RECENT ADVANCES IN COPPER-CATALYZED SYNTHESIS OF QUINAZOLINONES

DOI: http://dx.medra.org/10.17374/targets.2025.28.200

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Abstract. *Heterocyclic compounds have an inevitable place in organic chemistry due to their wide application in the different fields of science, particularly research on drug discovery, which has benefitted the most. Quinazolinones, the most important class of heterocyclic compounds, are intriguing compounds in pharmaceuticals and medicinal chemistry. Quinazolinone and its derivatives exhibit a wide range of biological and pharmacological activities, including anti-inflammatory, antitubercular, antiviral, and anticancer activities, etc. There are almost two hundred different types of quinazolinone in nature, and they exhibit intriguing biological characteristics. Recent research has revealed that several non-natural analogues of this heterocyclic compound framework also display intriguing biological and material features, leading to heightened interest in discovering a method to synthesize these molecules. In addition to the traditional classical approach, the latest development involves using the catalytic method with an organometallic reagent. In this regard, Cu-catalyzed techniques have demonstrated a significant contribution. Due to their inherent advantages, particularly their abundance and affordability, copper metal-based catalysts have recently garnered significant interest, particularly in the field of organic synthesis. In the last fifteen years, there have been noteworthy reports of the use of Cu-catalyst for the synthesis of quinazolinones. A variety of methods have been developed where Cu-catalysts are fully utilized as an electron donor. The present review specifically describes the synthesis of quinazolinone derivatives by using a Cu-based catalyst. We have categorized the key reactions into different sections and made every effort to incorporate the latest literature method.*

Contents

1. Introduction

Heterocyclic compounds play a significant role in the development of drugs and different kinds of materials for a variety of applications. More than 60% of approved small drugs are nitrogen-containing heterocycles.[1] Quinazolinones (1,3-diazanaphthalene-4-one), which are fused heterocyclic compounds, have a special prominence due to their presence in more than 200 natural alkaloids and wide range of biological properties. In the last few years, a good deal of interest has been elevated to develop methodologies to construct the framework of quinazolinones, particularly after the approval of a few unnatural derivatives as medicines *viz* rutaecarpine, (+)-febrifugine, afloqualone and raltitrexed ispinesib, raltitrexed, and tempostatin (Figure 1).[2] Furthermore, many other quinazolinone derivatives, such as tryptanthrin, luotonin A, rutaecarpine, euxylophoricine, and circumdatin also exhibit encouraging biological properties and are being investigated further to potentially become drugs. Thus, due to the wide array of its therapeutic potential *viz* in anticancer, antibacterial, antidiabetic, hypnotic, sedative, analgesic, anticonvulsant, antitussive, and anti-inflammatory activities, there is a high demand to synthesize unnatural heterocyclic compounds with quinazolinone scaffolds. Recently, a few quinazolinone derivatives have been also found with interesting photophysical properties, and thus these scaffolds further develop an upsurge of interest to develop as luminescent materials for the application in biosensors and imaging reagents.[3]

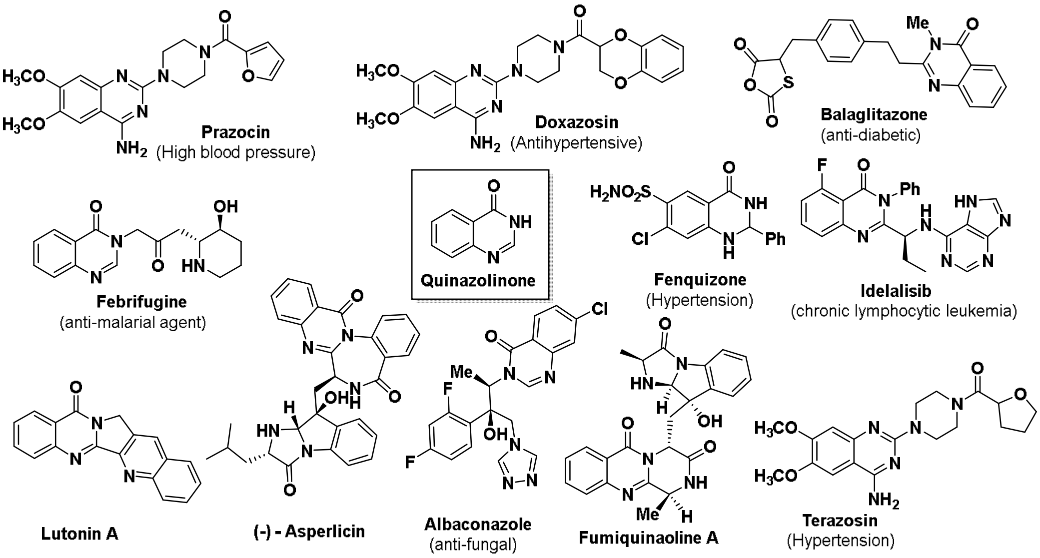


Figure 1. Representative examples of natural products and drugs with quinazolinone framework.

Quinazolinone derivatives are traditionally synthesized from the condensation reaction of 1,2-disubstituted anthranilic acid derivatives with formamide equivalents,[4] oxidative condensation of anthranilamide derivatives with corresponding carbonyl compounds, 2-aminobenzoic acid derivatives, 2-aminobenzonitrile, and 2-halogen-substituted anilines.[5,6] However, the use of these traditional methods was severely constrained due to the high temperature and lengthy reaction time.

Due to their significant interest, researchers have recently developed several methods to synthesize quinazolinone derivatives efficiently using both catalytic and non-catalytic approaches. There are only a few reviews available for the synthesis of quinazolinone.[7-13] The recent trend to synthesize quinazolinone derivatives is a catalytic approach that overcomes some of the above limitations, providing an opportunity to synthesize diverse varieties due to good substrate scope. One of the promising areas of research is the transition metal-catalyzed C−H activation and functionalization, which effectively forms C–C, C–X, and C–N bonds to create unique and novel organic compounds.[14,15,16-18] Thus, metal-based catalytic transformation specifically to quinazolinone derivatives is the centre of the development of methodologies, and various metals *viz* ruthenium,[19] vanadium,[20,21] zinc,[22,23] rhodium,[24,25] cobalt,[26] nickel,[27] gold,[25] iron,[25] iridium,[28,29] palladium,[30,31,32,33] and copper[34,35] have been utilized.[36] Copper salts, which are inexpensive, abundant, and possess low toxicity have generated a great deal of interest and have been widely used in organic reactions as well as in the synthesis of *N*-heterocycles as a catalyst[25,37,38,] The various Lewis acids copper catalysts, such as CuI, CuBr, CuCl, $Cu(OAc)_2$, and $Cu(OTf)_2$, were generally used in most of cases. This review describes the use of Cu- as a catalyst for the synthesis of quinazolinone derivatives.

2. General mechanism of copper catalyst mediated reactions

The C−H activation is a widely used method for the construction of C−N bonds and heterocyclic compounds using a Cu-catalyzed reaction. It is interesting to first summarize the general mechanism of Cu-catalyzed C−H functionalization since, under different sets of conditions, the mechanism may be complex because of the many oxidation states of copper [Cu(0), Cu(I), Cu(II), and Cu(III)]. The single electron transfer (SET) reaction mechanism is the most common in the case of a C−H activation reaction where the Cu(II)/Cu(I) catalytic cycle is involved. Thus, a common general process is the one-electron oxidation by Cu(II) by abstracting one electron from the substrate to afford a radical intermediate. The radical intermediate can then undergo several transformations involving cyclization and oxidation processes to afford the heterocycle product or, if the radical is reactive, it would then first transform into another radical and then follow cyclization and oxidation. The generated Cu(I) is subsequently oxidized by oxidants to regenerate the Cu(II) catalyst, which can be used in the next catalytic cycle (Figure 2a).

Recently, the two-electron transfer process of Cu-catalyst and C−H functionalization has gained increasing attention and here Cu(I)/Cu(III) catalytic cycle process is involved. First, two-electron transfers involving the oxidative addition of Cu(I) to halogenated substrate form an organocopper(III) intermediate through C−H functionalization. Then, reductive elimination of the organocopper(III) intermediate produces the heterocycle product and regenerates the Cu(I) species, closing the catalytic cycle. Another two-electron process has also been proposed, particularly for intermolecular C−H functionalization using the Cu(I)/Cu(III) catalytic cycle, where organocopper(III) intermediate undergoes C−H functionalization in the presence of strong oxidants (Figure 2b).

The more important one is the combination of one- and two-electron processes in Cu-catalyzed C−H functionalization. Researchers propose catalytic cycle that facilitates the process with the formation of an organocopper(III) intermediate serving as the key step. First, the substrate and Cu(II) form a Cu(II) intermediate involving C−H functionalization. The organocopper(III) intermediate is then formed by a Cu(II) disproportionation. The organocopper(III) intermediate undergoes reductive elimination to yield the heterocycle product and Cu(I) species, which oxidizes to Cu(II) to participate in the subsequent catalytic cycle (Figure 2c).[39,40]

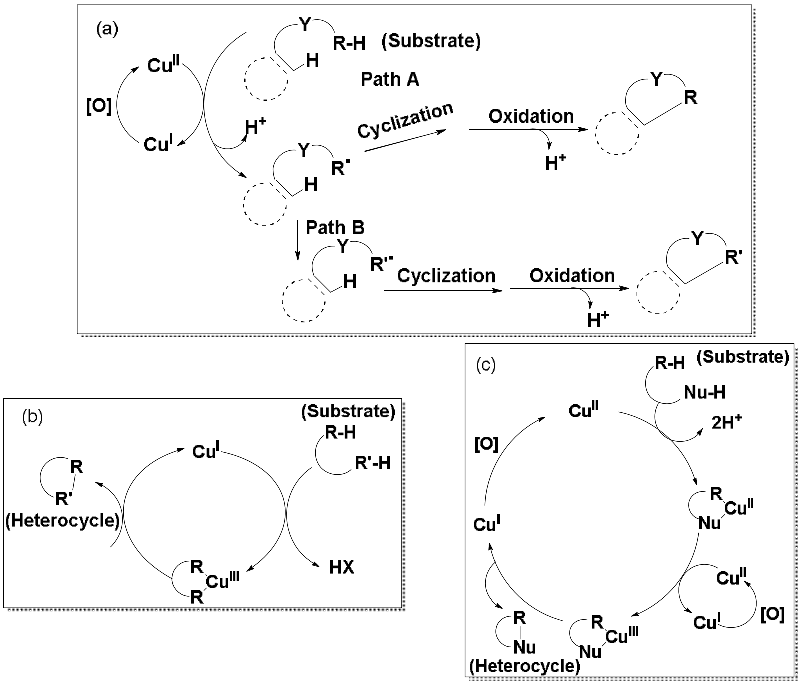


Figure 2. General reaction mechanism of Cu-catalyzed reactions: (a) one-Electron process in Cu-catalyzed C−H functionalization, (b) two-electron process in Cu-catalyzed C−H functionalization, (c) combination of one- and two-electron processes in Cu-Catalyzed C−H functionalization.

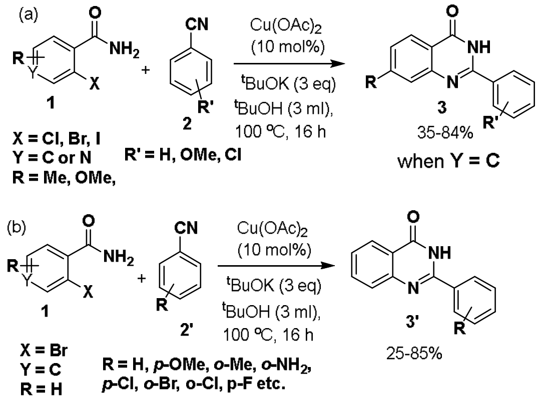
3. Synthesis of quinazolinones

The present review aims to summarize the use of copper catalysts in the synthesis of quinazolinones. The review is organized according to the type of reactions involved in the synthesis of quinazolinones where

Cu-catalyst as a prime or co-catalyst is used in the synthesis process. For some typical reactions, a mechanism will be also described.

3.1. Cu-Catalyzed cascade/tandem reactions

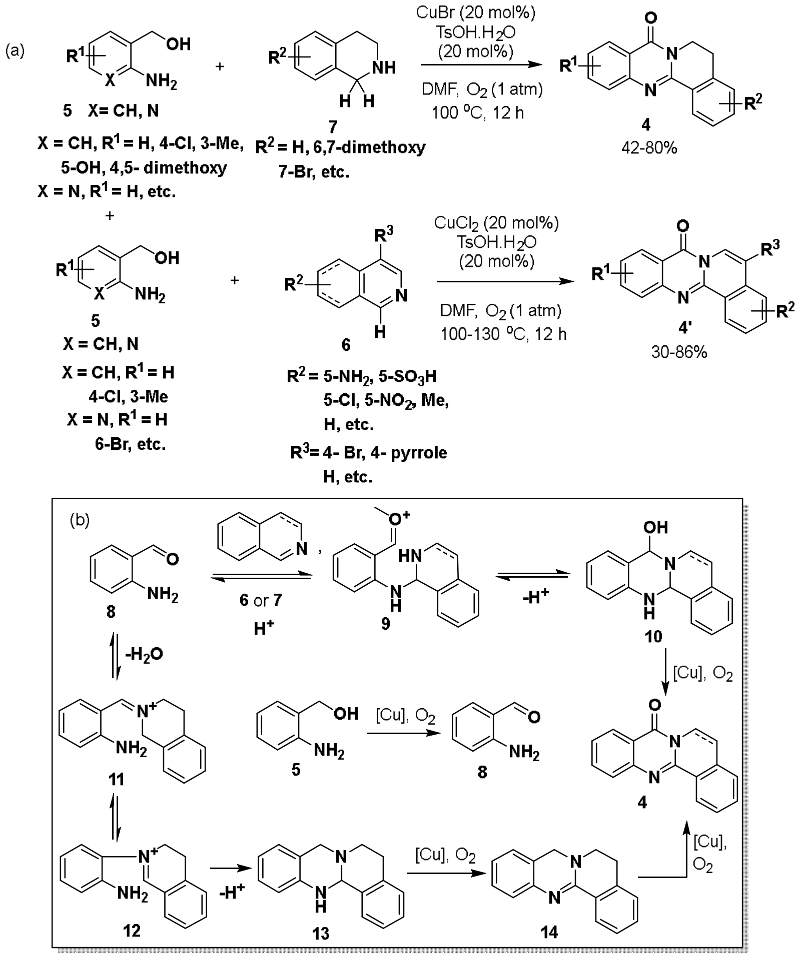
The 2-substituted halo derivatives were used regularly for the synthesis of quinazolinone derivatives. Bao *et al.* described a convenient method of the synthesis of quinazolinone derivatives **3** from simple and readily available 2-halo benzamides **1** and nitriles **2**. A Cu-catalyzed cascade reaction of nucleophilic addition of 2-halobenzamide to nitrile followed by S_NAr reaction in the presence of ^{t}BuOK was proposed for the synthesis of quinazolinones derivatives (Scheme 1a,b). After screening various Levis acid catalysts Cu(OAc)$_2$ was found to be the most suitable reagent. The method was found to be suitable for various kinds of substituents.[41]



Scheme 1. Use of 2-halobenzamides **1** and nitriles **2** for the synthesis of quinazolinone derivatives **3**.

Similarly, Fu and Jiang demonstrated the Cu-catalyzed cascade reactions of amidine hydrochlorides with substituted 2-halobenzaldehydes, 2-halophenylketones, or methyl 2-halobenzoates.[42] Fu *et al.* also utilized 2-halobenzamides containing (aryl)-methanamines or amino acids in their Cu-catalyzed cascade reactions.[43] Tripathi *et al.* recently demonstrated the synthesis of quinazoline-4(3*H*)-ones *via* a Cu-catalyzed one-pot reaction of 2-bromobenzamides with aldehydes, alcohols, or methyl arenes, using TMSN$_3$ as a nitrogen source.[44] The above reactions are Ullmann-type C–N coupling reactions, and Cu(I) salts were used as transition-metal catalysts. Ma *et al.* also used 2-halo-*N*-substituted benzamide with formamide for the synthesis of quinazolinone derivatives, which relied on a copper iodide/4-hydroxy-L-proline catalyzed aryl amidation reaction followed by subsequent spontaneous or HMDS/ZnCl$_2$ mediated condensative cyclization.[45] 2-Bromobenzoic acid or 2-iodobenzoic acid and acetamidine hydrochloride were chosen by Liu et. al. for the synthesis of quinazolinone derivatives in the presence of CuI and Cs$_2$CO$_3$.[46] Yao *et al.* demonstrated a one-pot Ullman-type *N*-alkylation reaction followed by intramolecular C–H amidation reaction protocol for the synthesis of 2-phenylquinazolinone and quinazolinone derivatives from *N*-substituted 2-iodobenzamides and benzylamines, allyl, and cinnamylamine reaction. An inexpensive reagent, such as CuSO$_4$·5H$_2$O was used in the reaction protocol.[47]

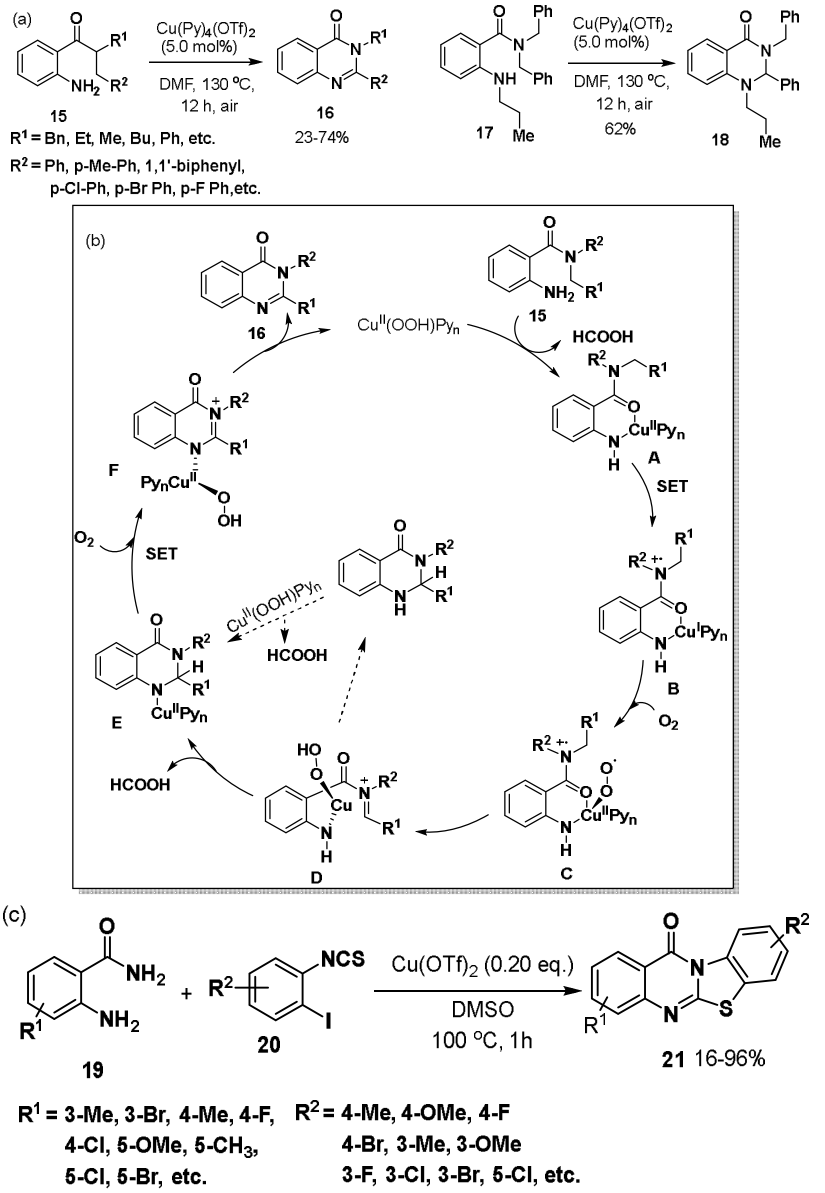
Pyrido-fused quinazolinone especially has particular pharmaceutical value. Also, 7,8-dehydrorutaecarpine, 1-hydroxy-7,8-dehydrorutaecarpine, euxylophoricine B, euxylophoricine E, and euxylophoricine F are important biologically active natural alkaloids bearing an 11*H*-pyrido[2,1-*b*]quinazolin-11-one fragment, and are isolated from plants.[48,49] Phan *et al.* synthesized a new set of pyrido-fused quinazolinones **4** *via* copper-catalyzed cascade Csp^2–H amination and annulation of 2-aminoarylmethanols **5** with isoquinolines **6** or pyridines. The commercially available CuCl$_2$ catalyst with molecular oxygen as a green oxidant was used. Moreover, the cross-coupling of 2-aminoarylmethanols with tetrahydroisoquinolines **7** was explored, and, in this case, CuBr was found to show a higher catalytic activity than CuCl$_2$. Several ring-fused quinazolinones were obtained following this protocol (Scheme 2a). Based on the control experiments, a plausible mechanism was proposed, which is shown in Scheme 2a. Therefore, using readily available reactants and catalysts, the aforementioned approach afforded a complex heterocyclic structure in a single synthetic step (Scheme 2b).[50]



Scheme 2. (a) Synthesis of pyrido-fused quinazolinone derivatives, (b) its mechanism.

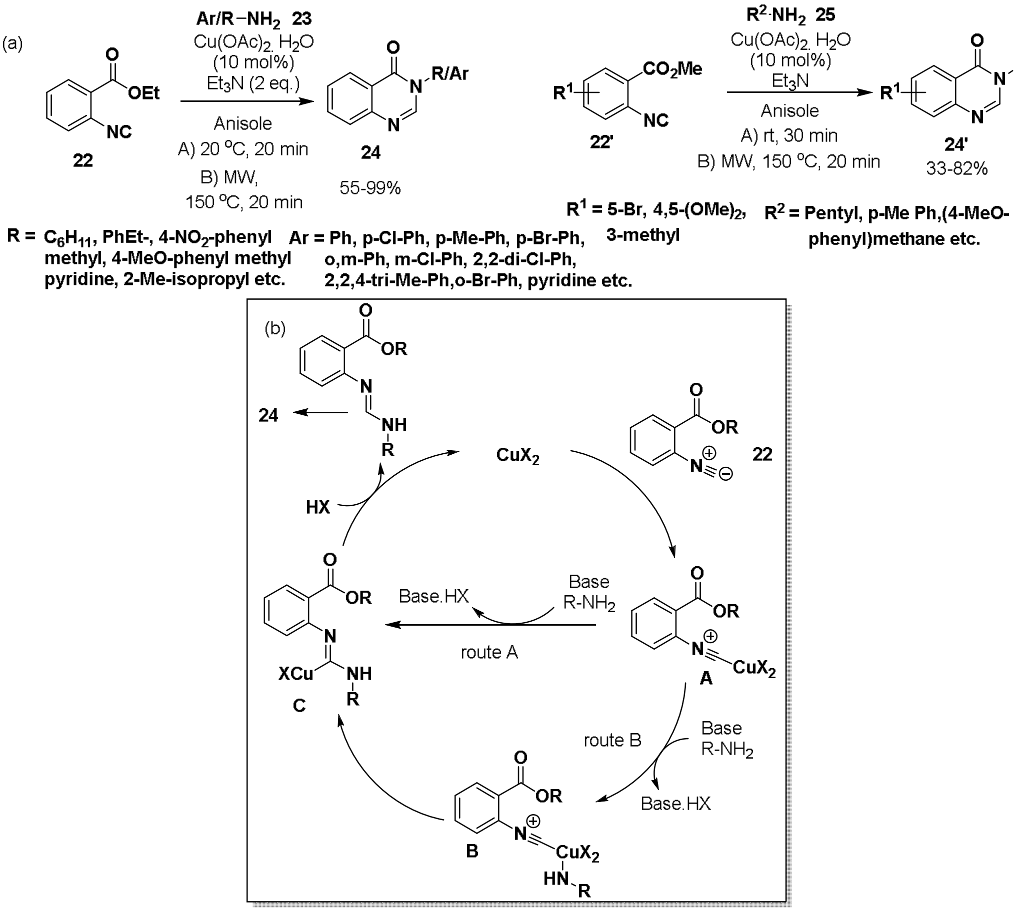
Previously, Cu-catalyzed pyrido-fused quinazolinone was also synthesized by Xu *et al.* by domino reaction from arylacetamides involving an aerobic benzylic oxidation/cyclization/decarbonylation process.[51] Huang *et al.*[52] also developed a simple and efficient synthesis of 11*H*-pyrido[2,1-*b*]quinazolin-11-ones by using $Cu(OAc)_2 \cdot H_2O$-catalyzed reaction of easily available substituted isatins and 2-bromopyridine derivatives. The reaction involves C–N/C–C bond cleavage and two C–N bond formations in a one-pot operation.

Kapdi *et al.* also used 2-amino substituted *N,N*-dialkylbenzamides **15** to synthesize 2,3-disubstituted-4(3*H*)-quinazolinones **16** *via* a $Cu(Py)_4(OTf)_2$ catalysed, Csp^3–H functionalisation/cyclisation reaction in the presence of oxygen. Substituted amine **17** also undergoes the reaction to give compound **18**. The method shows good functional group tolerance and and leads to diversely substituted quinazolinones under mild conditions. The mechanism of the reaction was also investigated, and was suggested to proceed through a double SET-type radical mechanism with an iminium-type intermediate involved in the rate-limiting step (Scheme 3a and b).[53] Very recently, Guo *et al.* also used 2-amino substituted benzamides **19** and 2-iodoisothiocyanates **20** for the Cu(OTf)$_2$-catalyzed synthesis of tetracyclic fused 12*H*-benzo[4,5]-thiazolo[2,3-*b*]quinazolin-12-ones **21** (Scheme 3c). The method utilized a domino double annulation strategy where C–N bond cleavage and the formation of a C–N/C–S bond are involved in one step. The control experiments and mechanistic investigation confirmed the intermolecular condensation of 2-amino benzamides with 2-iodoisothiocyanates, followed by an intramolecular Ullmann-type cross-coupling cyclization reaction.[54]



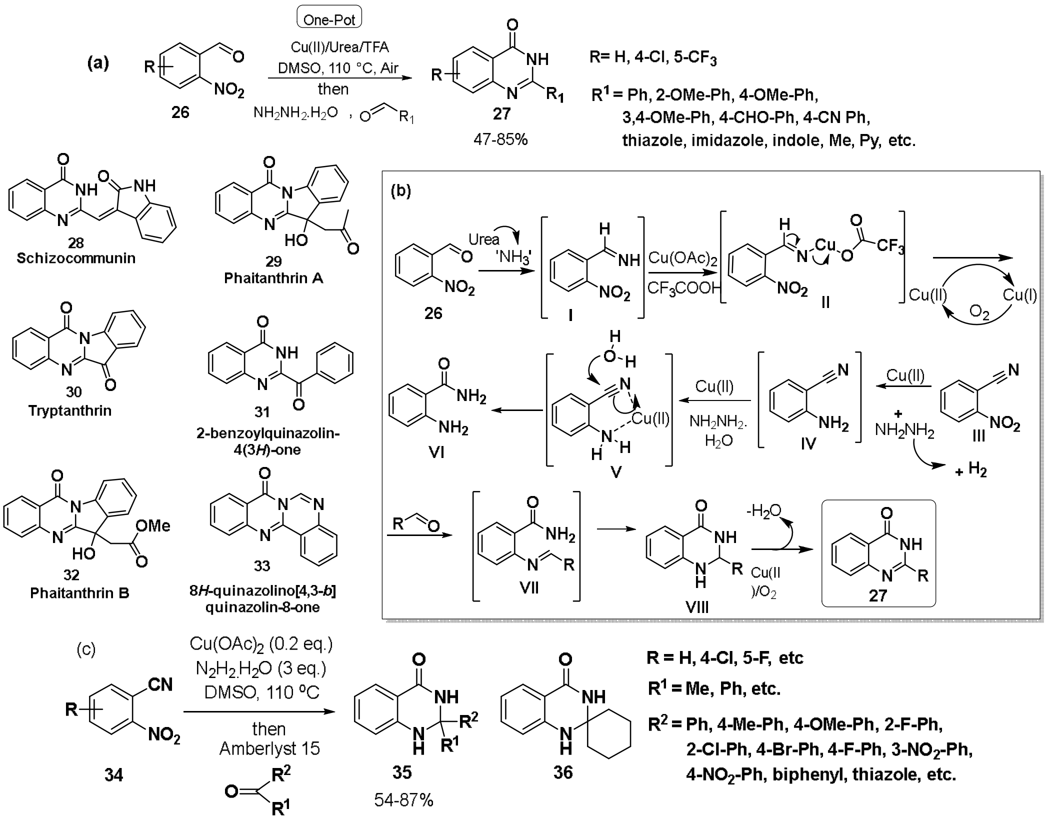
Scheme 3. (a) Synthesis of 2,3-disubstituted-4(3*H*)-quinazolinones, (b) its mechanism, (c) synthesis of fused 12*H*-benzo[4,5]-thiazolo[2,3-*b*]quinazolin-12-ones.

Recently, Orru *et al.* reported a novel Cu(II) acetate-catalyzed imidoylative cross-coupling/cyclocondensation between 2-isocyanobenzoates **22** and amines **23** which efficiently produces quinazoline-4-ones **24**. The reaction utilized Et_3N as an environmentally friendly catalyst and mild base and proceeded well in anisole as a sustainable solvent. The reaction could be performed even under non-anhydrous or inert atmosphere conditions. The scope of this reaction is broad and even aliphatic amines **25** were used for the synthesis of quizolinones derivatives (Scheme 4). The utility of methods was demonstrated by the synthesis of various natural products like echinozolinone, rutaecarpine, and pentacyclic luotonin A.[55]



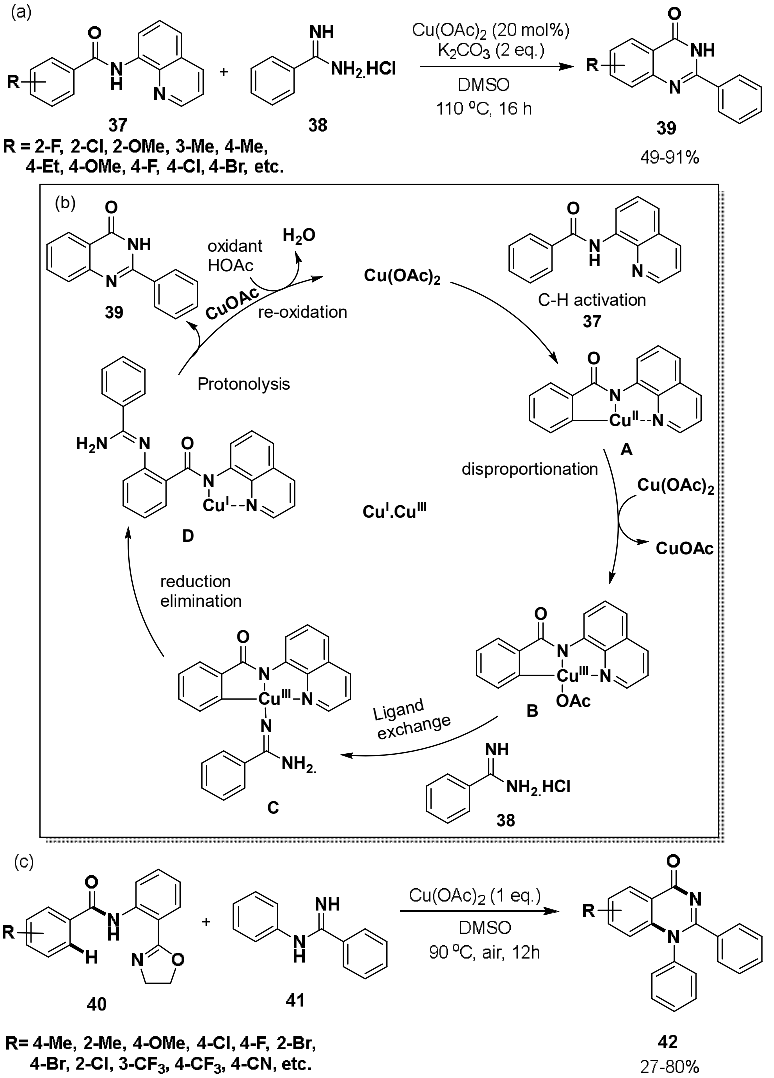
Scheme 4. (a) Synthesis of quinazoline-4-ones starting from 2-isocyanobenzoates, (b) its mechanism.

Pal *et al.* developed a useful method for the synthesis of quinazolinone derivatives **27** from 2-nitrobenzaldehydes **26** where a multi-step reaction in one pot was achieved.[56] First a method to convert aldehyde in 2-nitrobenzaldehyde derivative to nitrile III was developed under $Cu(OAc)_2$ and then method was extended to realize the one-step conversion of 2-nitrobenzaldehydes **26** to quinazolinone derivatives **27**. Based on control experiments, the mechanism was investigated. The steps involved were copper-catalyzed nitrile formation from aldehyde derivative in the presence of urea followed by reduction of the nitro group and hydrolysis of nitrile from hydrated hydrazine, supposed to give *o*-amino benzamide which on oxidative addition of aldehyde in the presence of atmospheric oxygen provided the quinazolinones. The method is suitable for wide variety of substarte with good functional group tolerance. The method was extended to the synthesis of natural products, namely, schizocommunin **28**, phaitanthrin-A **29**, tryptanthrin **30**, and phaitanthrin-B **31**. In addition, the method was applied to the regioselective synthesis of biheterocyclic 8*H*-quinazolino[4,3-*b*]quinazolin-8-one **32**, **33** in one step (Scheme 5a,b). Interestingly, DMSO was used as one carbon source to form product **32** under this copper-catalyzed reaction. The above method was extended to the synthesis of dihydroquinazolinones **35**, spiro-quinazolinones **36** and their bioactive molecular scaffolds starting from **34**. Thus reaction between 2-nitrobenzonitrile and hydrazine hydrate in the presence of ketone derivatives under Cu-catalyzed condition provided compounds **35**, **36** *etc.* in very good yields. This method has been used to synthesize a variety of electronically varied spiro- and dihydro-quinazolinones with high yield and functional group tolerance (Scheme 5c).[57]



Scheme 5. (a) Synthesis of quinazoline-4-ones starting from 2-nitrobenzaldehydes, (b) its mechanism, (c) synthesis of dihydroquinazolinones.

Huang *et al.* demonstrated the synthesis of quinazolinones derivatives **39** by the activation of *ortho* C–H bond in benzamide **38** linked with removable 8-aminoquinoline **37** directing by $Cu(OAc)_2$.[58] Thus, *ortho* C–H amination by using amidine hydrochlorides assisted by a removable 8-aminoquinoline **37** followed by the intramolecular nucleophilic addition led to a variety of quinazolinones derivatives **39** (Scheme 6a). The reaction was proposed to not follow the single electron pathway and, based on the different control experiments, a plausible mechanism was proposed (Scheme 6b). Huang *et al.* further extended the concept of C–H activation by using *N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)benzamide **40** as a bidentate-directing group and *N*-phenylbenzimidamide **41** for the synthesis of quinazolinones derivatives **42** in the presence of $Cu(OAc)_2$ as catalyst (Scheme 6c).[59] Additionally, the concept was extended to the synthesis of dihydro-quinazolinone derivatives, where acetophenone derivatives were employed. The method has also been applied to the synthesis of biologically active molecular scaffolds.

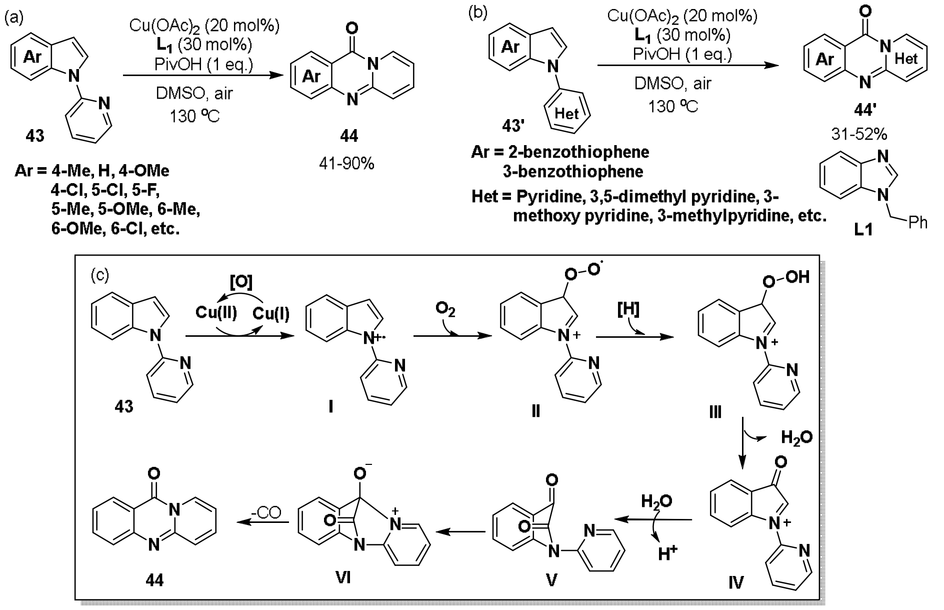


Scheme 6. (a) Synthesis of quinazolinones derivative from 8-aminoquinoline, (b) its mechanism, (c) synthesis of quinazolinones derivative from *N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)benzamide

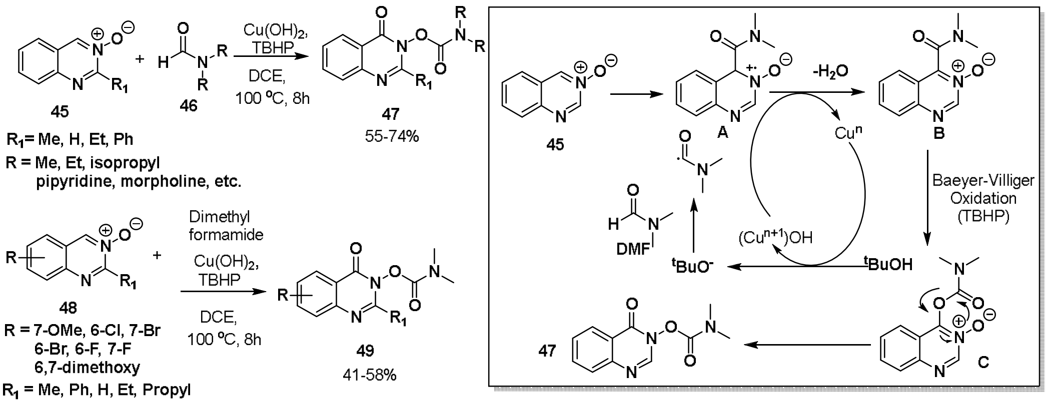
3.2. Cu-Catalysed aerobic oxidation

The metal-catalyzed sustainable approach with atom economy is one of the modern methods of organic synthesis. Methanol, a readily available carbon source in a reaction is a unique substrate that gives good atom economy and is considered as a green chemistry reactant. In a similar way, molecular oxygen has been recognized as the clean and ideal oxidant due to its abundance, lack of toxic by-products and low cost. Many catalyst have been used and Cu-based catalyst showed a significant result. Thus, combination of both molecular oxygen and Cu(II) as one-electron oxidant, the Cu(II)/O_2 catalytic system has been used in the construction of new C–O bond, C–N bond and C–C bond and extended to this effective system for successfully aerobic oxidation of C–H bond.[60] This combination of system have been also benefitted for the synthsis of quinazolinone derivatives.

Thus, Liu *et al.* demonstrated the effective use of Cu(II)/O_2 catalytic system toward the tandem aerobic oxidation of *N*-pyridylindole **43** to 11*H*-pyrido[2,1-*b*]quinazolin-11-one **44**. The reaction proceeded through the copper-catalyzed oxidation of *N*-pyridylindole *via* single-electron transfer to a radical-cation intermediate, which then takes up oxygen to generate the isatin product. Lastly, the extrusion of carbon monoxide releases the quinazolinone derivatives (Scheme 7).[61] Fu *et al.* developed an efficient strategy for the synthesis of *O*-quinazolinic carbamates **47** from quinazoline 3-oxides **45** and dialkyformamides **46** and extended to **49** from quinoxaline 3-oxide **48**. This protocol uses $Cu(OH)_2$ as a catalyst and TBHP as the oxidant. Three reaction sequence are involved *viz*-oxidative couplings comprised of radical addition, Baeyer-Villiger oxidation, and intramolecular acyl transfer (Scheme 8).[62]

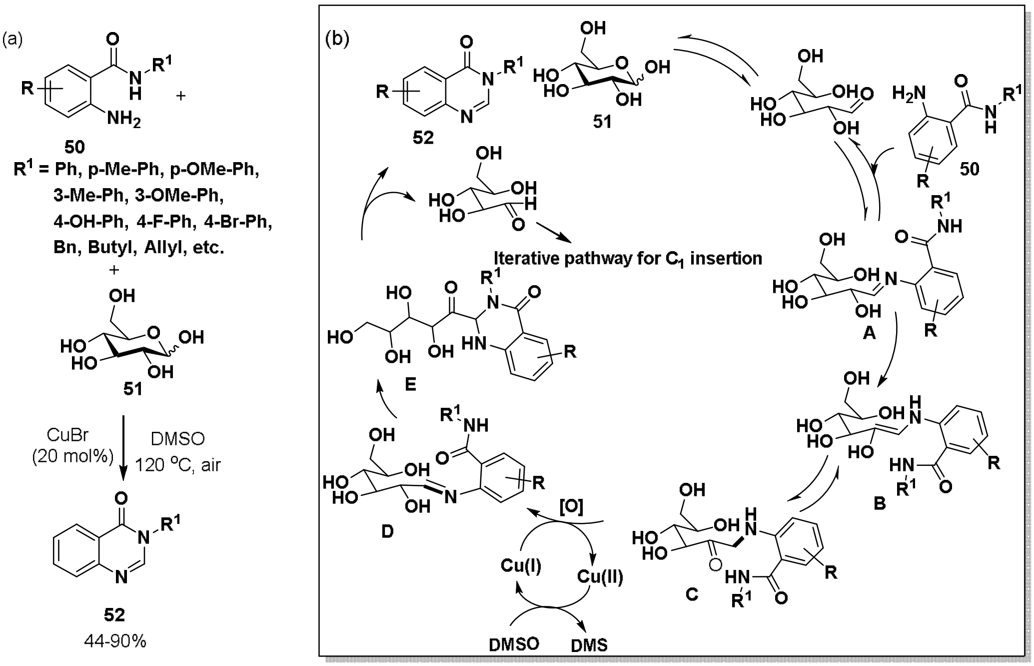


Scheme 7. (a) and (b) Synthesis of 11*H*-pyrido[2,1-*b*]quinazolin-11-one, (c) its mechanistic studies.



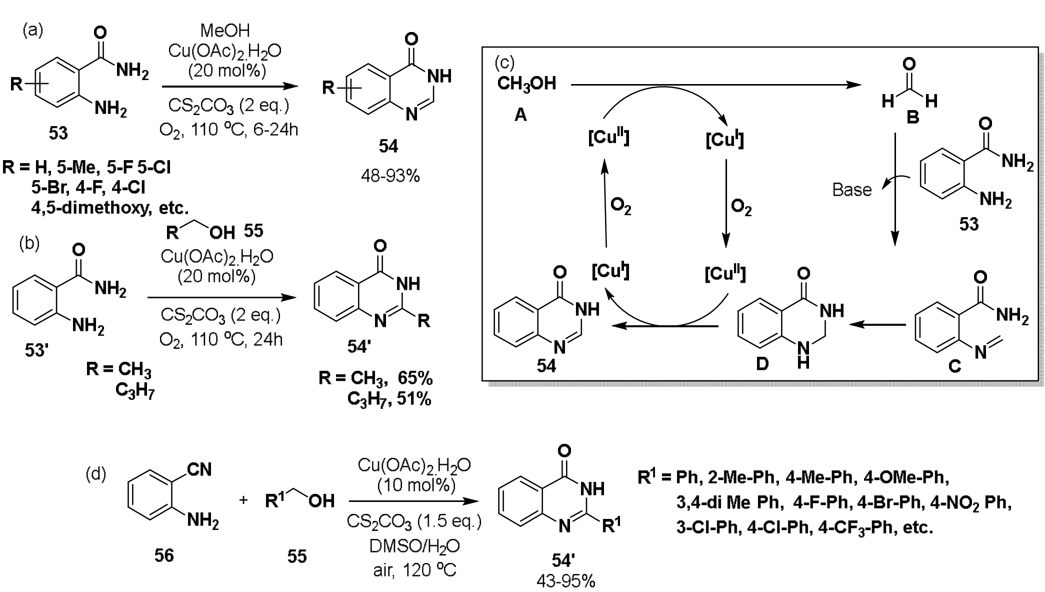
Scheme 8. (a) Synthesis of quinazolinic carbamates, (b) its mechanistic studies.

Senadi *et al.* developed an interesting reaction of copper-catalyzed oxidative coupling strategy for the synthesis of 4(3*H*)-quinazolinones **52** and benzoimidazoquinazoline using glucose **51** as a renewable C1 synthon and compound **50**. The use of control experiment and isotope labelling studies using $^{13}C_6$ D-glucose and DMSO-d_6, confirmed the role of D-glucose as a C1 source through CuBr/DMSO catalyzed the oxidative C−C cleavage. The significant features of this method include (i) utilization of 0.25 to 0.5 equiv., of D-glucose as a multi-C1 synthon; (ii) biomass-derived platform chemical as carbon synthon; (iii) atom-economical and benign conditions and; (iv) synthesis of naturally occurring alkaloid and precursor (Scheme 9).[63] This methodology has been used to synthesize a variety of electronically varied quinazolinones with high yield and functional group tolerance.



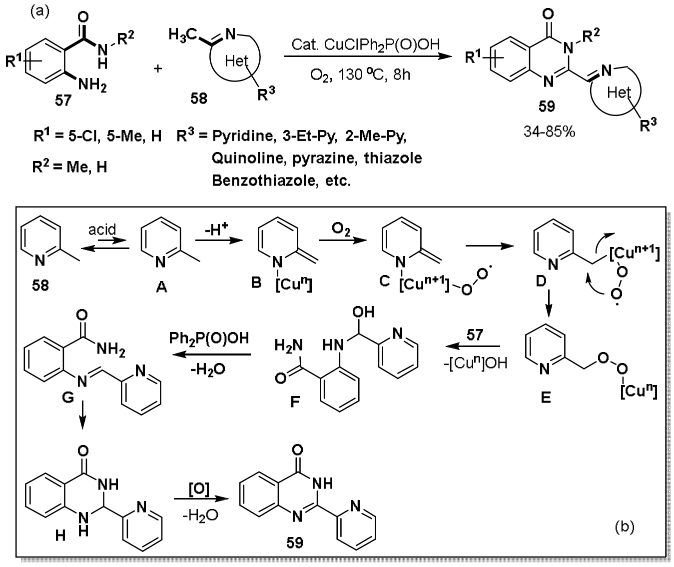
Scheme 9. (a) Synthesis of 4(3*H*)-quinazolinones derivative using glucose as synthon, (b) its mechanistic studies.

Kerdphon *et al.* reported the facile synthesis of quinazolinone derivatives **54** from 2-aminobezamides **53** and methanol which serves as both a C1 source and solvent for the reaction. The $Cu(OAc)_2$, Cs_2CO_3 and O_2 are the required and crucial materials used in the above process. A mechanism was proposed with the oxidation of methanol to produce formaldehyde by using a copper catalyst which afforded the imine intermediate with 2-aminobenzamide in the presence of a base. And finally, imine undergoes intramolecular cyclization to give dihydroquinazolinone (Scheme 10a,b,c).[64] Li *et al.* also used methanol as the C1-source and synthesized quinazolinones from 2-aminobenzamides. The reactions were carried out in a microwave reactor at 130 °C using an iridium catalyst.[65] Furthermore, Hu *et al.* also recently used benzyl alcohol **55** as the C1-source in the successful preparation of quinazolines from 2-aminobenzonitriles **56** using commercially available Cu(II) as catalysts (Scheme 10d).[66] Anandhan *et al.* developed a method where an *in-situ* generated ligand-copper superoxo complex absorbs visible light energy that activate the alpha Csp^3–H of MeOH and EtOH *via* hydrogen atom transfer (HAT) process for the synthesis of quinazolinones from oxidative cyclization of alcohol with *o*-aminobenzamide.[67] Kerdphon *et al.* developed microwave-assisted synthesis from 2-aminobenzamide derivatives and various alcohols such as benzyl alcohol and aliphatic alcohol derivatives using economical commercially available copper as a catalyst in the presence of a base, Cs_2CO_3.[68]



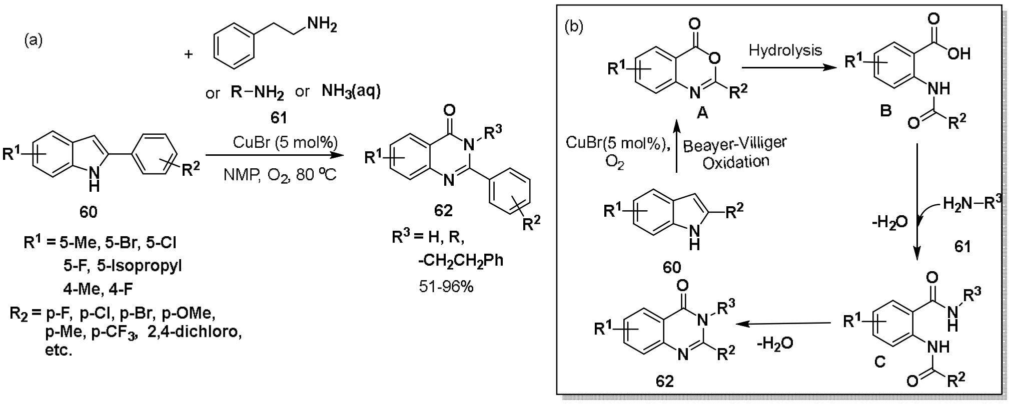
Scheme 10. (a) and (b) Synthesis of quinazolinone derivatives from alcohol as a C1 precursor, (c) its mechanism, (d) synthesis of quinazolinone derivatives from 2-aminobenzonitriles

A tandem oxidation amination cyclization strategy was developed by Yin *et al.* for the synthesis of 2-hetarylquinazolin-4(3*H*)-ones **59** *via* CuCl/Ph_2PO_2H catalyzed direct aerobic oxidative amination of C*sp*^{3}–H bonds from easily available 2-aminobenzamides **57** and (2-azaaryl)methanes **58**.[69] This procedure uses clean O_2 as an oxidant and thus provides convenient and environmentally friendly access to heterocyclic compounds. In addition to monosubstituted 2-methylpyridine, disubstituted 5-ethyl-2-methylpyridine and 2,6-dimethylpyridine also gave high yields of the corresponding products (Scheme 11).



Scheme 11. (a) Synthesis of 2-hetarylquinazolin-4(3*H*)-ones, (b) its mechanistic studies.

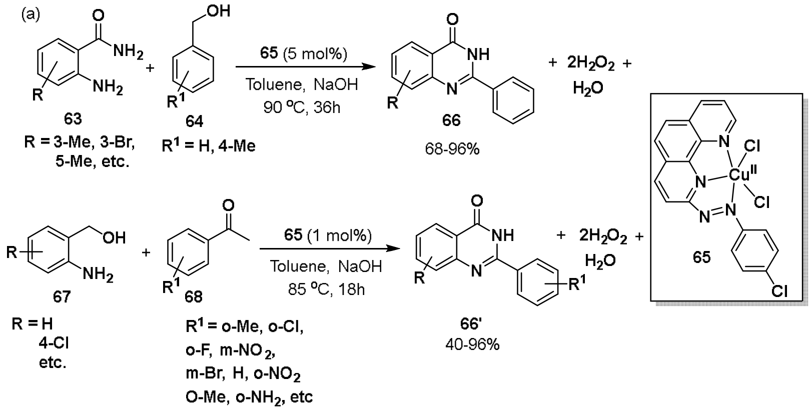
The control experiments confirmed that imine intermediate was involved in the above catalytic oxidative condensation process. Further, an interesting method was developed by Cui *et al.* to synthesize quinazolinone derivatives **62** where easily available 2-aryl indoles **60** and amines **61** or ammoniums were used. A novel copper-catalyzed (CuBr) synthesis uses molecular oxygen as an oxidant for Baeyer-Villiger oxidation followed by dehydration condensation reactions (Scheme 12).[70]

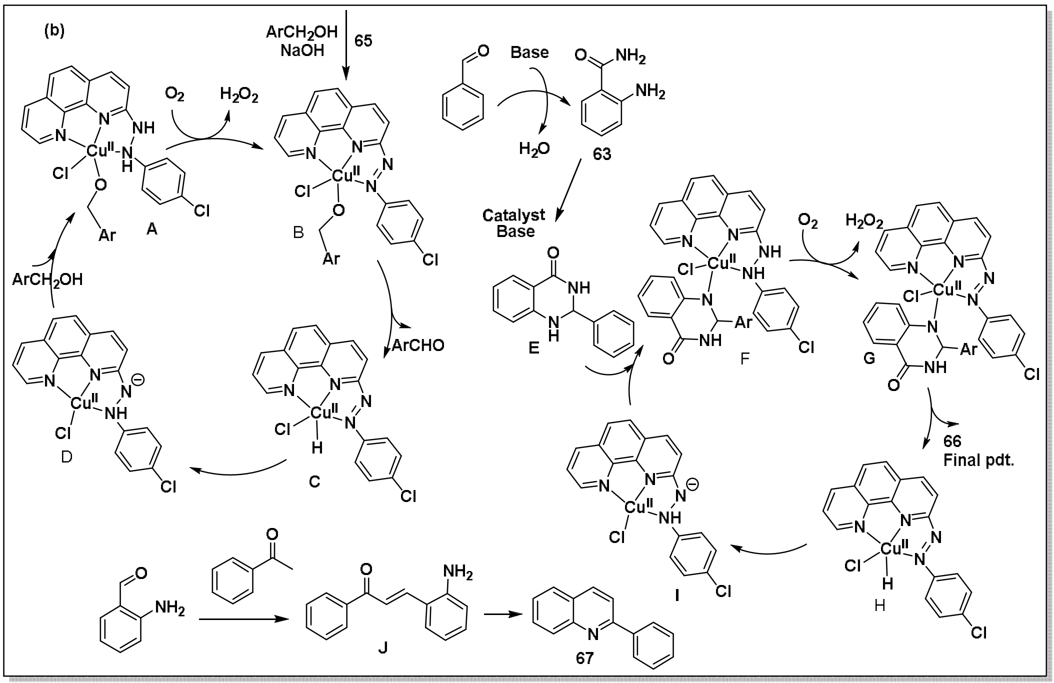


Scheme 12. (a) Synthesis of quinazoline-4(3*H*)-one derivatives, (b) its mechanistic studies.

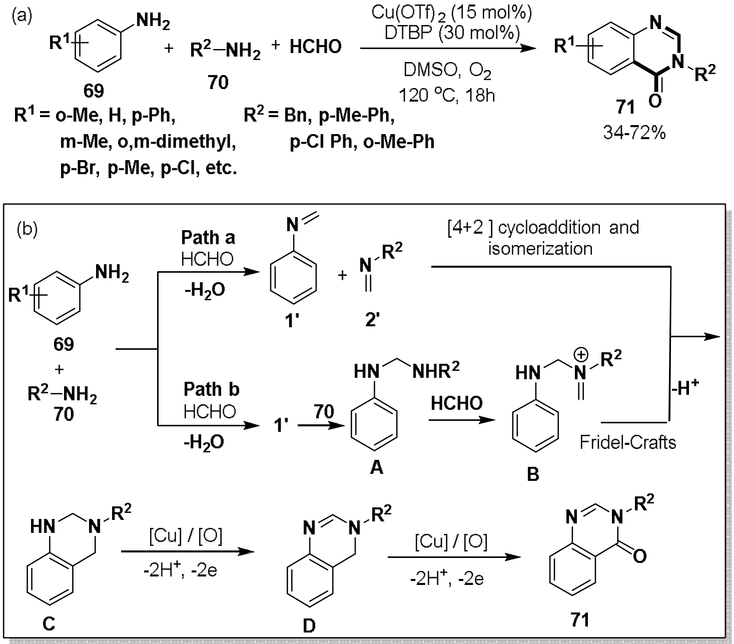
Paul *et al.* developed a method for the synthesis of quinazolinones **66** and quinoline derivatives from the dehydrogenative functionalization of alcohols **64** and 2-aminobenzamide **63** under relatively mild ($\leq$90 °C) aerobic conditions (Scheme 13a). The ketone **68** and benzyl alcohol derivative **67** were also used for the synthesis of quinazolinones **66'**. A simple metal–ligand cooperative approach was used where easy-to-prepare air-stable Cu(II) complexes featuring redox-active azo-aromatic scaffolds, 2-aryl azo-(1,10-phenanthroline) ($L^{1,2}$) **65**, are used as a catalyst. Control experiments confirm that both copper and the coordinated azo aromatic ligand participate cooperatively during the catalytic cycle. Based on the control experiments, a plausible reaction mechanism has been proposed and depicted in Scheme 13b.[71]

Zhang *et al.* developed a method for the direct aerobic copper-catalyzed, Cu(OTf)$_2$ oxidative multicomponent annulation reaction for the synthesis of quinazolinones **71** through an imine-protection strategy. The process makes use of bifunctional benzenes, and furnishes products from readily available anilines **69**, primary amines **70**, and HCHO (Scheme 14a). The construction of various products is achieved *via* the formation of three C–N and one C–C bond in conjunction with the benzylic functionalization. Based on the control experiments, a plausible reaction mechanism has been proposed and depicted in Scheme 14b.[72]



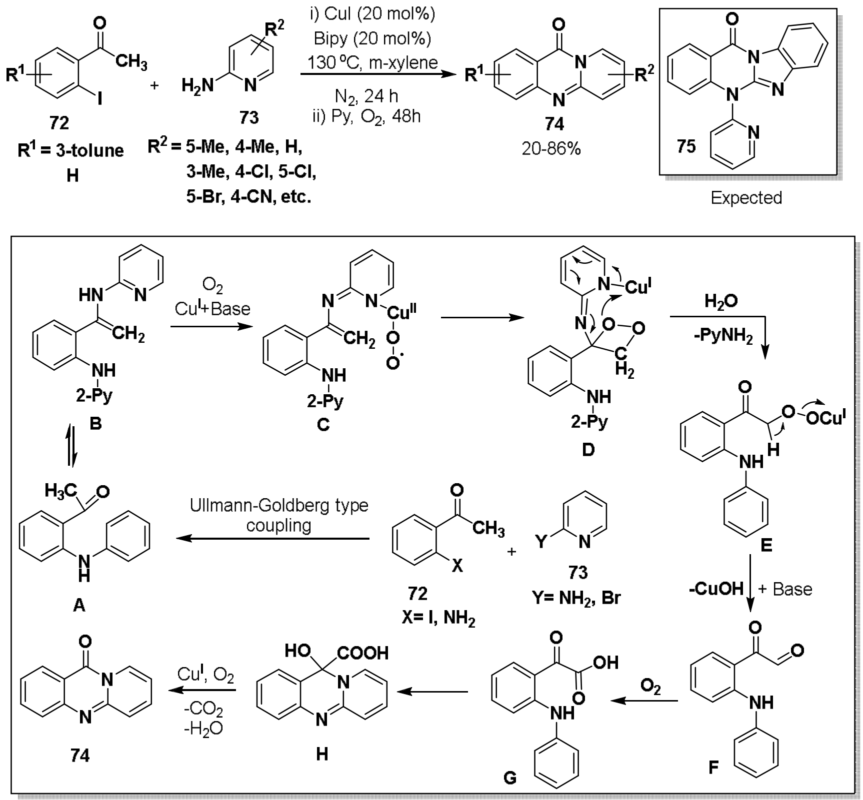


Scheme 13. (a) Synthesis of quinazolinones **66** and quinolines **67** by using Cu-catalyst **65**, (b) its mechanistic studies



Scheme 14. (a) Synthesis of quinazolinones from anilines, (b) its mechanistic investigation.

Kaliappan *et al.* developed a method for the direct one-pot CuI-catalyzed oxidative C–C bond cleavage leading to pyridoquinazolinones **74** instead of the expected fused benzimidazoquinazolinone **75**, starting from the *o*-iodo acetophenone derivatives **72** and anilines **73** (Scheme 15a). Here, the reaction followed a copper-catalyzed C–N coupling of Ullmann-Goldberg type coupling followed by concomitant Csp^3–H oxidation through SET transformation with Cu(I)/Py under oxygen atmosphere, amidation *via* oxidative C–C bond cleavage under O_2 atmosphere to deliver the target molecules in high yields. Based on the control experiments, a plausible reaction mechanism has been proposed and depicted in Scheme 15b.[73] Benzimidazoquinazolinones derivatives were also synthesised previously by Fu's, Qiao's and Kaliappan's groups.[74-76]

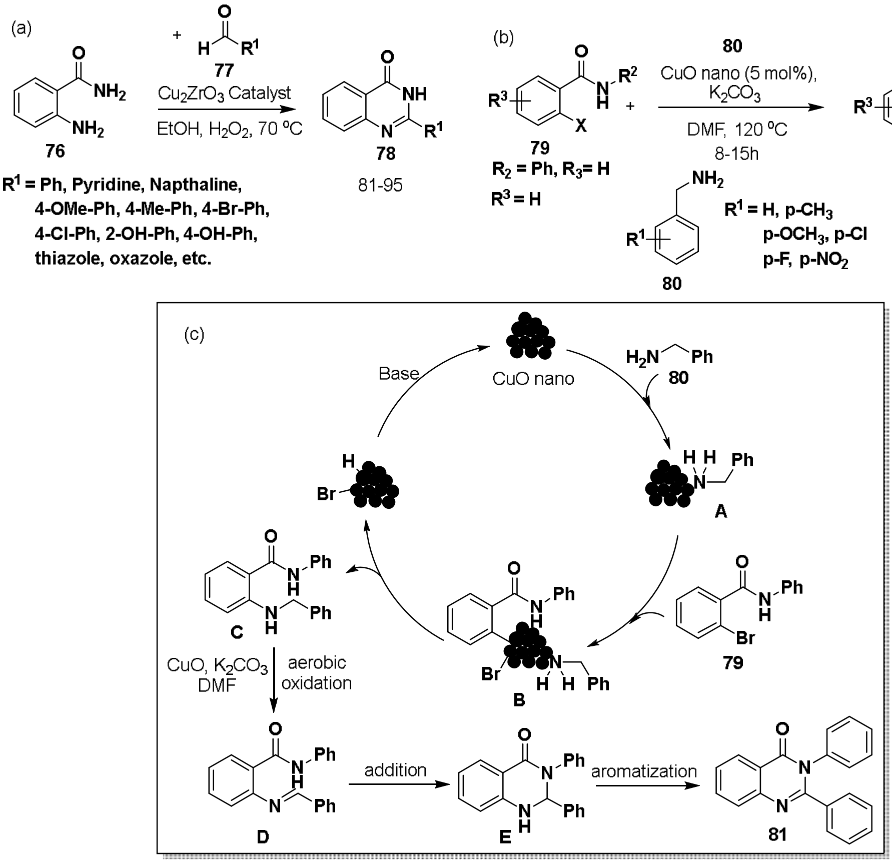


Scheme 15. (a) Synthesis of pyridoquinazolinones, (b) its mechanistic investigation.

3.3. Heterogeneous catalyst

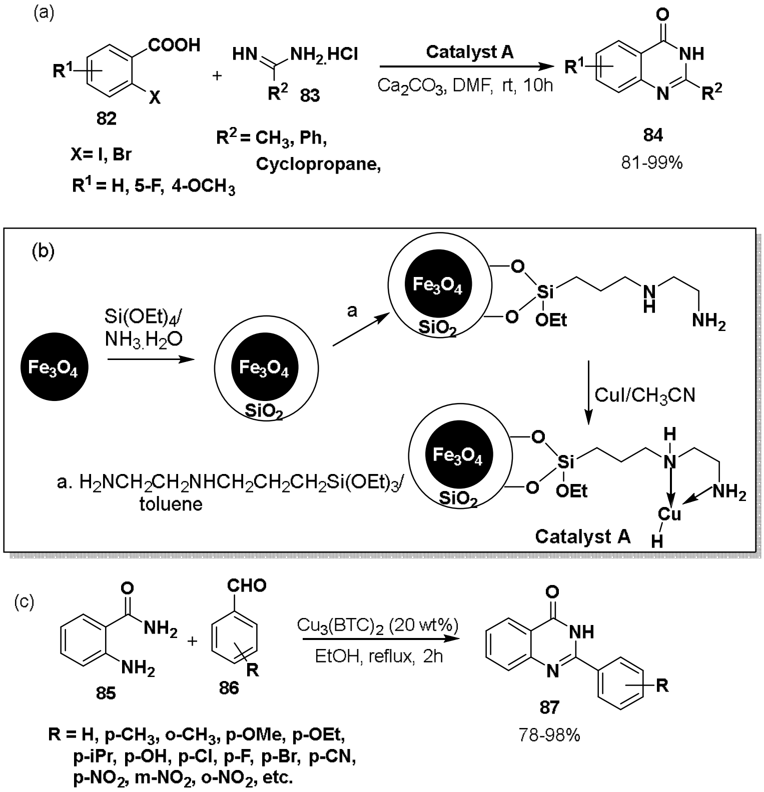
A heterogeneous catalytic system was also developed with the support of Cu-metal to synthesize the quinazolinone derivative. Heterogeneous catalytic systems have their own advantages, particularly having good dispersion of their active site, easy separation of the reaction mixture and catalyst recyclability compared with homogeneous systems. Furthermore, the large surface area, high reactivity, and high thermal resistance provide higher yields with better atom economy as compared to homogeneous catalysts. Catalyst recovery and reuse are the two most important features of many green synthetic methods. Heterogenization of the existing homogeneous catalysts, thus creating a heterogeneous catalytic system, has become one powerful way to solve these problems.

Sreenivasa *et al.* developed a reusable mesoporous ZrO_2-supported Cu_2O (Cu_2ZrO_3) system catalyst for the synthesis of quinazolinones derivative **78**. Thus, by use of anthranilamide **76** and different varieties of aldehyde **77** participated in the formation of quinazolinone **78** in the presence of H_2O_2 and Cu_2ZrO_3 catalysts in ethanol (Scheme 16a**)**. The present protocol showed good tolerance for various substituted aldehydes and good yields for quinazolinone derivatives. The catalyst was prepared by simple co-precipitation and characterized using techniques like XRD, TGA, BET, SEM and TEM. The catalyst was reused for five cycles without significant loss in the activity.[77] Further, Patel *et al.* used CuO nanoparticles for the synthesis of 2,3-disubstituted quinazolinones **81** from 2-halobenzamides **79** and (aryl)methanamines **80** under air atmosphere.[78] Reaction follows a sequential Ullmann coupling between 2-halobenzamide **79** and (aryl)methanamine **80**, where an active cluster of CuO nanoparticle undergoes oxidative addition of the *in situ* generated secondary amine to imine and then an intramolecular nucleophilic attack of the amidic N–H on to the imine carbon (C–N bond formation) resulting in the synthesis of 2,3-disubstituted quinazolinones. The catalytic efficiency of the recovered catalyst was examined up to three cycles (Scheme 16b,c).



Scheme 16. (a) Synthesis of quinazolinones by using a catalyst (Cu_2ZrO_3), (b) synthesis of quinazolinones by using catalyst CuO nanoparticle, (c) its mechanistic investigation.

Wang *et al.* used a magnetic nanoparticles (MNPs) of Fe_3O_4 supported by copper(I) catalyst, which has unique catalyst recovery, based on magnetic separation from the reaction mixture with an external permanent magnet. This approach is typically simpler and more effective than filtration or centrifugation as it prevents loss of the catalyst. The above system has been used in the cascade reactions of amidines **83** with substituted 2-halobenzoic acids **82** and 2-bromocycloalk-1-enecarboxylic acids to synthesize *N*-quinazolinones derivative **84**.[79] The reactions generated derivatives in good to excellent yields. In this case, the catalyst was able to recover and reuse at least ten times without significant loss of its reactivity (Scheme 17a,b). Suresh *et al.* used easily preparable $Cu_3(BTC)_2$ MOF as a sustainable solid-Lewis acid catalyst under mild conditions access quinazolinones **87** with aldehydes **86** and 2-aminobenzamides **85** (Scheme 17c).[80] It was proposed that the synthesis of the quinazolinone was catalyzed by coordinatively unsaturated open Cu(II) sites in $Cu_3(BTC)_2$ MOF. This uses minimum copper loading (0.07 mmol) without any harsh reaction conditions. A series of substituted quinazolinones were synthesized with good to excellent yields. In this case, the catalyst was able to recover and reuse at least six times without significant loss of its reactivity.

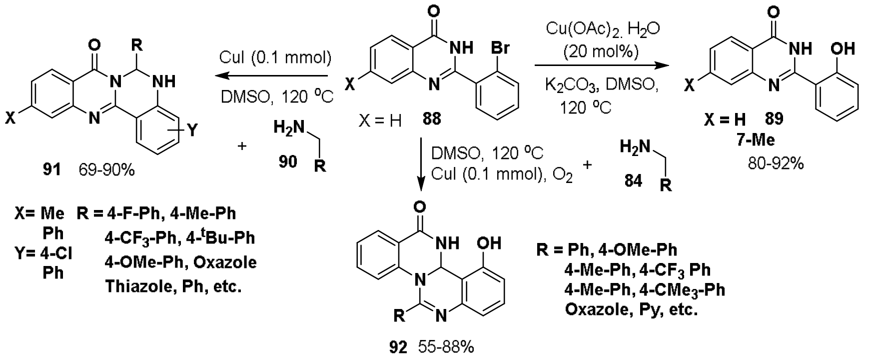


Scheme 17. (a) Synthesis of quinazolinones by using catalyst A, (b) synthesis of catalyst A, (c) synthesis of quinazolinones by using catalyst $Cu_3(BTC)_2$ MOF.

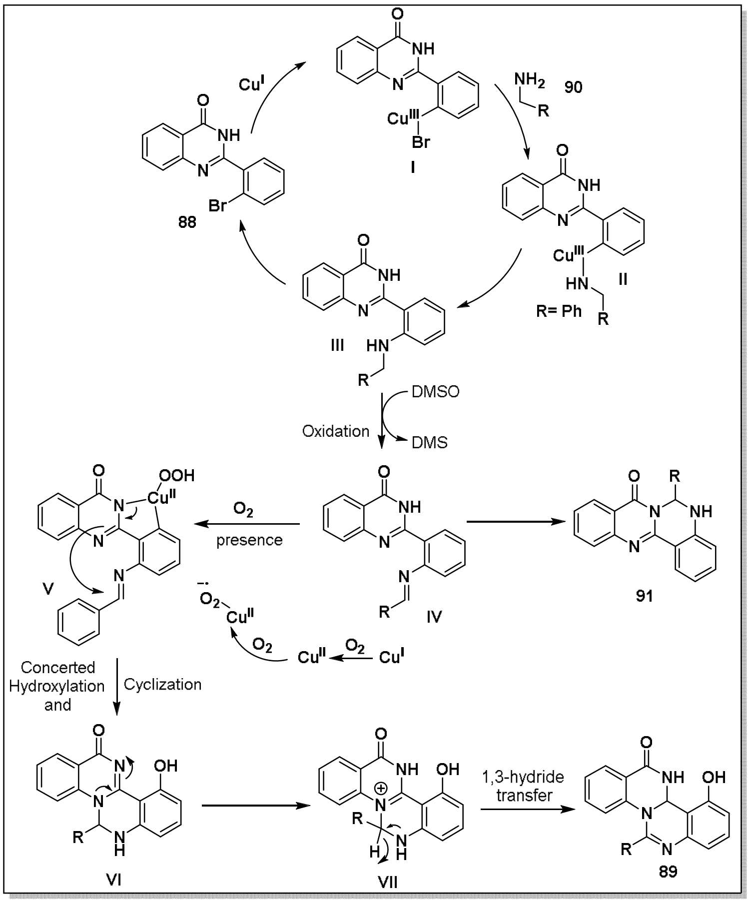
3.4. Modulation of quinazolinones

Quinazolinone derivatives have also been used for the modulation and synthesis of complex fused higher poly heterocycle derivatives. Most of the time, these varieties have their own special photophysical properties and thus open opportunities for use in different material science projects. Here, C–H functionalization also plays a critical role in the annulation and Cu-catalyst was also actively utilized.

Banerji *et al.*[81] developed a method to derivatise 2-(2-bromophenyl)quinazolin-4(3*H*)-one **88** into three diverse quinazolinone derivatives **89**, **91**, **92** in high yields by efficient copper-catalyzed modular methodology in the presence of amines **90**. Thus, it was found that, under the catalysis of CuI (20 mol %) in DMSO under the positive pressure of oxygen at 120 °C delivered the product **92**. Interestingly, under the same reaction conditions was utilized without the use of oxygen it afforded a new product **91**. Most of these compounds showed a solid-state fluorescence emission. Further, changing the catalyst from CuI to $Cu(OAc)_2 \cdot H_2O$, produced compound **89** with 92% yield (Scheme 18). Based on the control experiments, a plausible reaction mechanism has been proposed and depicted in Scheme 19. Further, aza-fused polycyclic heterocycles were also synthesized in a novel and elegant manner by Alla and co-workers *via* copper(I) catalyzed multicomponent reaction of substituted aldehydes, 2-(2-bromophenyl)quinazolines-4(3*H*)-one and various nitrogen sources under aerobic conditions.[82]

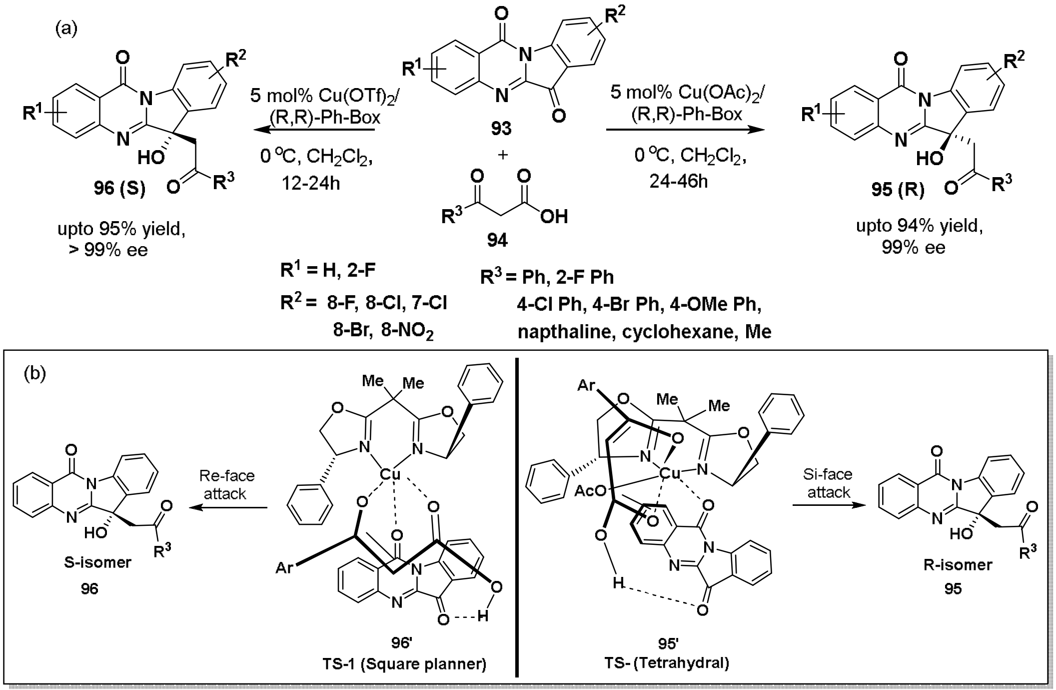


Scheme 18. Synthesis of higher analogues of quinazolinone derivatives **89**, **91**, **92**.



Scheme 19. Mechanistic studies of the synthesis of quinazolinone derivatives **89**, **91**, **92**.

Ma *et al.* developed a method for the asymmetric synthesis of a series of phaitanthrin A analogues from enantioselective decarboxylative aldol reaction of tryptanthrin **93** with aryl-substituted β-keto acids **94**. The Cu-bisoxazoline-catalyst was found to be the most suitable which provides a straightforward approach to deliver both enantiomers of the products **95** *R*, and **96** *S* with good to high enantioselectivity by simply changing the copper salts. Thus, the use of $Cu(OTf)_2$ provided *S*-phaitanthrin A, **96** analogues but $Cu(OAc)_2$ gave *R*-isomer **95**. Based on the X-ray crystallographic analysis of chiral Cu(II)-bisoxazoline complexes, the tentative stereochemical models were presented to account for the observed counteranion-induced switching in enantioselectivity (Scheme 20a,b).[83] Previously, Jiang and co-workers also concluded the asymmetric synthesis of *S*-phaitanthrin A and its derivatives *via* the aldol reactions of tryptanthrins with aliphatic ketones, malonic acid, or malonic acid half-oxy esters.[84-86]

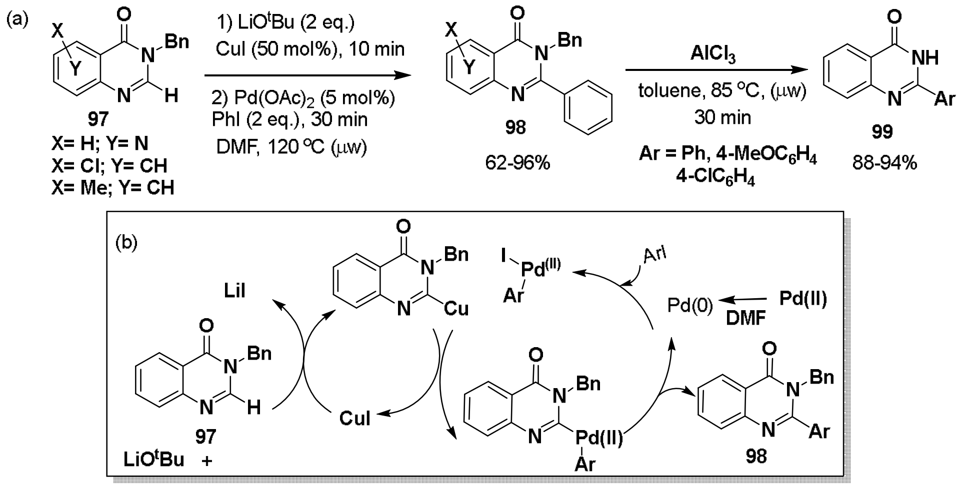


Scheme 20. (a) Synthesis of (S)-phaitanthrin A, **96** analogues and (R)-isomer **95**,
(b) mechanistic investigation to enantioselectivity of products.

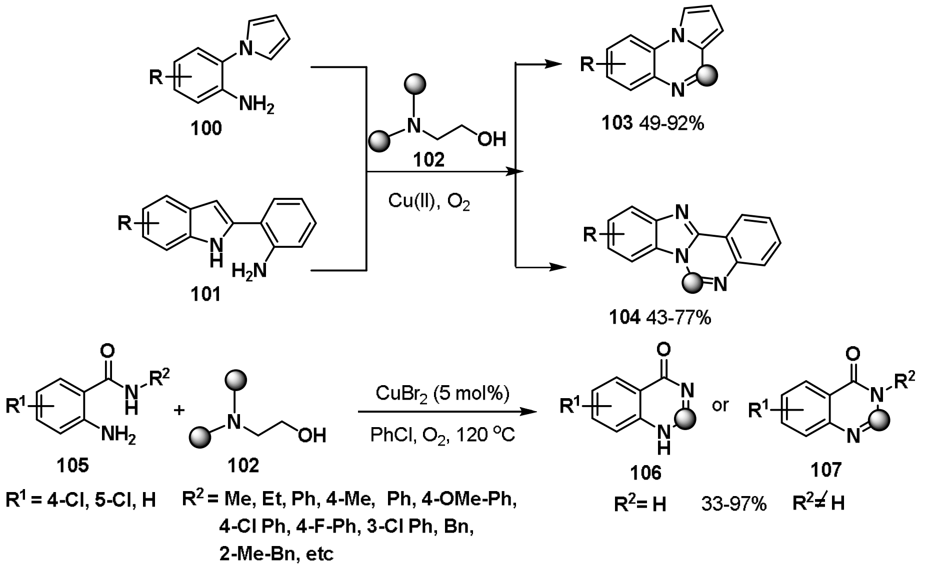
Besson *et al.*[87] developed a straightforward method for the functionalization of quinazolin **97** through the intermediate **98** followed by microwave-assisted method for the palladium-catalyzed and copper-assisted direct arylation. This method was found to be suitable for a wide range of aryl iodides and substituted (2*H*)-quinazolin-4-ones. This protocol provides a simple and efficient way to synthesize biologically relevant 2-arylquinazolin-4-one **99** backbones (Scheme 21a,b).

3.6. Miscellaneous methods

Ma *et al.* developed a protocol for the synthesis of quinazoline-4-ones **106**, **107** and as well as pyrrolo-[1,2-*a*]quinoxalines **103** and benzo[4,5]imidazoquinazoline **104** by changing the substrates. Thus, by using *N,N*-dimethylethanolamine (DMEA) **102** as a C1 synthon, a common starting material above three compounds were synthesized with compounds **105**, **100** and **101**, respectively, in the presence of a copper catalyst.[88] O_2 is used as a green oxidant which was found to be critical in these transformations since it facilitates the formation of a key reactive iminium ion intermediate (Scheme 22).

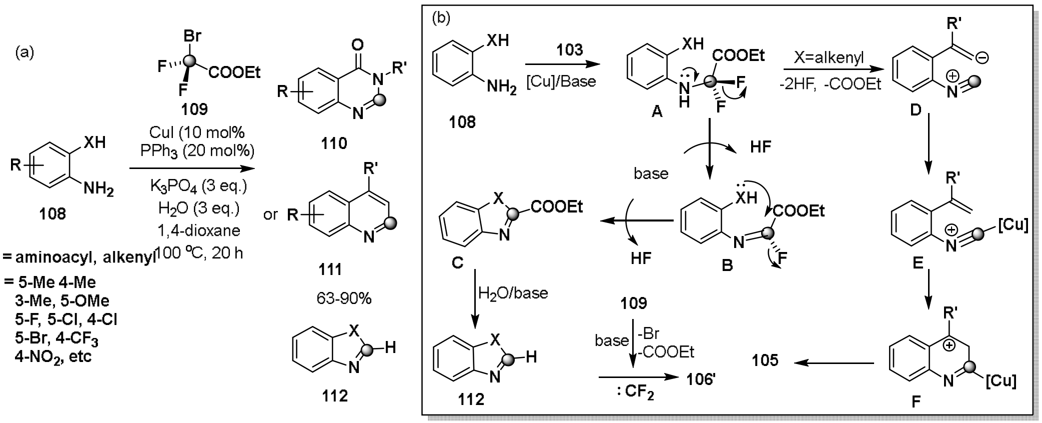


Scheme 21. (a) Synthesis of 2-arylquinazolin-4-one, (b) its mechanism.



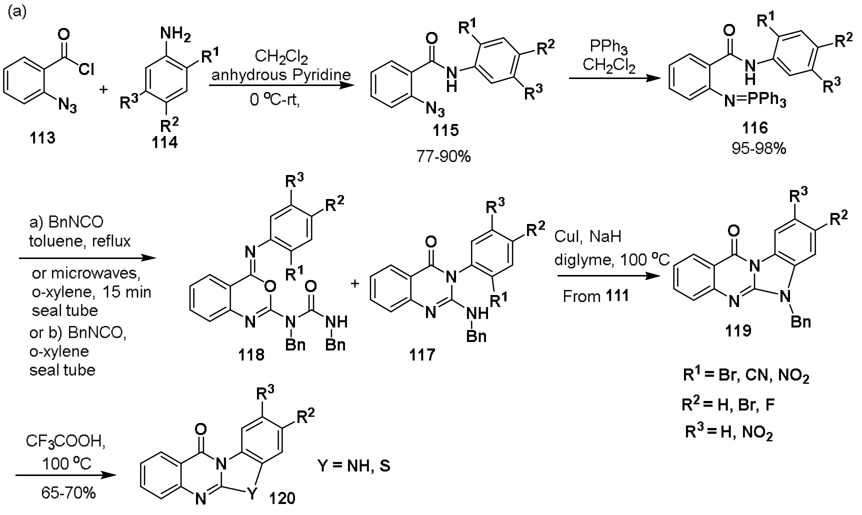
Scheme 22. Synthesis of quinazoline-4-ones and pyrrolo-[1,2-*a*]quinoxalines and benzo[4,5]imidazoquinazoline.

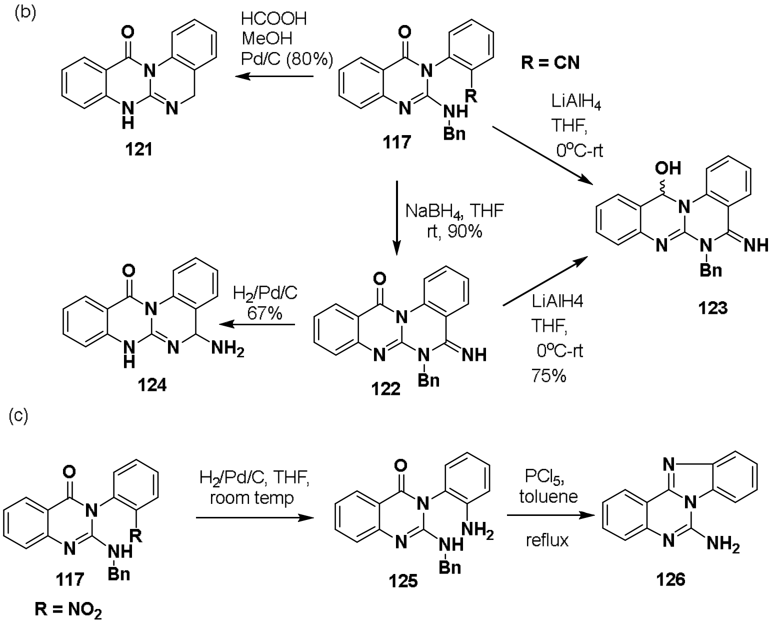
Tu *et al.* reported a unique method for the synthesis of quinazolin-4-ones through a copper-catalyzed carbocyclization strategy by using 2-functionalized anilines **108** with ethyl bromodifluoroacetate **109**. This transformation provides a simple and efficient protocol for the synthesis of various *N*-heterocycles, including quinazolinones **110**, benzimidazoles **111**, benzoxazoles, benzothiazoles, and benzimidazoles **112** (X=O, S, N). Moreover, this provides a method to afford *N*-difluoromethyl benzimidazoles with $BrCF_2COOEt$ playing dual roles as a C1 synthon and difluoromethyl source. Based on the control experiments, a plausible mechanism is presented below (Scheme 23a,b).[89]



Scheme 23. (a) Synthesis of quinazolinones, benzimidazoles, benzoxazoles, benzothiazoles, and quinolines, (b) its mechanistic study.

Molina *et al.* developed a method for the synthesis of linear quinazolinones fused to five-membered rings like benzimidazo[2,1-*b*]quinazolinones and benzothiazolo[2,3-b]quinazolinones **120** from iminophosphoranes **116**. The starting material **119** was derived from *N*-substituted *o*-azido benzamides **115**, easily prepared from compounds **113** and **114**, by a combination of the aza-Wittig methodology and CuI-catalysed heteroarylation. The presence of a nitrogen functionality in the *N*-aryl substituent of 4 promotes heterocyclization after an aza-Wittig reaction/reductive process, either across the 2-position, to afford quinazolino[2,1-b]quinazolinones **115-124**, or across the 4-position, to afford the benzimidazo[1,2-*c*]quinazoline **126** from the initially formed 3*H*-quinazolin-4-one **117**, followed by the intermediate **125**. When an acetyl group is present in the *N*-aryl substituent of **116**, aza-Wittig reactions with isocyanates lead directly to 4-methylene-4*H*-3,1-benzoxazines **117**; this transformation involves the initial formation of a carbodiimide, which undergoes ring-closure through the enol form of the carboxamide group and eventually an unprecedented imino benzoxazine/methylene benzoxazine rearrangement (Scheme 24a,b,c).[90]





Scheme 24. Synthesis of (a) benzimidazo[2,1-b]quinazolinones, benzothiazolo[2,3-*b*]quinazolinones (b) quinazolino[2,1-*b*]quinazolinones, (c) benzimidazo[1,2-*c*]quinazoline.

4. Conclusion

The introduction of nitrogen into organic compounds is always strategically beneficial for drug research and development. Many marketed drugs are heterocyclic compounds, and quinazolin-4-ones also have significant contributions. A number of designer compounds of the derivative quinazolinone have also been developed, and a few show a promising biological activity. This, along with its recent application in material science, has made the development of synthetic methods for the aforementioned heterocycles a hot topic in this area of organic chemistry. Recently a flood of methods has been reported which have a diverse variety, and most of them are metal-catalyzed methods of which a significant number are Cu-catalyzed methods. Here, we highlighted the different methods of Cu-catalyzed synthesis of quinazolinones which are divided mainly into four categories *viz* cross-coupling reactions, Cu-catalyzed aerobic oxidation, heterogeneous catalyst, and modulation of quinazolinones. It appears that Cu-catalyzed reactions are remarkably beneficial since they can adapt a wide variety of functionalities and can activate C–H as well as C–X (halogens) bonds. In recent years, we expect more methods will come which use more varieties of functional groups in compounds for the synthesis of quinazolinones.

Acknowledgements

Prof. S. Pal and Mr. S. K. Mondal are grateful to the Indian Institute of Technology (IIT)-Bhubaneswar for providing research infrastructures and facilities. Dr. G. Chandra and Ms. U. Rani thank the Central University of South Bihar (CUSB), Gaya, Bihar for providing research infrastructures and facilities. Mr. S. K. Mondal and Ms. U. Rani also thank to the MHRD, New Delhi and Council of Scientific and Industrial Research (CSIR)-New Delhi as well as CUSB respectively for providing research fellowship.

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