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N^NO Pincer Ligands Supported Palladium(II) Complexes: Direct Synthesis of Quinazolines via Acceptorless Double Dehydrogenative Coupling of Alcohols

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ABSTRACT: A sustainable approach for the synthesis of substituted quinazolines by a sequential acceptorless dehydrogenative coupling of 2-aminobenzyl alcohol with alcohols using new Pd(II)-NNO pincer type complexes as catalysts. The air-stable palladium(II) complexes with the general formula [Pd(L)(PPh₃)] (where L = 4-substituted methyl 2-pyrrolylbenzhydrazone ligands) have been synthesized and their compositions were recognized by analytical and spectral methods (FT-IR, NMR and HR-MS). Single crystal X-ray crystallography confirms the tridentate coordination of the ligands and the existence of square planar geometry around the metal ion. A wide range of substituted quinazoline derivatives has been synthesized from double dehydrogenation of benzyl alcohols by using 1.5 mol % of the catalyst loading with a maximum of 93% yield. The formation of an amino-benzaldehyde and benzaldehyde intermediates via double dehydrogenative coupling reaction was confirmed by control experiments.

INTRODUCTION

Synthesis of N-based heterocyclic compounds contributes to a wide range of biological applications in extensive fields of pharmacy and hence they are much engrossed by medicinal chemists and biologists.¹ The prevalence of N-heterocyclic compounds in biological activities is attributed to their stability and the operational efficiency in the human body as the nitrogen atom of the bioactive compound readily binds with biomolecules via hydrogen bonding.² Among the numerous N-heterocyclic compounds, quinazoline has been of much interest in the biological arena and its derivatives show a broad scale of biological activities (Figure 1).³

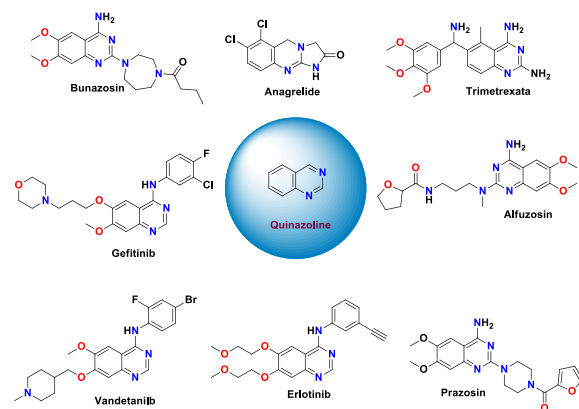


Figure 1. Representative examples of quinazoline drugs

A huge number of methods were described for the synthesis of quinazolines.⁴ However, they are not withstanding due

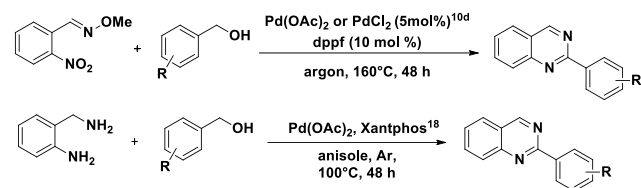
to the requirement of strong oxidising agents, inert atmospheric conditions, high catalyst loading, higher reaction temperature and the use of relatively unstable aldehyde. In recent years, researchers consider an environmentally friendly strategy for the synthesis of N-heterocycles⁵ via acceptorless dehydrogenation coupling (ADC) of alcohols. Readily accessibility of low-cost alcohols, the environmentally benign and atom economical nature of the catalytic reaction are the key characteristics of the ADC process.⁶ The *in situ* generation of more reactive carbonyl compounds further react with a suitable coupling partner to form the desired products in a sustainable manner is yet another advantage of this ADC protocol. Furthermore, either H₂ gas or H₂O is generated as the only chemical waste.

In the last decade, the transition metal catalysed synthesis of N-heterocycles has drawn great attention for the increasing efficiency and selectivity towards the large-scale synthesis in pharmaceuticals.⁷ Specifically, palladium metal is found to be more effective than several non-precious transition metal-catalyzed applications as palladium promotes the coupling of low reactivity substrates (like aryl chlorides). Palladium-catalyzed reactions furnished larger turnover numbers (TONs) at lower temperature find applications in large-scale synthesis.⁸ Prominently, palladium catalysed C-N cross-coupling reactions with diverse functional groups has a great impact on the synthesis of bioactive heterocyclic compounds.^{9,10}

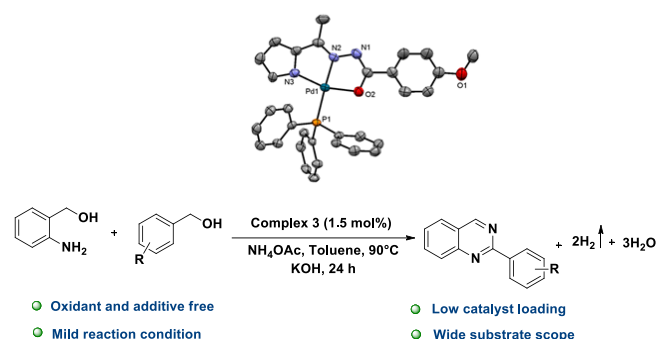
Further, palladium pincer complexes exhibit their outstanding catalytic activities in numerous organic transformation reactions.¹¹ In the past two decades,¹² the transition metal pincer chemistry is having a larger interest among the re-

searchers, especially, a pincer ligand with three donor sites coordinated to a metal centre in a meridional fashion which shows enhanced robustness. Also, the presence of three donor atoms in a single framework of the pincer ligand provides tunable electronic and steric properties for metal complexes. Taken together palladium pincer type complexes will undeniably be suitable for the acceptorless dehydrogenative coupling reactions.

Previous reports



This work



Scheme 1 Synthetic strategies for the synthesis of quinazoline

It is worth noting that aqueous ammonia and ammonium salts are inexpensive and suitable nitrogen sources for catalytic organic transformation reactions.¹³ Especially, ammonium acetate plays a vital role in the synthesis of N-heterocycles.¹⁴ To the best of our search, limited reports are available for the transition metal-catalyzed synthesis of quinazoline from alcohol and ammonia or ammonium salts. Wu and co-workers reported Cu-catalyzed construction of quinazoline derivatives from 2-aminophenyl methanol and aldehydes in presence of ammonium salt as nitrogen source.¹⁵ Zhenda and co-workers described the Ir-catalyzed hydrogen transfer-mediated annulation of 2-nitrobenzyl alcohols with alcohols and ammonia for quinazoline synthesis.¹⁶

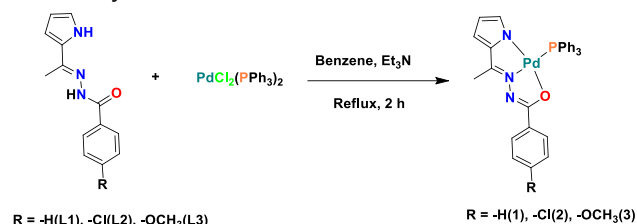
Fe, Mn, Ni, Ru, Ir based metal complexes were also reported as catalysts in acceptorless dehydrogenative coupling for the synthesis of quinazoline using 2-aminobenzyl alcohol/amine with benzamides, ketones, (hetero)aryl or alkyl nitriles, aldehyde, alcohol and benzylamines as a stable starting material.¹⁷ Exceptionally, Pd-catalyzed reaction for quinazolines from the reaction of primary alcohols with 2-aminobenzylamine was demonstrated by Kimura *et al.* However, these methods involve simple dehydrogenative oxidation reactions with limited substrate scope (Scheme 1).¹⁸ It is worth to note that, there are no reports available for the synthesis of quinazolines via alcohol with an ammonium source in the presence of palladium as a catalyst.

In continuation to our research on the catalytic behaviour of organometallic complexes for various cross coupling reactions,¹⁹⁻²¹ herein we report a sequential acceptorless dehydrogenation approach for the synthesis of quinazoline derivatives from readily available alcohols and 2-aminobenzyl alcohol by pincer type palladium catalysts using ammonium ace-

tate as a nitrogen source for the first time. Our protocol can be considered as more atom economical and environmentally benign approach as the present scheme releases water and hydrogen as the only by-products.

RESULTS AND DISCUSSION

The condensation reaction of methyl-2-pyrroleketone with benzhydrazides obtained benzhydrazone ligand derivatives and substituted benzhydrazides in the equimolar ratio in ethanol medium as reported in the literature.²² The obtained ligand derivatives were reacted with an equimolar ratio of Pd(II) precursor, PdCl₂(PPh₃)₂ in presence of Et₃N as a base. The above reaction yielded 85-89% of complexes with the general formula [Pd(L)(PPh₃)]₂ (Scheme 2). All the complexes were soluble in most of the organic solvents like MeOH, EtOH, CH₂Cl₂, CHCl₃, DMF and DMSO. The addition of triethylamine base to the reaction mixture assisted the tautomerization (amido-imidol) process and coordinates the imidolate oxygen effortlessly.



Scheme 2 Synthesis of Pd(II) pincer benzhydrazone complexes

Medium to strong bands for ν_{N-H} stretching vibrations were observed near 3420-3450 cm⁻¹ and 3218-3255 cm⁻¹ for hydrazone (Bz) and pyrrole (Py) moieties respectively of the hydrazine ligands. These bands were disappeared in the complexes indicating the coordination of pyrrole nitrogen with the Pd(II) ion. The IR spectral bands of the ligands near 1608-1640 cm⁻¹ and 1535-1567 cm⁻¹ were attributed for ν_{C=N} and ν_{C=O} stretching vibrations, respectively. The azomethine ν_{C=N} stretching frequency was shifted to a lower frequency (1530-1536 cm⁻¹) upon complexation confirming the involvement of imine nitrogen in coordination. The disappearance of ν_{C=O} bands and appearance of new bands near 1247-1287 cm⁻¹ for complexes confirm the coordination of imidolate oxygen with metal ions after tautomerization. Thus, the IR spectral data confirm that imidolate oxygen, imine nitrogen and pyrrole-nitrogen are coordinated to Pd(II) ion.

The NNO coordination modes of benzhydrazone ligands to palladium metal in the synthesized complexes (**1-3**) were further supported by NMR spectral data. In the proton NMR spectra of ligands, the -NH protons have appeared as singlets in the region δ 8.80-9.10 ppm. The absence of -NH protons in all the complexes (**1-3**) confirms the ligand coordination to Pd(II) ion *via* imidolate oxygen through enolization. Also, pyrrole N-H protons in all the complexes were disappeared which dictated the coordination of the N-H with palladium in an anionic manner. In addition to this, a singlet has appeared at δ 3.80 ppm attributed to the methoxy protons of complex **3**. The ¹³C NMR spectra showed the downfield shift for imidolate carbon (-C=N-N=C) at 175.77, 174.63, 175.77 and the upfield shift for imine carbon (-C=N) at 145.45, 145.32, 145.51 of complexes **1-3**, respectively. The shifts in NMR spectra of complexes were attributed to the complexation of the pyrrolyl benzhydrazone ligand with the precursor [PdCl₂(PPh₃)₂]. Also, the additional signal at 55.29 ppm for methoxy carbon (-OCH₃) was observed in the ¹³C NMR spectra of complex **3**.

Thus, the existence of coordination between benzhydrazone ligands and Pd(II) ion in a tridentate fashion was supported by the ^1H and ^{13}C NMR spectra.

The ESI-MS spectra of the synthesized benzhydrazone complexes (**1-3**) were taken to determine the composition of complexes, which exhibit molecular ion peaks at m/z 594.092 ($[\text{M}+\text{H}]^+$), 628.052 ($[\text{M}]^+$) and 624.10175 ($[\text{M}+\text{H}]^+$). There exists a good agreement between the calculated and experimental m/z values for all the complexes. Thus, the spectral studies of complexes (**1-3**) were in good arrangement with the proposed structural composition of the palladium(II) pin-cer benzhydrazone complexes.

X-ray Crystallographic Studies. The slow evaporation of complexes at room temperature in DCM/Methanol solution yielded single crystals of X-ray crystal quality. The complexes **1-3** were crystallized in the triclinic '*P*-1', space group, orthorhombic '*P* 21 21 21' space group and monoclinic '*P* 21/*c*' space group, respectively. The crystallographic data were provided in supplementary data Tables S1 and S2, respectively. The ORTEP diagrams in Figures 2-4 for complexes **1-3**, show that the ligands coordinate with the metal ion in a tridentate (NNO) fashion via the imidolate oxygen, imine nitrogen and pyrrole nitrogen which leads to the formation of two five-membered chelate rings. The bond parameters of the complexes reflect ONNP square-planar environment around Pd(II) ion similar to the other reported palladium square-planar complexes.²³

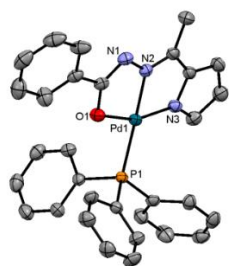


Figure 2 The ORTEP diagram of the complex **1** with 30% probability. All the hydrogen atoms are omitted for clarity. The selected bond distances (Å) and angles (°) N(2)-Pd(1) = 1.990(2), N(3)-Pd(1) = 2.003(3), O(1)-Pd(2) = 2.031(2), P(1)-Pd(1) = 2.2774(8), N(2)-Pd(1)-N(3) = 80.93(10), N(2)-Pd(1)-O(1) = 78.85(9), N(3)-Pd(1)-P(1) = 102.76(7), O(1)-Pd(1)-P(1) = 97.54(6).

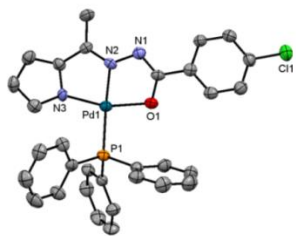


Figure 3 The ORTEP diagram of the complex **2** with 30% probability. All the hydrogen atoms are omitted for clarity. The selected bond distances (Å) and angles (°) N(2)-Pd(1)=1.976(5), N(3)-Pd(1)=1.999(4), O(1)-Pd(2) = 2.045(4), P(1)-Pd(1) = 2.2770(15), N2-Pd(1)-N(3) = 81.3(2), N(2)-Pd(1)-O(1) = 78.77(19), N(3)-Pd(1)-P(1) = 101.87(14), O(1)-Pd(1)-P(1) = 98.13(13).

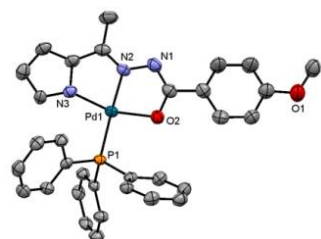
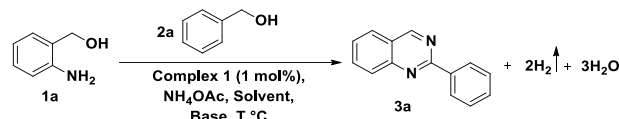


Figure 4 The ORTEP diagram of the complex **3** with 30% probability. All the hydrogen atoms are omitted for clarity. The selected bond distances (Å) and angles (°) N(2)-Pd(1) = 1.987(3), N(3)-Pd(1) = 2.014(3), O(1)-Pd(2) = 2.042(3), P(1)-Pd(1) = 2.2889(10), N(2)-Pd(1)-N(3) = 80.90(13), N(2)-Pd(1)-O(1) = 79.06(12), N(3)-Pd(1)-P(1) = 101.55(9), O(1)-Pd(1)-P(1) = 98.52(8).

Table 1. Optimization of reaction conditions^a



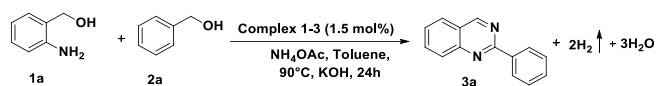
Entry	Solvent	Base	T (°C)	Yield ^b (%)
1	Toluene	NaOH	110	82
2	<i>m</i> -xylene	NaOH	140	72
3	Dioxane	NaOH	100	48
4	THF	NaOH	70	41
5	<i>t</i> -BuOH	NaOH	80	60
6	DMF	NaOH	150	17
7	Toluene	KOH	110	84
8	Toluene	KOH	90	80
9 ^c	Toluene	KOH	90	76
10	Toluene	KOH	70	65
11	Toluene	<i>t</i> -BuOK	110	73
12	Toluene	Na ₂ CO ₃	110	35
13	Toluene	K ₂ CO ₃	110	39
14	Toluene	Et ₃ N	110	10
15 ^d	Toluene	-	110	NR
16 ^e	Toluene	KOH	110	NR
17 ^f	Toluene	KOH	110	14
18 ^g	Toluene	KOH	110	22
19 ^h	Toluene	KOH	110	41

^aGeneral reaction conditions. 2-aminobenzyl alcohol **1a** (1.10 mmol), benzyl alcohol **2a** (1.10 mmol) complex **1** (1 mol %), NH₄OAc (1.5 mmol), Base (2.0 mmol), solvent (5 mL) at 70-150°C for 24 h under N₂ atm. ^bIsolated yield. ^cOpen atm., ^dNo base, ^eNo catalyst, ^fPdCl₂, ^gPd(OAc)₂ and ^h[PdCl₂(PPh₃)₂].

To investigate the best reaction conditions for the synthesis of quinazolines via double dehydrogenation, the reactions of 2-aminobenzyl alcohol (**1a**) and benzyl alcohol (**2a**) using 1 mol% of complex **1** were taken as bench-mark substrates (Table 1). In solvent screening, it was found that the non-polar toluene provided good yield than other solvents like *m*-xylene, 1,4-dioxane, THF, *t*-BuOH and DMF (Table 1, entry 1-6). This may be due to fact that toluene stabilizes the palladium complex during the course of the catalytic reaction. Different nitrogen sources including NH₄Cl, (NH₂)₂SO₄, NH₄CO₃ and

NH₄OAc were used in the catalytic reactions, in which NH₄OAc gave a better yield. The optimization of bases for the catalysis reaction shown in Table 1 (entries 1, 7 and 11-14) conveyed that KOH was more effective than the other bases examined. Hence, the catalytic conditions for coupling reactions were optimized with toluene /KOH at 90 °C using complex **1** as it provides a relatively high yield (Table 1, entry 8, 80%). **Only a marginal increase in the yield of the product was obtained when the reaction temperature is increased to 110°C with the optimized solvent and base (Table 1, entry 8).** It was found that no reaction has proceeded in the absence of either catalyst or base (Table 1, entries 15 and 16).

Table 2. Effect of the substituent of catalyst^a

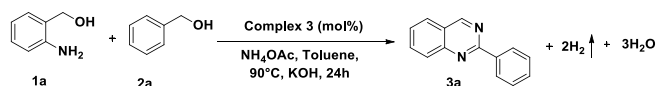


Entry	Pd complex	Yield (%) ^b
1	[Pd(L1)(PPh ₃)](1)	85
2	[Pd(L2)(PPh ₃)](2)	88
3	[Pd(L3)(PPh ₃)](3)	93

^aGeneral reaction conditions: 2-aminobenzyl alcohol **1a** (1.10 mmol), benzyl alcohol **2a** (1.10 mmol) catalyst (1.5 mol %), NH₄OAc (1.5 mmol), KOH (2.0 mmol) in toluene (5 mL) at 90°C for 24 h under N₂ atm. ^bisolated yields.

The influences of various substituents in the synthesized complexes **1-3** on the catalytic reaction were investigated in the optimized condition. Among them, complex **3** exhibits a relatively more yield than the other complexes (Table 2, entries 1-3) and this may be due to the presence of the electron-donating nature of the methoxy group. Therefore, complex **3** was considered as a representative catalyst to investigate the broad substrate scope using various alcohols. Catalyst loading experiments indicate that the reaction takes place effectively in 1.5 mol% among others (Table 3, entries 1-5).

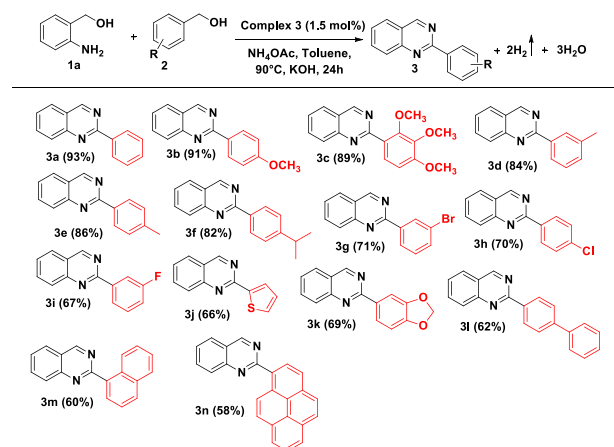
Table 3: Effect of catalyst loading^a



Entry	Complex 3 (mol %)	Yield % ^b
1	1.5	93
2	1	80
3	0.5	72
4	0.2	30
5	0.1	20

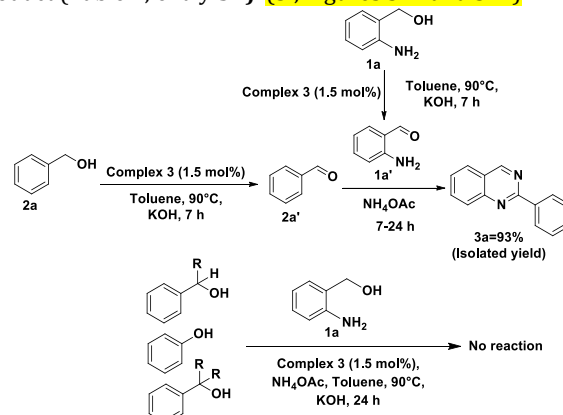
^aReaction conditions: 2-aminobenzyl alcohol **1a** (1.10 mmol), benzyl alcohol **2a** (1.10 mmol) catalyst (0.1-1.5 mol%), NH₄OAc (1.5 mmol), KOH (2.0 mmol) in toluene (5 mL) at 90°C for 24 h under N₂ atm. ^bIsolated yield.

Table 4. Double Dehydrogenative coupling of 2-aminobenzyl alcohol (**1a**) and benzyl alcohols (**2**) catalyzed by complex **3**^{a,b}



^aReaction conditions: 2-aminobenzyl alcohol **1a** (1.10 mmol), alcohols **2** (1.10 mmol), NH₄OAc (1.5 mmol), KOH (2.0 mmol), toluene (5 mL) at 90 °C for 24 h under N₂ atm. ^bIsolated yield.

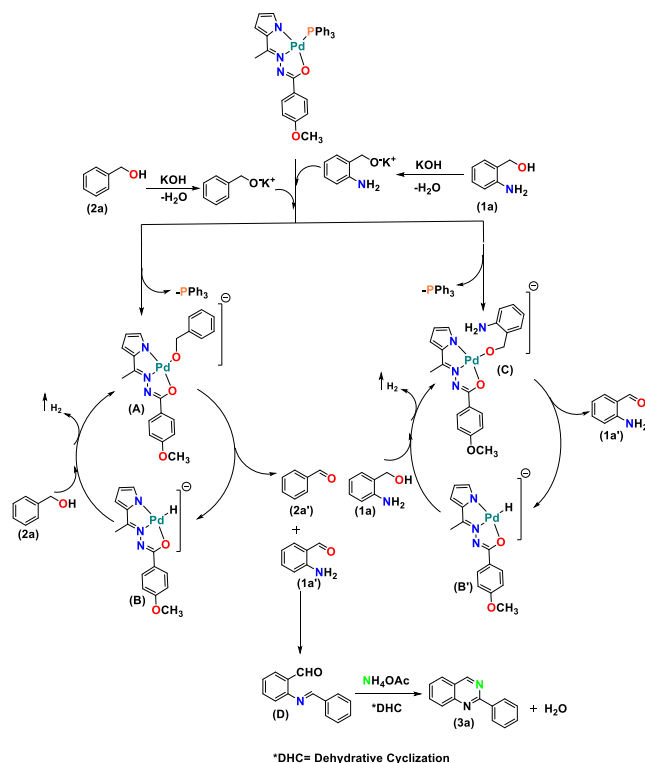
With the optimized reaction conditions, the coupling reactions of 2-aminobenzylalcohol with various (aromatic, polycyclic and heteroaromatic) alcohols (Table 4) were carried out via acceptorless double dehydrogenation reaction. The reaction of benzyl alcohol with 2-aminobenzyl alcohol resulted in the formation of 2-phenylquinazoline **3a** with a yield of 93%. Further, benzyl alcohols containing electron-donating groups such as 4-methoxy, 2,3,4-trimethoxy, 3-methyl, 4-methyl and 4-isopropyl benzyl alcohols were coupled efficiently with 2-aminobenzyl alcohol (Table 4; entries **3b-3f**) in 82-91% yields. Similarly, the reaction of benzyl alcohols with electron-withdrawing groups such as 3-bromo, 4-chloro and 3-fluoro alcohols with 2-aminobenzyl alcohol under the optimized condition to provide respective quinazoline (Table 4; entries **3g-3i**) in 67-71% yields. The reactions of polycyclic alcohols were also documented with this current reaction protocol. Further, we extended our scope of the catalytic reaction towards heterocyclic alcohols including thiophene-2-methanol and piperonyl alcohol with 2-aminobenzyl alcohol and resulted in good yields of quinazolines (Table 4; entries **3j** and **3k**) with good yields. Notably, polycyclic alcohols such as biphenyl-4-methanol and 1-naphthalenemethanol ended with corresponding quinazolines (Table 4; entries **3l** and **3m**) in 62% and 60% yields respectively. Interestingly, in the four-ring fused system, 1-pyrenemethanol reacts with 2-aminobenzyl alcohol to give the 58 % yield of quinazoline product (Table 4; entry **3n**). (SI, Figures S14 and S41)



Scheme 3 Control experiment for the mechanistic studies

Control experiments indicate that the coupling reaction was initiated through the formation of aldehydes intermediates. As represented in Scheme 3, catalyst 3 oxidized benzyl alcohol **2a** to the corresponding aldehyde intermediate **2a'** in 7 h (SI, Figures S10 and S11). Simultaneously, the alcohol oxidation reaction of 2-aminobenzyl alcohol **1a** led to 2-aminobenzaldehydes **1a'** (SI, Figures S12 and S13). Further, the reaction of **2a'** reacted with **1a'** from the oxidation product **1a**, the formation of product **3a** was accomplished in the presence of NH_4OAc when the reaction time was extended up to 24 h (Scheme 3). Hence, the coupling reactions involve alcohol dehydrogenation that proceeded through the double dehydrogenative coupling²⁴ pathway. Hence, the acceptorless dehydrogenation of alcohols leads to the formation of expected quinazolines using palladium catalysts.

Based on the control experiments, a plausible reaction pathway (Scheme 4) was proposed for the Pd(II)-catalyzed quinazoline (**3a**) formation via double dehydrogenative coupling of alcohols. Initially, At first, the formation of palladium alkoxide (**A**) from the reaction of palladium complex and benzyl alcohol in the presence of potassium hydroxide. The palladium-alkoxide (**A**) in turn generate benzaldehyde (**2a'**) with the formation of Pd-hydride species (**B**). Further, the oxidation of 2-aminobenzyl alcohol (**1a**) leads to 2-aminobenzaldehydes (**1a'**) by use of the palladium(II) catalyst. Next, the intermediate (**D**) was formed by the condensation of 2-aminobenzaldehyde (**1a'**) with benzaldehyde (**2a'**) and underwent dehydrative cyclization to yield quinazolines **3a** as the desired product. The intermediates **B** and **B'** further react with benzyl alcohol leading to alkoxides with the liberation of hydrogen gas. During the course of the reaction, the formation of hydrogen gas was confirmed by Gas chromatography (Figure S30)



Scheme 4 A plausible mechanism for quinazoline formation

Conclusions

Here, we have reported new palladium(II) NNO pincer catalysed the synthesis of quinazolines from 2-aminobenzyl alcohol with alcohols. A wide range of quinazoline derivatives has been constructed via acceptorless double dehydrogenative coupling methodology from various aromatic, heterocyclic and polycyclic alcohols with the maximum yield of 93% using 1.5 mol% palladium catalyst loading. Hence, the present environmentally benign approach has a great impact on the synthesis of diverse and valuable biologically important heterocycles using palladium(II) NNO pincer type catalysts.

Experimental

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

Synthesis of palladium (II) NNO pincer methyl 2-pyrrolyl benzhydrazone complexes

Upon dissolution of the appropriate methyl 2-pyrrolyl benzhydrazone ligands (1 equiv.), $[\text{PdCl}_2(\text{PPh}_3)_2]$ (1 equiv.) and Et_3N (0.2 mL) the mixture was refluxed in benzene (15-20 mL) for 2 h under air atmosphere. After that, the obtained orange solution was allowed to cool to room temperature to form an orange precipitate and filtered, washed with benzene and dried in a vacuum (Scheme 2). Yield: 85-89%.

Characterization of complexes (1-3).

Complex 1. Colour: Reddish-Orange solid. Yield: 77 mg, 85% M.p.:148°C, (with decomposition); calculated: $\text{C}_{31}\text{H}_{26}\text{N}_3\text{OPPd}$: C, 62.68, H, 4.41, N, 7.07% found: C, 62.37, H, 4.40, N, 7.05%. FT-IR (KBr, cm^{-1}): 1530 $\nu_{(\text{C}=\text{N})}$, 1287 $\nu_{(\text{C}-\text{O})}$, 1504 $\nu_{(\text{C}=\text{N}=\text{N}=\text{C})}$. ^1H NMR (CDCl_3 , δ ppm): 2.36 (s, 3H, Me), 5.36 (s, 1H, Pyrrole CH), 5.65 (m, 1H, Pyrrole CH), 6.39 (d, 1H, Pyrrole CH), 7.21-7.87 (m, 20H, aromatic). ^{13}C NMR (CDCl_3 , δ ppm): 175.77, 157.31, 145.45, 135.89, 134.70, 132.51, 131.33, 129.96, 129.73, 129.26, 128.90, 127.89, 115.57, 107.44, 11.84, 11.80. ESI-MS: displays a peak at m/z 594.09210 $[\text{M}+\text{H}]^+$ (calcd: 593.08483).

Complex 2. Colour: Reddish-Orange solid. Yield: 73 mg, 87%, M.p.: 168°C, (with decomposition); calculated: $\text{C}_{31}\text{H}_{25}\text{N}_3\text{OCIPPd}$: C, 59.25, H, 4.01, N, 6.69% found: C, 59.17, H, 4.00, N, 6.67%. FT-IR (KBr, cm^{-1}): 1535 $\nu_{(\text{C}=\text{N})}$, 1286 $\nu_{(\text{C}-\text{O})}$, 1573 $\nu_{(\text{C}=\text{N}=\text{N}=\text{C})}$. ^1H NMR (CDCl_3 , δ ppm): 2.35 (s, 3H, Me), 5.38 (s, 1H, pyrrole CH), 5.66 (q, 1H, pyrrole CH), 6.40 (dd, 1H, pyrrole CH) 7.18-7.79 (m, 19H, aromatic). ^{13}C NMR (CDCl_3 , δ ppm): 174.63, 157.60, 145.32, 132.09, 134.67, 131.38, 129.96, 129.61, 129.13, 128.91, 128.07, 115.82, 107.61, 11.78. ESI-MS: displays a peak at m/z 628.05243 $[\text{M}]^+$ (calcd: 628.04922).

Complex 3. Colour: Reddish-Orange solid. Yield: 76 mg, 89%, M.p.: 158°C, (with decomposition); calculated: $\text{C}_{32}\text{H}_{28}\text{N}_3\text{O}_2\text{PPd}$: C, 61.60, H, 4.52, N, 6.73% found: C, 61.37, H, 4.50, N, 6.71%. FT-IR (KBr, cm^{-1}): 1536 $\nu_{(\text{C}=\text{N})}$, 1247 $\nu_{(\text{C}-\text{O})}$, 1605 $\nu_{(\text{C}=\text{N}=\text{N}=\text{C})}$. ^1H NMR (CDCl_3 , δ ppm): Pyrrole ring protons: 2.35 (s, 3H, Me), 5.36 (s, 1H, pyrrole CH), 5.65 (q, 1H, pyrrole CH), 6.37 (dd, 1H, pyrrole CH), 6.73-7.82 (m, 19H, aromatic), 3.74 (d, 3H, OCH_3). ^{13}C NMR (CDCl_3 , δ ppm): 175.77, 161.15, 156.60, 145.54, 134.71, 131.30, 130.29, 129.76, 129.29, 128.88, 125.08, 115.15, 113.20, 107.27, 55.29, 11.27. ESI-MS: displays a peak at m/z 624.10175 $[\text{M}+\text{H}]^+$, (calcd 623.09540).

General procedure for the synthesis of quinazoline:

Synthesis of 2-phenylquinazoline (**3a**), in a 25 mL round-bottomed flask, a mixture of catalyst **3** (1.5 mol % with respect to 2-aminobenzyl alcohol), 2-aminobenzyl alcohol **1a** (1.10 mmol), KOH (2.0 mmol), benzyl alcohol **2a** (1.10 mmol)

and NH_4OAc (1.5 mmol) in 5.0 mL of toluene were taken in an oil bath and the mixture was heated at 90 °C for 24 h under N_2 atmosphere. The progress of the reaction was monitored by TLC and the mixture was concentrated. The product (**3a**) was separated by column with silica gel with hexane: ethylacetate (95:5) as an eluent. This protocol was used as a general procedure for the synthesis of quinazoline derivatives.

Characterization of the catalytic isolated product of quinazolines:

2-phenylquinazoline (**3a**).²⁵ Yellow solid (93%, 156 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.46 (s, 1H), 8.62 (dd, $J = 7.9, 1.6$ Hz, 2H), 8.09 (d, $J = 8.4$ Hz, 1H), 7.93 – 7.88 (m, 2H), 7.62 – 7.49 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 161.10, 160.55, 150.81, 138.07, 134.17, 130.66, 128.69, 128.61, 127.32, 127.17, 123.64.

2-(4-methoxyphenyl)quinazoline (**3b**).¹⁰ⁱ Pale yellow solid (91%, 175 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.41 (s, 1H), 8.57 (d, $J = 8.8$ Hz, 2H), 8.04 (d, $J = 8.4$ Hz, 1H), 7.87 (t, $J = 8.1$ Hz, 2H), 7.56 (t, $J = 7.5$ Hz, 1H), 7.04 (d, $J = 8.8$ Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.86, 160.89, 160.46, 150.85, 134.10, 130.73, 130.24, 128.42, 127.91, 127.18, 126.85, 123.34, 114.02, 55.45, 55.41.

2-(2,3,4-trimethoxyphenyl)quinazoline (**3c**).²⁶ Pale yellow solid (89%, 214 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.50 (s, 1H), 8.08 – 8.10 (m, 1H), 7.95 – 7.89 (m, 2H), 7.69 – 7.61 (m, 2H), 6.83 (d, $J = 8.8$ Hz, 1H), 3.96 – 3.93 (m, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ 161.69, 160.20, 155.20, 153.18, 150.69, 142.87, 134.07, 128.57, 127.40, 127.10, 126.79, 126.53, 123.01, 107.47, 61.83, 61.10, 56.14. **m/z** 298.5833 [$\text{M}+2\text{H}^+$] $^+$ (**calcd**: 296.1200).

2-(*m*-tolyl)quinazoline (**3d**).^{11j} White solid (84%, 150 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.36 (s, 1H), 8.32 (d, $J = 9.1$ Hz, 2H), 7.99 (d, $J = 7.9$ Hz, 1H), 7.80 (d, $J = 7.5$ Hz, 2H), 7.51 – 7.48 (m, 1H), 7.36 – 7.32 (m, 1H), 7.23 (d, $J = 6.6$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.25, 160.50, 150.80, 138.33, 137.99, 134.15, 131.49, 129.16, 128.64, 127.25, 127.17, 125.83, 123.60, 21.60.

2-(*p*-tolyl)quinazoline (**3e**).²⁷ Pale yellow solid (86%, 154 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.45 (s, 1H), 8.51 (d, $J = 8.2$ Hz, 2H), 8.07 (d, $J = 8.5$ Hz, 1H), 7.92 – 7.88 (m, 2H), 7.60 (t, $J = 7.3$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 161.19, 160.50, 150.84, 140.92, 135.34, 134.10, 129.46, 128.58, 128.55, 127.17, 127.10, 123.55, 21.54.

2-(4-isopropylphenyl)quinazoline (**3f**).^{11d} Yellow solid (82%, 165 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.43 – 9.24 (m, 1H), 8.54 (d, $J = 8.3$ Hz, 2H), 8.00 (dd, $J = 8.4, 0.7$ Hz, 1H), 7.74 (ddd, $J = 8.9, 5.2, 1.7$ Hz, 2H), 7.44 – 7.36 (m, 3H), 2.96 (dt, $J = 13.8, 6.9$ Hz, 1H), 1.28 (d, $J = 7.0$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 161.14, 160.48, 151.77, 150.80, 135.74, 134.09, 128.78, 128.55, 127.17, 127.06, 126.84, 123.49, 34.19, 23.97.

2-(3-bromophenyl)quinazoline (**3g**).¹¹ⁱ Yellow solid (71%, 163 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.41 (s, 1H), 8.77 (s, 1H), 8.53 (d, $J = 7.8$ Hz, 1H), 8.05 (d, $J = 8.8$ Hz, 1H), 7.89 (dd, $J = 7.6, 4.0$ Hz, 2H), 7.60 (t, $J = 7.5$ Hz, 2H), 7.38 (t, $J = 7.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.56, 159.53, 150.63, 140.09, 134.33, 133.48, 131.59, 130.16, 128.69, 127.68, 127.17, 127.12, 123.75, 122.96.

2-(4-chlorophenyl)quinazoline (**3h**).²⁸ White solid (70%, 136 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.39 (s, 1H), 8.50 (d, $J = 8.6$ Hz, 2H), 8.01 (d, $J = 8.4$ Hz, 1H), 7.88 – 7.86 (m, 2H), 7.57 (d, $J = 7.6$ Hz, 1H), 7.43 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.58, 160.10, 150.74, 136.88, 136.56, 134.31, 129.94, 128.87, 128.64, 127.51, 127.20, 123.67.

2-(3-fluorophenyl)quinazoline (**3i**).²⁸ Gray solid (67%, 122 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.38 (s, 1H), 8.35 – 8.33 (m,

1H), 8.25 (ddd, $J = 10.4, 2.5, 1.6$ Hz, 1H), 8.02 – 8.00 (m, 1H), 7.85 (ddd, $J = 9.7, 5.0, 1.4$ Hz, 2H), 7.56 (td, $J = 7.4, 1.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.53, 162.09, 160.60, 159.90, 150.69, 140.51, 140.44 (d, $J = 28$ Hz), 134.34, 130.15, 130.07 (d, $J = 32$ Hz), 128.72, 127.66, 127.19 (d, $J = 188$ Hz), 124.21, 124.18 (d, $J = 12$ Hz), 123.79, 117.61, 117.40 (d, $J = 84$ Hz), 115.55, 115.32 (d, $J = 92$ Hz).

2-(thiophen-2-yl)quinazoline (**3j**).²⁹ White solid (66%, 114 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.19 (s, 1H), 8.03 (d, $J = 2.9$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 7.70 (t, $J = 8.1$ Hz, 2H), 7.39 (dd, $J = 9.5, 5.4$ Hz, 2H), 7.07 – 7.05 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.54, 157.83, 150.58, 143.88, 134.38, 130.01, 129.29, 128.45, 128.15, 127.29, 127.01, 123.35.

2-(benzo[d][1,3]dioxol-5-yl)quinazoline (**3k**).¹¹ⁱ Yellow solid (69%, 140 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.36 (s, 1H), 8.21 (dd, $J = 8.2, 1.6$ Hz, 1H), 8.10 (d, $J = 1.5$ Hz, 1H), 8.01 – 7.99 (m, 1H), 7.86 – 7.82 (m, 2H), 7.54 (dd, $J = 11.2, 3.8$ Hz, 1H), 6.94 (d, $J = 8.2$ Hz, 1H), 6.03 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.52, 160.36, 160.34, 150.76, 149.92, 148.21, 134.09, 134.06, 132.54, 132.52, 128.45, 127.13, 127.12, 126.94, 126.92, 123.55, 123.40, 108.75, 108.34, 101.48, 101.47.

2-([1,1'-biphenyl]-4-yl)quinazoline (**3l**).^{11j} White solid (62%, 142 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.43 (s, 1H), 8.68 (d, $J = 8.4$ Hz, 2H), 8.07 (d, $J = 8.8$ Hz, 1H), 7.87 (dd, $J = 7.8, 6.4$ Hz, 2H), 7.76 (d, $J = 8.4$ Hz, 2H), 7.70 – 7.68 (m, 2H), 7.56 (t, $J = 7.5$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 7.36 (dd, $J = 10.6, 4.1$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.83, 160.55, 150.83, 143.27, 140.64, 137.03, 134.19, 129.11, 128.91, 128.66, 127.74, 127.39, 127.29, 127.25, 127.21, 123.64.

2-(naphthalen-1-yl)quinazoline (**3m**).^{11g} Pale yellow solid (60%, 125 mg). ^1H NMR (400 MHz, CDCl_3) δ 9.67 (s, 1H), 9.08 (d, $J = 9.4$ Hz, 1H), 8.73 (d, $J = 8.0$ Hz, 1H), 8.35 – 7.99 (m, 9H), 7.73 (t, $J = 7.4$ Hz, 1H), 7.26 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.51, 150.79, 134.43, 133.40, 132.47, 131.37, 130.91, 129.08, 128.77, 128.49, 127.83, 127.50, 127.24, 126.05, 125.61, 125.35, 124.94, 123.03.

2-(pyren-1-yl)quinazoline (**3n**).³⁰ Yellow solid (58% and 156 mg). ^1H NMR (400 MHz, CDCl_3) 9.61 (s, 1H), 8.69 – 8.66 (m, 1H), 8.17 (dd, $J = 9.7, 8.2$ Hz, 3H), 8.03 – 7.93 (m, 4H), 7.77 – 7.59 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.49, 150.60, 136.26, 134.47, 134.21, 130.45, 129.67, 128.68, 128.54, 127.85, 127.24, 126.92, 125.96, 125.90, 125.35, 123.18, 77.39, 77.07, 76.75.

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, quinazolines catalytic products and HRMS spectrum of complexes. CIF file for the complex. CCDC number for complexes **1**, **2** and **3** are is **1813178**, **1813179**, and **1565997** respectively. The materials may be downloaded free of charge at pubs.acs.org.

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Conflict of Interest

The authors declare no competing financial interests.

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Table of Contents Only (TOC)

N^NO Pincer Ligands Supported Palladium(II) Complexes: Direct Synthesis of Quinazolines via Double Dehydrogenative Coupling of Alcohols

One-pot synthesis of quinazolines using Pd(II) complexes via double dehydrogenative coupling of readily available benzyl alcohols and 2-aminobenzyl alcohol has been described. This approach unveiled a broad substrate scope to synthesize a wide variety of quinazoline derivatives with the maximum yield of 93% at 1.5 mol% catalyst loading.

