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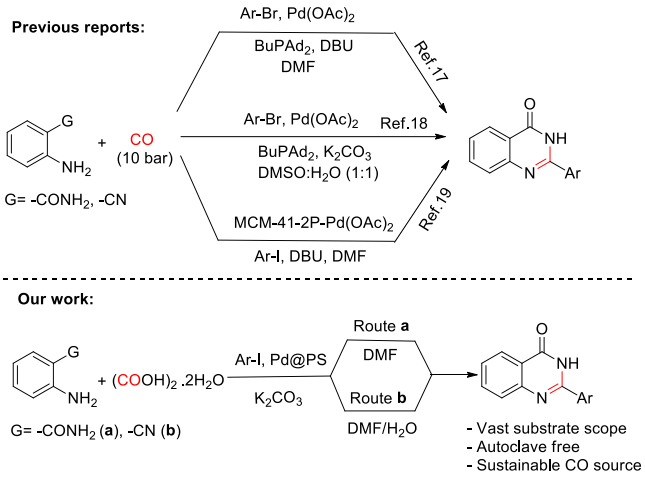
Polystyrene supported palladium (Pd@PS) catalyzed carbonylative annulation of aryl iodides using oxalic acid as a sustainable CO source for the synthesis of 2-aryl quinazolinones

Shankar Ram,[a,b] Shaifali,[a,b] Arvind Singh Chauhan,[a,b] Sheetal,[a,b] Ajay Kumar Sharma[a,b] and Dr. Pralay Das[a,b] *

Abstract: An efficient and convenient strategy for the synthesis of diversely substituted quinazolinones from o-carbamoyl/cyano aniline and aryl iodides using oxalic acid as a CO source under polystyrene supported palladium (Pd@PS) nanoparticles (NPs) catalyzed conditions has been developed. Under this study, we have employed oxalic acid as safe, economic, environmentally benign, sustainable and bench stable solid CO surrogate under Double-Layer-Vial (DLV) system for the synthesis of 2-aryl quinazolinones. This methodology does not require any special high-pressure equipment like autoclave, microwave etc. Moreover, simple procedure for catalyst preparation, catalyst recyclability, easy handling of reaction, additive and base free generation of CO, excellent to good yields and vast substrate scope are the additional features of developed protocol.

2-Aryl quinazolinone and its derivatives constitute an important class of nitrogen containing fused heterocycles existing in a variety of natural products and bioactive molecules.[1] These are also privileged structures for the development of drug candidates[2] due to their broad spectrum of biological and medicinal applications such as antiviral,[3] antimicrobial,[4] antimalarial,[5] anticancer,[6] anticonvulsant[7] etc. Furthermore, they are also used as ligand for benzodiazepine and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the central nervous system (CNS) for acquired epilepsy treatment or as DNA binders.[7a,8] Owing to broad applications of quinazolinones, various synthetic methods have been developed for their synthesis.[9] The traditional approach to obtain quinazolinones rely on the condensation of *o*-aminobenzamides with aldehydes,[10] benzyl alcohol,[11] aryl ketones,[12] benzyl amines,[13] and carboxylic acid[14] etc. However, most of these methods generally require some excess amount of oxidants, homogeneous catalytic system and additives.

During the last few decades, palladium catalyzed carbonylative transformation of organo-halides has become a powerful tool in the modern organic synthesis.[15] There are few reports available on the carbonylative synthesis of quinazolinones using carbon monoxide gas as C1 source. Zhu and co-workers reported an interesting palladium catalyzed intramolecular oxidative carbonylation of *N*-arylamidines to synthesize quinazolinones.[16] The reactions were carried out in the presence of palladium acetate together with one equivalent of CuO under one bar of CO gas. Later on, palladium catalyzed carbonylative coupling for the synthesis of 2-arylbenzoxazinones and its application for one pot synthesis of 2-arylquinazolinones was demonstrated by Beller and co-workers.[17a] In 2013, Wu *et al.* reported Pd-catalyzed carbonylative annulations of *o*-aminobenzamides with aryl bromides for the synthesis of quinazolinones using CO gas as C1 source.[17b] However, in case of aryl iodides they got only 30% yield of the desired product. Later, Wu and co-workers reported palladium(II)-catalyzed cascade synthesis of quinazolinone from *o*-aminobenzonitrile, CO and aryl bromide.[18] More recently, You *et al.* demonstrated carbonylative annulation reactions to synthesize quinazolinones using CO gas as C1 source under MCM-41-immobilized bidentate phosphine palladium(II) complex catalyzed conditions.[19] Most of these carbonylative annulation strategies for the synthesis of quinazolinones required high pressurized CO gas as C1 source.



Scheme1. Palladium catalyzed carbonylative synthesis of quinazolinones.

However, in most of the general lab practices the use of CO gas-based carbonylation reactions have been avoided because expensive high-pressure equipment is needed to perform such reactions and safety issues associated with this odorless, toxic and flammable gas as well. Therefore, owing to the limitation of

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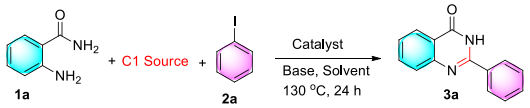
CO gas based carbonylation reactions, utilization of non-toxic, sustainable, economic and bench stable solid CO surrogate is desirable for the synthesis of quinazolinones. Furthermore, the application of homogeneous palladium complex in pharmaceutical industries remains a big challenge, as they are costly, non-recyclable and very difficult to separate from the reaction mixture.

In this context, for last few years our group have been continuously working on the development of polystyrene supported (PS) transition metal nanoparticles (NPs) as heterogeneous catalyst and their applications in different carbonylation and carboxylation reaction by utilizing oxalic acid as safe, sustainable and bench stable CO building block.[20] Recently, our group demonstrated Pd@PS catalyzed aminocarbonylation of aryl halides with amines using oxalic acid as *ex situ* CO surrogate under DLV(Double Layer Vial) system and their single-pot application in isoindolinone synthesis.[21] In continuation of our earlier development, herein, we report an efficient and convenient synthesis of 2-aryl quinazolinones from *o*-carbamoyl/cyano aniline and aryl iodides under Pd@PS catalyzed conditions using oxalic acid as bench stable solid CO surrogate.

The nano-catalyst Pd@PS was prepared by following our previously reported reduction deposition method (Supporting Information) and fully characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), high resolution transmission electron microscopy (HRTEM), energy dispersive spectroscopy (EDS) and selected area electron diffraction (SAED) studies.[20a, 22] In this study, the developed nano-catalyst Pd@PS was further applied to the carbonylative cyclization reaction for the synthesis of 2-aryl quinazolinones.

In a pursuit to develop convenient and efficient approach for the synthesis of quinazolinone, we began our investigation with a model reaction: 2-aminobenzamide (1 equiv.), iodobenzene (1.5 equiv.), Pd@PS (3 mol%), oxalic acid dihydrate (6 equiv.), DBU (2 equiv.) in DMF (2.0 mL) at 130 ^{o}C for 24 hrs. The targeted product 2-phenylquinazolinone (**3a**) formed in 30% isolated yield (Table1, entry1). In order to get optimum yield of the targeted product (**3a**), we further screened several reaction parameters such as catalyst concentration, C1 source, base, solvent, temperature and reaction time (Table1). We have evaluated different bases and solvents (Table1, entries 2-9), among them K_2CO_3 (2 equiv.) in DMF solvent was found to be the optimal base as the yield increased from 30 to 91% (Table1, entry 9). Decreasing the amount of base afforded the desired product **3a** in lower yield (Table1, entry 10). Further, replacing the oxalic acid with *N*-formyl saccharin and formic acid gave the desired product **3a** in 17% and 10% isolated yields respectively (Table 1, entries 12-13). These results revealed that oxalic acid was best CO surrogate among others as it decomposed easily to release CO and also compatible with the Pd@PS catalyst. We also screened different homogeneous and heterogeneous palladium catalysts such as $Pd(OAc)_2$, $Pd(OAc)_2$ with ligand (dppb), $Pd_2(dba)_3$, $Pd(PPh_3)_4$ $PdCl_2(PPh_3)_2$, Pd/C (5 wt%) and results summarized in Table1 (Entries 14-19). Among the screened catalysts, Pd@PS was found to be most effective in our standard reaction conditions for the

Table 1: Optimization of the reaction parameters[a]

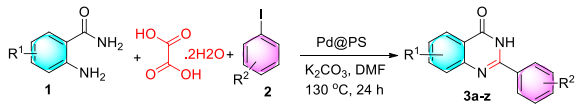


Entry	Catalyst (mol%)	CO source	Base (equiv.)	Solvent	Yield (%)[b]
1	Pd@PS (3)	$(COOH)_2.2H_2O$	DBU (2)	DMF	30
2	Pd@PS (3)	$(COOH)_2.2H_2O$	Et_3N (2)	DMF	10
3	Pd@PS (3)	$(COOH)_2.2H_2O$	K_3PO_4 (2)	DMF	47
4	Pd@PS (3)	$(COOH)_2.2H_2O$	Na_2CO_3 (2)	DMF	59
5	Pd@PS (3)	$(COOH)_2.2H_2O$	Cs_2CO_3 (2)	DMF	64
6	Pd@PS (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	PEG-400	37
7	Pd@PS (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	P-Xylene	30
8	Pd@PS (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMA	76
9	**Pd@PS (3)**	**$(COOH)_2.2H_2O$**	**K_2CO_3 (2)**	**DMF**	**91***
10	Pd@PS (3)	$(COOH)_2.2H_2O$	K_2CO_3 (1.5)	DMF	65
11	Pd@PS (2)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMF	48
12	Pd@PS (3)	N-formylsaccharine	K_2CO_3 (2)	DMF	17
13	Pd@PS (3)	Formic acid	K_2CO_3 (2)	DMF	10
14	$Pd(OAc)_2$ (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMF	61
15	$Pd(OAc)_2$ /dppb (3/3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMF	68
16	$Pd_2(dba)_3$ (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMF	56
17	$Pd(PPh_3)_4$ (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMF	39
18	$PdCl_2(PPh_3)_2$ (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMF	64
19	Pd/C (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMF	66
20	-	$(COOH)_2.2H_2O$	K_2CO_3 (2))	DMF	nd
21	Pd@PS (3)	-	K_2CO_3 (2)	DMF	nd
22[c]	Pd@PS (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMF	52
23[d]	Pd@PS (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMF	64
24[e]	Pd@PS (3)	$(COOH)_2.2H_2O$	K_2CO_3 (2)	DMF	60

[a]Reaction conditions: inner vial - *o*-aminobenzamide (0.36 mmol), aryl iodide (0.54 mmol), Pd@PS (3 mol%), K_2CO_3 (0.72 mmol), DMF (1.5 mL); outer vial - oxalic acid dihydrate (2.16 mmol), DMF (0.5 mL), 130 ^{o}C, 24 hrs; [b] Isolated yields; [c] Reaction temperature was 120 ^{o}C; [d] 4 equiv. oxalic acid was used; [e] Reaction time was 15 hrs. * Conversion = 100%.

selective synthesis of 2-phenylquinazolinone **3a**. This may be due to the good holding capacity of the oxalic acid over surface through ionic bonding and their simultaneous decomposition to produce CO and further adsorption inside the hydrophobic pocket of polymer matrix and the close vicinity of CO with Pd-catalyst on the same surface may enhance the availability of CO for the reaction to produce corresponding product, as also described in our previous reports.[20,21] We also tested the effect of temperature during the course of reaction and found that 130 ^{o}C was the optimal temperature. In the absence of Pd@PS catalyst, no desired product (**3a**) formation was noticed (Table 1, entry 20). The reaction also did not occur when oxalic acid dihydrate removed from the outer vial, which concluded that CO was coming from oxalic acid (Table 1, entry 21). On decreasing the reaction temperature (120 ^{o}C), reaction time (15 h), catalyst concentration (2 mol%) and proportion of oxalic acid dihydrate (4 equiv.), resulted in lower yields of desired product **3a** (Table 1, entries 11, and 22-24).

Table 2. Substrate scopes for 2-aryl quinazolinones synthesis from *o*-aminobenzamides and aryl iodides.[a]



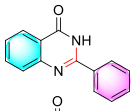
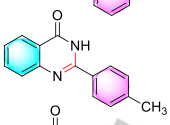
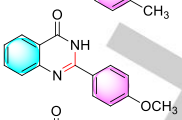
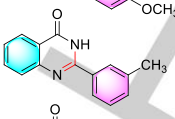
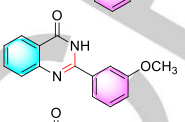
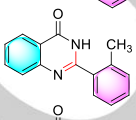
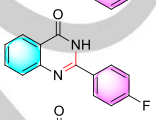
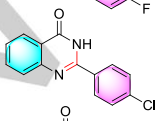
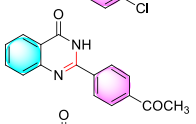
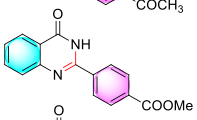
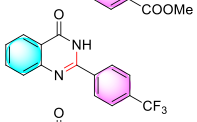
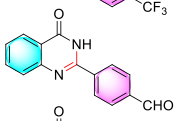
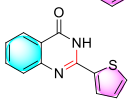
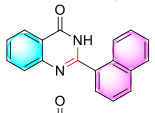
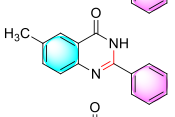
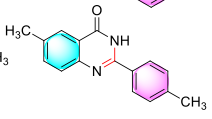
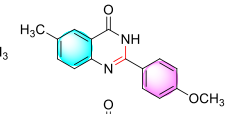
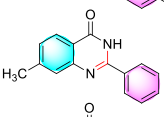
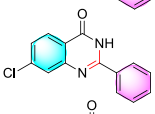
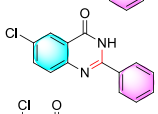
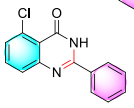
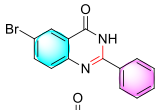
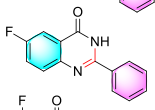
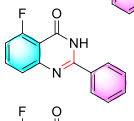
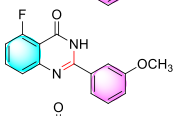
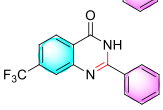
Entry	1	2	Product	3	Yields (%)[b]
1	**1a** R^1 = H	**2a** R^2 = H		**3a**	91
2	**1b** R^1 = H	**2b** R^2 = 4-CH_3		**3b**	84
3	**1c** R^1 = H	**2c** R^2 = 4-OCH_3		**3c**	76
4	**1d** R^1 = H	**2d** R^2 = 3-CH_3		**3d**	75
5	**1e** R^1 = H	**2e** R^2 = 3-OCH_3		**3e**	70
6	**1f** R^1 = H	**2f** R^2 = 2-CH_3		**3f**	60
7	**1g** R^1= H	**2g** R^2 = 4-F		**3g**	82
8	**1h** R^1 = H	**2h** R^2 = 4-Cl		**3h**	70
9	**1i** R^1 = H	**2i** R^2 = 4-$COCH_3$		**3i**	65
10	**1j** R^1= H	2j R^2 = 4-COOMe		**3j**	62
11	1k R^1= H	**2k** R^2 = 4-CF_3		**3k**	65
12	**1l** R^1= H	**2l** R^2 = 4-CHO		**3l**	73
13	**1m** R^1= H	**2m**		**3m**	67
14	**1n** R^1 = H	**2n**		**3n**	52
15	**1o** R^1 = 5-CH_3	**2o** R^2 = H		**3o**	80
16	**1p** R^1 = 5-CH_3	**2p** R^2 = 4-CH_3		**3p**	78

Table2 (Continued)

Entry	1	2	Product	3	Yields (%)[b]
17	**1q** R^1 = 5-CH_3	**2q** R^2 = 4-OCH_3		**3q**	55
18	**1r** R^1 = 4-CH_3	**2r** R^2 = H		**3r**	78
19	**1s** R^1 = 4-Cl	**2s** R^2 = H		**3s**	75
20	**1t** R^1 = 5-Cl	**2t** R^2 = H		**3t**	70
21	**1u** R^1 = 6-Cl	**2u** R^2 = H		**3u**	83
22	**1v** R^1= 5-Br	**2v** R^2 = H		**3v**	85
23	**1w** R^1 = 5-F	**2w** R^2 = H		**3w**	80
24	**1x** R^1 = 6-F	**2x** R^2 = H		**3x**	65
25	**1y** R^1= 6-F	**2y** R^2= 3-OCH_3		**3y**	76
26	**1z** R^1 = 4-CF_3	**2z** R^2 = H		**3z**	75

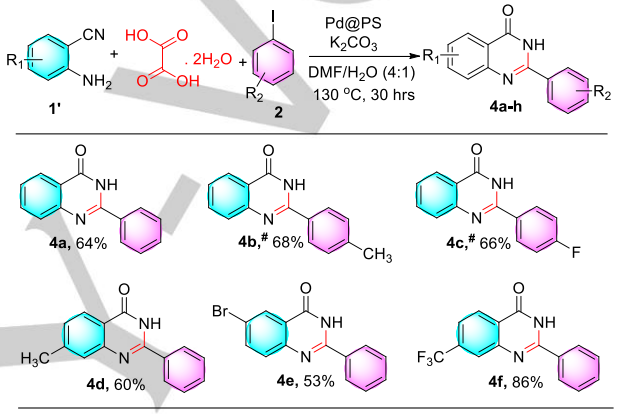
[a]Reaction conditions: inner vial - *o*-aminobenzamide (0.36 mmol), aryl iodide (0.54 mmol, 1.5 equiv.), Pd@PS (3 mol%), K_2CO_3 (0.72 mmol, 2 equiv.), DMF (1.5 mL); outer vial-oxalic acid dihydrate (2.16 mmol, 6 equiv.), DMF (0.5 mL), 130 °C, 24 hrs; [b] Isolated yields.

To explore the scope and generality of the developed protocol, we started the investigation of substrates for this transformation and a variety of *o*-aminobenzamides as well as aryl iodides were studied and results summarized in Table 2. Initially, we screened aryl iodides with o-aminobenzamide as a reaction partner under optimized reaction conditions. Excellent to good yields of target products were obtained with aryl iodides containing electron-donating groups. Aryl iodides having methyl or methoxy group at meta or para positions produced the desired products **3b-e** in 70-84% yields. Sterically hindered o-iodotoluene provided the corresponding product **3f** in 60% isolated yield. Para-fluoro and chloro substituted aryl iodides were well tolerated under the reaction conditions and procured the desired products **3g-h** in 82 and 70% yields respectively. Aryl iodides having electron withdrawing functionality are the challenging substrates for the carbonylative coupling reactions. In this context, some interesting aryl halides having electron withdrawing substituents such as 4-$COCH_3$, 4-$COOCH_3$, 4-CF_3, 4-CHO also applied under optimized reaction conditions. To our delight, these aryl halides found to be reactive under the

reaction conditions and provided the desired product **3i-3l** in 62-73% isolated yields. 2-Iodothiophene as well as 1-iodonaphthalene also successfully delivered the desired product **3m-n** in 67 and 52% yields respectively.

The optimized reaction condition was also applied to a series of *o*-aminobenzamides with aryl iodides. The *o*-aminobenzamide bearing electron donating substituents participated well in the reaction and provided the desired products **3o-p** and **3r** in 78-80% isolated yields. However, under the present condition *p*-iodoanisole with 5-methyl-2-aminobenzamide gave the desired product **3q** in 55% isolated yield. The fluoro, chloro and bromo substituted *o*-aminobenzamides regardless of their electronic properties and respective position of substituents, underwent carbonylative annulation reaction with aryl iodides efficiently to produce corresponding 2-aryl quinazolinones **3s-y** in 65-85% isolated yields. Interestingly, 5-bromo substituted *o*-aminobenzamide well tolerated under the reaction conditions and gave the desired product **3v** in good yield. Notably, trifluoromethyl (4-CF_3) substituted 2-aminobenzamide also reacted well, affording the desired product **3z** in 75% yield. Unfortunately, very poor yield (10%) of desired product obtained when reaction of *o*-aminobenzamide carried out with bromobenzene, whereas reaction did not occur with chlorobenzene under the standard reaction conditions.

Table 3. Carbonylative annulations reaction of *o*-aminobenzonitrile and aryl iodides using oxalic acid as CO source for the synthesis of quinazolinones.[a]



[a]Reaction conditions: inner vial- *o*-aminobenzonitrile (0.42 mmol), aryl iodide (0.63 mmol, 1.5 equiv.), Pd@PS (3 mol%), K_2CO_3 (1.26 mmol, 3 equiv.), DMF (1.2 mL), H_2O (0.3 mL); outer vial - oxalic acid dihydrate (2.52 mmol, 6 equiv.), DMF (0.5 mL), 130 °C, 30 hrs. # Benzoic acid of aryl halide was detected in traces.

During the substrates investigation, when we applied 2-iodo benzonitrile with *o*-aminobenzamides for carbonylative annulation reaction, no desired product formed but a small amount of benzamide formation was noticed. This may be due to the presence of water in the reaction mixture formed during the decomposition of oxalic acid dihydrate. Encouraged by these observations, we carried out a reaction of *o*-aminobenzonitrile with iodobenzene taking DMF:H_2O (4:1) as solvent system under the identical catalytic conditions and produced the desired product (2-aryl quinazolinones) in 40% isolated yield. After increasing the equivalency of base 2 to 3 equivalent and reaction time 24 to 30 h, yield of the desired product **4a** was increased from 40 to 64%. Notably, in this case we did not get benzoic acid which could be a side product of reaction. Next, we moved towards the scope and generality of this transformation by employing different *o*-aminobenzonitriles and aryl iodides under set reaction conditions (Table 3). A variety of substituents such as -CH_3, -F, -Br were well tolerated and furnished corresponding quinazolinones **4b-e** in 53-68% yields. However, in case of 4-Me and 4-F iodobenzene, we got respective benzoic acid derivatives in traces as side product. Interestingly, 4-trifluoromethyl-2-aminobenzonitrile with iodobenzene successfully delivered the desired product **4f** in 86% yield.

The recyclability experiments of polystyrene supported palladium (Pd@PS) nanoparticles (NPs) were carried out with o-aminobenzamide and iodobenzene under standard reaction conditions. After the completion of the reaction, the reaction mixture was quenched with water and the organic layer was extracted with ethyl acetate. Further the catalyst was filtered out and washed with water and acetone, then dried and reused for another reaction. The catalyst was found to be recycled upto five cycles with some loss in catalytic activity (Figure1). Very similar reason for loss in catalytic activity was noticed as mentioned in our earlier reports.[20c,20d]

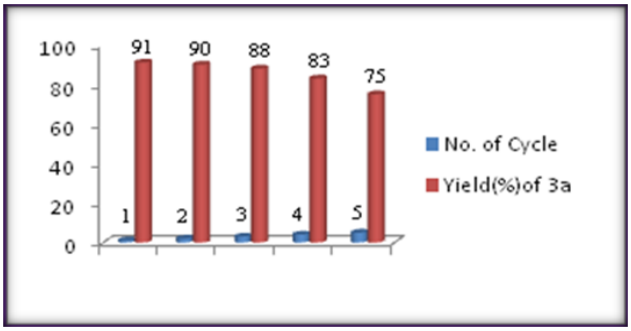


Figure1. Recyclability experiments of Pd@PS catalyst.

In summary, we have developed an operationally simple and efficient method for the synthesis of 2-aryl quinazolinones from *o*-aminobenzamides and aryl iodides, through Pd@PS NPs catalyzed carbonylative annulation reaction using oxalic acid dihydrate as cheap and bench stable CO surrogate. Following this method, a series of 2-aryl quinazolinones with electron sufficient or deficient substrates were performed with excellent to good yields. The developed methodology was also applied to different *o*-aminobenzonitriles and gave a variety of 2-aryl quinazolinones under single-pot reaction in considerably good yields. The catalyst can easily be prepared by simple procedure and recyclable up to 5 times with some loss in catalytic activity. Oxalic acid as bench stable solid CO surrogate in combination with the simple Double-Layer-Vial (DLV) reaction system could enhance the applicability of the reaction for general lab practices.

Experimental Section

Typical procedure for the synthesis of 2-phenylquinazolinone (3a): With a double layer vial system (DLV), 2-aminobenzamide (0.36 mmol, 50 mg), iodobenzene (0.55 mmol, 112.5 mg), Pd@PS (0.01 mmol, 246 mg), K_2CO_3 (0.73 mmol, 101 mg) and DMF (1.5 mL) was added in 2 mL vial (inner vial) and this vial was placed inside 5 mL reaction vessel (outer vial) containing oxalic acid dihydrate (2.20 mmol, 277 mg) and 0.5 mL of DMF. The 5 mL reaction vessel was tightened with solid PTFE cap and stirred at 130 ^oC for required time. The progress of reaction was monitored with the help of TLC. After the completion of reaction, the inner vial was taken out and reaction mixture was quenched with the help of water, organic layer was extracted with ethyl acetate. The extracted organic layer was dried over sodium sulphate and concentrated over rotary evaporator. The crude mixture was further purified by column chromatography using hexane:ethyl acetate (80:20) as elutent, afforded compound 3a as white solid (74 mg); yield: 91%; m.p: 248-250 ^oC.^1H (600 MHz, DMSO-d_6) δ (ppm) = 7.49-7.59 (m, 4H), 7.73-7.75 (m, 1H), 7.81-7.86 (m, 1H), 8.15-8.20 (m, 3H), 12.5 (brs, 1H).^{13}C (150 MHz, DMSO-d_6) δ (ppm) = 121.45, 126.30, 127.02, 127.96, 128.22, 129.04, 131.33, 133.18, 135.04, 149.20, 152.76, 162.68.The expected ESI-MS$(M+H)^+$ for $C_{14}H_{11}N_2O^+$ is 223.0866 and observed 223.0872.

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Keywords: palladium nanoparticles (NPs) • oxalic acid dihydrate • o-aminonenzamides • o-aminobenzonitriles • 2-aryl quinazolinones

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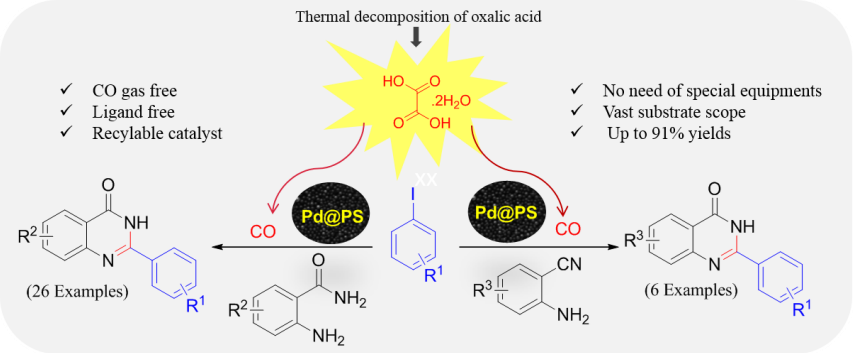

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Polystyrene supported palladium (Pd@PS) catalyzed carbonylative annulation of aryl iodides using oxalic acid as a sustainable CO source for synthesis of 2-aryl quinazolinones