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# A convenient palladium-catalyzed carbonylative synthesis of 4(3*H*)-quinazolinones from 2-bromoformanilides and organo nitros with $Mo(CO)_6$ as a multiple promoter†

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**A novel and convenient procedure for the synthesis of quinazolinones has been developed. Using 2-bromoformanilides and organo nitros as substrates and $Mo(CO)_6$ as a multiple promoter, the desired products were isolated in moderate to excellent yields in the presence of a palladium catalyst. Here, $Mo(CO)_6$ was not only a CO source, but also a nitro compound reducing reagent and a cyclization promoter.**

Nitrogen-containing heterocycles are widely distributed in nature and are essential to life, playing a vital role in the metabolism of all living cells. Among these, 4(3*H*)-quinazolinones represent one of the most prevalent compounds found in natural products and biologically active pharmaceuticals (Fig. 1).[1] They are now known to have a wide range of useful biological properties, *e.g.* anticancer, antiviral, anti-inflammatory, anti-microbial cholinesterase inhibitors, antifolate, antitumor, protein kinase inhibitors and many others.[2] In view of their importance, a number of methods for 4(3*H*)-quinazolinone preparation have been developed. These routes, however, mainly rely on using anthranilic acid or its derivatives as the starting materials, and generally suffer from low yields and multistep reactions.[3] The search for new methodologies to synthesize this class of compounds is a research field of undoubted current attention.

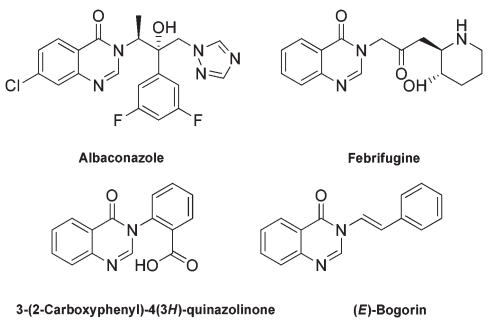


**Fig. 1** Selected examples of bio-active quinazolinones.

Palladium-catalyzed carbonylative transformation has already become a unique, powerful, and versatile tool for the synthesis of carbonyl containing compounds.[4] In contrast to the traditional use of carboxylic acids to form nucleophile-acyl bonds, aryl halide carbonylation generates these same products with palladium catalysts and CO. Regrettably, the high toxicity and the cumbersome handling of CO gas severely limit the usefulness of this transformation in drug discovery and other small-scale applications. Therefore, solid reagents that can release CO in a controlled manner have gained considerable interest over the past few decades. Among them, $Mo(CO)_6$ has emerged as an ideal candidate and has been previously demonstrated in a wide range of carbonylative reactions.[5] However, to date, the application of $Mo(CO)_6$ as the CO supplier for the synthesis of carbonyl containing heterocycles is rarely exploited.

Regarding the nitrogen sources, nitro compounds are attractive due to their low cost and wide availability.[6] In industry, they are used as the major raw materials for the synthesis of a wide range of N-containing compounds.[7] But compared to the impressive progress being made in the palladium-catalyzed aminocarbonylation (a key step in the N-containing heterocycle synthesis) with amines as starting materials, there are scarcely available reports dealing with the direct use of organo nitros for such transformations. This is not surprising as the selective reduction of the nitro group in the presence of other sensitive competing functionalities is still a challenging problem.[8] Moreover, the compatibility between the conditions of nitro reduction and aminocarbonylation is generally hard to be

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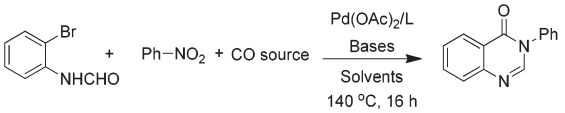
achieved. To address these critical issues, we wish to report here our discovery on palladium-catalyzed carbonylative synthesis of quinazolinones. In this new procedure, nitro compounds (aromatic and aliphatic) and 2-bromoformanilides were applied as the substrates and $Mo(CO)_6$ as a multirole reactant, the desired quinazolinones were formed in moderate to excellent yields.

Initially, the direct transformation of nitrobenzene, 2-bromoformanilide and $Mo(CO)_6$ in 1,4-dioxane using $NEt_3$ as a base was investigated as a model reaction to identify the potential catalysts. Summarizing these experiments, we observed that the $Pd(OAc)_2$/$BuPAd_2$ catalyst system gave an impressive conversion of starting materials to afford the desired product 4(3*H*)-quinazolinone in 87% isolated yield at 140 °C within 16 h (Table 1, entry 1). In the absence of a ligand only traces of the product are observed (Table 1, entry 2). Other monodentate and bidentate phosphine ligands including $PPh_3$, $PCy_3$, Xantphos, DPPB, BINAP and DPPF gave poor yields (Table 1, entries 3–8). Variations of bases and solvents were also examined, but no better yields were obtained, except in the case of using DiPEA as a base (Table 1, entries 9–15).

Notably, using CO gas (either 10 bar, 5 bar, or 2 bar) instead of $Mo(CO)_6$, only 10–13% of the corresponding quinazolinone was produced with low conversion of starting materials (nitrobenzene and 2-bromoformanilide) (Table 1, entries 16–18). This scenario, in conjunction with the significantly retarded yield identified for using other metal carbonyl compounds as the CO sources (Table 1, entries 19, 20), strongly suggests that the $Mo(CO)_6$ is not just a solid CO in the title reaction. To clarify this point, we investigated the catalytic performance in the absence of $Pd(OAc)_2$/$BuPAd_2$. Although $Mo(CO)_6$ did not promote the carbonylation step, the complete reduction of nitrobenzene to aniline went smoothly. Taken together, these results indicate that the cooperation between the palladium-catalyzed aminocarbonylation and the $Mo(CO)_6$-mediated reduction is essential to facilitate the desired reaction in a domino fashion. The attempt to decrease the temperature was performed in the last stage, decreased conversion and yield were observed if the reaction was performed at 120 °C (Table 1, entry 21).

**Table 1** Cross-coupling of 2′-bromoformanilide with nitrobenzene under various conditions[a]




| Entry | CO source | Ligands | Bases | Solvents | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 | $Mo(CO)_6$ | $BuPAd_2$ | $NEt_3$ | Dioxane | 94(87) |
| 2 | $Mo(CO)_6$ | — | $NEt_3$ | Dioxane | Trace |
| 3 | $Mo(CO)_6$ | $PPh_3$ | $NEt_3$ | Dioxane | 15 |
| 4 | $Mo(CO)_6$ | $PCy_3$ | $NEt_3$ | Dioxane | 8 |
| 5 | $Mo(CO)_6$ | Xantphos | $NEt_3$ | Dioxane | 33 |
| 6 | $Mo(CO)_6$ | DPPB | $NEt_3$ | Dioxane | 20 |
| 7 | $Mo(CO)_6$ | BINAP | $NEt_3$ | Dioxane | 31 |
| 8 | $Mo(CO)_6$ | DPPF | $NEt_3$ | Dioxane | 41 |
| 9 | $Mo(CO)_6$ | $BuPAd_2$ | $K_3PO_4$ | Dioxane | 9 |
| 10 | $Mo(CO)_6$ | $BuPAd_2$ | $Na_2CO_3$ | Dioxane | 25 |
| 11 | $Mo(CO)_6$ | $BuPAd_2$ | DiPEA | Dioxane | 91 |
| 12 | $Mo(CO)_6$ | $BuPAd_2$ | $NEt_3$ | DMF | 11 |
| 13 | $Mo(CO)_6$ | $BuPAd_2$ | $NEt_3$ | Mesitylene | 41 |
| 14 | $Mo(CO)_6$ | $BuPAd_2$ | $NEt_3$ | DMSO | 7 |
| 15 | $Mo(CO)_6$ | $BuPAd_2$ | $NEt_3$ | THF | 34 |
| 16 | CO (10 bar) | $BuPAd_2$ | $NEt_3$ | Dioxane | 11 |
| 17 | CO (5 bar) | $BuPAd_2$ | $NEt_3$ | Dioxane | 10 |
| 18 | CO (2 bar) | $BuPAd_2$ | $NEt_3$ | Dioxane | 13 |
| 19 | $Co_2(CO)_8$ | $BuPAd_2$ | $NEt_3$ | Dioxane | 19 |
| 20 | $Fe_3(CO)_{12}$ | $BuPAd_2$ | $NEt_3$ | Dioxane | 6 |
| 21 | $Mo(CO)_6$ | $BuPAd_2$ | $NEt_3$ | Dioxane | 59[c] |

[a] 2′-Bromoformanilide (1 mmol), nitrobenzene (1.1 mmol), CO source (1 mmol), $Pd(OAc)_2$ (2 mol%), ligand (6 mol%), solvent (2 mL), base (2 mmol), $N_2$ (10 bar). [b] Yields were determined by GC analysis using hexadecane as an internal standard (number in parenthesis refer to an isolated yield). [c] 120 °C.

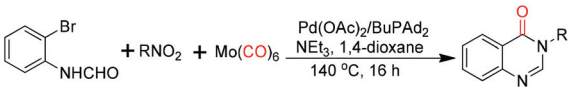
Once suitable reaction conditions for the model system are identified, the scope and limitations of this novel procedure are explored (Tables 2 and 3). Several alkyl substituted nitrobenzenes, such as methyl-, isopropyl-, and *tert*-butyl-, were tested at the first stage, 61–97% of the desired quinazolinones were isolated (Table 2, entries 2–6). 1-Nitronaphthalene can be applied as a substrate as well and gave the corresponding 3-(naphthalen-1-yl)quinazolin-4(3*H*)-one in 81% isolated yield (Table 2, entry 8). Several electron-withdrawing group substituted aromatic nitro compounds were tested subsequently. Moderate to excellent yields can be achieved without further optimization (Table 2, entries 9–13). However, this procedure seems quite sensitive to the steric properties of the substrates. In detail, 41% of the product was isolated from *ortho*-chloro substituted nitrobenzene while 95% yield was achieved with the *meta*-chloro substituted substrate (Table 2, entries 9 and 10). Additionally, groups like hydroxyl and alkene, which are potentially active in palladium-catalyzed coupling reactions, can be tolerated under our conditions and gave the corresponding quinazolinones in 53–59% yields (Table 2, entries 14 and 15). More interestingly, in addition to aromatic nitro compounds, aliphatic nitro compounds can be applied as substrates as well (Table 2, entries 16 and 17). 53–74% of the desired quinazolinones were isolated from the reaction between 2′-bromoformanilide and the corresponding alkyl nitros.

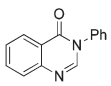
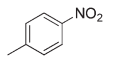
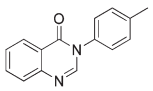
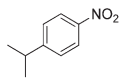
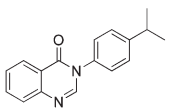
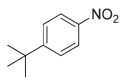
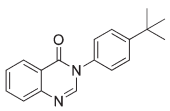
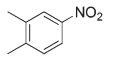
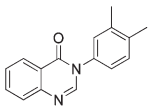
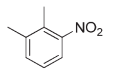
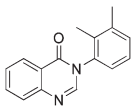
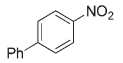
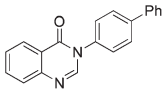
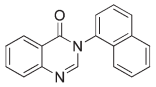
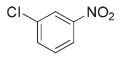
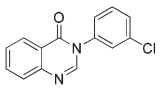
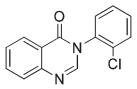
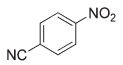
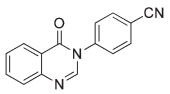
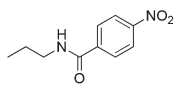
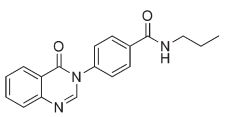
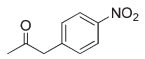
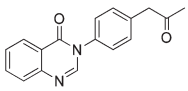
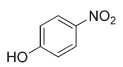
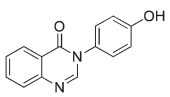
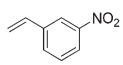
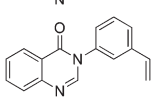
We then choose nitrobenzene as the model substrate to test with various 2′-bromoformanilides (Table 3). In general, 63–83% of different substituted quinazolinones were isolated. Both electron-donating and withdrawing functional groups are tolerable (Table 3, entries 1–3). Of particular note is the utility of our method for the preparation of fluorinated 4(3*H*)-quinazolinones from 2-bromoformanilides. It is well known that fluorine-containing functional groups can drastically change both the biological and physical properties of organic molecules. We are pleased to find that all six 2-bromoformanilides bearing fluoro, trifluoromethyl and trifluoromethoxyl are suitable substrates for this procedure (Table 3, entries 4–9).

In order to understand the reaction in more detail, several control experiments on nitrobenzene reduction were carried out (Scheme 1). Under our standard reaction conditions, 43%

**Table 2** Palladium-catalyzed, $Mo(CO)_6$-mediated carbonylative coupling of 2′-bromoformanilide with nitro compounds[a]




| Entry | Nitro compounds | Product | Yield[b] [%] |
|---|---|---|---|
| 1 |  |  | 87 |
| 2 |  |  | 79 |
| 3 |  |  | 90 |
| 4 |  |  | 97 |
| 5 |  |  | 61 |
| 6 |  |  | 63 |
| 7 |  |  | 80 |
| 8 |  |  | 81 |
| 9 |  |  | 95 |
| 10 |  |  | 41 |
| 11 |  |  | 57 |
| 12 |  |  | 49 |
| 13 |  |  | 71 |
| 14 |  |  | 59 |
| 15 |  |  | 53 |

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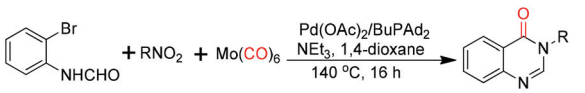
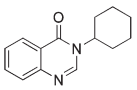
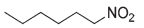
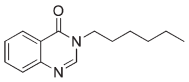



| Entry | Nitro compounds | Product | Yield[b] [%] |
|---|---|---|---|
| 16[c] |  |  | 53 |
| 17[c] |  |  | 74 |

[a] 2′-Bromoformanilide (1 mmol), nitro compounds (1.1 mmol), $Mo(CO)_6$ (1 mmol), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 1,4-dioxane (2 mL), $NEt_3$ (2 mmol), $N_2$ (10 bar). [b] Isolated yield. [c] 2′-Bromoformanilide (0.5 mmol), nitro compounds (0.55 mmol), $Mo(CO)_6$ (1 mmol), $Pd(OAc)_2$ (4 mol%), ligand (12 mol%), 1,4-dioxane (2 mL), $NEt_3$ (1 mmol), $N_2$ (10 bar).

of aniline was produced from nitrobenzene with $Mo(CO)_6$ as the reductant (Scheme 1, **a**); and the yield of aniline can be improved to 96% by adding 3 mmol of water (Scheme 1, **b**). These results indicated the importance of water for nitro reduction, as the solvent was used as received and the already present water can initiate the reaction. The water will be regenerated after intramolecular condensation; this explains why we do not need to add additional water in our reaction system. The presence of a palladium catalyst was found not necessary for nitro reduction while the presence of a base was proved to be crucial (Scheme 1, **a** *vs.* **c** *vs.* **d**).

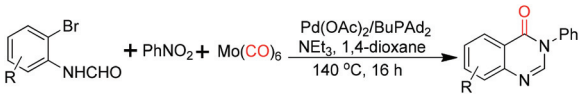
Then aniline was tested in place of nitrobenzene under our typical conditions (Scheme 2). To our delight, 67% of the desired quinazolinone was formed without any optimization. This result further proves that nitro compounds were reduced to the corresponding amines initially and were then ready for further transformations.

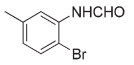
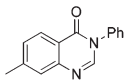
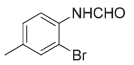
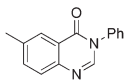
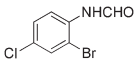
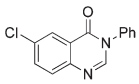
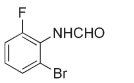
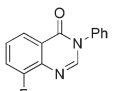
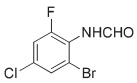
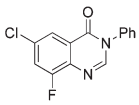
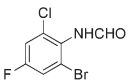
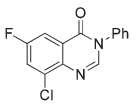
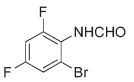
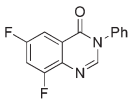
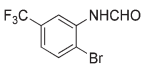
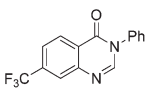
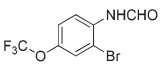
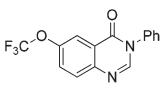
Based on the previous mechanistic studies on palladium-catalyzed carbonylations,[9] a most possible reaction pathway is proposed and shown in Scheme 3. The reaction started with the oxidative addition of 2′-bromoformanilide to Pd(0) to give the organopalladium intermediate. Then followed by the coordination and insertion of CO which was released from $Mo(CO)_6$; the acylpalladium complex was formed as the key intermediate. At the same time, the nitro compound was reduced by $Mo(CO)_6$ under this condition and the formed amine nucleophilically attacked the acylpalladium complex. Finally, the eliminated 2-formamido-*N*-phenylbenzamide gave the final quinazolinone product after intramolecular condensation, which is promoted either by palladium or molybdenum salts as Lewis acids.

## Conclusions

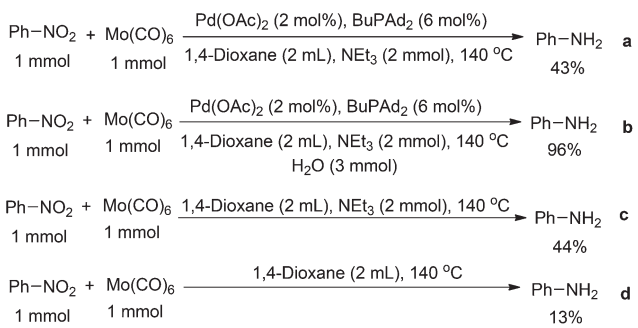
In conclusion, an interesting and convenient procedure for the synthesis of quinazolinones from 2′-bromoformanilides and

**Table 3** Palladium-catalyzed, $Mo(CO)_6$-mediated carbonylative coupling of 2′-bromoformanilides with nitrobenzene[a]



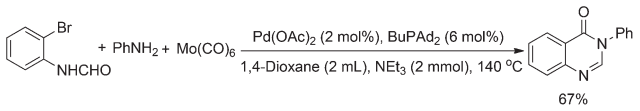

| Entry | 2′-Bromoformanilides | Product | Yield[b] [%] |
|---|---|---|---|
| 1 |  |  | 69 |
| 2 |  |  | 76 |
| 3 |  |  | 70 |
| 4 |  |  | 68 |
| 5 |  |  | 74 |
| 6 |  |  | 74 |
| 7 |  |  | 63 |
| 8 |  |  | 77 |
| 9 |  |  | 83 |

[a] 2′-Bromoformanilides (1 mmol), nitrobenzene (1.1 mmol), $Mo(CO)_6$ (1 mmol), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 1,4-dioxane (2 mL), $NEt_3$ (2 mmol), $N_2$ (10 bar). [b] Isolated yield.

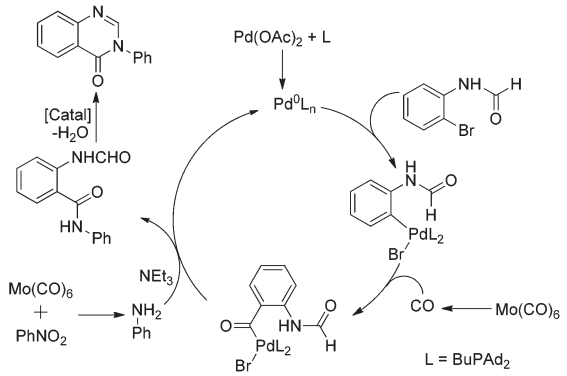



**Scheme 1** Reduction of nitrobenzene with $Mo(CO)_6$.

nitro compounds has been developed. 26 examples of the desired products were isolated in 41–97% yields. Not only aromatic nitros but also aliphatic nitros are suitable substrates




**Scheme 2** Palladium-catalyzed, $Mo(CO)_6$-mediated carbonylative coupling of 2′-bromoformanilides with aniline.




**Scheme 3** Proposed reaction mechanism.

for this novel transformation. Both electron-donating and withdrawing substituents are tolerable under our conditions. Notably, $Mo(CO)_6$ plays a role as more than a CO source in this system.

### General procedure for the synthesis of quinazolinone

A 12 mL vial was charged with $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 2′-bromoformanilide (1 mmol), $Mo(CO)_6$ (1 mmol) and a stirring bar. Then, nitro compounds (1.1 mmol), $NEt_3$ (2 mmol) and 1,4-dioxane (2 mL) were injected using a syringe under argon. The vial (or several vials) was placed in an alloy plate, which was transferred to a 300 mL autoclave of the 4560 series from Parr Instruments® under an argon atmosphere. After flushing the autoclave three times with $N_2$, a pressure of 10 bar $N_2$ was adjusted at ambient temperature. Then, the reaction was performed for 16 h at 140 °C. After completion of the reaction, the autoclave was cooled down to room temperature and the pressure was released carefully. The solution was extracted 3–5 times with 2–3 mL of ethyl acetate. After evaporation of the organic solvent the residue was adsorbed on silica gel and the crude product was purified by column chromatography.

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