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# Recent advances in the application of β-ketonitriles as multifunctional intermediates in organic chemistry

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This review discusses the diverse applications of β-ketonitriles in organic synthesis, highlighting protocols that generate various compounds, including cyclic hydrocarbons, aromatic compounds, heterocycles, spirocycles, and fused heterocycles. These compounds serve as valuable building blocks for biologically active scaffolds like chromenes, quinolines, and natural products. It provides an overview of 69 research articles published from 2014 to 2023, focusing on reactions involving benzoyl acetonitrile derivatives and other β-ketonitriles. The methodologies include cascade, domino, and sequential reactions facilitated by different catalysts, showcasing the versatility of β-ketonitriles in organic chemistry.



## 1. Introduction

β-Ketonitriles are used as soluble molecules in water and are used in the synthesis of organic compounds, pharmacology, pure chemistry, and applied chemistry.[1]

These compounds are used as precursors for the production of anti-cancer,[2] anti-inflammatory,[3] and antimalarial drugs,[4] and anti-HIV agents.[5] Additionally, β-ketonitriles have been studied extensively in medicinal chemistry due to their potential therapeutic applications. For example, some derivatives have shown promising activity against cancer cells, while others have been studied for their potential as anti-inflammatory agents or as inhibitors of enzymes involved in various disease pathways.[6] Ongoing research in this area may lead to the development of new drugs with improved efficacy and reduced side effects. Various methods have been presented for synthesizing β-ketonitriles.[7] Kiyokawa *et al.* completely summarized the synthesis of these valuable compounds in a review.[8] One well-known β-ketonitrile is benzoylacetonitrile, utilized as a starting material for synthesizing various heterocyclic compounds. It can undergo different reactions to produce various types of heterocycles such as pyridines,[9] pyrimidines,[10] and pyrazoles.[11] One common reaction is the condensation of benzoylacetonitrile with aldehydes or ketones to form pyridine. This reaction is known as the Hantzsch synthesis and involves the formation of a dihydropyridine intermediate, which is then oxidized to the pyridine product.[9] Benzoylacetonitrile can also undergo cyclization reactions with different reagents to form various heterocyclic compounds. For example, a reaction with hydrazine derivatives can lead to the formation of pyrazoles,[11] while a reaction with urea or thiourea can lead to the formation of pyrimidines.[10] In addition, benzoylacetonitrile can be used as a starting material for the synthesis of benzonitriles.[12] Overall, benzoylacetonitrile is a versatile starting material for synthesizing a wide range of heterocyclic compounds with potential applications in pharmaceuticals and agrochemicals.[13] In 2013, Bakr F. and colleagues successfully synthesized various heterocycles such as pyran, pyridazine, pyrimidine, pyrazine, and triazine compounds using benzoylacetonitrile as a precursor.[14] They conducted a review of the use of benzoyl acetonitrile from 1985 to 2013. In the last decade, many efforts have been made in this field, leading to numerous interesting results. Benzoylacetonitrile was used as a precursor in several multicomponent and one-pot reactions that led to the construction of functionalized cyclic molecules. In addition to some common carbocyclic and heterocyclic compounds, other unusual compounds, such as propellanes, carbazoles, quinoxalines, benzofuropyrroles, N-fused bicyclic systems, and other polycyclic heterocycles, were also reported. To provide a better understanding of the topic, this review is mainly organized according to different product structures.

## 2. Acyclic compounds

### 2.1. α-Ketoesters

α-Ketoesters are valuable in the synthesis of drugs and organic compounds because they are good precursors for α-hydroxy esters, chiral compounds, and heterocycles. Due to their versatile applications, several methods have been developed for their synthesis.[15] In this review, we will discuss two optimized methods that use β-ketonitriles. Xie and their colleagues report a facile and straightforward approach to obtaining α-ketoesters and α-ketoamides **3** from β-ketonitriles **1**, phenyliodine(III) diacetate (PIDA) **2**, and alcohols and amines under refluxing conditions (Scheme 1).[16]

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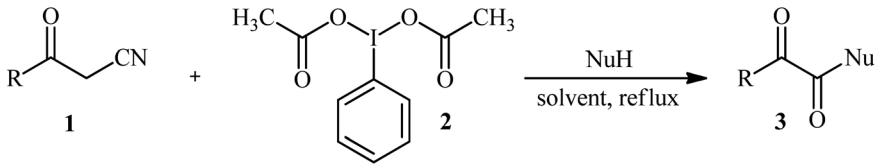
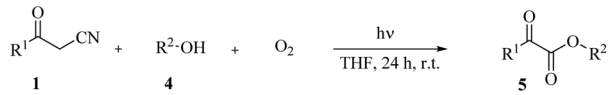


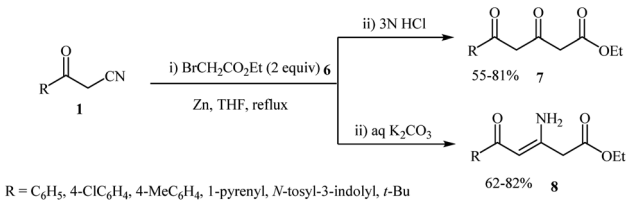

R = Ph, 4-$ClC_6H_4$, 2-$MeC_6H_4$, 3-$MeC_6H_4$, 4-$MeC_6H_4$, 4-$FC_6H_4$, 4-$IC_6H_4$, naphthyl, 2-thienyl
NuH = EtOH, MeOH, $PhCH_2OH$, *t*-BuOH, *n*-$BuNH_2$, *N*-Methyl, piperazine
Solvent = EtOH, MeOH, $CH_2Cl_2$

Scheme 1 Synthesis of α-ketoesters **3** with phenyliodine(III) diacetate.




$R^1$ = $C_6H_5$, 4-$ClC_6H_4$, 4-$MeC_6H_4$. 3-$MeC_6H_4$, 4-$FC_6H_4$, 4-$MeOC_6H_4$
$R^2$ = Me, Et, isopropyl, *tert*-butyl, benzyl

Scheme 2 Reactions of β-ketonitriles and alcohols for constructing α-ketoesters **5**.




R = $C_6H_5$, 4-$ClC_6H_4$, 4-$MeC_6H_4$, 1-pyrenyl, *N*-tosyl-3-indolyl, *t*-Bu

Scheme 3 Synthesis of 3,5-dioxopentanoates **7** (3,5-diketo esters) and 3-amino-5-oxopent-3-enoates **8**.

The following year, Cheng Guo *et al.* reported a new method for esterification that does not require transition metals or photocatalysts. This process involves using visible light to facilitate the decyanation of aryl ketonitriles **1** in the presence of dioxygen and alcohols **4** at room temperature, forming α-ketoesters **5** (53–93% yield). This reaction enables C–H bond functionalization, C–C σ-bond cleavage, and dioxygen activation to be achieved in a single step, cleavage, and dioxygen activation to be achieved in a single step (Scheme 2).[17]

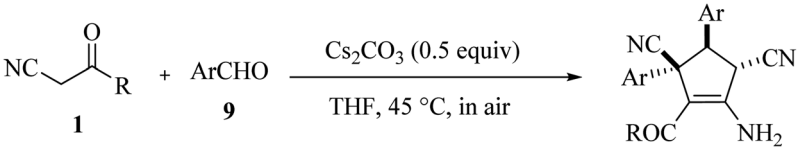
### 2.2. 3,5-Diketoesters

In 2016, Rao and colleagues successfully developed a simple and convenient method for synthesizing various 3,5-dioxopentanoates **7** (3,5-diketo esters) and 3-amino-5-oxopent-3-enoates **8**. This is achieved through a zinc-mediated condensation of β-ketonitriles **1** (also known as α-cyano ketones) with ethyl bromoacetate **6**. By using an acidic workup, the reaction yields 3,5-dioxopentanoates (55–81%), while a basic workup yields ethyl (3*Z*)-3-amino-5-oxo-5-pent-3-enoates (62–82%). This method allows for direct and regioselective synthesis of 3,5-dioxopentanoates or the corresponding enamines (Scheme 3).[18] Further investigation of this method has shown that the keto and nitrile functional groups are in a geminal relationship, leading to enolization and the possibility of the Blaise process.

## 3. Carbocyclic compounds

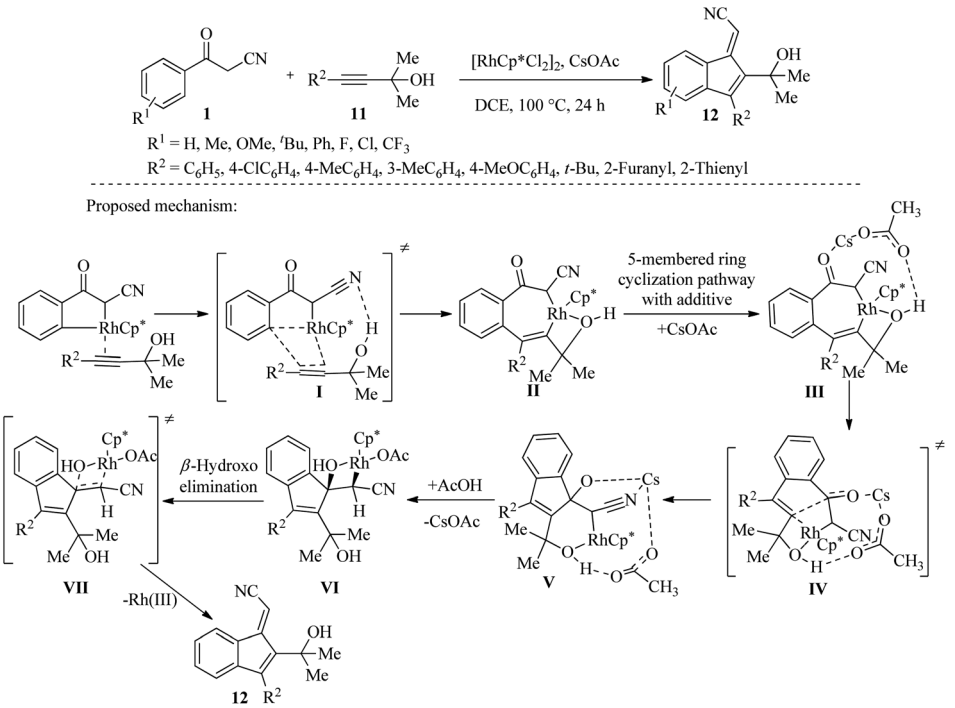
### 3.1. Aliphatic carboxylic compounds

Gao *et al.* have developed a green cascade approach for the preparation of a variety of diastereoselective polysubstituted cyclopentene derivatives through metal-free oxidative [2 + 1 + 1 + 1] annulation of aldehydes **9** and β-ketonitriles **1**. According to their research, different groups at the para-position of the aromatic aldehyde ring were better tolerated than the substituents at the *meta*-position, resulting in the corresponding para-substituted diphenylcyclopentene products in higher yields compared to the *meta*-substituted analogs. To confirm the application of this method, they selected certain substrates such as 2-naphthaldehyde, cyclohexane-carboxaldehyde, and 3-thiophenecarboxaldehyde instead of the aromatic aldehyde ring. Except for cyclohexane, other substitutions produced the desired product in moderate yields with high stereoselectivities (>95 : 5 dr). Other carbonyl acetonitrile substrates such as benzoyl acetonitrile, furanylacetonitrile, and phenyl nitrile acetate, also showed good reactivity in this reaction. The mechanism of this method involves a four-step cascade reaction




Ar = $C_6H_5$, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 4-$FC_6H_4$, 4-$ClC_6H_4$, 4-$BrC_6H_4$, naphthyl, thienyl
R = OMe, OEt, Ph, OPh, 3-$MeC_6H_4$, furyl.

Scheme 4 Synthesis of diastereoselective polysubstituted cyclopentenes **10**.



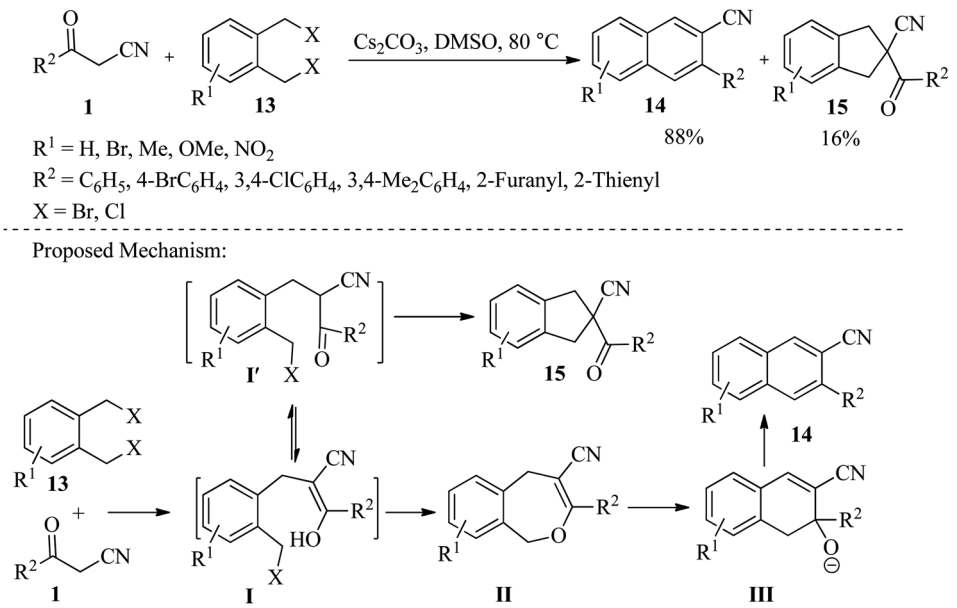

Scheme 5 Synthesis of functionalized benzofulvenes **12**.

involving air oxidation and Michael addition to obtain the final product (Scheme 4).[19]

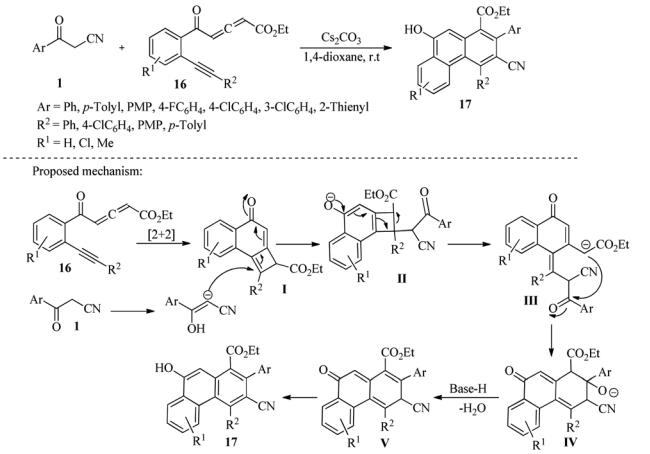
### 3.2. Aromatic carboxylic compounds

**3.2.1. Synthesis of functionalized benzofulvenes.** In 2019, Zhang and colleagues carried out a Rh(III)-catalyzed synthesis of functionalized benzofulvenes (40–83%) **12** using benzoyl acetonitrile **1** and propargyl alcohols **11**. The researchers used density functional theory (DFT) calculations to perform mechanical modeling and found that the hydroxyl group and CsOAc played crucial roles in mediating the 5-membered ring cyclization. These two components formed a thermodynamically stable Rh(III) intermediate that was essential for the reaction (Scheme 5).[20]

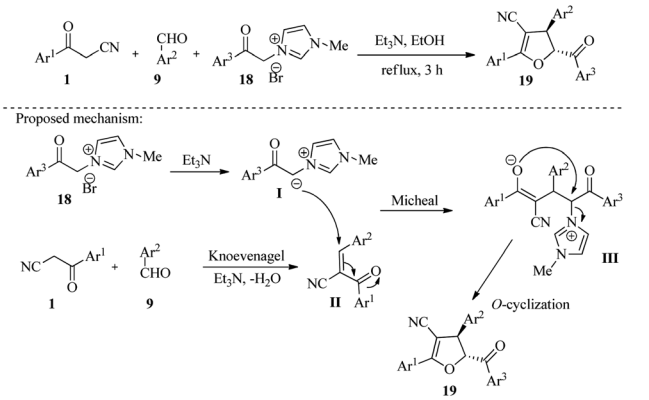
**3.2.2. Synthesis of substituted naphthalenes.** An efficient and practical method for synthesizing cyano-substituted




Scheme 6 Synthesis of substituted naphthalenes **14**.




Scheme 7 Synthesis of substituted phenanthrene-1-carboxylates **17**.




Scheme 8 Synthesis of multi-substituted 4,5-dihydrofurans **19**.

naphthalene derivatives is described by reactions of β-ketonitriles **1** and 1,2-bis(halomethyl)benzenes **13** including a rearrangement aromatization of benzo[*c*]oxepine in present $Cs_2CO_3$ in DMSO at 40 °C. The mechanism of this method involves the *C*-alkylation of compound **13** provided intermediate **I**, which appeared in two tautomeric forms: **I** and **I′**. The subsequent *O*-alkylation of enolic formed **I** and presented as the seven-membered ring **II**. Meanwhile, the competing *C*-alkylation yielded the five-membered ring **15** as a by-product. Finally, rearrangement of **I** followed by aromatization in the presence of $Cs_2CO_3$ afforded the desired naphthalene-based product **14** (Scheme 6).[21]

**3.2.3. Synthesis of substituted phenanthrene-1-carboxylates.** Shu-Jiang Tu *et al.* have developed a mild reaction condition to prepare a wide range of phenanthrene-1-carboxylates. The method involves a metal-free [2 + 2] cycloaddition/ring expansion sequence of yne-allenone esters **16** with β-keto nitriles **1**, using 1.0 equivalent of $Cs_2CO_3$ as a base promoter. The reaction is carried out in 1,4-dioxane at room temperature for 2.5 hours under air conditions. The final product, phenanthrene-1-carboxylates **17**, is obtained with a 56–97% yield (Scheme 7).[22]

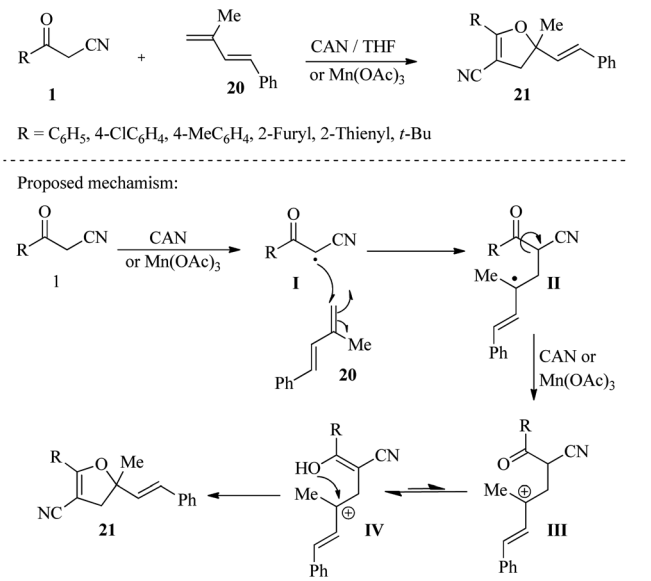
# 4. Heterocyclic compounds

## 4.1. Five-membered rings

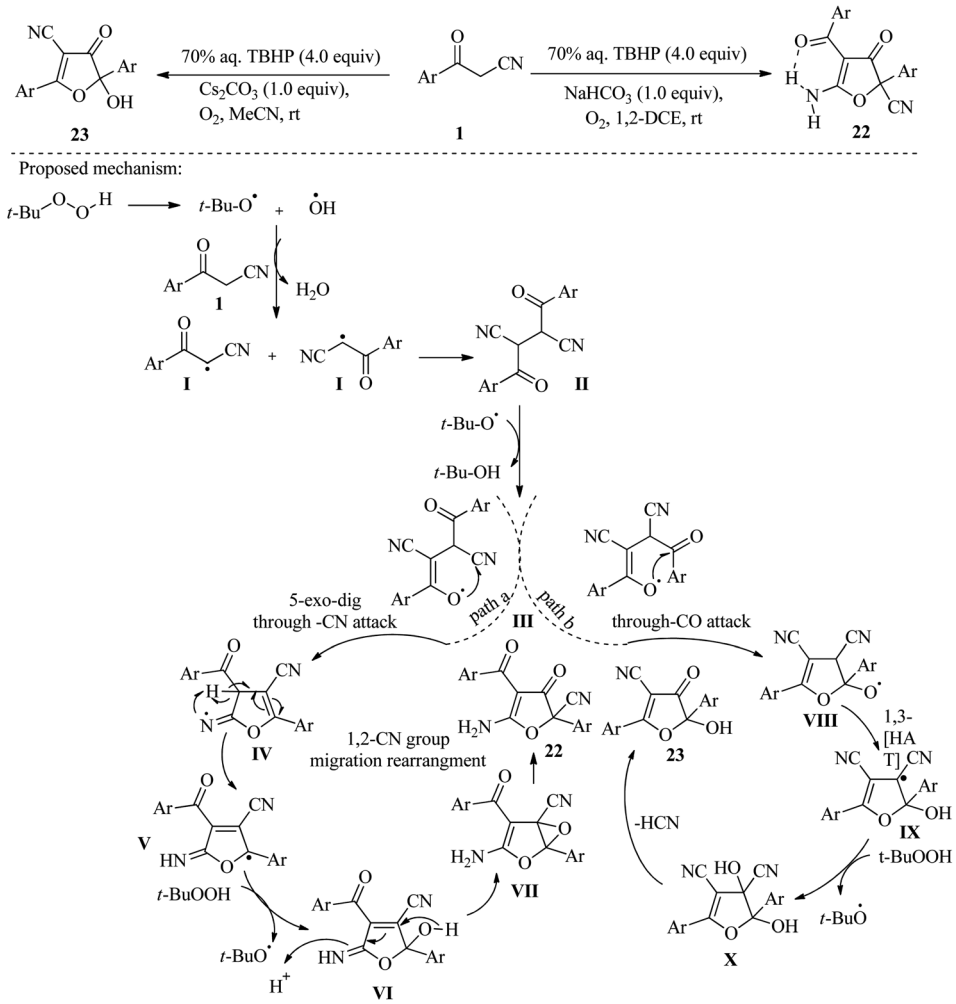
### 4.1.1. Five-membered rings with one hetero atom

*4.1.1.1. Polysubstituted furans, dihydrofurans, furo[2,3-b] furans.* In 2021, Sathiyamoorthi and colleagues developed a new chemical reaction that produces highly substituted dihydrofuran derivatives **19** in 90–97% yield. The reaction involves a one-pot three-component tandem strategy that uses aroyl acetonitriles **1**, aromatic aldehydes **9**, and 1-methyl-3-(2-oxo-2-phenylethyl)-1*H*-imidazol-3-ium bromides **18**. The reaction mechanism follows a convergence condensation-Michael addition-*O*-cyclization process, which results in the formation of three new bonds (two C–C and one C–O) to produce the final product (Scheme 8).[23]

In a different study, Hocaoglu and colleagues utilized the radical addition of β-ketonitriles **1** to conjugated dienes **20** to produce 5-ethenyl-4,5-dihydrofuran-3-carbonitriles **21** in yields ranging from low to good. In this method, $Mn(OAc)_3$ and CAN were used as radical oxidants in the reactions. Based on these results, the authors concluded that $Mn(OAc)_3$ is effective in reactions of 3-oxopropanenitriles with dienes that contain a thiophen-2-yl group. Conversely, CAN is more efficient with dienes that do not contain thiophen-2-yl (Scheme 9).[24] Wang and their team have reported on a solvent/base-switchable platform that allows for the selective conversion of β-ketonitriles **1** to multi-substituted 2,3-dihydrofuran-2-carbonitriles **22** and 4,5-dihydrofuran-3-carbonitriles **23** without the use of metals. By simply changing the solvent and reaction base, the same oxidant (TBHP) can produce the desired products through two distinct pathways. Through mechanistic exploration, this method has shown that the reaction of β-ketonitriles under



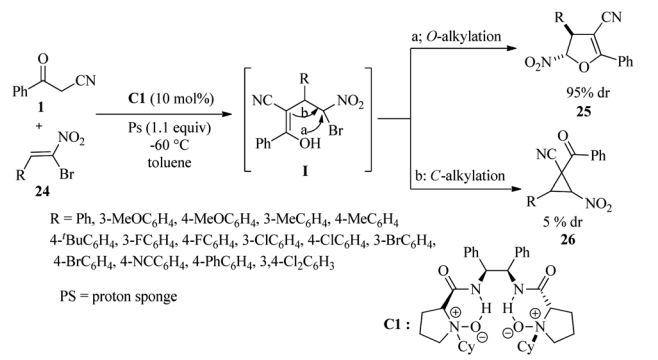

Scheme 9 Synthesis of 5-ethenyl-4,5-dihydrofuran-3-carbonitriles **21**.



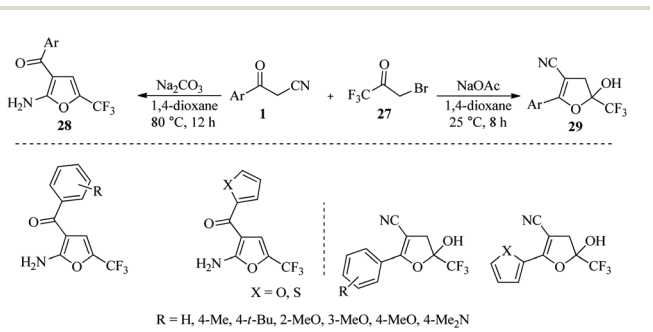

Scheme 10 Synthesis of multi-substituted 2,3-dihydrofuran-2-carbonitriles **22** and 4,5-dihydrofuran-3-carbonitriles **23**.

non-polar and polar solvents leads to unexpected rearrangement of the –CN group migration and hydroxylation, respectively, resulting in different products of hydrofurans (Scheme 10).[25]

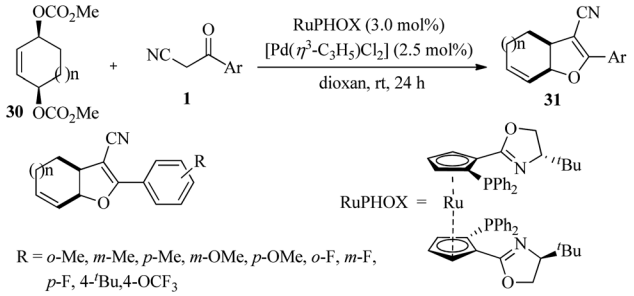
In 2016, Feng and coworkers obtained regio-diastereo and enantioselective 2,3-dihydro-furans **25** in 93–92% yield from the reaction of substituted β-ketonitriles **1** with bromonitrostyrenes **24** in toluene solvent at 60 °C for 72 h by using achiral *N*,*N*′-dioxide as organocatalyst. In the mechanical exploration of this reaction, bromonitrostyrenes are first added to substituted β-ketonitrile from Michael's process (C–C bond formation). Then, by adjusting the reaction conditions, the *O*-alkylation path is preferred to the *C*-alkylation path. With this strategy, the



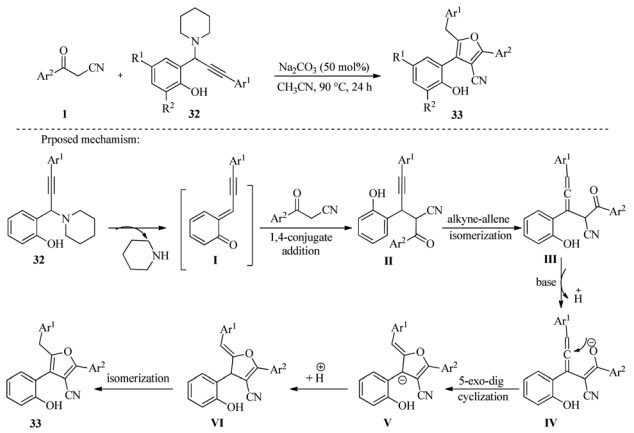

Scheme 11 Synthesis of 2,3-dihydrofurans **25**.



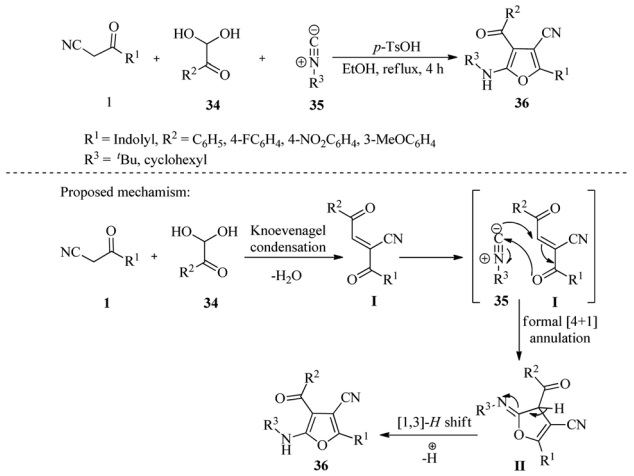

Scheme 12 Synthesis of trifluoromethylated furans **28** and dihydrofuranols **29**.




Scheme 13 Synthesis of bicyclic dihydrofurans **31**.



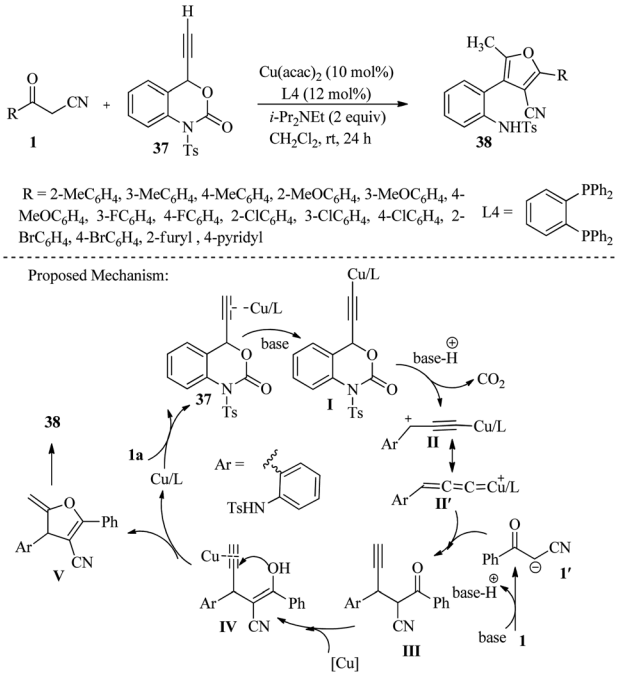

Scheme 14 Synthesis of polysubstituted furans **33**.




Scheme 15 Synthesized highly substituted furan-linked biheteroaryls **36**.

desired chiral 2,3-dihydrofurans **25** were obtained in up to 95% yield with 95 : 5 dr and 93% ee (Scheme 11).[26]

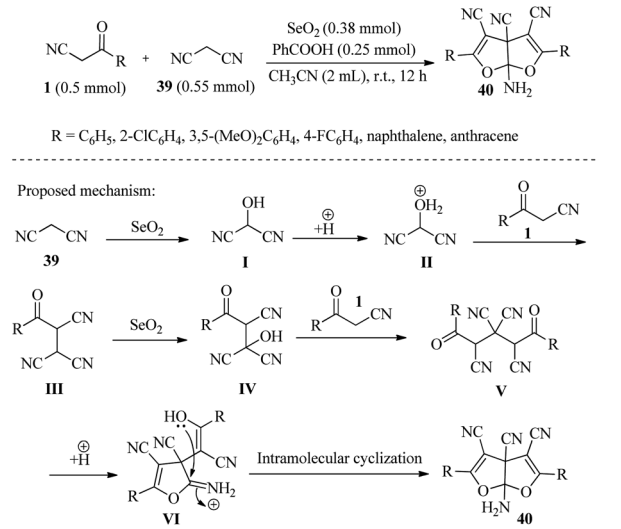
In a different research, Weng *et al.* discovered that by using two different bases, $Na_2CO_3$ and NaOAc, in the reaction of β-ketonitriles **1** with 3-bromo-1,1,1-trifluoroacetone **27**, it becomes possible to selectively synthesize two trifluoromethylated furans **28** and dihydrofuranols **29** without using any metals (Scheme 12).[27]



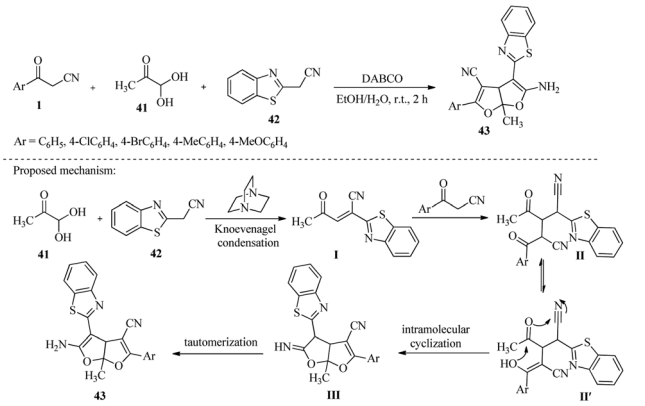

Scheme 16 Synthesis of tetrasubstituted furan **38**.

Zhang and colleagues have developed a new method for synthesizing chiral bicyclic dihydrofurans **31** with two vicinal carbon stereocenters. The method involves a Pd-catalyzed asymmetric allylic substitution cascade reaction of allylic dicarbonates **30** with β-ketonitriles **1**. The products are obtained in high yields and with up to 97% ee (Scheme 13).[28]

The following year, Xinwei He *et al.*, synthesized a series of polysubstituted furans **33** by the reactions of propargylamines **32** with β-ketonitriles **1** in the presence of $Na_2CO_3$ under heating at 90 °C for 24 h. Further exploration of the mechanism of this reaction indicates that it proceeds through




Scheme 17 Synthesis of substituted-furo[2,3-*b*]furans **40**.




Scheme 18 Synthesis of heterocyclic furo(2,3-*b*)furan derivatives **43**.

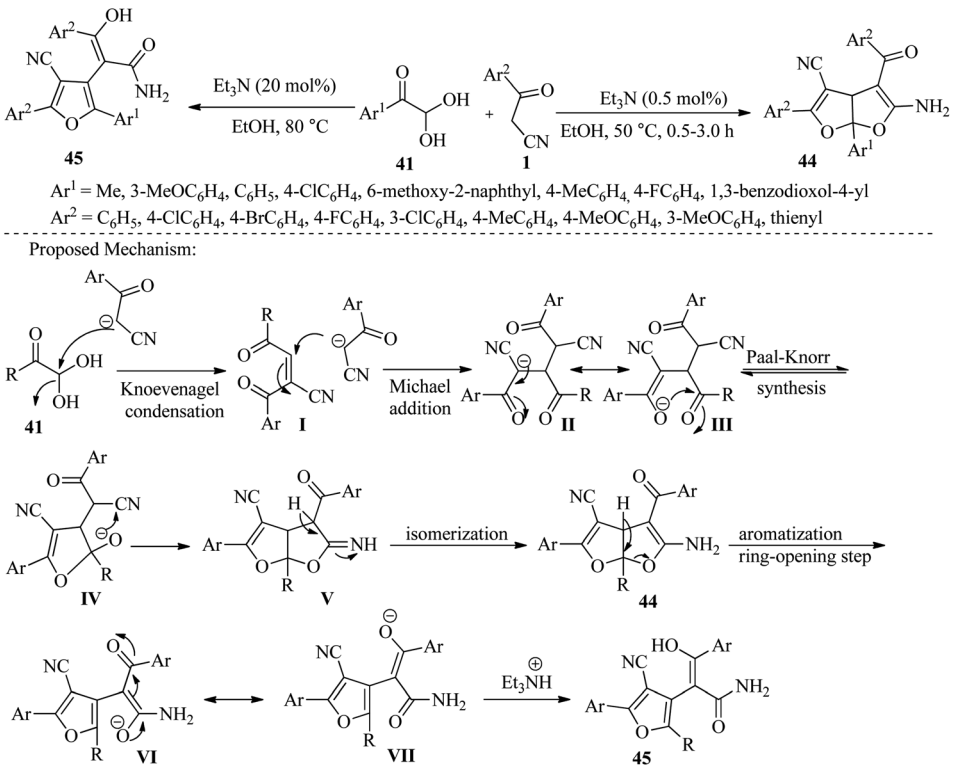
a sequence of steps. First, there is a 1,4-conjugate addition of β-ketonitriles **1** to propargylamines **32**, followed by a 5-*exo*-dig annulation/isomerization to form the fully substituted furans **33** (Scheme 14).[29]

In 2019, Jeong and coworkers synthesized highly substituted furan-linked biheteroaryls **36** by a three-component cascade reaction of aryl glyoxals **34**, isonitriles **35**, and aroyl or heteroaryl β-ketonitriles **1** in the presence of *p*-TsOH and EtOH under reflux condition for 4 h. The reaction sequence involves a Knoevenagel condensation of aryl glyoxals **34** with β-ketonitriles **1** followed by an isocyanide **35** insertion *via* formal [4 + 1] cycloaddition, and then a rapid [1,3]-*H* shift to afford novel biheterocycles with unique decorations (Scheme 15).[30]

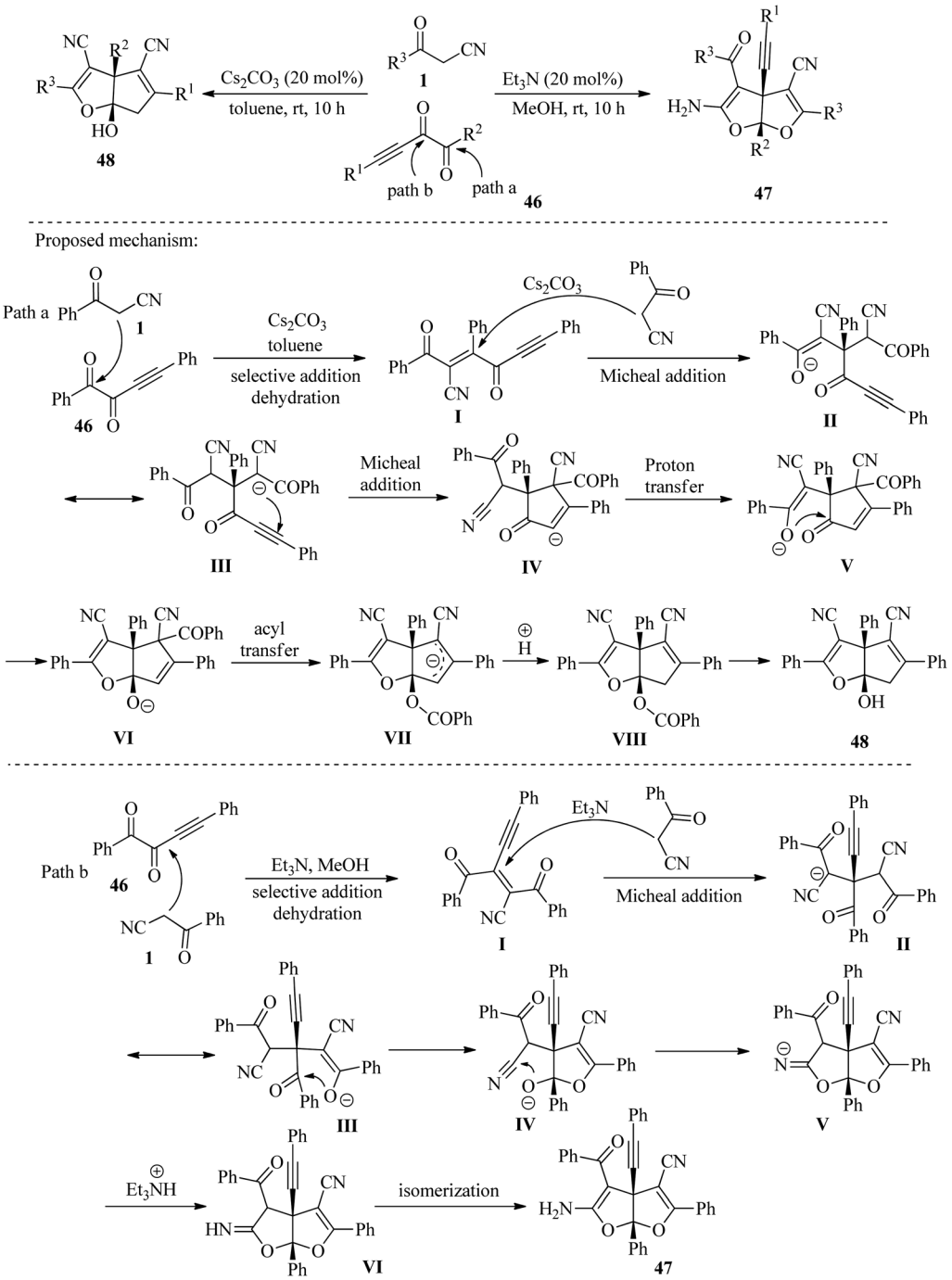
In 2020, Zhong and colleagues achieved moderate to high yields of tetrasubstituted furan derivatives **38** through [3 + 2] annulation of ethynyl benzoxazinanones **37** with β-ketonitriles **1**. This was done in the presence of $Cu(acac)_2$ as a catalyst and *i*-$Pr_2NEt$ in $CH_2Cl_2$ at room temperature over 24 hours. It was found that intermediate copper allenylidines acted as a C2 synthon during the cycloaddition reaction (Scheme 16).[31]

In 2021, Wan *et al.* reported the synthesis of substituted-furo [2,3-*b*]furans **40** by oxidizing malononitrile **39** to 2-hydroxy-malononitrile **I**, which can then react with β-ketonitriles **1** in $CH_3CN$ in the presence of 0.5 equiv. of benzoic acid at room temperature for 12 h. In the mechanistic exploration of this reaction, it was hypothesized that $SeO_2$ oxidizes malononitrile to 2-hydroxy-malononitrile, which can then react with β-ketonitriles **1** and during the two processes of Michael addition and intramolecular cyclization, it provides target compounds with 27–56% efficiency. The authors have highlighted that the synthesized compounds exhibit interesting photoluminescence properties in both solution and solid-state (Scheme 17).[32]

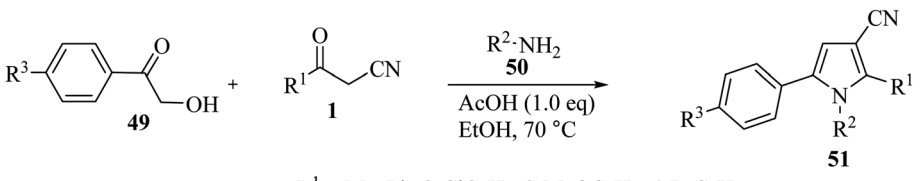
In a recent study, Gnanasambandam and his colleagues synthesized heterocyclic furo(2,3-*b*)furan derivatives **43** with an efficiency rate of 60–80%. They achieved this through a three-component reaction that involved methylglyoxal **41**, benzothiazole acetonitrile **42**, and β-ketonitriles **1**, with the use of DABCO (1,4-diazabicyclo[2.2.2]octane) as a base and $EtOH/H_2O$ solvent mixture at room temperature for two hours. The




Scheme 19 Synthesis of functionalized dihydrofuro[2,3-*b*]furans **44** and substituted phenyl furan 3-hydroxy-3-phenylacrylamides **45**.

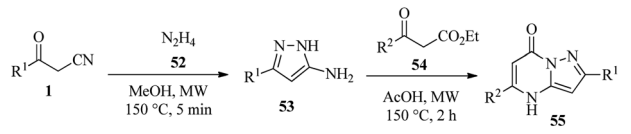



Scheme 20 Synthesis of dihydrofurofurans **47** and dihydrocyclopentafuranols **48**.



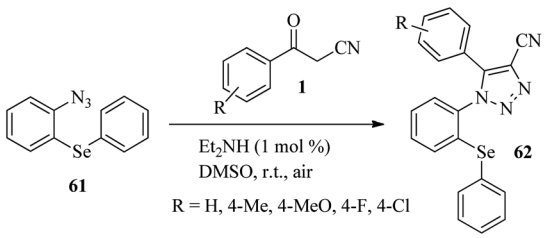

$R^1$ = Me, Ph, 2-$ClC_6H_4$, 3-$MeOC_6H_4$, 4-$BrC_6H_4$
$R^2$ = Alkyl, 2-Phenyl, propargyl, Ph
$R^3$ = H, Me, MeO, F, Cl

Scheme 21 Synthesis of functionalized 3-cyanopyrroles **51**.

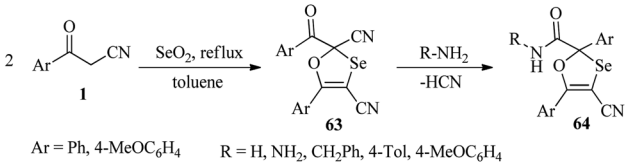



$R^1$ = $C_6H_5$, 3-$ClC_6H_4$, 4-$FC_6H_4$, 4-$MeC_6H_4$, 2-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-furyl, 2-thienyl, *t*-Bu, Me
$R^2$ = Me, $C_6H_5$, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 2,3,4,5-$F_4C_6H$, 3,5-$(F_3C)_2C_6H_4$

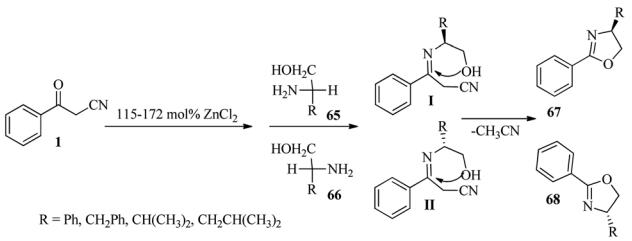
Scheme 22 Synthesis of 5-amino pyrazoles **53** and pyrazolo[1,5-*a*] pyrimidinones **55**.



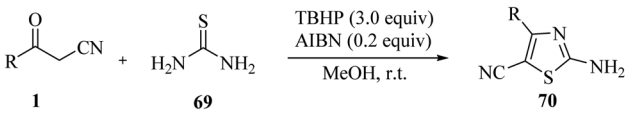

Scheme 24 Synthesis of phenylselanyl-1*H*-1,2,3-triazole-4-carbonitriles **62**.




Scheme 25 Synthesis of 1,3-oxaselenoles **63** and **64**.




Scheme 26 Synthesis of 2-oxazolines **67** and **68**.




Scheme 27 Synthesis of substituted 2-aminothioazoles **70**.

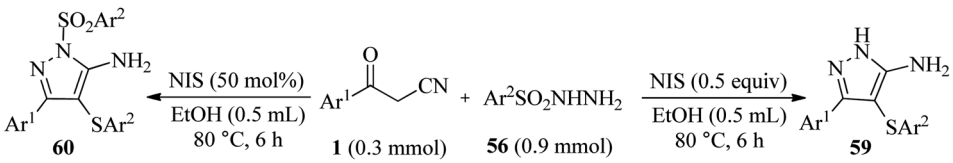
reaction involved Knoevenagel condensation, Michael addition, intramolecular cyclization, and tautomerization processes (Scheme 18).[33]

Followed by Jeong *et al.* have disclosed a highly efficient one-step protocol for constructing highly functionalized dihydrofuro[2,3-*b*]furans **44** and substituted phenyl furan 3-hydroxy-3-phenylacrylamides **45**. This is achieved through a three-component cascade reaction between aromatic or aliphatic glyoxals **41**, β-ketonitriles **1**, and two different equivalent amounts of triethylamine. The reaction can be performed in two different conditions: at room temperature or under reflux, with excellent yields obtained in both cases. The protocol involves a Knoevenagel and Michael adduct *via* Paal–Knorr cyclization with aromatic or aliphatic glyoxal and β-ketonitriles under mild heating conditions. The final product can be easily obtained through a simple filtration method (Scheme 19).[34]

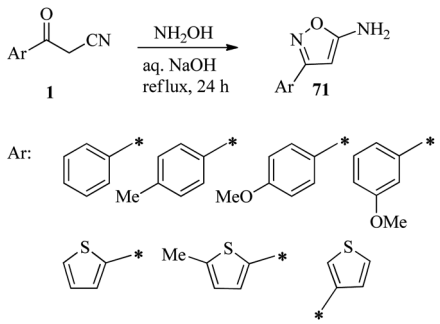
Also, Fang and their team have successfully developed a novel method to create a large variety of cyclic molecules, such as dihydrofurofurans **47** dihydrocyclopentafuranols **48** and, by performing regioselectivity-switchable reactions between alkynyl α-diketones **46** and β-ketonitriles **1**. This approach provides a platform for generating a broad range of structurally diverse heterocycles with new dihydrofuran-cyclopentenone skeletons and dihydrofurofurans.

The study also revealed that base and solvent play a critical role in modulating the regioselectivity of this reaction (Scheme 20).[35]

*4.1.1.2. Synthesis of cyanopyrroles.* In 2022, Moussa and their colleagues discovered a simple and efficient three-component reaction involving α-hydroxyketones **49**, β-ketonitriles **1**, and primary amines **50**. The result of the reaction is a selective production of densely functionalized 3-cyanopyrroles **51** with isolated yields ranging from 55–90%. The reaction has a wide substrate scope and can be carried out under mild reaction conditions. AcOH is used as a catalyst and the reaction is performed using EtOH at 70 °C for 3 hours. The mechanism of this reaction can be explained based on three processes: A, B, and C. Additionally, the high atomic efficiency of this reaction suggests that the only molecule lost during the process is water (Scheme 21).[36]



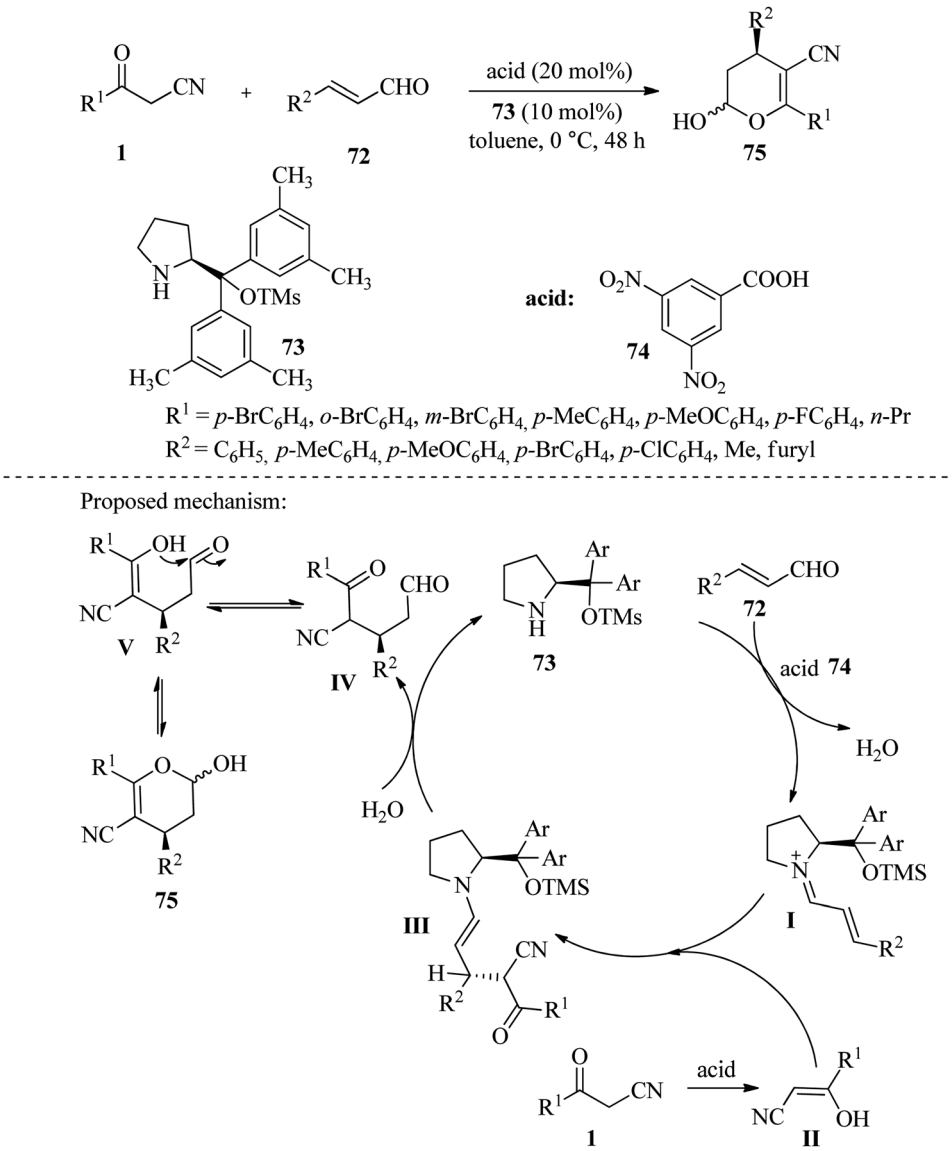

Scheme 23 Synthesis of 3-aryl-4-(arylthio)-1*H*-pyrazol-5-amine derivatives **59** and 3-phenyl-1-(phenylsulfonyl)-4-(phenylthio)-1*H*-pyrazol-5-amines **60**.



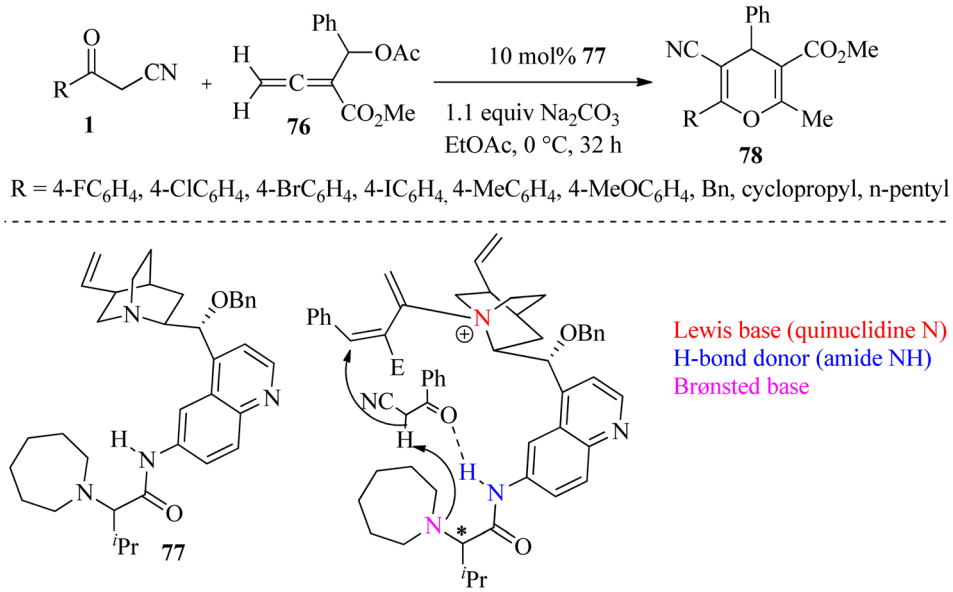

Scheme 28 Synthesis of substituted isoxazole-5-amines **71**.

#### 4.1.2. Five-membered rings with two hetero atom

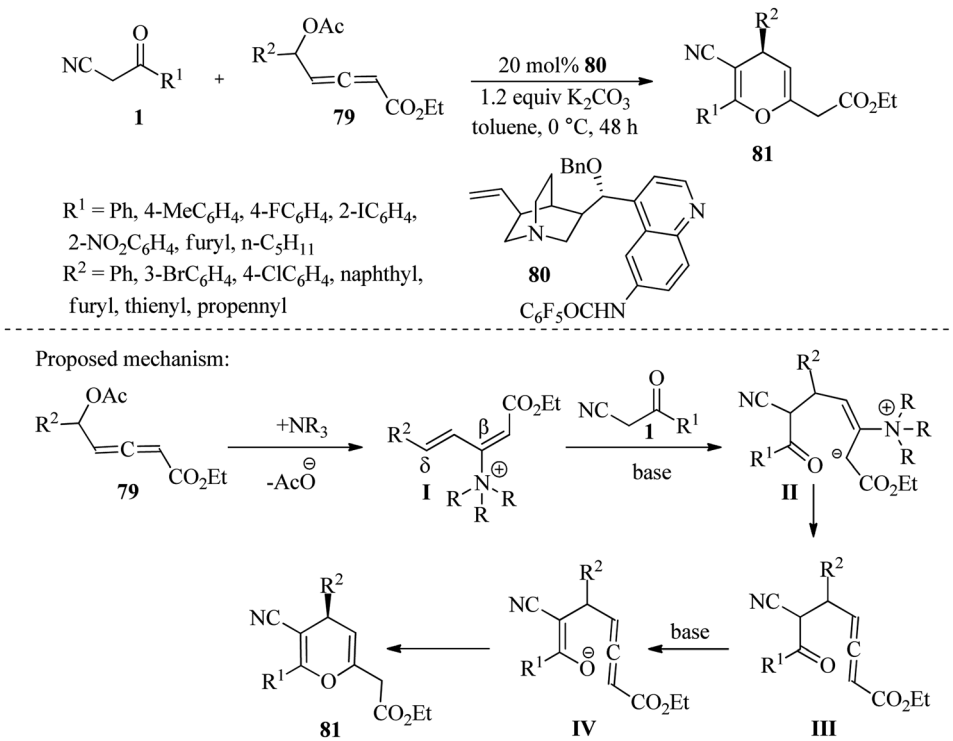
*4.1.2.1. Synthesis of 5-aminopyrazole and pyrazolo[1,5-a]pyrimidinones.* One of the important applications of β-ketonitriles derivatives is their use as intermediates for the synthesis of 5-amino pyrazoles. To prepare 5-amino pyrazoles, β-ketonitrile **1** is heated with hydrazine in various ways, either in a solvent or with the help of microwaves.[37] Reports indicate that 5-amino pyrazoles play an important role in the synthesis of nitrogen-containing heterocyclic compounds, including pyrazolopyrimidinones. For example, Kelada *et al.* reacted the derivatives of β-ketonitriles **1** (0.9 mmol, 1.0 equiv.), hydrazine **52** (1.2 mmol, 1.3 equiv.), MeOH (1 mL) under microwave conditions (100 W, 150 °C) for 5 min have reported the synthesis of 5-amino pyrazoles **53**. After obtaining this intermediate, they continued this process by adding AcOH (0.5 mmol, 0.6 equiv.) and ketoester derivatives **54** (0.9 mmol, 1.0 equiv.) under microwave conditions (100 W, 150 °C) for 2 h and various heterocycles of pyrazolopyrimidinones **55** have been synthesized (Scheme 22).[38]




Scheme 29 Synthesis of 3,4-dihydropyrans **75**.



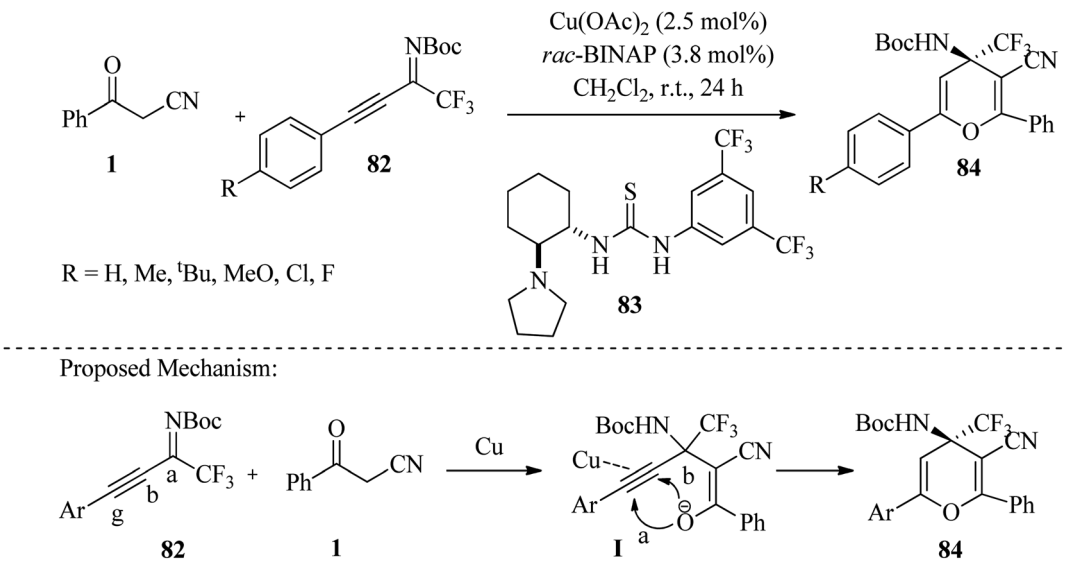

Scheme 30 Synthesis of 4*H*-pyran derivatives **78** by using 6′-deoxy-6′-[(L)-*N*,*N*-(2,2′-oxydiethyl)-valine amido]quinine **77** as a catalyst.



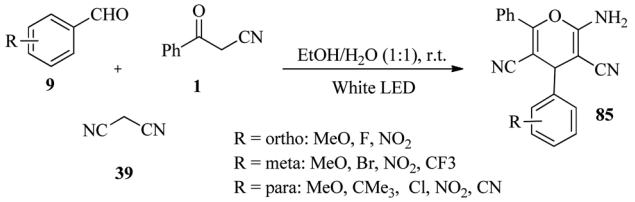

Scheme 31 Synthesis of 4*H*-pyrans **81** by using 6′-deoxy-6′ perfluorobenzamido-quinine **80** as a catalyst.

In a separate study, Liu and colleagues used NIS to accomplish a quasi-three-component reaction of β-ketonitriles **1** and aryl sulfonyl hydrazides **56** in ethanol solvent under reflux conditions, yielding 3-aryl-4-(arylthio)-1*H*-pyrazol-5-amine derivatives **59** and 3-phenyl-1-(phenylsulfonyl)-4-(phenylthio)-1*H*-pyrazol-5-amines **60**. In the mechanistic investigation of this method, it was discovered that the process involves a sequence of cyclization, sulfonylation, and removal of aryl sulfonyl in the presence of NIS (Scheme 23).[39]

*4.1.2.2. Synthesis of triazoles, oxaselenoles, oxazolines, thiazoles, isoxazos.* Savegnago and his colleagues studied the synthesis, chemical diversity, and antioxidant properties of




Scheme 32 Synthesis of 4*H*-pyran derivatives **84** with a quaternary $CF_3$-containing center.



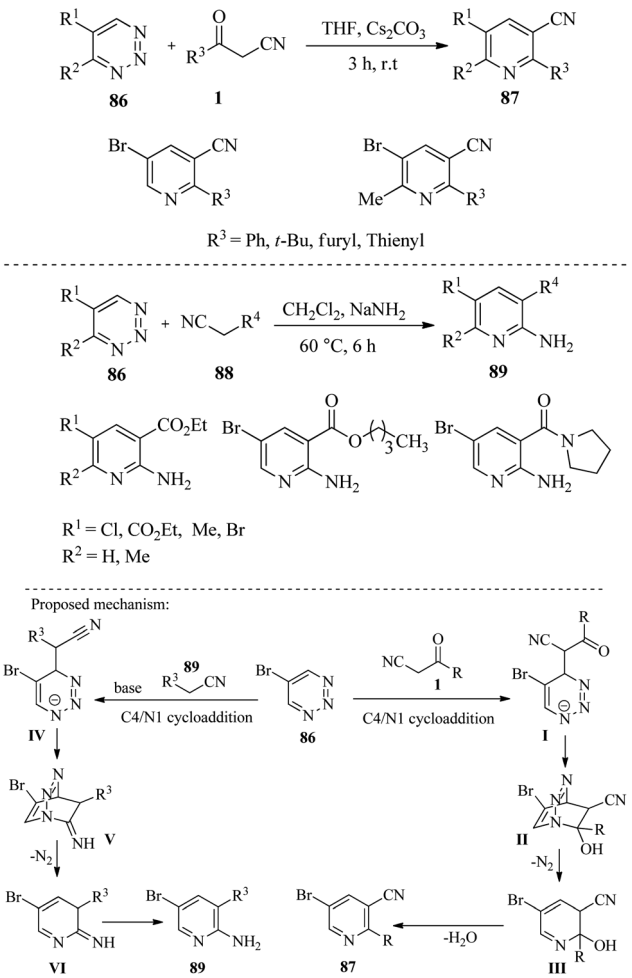

Scheme 33 Synthesis of 2-amino-4*H*-pyran-3,5-dicarbonitrile derivatives **85**.

phenylselenyl-1*H*-1,2,3-triazole-4-carbonitriles **62**. They synthesized these compounds in high yield by reacting azidophenylphenylselenides **61** with a range of β-ketonitriles **1** in the presence of DMSO as a solvent and a catalytic amount of $Et_2NH$ (1 mol%) (Scheme 24).[40]

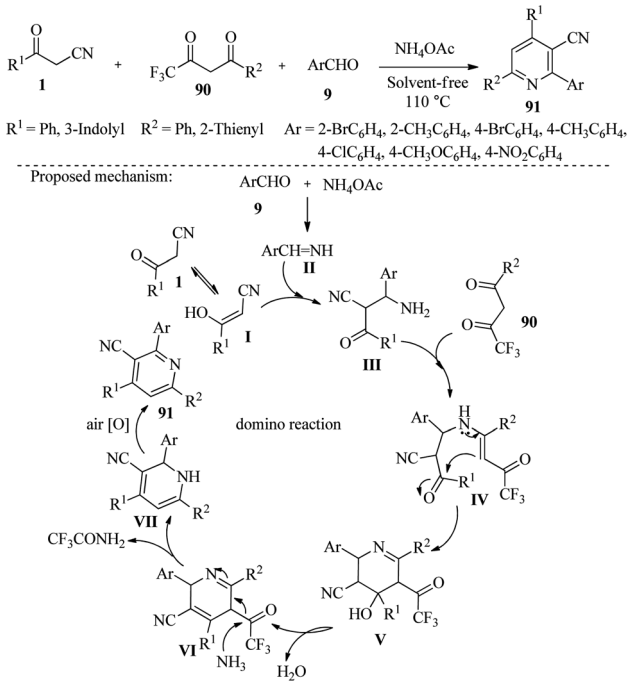
Kachanov *et al.* produced 1,3-oxaselenole heterocycles **63** and **64** in good yield with a cyano group using aroyl acetonitrile **1** and selenium(IV) oxide. The resulting products were found to react with ammonia, hydrazine, or primary amines, during which an aryl rearrangement was observed (Scheme 25).[41]

In another study, a series of 2-oxazolines (**67** and **68**) were produced using a simple one-pot method under inert and non-moisture conditions from β-ketonitrile **1** and β-amino alcohols **65** and **66** with 115–172 mol% $ZnCl_2$ (Scheme 26).[42]

An effective oxidative system, which does not require the use of metals, has been developed using TBHP and AIBN. This system has allowed for the successful synthesis of substituted 2-aminothioazoles **70** by reacting β-ketonitrile **1** with thiourea **69**. Mechanistic studies have shown that the reaction proceeds through the formation of a C–S bond *via* a radical process, followed by the formation of a C–N bond through an intramolecular condensation reaction (Scheme 27).[43]

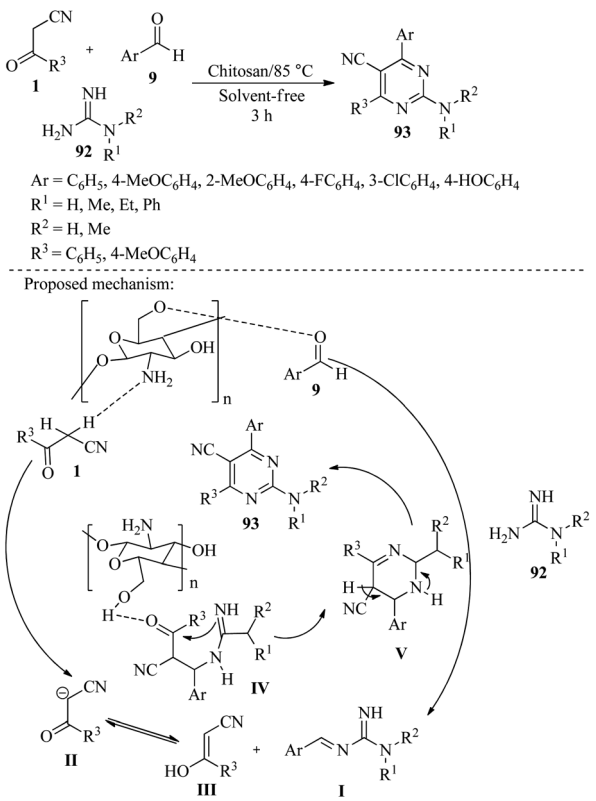



Scheme 34 Synthesis of highly substituted pyridines **87** and **89**.

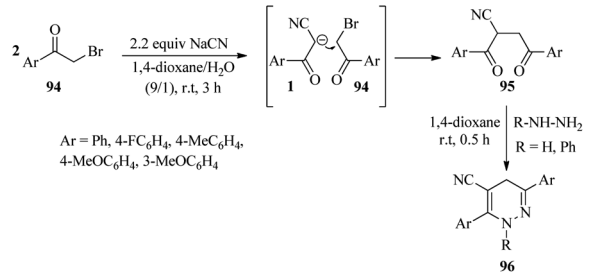



Scheme 35 Synthesis of 2,6-diaryl-4-(1*H*-indol-3-yl)-3-cyanopyridines **91**.

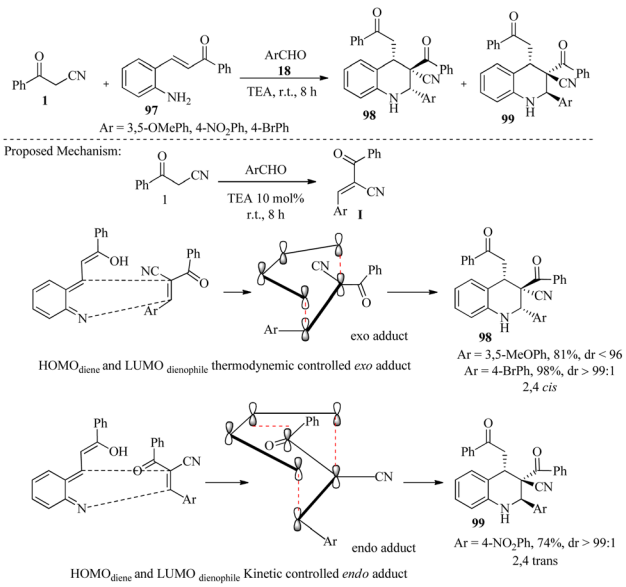
Krasavin *et al.* have prepared a set of isoxazole-5-amines **71** by reacting readily available β-ketonitriles **1** with hydroxylamine in 15% aqueous NaOH solution at reflux for 14 hours (Scheme 28).[44]



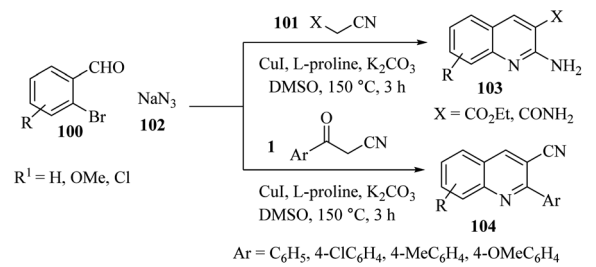

Scheme 36 Synthesis of 2-aminopyrimidine carbonitriles **93**.




Scheme 37 Synthesis of dihydropyridazines **96**.




Scheme 38 Synthesis of tetrahydroquinoline isomers exo **98** and endo **99**.

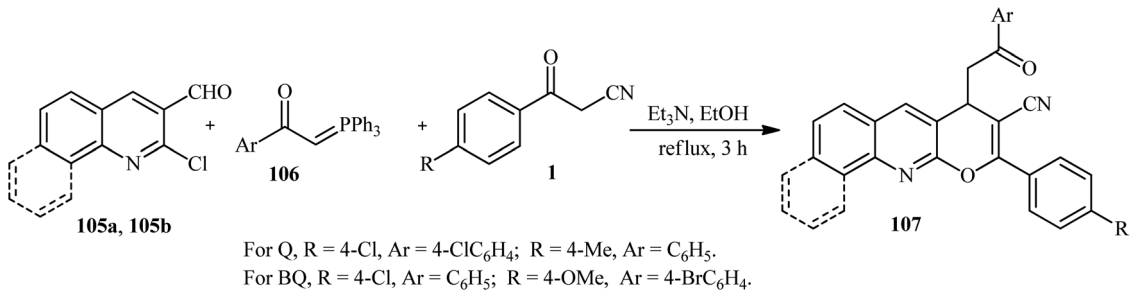



Scheme 39 Synthesis of 2-aminoquinolines **103** and 2-arylquinoline-3 carbonitriles **104**.

## 4.2. Six-membered rings

### 4.2.1. Six-membered rings with one heteroatom

*4.2.1.1. Synthesis of dihydropyrans and pyrans.* In 2014, a highly efficient synthesis of 3,4-dihydropyrans **75** was reported by catalyzing L-diphenylprolinol trimethylsilyl ether **73** through the Michael addition of β-ketonitriles **1** to β-unsaturated aldehyde derivatives **72.**



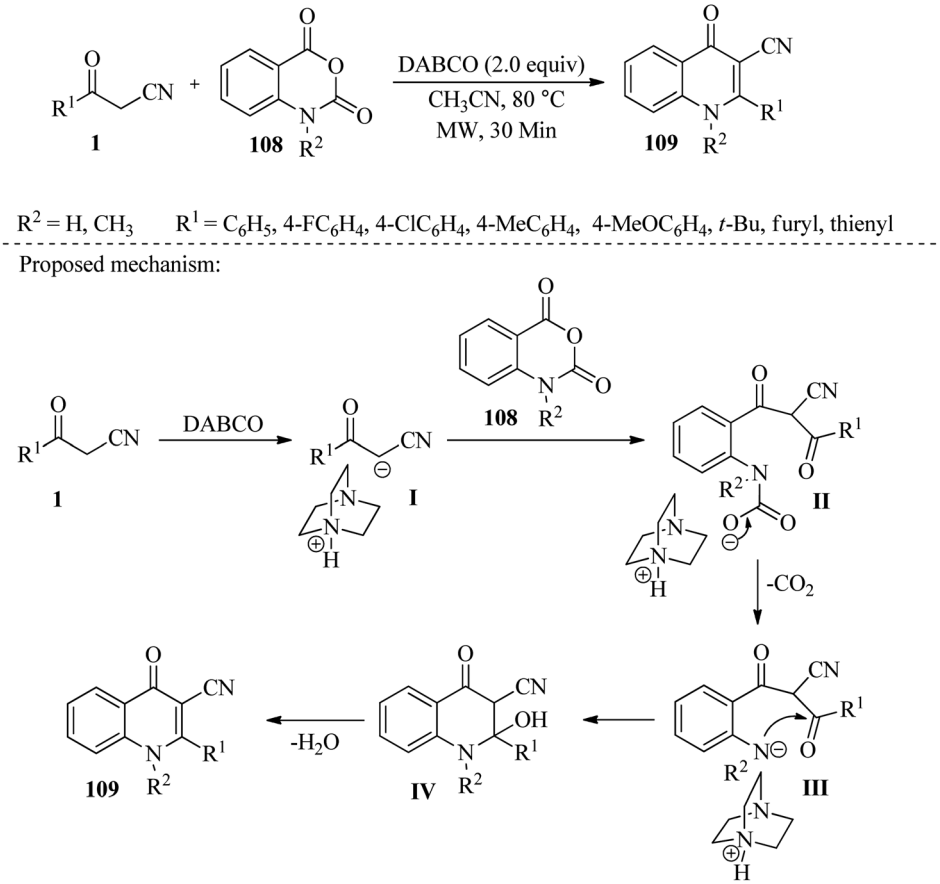

Scheme 40 Synthesis of functionalized pyrano[2,3-*b*]quinoline and benzo[*h*]pyrano[2,3-*b*]quinoline derivatives.

The desired compounds were acquired with exceptional yields (up to 91%) and enantioselectivities (up to 98% ee) (Scheme 29).[45]

In 2016, Tong *et al.* found that by using 6′-deoxy-6′-[(L)-*N*,*N*-(2,2′-oxydiethyl)-valine amido]quinine **77** as the catalyst, the formation of 4*H*-pyrans **78** through (3 + 3) annulations of β′-acetoxy allenoates **76** with β-ketonitriles **1** can occur quickly and with excellent enantioselectivity. Catalyst **77** has three functions, including Lewis base (quinuclidine N), H-bond donor (amide NH), and Brønsted base (morpholine N), each playing crucial roles in the chemo- and enantio-selectivity for the construction of 4*H*-pyrans **78** (Scheme 30).[46]

The following year, Zhou *et al.* discovered that using 6′-deoxy-6′ perfluorobenzamido-quinine **80** as a catalyst can result in the quick formation of 4*H*-pyrans **81** through [3 + 3] annulations of δ-acetoxy allenoates **79** and β-ketonitriles **1** with excellent enantioselectivity. The researchers found that the amide NH of **80** plays a crucial role as an H-bond donor, facilitating the formation of cationic intermediate **I** and increasing the electrophilicity of its δ-position (Scheme 31).[47]

In 2022, Zhang *et al.* realized that using $Cu(OAc)_2$ as the catalyst can result in the quick formation of polysubstituted 4*H*-pyran derivatives **84** with a quaternary $CF_3$-containing center through (3 + 3) annulations of alkynyl ketimines **82** and β-




Scheme 41 Synthesis of 3-cyano-4-quinolone derivatives **109**.

ketonitriles **1** with excellent yields (86–99%) and good enantioselectivities (71–78% ee). The researchers found that the reaction involves a process with a base-catalyzed or chiral thiourea-catalyzed Mannich-type reaction followed by a highly regioselective copper-catalyzed ring-closing reaction on the alkynyl moiety in a 6-*endo*-dig fashion (Scheme 32).[48]

In 2019, the same group synthesized derivatives of 2-amino-4*H*-pyran-3,5-dicarbonitrile **85** through a three-component reaction. This reaction involved aldehydes **9**, malononitrile **39**, and β-ketonitriles **1** and was carried out in a mixture of ethanol and water at room temperature. The resulting products had a wide range of functional groups and were obtained in high yields (Scheme 33).[49]

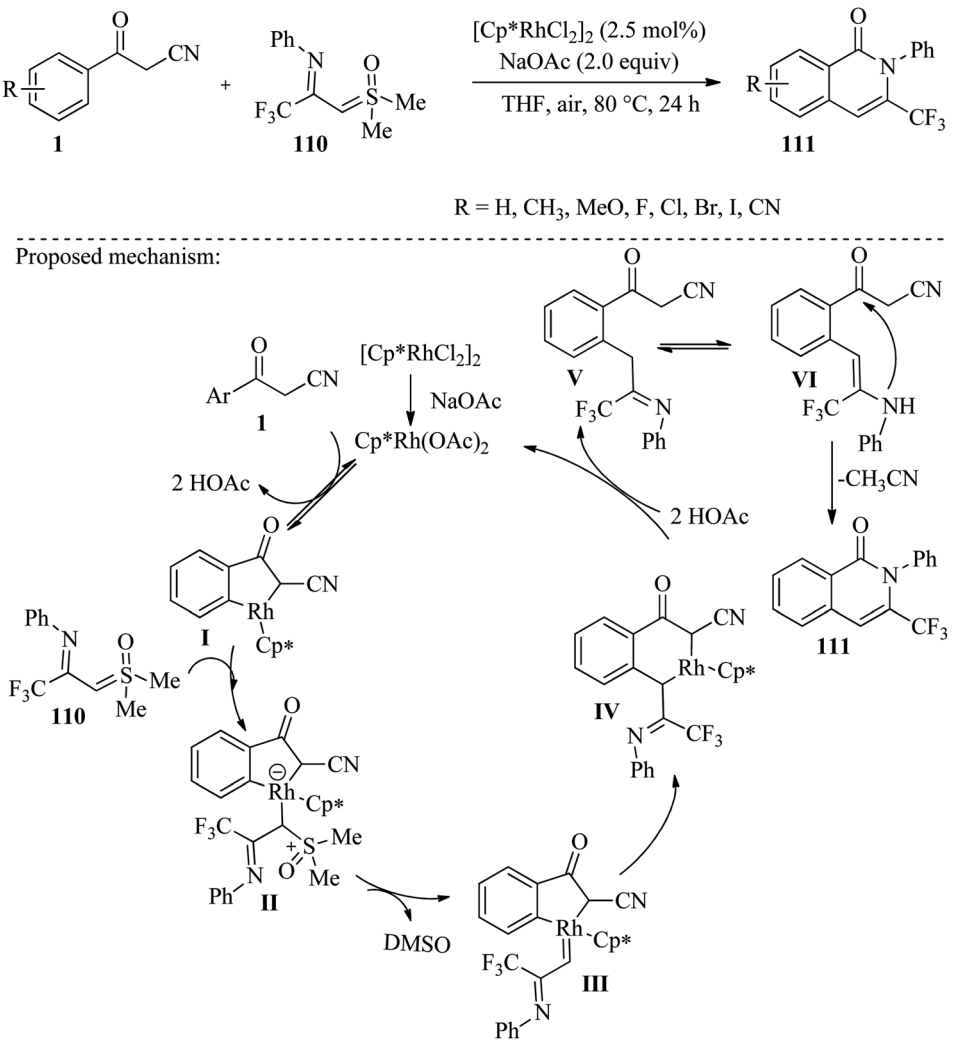
*4.2.1.2. Synthesis of pyridines.* In 2019, Zhang and colleagues conducted a study on the cascade nucleophilic addition reactions of 1,2,3-triazines **86** with activated β-ketonitriles **1** or ketones **88**. This approach enabled the construction of highly substituted pyridines **87** and **89**, which are not easily accessible by traditional methods. The study addressed some structural diversity issues that currently exist in medicinal chemistry. The resulting pyridines could be used as convenient precursors for the synthesis of related pharmaceuticals (Scheme 34).[50]

Bharkavi *et al.* reported a series of new compounds called 2,6-diaryl-4-(1*H*-indol-3-yl)-3-cyanopyridines **91**. These compounds were produced in good yields through the domino reactions of β-ketonitriles **1**, 4,4,4-trifluoro-1-phenylbutane-1,3-dione **90**, and aromatic aldehydes **9** in the presence of ammonium acetate without the use of solvents. This process creates two C–C and two C–N bonds, leading to the formation of a six-membered ring in a single operation (Scheme 35).[51]

### 4.2.2. Six-membered rings with two heteroatom

*4.2.2.1. Synthesis of pyrimidines.* In 2014, Siddiqui *et al.* applied the Friedlander reaction of guanidines, aldehydes, and cyano ketones under solvent-free conditions at 85 °C in the presence of chitosan as a green catalyst to get 2-amino-pyrimidine carbonitriles **93**.

In the mechanistic study of this reaction, it is explained that the hydroxyl group of chitosan activates the carbonyl group of aldehyde 9 at first, which then undergoes condensation with




Scheme 42 Synthesis of 3-trifluoromethyl-isoquinolines **111**.

guanidine 92 leading to the formation of intermediate I. The amine group present on the surface of chitosan facilitates the formation of III. The final step involves the addition of intermediates I and III to form a new intermediate IV, which undergoes intramolecular cyclization followed by aromatization V to produce the desired product 93 in good yield (Scheme 36).[52]

*4.2.2.2. Synthesis of dihydropyridazines.* A new synthetic route has been developed by Chan and his colleagues for the construction of functionalized 2-cyano-1,4-diketones **95**. The route involves the nucleophilic substitution of 2-bromoacetophenones **94** with NaCN, *via* in situ-generated β-ketonitriles **1**. By using 2-cyano-1,4-diketone **95** as an intermediate and titrating it with hydrazine, the team successfully synthesized six-membered heterocycles of dihydropyridazines **96**. The successful synthesis of these heterocycles is a significant advancement in the field of organic chemistry (Scheme 37).[53]

### 4.3. Synthesis of quinoline and isoquinoline derivatives

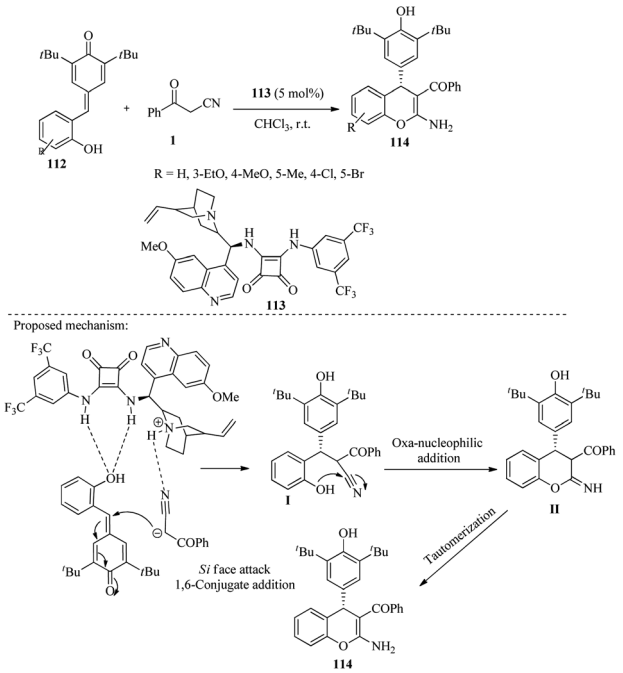
Palanimuthu and his colleagues have developed a simple and efficient method for synthesizing new, densely functionalized tetrahydroquinoline derivatives. This is achieved through the aza-Diels–Alder reaction between β-ketonitriles **1** aromatic aldehydes **9**, and 2-alkenyl amines **97**. The reaction uses a catalytic amount of TEA and takes place under very mild conditions. The resulting tetrahydroquinoline isomers exo **98** and endo **99** are synthesized with excellent diastereoselectivity and high yields (Scheme 38).[54]

In 2016, Dhiman used copper as a catalyst for the three-component domino reactions of 2-bromobenzaldehydes **100**, active methylene nitriles (**1** and **101**), and sodium azide **102**. The reactions were performed in DMSO under reflux at 150 °C in the presence of L-proline and $K_2CO_3$ leading to the synthesis of 2-aminoquinolines **103** and 2-arylquinoline-3 carbonitriles **104**. Mechanistic exploration of this reaction shows that the formation of substituted quinolines involves Knoevenagel condensation of *ortho*-bromobenzaldehyde with active methylene nitriles followed by copper-catalyzed reductive amination and intramolecular cyclization (Scheme 39).[55]

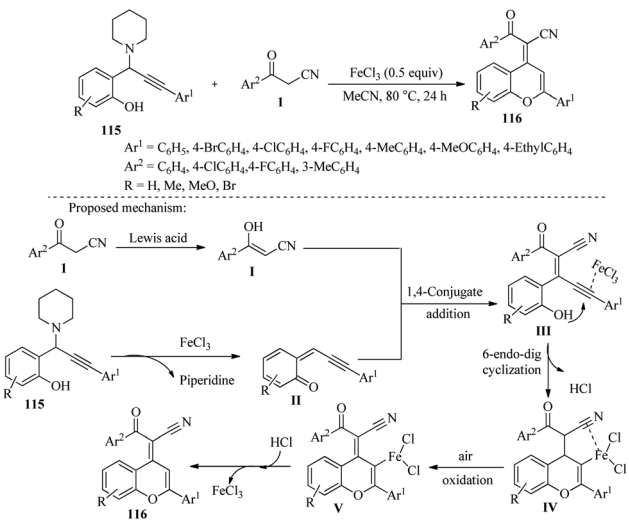
Recently, our group reported an efficient synthesis of functionalized pyrano[2,3-*b*]quinoline and benzo[*h*]pyrano[2,3-*b*]quinoline derivatives **107a** and **107b** by using 2-chloroquinoline-3-carbaldehyde or 2-chlorobenzo[*h*]quinoline-3-carbaldehyd **105a** and **105b**, 1-aryl-2-(1,1,1-triphenyl-$\lambda^5$-phosphanylidene)ethan-1-one (Wittig reagent) **106** and β-ketonitriles **1** in EtOH under reflux at 80 °C in the presence of $Et_3N$ in good to excellent yields. The mechanical of this reaction involves the two processes of C–C bond formation (Michael addition) and intramolecular cyclization (by attacking the oxygen atom of active methylene compounds) (Scheme 40).[56]

Hussain *et al.* have developed an efficient method to produce 3-cyano-4-quinolone derivatives **109**. This is achieved through decarboxylative cyclization of isatoic anhydrides **108** with β-ketonitriles **1** using DABCO as a non-toxic, eco-friendly, and inexpensive reagent under microwave conditions. The reaction is performed in $CH_3CN$ under reflux at 80 °C for 30 minutes. This approach provides an easy pathway for making this class of compounds in good to high yield from readily available starting materials in short reaction times (Scheme 41).[57]

Yang *et al.* conducted a study on synthesizing 3-trifluoromethyl-isoquinolines **111**, which are important compounds in biology, using an Rh(III)-catalyzed annulation of β-ketonitriles **1** and $CF_3$-substituted imidoyl sulfonium ylides (TFISYs) **110**. The reaction was conducted in THF solvent with NaOAc at 60 °C for 24 hours. The transformation involved




Scheme 43 Synthesis of 2-amino-4-aryl-4*H*-chromenes **114**.




Scheme 44 Synthesis of functionalized 2-aryl-4*H*-chromenes **116**.

removing a C–H bond and an unusual C–C bond from benzoyl acetonitrile, while also removing a molecule of dimethyl sulfoxide (DMSO) and acetonitrile ($CH_3CN$). This reaction has several advantages, including low catalyst loadings, mild conditions, wide substrate scope, high efficiency, and scalability (Scheme 42).[58]

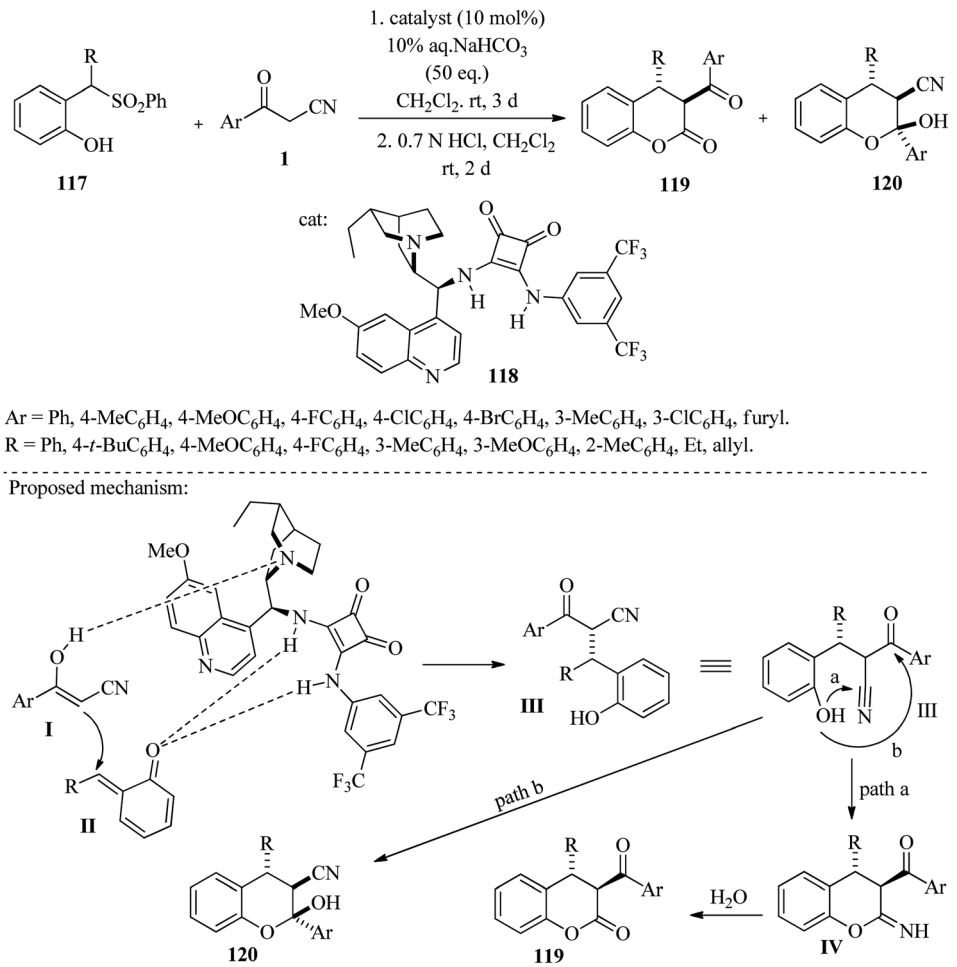
### 4.4. Synthesis of chromene derivatives

Duan *et al.* have developed an efficient method to produce 2-amino-4-aryl-4*H*-chromenes **114**. This is achieved through reactions of ortho-hydroxyl-substituted *p*-QMs **112** with β-ketonitriles **1**, using asymmetric organocatalytic chiral **113** at mild conditions in $CHCl_3$ solvent. The process involves 1,6-conjugate addition/annulation/tautomerization (Scheme 43).[59]

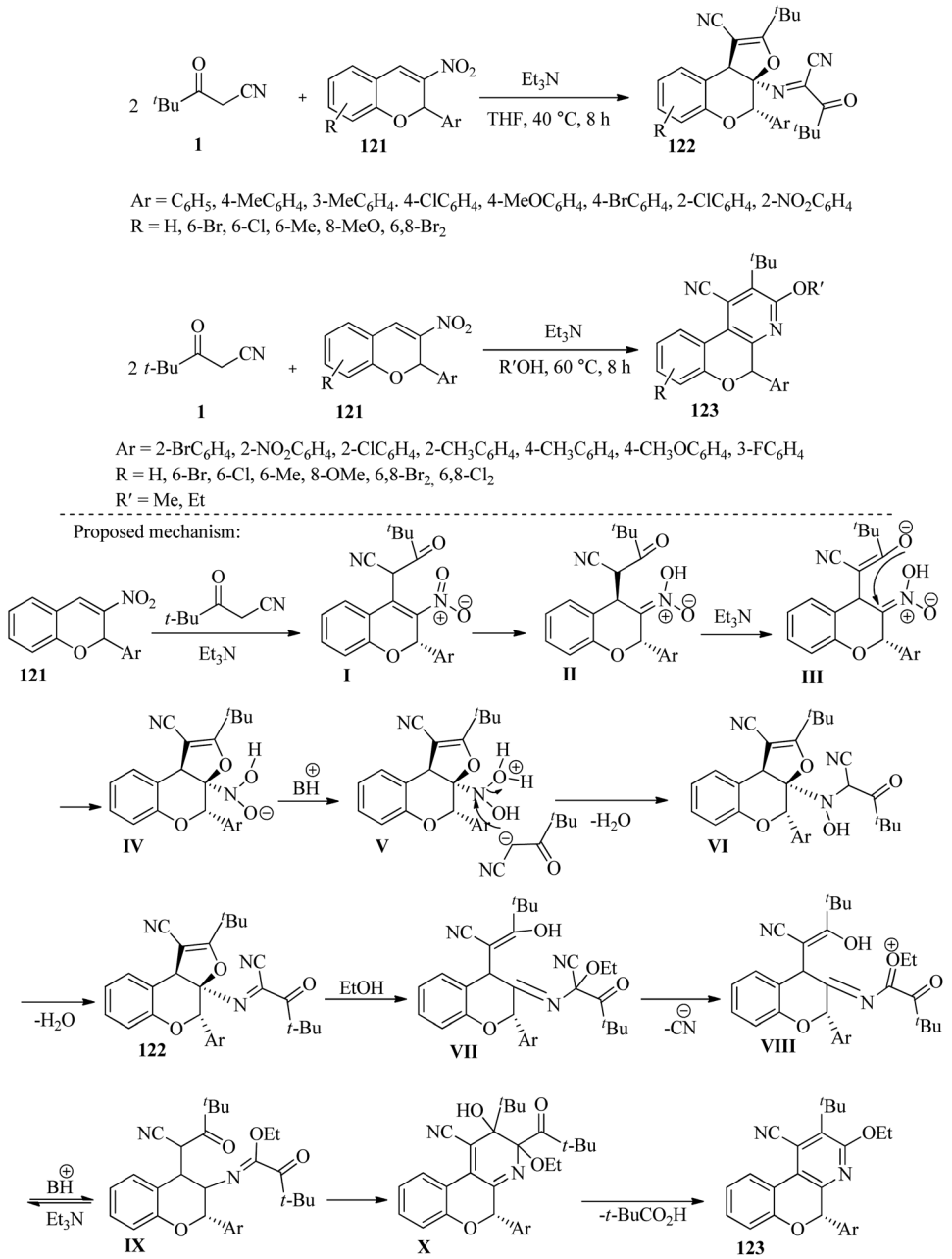
In 2018, He *et al.* developed a concise and efficient method for synthesizing functionalized 2-aryl-4*H*-chromenes **116** using propargylamines **115** and β-ketonitriles **1** in the presence of $FeCl_3$ as a catalyst. This method is environmentally friendly and utilizes $CH_3CN$ solvent for 24 hours under reflux conditions. The reaction features a highly efficient tandem sequence of 1,4-conjugate addition, 6-*endo*-dig cyclization, and oxidation. This protocol accommodates various functional groups, rendering it a practical and effective method for synthesizing 2-aryl-4*H*-chromene skeletons **116** (Scheme 44).[60]

The Pan group recently developed an organocatalytic method for the synthesis of chiral 3,4-dihydrocoumarins **119** and tetrasubstituted chromas **120**. This process involves Michael addition and intramolecular cyclization of β-ketonitriles **1** and 2-sulfonyl methyl phenols **117**. The reaction takes place in dichloromethane with sodium bicarbonate at room temperature. In the reaction mechanism, the amino group of catalyst **118** activates the carbonyl groups and acts as a Lewis acid to facilitate the reaction (Scheme 45).[61]

Jiang and his team conducted research on the domino reaction of two molecules of β-ketonitriles **1** and one molecule of 2-aryl-3-nitro chromene **121**, in the presence of triethylamine. They performed this reaction in tetrahydrofuran solvent to synthesize various derivatives of dihydrofuro[2,3-*c*]chromenes **122**, and by using polar protic solvents such as ethanol and methanol, to synthesize chromeno[3,4-*b*] substituted pyridines




Scheme 45 Synthesis of chiral 3,4-dihydrocoumarins **119** and tetrasubstituted chromas **120**.



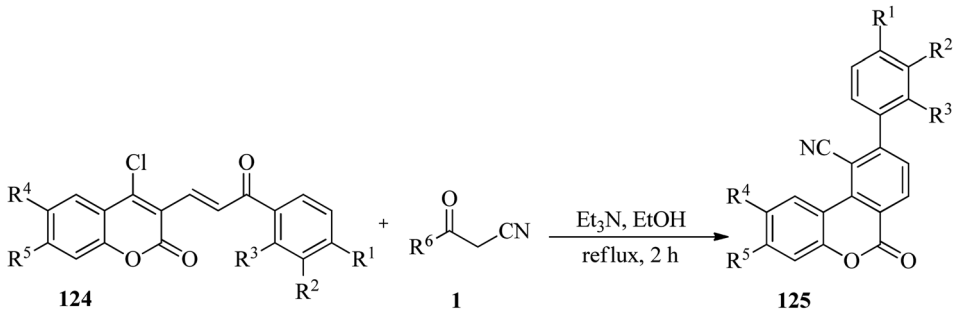

Scheme 46 Synthesis of dihydrofuro[2,3-*c*]chromene **122** and chromeno[3,4-*b*] substituted pyridines **123**.

**123**. These products were obtained under mild conditions. One of the most significant advantages of this process is the wide range of products produced with satisfactory efficiency (Scheme 46).[62]

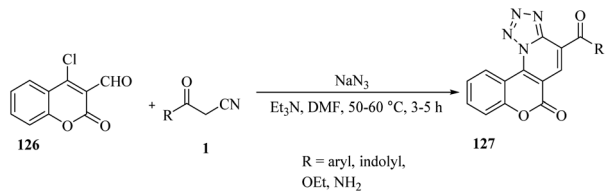
Also, our research group a general and efficient method for the chemoselective synthesis of benzo[*c*]chromen-6-ones **125** has been developed. The reactions were accomplished in the presence of $Et_3N$ in EtOH under reflux conditions to afford functionalized benzo[*c*]chromen-6-ones **125** in 70–91% yield. The mechanism of this reaction includes a base-promoted nucleophilic substitution/deprotonation/intramolecular aldol condensation/carboxylic acid or alkyl hydrogen carbonate elimination/aromatization reaction of β-ketonitriles **1** and α,β-unsaturated coumarins **124** (Scheme 47).[63]

Bhuyan and colleagues have developed an effective and versatile method for the selective synthesis of tetrazole-fused pyrido[3,2-*c*]coumarin derivatives **127**.

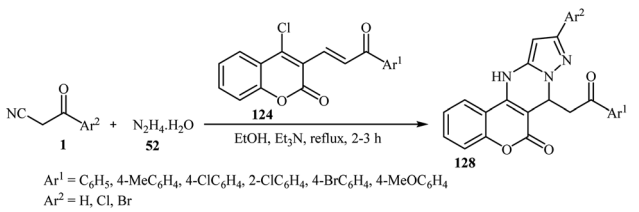
This is achieved through a one-pot three-component reaction of 4-chloro-3-formylcoumarin **126** *via* intramolecular 1,3-cycloaddition reaction of azides to β-ketonitriles **1**. The reactions were carried out in DMF under mild conditions with the addition of one drop of $Et_3N$. The resulting products were obtained with yields ranging between 75-86% (Scheme 48).[64]



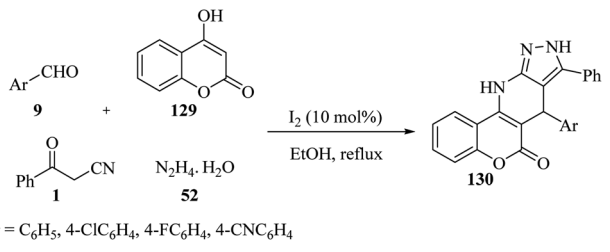

Scheme 47 Synthesis of benzo[*c*]chromen-6-ones **125**.




Scheme 48 Synthesis of tetrazole-fused pyrido[3,2-*c*]coumarin derivatives **127**.



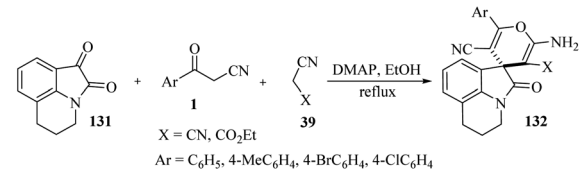

Scheme 49 Synthesis of dihydro-6*H*-chromeno[4,3-*d*]pyrazolo[1,5-*a*]pyrimidin-6-ones **128**.



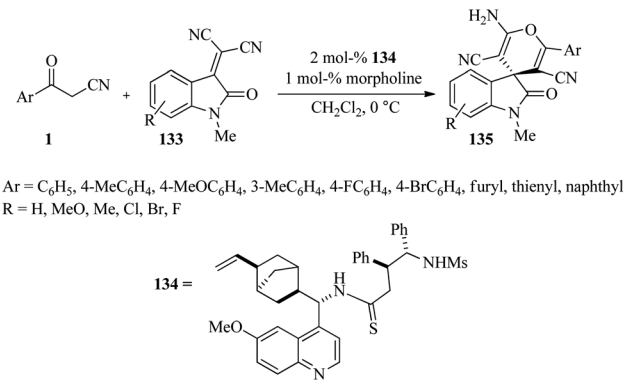

Scheme 50 Synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones **130**.

In another study Alizadeh and Rostampoor developed a method for synthesizing dihydro-6*H*-chromeno[4,3-*d*]pyrazolo[1,5-*a*]pyrimidin-6-ones **128** through a three-component reaction involving α,β-unsaturated coumarins **124**, β-ketonitriles **1**, and hydrazine hydrate **52**. This process includes 1,4-addition and aza-Michael addition, forming two carbon–nitrogen (C–N) bonds. The reactions were accomplished in the presence of $Et_3N$ in EtOH under reflux conditions to afford products up to 77–92% yield (Scheme 49).[65]

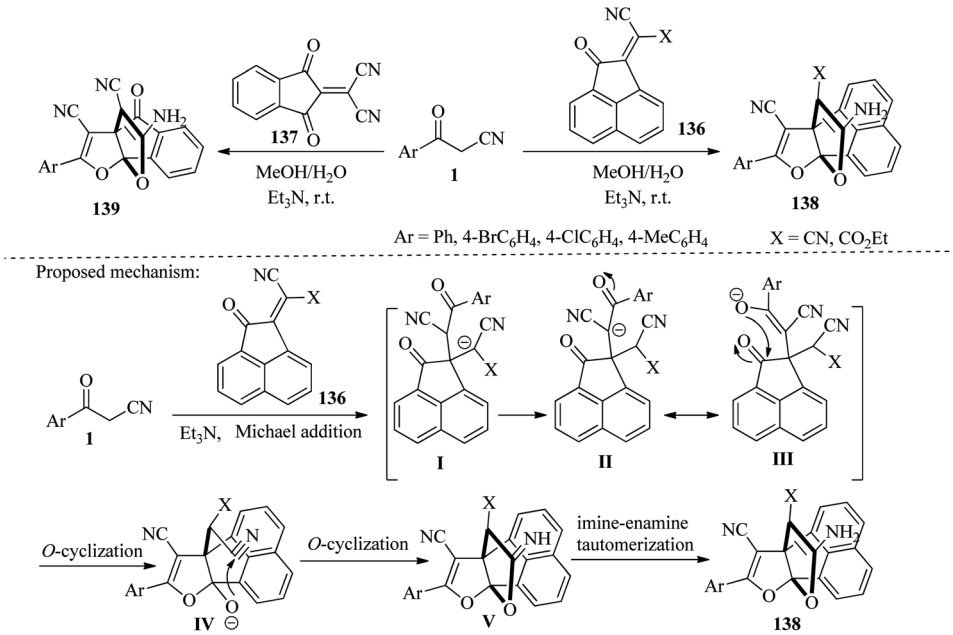
Choudhury and his team developed a concise method using molecular iodine to synthesize dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones **130** through a four-component reaction involving aromatic aldehydes **9**, 4-hydroxycoumarin **129**, β-ketonitriles **1**, and hydrazine hydrate **52** in EtOH under



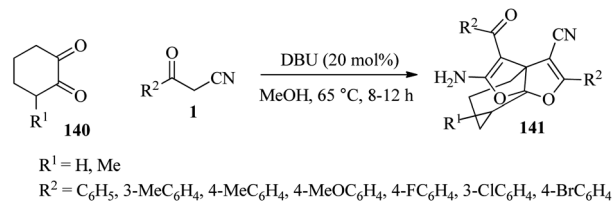

Scheme 51 Synthesis of spiro[4*H*-pyran-3,3′-oxindoles] **132**.



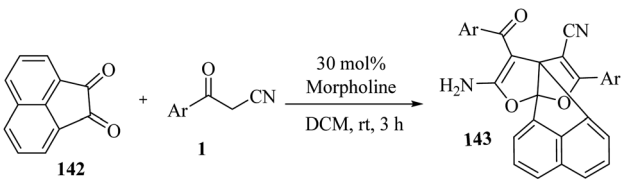

Scheme 52 Synthesis of chiral spiro[4*H*-pyran-oxindole] derivatives **135**.



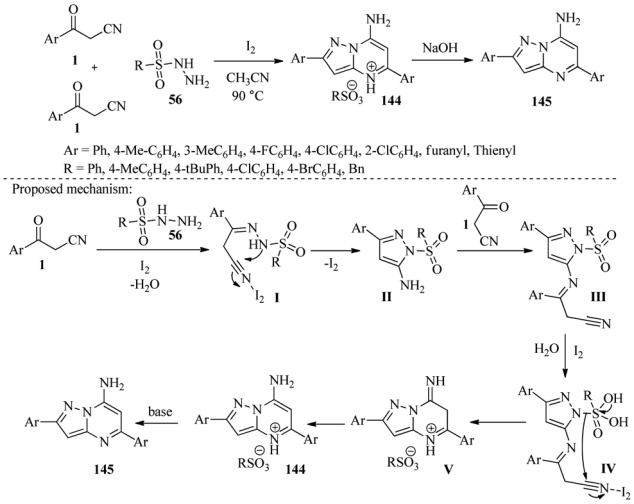

Scheme 53 Synthesis of dioxopropanes **138** and **139**.




Scheme 54 Synthesis of substituted heterocyclic[4.3.3]propellane **141**.




Scheme 55 Synthesis of fused (epoxyetheno)indeno-furans **143**.



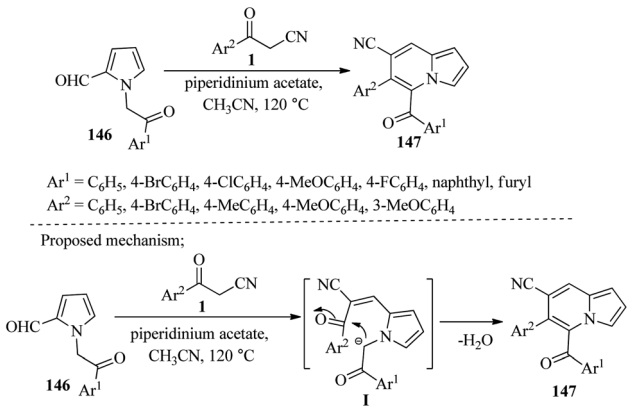

Scheme 56 Synthesis of functionalized pyrazolo[1,5-*a*]pyrimidine-4-iome sulfonates **144** and pyrazolo[1,5-*a*]pyrimidines **145**.

reflux conditions. The synthesis process involves Knoevenagel condensation, Michael addition, and intramolecular condensation (Scheme 50).[66]

### 4.5. Synthesis of spiro compounds

Baradarani and his team developed a simple and concise method catalyzed by DMAP for synthesizing a series of spiro [4*H*-pyran-3,3′-oxindoles] **132**. This was achieved through a three-component reaction of isatin (5,6-dihydro-4*H*-pyrrolo [3,2,1-*ij*]quinoline-1,2-dione) **131** with various β-ketonitriles **1** and malononitrile derivatives **39** in ethanol under reflux. The synthesis process involves Knoevenagel condensation, Michael addition, and intramolecular condensation (Scheme 51).[67]

Wu and colleagues developed a method using just 2 mol% of a chiral organocatalyst **134**, producing chiral spiro[4*H*-pyran-oxindole] derivatives **135** with 97–99% yields and 76–97% enantioselectivities. This is achieved through a one-pot reaction of β-ketonitriles **1** and isatylidene malononitriles **133** in $CH_2Cl_2$ at −10 °C and adding 1 mol% morpholine. The addition of

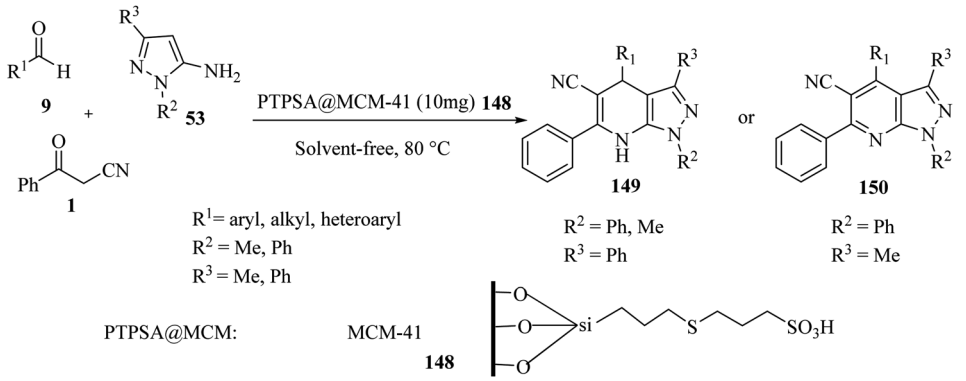



Scheme 57 Synthesis of 5-acylindolizine-7-carbonitrile **147**.

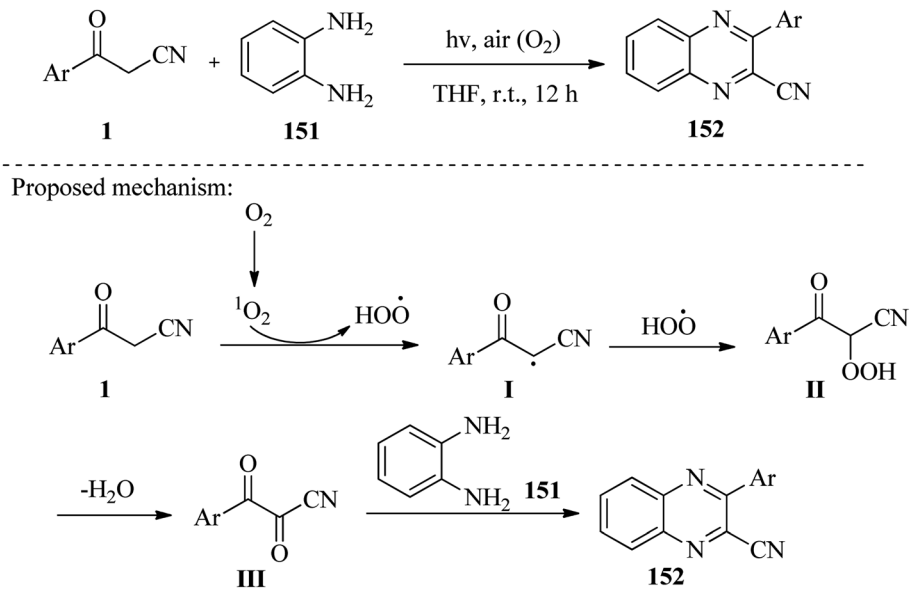
2% mol of tertiary amine catalyst **134**, which contains many hydrogen bond donors, activates the carbonyl β-ketonitrile **1** group. This activation promotes the Michael addition process, resulting in the formation of spirooxindole through intramolecular cyclization (Scheme 52).[68]

### 4.6. Synthesis of propellanes

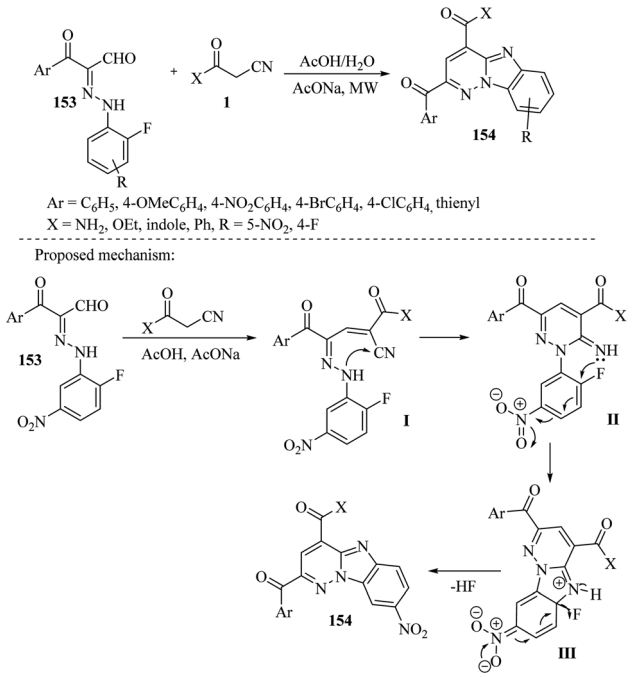
In 2017, Yavari and his team revealed a method for synthesizing dioxopropanes **138** and **139** that is highly chemoselective and regioselective. The process involves reacting adducts of acenaphthoquinolidene malonitriles **136** (and ninhydrylidene malonitriles **137**) with β-ketonitriles **1** in 70% aqueous MeOH at room temperature. The reaction mechanism involves three processes: Michael addition and two molecular cyclization




Scheme 58 Synthesis of dihydro-1*H*-pyrazolo-[3,4-*b*]pyridines **149** and 1*H*-pyrazolo-[3,4-*b*]pyridines.




Scheme 59 Synthesis of synthesis of quinoxaline derivatives **152**.




Scheme 60 Synthesis of benzo[4,5]imidazo[1,2-*b*]pyridazines derivatives **154**.

processes that form one C–C bond and two C–O bonds (Scheme 53).[69]

Jeong and his team developed a simple and concise method catalyzed by DBU for synthesizing new substituted heterocyclic [4.3.3]propellane **141**. This was done through a one-pot reaction of *a*-diketones **140** with variously substituted β-ketonitriles **1** in MetOH under reflux conditions for 8–12 h. The synthesis process involves Knoevenagel, Michael, and intramolecular/Paal–Knorr cyclization (Scheme 54).[70]

In 2022, the same group synthesized fused (epoxyetheno) indeno-furans **143** by reacting acenaphthoquinolidene **142** and β-ketonitriles **1**. The reaction was carried out in the presence of 30 mol% morpholine in DCM under mild conditions for 3 hours. The reaction mechanism is similar to Scheme 54 and involves three processes: Knoevenagel, Michael, and intramolecular/Paal–Knorr cyclization (Scheme 55).[71]

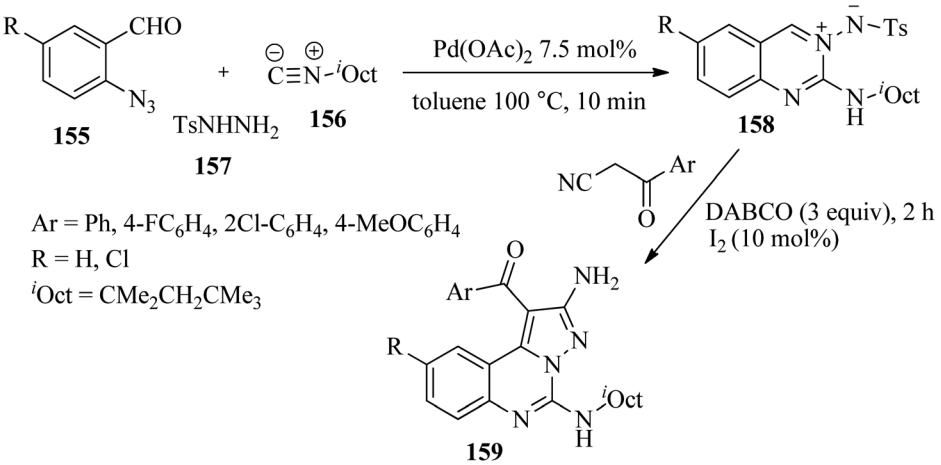
### 4.7. Nitrogen-containing heterocycles

**4.7.1. Bicyclic system.** Sun and colleagues developed an iodine-catalyzed three-component bi-cyclization of β-ketonitriles **1** with sulfonylhydrazides **56** to synthesize a range of functionalized pyrazolo[1,5-*a*]pyrimidine-4-iome sulfonates **144** in a highly regioselective manner. These sulfonates can be quantitatively converted into densely functionalized pyrazolo [1,5-*a*]pyrimidines **145** in the presence of bases (Scheme 56).[72]

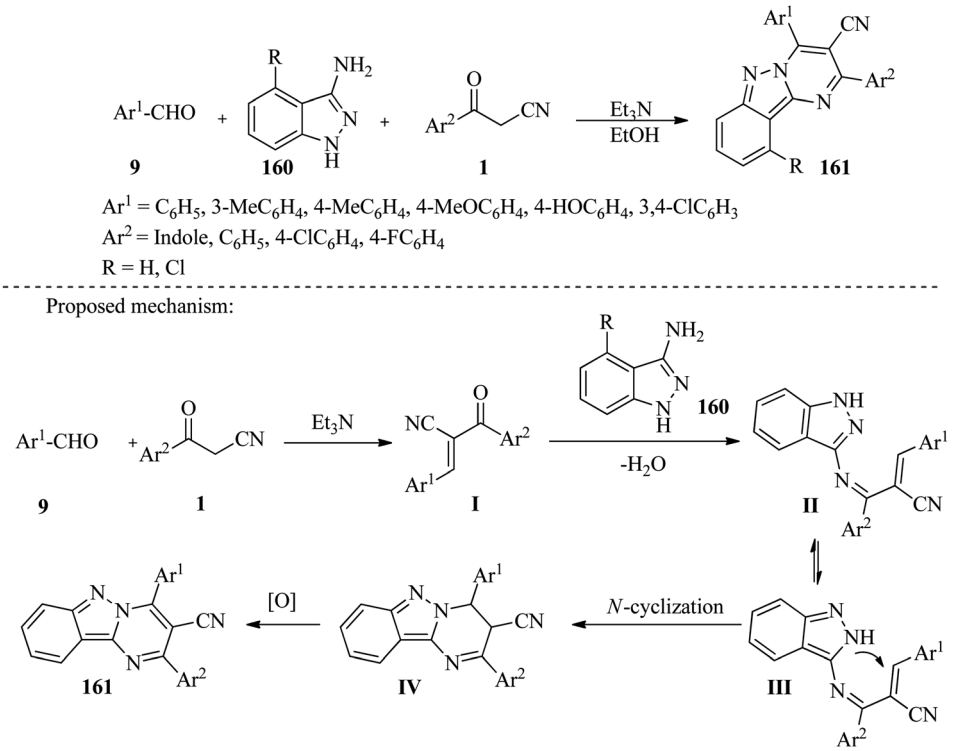
In 2021, Kim and his colleagues developed a reaction between β-ketonitriles **1** and N-substituted pyrrole-2-carboxaldehyde **146** in $CH_3CN$, in the presence of piperidinium acetate, which allows selective access to 5-acylindolizine-7-carbonitrile **147** through a Knoevenagel condensation–intramolecular aldol cyclization sequence (Scheme 57).[73]

In a recent study, Khosropour and his colleagues developed a novel catalyst named 3-(propylthio)propane-1-sulfonic acid-functionalized MCM-41 (PTPSA@MCM-41) **148** which was found to be effective and reusable. This catalyst was used for the multicomponent synthesis of dihydro-1*H*-pyrazolo-[3,4-*b*]pyridines **149** and 1*H*-pyrazolo[3,4-*b*]pyridines **150** through the reaction of aldehydes **9**, β-ketonitriles **1**, and 1*H*-pyrazol-5-amines **53** at 80 °C under solvent-free conditions. One significant advantage of this catalytic system is its high catalytic activity and reusability, mild reaction conditions, simple operation, and benign environmental impact (Scheme 58).[74]

A selective protocol has been developed for the synthesis of quinoxaline derivatives **152** under the same reaction conditions simply from the reaction of phenylenediamine **151** with various derivatives of β-ketonitriles **1** in the presence of visible




Scheme 61 Synthesis of pyrazolo[1,5-*c*]quinazolines derivatives **159**.




Scheme 62 Synthesis of pyrimido[1,2-*b*]indazol-3-carbonitrile derivatives **161**.

light in THF solvent and room temperature. This is a novel protocol that accommodates various β-ketonitriles **1** and binary aromatic amines *via* visible light-induced electron transfer and oxidative coupling. This metal-free method works at room temperature with various substrates and does not require extra oxidants. It typically gives moderate to good yields (Scheme 59).[75]

**4.7.2. Tricyclic system.** A team of researchers led by Behbehan *et al.* has developed a simple and efficient method for synthesizing benzo[4,5]imidazo[1,2-*b*]pyridazines **154** using intramolecular SNAr. They used either $H_2O$/AcONa or AcOH/AcONa as the reaction medium and microwave irradiation as an energy source. The entire process involves only one step, which is the reaction between 3-oxo-2-arylhydrazonopropanals **153** and β-ketonitriles **1** such as (3-oxo-3-phenylpropionitrile, 3-oxo-3-hetarylpropionitrile, ethyl cyanoacetate, and 2-cyanoacetamide). The final compounds were produced with an overall yield of 89% to 99% (Scheme 60).[76]

Singh and his team synthesized a series of pyrazolo[1,5-*c*]quinazolines **159** that function as inhibitors for EGFR. They used a highly efficient multicomponent route involving a palladium-catalyzed four-component one-pot tandem reaction.

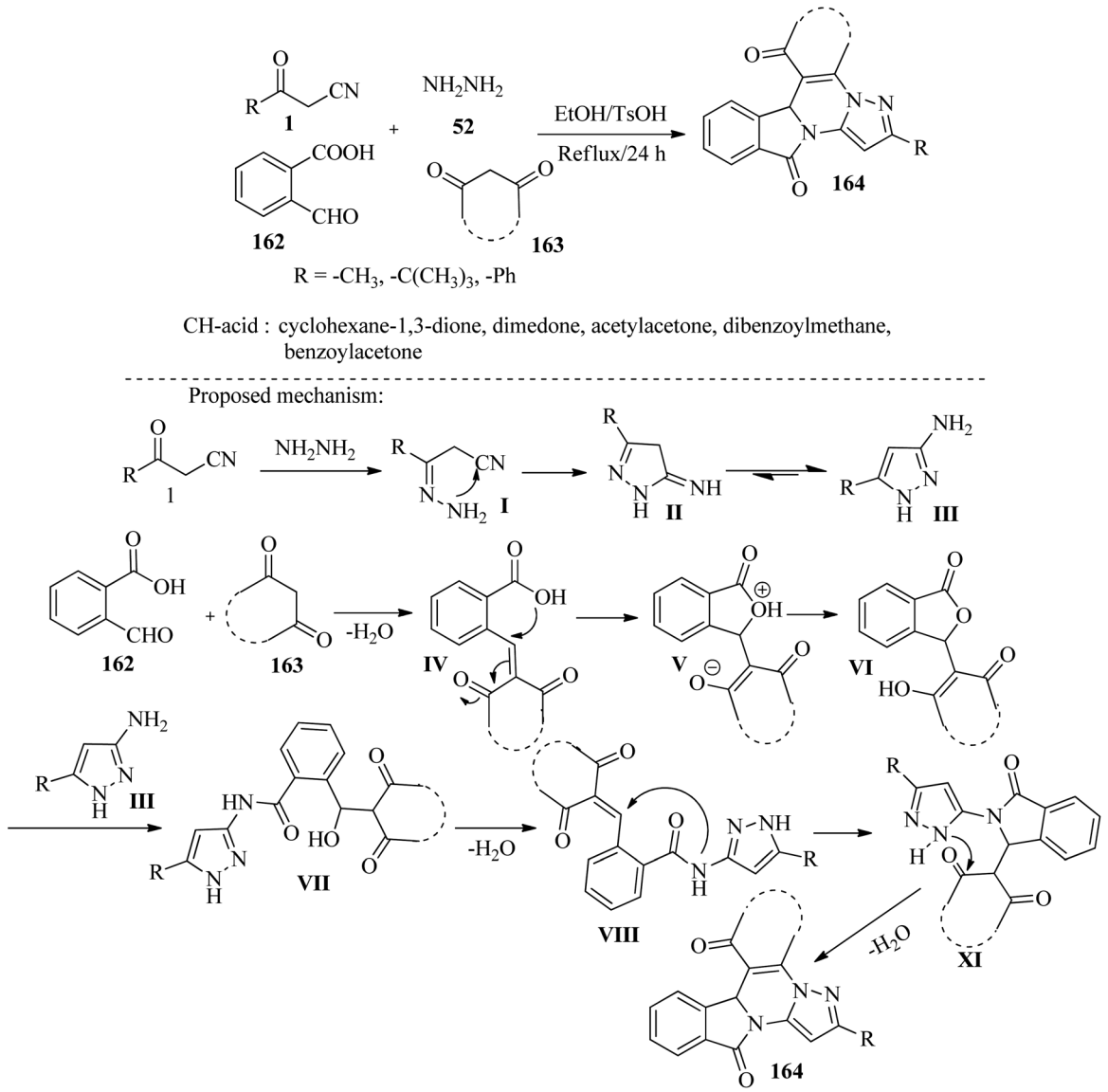
In this one-pot process, they first formed azomethine **158** by reacting azidobenzaldehyde derivatives **155**, isocyanides **156**, and arylsulfonylhydrazides **157** in the presence of $Pd(OAc)_2$ (7.5 mol%) in the toluene solvent. Then, they added β-ketonitriles **1** to the reaction mixture in the presence of DABCO, which resulted in pyrazolo[1,5-*c*]quinazoline formation. The target compounds were screened against MDA-MB-231, A549, and H1299 cancer cell lines (Scheme 61).[77]

In 2017, Rong and co-workers developed a simple and efficient method for the synthesis of pyrimido[1,2-*b*]indazol-3-carbonitrile derivatives **161** from aromatic aldehydes **9**, 1*H*-indazol-3-amine (4-chloro-1*H*-indazol-3-amine) **160** and β-ketonitriles **1** (3-(1*H*-indol-3-yl)-3-oxopropanenitrile or 3-oxo-3-arylpro-panenitrile) under metal-free conditions. This was a very successful technique for making pyrimido[1,2-*b*]indazole compounds **161** using only ethanol and triethylamine in a typical laboratory setting. This process has many advantages, including simple operation, high efficiency, easy isolation, and a wide range of substrates (Scheme 62).[78]

**4.7.3. Tetracyclic system.** New N-fused heterocyclic compounds (pyrazolo[5′,1′:2,3]pyrimido[6,1-*a*]isoindol derivatives) **164** have been synthesized through a simple one-pot four-component reaction involving hydrazine hydrate **52**, 3-oxoalkanonitriles 1,2-phthaldehydic acid **162**, and various CH-acids **163** in ethanol, using 4-toluenesulfonic acid as a catalyst. Researchers found the most important advantage of this reaction is the formation of all rings during the reaction time and the use of 4-toluenesulfonic acid as an available and cheap catalyst and ethanol as a green organic solvent (Scheme 63).[79]

### 4.8. Polycyclic system

Yang *et al.* have developed an efficient method for synthesizing polysubstituted cyanocarbazoles **167**. The reaction can be carried out in two steps using $Cs_2CO_3$ and $FeBr_2$ (5 mol%) as




Scheme 63 Synthesis of pyrazolo[5′,1′:2,3]pyrimido[6,1-*a*]isoindol derivatives **164**.

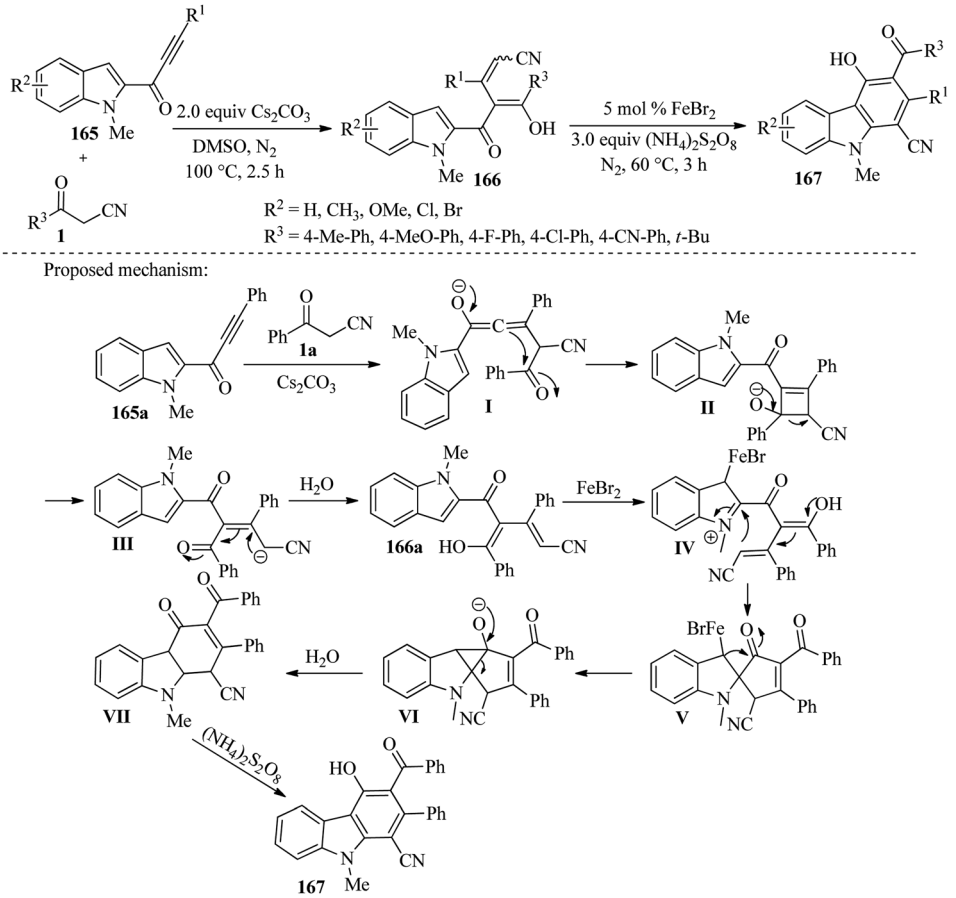
catalysts. The process involves reacting indolyl alkynyl ketones **165** with β-ketonitriles **1** in the presence of nitrogen gas and DMSO solvent under reflux conditions. The transformation involves $Cs_2CO_3$-promoted C–C σ-bond activation of α β-ketonitriles, followed by Fe-catalyzed selective C–H and/or C–C bond activations. This selective C–C σ-bond insertion and C–H activation could have broad implications for discovering new routes in organic chemistry that lead to advanced molecular scaffolds (Scheme 64).[80]

In another study, Jeong *et al.* have developed a one-pot coupling method that involves three components: 2-hydroxybenzaldehydes **168**, β-ketonitriles **1**, and isonitriles **156**. This method results in the construction of a new tricyclic 2-phenyl-1*H*-benzofuro[2,3-*b*]pyrrole ring **169**. The reaction sequence begins with a Knoevenagel condensation of 2-hydroxybenzaldehydes **168** with β-ketonitriles **1**, followed by the nucleophilic addition of the divalent isocyanic carbon **156**. This reaction produces a reactive nitrilium carbon that can be easily trapped by a nearby phenolic group of 2-hydroxybenzaldehydes **168**, yielding diverse benzofuro[2,3-*b*]pyrroles **169** in a single step (Scheme 65).[81]

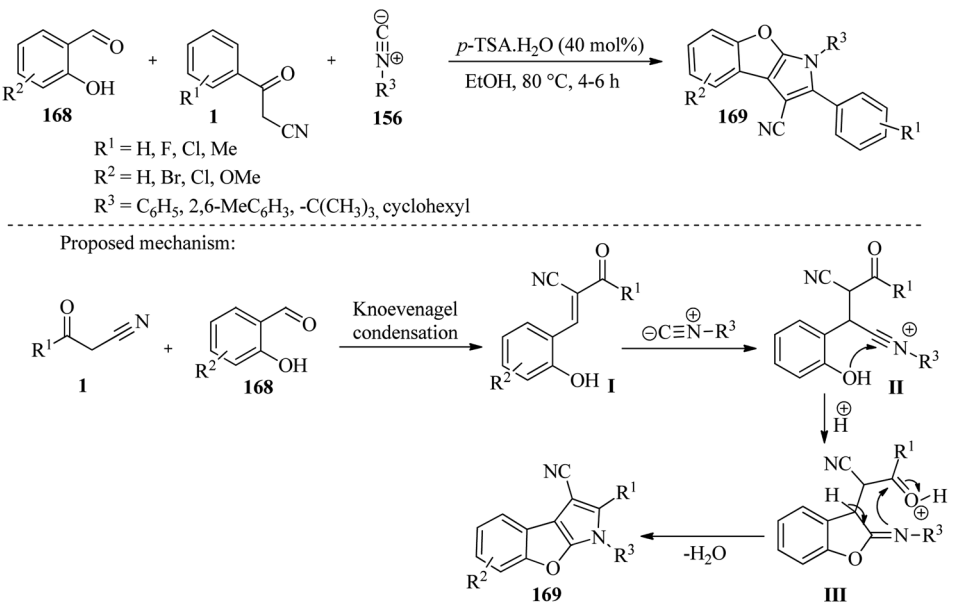
According to Wang *et al.*, the use of an iridium catalyst facilitates the cascade annulation reactions of β-ketonitriles **1** with diazo compounds **170** and **171**, leading to the formation of substituted naphtho[1,8-*bc*]pyrans **172** and **173**. The reactions involve sequential cleavage of $C(sp^2)$–H/$C(sp^3)$–H and $C(sp^2)$–H/O–H bonds, resulting in the production of different types of naphtho[1,8-*bc*]pyrans **172** and **173** depending on whether cyclic or open-chain diazo compounds are used. The researchers found that the reactions yield most products in moderate to good amounts and work well with a wide range of substrates (Scheme 66).[82]

Continuing research in this field, Zhang and colleagues have developed an efficient approach for synthesizing functionalized

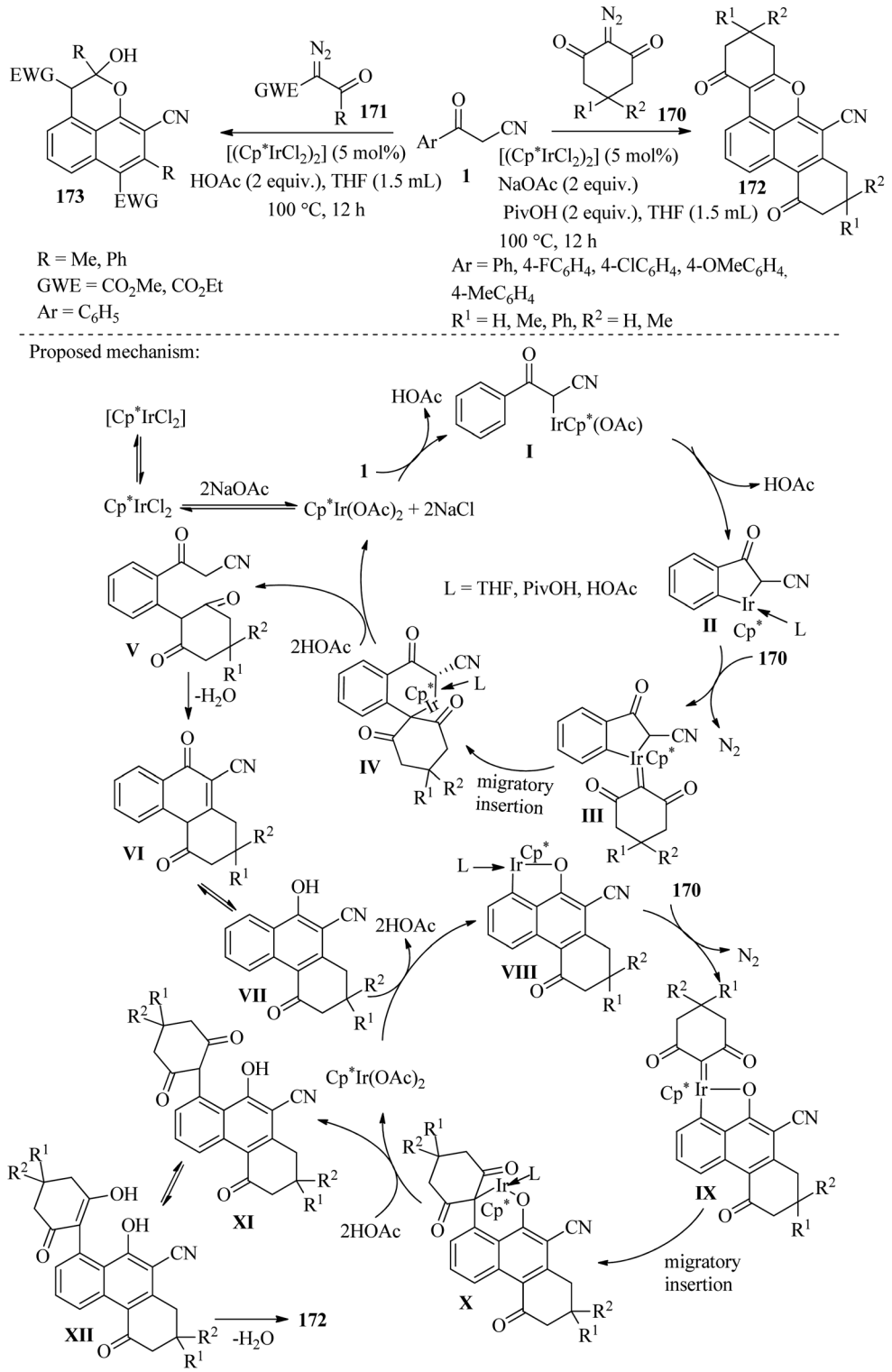
naphtho[1,8-*bc*]pyrans **172** through Rh(III)-catalyzed cascade reactions of β-ketonitriles **1** with cyclic 2-diazo-1,3-dicarbonyl compounds **170**. The formation of the title compounds involves a cascade process that goes through two steps. The process begins with the cleavage of C($sp^2$)AH/C($sp^3$)AH bonds, followed by metalation and carbenoid insertion of **170** with **I**,




Scheme 64 Synthesis of polysubstituted cyanocarbazoles **167**.

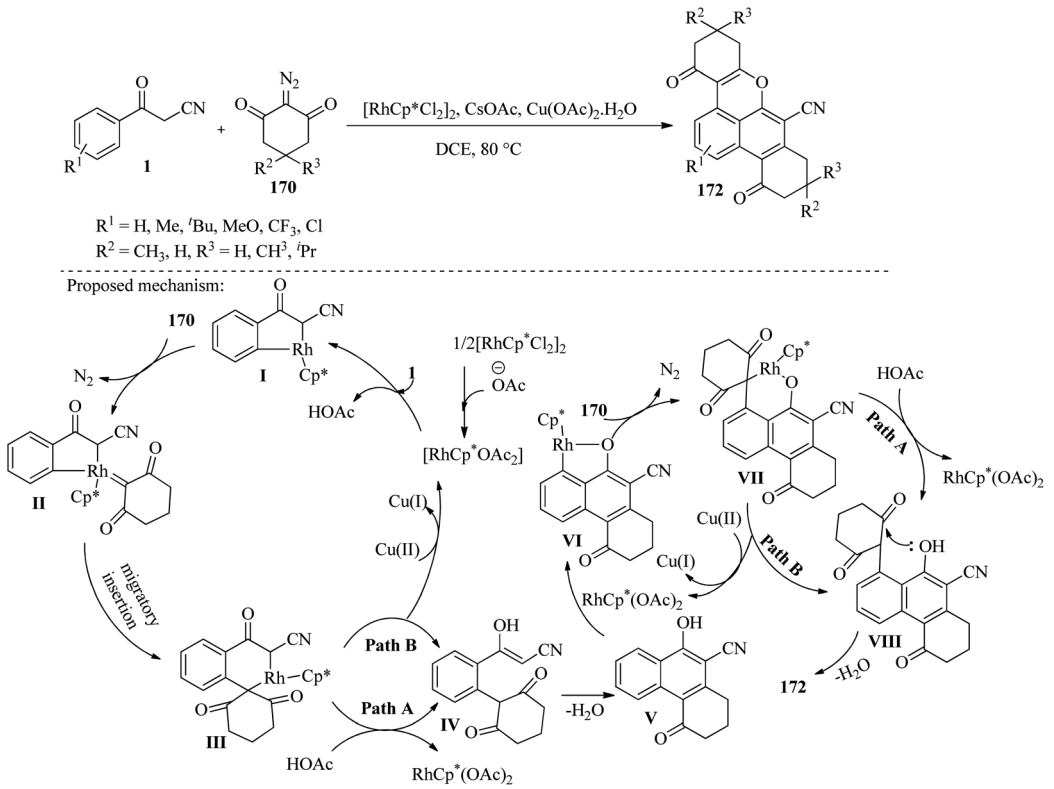



Scheme 65 Synthesis of polysubstituted benzofuro[2,3-*b*]pyrroles **169**.

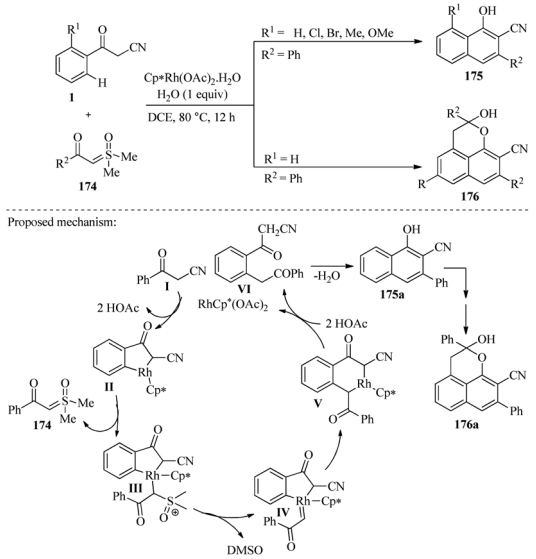



Scheme 66 Synthesis of polysubstituted naphtho[1,8-*bc*]pyrans **172** and **173**.

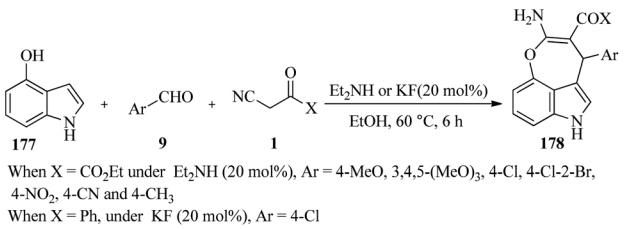
resulting in intramolecular annulation to yield substituted 1-naphthol **V** as a key intermediate. In the second step, the *in situ* formed 1-naphthol intermediate **V** undergoes C($sp^2$)AH/OAH bonds cleavage, metalation, carbenoid insertion with **170**, and an intramolecular cyclization to give the naphtho[1,8-*bc*]pyran product. According to the authors, this new method for synthesizing naphtho[1,8-*bc*]pyran derivatives **172** offers several advantages over previously reported methods, including a simple operating method, readily available substrates, high efficiency, and excellent atom economy (Scheme 67).[83]




Scheme 67 Synthesis of polysubstituted naphtho[1,8-*bc*]pyrans **172**.




Scheme 68 Synthesis of naphthols **175** and 2,3-dihydronaphtho[1,8-*bc*]pyrans **176**.




Scheme 69 Synthesis of 3,4-fused tricyclic indoles **178**.

In a recent report, Wang and colleagues demonstrated the successful application of rhodium(III) catalysis in the synthesis of naphthols **175** and 2,3-dihydronaphtho[1,8-*bc*]pyrans **176**.

The process is involved the cascade activation of β-ketonitriles **1** and annulation with sulfoxonium ylides **174**. This study shows that this method is very efficient, selective, and versatile, and a wide range of β-ketonitrile **1** and sulfoxonium ylide **174** have been successfully employed. The redox-neutral conditions and broad substrate scope make this approach suitable for the synthesis of complex structures that are otherwise challenging to access (Scheme 68).[84]

Bai *et al.* have reported the development of three-component reactions that involve 4-hydroxyindole **177**, aldehydes **9**, and β-ketonitriles **1** for the synthesis of 3,4-fused tricyclic indoles **178**. These reactions utilize either potassium fluoride or diethylamine as a catalyst, offering straightforward access to 3,4-fused tricyclic indoles with good to excellent yields (Scheme 69).[85]

## 5. Conclusion

This review summarizes the last decade of advancements in using β-ketonitriles as vinylogous nucleophiles for synthesizing

biologically active scaffolds such as functionalized coumarins, quinolines, five and six-membered heterocycles, spiro and polycyclic heterocycles, propellanes and other useful cyclic and acyclic compounds, as well as natural products.

The dual reactivity of β-ketonitriles, serving as both electrophiles from the CN moiety and nucleophiles from hydroxyl and CH groups, enables the design of novel tandem reactions. Their high reactivity and ability to coordinate with catalysts through hydrogen bonding and acid-base interactions make them valuable substrates in synthetic organic chemistry, particularly for synthesizing chiral scaffolds.

## Data availability

No primary research results, software, or code have been included and no new data were generated or analyzed as part of this review.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We are grateful to the Research Council of Tarbiat Modares University for its support of this work.

## Notes and references

1 M. H. Elnagdi, M. R. H. Elmoghayar and G. E. H. Elgemeie, *Synthesis*, 1984, **1984**, 1–26.
2 N. R. Mohamed, N. Y. Khaireldin, A. F. Fahmy and A. A. El-Sayed, *Pharma Chem.*, 2010, **2**, 400.
3 R. E. Khidre, B. F. Abdel-Wahab and F. A.-R. Badria, *Lett. Drug Des. Discovery*, 2011, **8**, 640.
4 B. Zarranz, A. Jaso, I. Aldana, A. Monge, S. Maurel, E. Deharo, V. Jullian and M. Sauvain, *Chem. Abstr.*, 2006, **144**, 266586.
5 F. Al-Omran, A.-Z. A. Elassar and A. A. El-Khair, *Tetrahedron*, 2001, **57**, 10163.
6 (*a*) R. E. Khidre and B. F. Abdelwahab, *Turk. J. Chem.*, 2013, **37**, 685–711; (*b*) M. H. Elnagdi, M. R. H. Elmoghayar and G. E. H. Elgemeie, *Synthesis*, 1984, **1984**, 1–26; (*c*) C. R. Hauser and C. J. Eby, *J. Am. Chem. Soc.*, 1957, **79**, 728–731.
7 I. Yavari, S. Shaabanzadeh and S. Sheikhi, *ChemistrySelect*, 2020, **5**, 564–568.
8 K. Kiyokawa, T. Nagata and S. Minakata, *Synthesis*, 2018, **50**, 485–498.
9 J. M. Robinson, M. Ahmed, N. J. Alaniz, T. R. Boyles, C. D. Brasher, K. A. Floyd and C. D. Wright, *J. Heterocycl. Chem.*, 1998, **35**, 65–69.
10 S. V. Ryabukhin, A. S. Plaskon, E. N. Ostapchuk, D. M. Volochnyuk, O. V. Shishkin, A. N. Shivanyuk and A. A. Tolmachev, *Org. Lett.*, 2007, **9**, 4215–4218.
11 P. S. N. Reddy and P. Reddy, *Heterocycl. Commun.*, 2004, **10**, 163–166.
12 Q. Jia and J. Wang, *Org. Lett.*, 2016, **18**, 2212–2215.
13 R. E. Khidre and B. F. Abdel-Wahab, *Curr. Org. Chem.*, 2013, **17**, 430–445.
14 B. F. Abdel-Wahab, M. F. El-Mansy and R. E. Khidre, *J. Iran. Chem. Soc.*, 2013, **10**, 1085–1102.
15 (*a*) A. Raghunadh, S. B. Meruva, N. A. Kumar, G. S. Kumar, L. V. Rao and U. S. Kumar, *Synthesis*, 2012, **44**, 283–289; (*b*) C. Zhang, P. Feng and N. Jiao, *J. Am. Chem. Soc.*, 2013, **135**, 15257–15262; (*c*) A. Nagaki, D. Ichinari and J. I. Yoshida, *Chem. Commun.*, 2013, **49**, 3242–3244.
16 Y. Xie, J. Liu, Y. Huang and L. Yao, *Tetrahedron Lett.*, 2015, **56**, 3793–3795.
17 C. Xu, N. N. Zhang, X. J. Li, Y. Q. Ge, P. H. Diao and C. Guo, *Synlett*, 2018, **29**, 1065–1070.
18 H. S. P. Rao and N. Muthanna, *Synlett*, 2016, **27**, 2014–2018.
19 N. Gao, X. Liu, X. Yuan, B. Hu, P. Jiang, J. Lin and Y. Jin, *J. Org. Chem.*, 2022, **87**, 10298–10308.
20 X. Song, B. N. Do Doan, X. Zhang, R. Lee and X. Fan, *Org. Lett.*, 2020, **22**, 46–51.
21 J. Wang, J. Xiang, M. Wang, J. Guan and A. Wu, *Tetrahedron*, 2014, **70**, 1412–1417.
22 H. K. Sha, T. Xu, F. Liu, B. Z. Tang, W. J. Hao, S. J. Tu and B. Jiang, *Chem. Commun.*, 2018, **54**, 10415–10418.
23 S. Sathiyamoorthi, A. I. Almansour, S. K. Raju, A. Natarajan and R. R. Kumar, *Synth. Commun.*, 2021, **51**, 234–244.
24 B. Hocaoglu and M. Yilmaz, *Synth. Commun.*, 2019, **49**, 1938–1946.
25 B. S. Gore, C. Y. Kuo, A. M. Garkhedkar, Y. L. Chang and J. J. Wang, *Org. Lett.*, 2020, **22**, 6160–6165.
26 J. Feng, X. Yuan, W. Luo, L. Lin, X. Liu and X. Feng, *Chem.–Eur. J.*, 2016, **22**, 15650–15653.
27 J. Wang, S. Chen, W. Wu, S. Wen and Z. Weng, *J. Org. Chem.*, 2019, **84**, 15685–15696.
28 K. Xu, H. Liu, Y. Hou, J. Shen, D. Liu and W. Zhang, *Chem. Commun.*, 2019, **55**, 13295–13298.
29 Q. Li, X. He, J. Tao, M. Xie, H. Wang, R. Li and Y. Shang, *Adv. Synth. Catal.*, 2019, **361**, 1874–1886.
30 S. G. Balwe, J. S. Kim, Y. I. Kim and Y. T. Jeong, *Tetrahedron*, 2019, **75**, 797–807.
31 D. Zhong, F. Jiang, S. Shen, L. Wang, W. Wang, Y. Wu and H. Guo, *Adv. Synth. Catal.*, 2020, **362**, 5026–5030.
32 J. Zhou, M. Huang, X. Zhu and Y. Wan, *Chin. Chem. Lett.*, 2021, **32**, 445–448.
33 L. Palanivel and V. Gnanasambandam, *Org. Biomol. Chem.*, 2020, **18**, 3082–3092.
34 M. B. Yadav and Y. T. Jeong, *Org. Biomol. Chem.*, 2021, **19**, 7409–7419.
35 S. Nagaraju, S. Liu, J. Liu, S. Yang, R. Liu, Z. Chen and X. Fang, *Org. Lett.*, 2019, **21**, 10075–10080.
36 M. Xia, Z. Moussa and Z. Judeh, *Molecules*, 2022, **27**, 5285.
37 A. Shaabani, M. T. Nazeri and R. Afshari, *Mol. Diversity*, 2019, **23**, 751–807.
38 (*a*) M. Kelada, J. M. Walsh, R. W. Devine, P. McArdle and J. C. Stephens, *Beilstein J. Org. Chem.*, 2018, **14**, 1222–1228; (*b*) Z. He, C. Charleton, R. W. Devine, M. Kelada, J. M. Walsh, G. E. Conway and J. F. Curtin, *Eur. J. Med. Chem.*, 2021, **224**, 113736–113747.

39 Y. Wei, P. Liu, Y. Liu, J. He, X. Li, S. Li and J. Zhao, *Org. Biomol. Chem.*, 2021, **19**, 3932–3939.
40 L. Savegnago, M. do Sacramento, L. M. Brod, M. G. Fronza, N. Seus, E. J. Lenardao and D. Alves, *RSC Adv.*, 2016, **6**, 8021–8031.
41 A. V. Kachanov, A. V. Zamaraev, A. V. Gerasimenko, K. V. Maslov, O. Y. Slabko and V. A. Kaminskii, *Synlett*, 2018, **29**, 2035–2038.
42 M. Luo, J. C. Zhang and H. Yin, *J. Chem. Sci.*, 2015, **127**, 163–166.
43 J. Sun, H. Ge, X. Zhen, X. An, G. Zhang, D. Zhang-Negrerie and K. Zhao, *Tetrahedron*, 2018, **74**, 2107–2114.
44 M. Krasavin, M. Korsakov, Z. Zvonaryova, E. Semyonychev, T. Tuccinardi, S. Kalinin and C. T. Supuran, *Bioorg. Med. Chem.*, 2017, **25**, 1914–1925.
45 Z. Niu, X. He and Y. Shang, *Tetrahedron: Asymmetry*, 2014, **25**, 796–801.
46 C. Ni and X. Tong, *J. Am. Chem. Soc.*, 2016, **138**, 7872–7875.
47 W. Zhou, C. Ni, J. Chen, D. Wang and X. Tong, *Org. Lett.*, 2017, **19**, 1890–1893.
48 C. Sheng, Z. Ling, T. Ahmad, F. Xie and W. Zhang, *Chem.–Eur. J.*, 2022, **28**, e202200128, DOI: **10.1002/chem.202200128**.
49 M. Zhang, M. N. Chen, J. M. Li, N. Liu and Z. H. Zhang, *ACS Comb. Sci.*, 2019, **21**, 685–691.
50 Y. Zhang, H. Luo, Q. Lu, Q. An, Y. Li, S. Li and B. Li, *Chin. Chem. Lett.*, 2021, **32**, 393–396.
51 C. Bharkavi, P. Gunasekaran, S. V. Kumar, M. Sakthi and S. Perumal, *Tetrahedron Lett.*, 2014, **55**, 5486–5490.
52 I. R. Siddiqui, P. Rai and A. Srivastava, *New J. Chem.*, 2014, **38**, 3791–3795.
53 C. K. Chan, Y. L. Chan, Y. L. Tsai and M. Y. Chang, *J. Org. Chem.*, 2016, **81**, 8112–8120.
54 A. Palanimuthu, C. Chen and G. H. Lee, *Tetrahedron Lett.*, 2021, **72**, 153063.
55 S. Dhiman, H. K. Saini, N. K. Nandwana, D. Kumar and A. Kumar, *RSC Adv.*, 2016, **6**, 23987–23994.
56 A. Alizadeh and A. Rostampoor, *J. Iran. Chem. Soc.*, 2022, **19**, 1239–1249.
57 M. S. Rao and S. Hussain, *Tetrahedron Lett.*, 2021, **76**, 153187.
58 Z. Yang, P. Li, Z. Chen and X. F. Wu, *J. Catal.*, 2023, **427**, 115098.
59 C. Duan, L. Ye, W. Xu, X. Li, F. Chen, Z. Zhao and X. Li, *Chin. Chem. Lett.*, 2018, **29**, 1273–1276.
60 X. He, H. Wang, X. Cai, Q. Li, J. Tao and Y. Shang, *Org. Biomol. Chem.*, 2018, **16**, 7191–7202.
61 C. Gharui, C. Parida and S. C. Pan, *J. Org. Chem.*, 2021, **86**, 13071–13081.
62 W. Jiang, J. Sun, R. Z. Liu and C. G. Yan, *Org. Biomol. Chem.*, 2018, **16**, 5816–5822.
63 A. Alizadeh and B. Farajpour, *ChemistrySelect*, 2021, **6**, 6150–6153.
64 P. Borah, P. S. Naidu and P. J. Bhuyan, *Tetrahedron Lett.*, 2012, **53**, 5034–5037.
65 A. Alizadeh and A. Rostampoor, *ChemistrySelect*, 2022, 7, DOI: **10.1002/slct.202200299**.
66 S. Pal, M. N. Khan, S. Karamthulla and L. H. Choudhury, *RSC Adv.*, 2013, **3**, 15705–15711.
67 P. Zafari, B. E. Saatluo, A. Rashidi, M. M. Baradarani and J. A. Jouleb, *Arkivoc*, 2021, 9–16.
68 J. Xie, W. L. Xing, F. Sha and X. Y. Wu, *Eur. J. Org Chem.*, 2016, **2016**, 3983–3992.
69 I. Yavari, A. Khajeh-Khezri, S. Bahemmat and M. R. Halvagar, *Synlett*, 2017, **28**, 1785–1788.
70 M. B. Yadav, S. R. Bhosle and Y. T. Jeong, *Tetrahedron Lett.*, 2022, **98**, 153815.
71 M. B. Yadav, S. S. Vagh and Y. T. Jeong, *Eur. J. Org Chem.*, 2022, **2022**, e202101534.
72 J. Sun, J. K. Qiu, B. Jiang, W. J. Hao, C. Guo and S. J. Tu, *J. Org. Chem.*, 2016, **81**, 3321–3328.
73 S. Kim, J. H. Lee, S. H. Yoon and I. Kim, *Org. Biomol. Chem.*, 2021, **19**, 5806–5817.
74 S. Safaei, I. Mohammadpoor-Baltork, A. R. Khosropour, M. Moghadam, S. Tangestaninejad and V. Mirkhani, *J. Iran. Chem. Soc.*, 2017, **14**, 1583–1589.
75 C. Zhou, P. Diao, X. Li, Y. Ge and C. Guo, *Chin. Chem. Lett.*, 2019, **30**, 371–374.
76 H. Behbehani and H. M. Ibrahim, *RSC Adv.*, 2015, **5**, 89226–89237.
77 A. J. Ansari, G. Joshi, U. P. Yadav, A. K. Maurya, V. K. Agnihotri, S. Kalra and D. M. Sawant, *Bioorg. Chem.*, 2019, **93**, 103314.
78 L. Li, H. Xu, L. Dai, J. Xi, L. Gao and L. Rong, *Tetrahedron*, 2017, **73**, 5358–5365.
79 M. Alizadeh-Kouzehrash and A. Rahmati, *Tetrahedron*, 2020, **76**, 130923.
80 Y. Yang, J. Huang, H. Tan, L. Kong, M. Wang, Y. Yuan and Y. Li, *Org. Biomol. Chem.*, 2019, **17**, 958–965.
81 S. G. Balwe and Y. T. Jeong, *New J. Chem.*, 2020, **44**, 3632–3636.
82 K. Yan, B. Li and B. Wang, *Adv. Synth. Catal.*, 2018, **360**, 2272–2279.
83 B. Zhang, B. Li, C. Guo, X. Zhang and X. Fan, *Tetrahedron Lett.*, 2018, **59**, 3094–3099.
84 P. Hu, Y. Zhang, Y. Xu, S. Yang, B. Liu and X. Li, *Org. Lett.*, 2018, **20**, 2160–2163.
85 R. Bai, J. Yang, L. Min, C. Liu, F. Wu and Y. Gu, *Tetrahedron*, 2016, **72**, 2170–2177.