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Pd/C as an Efficient Heterogeneous Catalyst for Carbonylative Four-Component Synthesis of 4(*3H*)-Quinazolinones

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Abstract: Quinazolinones are of interest in the fields of pharmaceuticals and medicinal chemistry. The application of palladium on activated charcoal (Pd/C) as a heterogeneous catalyst was investigated for the carbonylation of 2-iodoanilines with trimethyl orthoformate and amines *via* multicomponent reaction approach in providing excellent yields of 4(3*H*)-quinazolinones. It avoids the use of expensive phosphine ligands with an additional advantage of catalyst recovering. Furthermore, >5 new quinazolinone scaffolds containing trifluoroethyl group were introduced by this procedure and gram scale experiments were successfully performed as well.

Ever since the pioneering work of Heck and Schoenberg in 1974, palladium-catalyzed carbonylations have experienced impressive progress during the past decades.[1] By carbonylative transformations, CO, as one of the cheapest C1 source, can be incorporated into the parent molecules and contribute to increasing the diversity of accessible compounds in many ways. With carbonylation reactions, various carbonyl-containing compounds can be prepared easily, including valuable heterocycles. As heterocyclic compounds are holding numerous applications in various areas, the integration of cheap CO into valued heterocycles is like transform 'stone' into 'gold'.[2]

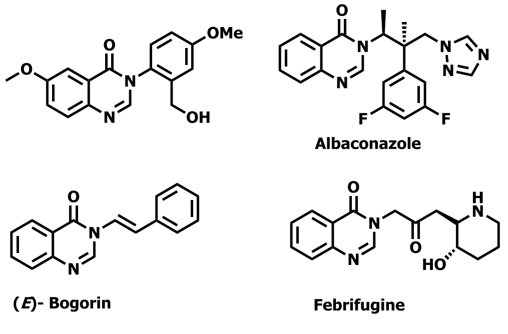


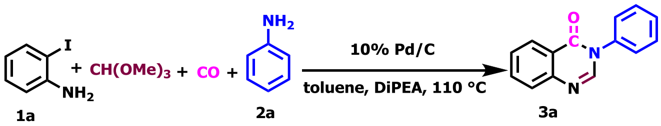
Figure 1: Selected structures of biologically important quinazolinones

Among all the known heterocycles, quinazolinone core and its derivatives consist an important class of compounds, as they are existing in a large family of products with extensive biological activities (Figure 1).[3] They generally display useful therapeutic and pharmacological properties such as anti-inflammatory, anti-convulsant, antihypertensive and antimalarial activities.[4] Due to the wide range and applicability of quinazolinones and its related derivatives, their synthesis has drawn interests from organic chemists.[5] Among the developed procedures, most of the synthetic routes rely on using anthranilic acid or its derivatives as the starting materials and generally suffering from low yields, multistep reactions, or relatively harsh reaction conditions. Therefore new methodologies for quinazolinones synthesis are still under request.

As the above mentioned importance of carbonylations and quinazolinones, the application of carbonylation in quinazolinones synthesis will be interesting. This idea has been realized by other chemists as well and many procedures have been reported. For example, Willis and co-workers reported a straightforward procedure for the synthesis of quinazolinones with *N*-(*o*-halophenyl)-imidates as their substrates.[6] Alper's group developed several carbonylative procedures for quinazolinones synthesis based on *N*-(2-iodophenyl)-*N*′-phenylcarbodiimides,[7a] *o*-iodoanilines and carbodiimides,[7b] or *N*-(2-bromophenyl)pyridine-2-amines as the substares.[8] Zhu and co-workers succeeded in carbonylative synthesis of quninazolinones *via* C-H activation.[9,10] With *N*-aryl-2-aminopyridines or *N*-arylamidines as the starting materials, the corresponding quinazolinones were produced in good yields. Our group developed several carbonylative procedures for the preparation of quinazolinones as well.[11] In the presence of palladium catalyst; good yields of the desired products can be produced. However, the discussed procedures are all homogeneous palladium catalyst based, which have disadvantages include phosphine ligands relied and not recyclable. Then Pd/C as a readily available inexpensive heterogeneous catalyst comes into our interest.[12] Here we wish to report our new results on Pd/C-catalyzed carbonylative four-component synthesis of 4(3*H*)-quinazolinones. With 2-iodoanilines, trimethyl orthoformate and amines as the substrates, the desired products were isolated in good to excellent yields. Notably, gram scale and catalyst reuse experiments were performed successfully as well.

Initially, with 2-iodoaniline (**1a**), trimethyl orthoformate and aniline (**2a**) in the presence of DiPEA as base as the reaction system, various heterogeneous palladium catalysts were screened (Table 1, entries 1, 8–10). Among them, (10%) Pd/C was found to be the best catalyst providing an excellent yield of the desired product (Table 1, entry 1). The same yield can be achieved even with 1 mol% of palladium catalyst (Table 1, entry 5). However, the yield has been relatively dropped with 0.5 mol% catalyst loading (Table 1, entry 6).

Table 1: Effect of catalyst on the palladium-catalyzed carbonylative coupling of 2-idoanilines with amines, trimethyl orthoformate, and CO.[a]



Entry	Catalyst	**3a** Yield (%)[b]
1	Pd/C (5 mol%)	96
2	Pd/C (2.5 mol%)	94
3	Pd/C (2 mol%)	94
4	Pd/C (1.5 mol%)	94
5	**Pd/C (1 mol%)**	**94**
6	Pd/C (0.5 mol%)	87
7	-	No reaction
8	Pd/1,10 Phenonthroline	22
9	Pd/CeO_2	56
10	Pd/TiO_2	44

Reaction conditions: 2-Iodoaniline (1 mmol), aniline (1.2 mmol), trimethyl orthoformate (2 mmol), DiPEA (3.0 mmol), toluene (3 mL), 110 °C, CO (10 bar), 20 h.

Then different solvents and bases were tested to show their effect on this reaction. Solvents like acetonitrile, DMF, 1,4-dioxane, THF DMSO and Xylene provided relatively lower yields of the expected product (Table 2, entries 1-4, 6-7). Toluene was found to be the optimal solvent (Table 2, entry 5) and used for further studies. In the various tested organic and inorganic bases, no better yield can be achieved than DiPEA (Table 2, entries 9-14). With the conditions in entry 5 (Table 2), lower pressure of CO were tested; 80% of quinazolinone can be formed under 5 bar of CO and the yield decreased to 21% when perform the reaction under 1 bar of CO.

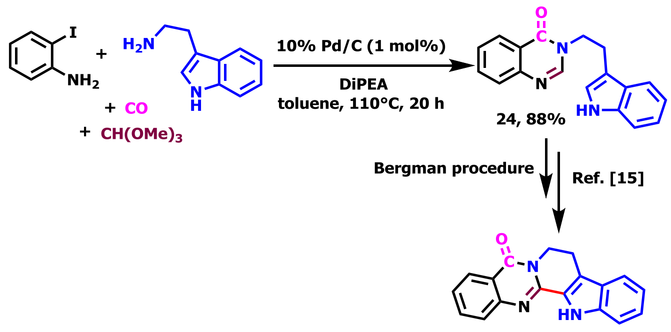
Table 2. Optimization of palladium-catalyzed carbonylative coupling of 2-iodoanilines with amines, trimethyl orthoformate, and CO under various reaction conditions.[a]

Entry	Base	Solvent	**3a** Yield (%)
1	DiPEA	Acetonitrile	42
2	DiPEA	DMF	29
3	DiPEA	1,4 dioxane	75
4	DiPEA	THF	61
5	**DiPEA**	**Toluene**	**94**
6	DiPEA	DMSO	27
7	DiPEA	Xylene	90
8	DiPEA	H_2O	No reaction
9	DBU	Toluene	56
10	DABCO	Toluene	64
11	TEA	Toluene	81
12	K_2CO_3	Toluene	45
13	Cs_2CO_3	Toluene	59
14	Na_2CO_3	Toluene	41
15	-	Toluene	No reaction

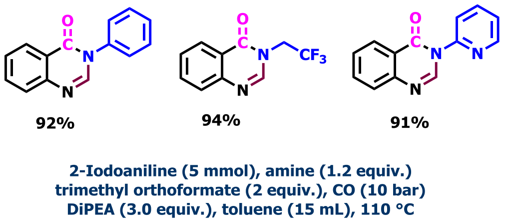
Reaction conditions: 1a (1 mmol), 2a (1.2 mmol), trimethyl orthoformate (2 mmol), base (3.0 mmol), solvent (3 mL), 110 °C, CO (10 bar), 20 h.

With the optimized reaction conditions in the hand, we extended this straight forward synthesis of 4(3*H*)-quinazolinones to a wider range of amines and 2-iodoanilines (Table 3). As depicted in Table 3, this 10% Pd/C catalytic system was surprisingly versatile. Structurally diverse amines, including aromatic and aliphatic ones reacted with 2-iodoaniline to give the desired products in good to excellent yields (Table 3,entries 1–24).Various anilines, regardless of the presence of electron-donating or electron-withdrawing groups reacted efficiently to give 84–98% isolated yields of the desired products (Table 3, entries 1–9). Notably, trifluoromethyl group can be effectively installed into the quinazolinone scaffolds by using trifluoroethyl amine as the reaction partner as well (Table 3, entries 14-18).[13] To the best of our knowledge, these kind of quinazolinone compounds are scarcely reported in the literature. To further demonstrate the general applicability of this procedure, we then choose aniline as a standard substrate to perform the reactions with different 2-iodoanilines. Both electron-donating and electron-withdrawing substituents are tolerable under the present reaction conditions (Table 3, entries 19–24). However, no reaction occurred when 2-bromoaniline was applied as the substrate. In the case of with strongly activated 3-amino-4-bromobenzonitrile, still only trace of the desired quinazolinone was detected.

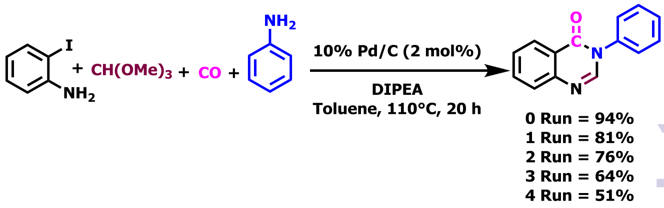
Given the importance of the 4(3*H*)-quinazolinone nucleus in many natural products, we were interested to utilize our efficient synthetic protocol for the synthesis of a pharmaceutically relevant alkaloids. One such target with fundamental biological interest is dihydrorutecarpin, a quinazolino carboline alkaloid which was used for more than 2000 years in Chinese medical practice as a remedy for gastrointestinal disorders (abdominal pain, dysentery), headache, amenorrhea, and postpartum hemorrhage.[14] By the present convergent synthetic approach, carbonylative coupling of 2-iodoaniline and trimethyl orthoformate with tryptamine under 10 bar of CO provides *3-[2-(3-indolyl)ethyl]-4(3H)-quinazolinone* (24) in 88% yield (Scheme 1). The treatment of 24 with trifluoroaceticanhydride effected cyclization to (trifluoroacetyl)-13b, l, 4-dihydrorutaecarpin, which can be readily hydrolyzed to the desired dihydrorutaempine according to the Bergman procedure.[15] Additionally, we performed 1-g scale reactions for selected substrates too. As shown in Scheme 2 in all these cases we have obtained in excellent yields. Moreover, Pd/C was found to be effectively recycled for four consecutive cycles in our recycling experiments (Scheme 3).



Scheme 1: Palladium-catalyzed four-component carbonylative coupling reaction for the synthesis of dihydrorutecarpin.



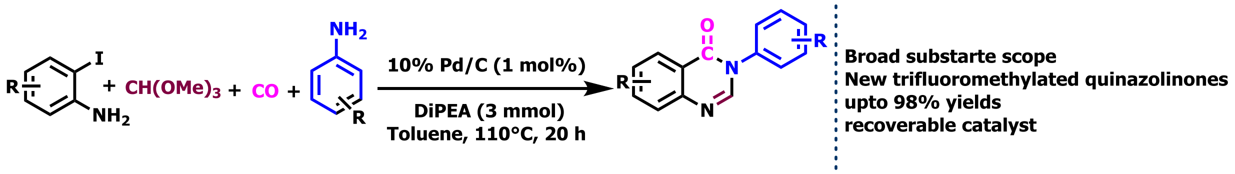
Scheme 2: Gram scale reactions.

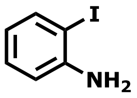
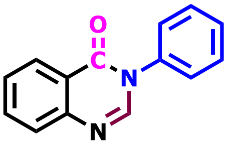
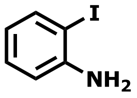
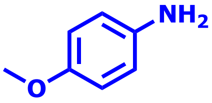
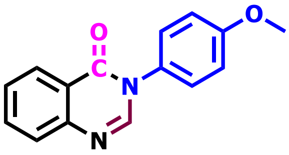
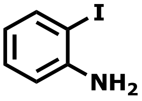
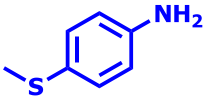
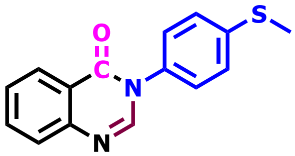


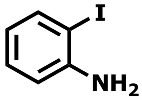
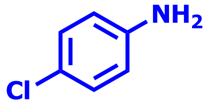
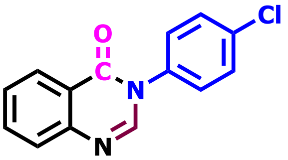
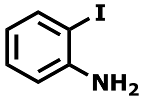
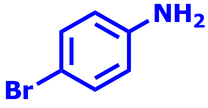
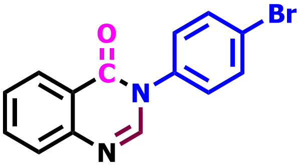
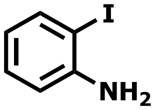
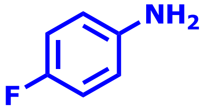
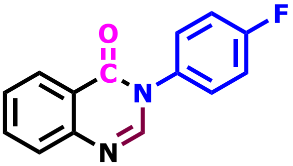
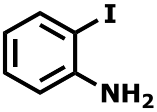
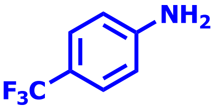
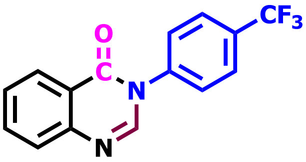
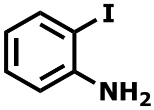
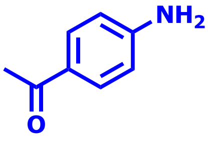
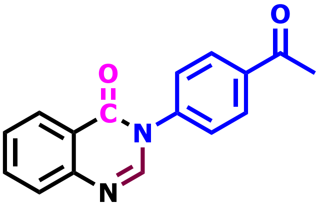
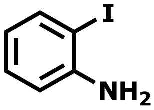
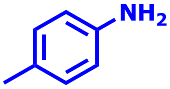
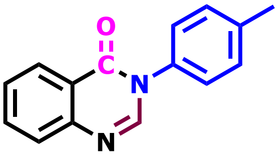
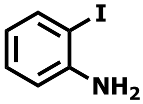
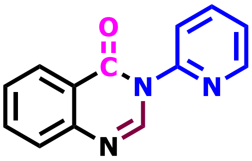
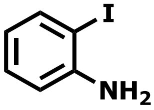
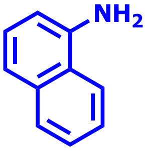
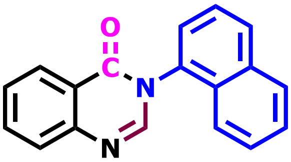
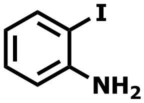
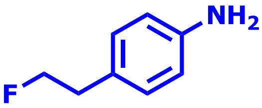
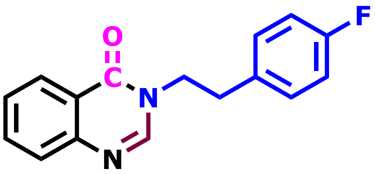
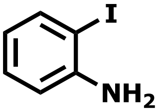
Scheme 3: Recyclability study of Pd/C catalyst.

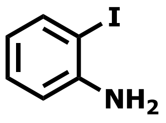
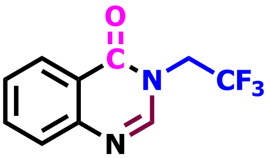
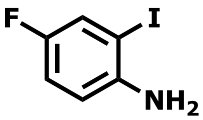
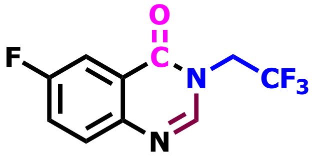
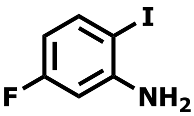
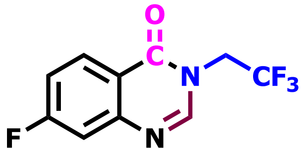
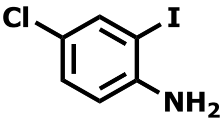
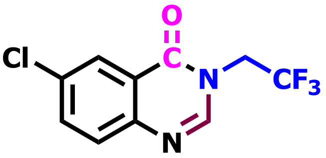
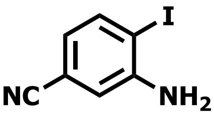
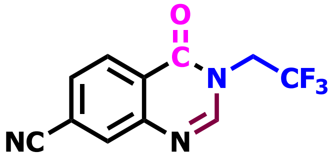
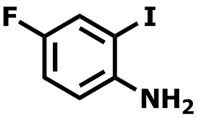
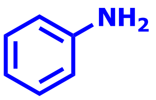
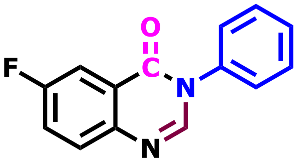
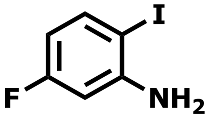
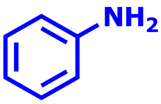
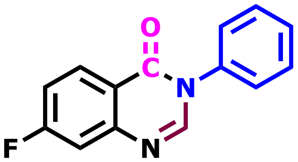
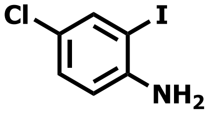
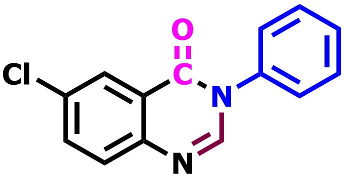
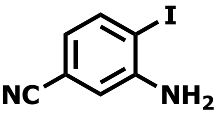
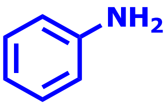
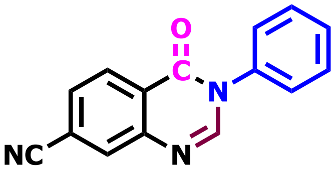
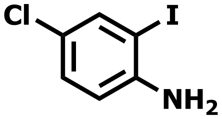
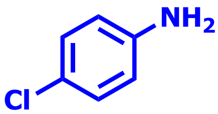
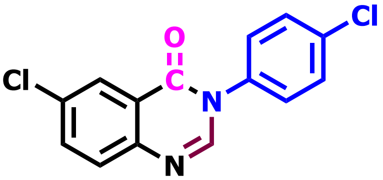
In summary, we have developed a relatively mild, operationally simple, phosphine-free and recyclable catalytic system for the carbonylative synthesis of 4(3*H*)-quinazolinones. With 2-iodoanilines, trimethyl orthoformate, and amines as the substrates, the desired quinazolines were formed in good to excellent yields. Additionally, gram scale and catalyst reuse experiments were performed successfully as well.

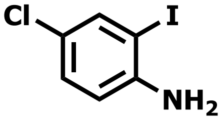
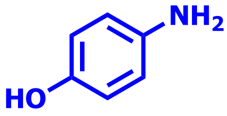
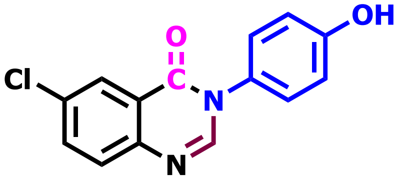
Table 3: Palladium-catalyzed carbonylative coupling of various amines with 2-iodoanilines, trimethylorthoformate, and CO



Entry	2-iodoaniline	Amine	Product	Yield[b]
1				97
2				98
3				96

4				93
5				91
6				97
7				93
8				84
9				87
10				95
11				90
12				98
13				98

14				96
15				97
16				93
17				96
18				98
19				97
20				93
21				96
22				98
23				95

24				91

Reaction conditions: 2-iodoaniline or substituted 2-iodoaniline (1 mmol), amine (1.2 mmol), trimethyl orthoformate (2 mmol), DiPEA (3.0 mmol), toluene (3 mL), 110 °C, CO (10 bar), 20h.

General information

Reactions were run under an argon/N_2 atmosphere with exclusion of moisture from reagents and autoclaves. All substrates were purchased from Sigma–Aldrich, were used as received. Solvents were dried from molecular sieves and kept under argon. NMR spectra were recorded on the Bruker AV 300 spectrometers. All chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) in Hz. All chemical shifts are reported relative to tetramethylsilane (δ 0.0 for 1H NMR in DMSO-d^6, $CDCl_3$) and d-solvent peaks (δ 77.00 for ^{13}C NMR, chloroform and for DMSO-$d^{6,}$ δ 40.00), respectively. All measurements were carried out at room temperature unless otherwise stated. Mass spectra were recorded on an AMD 402/3 or a HP 5989A mass selective detector. Gas chromatographic analysis was performed on an Agilent HP-5890 instrument with an FID detector and an HP-5 capillary column (poly(dimethylsiloxane) with 5% phenyl groups, 30 m, 0.32 mm i.d., 0.25 mm film thickness) with argon as the carrier gas. The chemicals are ordered from Aldrich.

Experimental section

A 12 mL vial was charged with 10 wt. % Pd/C (1 mol%; 10 mg), 2-iodoaniline (1 mmol) and a stirring bar. Then, aniline (1.1 mmol), trimethyl orthoformate (2 mmol), DiPEA (3 mmol), and toluene (3 mL) were injected by syringe under argon. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments® under argon atmosphere. After flushing the autoclave three times with CO, a pressure of 10 bar CO was adjusted at ambient temperature. Then, the reaction was performed for 20 h at 110 °C. After the reaction finished, the autoclave was cooled down to room temperature and the pressure was released carefully. The solution was filtered through whatmann filter paper and washed the reaction mixture with acetone (2-3 ml). After evaporation of the organic solvent the residue was adsorbed on silica gel and the crude product was purified by column chromatography using n-heptane/ethyl acetate (7:3) as eluent.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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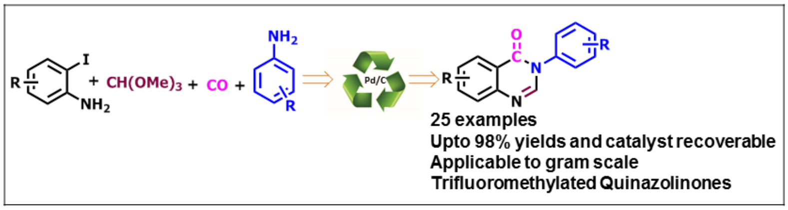

A relatively mild, operationally simple, phosphine-free and recyclable catalytic system for the carbonylative synthesis of 4(3*H*)-quinazolinones with 2-iodoanilines, trimethyl orthoformate, and amines as the substrates has been developed.