Multicomponent Reactions

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Highly Efficient Four-Component Synthesis of 4(3*H*)-Quinazolinones: Palladium-Catalyzed Carbonylative Coupling Reactions**

Lin He, Haoquan Li, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu**

Abstract: *Given the importance of quinazolinones and carbonylative transformations, a palladium-catalyzed four-component carbonylative coupling system for the synthesis of diverse 4(3H)-quinazolinone in a concise and convergent fashion has been developed. Starting from 2-bromoanilines (1 mmol), trimethyl orthoformate (2 mmol), and amines (1.1 mmol), under 10 bar of CO, the desired products were isolated in good yields in the presence of $Pd(OAc)_2$ (2 mol %), $BuPAd_2$ (6 mol %) in 1,4-dioxane (2 mL) at 100 °C, using N,N-diisopropylethylamine (2 mmol) as the base. Notably, the process tolerates the presence of various reactive functional groups and is very selective for quinazolinones, and was used in the synthesis of the precursor to the bioactive dihydrorutaempine.*

The pursuit of sustainable chemistry has stimulated the development of new strategies and technologies for the synthesis of useful products in a safe, compact, and energy-efficient manner. In this regard, multicomponent reactions (MCRs)[1] which directly yield the target products by domino or cascade reaction sequences offer significant advantages over conventional linear-step syntheses. The resulting reduced number of synthetic and purification steps for a given molecule increases the attractiveness and practicability of the process.[2] In the ideal situation, a MCR occurs when the different transformations are mediated by the same catalytic precursor in a one-pot, one-step operation. Significant success has been achieved under this paradigm as illustrated by the growing number of processes for three-component reactions.[3] In contrast, a rather limited number of MCRs involving four or more reagents have thus far proved to be reliable enough to be among the usual synthetic tools.[4] This clearly demonstrates the increasing difficulty in finding a suitable catalytic system when increasing the number of components. Not surprisingly though, the balance between activity and selectivity is generally hard to achieve, as a sharp penalty has to be paid because of side reactions. Thus, the implementation of a straightforward MCR strategy with efficient catalytic control remains a formidable challenge.

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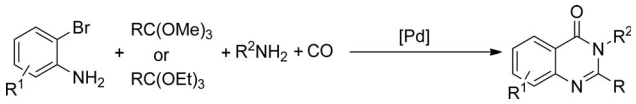
Over the years, the transition-metal-catalyzed MCRs have emerged as a powerful approach for the construction of C–X (X = C, N, O, etc.) bonds.[5] One representative example is the palladium-catalyzed carbonylative reactions, which hold an important status because of the high levels of selectivity generally observed, and the variety of bond-forming processes available.[6] Furthermore, concomitant incorporation of CO (one of the cheapest C1 source) into the final products may contribute to increasing the diversity of accessible compounds in many ways. Indeed, many elegant three-component carbonylative coupling reactions have been developed, thus providing rapid and convergent syntheses of complex organic molecules from readily available starting materials.[7] In this contribution, our laboratory and other research groups have presented several strategic options for the preparation of various heterocycles.[8,9] In pursuing our interest in finding more sophisticated MCRs, we sought to use palladium-catalyzed carbonylative reactions for the concise one-pot, four-component synthesis of valuable N-containing heterocyclic compounds. To date, only rare examples of such reactions (mainly performed in two steps manner) have been reported.[10]

As one of the most frequently encountered heterocycles in medicinal chemistry, 4(3*H*)-quinazolinones are present in a large family of products with broad pharmacological properties including antimalarial, antitumor, anticonvulsant, fungicidal, antimicrobial, and anti-inflammatory.[11] Furthermore, the heterocyclic core constitutes more than 40 alkaloids isolated from natural products.[12] 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, multistep reactions, or harsh reaction conditions.[13] Recently, Willis and co-workers reported a straightforward procedure for the synthesis of quinazolinones.[14] They used *N*-(*o*-halophenyl)-imidates as their substrates, and the desired products were produced in good yields. Herein, we wish to report our new achievement in the carbonylative synthesis of quinazolinones. We started from commercially available 2-bromoanilines, amines, and *ortho*-esters, and various 4(3*H*)-quinazolinones were isolated in moderate to excellent yields from palladium-catalyzed aminocarbonylation reactions (Scheme 1).

Initially, the reaction was carried out with 2-bromoaniline (1 mmol), aniline (1.1 mmol), CO (10 bar), and triethyl orthoformate (2 mmol) in the presence of $Pd(OAc)_2$ (2 mol %), $BuPAd_2$ (CataCXium A, 6 mol %) at 120 °C for 16 hours. The expected four-component reaction occurred and 3-phenyl-4(3*H*)-quinazolinone (**1**) was formed as the major product (63 % GC yield) by using NEt_3 (2 mmol) as the

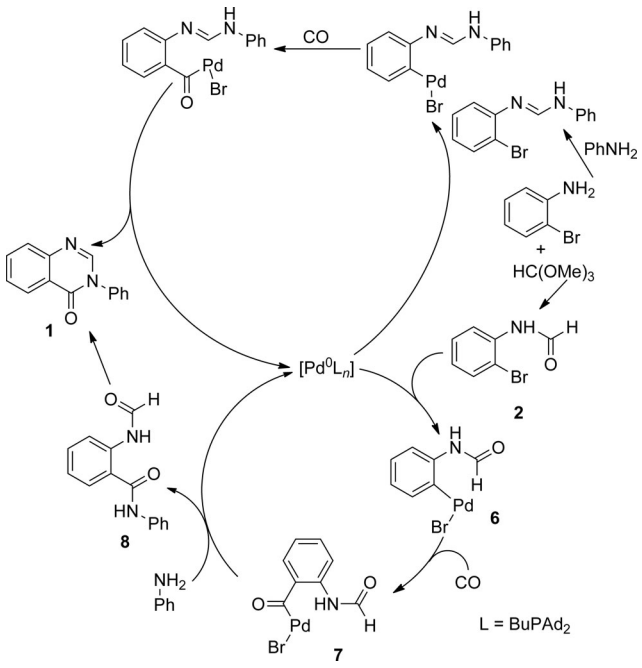


Scheme 1. Concept of the catalytic multicomponent coupling reaction for the synthesis of 4(3*H*)-quinazolinones.

base in 1,4-dioxane (2 mL). Among numerous by-products, four of them, namely *N*-(2-*b*romophenyl)formamide (**2**), *N*-phenylformamide (**3**), ethyl 2-aminobenzoate (**4**), and ethyl 2-formamidobenzoate (**5**) were identified by GC-MS (6–9% yield). This result was encouraging, since it is not easy to avoid side reactions for a reaction of such complexity. To our delight, by replacing triethyl orthoformate with trimethyl orthoformate, the desired 4(3*H*)-quinazolinone can be obtained in remarkably high yield (86% yield upon isolation, 94% GC yield). The yield of the isolated product could be further improved to 92% by using 2 mmol of DIPEA (*N*,*N*-diisopropylethylamine) as a base under milder reaction conditions (100 °C), whereas a decreased yield was observed when either K_3PO_4 or Na_2CO_3 was used. In the presence of DIPEA, the air-stable $BuPAd_2$ showed superior performance compared to ligands such as PPh_3 and DPPP. The high selectivity of the present four-component system, coupled with its ability to react under mild reaction conditions, significantly improves the economic and environmental impacts of this palladium-catalyzed carbonylative coupling process.

To gain insight into a reaction mechanism, control experiments were conducted. It was confirmed that the direct conversion of 2-bromoaniline and *N*-phenylformamide (**2**) under 10 bar of CO afford the desired product, while the combination of aniline, CO (10 bar), and *N*-(2-bromophenyl)formamide (**3**), which is the condensation product of 2-bromoaniline with trimethyl orthoformate through an ether cleavage of the imidate motif, led to **1** in near quantitative yield (95% GC yield) under the optimized reaction conditions. On the basis of the above observations and the known chemistry of the palladium-catalyzed carbonylative cyclizations, a possible reaction mechanism has been proposed in Scheme 2. Initially, the reaction of 2-bromoaniline with trimethyl orthoformate gave **2** as the intermediate. Then, oxidative addition of the in situ generated active Pd^0 complex to **2** results in the arylpalladium complex **6**. After the coordination and insertion of CO, the acylpalladium complex **7** is produced. After nucleophilic attack of aniline on the acylpalladium complex, **8** was eliminated and gave the terminal product **1** after intramolecular condensation. Pd^0 can be regenerated with the assistance of a base and thus starts the next catalytic cycle. A catalytic cycle involving (*E*)-*N*′-(2-bromophenyl)-*N*-phenylformimidamide as an intermediate cannot be excluded.

With these findings in hand, we extended this straightforward synthesis of 4(3*H*)-quinazolinones to a wider range of amines and 2-bromoanilines. As depicted in Table 1 and Table 2, the present $Pd(OAc)_2$/$BuPAd_2$ catalytic system was surprisingly versatile. Structurally diverse amines, including aromatic and aliphatic ones react with 2-bromoaniline to give

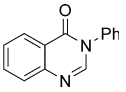
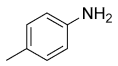
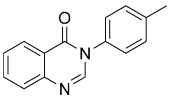
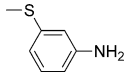
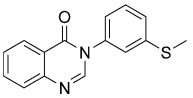
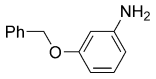
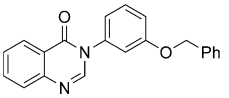
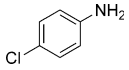
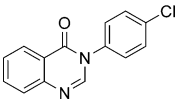
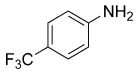
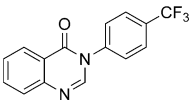
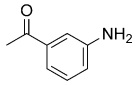
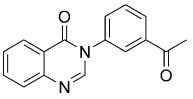
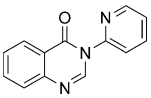
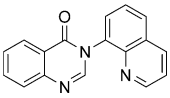
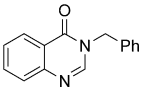
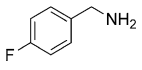
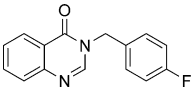
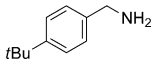
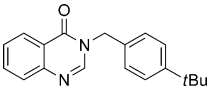
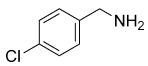
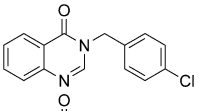
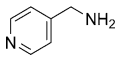
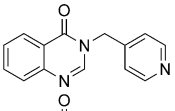
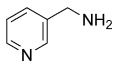
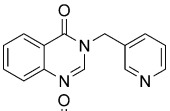
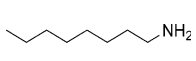
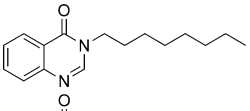
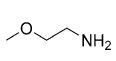
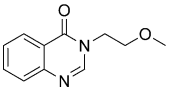


Scheme 2. Proposed reaction mechanism.

the desired products in good to excellent yields (Table 1, entries 1–17). Various anilines, regardless of the presence of electron-donating or electron-withdrawing groups reacted smoothly to give 71–92% yields of the isolated products (entries 2–7). Strikingly, a wide range of synthetically useful functional groups including thioether, benzyloxy, halide, and trifluoromethyl groups, as well as ketone moieties remained intact during the reaction. Also, the present system shows excellent promise for the transformation of heteroaromatic amines (entries 8 and 9). Notably, the notoriously difficult benzylamines were successfully converted into the corresponding 4(3*H*)-quinazolinones (60–73% yields; entries 10–15). When alkylamines were employed, it was found that N-alkylquinazolinones could be obtained in excellent yields (80–84%, entries 16 and 17). More importantly, this one-pot, four-component synthesis of 4(3*H*)-quinazolinone could be easily scaled up. For example, by using DIPEA (20 mmol) as a base, the direct conversion of 2-bromoaniline (10 mmol), aniline (11 mmol), triethyl orthoformate (20 mmol), and CO (10 bar) in the presence of $Pd(OAc)_2$ (2 mol%), and $BuPAd_2$ (Cata-CXium A, 6 mol%) proceeded smoothly in 1,4-dioxane (20 mL) at 120 °C, thus affording 3-phenyl-4(3*H*)-quinazolinone in 70% yield within 24 h (Table 1, entry 1).

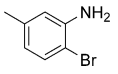
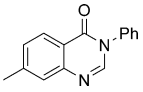
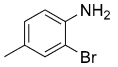
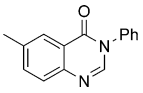
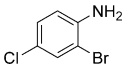
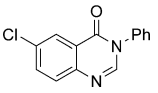
To further demonstrate the general applicability of this procedure, we then choose aniline as a standard substrate to perform the test reactions with different 2-bromoanilines (Table 2). Both electron-donating and electron-withdrawing substituents are tolerable under the present reaction conditions (Table 1, entries 1–9). Of particular note is the utility of our method for the preparation of fluorinated 4(3*H*)-quinazolinones from commercially available 2-bromoanilines. It is well known that fluorine-containing functional groups can drastically change both the biological and physical properties of organic molecules.[15] We were pleased to find

Table 1: Palladium-catalyzed carbonylative coupling of various amines with 2-bromoanilines, trimethyl orthoformate, and CO.[a]

Entry	Amine	Product	Yield [%][b]
1			92 70[c]
2			81
3			82
4			71
5			83
6			85
7			79
8			68
9			80
10			60[d]
11			71[d]
12			68[d]
13			67[d]
14			73[d]
15			69[d]
16			84[d]
17			80[d]

[a] 2-Bromoaniline (1 mmol), trimethyl orthoformate (2 mmol), amine (1.1 mmol), CO (10 bar), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 1,4-dioxane (2 mL), DIPEA (2 mmol), 100°C, 16 h. [b] Yields of isolated products. [c] 10 mmol scale. [d] NEt_3 (2 mmol), 120°C.

Table 2: Palladium-catalyzed carbonylative coupling of various 2-bromoanilines with trimethyl orthoformate, aniline, and CO.[a]

Entry	2-Bromoaniline	Product	Yield [%][b]
1			70
2			73
3			72
4			84
5			69
6			65
7			75
8			80
9			85

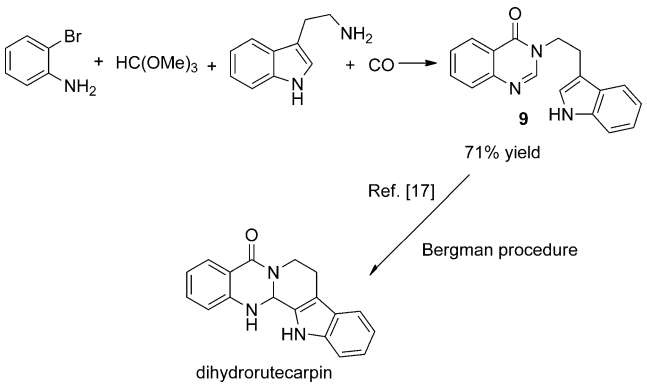
[a] 2-Bromoaniline (1 mmol), trimethyl orthoformate (2 mmol), aniline (1.1 mmol), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 1,4-dioxane (2 mL), DIPEA (2 mmol), 100°C, CO (10 bar), 16 h. [b] Yields of isolated products.

that all five 2-bromoanilines bearing fluoro, trifluoromethyl, and trifluoromethoxyl groups are suitable substrates for this procedure (65–84% yields of isolated products, entries 4–8). As a representative example of a heterocycle, 3-bromopyridin-2-amine can also be used as a substrate and resulted in the desired products in 85% yield. This result is remarkable, considering that the strong coordinating capability of such generally makes the reaction more difficult to proceed.

Besides trimethyl orthoformate, other *ortho* esters including trimethyl orthoacetate, trimethyl orthopropionate, and trimethyl orthobenzoate can also be used in the process. However, the yields of the corresponding 4(3*H*)-quinazolinones were around 15% under standard reaction conditions. The yields can be improved to 30–35% by using 2 equivalents of 2-bromoaniline.

Given the importance of the 4(3*H*)-quinazolinone nucleus in many natural products, we wanted to demonstrate the utility of this method 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.[16] By the present convergent synthetic approach, carbonylative coupling of 2-bromoaniline and trimethyl orthoformate with tryptamine under 10 bar of CO provides 3-[2-(3-indolyl)ethyl]-4(3*H*)-quinazolinone (**9**) in 71% yield (Scheme 3). The treatment of **9** with trifluoroacetic anhydride effected cyclization to (trifluoroacetyl)-13*b*,l4-dihydrorutaecarpin, which can be readily hydrolyzed to the desired dihydrorutaempine according to the Bergman procedure.[17]



Scheme 3. Palladium-catalyzed four-component carbonylative coupling reaction for the synthesis of dihydrorutecarpin.

In summary, we have developed a novel palladium-catalyzed four-component carbonylative coupling system for the selective construction of 4(3*H*)-quinazolinones in a one-pot fashion. The easy generation of molecular diversity along with the importance of 4(3*H*)-quinazolinones in medicinal chemistry makes the reaction described herein an appropriate alternative for the synthesis of potentially bioactive compounds. In this context, and considering the simplicity of the starting materials, the reaction is suitable for the synthesis of small libraries of functionalized 4(3*H*)-quinazolinones. Notably, this interesting procedure can be easily scaled up and its application in the synthesis of the bioactive dihydrorutaempine precursor was successful.

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