Palladium(II) N^O chelating complexes catalyzed One-pot Approach for synthesis of Quinazolin-4(3H)-ones via acceptorless dehydrogenative coupling of Alcohols and 2-Aminobenzamide

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ABSTRACT: A convenient protocol for the one-pot synthesis of quinazolin-4(3H)-ones using palladium(II) complexes via dehydrogenative coupling of readily available benzyl alcohols and 2-aminobenzamide has been described. New structurally related Pd(II) N^O chelating complexes of general configuration [Pd(L)Cl(PPh₃)] (where L = dimethylamino benzoylhydrazone ligands) have been designed and synthesized. The formation of the complexes has been recognized by analytical and spectral methods (FT-IR, NMR & HR-MS). The presence of a square-planar geometry around palladium (II) ion was confirmed by single crystal X-ray diffraction study. A wide range of substituted quinazolinones have been successfully achieved from diverse range of benzyl alcohols in good to excellent yields using 1.0 mol% of catalyst loading under aerobic conditions. Furthermore, control experiments reveal that the dehydrogenative coupling reaction involves initially via the formation of aldehyde intermediate and subsequent formation of cyclic aminal intermediate.

INTRODUCTION

Nitrogen heterocycles exhibit momentous interest over the years due to their presence in extensive range of synthetic and natural organic compounds.¹ Among them, quinazolinones and their derivatives are important class of compounds found in a large number of natural products.² Significantly, a diverse range of molecules with quinazolin-4(3H)-ones displaying a broad spectrum of bioactivities.³⁻⁹ (Figure 1) Therefore, a vast number of synthetic approaches have been established¹⁰ due to the immense biological needs of quinazolinone and its derivatives in various fields.^{9,10d} However, all these methodologies suffer in providing the desired products of quinazolinone due to low yield, long reaction time, multistep reaction sequences, need of oxidants like DDQ,^{11a} CuCl₂,^{11b} MnO₂,^{11c} KMnO₄,^{11d} I₂,^{11e} and t-BuOOH,^{11f-h}. Further, limitation associated with the above synthetic routes is the use of unstable aldehydes through oxidation of alcohols using toxic oxidants.

To accomplish the greener strategy, transition metal catalyzed acceptorless alcohol dehydrogenation (AAD) methodology¹² is one of the attractive and convenient methodologies for the synthesis of quinazolinone and other N-heterocycles.¹³ Zhou and co-workers disclosed the synthesis of quinazolinones using 2.5 mol% of Ir catalyst from the coupling of benzyl alcohols and 2-aminobenzamides under inert condition.¹⁴ Watson and co-workers achieved the access of quinazolinones using 5 mol% of ruthenium-catalyst under N₂ atmosphere.¹⁵ Wu and co-workers developed ZnI₂/TBHP catalyst for the synthesis of quinazolinones from the reaction of

2-aminobenzamide and benzyl alcohols.¹⁶ Iron catalysed oxidative synthesis of quinazolinones from primary alcohols has been reported in presence of expensive TBHP oxidant.¹⁷ Hu and co-workers have described a report on the synthesis of quinazolinones from alcohols and 2-aminobenzamides with Iron nitrate/TEMPO.¹⁸ Zang *et al.* has reported ruthenium-catalyzed dehydrogenative coupling of 2-aminobenzamides and allylic alcohols.²⁰ Recently, direct access of quinazolinones from aromatic primary alcohols were documented by Paul and co-workers using nickel(II) (5 mol %) and copper(II) (5 mol %) catalysts.^{19,21} (Scheme 1).

Figure 1. Examples of bioactive quinazolinones.

Remarkably, the Pd-catalysed cross coupling reaction have given a great contribution in the construction of heterocyclic compounds,²² especially for the synthesis of quinazolinones.²³ Yokoyama *et al.* investigated quinazolinone synthesis from the

reaction of 2-aminobenzamide and excess of alcohol at the expense of 5 mol% of $\text{Pd}(\text{OAc})_2/\text{TPPMS}$ catalyst in H_2O medium.^{24a} Beller *et al.* synthesized quinazolinone from the coupling reaction of 2-aminobenzamide and aryl halide under catalytic condition of $\text{Pd}(\text{OAc})_2/\text{BuPAD}_2$ and carbon monoxide (10 bar) atmosphere in DMF.^{24b} Zhu *et al.* reported the synthesis of quinazolinone from multi component reaction of anthranilamide, aryl halide and tert-butyl isocyanide with optimal catalytic condition of PdCl_2 (5 mol %)/DPPP and CaCl_2 as an additive in toluene at 145 °C under N_2 atmosphere.^{24c} Liu *et al.* described quinazolinones synthesis using $\text{Pd}(\text{TFA})_2$ (10 mol%) and bpy (20 mol %) under oxygen atmosphere.^{24d} Zhu *et al.* examined the synthesis of quinazolinone from multi component reaction of substituted anthranilamide with arylboronic acids, tertbutylisocyanide and $\text{Cu}(\text{OAc})_2$ with the reaction condition of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ under a N_2 atmosphere in DMF.^{24e} The same research group has reported the synthesis of quinazolinone from 2-aminobenzamide, bromobenzene, $\text{Mo}(\text{CO})_6$ under the condition of $\text{PdCl}_2/\text{BuPAD}_2$ and DBU in DMF under air.^{24f} (Scheme 1)^{a-f}

Hence, the synthesis of quiazolinones from the dehydrogenative coupling of alcohols with 2-aminobenzamide under aerobic condition using palladium(II) complexes has not been well explored in the literature. Therefore, in continuation of our previous reports,^{25,26} we wish to describe the easy access of a wide range of quinozolinones via dehydrogenation of benzylalcohols under mild reaction conditions by newly synthesised palladium(II) benzoylhydrazone complexes. Gratifyingly, the present methodology is considered as atom-economical and environmentally benign protocol which releases water as the only byproduct.

Previous report

Scheme 1. Synthetic strategies for quinazolinone formation.

RESULTS AND DISCUSSION

The dimethylamino benzoylhydrazone ligands were easily prepared from the condensation of dimethylaminobenzaldehyde and 4-substituted benzhydrazide in ethanol.²⁷ Complexation was accomplished by reacting these ligands with the palladium(II) precursor $[\text{PdCl}_2(\text{PPh}_3)_2]$ in a 1:1 molar ratio in the

presence of an equivalent of Et_3N as a base. The resulted red-dish orange complexes of common formula, $[\text{Pd}(\text{L})\text{Cl}(\text{PPh}_3)]$ (Scheme 2) were obtained in good yields. The addition of Et_3N in the reaction mixture assists the amido-imidol tautomerization for effortless coordination of imidolate oxygen. All the palladium complexes are stable in air and readily dissolved in most organic solvents. The newly formed palladium benzoylhydrazone complexes were authenticated with the help of analytical and different spectral techniques.

Scheme 2. Synthesis of Pd(II) benzoylhydrazone complexes.

A medium to strong band is observed in the region 3034–3095 cm^{-1} due to $\nu_{\text{N-H}}$ of hydrazone moiety of the ligands. In addition, the $\nu_{\text{C=N}}$ and $\nu_{\text{C=O}}$ absorptions frequencies of the ligands appear around 1610–1642 cm^{-1} and 1539–1568 cm^{-1} respectively. The $\nu_{\text{C=N}}$ stretching frequencies were decreased to 1579–1582 cm^{-1} upon complexation confirm that imine nitrogen is coordinated to palladium ion. Furthermore, the disappearance of $\nu_{\text{C=O}}$ bands and appearance of new bands in the region of 1341–1345 cm^{-1} indicated the coordination of imidolate oxygen via tautomerization. It is inferred from the IR spectra that the imine nitrogen and imidolate oxygen of the benzoylhydrazone ligand coordinate to the palladium(II) ion.

The NMR spectral studies support the bidentate coordinating character of the ligand to metal in the synthesized palladium(II) benzoylhydrazone complexes. In the ^1H -NMR spectra of complex **1-3**, aromatic protons of the phenyl group of triphenylphosphine and benzoylhydrazone ligands were observed as multiplets at δ 6.70–8.32 ppm. Azomethine proton ($\text{N}=\text{C}-\text{H}$) observed as a doublet²⁸ at δ 7.90–7.94 ppm in all three complexes. After the complex formation, absence of signal around 10.29–11.55 ppm indicates the disappearance of $-\text{NH}$ proton of ligands due to coordination of imidolate oxygen to palladium ion through enolization. In addition, complex **3** displayed a methoxy signal of the benzoylhydrazone ring as singlet at δ 3.80 ppm. (ESI, Figures S1–S3). Further, carbon NMR of the complexes **1-3** shown a downfield shift of carbonyl group to 175.0, 173.94, 174.98 ppm respectively which results from the reduced bond order ($-\text{N}=\text{C}-\text{O}$) upon complexation ($-\text{NH}-\text{C}=\text{O}$) with Pd. In contrast, the up field shift of imine carbon ($\text{C}=\text{N}$) to 152.26, 152.54, 151.92 was observed during the nitrogen coordination of benzoylhydrazone ligand with palladium precursor. Moreover, the complex **3** showed that additional signal at δ 55.30 ppm due to the presence of methoxy carbon. (ESI, Figures S4–S6).

Furthermore, the composition of the complexes has been established by high resolution mass spectrometry (HRMS) analysis (ESI, Figures S7–S9). Mass spectrometric measurement was carried out under positive ion ESI mode using acetonitrile. The mass spectra of all the complexes show a well-defined molecular ion peak at $m/z=675.1507$ ($[\text{M}+2\text{H}]^+$), 709.1116 ($[\text{M}+2\text{H}]^+$) and 705.1604 ($[\text{M}+2\text{H}]^+$), peak fragments. Hence, the mass spectral data are in good agreement with the structural composition of the complexes.

X-ray crystallographic studies

Single crystals of complex **2** and **3** were isolated from CH₂Cl₂/methanol mixture at room temperature. The solid-state molecular structure of palladium(II) benzoylhydrazone complexes **2** and **3** were resolved by X-ray crystallography. The summary of the crystallographic data and refinement parameters are given in, Table S1 and the selected bond lengths along with bond angles are gathered in Table S2. The complex **2** crystallize in triclinic form with the P-1 space group while complex **3** crystallize in the monoclinic space group P21/n space group. The ORTEP view of the complexes have been shown in Figure 2 and 3, which clearly indicate that the ligand binds to palladium metal in a bidentate(N^O) manner through the imine nitrogen and imidolate oxygen with a formation of a five-membered chelate ring. The bite angles of N(2)-Pd(1)-O1(1) and N(12)-Pd(1)-O1(1) in complexes **2** and **3** are 78.77 ° and 78.90 ° respectively. The other positions were occupied by chloride and phosphine ligands. Eventually, the palladium (II) ion is present in a ONPCL square planar environment as reflected in all the bond parameters.²⁹

Figure 2. ORTEP diagram of the complex **2** with 30% probability. All the hydrogen atoms were omitted for clarity. The bond angles around the Pd(1) ion: O(1)-Pd(1)-N(2)= 78.77(8), O(1)-Pd(1)-P(1)= 97.53(5), N(2)-Pd(1)-P(1)= 175.92(6), O(1)-Pd(1)-Cl(2)= 174.95(5), N(2)-Pd(1)-Cl(2)= 96.18(6), P(1)-Pd(1)-Cl(2)= 87.50(2), Bond lengths: N(2)-Pd(1)= 2.059(2), O(1)-Pd(1)= 2.0106(18), P(1)-Pd(1)= 2.2650(7), Cl(1)-Pd(1)= 2.2806(7).

Figure 3. ORTEP diagram of the complex **3** with 30% probability. All the hydrogen atoms were omitted for clarity. The bond angles around the Pd(1) ion: O(1)-Pd(1)-N(1)= 78.90(8), O(1)-Pd(1)-P(1)= 95.35(5), N(1)-Pd(1)-P(1)= 174.25(6), O(1)-Pd(1)-Cl(1)= 175.22(5), N(1)-Pd(1)-Cl(1)= 96.34(6), P(1)-Pd(1)-Cl(1)= 89.40(3). Bond lengths: N(1)-Pd(1)= 2.055(2), O(1)-Pd(1)= 2.0100(18), P(1)-Pd(1)= 2.2561(7), Cl(1)-Pd(1)= 2.2790(7).

The remarkable applications of palladium catalysts to an extensive variety of coupling reactions motivated us to tune the present Pd(II)hydrazone complexes as catalysts in the direct synthesis of bioactive quinazolinones via dehydrogenative coupling substituted benzyl alcohols and 2-aminobenzamide under aerobic condition.

Table 1. Optimization of reaction conditions^a

Entry	Solvent	Base	T(°C)	Time (h)	Yield ^b (%)
1	m-xylene	NaOH	140	24	82
2	Toluene	NaOH	140	24	61
3	Dioxane	NaOH	140	24	40
4	THF	NaOH	140	24	26
5	Acetonitrile	NaOH	140	24	65
6	Methanol	NaOH	140	24	15
7	Ethanol	NaOH	140	24	12
8	DMF	NaOH	140	24	75
9	DMSO	NaOH	140	24	63
10	H ₂ O	NaOH	140	24	30
11	m-xylene	Na ₂ CO ₃	140	24	50
12	m-xylene	K ₂ CO ₃	140	24	55
13	m-xylene	NaHCO ₃	140	24	45
14	m-xylene	KOH	140	24	90
15	m-xylene	CS ₂ CO ₃	140	24	69
16	m-xylene	^t BuOK	140	24	77
17	m-xylene	Et ₃ N	140	24	15
18	m-xylene	KOH	110	24	88
19	m-xylene	KOH	80	24	50
20 ^c	m-xylene	-	110	24	<10
21 ^d	m-xylene	KOH	110	24	NR

^aGeneral reaction conditions. 2-aminobenzamide **1a** (1 mmol), benzyl alcohol **2a** (1.10 mmol) complex **1** (1 mol %), KOH (1.5 mmol) in m-xylene at 70-130 °C for 24 h under open air.

^bIsolated yield. ^cNo base and ^dNo catalyst was used.

To initiate the optimization of reaction condition, we have selected the formation of 2-phenylquinazolin-4(3H)-one from there action of 2-aminobenzamide (**1a**) and benzyl alcohol (**2a**) as a bench-mark substrate using 1 mol% of complex **1** (Table 1). The satisfactory yield (Table 1, Entry 1) of synthesized quinazolinone helped us to investigate various catalytic parameters such as bases, solvents and reaction temperatures (Table 1) Further, the screening of solvents dictated that non-polar m-xylene outperformed the other solvents (toluene, 1,4-dioxane, THF, acetonitrile, methanol, ethanol, DMF, DMSO and H₂O) that examined in this catalytic reaction (Table 1, entry 1-10). Also, the optimization of different bases revealed that KOH found to be effective than other bases including NaOH, ^tBuOK, CS₂CO₃, K₂CO₃, Na₂CO₃, NaHCO₃, Et₃N) (Ta-

ble 1, entries 1 and 11-17) employed in the reaction. Therefore, we are pleased to compromise that the complex 1 is found to exhibit relatively high yield (Entry 18, 88%) of desired quinazolinone under the catalytic condition of m-xylene/KOH at 110 °C. The coupling reaction was unsuccessful in the absence of either catalyst or base (Table 1, entries 21 and 20).

Table 2. Effect of the substituent of catalyst^a

Entry	Pd complex	Yield(%) ^b
1	[Pd(L1)Cl(PPh ₃)] (1)	82
2	[Pd(L2)Cl(PPh ₃)] (2)	86
3	[Pd(L3)Cl(PPh ₃)] (3)	91

^aGeneral reaction conditions: 2-aminobenzamide **1a** (1 mmol), benzyl alcohol **2a** (1.10 mmol) catalyst (1 mol %), KOH (1.5 mmol) in m-xylene at 110 °C for 24 h under open air. ^bIsolated yields.

Once the various catalytic parameters were optimized, the effect of substituents of all the complexes on the catalytic reaction has been investigated. At most, all the complexes (**1-3**) showed good catalytic activity in the formation of quinazolinone product with appreciable yields. However, based on experimental results, the complex **3** relatively provided a better yield than complex **1** and complex **2** due to the presence of electron donating methoxy group (Table 2, entries 1-3). Hence, the complex **3** was kept as a representative catalyst to explore the broad substrate scope using a diverse range of alcohols. Furthermore, effect of catalyst loading was verified under optimal reaction condition. From the results, the catalytic reaction proceeds well with 1 mol % and drop in the yields upon decreasing the catalyst loading to 0.5, 0.2, 0.1, or 0.05 mol % (Table 3, entries 1–5).

Table 3: Effect of catalyst loading^a

Entry	Complex 3 (mol %)	Yield % ^b
1	1	91
2	0.5	66
3	0.2	41
4	0.1	25
5	0.05	14

^a Reaction conditions: 2-aminobenzamide **1a** (1mmol), benzyl alcohol **2a** (1.10 mmol) catalyst (0.05-1 mol%), KOH (1.5 mmol) in m-xylene at 110 °C for 24 h under open air. ^bIsolated yield.

Table 3. Dehydrogenative coupling of 2-aminobenzamide **1a** and various benzyl alcohols **2a** catalyzed by complex **3**^a

^aReaction conditions: 2-aminobenzamide **1a** (1 mmol), alcohol **2a** (1.10 mmol), base (1.5 mmol), m-xylene at 110 °C for 24 h under open air. ^bIsolated yield.

Having optimized condition in our hand, the scope of palladium catalysed acceptorless dehydrogenate reaction was interestingly probed for the coupling of 2-aminobenzamide with various aromatic, polycyclic and heterocyclic aromatic alcohols (Table 3). It is noted that the benzyl alcohol and their derivatives were found to be effective coupling partner with o-aminobenzamide to provide a respective quinazolinone with good yield. The reaction of benzyl alcohol with o-aminobenzamide resulted in the formation 2-phenylquinazolin-4(3H)-one **3a** in 91% yield. Further, the benzyl alcohols bearing electron donating substituents at ortho, meta and para positions effectively reacted with 2-aminobenzamide to give corresponding quinazolinone **3b-3h** in 71-89% yields. Gratifyingly, the catalytic efficiency was proved for the reaction of sterically hindered 3,4,5-trimethoxybenzyl alcohol with 2-aminobenzamide to give the desired **3i** in 77% yield. In case of benzyl alcohol with electron-withdrawing substituents such as 3-fluorobenzyl alcohol, 4-chlorobenzyl alcohol and 2-bromobenzyl alcohol, the yield of respective quinazolinones **3l-3j** in 58-69%. More interestingly, we use the current catalytic protocol for introducing heterocyclic ring in the quinazolin-4(3H)-one. Hence, the heterocyclic aromatic alcohols such as 2-pyridine methanol, 2-thiophene methanol, furfuryl alcohol smoothly coupled with 2-aminobenzamide gave the corresponding products **3m-3o** in 65-67% yields. In addition, the coupling reaction of piperonyl alcohol with 2-aminobenzamide afforded the respective quinazolinone **3p** in 55% yield. Noticeably, reactions of polycyclic alcohols namely, 2-naphthalenemethanol and 9-anthracenemethanol underwent dehydrogenative coupling with 2-aminobenzamide to

give moderate yield of quinazolinones **3q** and **3r** as 59% and 56% respectively. In addition, application of biphenyl-4-methanol in catalysis course, resulted the preferred product **3s** with 58% yield. The reaction of indole-3-carbinal with 2-aminobenzamide resulted in product **3t** in 54% yield. (ESI, Figures S14-S53)

Scheme 3. Control experiments for mechanistic studies

Control experiments were carried out in order to investigating the mechanism behind the catalytic acceptorless dehydrogenation coupling reaction. In the absence of 2-aminobenzamide **2a**, benzyl alcohol **1a** gives rise to the corresponding aldehyde intermediate **1a'** in 6h under optimized reaction conditions (Figures S10 and S11). Further, **1a'** and amide **2a** yielded the cyclic aminal intermediate **2a'** in 6 - 12 h (Figures S12, S13 and S54). Furthermore, the completion of quinazolin-4(3H)-ones product **3a** was reached when the reaction time was extended up to 24 h (Scheme 3). Hence, we strongly believe that the synthesis of the quinazolinones occurs via alcohol dehydrogenation along with the formation of cyclic aminal intermediate proceeds through dehydrogenative pathway.¹⁹

To get more understanding about the impact of electron donating and electron withdrawing substituents of substrates on catalytic reactivity, an intermolecular competitive experiment has been carried out under optimized reaction condition using benzyl alcohol bearing electron donating (4-methoxy) **2e** and electron withdrawing (4-chloro) **2k** with 2-aminobenzamide. The outcome of control reaction proves that the electron-rich substrate **3e** shows more reactivity than the electron-deficient substrate **3k** (Scheme 4).

Scheme 4. Competitive control experiment between EDG and EWG.

On the basis of the control experiments and previous reports, a possible reaction mechanism has been depicted in Scheme 5 for the dehydrogenative coupling of 2-aminobenzamide with primary alcohol using the palladium catalyst. The coupling reaction is supposed to begin with the formation of palladium – alkoxy species (**B**). Then, the (**B**) undergoes β -H elimination to provide benzaldehyde (**B'**) along with the formation of a palladium – hydride species (**C**). Further, the in situ formed benzaldehyde (**B'**) condense with 2-aminobenzamide to form cyclic aminal intermediate (**C'**) with removal of a water molecule. Thereafter, the (**C**) reacts with cyclic aminal intermediate (**C'**) and affords an amino palladium species (**D**) which undergoes dehydrogenation to form quinazolin-4(3H)-one (**E**) with the release of water.

Scheme 5. Plausible mechanism for the synthesis of quinazolinone

Conclusions

In summary, we report palladium(II) benzoylhydrazone complexes as efficient catalysts for the direct synthesis of quinazolin-4(3H)-ones from acceptorless dehydrogenative coupling of substituted benzyl alcohols and 2-aminobenzamide. This approach unveiled a broad substrate scope to synthesize a wide variety of quinazolinone derivatives with the maximum yield of 91% at 1 mol% catalyst loading. This straightforward protocol operates at aerobic conditions and water is the only byproduct. Control experiments and the mechanistic investigation indicate the coupling reaction proceeds via dehydrogenation of alcohols. The present results undoubtedly explore a chance for the creation of distinct and valuable biologically important heterocycles using palladium catalysts.

Experimental

Materials, methods, and crystal data collection were given in the Supporting Information (ESI-S2).

Synthesis of new palladium(II) benzoylhydrazone complexes:

Upon dissolution of the dimethylamino benzoylhydrazone ligands (1 mmol) in benzene (15-20 mL), $[\text{PdCl}_2(\text{PPh}_3)_2]$ (1 mmol) was added and the resultant mixture was refluxed for 3 h under open air. The completion of the complexation was monitored by TLC, reaction color changes from yellow to orange, the resulting orange solution was dried in *vacuo* and treated for column chromatography to get the complexes with good yields (85-90%). All the complexes were highly soluble in CH_3OH , CH_2Cl_2 , CHCl_3 and acetone (Scheme 2).

Characterization of complexes (1-3). Complex **1**. Reddish-Orange solid. Yield: 43 mg, 85% M.p.: 233 °C, (with decomposition); Anal. calcd: $\text{C}_{34}\text{H}_{31}\text{N}_3\text{OClPdP}$: C, 60.90, H, 4.66, N, 6.26% found: C, 60.75, H, 4.51, N, 6.15%. FT-IR (KBr, cm^{-1}): 1579 $\nu_{\text{C=N}}$, 1342 $\nu_{\text{C-O}}$, 1521 $\nu_{\text{C=N=N=C}}$. ^1H NMR (CDCl_3 , δ

ppm): 8.31 (d, $J = 9.0$ Hz, 2H, Ligand Ar-H), 7.94 (d, $J = 5.7$ Hz, 1H, CH=N), 7.81-7.72 (m, 8H), 7.54 – 7.43 (m, 10H), 7.26 (dd, $J = 9.1, 5.9$ Hz, 2H), 6.72 (d, $J = 9.0$ Hz, 2H, Ligand Ar-H), 3.06 (s, 6H, N(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃, δ , ppm): 175.00 (N=C=O), 154.26 (C=N), 135.48, 135.15, 135.09, 135.02, 134.88, 134.77, 132.06, 131.11, 131.08, 130.57, 130.11, 129.17, 129.01, 128.64, 128.50, 128.39, 128.17, 128.11, 128.06, 127.76, 119.22, 119.16, 111.10, 40.04. ESI-MS: displays a peak at m/z 675.1507([M+2H]⁺)(calcd: 673.0907).

Complex **2**. Reddish-Orange solid. Yield: 41 mg, 88%, M.p: 248 °C, (with decomposition); Anal. calcd: C₃₄H₃₀N₃OCl₂PdP: C, 57.93, H, 4.28, N, 5.96% found: C, 57.77, H, 4.11, N, 5.90% FT-IR (KBr, Cm⁻¹): 1582 $\nu_{(C=N)}$, 1341 $\nu_{(C-O)}$, 1518 $\nu_{(C=N=N=C)}$. ¹H NMR (CDCl₃, δ ppm): 8.27 (d, $J = 8.9$ Hz, 2H, Ligand Ar-H), 7.93 (d, $J = 5.7$ Hz, 1H, CH=N), 7.78 (dd, $J = 11.9, 7.3$ Hz, 6H), 7.63 (d, $J = 8.5$ Hz, 2H), 7.55-7.44 (m, 9H), 7.26 – 7.21 (m, 2H), 6.72 (d, $J = 9.0$ Hz, 2H, Ligand Ar-H), 3.07 (s, 6H, N(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃, δ , ppm): 173.94 (N=C=O), 152.54 (C=N), 136.07, 135.47, 134.87, 134.76, 131.15, 131.12, 130.63, 130.29, 129.06, 128.50, 128.39, 127.96, 119.00, 111.10, 40.03. ESI-MS: displays a peak at m/z 709.1116 ([M+2H]⁺)(calcd: 707.0542).

Complex **3**. Reddish-Orange solid. Yield: 42 mg, 90%, M.p: 240 °C, (with decomposition); Anal. calcd: C₃₅H₃₃N₃O₂ClPdp: C, 60.0, H, 4.74, N, 6.02 % found: C, 59.80, H, 4.65, N, 6.5% FT-IR (KBr, Cm⁻¹): 1579 $\nu_{(C=N)}$, 1345 $\nu_{(C-O)}$, 1495 $\nu_{(C=N=N=C)}$. ¹H NMR (CDCl₃, δ ppm): 8.30 (d, $J = 8.9$ Hz, 2H, Ligand Ar-H), 7.90 (d, $J = 5.8$ Hz, 1H, CH=N), 7.81 – 7.76 (m, 6H), 7.68 (d, $J = 8.8$ Hz, 2H), 7.54 – 7.43 (m, 9H), 6.74 (dd, $J = 22.6, 8.9$ Hz, 4H, Ligand Ar-H), 3.06 (s, 6H, N(CH₃)₂). ¹³C NMR (100 MHz, CDCl₃, δ , ppm): 174.98 (N=C=O), 161.27 (C=OCH₃), 151.92 (C=N), 135.31, 134.88, 134.77, 131.08, 131.06, 130.64, 129.21, 128.69, 128.48, 128.37, 124.56, 119.33, 119.27, 113.08, 111.08, 55.30 (OCH₃), 40.03. ESI-MS: displays a peak at m/z 705.1604([M+2H]⁺), (calcd .703.1037).

General Protocol for synthesis of Quinazolinones: Under open air atmosphere, a mixture of [Pd(L)Cl(PPh₃)] (0.005 mmol), KOH (1.5 mmol), alcohol (1.10 mmol) and 2-aminobenzamide (1.0 mmol) was dissolved in 10 mL of *m*-xylene and the mixture was placed in an oil bath and heated at 110 °C for 24 h. After the completion of the reaction by TLC, the resulting mixture was concentrated and the formed quinazolinone was isolated by column chromatography using silica gel with hexane:ethylacetate (85:15) as an eluent.

Competitive control experiment between EDG and EWG. 4-Methoxybenzyl alcohol **2e** (1.10 mmol), 4-chlorobenzyl alcohol **2k** (1.10 mmol), 2-aminobenzamide (2 mmol), KOH (3 mmol), catalyst **3** (1 mol%), were stirred in *m*-xylene at 110 °C (oil bath) for 18 h under open air. The completion of the reaction was monitored by TLC and the formed **3e** and **3k** was isolated by column chromatography using with hexane:ethylacetate (85:15) as an eluent with 41% and 18 % isolated yields, respectively.

Spectral data for 2-phenyl-2,3-dihydroquinazolin-4(1H)-one. (2a)¹⁴ ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) = 8.35 (s, 1H), 7.66 – 7.64 (m, 1H), 7.52 (d, $J = 6.9$ Hz, 2H), 7.43 – 7.34 (m, 3H), 7.28 – 7.24 (m, 1H), 7.16 (s, 1H), 6.78 (d, $J = 8.0$ Hz, 1H), 6.70 (t, $J = 7.4$ Hz, 1H), 5.78 (s, 1H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆): δ (ppm) = 163.63, 147.85, 147.57, 133.33, 128.45, 128.32, 127.35, 126.85, 117.12,

114.90, 114.39, 66.53. Calcd. m/z for C₁₄H₁₂N₂O: 224.1050). Found: 225.1021([M+H]⁺).

Characterization of the catalytic isolated product of quinazolinones:

2-phenylquinazolin-4(3H)-one (**3a**).^{24f} White solid (91%, 148 mg). ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 12.57 (s, 1H), 8.22 – 8.17 (m, 3H), 7.86 – 7.83 (m, 1H), 7.76 (d, $J = 7.9$ Hz, 1H), 7.60 – 7.52 (m, 4H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆) δ (ppm) = 162.26, 152.29, 148.67, 134.53, 132.68, 131.34, 128.55, 127.73, 127.45, 126.52, 125.82, 120.93.

2-(*o*-aminophenyl)quinazolin-4(3H)-one (**3b**).³⁰ Yellow solid (76%, 132 mg), ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 12.16 (s, 1H), 8.14 (d, $J = 7.9$ Hz, 1H), 7.81-7.70 (m, 3H), 7.47 (t, $J = 7.4$ Hz, 1H), 7.20 (t, $J = 7.6$ Hz, 1H), 7.10 (s, 2H), 6.86 (d, $J = 8.2$ Hz, 1H), 6.61 (t, $J = 7.5$ Hz, 1H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆) δ (ppm) = 162.13, 153.61, 149.40, 147.95, 134.44, 131.80, 128.85, 126.74, 126.14, 125.71, 120.40, 116.61, 115.02, 112.34.

2-(3-(dimethylamino)phenyl)quinazolin-4(3H)-one (**3c**).³¹ White solid (74%, 144 mg), ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 12.48 (s, 1H), 8.15 (d, $J = 7.8$ Hz, 1H), 7.81 (t, $J = 7.6$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.52 – 7.47 (m, 3H), 7.32 (t, $J = 7.9$ Hz, 1H), 6.90 – 6.88 (m, 1H), 2.97 (s, 6H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆) δ (ppm) = 162.35, 152.92, 150.38, 148.73, 134.49, 133.22, 129.12, 127.39, 126.35, 125.58, 120.87, 115.53, 115.04, 111.09.

2-(2-methoxyphenyl)quinazolin-4(3H)-one (**3d**).³² White solid (75%, 138 mg), ¹H NMR (400 MHz, DMSO-d₆) (ppm): 12.12 (s, 1H), 8.15 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.85 – 7.81 (m, 1H), 7.71 (dd, $J = 7.6, 1.7$ Hz, 2H), 7.56 – 7.53 (m, 2H), 7.20 (d, $J = 8.4$ Hz, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 3.86 (s, 3H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆) (δ ppm): 161.26, 157.09, 152.33, 134.39, 132.20, 130.41, 126.53, 125.75, 122.57, 120.93, 120.40, 111.82, 55.73.

2-(4-methoxyphenyl)quinazolin-4(3H)-one (**3e**).^{24f} White solid (89%, 165 mg). ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 12.43 (s, 1H), 8.20 (d, $J = 8.9$ Hz, 2H), 8.13 (dd, $J = 7.9, 1.0$ Hz, 1H), 7.83 – 7.79 (m, 1H), 7.70 (d, $J = 7.9$ Hz, 1H), 7.48 (t, $J = 7.1$ Hz, 1H), 7.09 (d, $J = 8.9$ Hz, 2H), 3.85 (s, 3H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆) δ (ppm) = 162.54, 152.08, 148.86, 134.45, 129.42, 127.12, 126.03, 125.80, 124.92, 120.63, 113.94, 55.42.

2-(*m*-tolyl)quinazolin-4(3H)-one (**3f**).¹⁹ White solid (73%, 126 mg). ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 12.46 (s, 1H), 8.15 (d, $J = 7.9$ Hz, 1H), 7.99 (s, 1H), 7.94 (d, $J = 7.2$ Hz, 1H), 7.83 (t, $J = 7.6$ Hz, 1H), 7.74 (d, $J = 8.1$ Hz, 1H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.44 – 7.38 (m, 2H), 2.39 (s, 3H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆) δ (ppm) = 162.33, 152.47, 148.60, 137.94, 134.61, 132.57, 132.00, 128.51, 128.21, 127.31, 126.54, 125.81, 124.83, 120.82, 20.91.

2-(*p*-tolyl)quinazolin-4(3H)-one (**3g**).^{24d} White solid (85%, 147 mg). ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) = 12.53 (s, 1H), 8.20 (d, $J = 7.0$ Hz, 1H), 8.14 (d, $J = 8.1$ Hz, 2H), 7.87 (dd, $J = 11.1, 4.1$ Hz, 1H), 7.78 (d, $J = 7.8$ Hz, 1H), 7.56 (t, $J = 7.0$ Hz, 1H), 7.40 (d, $J = 7.9$ Hz, 2H), 2.44 (s, 3H). ¹³C{¹H} NMR (100 MHz, DMSO-d₆) δ (ppm) = 162.32, 152.25, 148.70, 141.44, 134.55, 129.83, 129.16, 127.63, 127.28, 126.37, 125.80, 120.80, 20.94.

2-(4-isopropylphenyl)quinazolin-4(3H)-one (**3h**).^{24f} White solid (71%, 138 mg). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 12.24 (s, 1H), 8.22 (d, $J = 7.7$ Hz, 1H), 8.15 (d, $J = 8.3$ Hz, 2H), 7.72-7.64 (m, 2H), 7.39 – 7.35 (m, 1H), 7.31 (d, $J = 8.3$ Hz, 2H), 2.90 (dt, $J = 13.8, 6.9$ Hz, 1H), 1.21 (d, $J = 6.9$

Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ (ppm) = 164.43, 152.87, 152.06, 149.76, 134.79, 130.39, 127.93, 127.72, 127.08, 126.47, 126.35, 120.77, 34.19, 23.83.

2-(3,4,5-trimethoxyphenyl)quinazolin-4(3H)-one (**3i**).³³ White solid (77%, 177 mg), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 12.58 (s, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.88 (t, J = 7.5 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.61 (s, 2H), 7.56 (t, J = 7.4 Hz, 1H), 3.95 (s, 6H), 3.80 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 162.35, 152.82, 151.70, 148.57, 140.14, 134.58, 127.62, 127.38, 126.44, 125.81, 120.75, 105.10, 103.35, 60.11, 56.06.

2-(3-fluorophenyl)quinazolin-4(3H)-one (**3j**).³² White solid (69%, 122 mg). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 12.59 (s, 1H), 8.15 – 7.99 (m, 3H), 7.78 (d, J = 33.8 Hz, 2H), 7.58 – 7.42 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 162.22, 151.10, 148.34, 134.64, 130.75, 127.47, 126.87, 125.83, 123.88, 121.03, 118.10, 114.60, 114.36.

2-(4-chlorophenyl)quinazolin-4(3H)-one (**3k**).³³ White solid (68%, 128 mg). ^1H NMR (400 MHz, DMSO-d_6) (ppm): 8.28 (d, J = 8.6 Hz, 2H), 8.09 – 8.07 (m, 1H), 7.71 – 7.67 (m, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.39 – 7.35 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 166.50, 155.55, 149.91, 135.14, 135.01, 132.89, 129.57, 128.19, 126.70, 125.82, 124.87, 121.26.

2-(2-bromophenyl)quinazolin-4(3H)-one (**3l**).²¹ White solid (58%, 128 mg). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 12.59 (s, 1H), 8.21 (t, J = 8.8 Hz, 3H), 7.87 (t, J = 7.6 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.63–7.54 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 162.22, 152.27, 148.69, 137.88, 134.56, 132.67, 131.36, 128.57, 128.46, 128.25, 127.73, 127.47, 126.55, 125.82, 124.85, 120.93.

2-(pyridin-3-yl)quinazolin-4(3H)-one (**3m**).³⁴ Yellow solid (67%, 110 mg), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.70 (s, 1H), 8.51 – 8.44 (m, 2H), 8.14 (d, J = 6.9 Hz, 1H), 7.95 (s, 1H), 7.73 (d, J = 18.4 Hz, 2H), 7.45 (d, J = 41.1 Hz, 1H), 6.96 (s, 1H), 6.56–6.38 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = ^{13}C NMR (101 MHz, DMSO) δ 172.38, 166.98, 153.00, 149.98, 148.88, 137.23, 136.24, 132.87, 131.72, 129.74, 126.87, 125.92, 125.10, 123.69, 122.61, 121.75, 120.63, 115.23, 113.87.

2-(furan-3-yl)quinazolin-4(3H)-one (**3n**).³⁴ Yellow solid, (65%, 101 mg), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 12.58(s, 1H), 8.18 (d, J = 7.9 Hz, 1H), 8.06 (s, 1H), 7.90 – 7.85 (m, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 3.4 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 6.81 (dd, J = 3.5, 1.7 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 161.87, 151.34, 146.74, 144.00, 143.73, 134.83, 134.47, 127.12, 126.46, 125.90, 121.07, 114.48, 112.51.

2-(thiophen-3-yl)quinazolin-4(3H)-one (**3o**).³⁴ Yellow solid (66%, 111 mg). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.06 (dd, J = 8.0, 1.8 Hz, 2H), 7.69 – 7.63 (m, 2H), 7.56 (d, J = 8.1 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.16 (dd, J = 5.0, 3.8 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 166.30, 152.84, 149.89, 141.79, 132.96, 130.12, 128.05, 126.11, 125.89, 124.50, 121.16.

2-(benzo[d][1,3]dioxol-5-yl)quinazolin-4(3H)-one (**3p**).³¹ White solid (55%, 107 mg), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.12 (d, J = 7.7 Hz, 1H), 7.80 (dd, J = 11.1, 4.3 Hz, 2H), 7.74 (d, J = 1.4 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.13 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 162.77, 152.10, 149.91, 148.76, 147.60, 134.38, 127.11, 125.79, 122.77, 120.68, 108.21, 107.53, 101.79.

2-(naphthalen-2-yl)quinazolin-4(3H)-one (**3q**).³⁴ White solid (59%, 118 mg), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 12.67 (s, 1H), 8.24 – 8.16 (m, 2H), 8.12 (d, J = 8.2 Hz, 1H), 8.05 (dd, J = 6.4, 2.8 Hz, 1H), 7.89 – 7.85 (m, 1H), 7.80 (d, J = 7.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.67–7.57 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 162.08, 153.82, 148.63, 134.49, 133.10, 131.74, 130.34, 130.22, 128.31, 127.63, 127.31, 127.04, 126.75, 126.34, 125.15, 125.05, 121.15.

2-(anthracen-9-yl)quinazolin-4(3H)-one (**3r**).¹⁹ White solid (56%, 132 mg), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 12.89 (s, 1H), 8.87 (s, 1H), 8.35 (d, J = 7.5 Hz, 1H), 8.25 (d, J = 8.1 Hz, 2H), 7.95 (t, J = 7.2 Hz, 1H), 7.79–7.85 (dd, J = 17.4, 8.2 Hz, 3H), 7.69 (t, J = 7.5 Hz, 1H), 7.57 – 7.64 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 161.75, 153.04, 148.86, 134.56, 130.56, 128.98, 128.70, 128.52, 127.50, 127.04, 126.00, 125.65, 125.02, 121.62.

2-([1,1'-biphenyl]-4-yl)quinazolin-4(3H)-one (**3s**).^{24f} White solid (58%, 127 mg), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 12.61(s, 1H), 8.31 (s, 1H), 8.18 (d, J = 7.5 Hz, 1H), 7.77 – 7.88 (m, 7H), 7.43 – 7.56 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 162.20, 151.88, 148.75, 142.80, 138.93, 134.60, 131.51, 129.04, 128.35, 127.49, 126.82, 126.72, 125.84, 120.97.

2-(1H-indol-3-yl)quinazolin-4(3H)-one (**3t**).³⁵ Yellow solid (54%, 103 mg), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 12.28 (s, 2H), 8.12 (d, J = 7.6 Hz, 1H), 7.51–7.80 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6) δ (ppm) = 160.73, 148.69, 145.37, 134.29, 127.17, 126.71, 125.80, 122.56.

ASSOCIATED CONTENT

Supporting Information

Complete details of materials, methods, and crystal data collection. Tables for crystallographic data, refinement parameters, selected bond lengths and bond angles. Figures illustrating the NMR spectra of complexes, intermediates and quinazolinone catalytic products. HRMS spectra of complexes and cyclic amination intermediate. CIF file for complex. CCDC number for complex **2** is **1833169** and **3** is **1565995**. The materials may be downloaded free of charge at pubs.acs.org.

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For Table of Contents Only (TOC)

Palladium(II) N[^]O chelating complexes catalyzed One-pot Approach for synthesis of Quinazolin-4(3H)-ones via acceptor-less dehydro-genative coupling of Alcohols and 2-aminobenzamide

One-pot synthesis of quinazolin-4(3H)-ones using Pd(II) complexes via dehydrogenative coupling of readily available benzyl alcohols and 2-aminobenzamide has been described. This approach unveiled a broad substrate scope to synthesize a wide variety of quinazolinone derivatives with the maximum yield of 91% at 1 mol% catalyst loading under aerobic conditions.

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