Review

Ibrahim M. Abdou* and Shaikha S. Al-Neyadi

Synthesis of quinazolines and quinazolinones via palladium-mediated approach

Abstract: Quinazoline derivatives have drawn attention in the field of heterocyclic chemistry because of their unique skeleton and interesting biological applications. This review summarizes the recent palladium-catalyzed reactions used to construct quinazoline and its related 4(3*H*)-quinazolinone analogues. The mechanisms of some Pd-catalyzed reactions are also discussed.

Keywords: palladium catalysis; quinazolines; quinazolinones; reaction mechanism; synthesis.

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Introduction

Heterocyclic chemistry covers at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical, and veterinary products. Quinazoline (**1**) and related 4(3*H*)-quinazolinone (**2** in Scheme 1) are classes of fused heterocycles that are of considerable interest because of the diverse range of biological properties of their derivatives, including anticancer [1], diuretic, anti-inflammatory [2], anticonvulsionary, lung antifibrotic [3], antimicrobial [4], antimalarial [5], antiepileptic [6], and antihypertensive [7] activities.

This review surveys the literature to summarize newer methods for constructing quinazoline and 4(3*H*)-quinazolinone ring structures [8]. The traditional synthetic routes to the quinazoline compounds are as follows: (i) reaction of nitriles with lithiated anthranilamides [9]; (ii) cyclization of anthranilamides with aldehydes, ketones, or acid chlorides under acidic or basic conditions [10]; (iii) thermolysis of 3-(arylidene)amino-1,2,3-benzotriazin-4-ones [11]; and (iv) SmI_2-promoted reaction between *o*-nitrobenzamide and benzyl nitriles [12]. These traditional methods often suffer from multistep reactions, difficult workup, or harsh reaction conditions. Recently, several new synthetic methods have been reported, including metal-catalyzed solid-phase synthesis [13] and microwave irradiation [14].

A few examples of transition metal-catalyzed routes to form 4(3*H*)-quinazolinones have been reported, including the use of $PdCl_2$-$(PPh_3)_2$ and $SnCl_2$ catalysis [15]. 4(3*H*)-quinazolinones have also been synthesized using dicobalt octacarbonyl ruthenium, platinum complexes, or titanium catalysts [16]. Some of these procedures have clear technical advantages over traditional methods in terms of yield and versatility, but they do not use new chemistry in the construction of the ring systems. However, the use of combinatorial synthesis, microwave-enhanced processes, and new catalytic methodologies in the preparation of these heterocycles is a clear indication that significant advancements have been made in recent years.

Palladium-catalyzed coupling reactions have become a powerful tool in organic synthesis [17]. There are numerous applications of palladium catalysts in the preparation of pharmaceuticals, agrochemicals, and advanced materials on laboratory and industrial scales. The importance of palladium catalysis was underlined by the 2010 Nobel Prize to R. Heck, A. Suzuki, and E. Negishi for their pioneering work in this field [18]. Considering the importance of the Pd-catalyzed reactions, here we summarize the contributions of the quinazoline system to Pd-catalyzed construction. The syntheses of both quinazolines and their quinazolinone analogues are classified into four categories based on the substitution patterns of the ring system:

- Quinazoline and quinazolinone
- Monosubstituted quinazolines and quinazolinones
- Disubstituted quinazolines and quinazolinones
- Ring-fused quinazolinones

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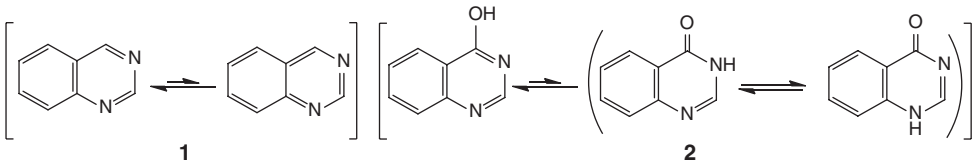
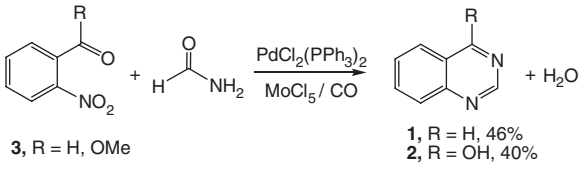


Scheme 1 Quinazoline (**1**) and 4(3*H*)-quinazolinone (**2**).



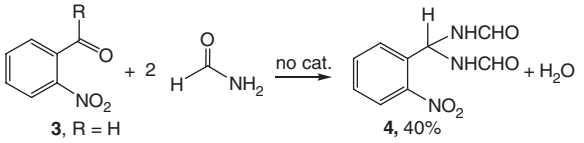
Scheme 2 Synthesis of quinazoline (**1**) and 4(3*H*)-quinazolinone (**2**).

Quinazoline and quinazolinone

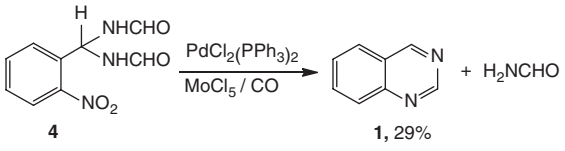
The application of palladium-catalyzed carbonylation reactions in the synthesis of quinazolines was reported by Akazome et al. [19]. A novel palladium-catalyzed method was designed to construct quinazoline (**1**) by using an intermolecular reductive *N*-heterocyclization. A palladium complex of $PdCl_2(PPh_3)_2$ with $MoCl_5$ shows high catalytic activity for the *N*-heterocyclization of 2-nitrobenzaldehyde (**3**, R = H) or methyl 2-nitrobenzoate (**3**, R = OMe) with formamide to afford the corresponding quinazolines **1** and **2** (Scheme 2).

In the absence of the palladium catalyst, 2-nitrobenzaldehyde (**3**, R = H) undergoes a reaction with formamide to give the bis-formamide product **4** (Scheme 3).

Quinazoline (**1**) is formed upon heating formamide **4** in the presence of $PdCl_2(PPh_3)_2/MoCl_5$ and CO at 100°C for 16 h (Scheme 4). This result indicates that compound **4** is a possible intermediate in the catalytic reductive *N*-heterocyclization.



Scheme 3 Formation of bis-formamide **4**.



Scheme 4 Catalytic reductive *N*-heterocyclization of **4** using $PdCl_2(PPh_3)_2/MoCl_5$.

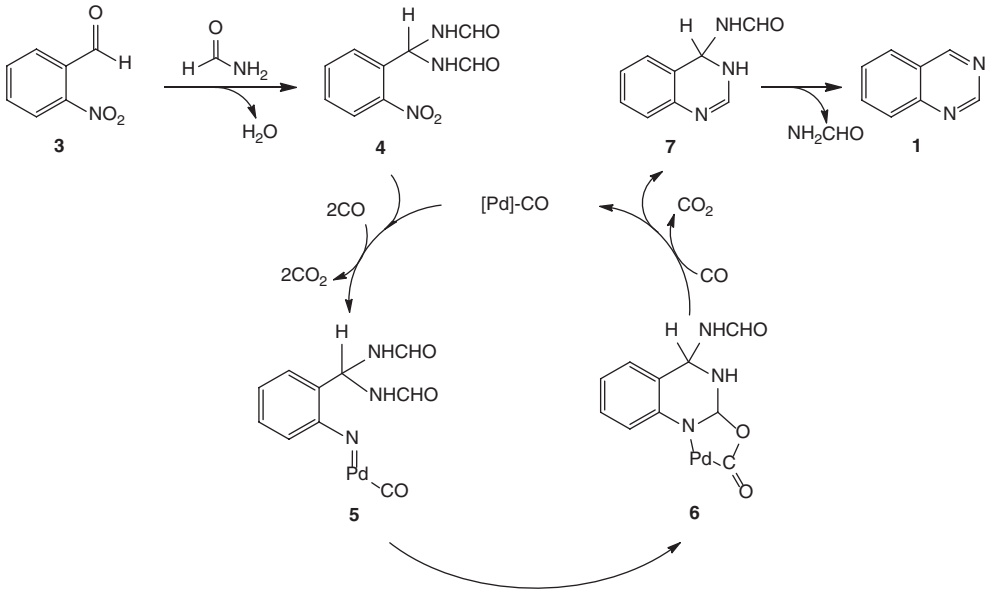
The reductive *N*-heterocyclization mechanism for **1** is believed to start with the reaction between a carbonyl group of the 2-nitrobenzaldehyde **3** (R = H) and formamide to give the corresponding bis-amide **4** (Scheme 5). Then a nitrene intermediate **5** is generated by the deoxygenation of the nitro group by the reaction with carbon monoxide. Lewis acid $MoCl_5$ is coordinated with the oxygen atoms of the nitro group, which weaken the N-O bond and thereby assist the deoxygenation process. An intramolecular nucleophilic addition of the nitrene to the carbonyl group of the bis-amide followed by the generation of metallacyclic intermediate **6** and then the decarboxylation of **6** results in the formation of another intermediate product **7** and regeneration of the active catalyst. In the final step, quinazoline (**1**) is produced by the dehydroamidation of **7**.

Monosubstituted quinazolines and quinazolinones

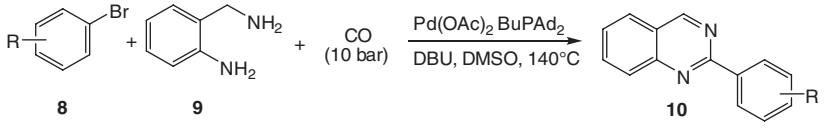
2-Substituted quinazolines

A new strategy toward the synthesis of quinazolines **10** has been discovered by Chen et al. [20]. This reaction involves palladium-catalyzed carbonylative coupling of aryl bromides **8** with 2-aminobenzylamine **9** (Scheme 6). The palladium catalyst is a ternary complex of palladium acetate/1,1′-bis(diphenylphosphino)ferrocene/1,8-diazabicyclo[5.4.0]undec-7-ene [$Pd(OAc)_2$/dppf/DBU]. 2-Substituted quinazolines **10** are produced in yields 61–92%. The reaction proceeds via an aminocarbonylation-condensation-oxidation sequence as a one-pot procedure. Preliminary investigations have shown that DMSO serves as a solvent and an oxidant in this preparation (Scheme 6).

Aryl bromides **8** substituted with an electron-donating group such as methoxy, dimethylamino, or *tert*-butyl undergo reaction with 2-aminobenzylamine (**9**) to give the corresponding quinazolines **10** in yields 61–91%. The



Scheme 5 Proposed mechanism for palladium-catalyzed synthesis of quinazoline (**1**).



R = H, 4-OMe, 4-Cl, 4-*tert*-Bu, 4-N(Me)$_2$, 2-OMe, 4-CF$_3$, 4-CN, 4-COC$_6$H$_5$, yields 61-92%

Scheme 6 A convenient palladium-catalyzed carbonylative synthesis of 2-substituted quinazolines **10**.

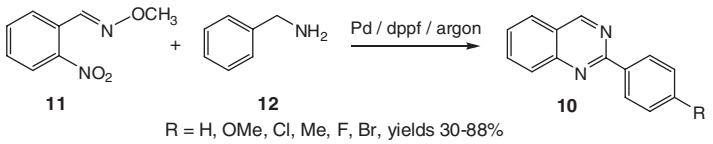
presence of electron-withdrawing substituents such as a trifluoromethyl or cyano group at **8** gives rise to the corresponding 2-substituted quinazolines in yields 65–81%.

Similar 2-arylquinazolines **10** have been synthesized via hydrogen transfer methodology using a Pd-catalytic system [21]. In this method, various (*E*)-2-nitrobenzaldehyde *O*-methyl oximes **11** are allowed to react with benzyl amines **12** to produce compounds **10** in good yields (Scheme 7).

2-Substituted quinazolinones

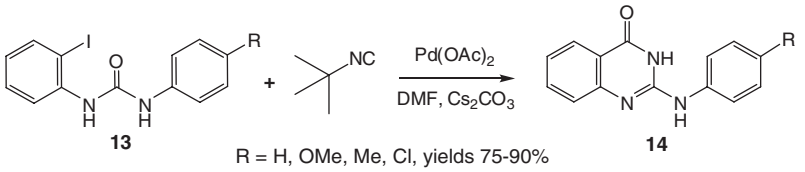
An efficient approach to the synthesis of 2-substituted 4(3*H*)-quinazolinones **14** (Scheme 8) involves a palladium-catalyzed coupling method developed by Sharma and Jain [22]. In this methodology, substituted urea derivatives **13** are allowed to react with *tert*-butyl isocyanide in the presence of Pd(OAc)$_2$ and Cs$_2$CO$_3$ in DMF to produce 2-substituted quinazolinones **14** in yields 75–90% (Scheme 8).

A mechanism for this synthesis is proposed in Scheme 9. The first step involves the oxidative insertion of Pd to the urea derivative **13** forming complex **15**. Isocyanide insertion of *tert*-butyl isocyanide on complex **15** produces Pd(II) species **16**. The subsequent reductive elimination of **16** via intramolecular cyclization provides the intermediate product **17**, which undergoes rearrangement to **18**. The intermediate product **18** is a direct precursor to the final quinazoline **14**.



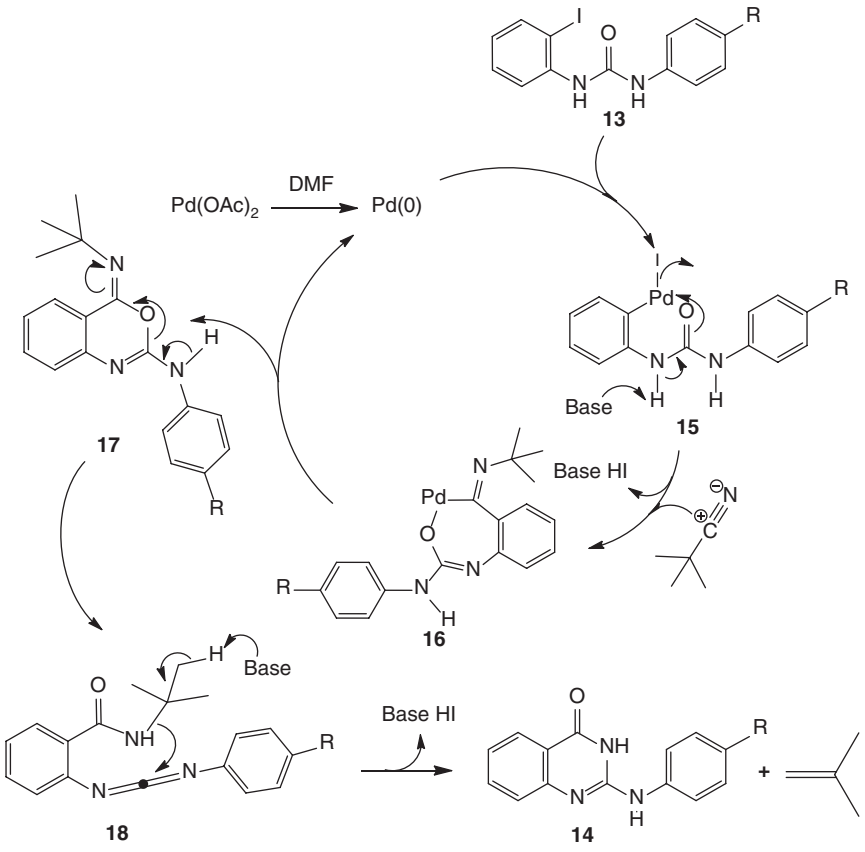
R = H, OMe, Cl, Me, F, Br, yields 30-88%

Scheme 7 Palladium-catalyzed hydrogen transfer synthesis of 2-substituted quinazolines **10**.



13 14

Scheme 8 An efficient palladium-catalyzed synthesis of 2-substituted-4(3*H*)-quinazolinones **14** from disubstituted ureas **13** and *tert*-butyl isocyanide.

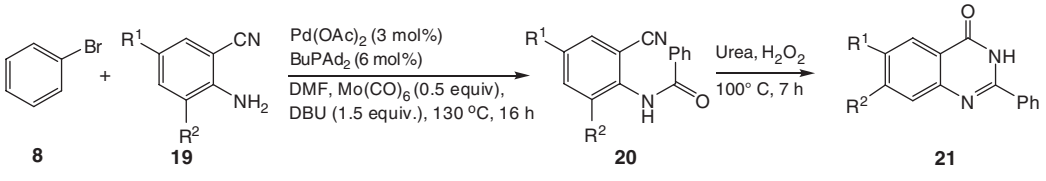


13 15 16 17 18 14

Scheme 9 Plausible reaction pathway for the synthesis of 2-substituted-4(*3H*)-quinazolinones **14**.

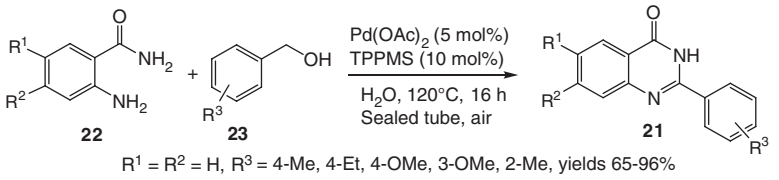
A convenient one-pot method to synthesize 4(3*H*)-quinazolinones has been developed [23]. The aminocarbonylation of bromobenzene **8** using substituted amines **19** in the presence of $Pd(OAc)_2$ and $Mo(CO)_6$ as solid CO source produces *N*-(2-cyanoaryl)benzamides **20**. The cyclization of **20** using urea-hydrogen peroxide (UHP) yields the corresponding 2-phenyl-4(3*H*)-quinazolinones **21** in moderate to good yield (Scheme 10).

A novel method for the synthesis of similar 2-substituted-4(3*H*)-quinazolinones **21** via a palladium-catalyzed



8 19 20 21

Scheme 10 Synthesis of 2-substituted-4(3*H*)-quinazolinones **21**.



Scheme 11 Palladium-catalyzed reaction of benzyl alcohol with 2-aminobenzamide.

reaction of *o*-aminobenzamide **22** with benzyl alcohols **23** has been developed by Hikawa et al. [24]. Results for the reaction of *o*-aminobenzamides **22** with several benzyl alcohols **23** using $Pd(OAc)_2$ (5 mol%) and sodium (diphenylphosphino)benzene-3-sulfonate (TPPMS; 10 mol%) in water for 16 h under air in a sealed tube are summarized in Scheme 11. Reactions of benzyl alcohols **23** substituted at position 4 with an electron-donating group such as methyl, ethyl, or methoxy group afford the quinazolinones **21** in the respective yields of 90%, 96%, and 88%.

The mechanism involves *N*-benzylation, benzylic C-H amidation, and dehydrogenation in water, which may play an important role in the smooth generation of the (η3-benzyl) palladium species by activation of the hydroxyl group of the benzyl alcohol. In the first step, the reaction with Pd(0) with **23** results in the formation of a benzyl-Pd complex **25**. The complex **25** undergoes a reaction with 2-(*o*-benzylamino)benzamide (**24**), derived from **22** to form another intermediate complex **26**. This cascade of transformations is followed by the amidation/dehydrogenation of **26** affording the quinazolinone product **21** in almost a quantitative yield (Scheme 12).

3-Substituted quinazolinones

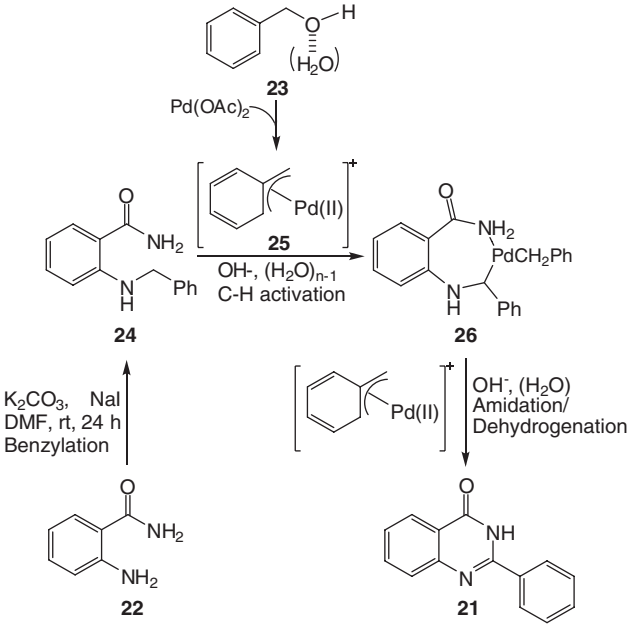
He et al. [25] have developed a palladium-catalyzed four-component carbonylative coupling system for the selective construction of 3-aryl-4(3*H*)-quinazolinones **29** in a one-pot fashion. The treatment of a mixture of 2-bromoaniline (**27**), arylamine **28**, triethyl orthoformate, and CO with a complex palladium acetate/di(1-adamantyl)-*n*-butylphosphine [$Pd(OAc)_2$/($BuPAd_2$)] at 100°C affords 3-substituted-4(3*H*)-quinazolinone **29** in high yield (Scheme 13).

A convenient transformation of 2-bromoformanilide **30** and nitro compounds **31** into the corresponding 3-substituted-4(3*H*)-quinazolinones **29** using the catalyst $Pd(OAc)_2$/$BuPAd_2$ and $Mo(CO)_6$ as a solid source of CO in a mixture of 1,4-dioxane and Et_3N is summarized in Scheme 14 [26].

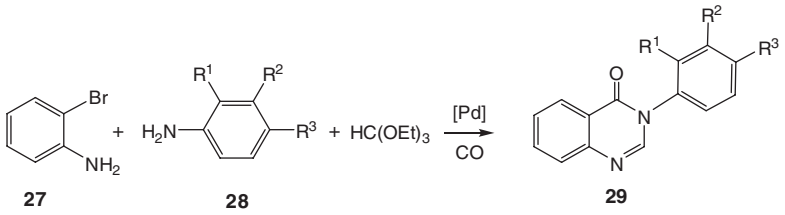
A reaction pathway is proposed in Scheme 15. First, the oxidative addition of 2-bromoformanilide **30** to Pd(0) generates the organopalladium intermediate **32**. The insertion of CO generated from $Mo(CO)_6$ to intermediate **32** results in the formation of the acylpalladium complex **33** as the key intermediate product. At the same time, the nitro compound **31** is reduced by $Mo(CO)_6$, and the resulting amine undergoes an attack by the acylpalladium complex **33**, forming 2-formamido-*N*-phenylbenzamide (**34**) with regeneration of the Pd(0) catalyst. The quinazolinone **29** is produced in an intramolecular nucleophilic condensation of the bis-amide **34**.

4-Substituted quinazolines

Another approach to synthesize 4-substituted quinazolines **35** has been reported by Akazome et al. [19]. The chemistry involves an intermolecular reductive *N*-heterocyclization, specifically the reaction of 2-nitrophenyl ketones **3** (R = Me, Et) with formamide in the presence of a complex $PdCl_2(PPh_3)_2$ and $MoCl_5$ to afford the corresponding 4-substituted quinazolines **35** (Scheme 16).

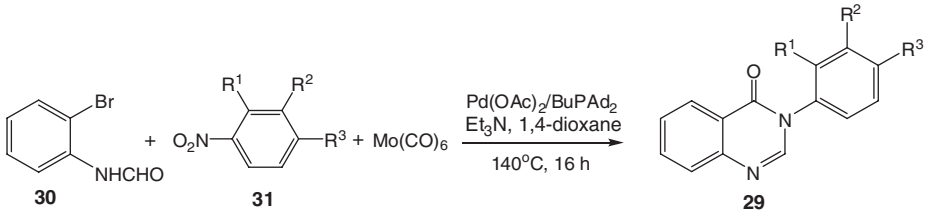


Scheme 12 Suggested mechanism for the palladium-catalyzed synthesis of quinazolines **21** from substrates **22** and **23**.



$R^1 = R^2 = R^3 = H$; $R^1 = R^2 = H$, R^3 = 4-CF_3-C_6H_4; $R^1 = R^2 = H$, R^3 = 4-Cl-C_6H_4; $R^1 = R^2 = H$, R^3 = 3-OAc-C_6H_4; $R^1 = R^2 = H$, $R^3 = CH_2$-C_6H_5; $R^1 = R^2 = H$, R^3 = 4-F-benzyl, yields 60-92%

Scheme 13 Palladium-catalyzed carbonylative coupling of anilines with 2-bromoaniline.



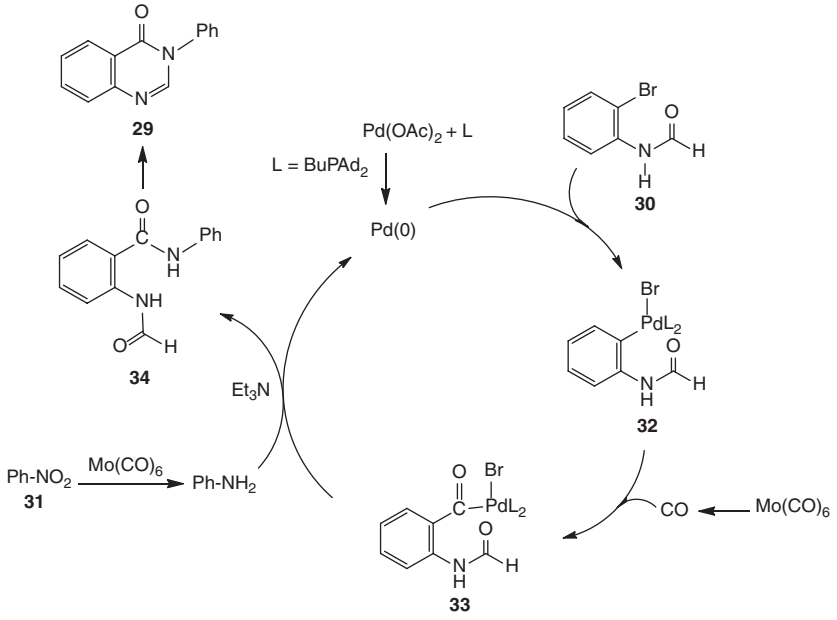
$R^1 = R^2 = R^3 = H$; $R^1 = R^2 = H$, R^3 = Me; $R^1 = R^2 = H$, R^3 = isopropyl; $R^1 = R^2 = H$, R^3 = *tert*-Bu; R^1 = H, $R^2 = R^3$ = Me; $R^1 = R^2$ = Me, R^3 = H, yields 61-97%

Scheme 14 Palladium-catalyzed formation of 3-substituted-4(3*H*)-quinazolinones **29**.

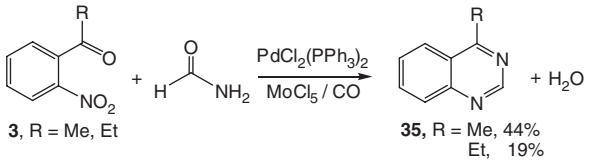
Disubstituted quinazolines

2,3-Disubstituted-4(3*H*)-quinazolinones

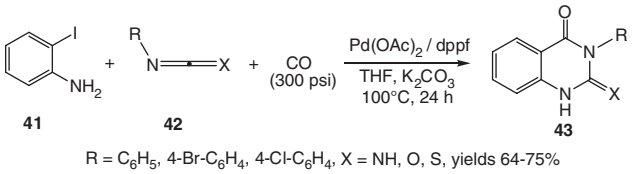
There are many procedures using a palladium-catalyzed carbonylation system that were developed for the synthesis of 2,3-disubstituted-4(3*H*)-quinazolinones. Hikawa et al. [24] reported in 2012 that 2,3-disubstituted-4(3*H*)quinazolinones **37** are obtained in excellent yields by the reaction of 2-amino-*N*-methylbenzamide (**36**), a benzyl alcohol **23**, $Pd(OAc)_2$ (5 mol%), and TPPMS (10 mol%) in water for 16 h under air in a sealed tube (Scheme 17).



Scheme 15 Suggested mechanism for palladium-catalyzed synthesis of 3-phenyl-4(3*H*)-quinazolinone **29**.



Scheme 16 Synthesis of 4-substituted quinazolines **35**.



Scheme 19 Synthesis of 4(3*H*)-quinazolinone derivatives **43**.

Sadig et al. [27] reported a new method for the construction of 2,3-disubstituted-4(3*H*)-quinazolinones **40** via a palladium-catalyzed reaction of (*Z*)-methyl-*N*-(2-bromophenyl)benzimide **38** with a variety of amines **39**. The ease of synthesis of the precursors **38** from a readily available starting material **27** makes them attractive building blocks for heterocycle preparation (Scheme 18).

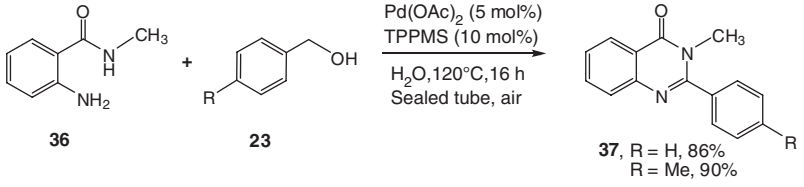
In 2000, Larksarp and Alper [28] developed a palladium acetate/1,1′-bis(diphenylphosphino)ferrocene (dppf) catalyst system for the cyclocarbonylation of 2-iodoaniline (**41**) with heterocumulenes **42** to afford 4(3*H*)-quinazolinone derivatives **43** (Scheme 19). This synthesis is conducted at 100°C for 24 h under a carbon monoxide pressure to produce products **43** in good yields.

Using carbodiimides **42** with electron-withdrawing groups substituted on the phenyl ring does not have any effect on the selectivity of the reaction. The reaction is inefficient for the starting carbodiimides bearing electron-donating substituents.

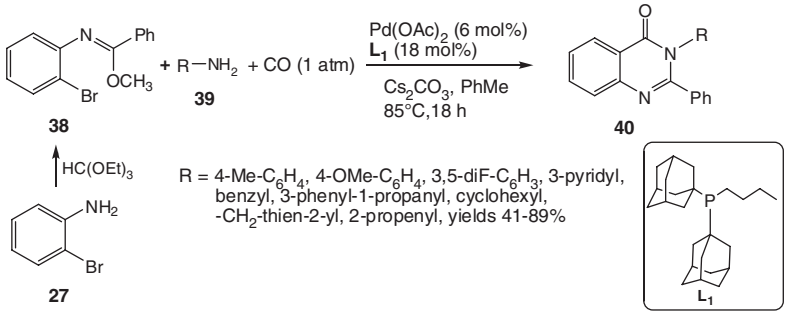
A possible mechanism for the palladium-catalyzed cyclocarbonylation reaction of 2-iodoaniline with carbodiimides is presented in Scheme 20. In the first step, compound **41** undergoes a reaction with carbodiimide **42** to produce a guanidine intermediate **44**, which is followed by the oxidative addition of the palladium catalyst into the C-I bond to give **45**. There is also the possibility of coordination between the NHPh moiety and the palladium in the aroylpalladium intermediate **46**; the subsequent reductive elimination would result in the formation of the intermediate product **43**. This intermediate **43** undergoes tautomerization to the more stable 2-amino-4(3*H*)-quinazolinone **47** (Scheme 20).

In an extension of this methodology, a ketenimine **48** is allowed to react with 2-iodoaniline **41** and CO in the presence of a palladium catalyst (Scheme 21) to give a 2,3-disubstituted-4(3*H*)-quinazolinone **49** in excellent yield in most cases studied.

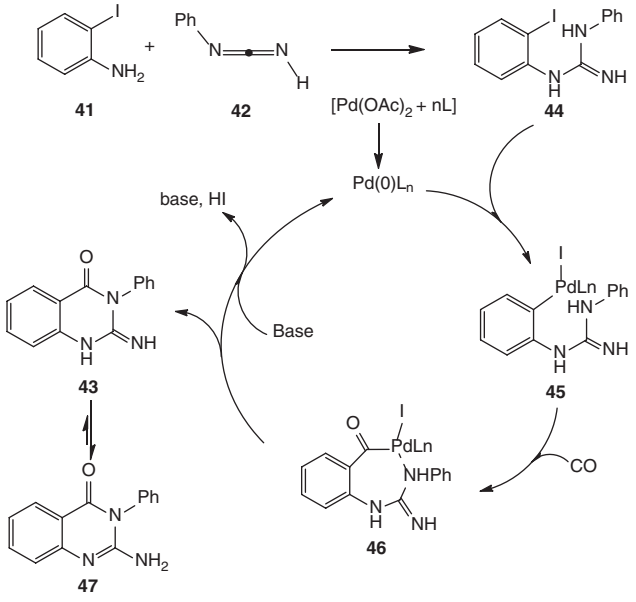
This reaction may proceed in a similar way to that described for carbodiimides. It can be suggested that two intermediate amidines **51** and **52** are formed by the reaction of 2-iodoaniline **41** with the ketenimine **48** by a process of oxidative addition and carbonyl insertion



Scheme 17 Synthesis of 2,3-disubstituted-4(*3H*)-quinazolinones **37**.



Scheme 18 Synthesis of 2,3-disubstituted-4(*3H*)-quinazolinones **40**.



Scheme 20 Suggested mechanism for the palladium-catalyzed cyclocarbonylation reaction of 2-iodoaniline with carbodiimide.

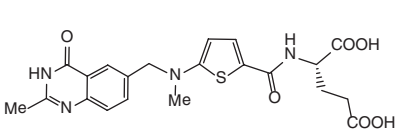
(Scheme 22). The intermediate product **51** would undergo reductive elimination to afford **53.** This intermediate product would then undergo rearrangement to give the more stable 2,3-disubstituted-4(3*H*)-quinazolinone **49**. An alternative route to **49** may involve oxidative addition followed with carbonyl insertion to afford intermediate product **52**. The base-catalyzed intramolecular cyclization of **52** would afford final product **49** (Scheme 22).

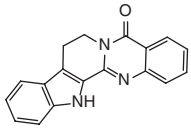
Zhaoyan and Howard [29] developed a one-step carbonylation procedure to synthesize 2,3-disubstituted-4(3*H*)-quinazolinones **56** from 2-iodoanilines **41** and readily available imidoyl chlorides **54** by a palladium-catalyzed three-component process. The method tolerates a range of functional groups, and 2,3-disubstituted-4(*3H*)-quinazolinones **56** were obtained in 63–91% yields. The reaction is catalyzed by the system $Pd(OAc)_2$/PPh_3/Et_3N (Scheme 23). Studies have suggested that this cyclocarbonylation reaction may involve the intermediate amidine **55**.

The mechanism for the formation of 2,3-disubstituted 4(3*H*)-quinazolinones **56** is suggested in Scheme 24. In the first step, the base-catalyzed reaction of imidoyl chloride and aromatic amine generates an aryl amidine **55**. The oxidative addition of **55** to the *in situ* generated palladium(0) species leads to aryl amidine-palladium complex **57**. Carbon monoxide insertion into the aryl carbon-palladium bond of **57** affords the aroylpalladium iodide complex **58**. The base-catalyzed intramolecular cyclization of **58** gives a palladacycle **59**, which then undergoes reductive elimination affording 4(3*H*)-quinazolinone **56** with regeneration of palladium(0).

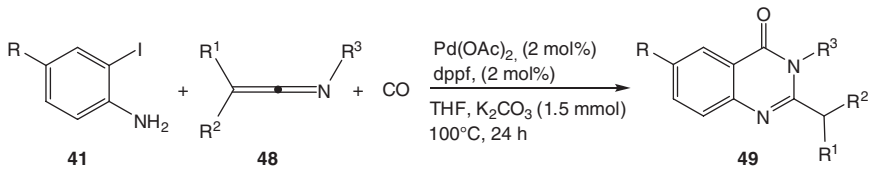
Pd(II)-catalyzed *ortho*-carboxylation in anilides to form *N*-acylanthranilic acids has been developed by Giri et al. [30]. The reaction protocol enables the generation of an array of biologically active benzoxazinone and quinazolinone derivatives from simple anilides (Scheme 25).

Quinazoline heterocyclic scaffolds exemplified by raltitrexed and rutaecarpine are substantial structures in medicinal chemistry [31]. Readily available acyl-protected aniline derivatives can be used as substrates for the construction of the quinazoline system via carboxylation [32]. Diverse synthetic methods have been developed with anthranilic acid as the crucial substrate for carboxylation to access quinazolines (Scheme 26).



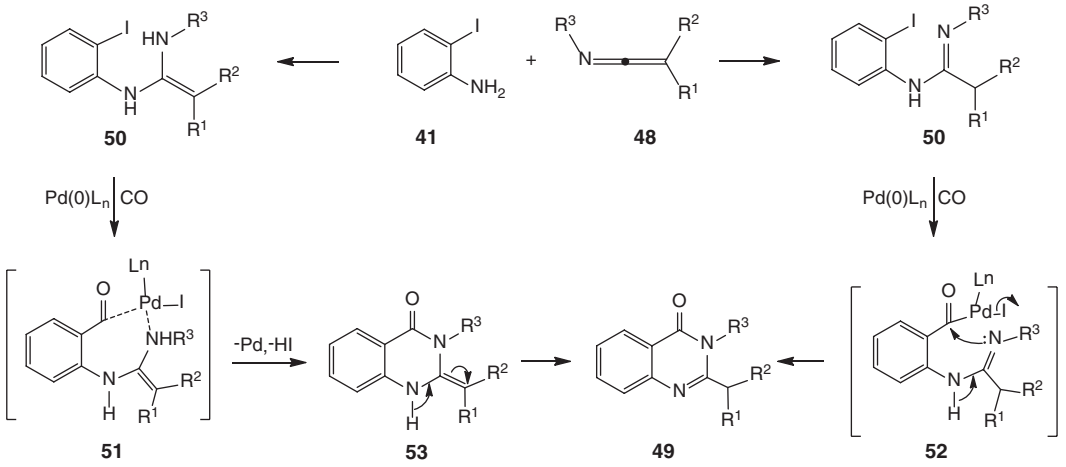


Early attempts were discouraging because acetanilides **60** failed to undergo *ortho*-carboxylation under the standard conditions (Ag_2CO_3/K_2CO_3/NaOAc/dioxane) [33]. It is well known from the pioneering works of Tremont et al. [34], Boele et al. [35], and Zaitsev et al. [36] that anilides are amenable to *ortho*-C-H cleavage in the presence of Pd(II) catalysts under various conditions. However, *ortho*-C-H activation of acetanilide **60** was initially unsuccessful in the presence of CO. It became evident that the presence



R = H, Cl; R^1 = Me, R^2 = CO_2Et, R^3 = C_6H_5; R = H, R^1 = Me, R^2 = CO_2Et, R^3 = *n*-Bu; R = H, R^1 = Me, R^2 = COC_6H_5, R^3 = C_6H_5; R = H, R^1 = R^2 = CO_2Et, R^3 = C_6H_5, yields 71-98%

Scheme 21 Synthesis of 2,3-disubstituted-4(3*H*)-quinazolinones **49**.

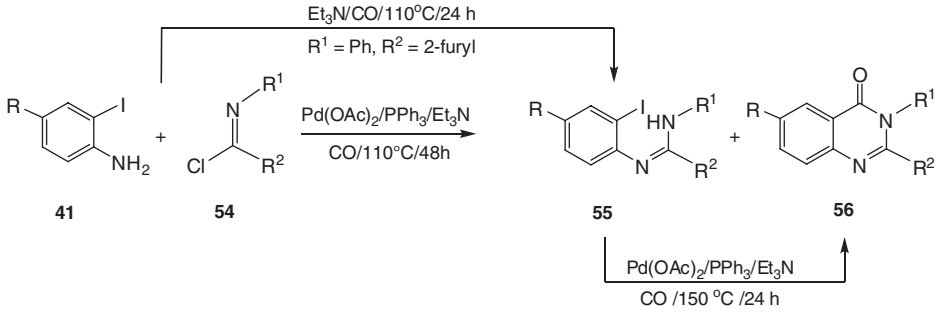


Scheme 22 Proposed mechanism for the synthesis of 2,3-disubstituted-4(3*H*)-quinazolinones **49**.

of CO hinders the C-H activation process and affects the reduction of $Pd(OAc)_2$ to Pd(0) in both stoichiometric and catalytic experiments [37]. To overcome this problem, reaction conditions were investigated that would promote the cleavage of C-H bonds over the reduction of $Pd(OAc)_2$. Highly electrophilic cationic Pd(II) species generated under acidic conditions are known to be more reactive toward C-H activation [38]. The successful study involved the reaction of acetanilide **60** with a stoichiometric amount of $Pd(OAc)_2$ in trifluoroacetic acid (TFA) under 1 atm of CO. Recently, Houlden et al. [39] have reported a urea-directed *ortho*-carbonylation and 1,2-dicarboamination of dienes via *ortho*-C-H activation of phenylurea derivatives [40]. A variety of anilides **60** undergo carboxylation to *N*-acylanthranilic acids **61**, the treatment of which with PCl_3 in the presence of anilines **39** furnishes quinazolinones **62** in high yields (85–96%) (Scheme 26).

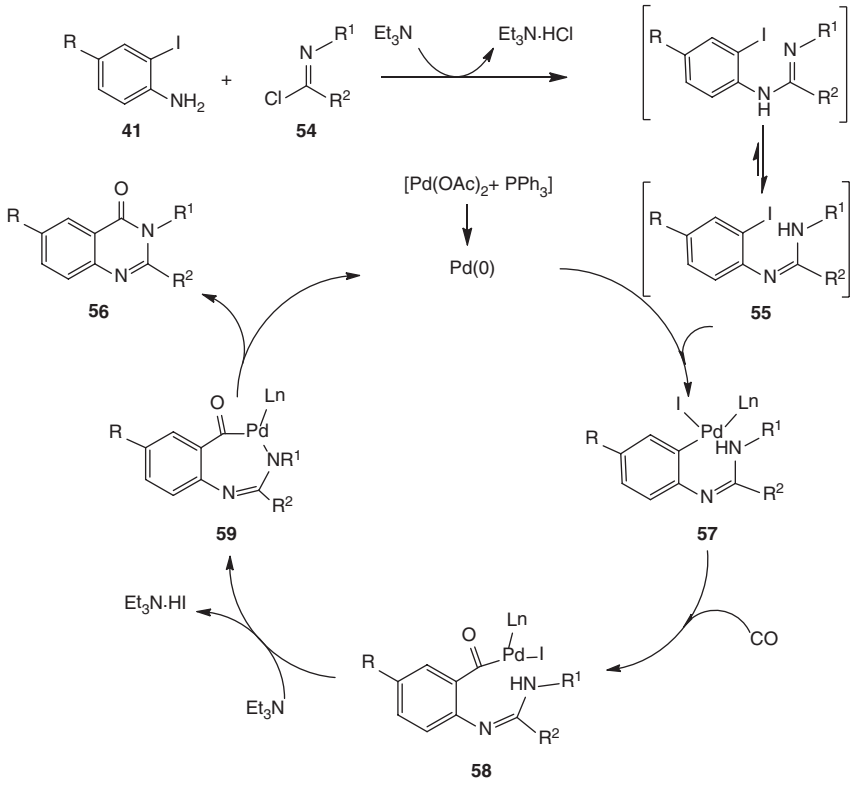
2,4-Disubstituted quinazolines

2,4-Disubstituted quinazolines exist in many biologically active scaffolds, including some anticancer agents [41]. An efficient method for the synthesis of 2,4-disubstituted quinazolines from readily available *N*-arylamidines and isonitriles via palladium-catalyzed intramolecular cyclization was published by Wang et al. [42] in 2011. 4-Amino-2-arylquinazolines with a broad substrate scope and good

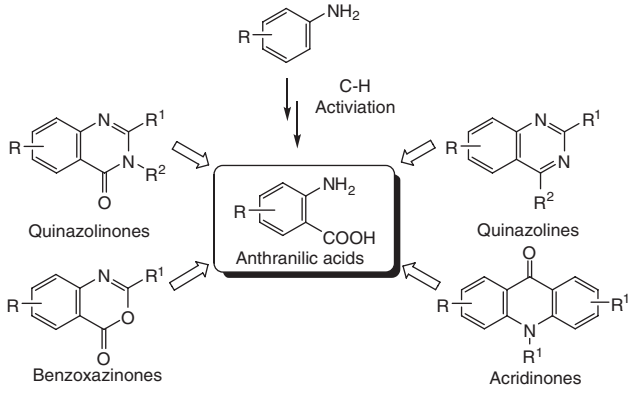


R = H, $R^1 = R^2 = C_6H_5$; R = H, R^1 = 4-OMe-C_6H_4, $R^2 = C_6H_5$; R = H, R^1 = 4-Me-C_6H_4, $R^2 = C_6H_5$; R = H, $R^1 = R^2$ = 4-Me-C_6H_4; R = H, R^1 = 4-Cl-C_6H_4, $R^2 = C_6H_5$; R = H, $R^1 = C_6H_5$, R^2 = 4-Cl-C_6H_4; R = H, $R^1 = R^2$ = 4-Cl-C_6H_4; R = H, R^1 = isopropyl, $R^2 = C_6H_5$; R = H, R^1 = n-Bu, $R^2 = C_6H_5$; R = H, $R^1 = C_6H_5$, R^2 = *tert*-Bu; R = H, $R^1 = C_6H_5$, R^2 = 2-furyl; R = CH_3, $R^1 = R^2$ = 4-Me-C_6H_4; R = Cl, $R^1 = R^2$ = 4-Me-C_6H_4; R = CN, $R^1 = R^2$ = 4-Me-C_6H_4; yields 63-91%

Scheme 23 Synthesis of 2,3-disubstituted-4(*3H*)-quinazolinones **56** *via* palladium-catalyzed cyclocarbonylation of 2-iodoanilines **41** with imidoyl chlorides **54**.



Scheme 24 Proposed mechanism of 2,3-disubstituted-4(*3H*)-quinazolinones **56**.

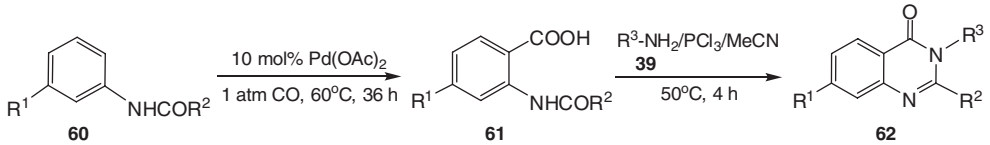


Scheme 25 Anthranilic acid as precursor to heterocyclic frameworks.

functionality tolerance are efficiently obtained by using this method.

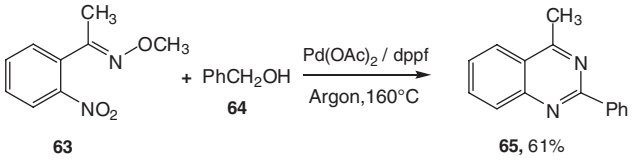
Recently, Wang et al. [21] proposed an easy method producing 2,4-disubstituted quinazoline **65** by reacting (*E*)-1-(2′-nitrophenyl)ethanone *O*-methyl oxime (**63**) and benzyl alcohol (**64**) in the presence of $Pd(OAc)_2$/dppf under argon at 160°C. In this reaction, the nitro group is reduced *in situ* by hydrogen generated by the alcohol dehydrogenation step (Scheme 27).

A suggested mechanism for 2,4-disubstituted quinazoline **65** is given in Scheme 28. The dehydrogenation of benzyl alcohol generates benzaldehyde and causes the reduction of **63** to the intermediate product **66**. The condensation of benzaldehyde with **66** affords



61: R^1 = H, R^2 = CH_3, R^1 = H, R^2 = C_6H_5; R^1 = OMe, R^2 = 3-Cl-C_6H_4 yields 73-96%
62: R^1 = H, R^2 = C_6H_5, R^3 = 4-OMe-C_6H_4; R^1 = H, R^2 = C_6H_5, R^3 = 3,5-CF_3-C_6H_3; R^1 = OMe, R^2 = 3-Cl-C_6H_4, R^3 = C_6H_5; R^1 = OMe, R^2 = 3-Cl-C_6H_4, R^3 = 4-OMe-C_6H_4; R^1 = OMe, R^2 = 3-Cl-C_6H_4, R^3 = 3,5-CF_3-C_6H_3; yields 85-96%

Scheme 26 Synthesis of 2,3-disubstituted-4(3*H*)-quinazolinones **62**.



Scheme 27 Synthesis of 2,4-disubstituted quinazoline **65**.

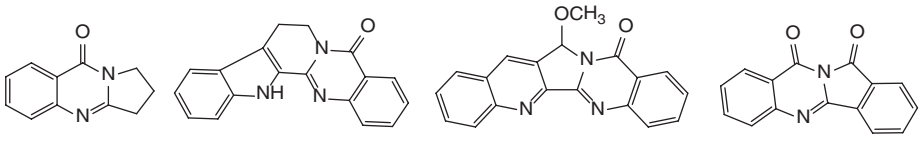
an imine intermediate **67**, the oxidative addition of which to Pd(0) affords complex **68**. The intramolecular cyclization of **68** followed by the reductive elimination of the resultant intramolecular complex **69** yields the final product **65**.

A method for the Pd-catalyzed *N*-arylation of both aryl and alkyl amidines with a wide range of aryl bromides, chlorides, and triflates has been described by the Buchwald group [43]. The reaction proceeds with excellent selectivity for monoarylation (Scheme 29). The resultant *N*-arylamidines (**72**) can serve as precursors for the synthesis of biologically important heterocycles such as imidazoles [44], benzimidazoles [45], quinazolines [46], and quinazolinones [47]. Traditionally, *N*-arylamidines have been prepared by an additional reaction of aniline to an activated nitrile or amide or by the addition of thioimidic ester [48]. Recently, trihaloethyl imidates have also been selected as excellent reagents for the synthesis of substituted amidines [49]. There have been several recent reports of successful amidine *N*-arylation, particularly using copper catalysis [50]. Most of these reactions require the presence of an *ortho*-directing group in the molecule [51] or 1,2-dihaloarene electrophiles [52] to provide fused heterocycles directly, as shown in Scheme 29. The synthesis of **72** is conducted efficiently in the presence of a biarylphosphine ligand **L2** [45]. The application of compounds **72** in the synthesis of quinazolines **74** is illustrated in Schemes 30 and 31. Scheme 31 shows a greatly improved one-pot synthesis of products **74**.

The scope of reactions of *N*-aryl substituted benzamidines **72** was improved by using *tert*-butylisonitrile, $Pd(OAc)_2$, and Cs_2CO_3 under a slight pressure of molecular oxygen in toluene to form the corresponding 4-(*N*-*tert*-butylamino)-2-phenylquinazolines **76** (Scheme 32). A mechanism is suggested in Scheme 33.

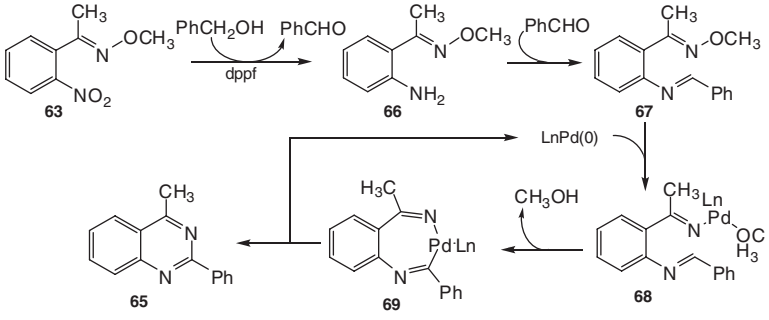
Ring-fused quinazolinones

Ring-fused quinazolinones represent an important class of heterocyclic motifs that were found as the core structural skeletons in a variety of natural products. Examples are deoxyvasicinone isolated from *Adhatoda vasica*, rutecarpine isolated from *Evodia rutaecarpa*, luotonin A isolated from *Peganum nigellastrum*, and tryptanthrin isolated from *Couropita guianensis* [53]. There are several approaches developed for the synthesis of ring-fused quinazolinones [53, 54].

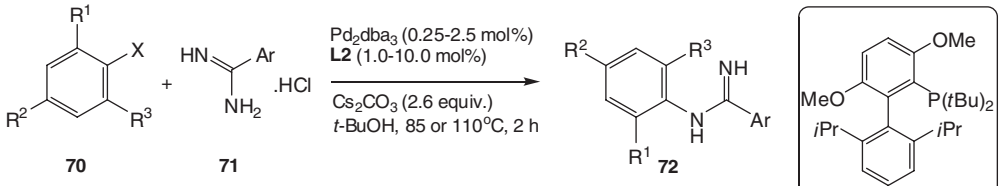


Tricyclic quinazolinones

A new approach for the facile synthesis of fused quinazolinone scaffolds **82** and **83** has recently been discovered

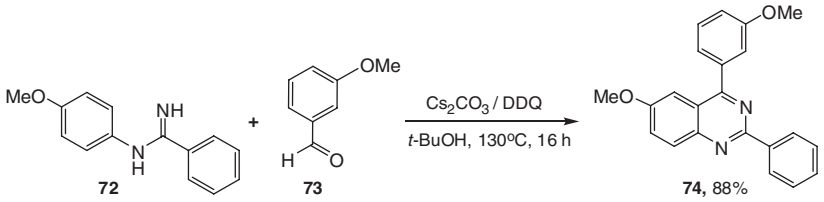


Scheme 28 A suggested mechanism for 2,4-disubstituted quinazoline **65**.

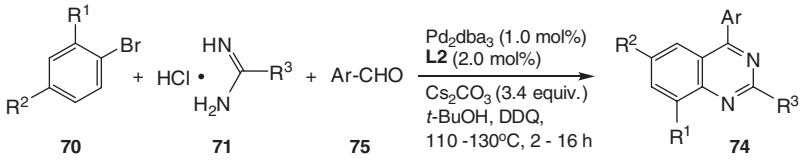


X = Br, $R^1 = R^3 = H$, R^2 = Me, Ar = C_6H_5; X = Cl, $R^1 = R^3 = H$, R^2 = Me, Ar = C_6H_5; X = OTf, $R^1 = R^3 = H$, R^2 = Me, Ar = C_6H_5; X = Br, $R^1 = R^3 = H$, R^2 = CN, Ar = C_6H_5; X = Br, $R^1 = R^3 = H$, R^2 = OMe, Ar = C_6H_5; X = Br, $R^1 = R^3 = H$, R^2 = OMe, Ar = 4-pyridyl; X = Cl, $R^1 = R^3 = H$, R^2 = OMe, Ar = 4-pyridyl; X = Br, $R^1 = R^2$ = Me, $R^3 = H$, Ar = 3-pyridyl; yields 70-93%

Scheme 29 Synthesis of *N*-monoarylamidines **72**.



Scheme 30 Synthesis of 2,4-disubstituted quinazoline **74**.

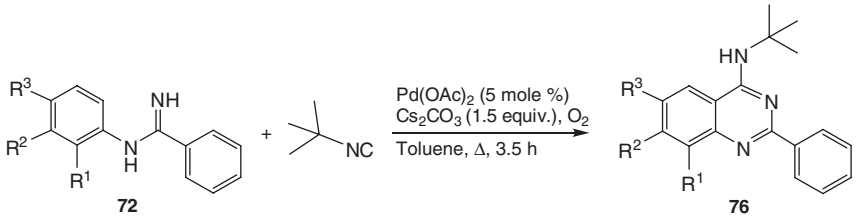


R^1 = H, R^2 = OMe, $R^3 = C_6H_5$, Ar = 3-OMe-C_6H_4; $R^1 = R^2$ = Me, R^3 = 3-pyridyl, Ar = 3-OMe-C_6H_4; R^1 = H, R^2 = OMe, R^3 = 2-thienyl, Ar = 2-pyridyl; R^1 = H, R^2 = OMe, R^3 = isopropyl, Ar = 4-quinolinyl; R^1 = H, R^2 = *n*-Bu, R^3 = cyclopropyl, Ar = 2-Br,5-F-C_6H_3; yields 32-55%

Scheme 31 One-pot synthesis of 2,4-disubstituted quinazolines **74**.

through a palladium-catalyzed carbonylative coupling followed by an intramolecular nucleophilic aromatic substitution [55]. The base serves as the key modulator. In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the linear isomers **82** are preferentially obtained, while Et_3N promotes the preferential formation of angular products **83** (Scheme 34).

The proposed catalytic cycle mechanism for this palladium-catalyzed carbonylation reaction is shown in Scheme 35. The formation of the active catalyst takes place by the reduction of Pd(II) to Pd(0) with CO or amines. The oxidative addition of 1-bromo-2-fluorobenzene (**80**) to Pd(0) leads to the corresponding organopalladium species **84**. By the coordination and insertion of CO, the key intermediate acyl palladium complex **85** is formed. In the presence of DBU, 2-imino-2*H*-pyridin-1-ide (**86**) undergoes nucleophilic attack on the acyl palladium complex **85** forming intermediate **87**. On the other hand, in the presence of Et_3N, the



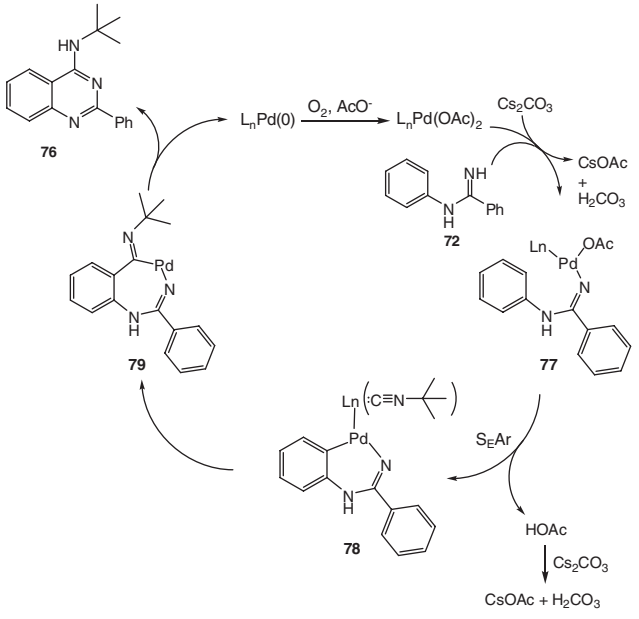
$R^1 = R^2 = R^3 = H$; $R^1 = R^2 = H$, R^3 = Me; $R^1 = R^2 = H$, R^3 = OMe; $R^1 = R^2 = H$, R^3 = F; $R^1 = R^2 = H$, R^3 = Cl; $R^1 = R^3 = H$, R^2 = Me; $R^1 = R^3 = H$, R^2 = OMe; $R^1 = R^3 = H$, R^2 = Cl; R^1 = Me, $R^2 = R^3 = H$; R^1 = *tert*-Bu, $R^2 = R^3 = H$; R^1 = F, $R^2 = R^3 = H$; yields 42-96%

Scheme 32 Synthesis of 2,4-disubstituted quinazolines **76**.

nucleophilic reaction of 2-aminopyridine (**81**) with the acyl palladium complex **85** yields intermediate **88**. Finally, the intramolecular nucleophilic aromatic substitution of intermediate **87** or **88** affords the respective terminal linear **82** or the angular **83** product. The active Pd(0) catalyst is regenerated with the assistance of the base.

In 1987, Tilley et al. [56] reported an interesting protocol for the synthesis of pyrido[2,1-*b*]quinazolinones **91** starting from *N*-(2-bromoaryl)pyridin-2-amines **89** under carbonylative conditions (Scheme 36). Another efficient catalytic protocol for the synthesis of **91** uses similar substrates **90** [57]. The C–H pyridocarbonylation reaction takes place smoothly under an atmospheric pressure of CO in the presence of $Pd(OAc)_2$ and $K_2S_2O_8$ as an oxidant in TFA. A range of substituted pyrido[2,1-*b*]quinazolin-11-ones **91** has been obtained in moderate to good yields (47–57%).

The mechanism (Scheme 37) involves the oxidative addition of **89** to the activated palladium forming the aryl palladium species **92**, which is followed by the insertion of the coordinated CO molecule to the aryl-Pd bond leading to Pd-complex **93**. The pyridine nitrogen atom coordinates with Pd, which results in the formation of the seven-atom palladocycle intermediate **94**. The subsequent reductive elimination of **94** that regenerates palladium(0) results in the formation of the quinazoline product **91**. An alternative mechanism may involve the initial chelation of the pyridine nitrogen atom with the CO ligated Pd(II) complex **95** followed by electrophilic cyclopalladation on the phenyl ring to form the intermediate product **96**. The migratory insertion of the coordinated CO molecule into the aryl-Pd bond generates a seven-numbered palladocycle **97**. Reductive elimination leads to product **91** with the concurrent formation of a Pd(0) species, which is reoxidized to the Pd(II) complex by $K_2S_2O_8$ in the presence of CO and TFA.



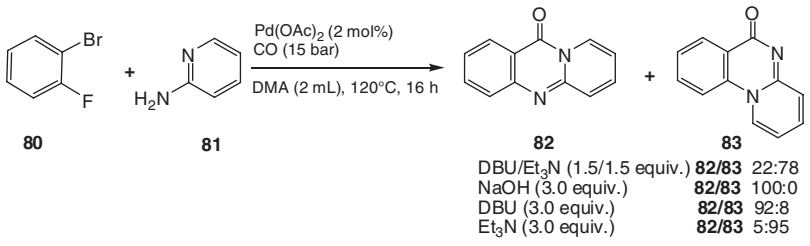
Scheme 33 A suggested mechanism for quinazoline **76**.

Tetracyclic quinazolinones

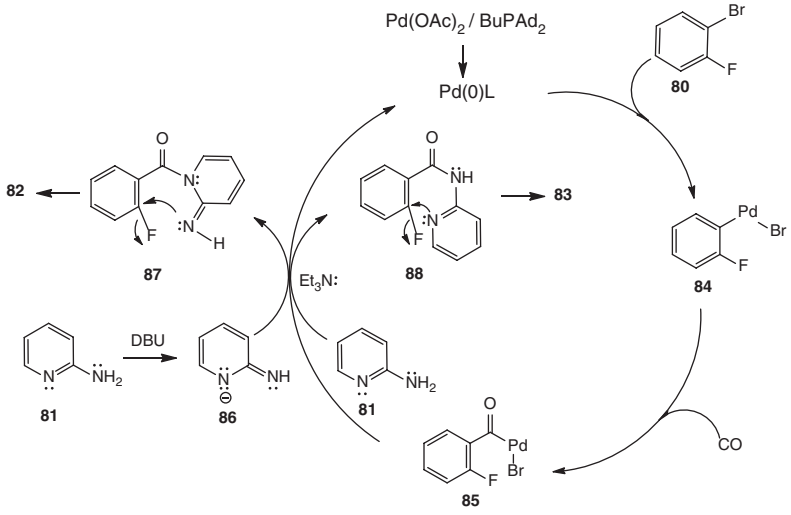
Larksarp and Alper [28] developed a highly efficient palladium-catalyzed domino process for the synthesis of quinazolino[3,2-*a*]quinazolinones in which five new bonds are formed in a single step. This protocol displays good functional group compatibility and provides a facile and straightforward access to potentially important aza-fused tetracyclic quinazoline derivatives. The starting carbodiimides **100** are prepared in 87–93% yields by the reaction of the corresponding isocyanates **98** with *N*-(2-iodoaryl)triphenyliminophosphoranes **99** (Scheme 38).

The cyclization of carbodiimides **100** by the reaction with a variety of amines under Pd-catalyzed conditions to form quinazolino[3,2-*a*]quinazolinones **101** is shown in Scheme 39.

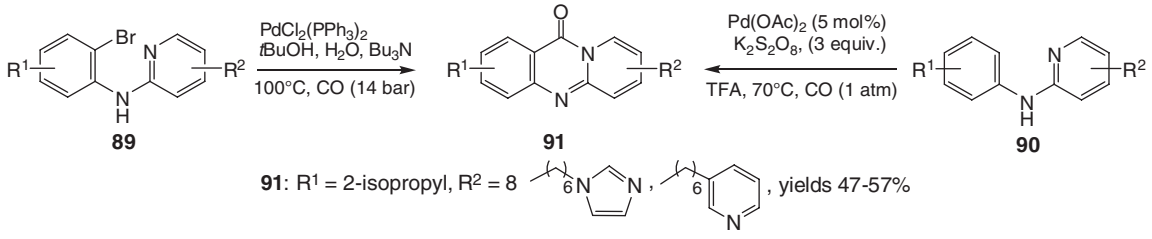
The first palladium-catalyzed double-carbonylation process for the synthesis of quinazolinediones has been developed by Li et al. [58]. Starting from commercially available 2-bromoanilines **27** and 2-bromobenzonitrile **102,** a series of isoindolo[1,2-*b*]quinazoline-10, 12-diones



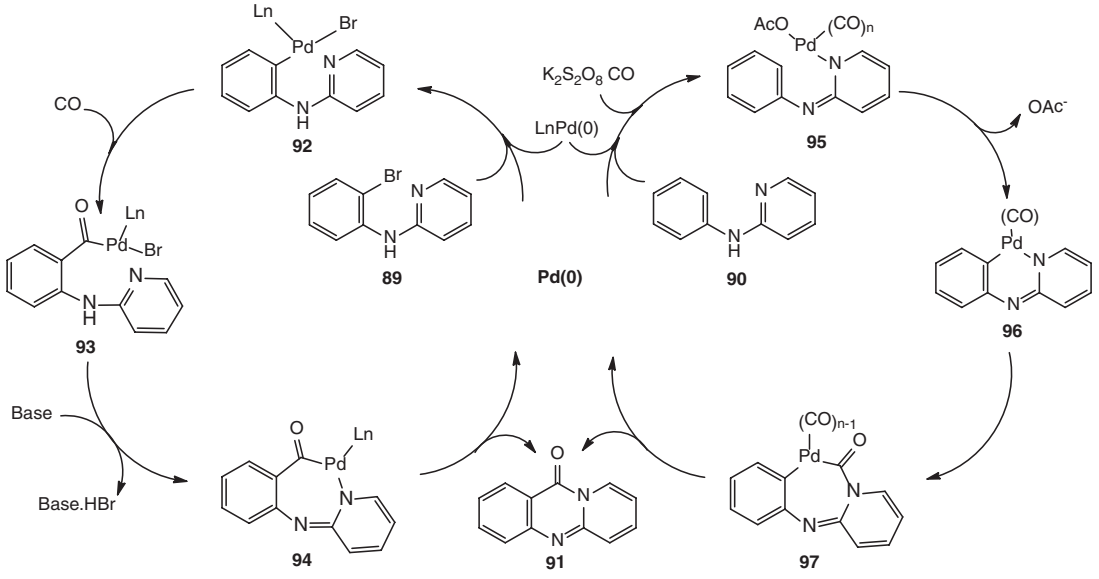
Scheme 34 Synthesis of linear **82** and angular **83** quinazolinones.



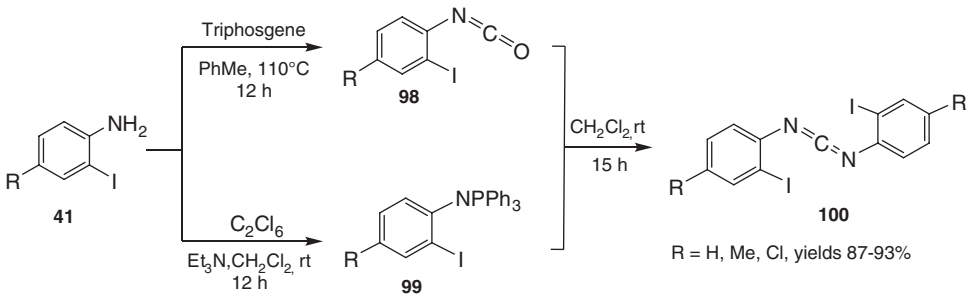
Scheme 35 A suggested mechanism for quinazolines **82** and **83**.



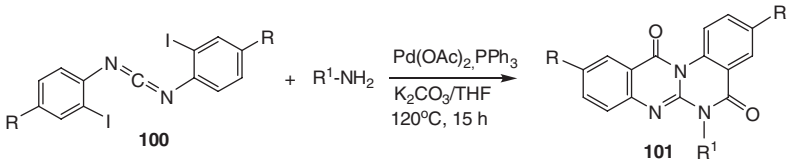
Scheme 36 Two pathways for palladium-catalyzed carbonylative synthesis of pyrido[2,1-*b*]quinazolinones **91**.



Scheme 37 Two pathways suggested for palladium-catalyzed carbonylative synthesis of pyrido[2,1-*b*]quinazolinone **91**.



Scheme 38 Synthesis of carbodiimides **100**.



R = H, R^1 = *n*-hexyl; R = H, R^1 = isopropyl; R = H, R^1 = cyclohexyl; R = H, R^1 = *tert*-butyl; R = H, R^1 = benzyl; R = H, R^1 = 4-OMe-benzyl; R = H, R^1 = 4-Me-benzyl; R = H, R^1 = 4-F-benzyl; R = H, R^1 = C_6H_5; R = H, R^1 = 2-propenyl; R^1 = Me, R^2 = *n*-hexyl; R = Me, R^1 = isopropyl; R^1 = Cl, R^2 = *n*-hexyl; R = Cl, R^1 = isopropyl, yields 38-89%

Scheme 39 Synthesis of tetracyclic quinazolinones **101**.

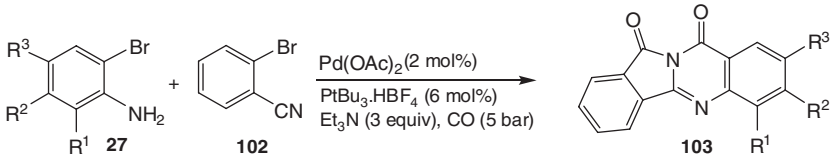
103 can be obtained in a straightforward manner with good isolated yields (Scheme 40). In this novel domino process, both inter- and intramolecular carbonylation reactions take place, and two CO molecules are incorporated in the final product **103**. Considering that five different C-C and C-N bonds are formed, each of the individual reaction steps proceeds with high selectivity and excellent yield.

In the proposed mechanism, the first aminocarbonylation of **102** generates amide **104** (Scheme 41, Cycle A). It can be noted that the oxidative insertion of the active palladium species occurs preferentially with **102** because of its high reactivity forming *o*-cyanobenzoyl aniline **104**. This reaction is followed by the base-catalyzed isomerization-cyclization of **104** to form the iminoisoindolinone **105**. Interestingly, the intermediate product **105** does not undergo a second carbonylation reaction; instead, the isomerization of **105** to **106** occurs, probably because of steric effects. Subsequent intramolecular carbonylative coupling furnishes **103** as the final product (Scheme 41, Cycle B).

A convenient procedure for the carbonylative synthesis of isoindoloquinazolinones **108** has been developed by Chen et al. [59]. Using 2-aminobenzylamine (**9**) and 1,2-dibromobenzene (**107**) as substrates and $Pd(OAc)_2$/$BuPAd_2$ as catalyst, the quinazoline product **108** is isolated in a good yield. This is the first example of the carbonylative synthesis of batracylin analogues (Scheme 42).

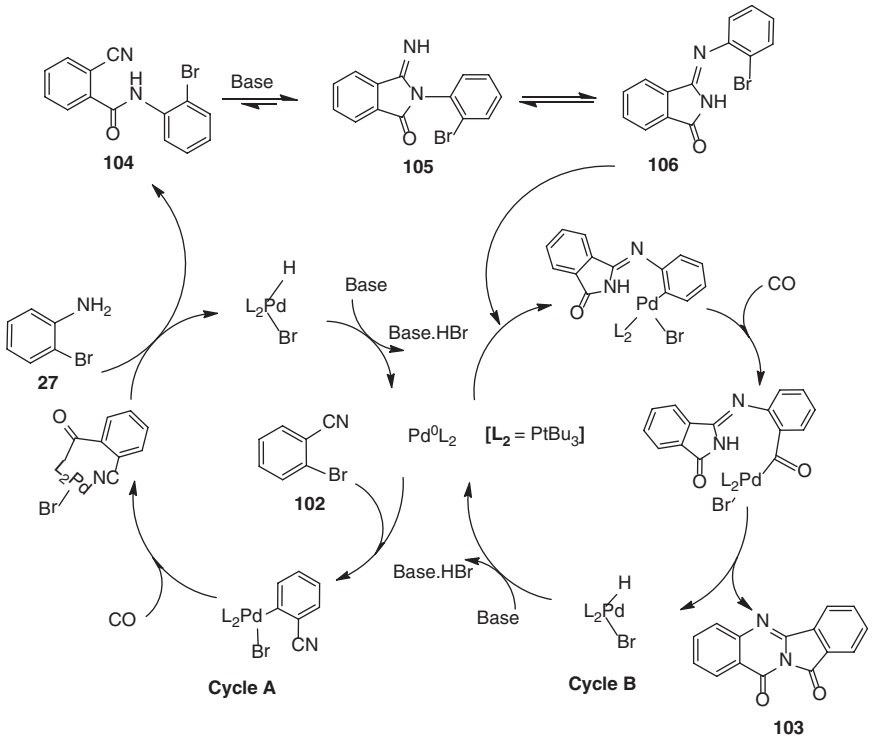
Conclusions

Here we have summarized the major developments of palladium-catalyzed syntheses of quinazolines and

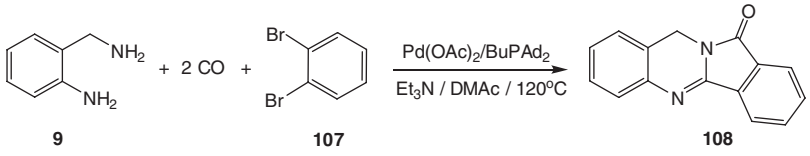


R^1 = R^2 = R^3 = H; R^1 = R^2 = H, R^3 = Cl; R^1 = R^2 = H, R^3 = Ac; R^1 = R^2 = H, R^3 = CN; R^1 = R^2 = H, R^3 = Me; R1 = R^3 = H, R^2 = Me; R^1 = R^2 = H, R^3 = CF_3; R^1 = R^3 = F, R^2 = H; R^1 = Cl, R^2 = H, R^3 = F, yields 37-87%

Scheme 40 Pd-catalyzed carbonylative synthesis of quinazolinedione **103**.



Scheme 41 Proposed mechanism for palladium-catalyzed synthesis of **103**.



Scheme 42 Pd-catalyzed double carbonylative synthesis of batracylin analogue **108**.

quinazolinones. Among all palladium-catalyzed coupling reactions, carbonylation reactions have experienced improvements since the pioneering work by Heck and co-workers in 1974. The advantages of carbonylations are twofold: (i) this potent methodology for the synthesis of carbonyl containing aryl/heteroaryl compounds introduces several carbon atoms at the same time, and (ii) carbon monoxide is used as an inexpensive and readily available C1 source, which is also in agreement with the green chemistry principles. The carbonylation chemistry is of interest not only in academic laboratories but also in industry. Hence, it is not surprising that many carbonylation reactions are used on an industrial scale. In general, these reactions use inexpensive carbon monoxide as the substrate and are conducted in the presence of reusable palladium catalysts.

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