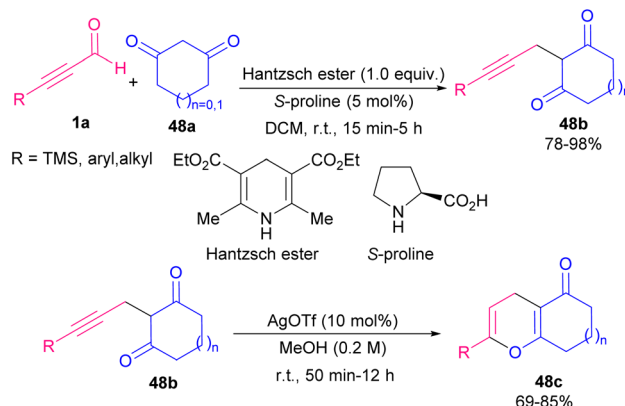


Review

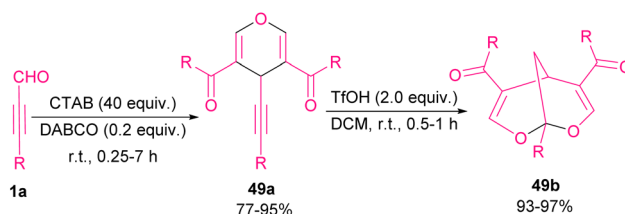


Scheme 63 NHC-catalyzed tandem Michael addition/lactonization.

In 2019, Ramachary *et al.* developed a three-component coupling reaction between ynals **1a**, cyclic-1,3-diketones **48a** and Hantzsch ester (Scheme 65).⁷⁸ In this reaction, *S*-proline acted as an efficient amino acid catalyst for the chemoselective synthesis of 2-(3-aryl/alkylprop-2-yn-1-yl)cycloalkane-1,3-diones **48b** in good to excellent yields. Afterward, by the addition of AgOTf as a catalyst, annulative esterification of **48b** occurred to yield dihydropyran structures **48c**. Green and sustainable synthesis of pyran derivatives from ynals **1a** as starting materials access to 4*H*-pyrans **49a** and then bioactive 2,8-dioxabicyclo[3.3.1]nona-3,6-diene scaffolds **49b** was developed in 2021 (Scheme 66).⁷⁹ In this method, trimerization of ynals **1a** utilizing a cationic micelle like cetrimonium bromide (CTAB), and 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base in water as a solvent led to 4*H*-pyrans **49a**. In the next step, obtained pyrans underwent a rearrangement process in the presence of 2.0 equivalent triflic acid (TfOH) in CH₂Cl₂ at room temperature to furnish 2,8-dioxabicyclo[3.3.1]nona-3,6-diene natural products **49b**. The reaction started with Michael-type addition to ynal **1a** to yield a zwitterionic allene intermediate **A**. Hereafter, Michael-type hydration and DABCO elimination in **A** led to β-keto

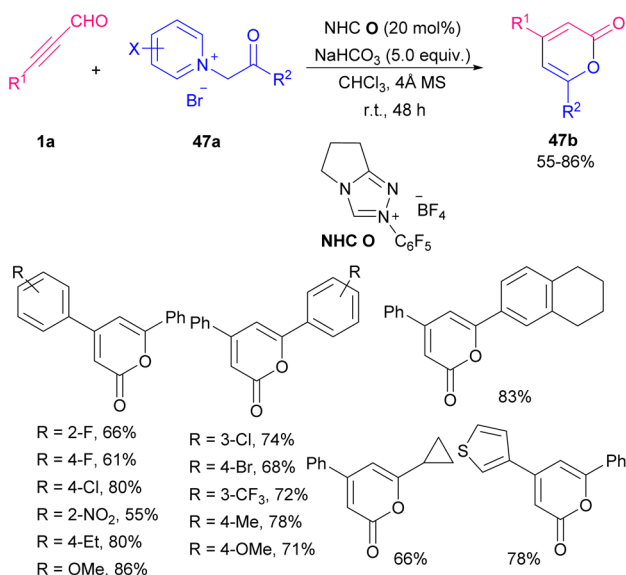
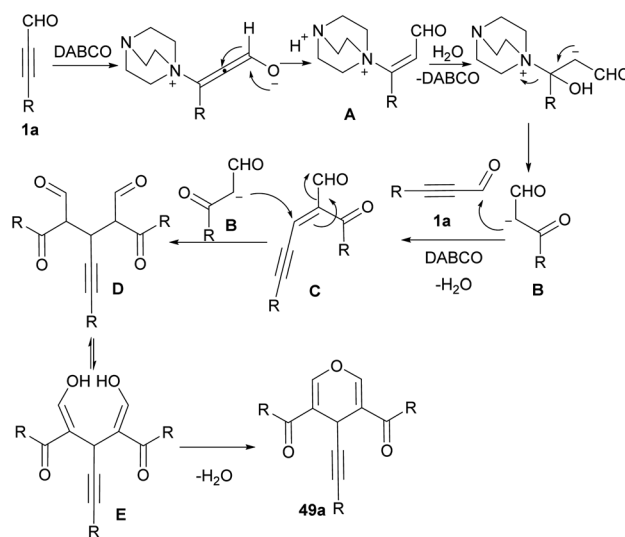


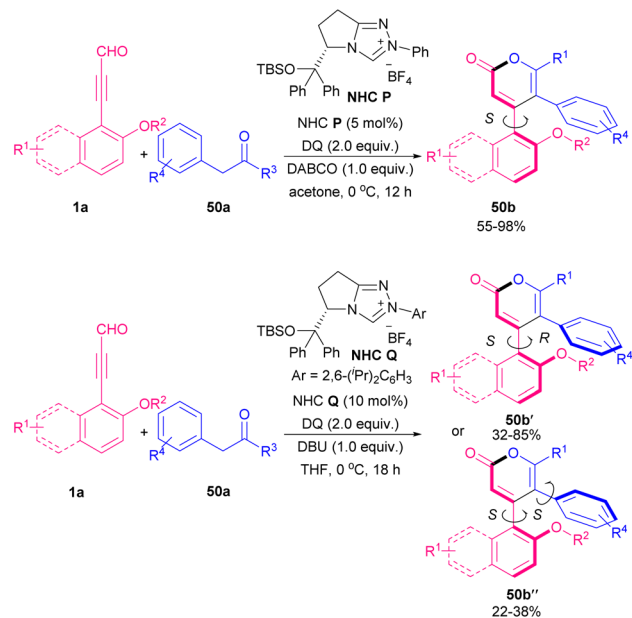
Scheme 65 Three-component coupling reaction between ynals, cyclic-1,3-diketones and Hantzsch ester.

Scheme 66 Synthesis of 4*H*-pyrans and 2,8-dioxabicyclo[3.3.1]nona-3,6-dienes starting from ynals.

aldehyde intermediate **B**. Aldol condensation between **B** and **9** rendered intermediate **C**. Afterward, **C** underwent second Michael-type addition with **B** to form intermediate **D**. Enolization of **D** to **E** and subsequent cyclodehydration produced 4*H*-pyran **49a** (Scheme 67).

Very recently, Wong and Lu's research group introduced a protocol for the synthesis of axially chiral triaryl-2-pyrone frameworks by the employment of an oxidative organo-catalysis system (Scheme 68).⁸⁰ The products obtained *via* [3 + 3]

Scheme 64 NHC-promoted the construction of 4,6-disubstituted α -pyrones.Scheme 67 Possible mechanism for synthesis of 4*H*-pyrans.



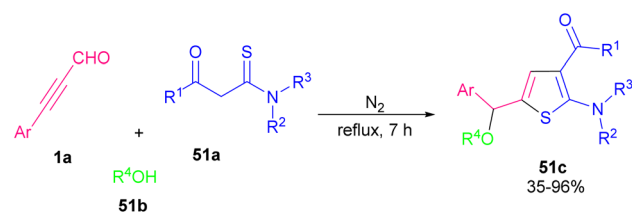
Scheme 68 NHC-catalyzed synthesis of axially chiral triaryl-2-pyrones.

annulation of alkynyl aldehydes **1a** and 2-aryketones **50a**, and contained one axis or two axes. After screening several NHC organocatalysts, chiral NHCs **P**, and **Q** were chosen for this transformation. The authors also investigated stereoisomer's energies, and rotational barriers by DFT calculation. Stereoisomer (*S,R*)-**50b** had the highest percentage (99.9%) compared to other stereoisomers.

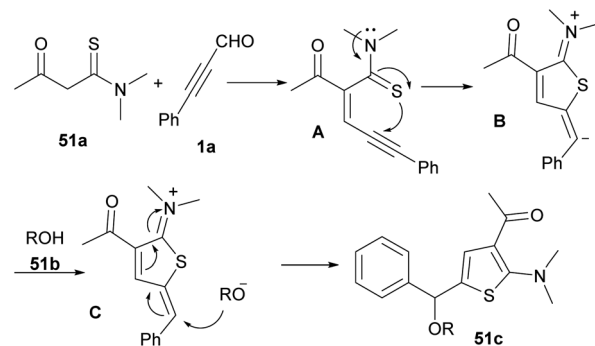
4. Synthesis of *S*-heterocyclic compounds

4.1. Synthesis of thiophenes

Thiophene derivatives are important heterocyclic compounds and exhibit various properties and applications. Compounds containing thiophene ring system show several pharmaceutical properties, including anticancer,⁸¹ anti-inflammatory,⁸² antihypertensive,⁸³ antimicrobial,⁸⁴ and anti-atherosclerotic properties.⁸⁵ In 2015 Luo and Deng and co-workers proposed an approach for the synthesis of functionalized 2-aminothiophene derivatives **51c** (Scheme 69).⁸⁶ They reported a simple, regioselective, and transition metal-free synthesis of multiubstituted 2-



Scheme 69 Aldol condensation/intramolecular cyclization/conjugate addition reaction of 2-ynals and thioamides.



Scheme 70 Plausible mechanism for aldol condensation/intramolecular cyclization/conjugate addition reaction of 2-ynals and thioamides.

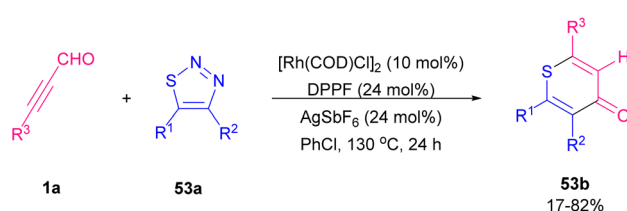
aminothiophenes **51c** through a one-pot aldol condensation/intramolecular cyclization/conjugate addition cascade reaction of propargyl aldehydes **1a**, thioamides **51a**, and alcohols **51b** in high yields. A possible mechanism for this transformation is depicted in Scheme 70. Aldol condensation of **1a** with **51a** produced the key intermediate **A**, which was exposed to spontaneous intramolecular cyclization and followed protonation to give intermediate **C**. The conjugate addition of alcohols **51b** to intermediate **C** yielded the 2-aminothienyl ethers **51c**.

4.2. Synthesis of thiopyrans

In 2001, Ishino *et al.* developed a procedure for selective ring formation *via* intermolecular cycloaddition of α,β -unsaturated aldehydes **1a**, and **44c** and arenethiols **52a** in the presence of a catalytic quantity of *p*-toluenesulfonic acid (*p*-TsOH) to afford the corresponding 4-thioaryl-2,3,4-trihydro-1-benzothiopyrans

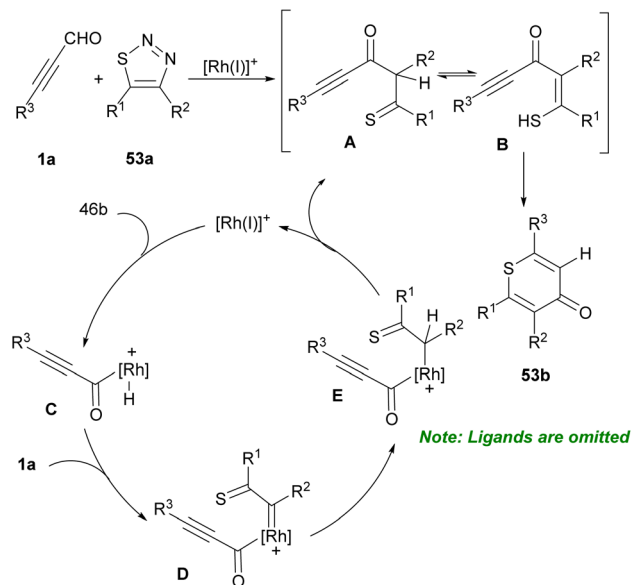


Scheme 71 Intermolecular cycloaddition of α,β -unsaturated aldehydes with arenethiols.



Scheme 72 Rh-catalyzed reaction of 1,2,3-thiadiazoles with alkynyl aldehydes.





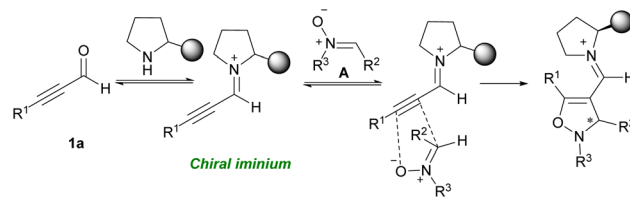
Scheme 73 Tentative mechanism for Rh-catalyzed reaction of 1,2,3-thiodiazoles and alkynyl aldehydes.

52b, and **52c** in good to excellent product yields (Scheme 71).⁸⁷ This method is characterized by the employment of a catalytic amount of acids, an easy and convenient reaction procedure, mild conditions, and selective ring formation by readily available substrates, and good product yields. In 2019, Xu and Yang *et al.* found that 1,1-hydroacylation of thioacyl carbenes derived from 1,2,3-thiodiazoles **53a** with alkynyl aldehydes **1a** generated thioketones that can undergo 6-*endo*-dig cyclization to deliver [3 + 3] transannulation 4*H*-thiopyran-4-one products **53b** as important subunits in a variety of advantageous compounds (Scheme 72).⁸⁸ Similar transformations of alkenyl aldehydes also occurred to yield valuable products. In a tentative mechanism for 1,1-hydroacylation, oxidative addition of Rh(i) into alkynyl aldehydes **1a** led to rhodium hydrides **C**, which further decomposed thiodiazoles **53a** to obtain carbene complexes **D**. Migratory insertion of hydride into carbenic center formed **E**, followed by reductive elimination to regenerate catalysts and gave 1,1-hydroacylation compounds **53b** (Scheme 73).

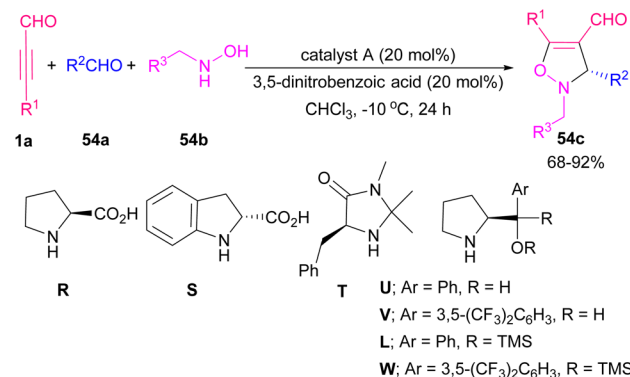
5. Synthesis of O,N-heterocyclic compounds

5.1. Synthesis of isoxazolines, isoxazoles, and oxazoles

An iminium activation pathway was described for enantioselective dipolar [3 + 2] cycloaddition between aryl/alkyl alkynyl aldehydes **1a** and *in situ* generated nitrones **A** toward chiral 4-isoxazolines **54c** (up to 96% ee) (Scheme 74).⁸⁹ A series of organocatalysts such as prolines **R**, and **S**, imidazolidine **T**, prolinols **U**, and **V**, and related ethers **L**, and **W** were utilized for this procedure. Among them, *L*- α,α -bis(3,5-ditrifluoromethylphenyl)prolinol **W** catalyzed the reaction in the presence of 3,5-dinitrobenzoic acid as an additive (Scheme 75). Meantime, the employment of pyrrolidines as the efficient catalysts to make



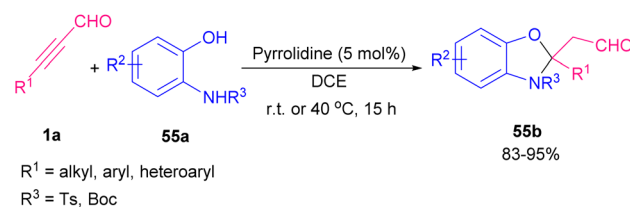
Scheme 74 An iminium activation pathway for constructing chiral 4-isoxazolines.



Scheme 75 Use of organocatalyst for constructing chiral 4-isoxazolines.

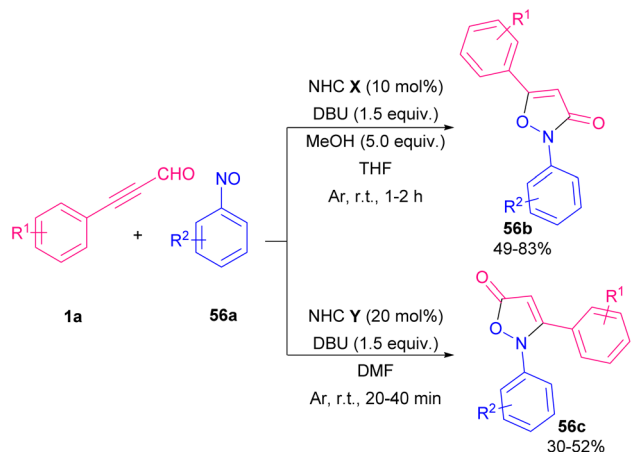
isoxazoline rings from aryl/alkyl alkynyl aldehydes and aryl nitrones was reported by Aleman and Fraile's research group.⁹⁰ Pyrrolidine iminium activation procedure also used by Wang *et al.* for synthesizing biologically important benzoxazole **55b** compounds from [4 + 1] annulation between 2-aminophenols **55a** and alkyl/aryl alkynyl aldehydes **1a** (Scheme 76).⁹¹

In 2013, She's research group developed a formal [3 + 2] annulation of aryl alkynyl aldehydes **1a** and nitrosobenzenes **56a** *via* C–O and C–N bond formation in the presence of NHC catalysis system (Scheme 77).⁹² A variety of 2,3-disubstituted isoxazol-5(2*H*)-ones **56b** and 2,5-disubstituted isoxazol-3(2*H*)-ones **56c** were prepared by this method. A mechanism for the regioselective Umpolung is illustrated in Scheme 78. In the presence of NHCs, intermediate **H** is generated. In cycle I, when catalyst **B** was used, acyl anion **E** formed, which reacted with **56a** to form **F**. After releasing the NHC catalyst, product **56b** was achieved. While in cycle II, the reaction of **D** with **56a** resulted in the formation of **C** followed by a cyclization process to give product **56c**.

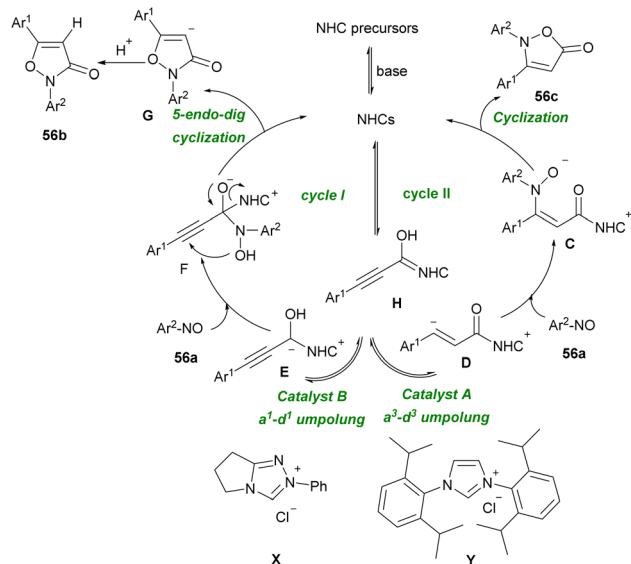


Scheme 76 Amine-catalyzed [4 + 1] annulation for synthesizing benzoxazoles.





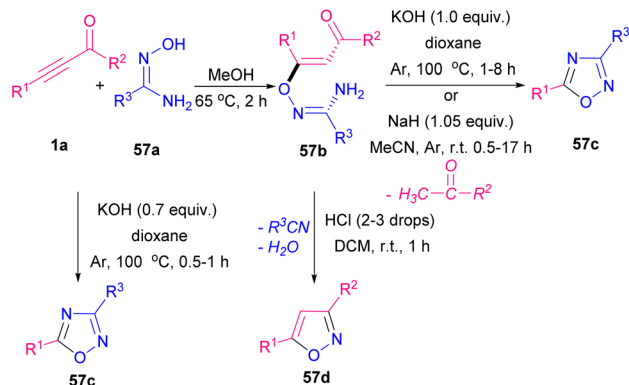
Scheme 77 NHC-catalyzed [3 + 2] annulation of aryl alkynyl aldehydes with nitrosobenzenes.



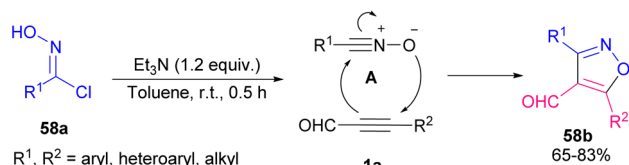
Scheme 78 Proposed mechanism for NHC-catalyzed [3 + 2] annulation of aryl alkynyl aldehydes with nitrosobenzenes.

A new strategy in metal-free constructing 1,2,4-oxadiazoles 57c and isoxazoles 57d was established by Zora and Kivrak (Scheme 79).⁹³ The protocol employed amidoximes 57a and α,β -alkynic aldehydes 1a, or ketones as the starting materials to form conjugate addition products in the first step. Then, in the presence of KOH or NaH, 1,2,4-oxadiazoles 57c and isoxazoles 57d were obtained *via* a ketone group elimination. It is found that 1,2,4-oxadiazoles 57c also could synthesize using a base in one step. The transformation also proceeded by the addition of 2–3 drops of HCl, which after nitrile and water release, isoxazole rings were furnished.

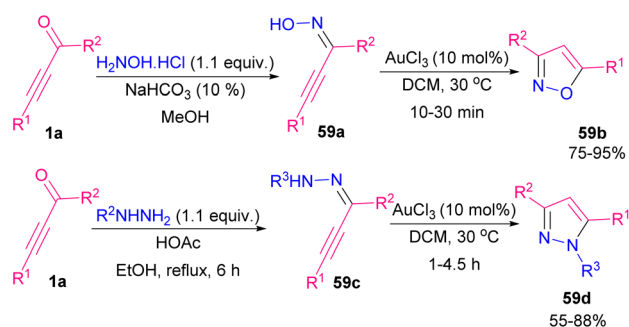
Reactive nitrile oxides **A** can be generated *in situ* from chloro-oximes 58a to participate in [1,3]-dipolar cycloaddition with α,β -acetylenic aldehydes 1a toward 1,2-oxazols 58b. Both alkynyl aldehydes 1a and oximes 58a bearing aryl, heteroaryl and alkyl groups were compatible in this transformation (Scheme 80).⁹⁴



Scheme 79 Construction of 1,2,4-oxadiazoles and isoxazoles.

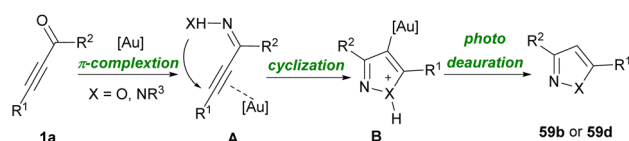


Scheme 80 Construction of 1,2,4-oxadiazoles and isoxazoles.



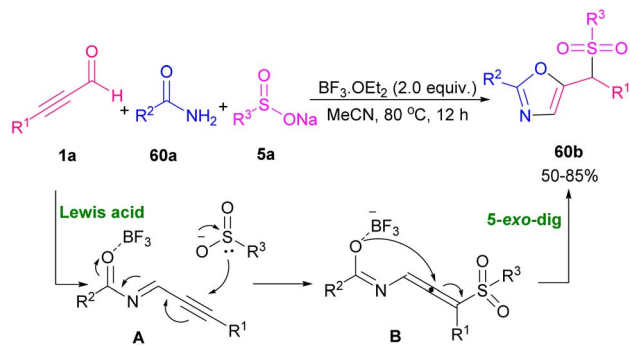
Scheme 81 Preparation of isoxazoles and pyrazoles.

Preparation and cytotoxic evaluation of isoxazoles 59b and pyrazoles 59d were performed by Praveen *et al.* (Scheme 81).⁹⁵ In this regard, they investigated the capability of AuCl₃ in the cycloisomerization of α,β -acetylenic oximes 59a and α,β -acetylenic hydrazones 59c. The reaction initiated by the activation of alkyne 1a to generate π -complex **A**. Meantime, an intramolecular nucleophilic attack of OH or NHR³ resulted in a cyclization process, in which proto-deauration of **B** led to producing 59b or 59d (Scheme 82). They also evaluated the cytotoxic potential of selected products toward cancer cells. Very

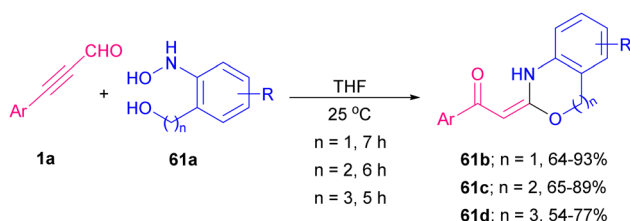


Scheme 82 Possible mechanism for preparing isoxazoles and pyrazoles.





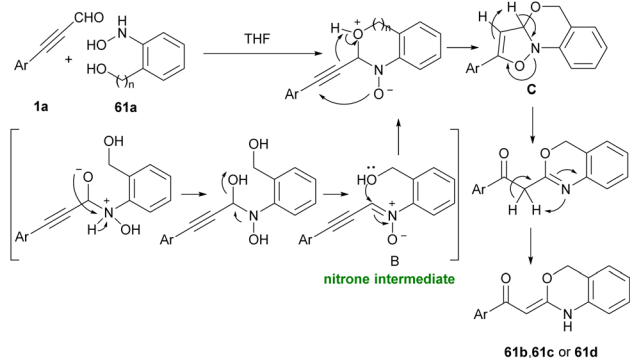
Scheme 83 Lewis acid-promoted synthesis of oxazole derivatives.



Scheme 84 Synthesis of benzo-oxazine, benzo-oxazepine and benzo-oxazocine.

recently, another interesting type of Lewis acid catalyzed the construction of 2,5-disubstituted oxazoles **60b** was reported by Zhu and Cao *et al.* (Scheme 83).⁹⁶ Broad substrate scope including propargyl aldehydes **1a**, aromatic amides **60a**, and aryl/alkyl-substituted sodium sulfonates **5a** worked well in this metal-free cyclization reaction. The reaction proceeded *via* the formation of intermediate **A**, the addition of **5a** into **A**, and 5-*exo-dig* cyclization.

Very recently, the synthesis of a series of six, seven, and eight-membered *N,O*-heterocyclic compounds, including benzo-oxazine **61b**, benzo-oxazepine **61c** and benzo-oxazocine **61d** from easily available ynals **1a** and 2-(hydroxyamino)phenyl alcohols **61a** was explained by Dateer and co-workers (Scheme 84).⁹⁷ Synthetic utility of benzo-oxazine was demonstrated by gram-scale synthesis and further conversion into the pyrazole



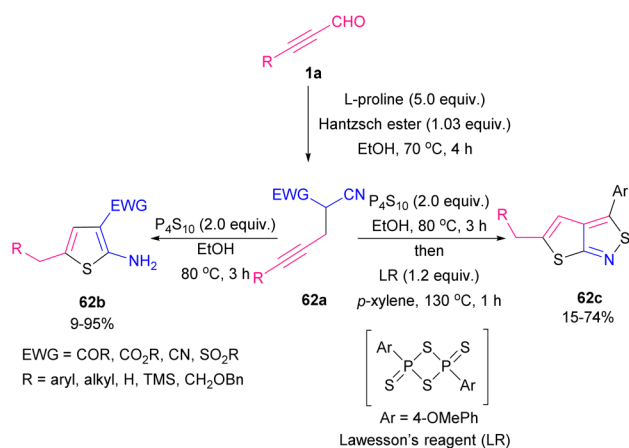
Scheme 85 Possible mechanism for synthesis of benzo-oxazine, benzo-oxazepine and benzo-oxazocine.

derivative. A mechanism for this catalyst and additive-free method is illustrated in Scheme 85. The reaction commenced with the interaction of ynals **1a** and 2-(hydroxyamino)phenyl alcohol **61a** to generate nitron intermediate **A**. Afterward, an intramolecular nucleophilic attack of OH on electron-deficient imine carbon and oxygen atom transfer to alkyne furnished dihydrobenzo[*d*]isoxazol intermediate **B**. Finally, N–O bond cleavage, and rearrangement led to benzo-oxazine **61b**, **61c**, or **61d**.

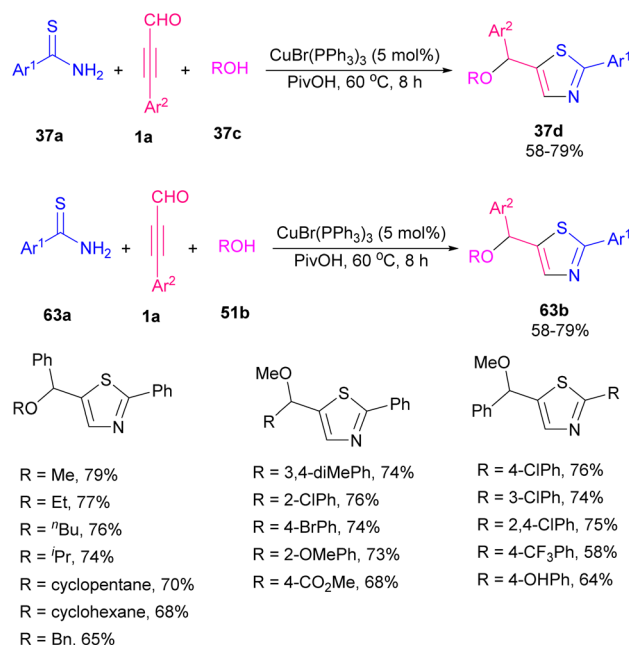
6. Synthesis of S, N-heterocyclic compounds

6.1. Synthesis of isothiazoles

An unprecedented temperature-controlled thiation of α -cyano- β -alkynyl carbonyl compounds **62a** was explored by Shia and



Scheme 86 Synthesis of 2-aminothiophenes and thieno[2,3-c]isothiazoles.



Scheme 87 Cu-catalyzed construction of functionalized thiazoles.



Wu *et al.* (Scheme 86).⁹⁸ For this purpose, they examined phosphorus decasulfide and Lawesson's reagent as the sulfur-transferring reagents. In the case of 2-aminothiophene products **62b**, the temperature was set at 80 °C in EtOH as the reaction solvent. When the temperature was enhanced to 130 °C, with the addition of *p*-xylene as the replaced solvent, thieno [2,3-*c*]isothiazole derivatives **62c** were formed. It seems that the LR was responsible for the oxidation in the current procedure. Also, other thiation reagents like sodium sulfide and octasulfur did not effective. For producing functionalized thiazoles **63b** via Cu-catalyzed C–N, C–O, and C–S bond formation, thioamides **63a**, aryl alkynyl aldehydes **1a**, and alcohols **51b** were used (Scheme 87).⁹⁹ Various aromatic and heteroaromatic groups in substrates tolerated well in such transformation and cyclized products achieved with good regioselectivity.

7. Conclusions

This comprehensive review has described the progress in synthesis processes to access N-, O-, and S-heterocycles from readily accessible alkynyl aldehydes by C–N/C–O/C–S/C–C bond formation. In this regard, a variety of transition metal-catalyzed, metal-free-promoted, and visible-light-mediated syntheses are highlighted in this concept. Challenging mechanistic insights as well as the scope of some substrate ranges showed. It is noted that NHC-catalyzed methodologies presented extensive potential applications compared to metal-catalyzed strategies that led to the green synthetic routes for constructing a vast number of N-, O-, and S-heterocycles. In our opinion, the design, and use of more simple NHC organocatalysts for alkynyl aldehyde reactions could strongly expand the scope of these synthetic applications. Despite recent progress, due to the importance of N-, O-, and S-heterocyclic frameworks in pharmaceutical and material chemistry, further developing new environmentally friendly and high atom-economic systems involving commercially available alkynyl aldehyde motifs is still required in this area. Also, it seems study on S-heterocyclic compounds from alkynyl aldehydes remain less explored in comparison to N-heterocycles. We hope that current review will open opportunities for medicinal and organic chemists to work in the field of N-, O-, and S-heterocycles synthesis.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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