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VIP

A Convenient and General Palladium-Catalyzed Carbonylative Coupling for the Synthesis of 2-Arylbenzoxazinones

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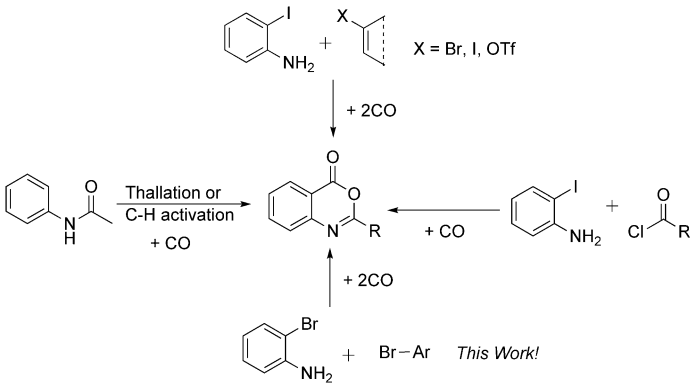
Benzoxazinones represent a class of annulated nitrogen heterocycles that are of interest to organic synthesis owing to their various biological activities.[1] Among the different methodologies developed for their preparation,[2] cyclization of anthranilic acid, *N*-acylanthranilic acid, or isotonic anhydride are most accepted.[3] Although alternative methodologies are known,[4] the availability of substrates and required reaction conditions limited their application so far.

Palladium-catalyzed carbonylation reactions allow for a general synthesis of all kinds of benzoic acid derivatives starting from easily available (hetero)aryl halides and inexpensive carbon monoxide.[5] Combining such carbonylative processes with subsequent intramolecular cyclization reactions permits an efficient access to different heterocycles.[6] In this respect, also few palladium-catalyzed carbonylative syntheses of benzoxazinones are known (Scheme 1).[7]

The first example consisting of a stoichiometric thallation and subsequent carbonylation of *N*-acetylaniline was reported by Larock and Fellows.[7a] Later on, Cacchi and co-workers published a general method for the carbonylative coupling of 2-iodoanilines with unsaturated halides or triflates.[7b,g] In addition, similar carbonylative coupling reactions of 2-iodoanilines with acid chlorides were developed by Alper and Petricci and their co-workers.[7c,d] More recently, interesting palladium-catalyzed carbonylative C–H activation of benzanilides and aryl urea derivatives were independently disclosed by Yu and co-workers,[7f] as well as Lloyd-Jones and Booker-Milburn and their co-workers.[7e] Despite these elegant achievements, it is still desirable to extend known protocols for benzoxazinone synthesis. Based on our ongoing interest in palladium-catalyzed carbonylation reactions,[8] we wish to present a new double carbonylation procedure, which allows for a general synthesis of 2-(hetero)arylbenzoxazinones starting from easy available 2-bromoanilines and (hetero)aryl bromides.



Scheme 1. Synthesis of benzoxazinones by means of Pd-catalyzed carbonylation sequences.

Initial experiments were carried out using the carbonylation of 2-bromoaniline and bromobenzene as a model reaction. Some years ago, we introduced Pd/diadamantylalkylphosphine catalysts for coupling reactions.[9] Recently, we have shown that the Pd/$BuPAd_2$ catalyst system is well suited for different carbonylations.[10] Hence, we tested this catalyst system in a model reaction at 100 °C in the presence of K_2CO_3 in various solvents (Table 1, entries 1–4). In all cases the desired 2-phenylbenzoxazinone (**2**) was formed; however, significant amounts of the aminocarbonylated intermediate **1** were observed as a side product. By simply increasing the temperature to 110 °C in NMP full conversion of bromobenzene and 69 % yield of product **2** was achieved (Table 1, entry 5). Notably, other polar solvents at this temperature still gave a mixture of **1** and **2** (Table 1, entries 6 and 7). Variation of ligands showed that other phosphine ligands such as PCy_3 and $P(tBu)_3$ were also successful in this reaction, but $BuPAd_2$ gave slightly better product yields (Table 1, entries 5 and 8–11). Finally, it was found that applying toluene in the presence of organic amines as base gave the best yields (79–86 %; Table 1, entries 14–16). However, at lower catalyst loading again a mixture of starting materials and **1** and **2** was formed (Table 1, entry 17). Apparently, the key intermediate of this carbonylative sequence towards 2-phenylbenzoxazinone is *N*-(2-bromophenyl)benzamide (**1**). Indeed, further carbonylation of isolated **1** under the optimized conditions resulted in 92 % yield of the desired product **2** (Scheme 2).

Hence, the following mechanism is proposed for this new domino transformation (Scheme 3). The reaction starts with an initial oxidative addition of a Pd^0 species to bromobenzene to give the ligated phenylpalladium(II)bromide complex. Insertion of carbon monoxide leads to the respective

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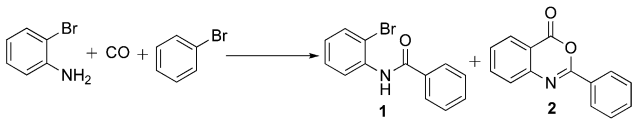
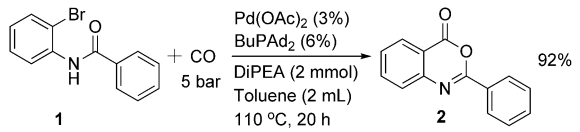
Table 1. Palladium-catalyzed carbonylative coupling of 2-bromoaniline and bromobenzene.[a]

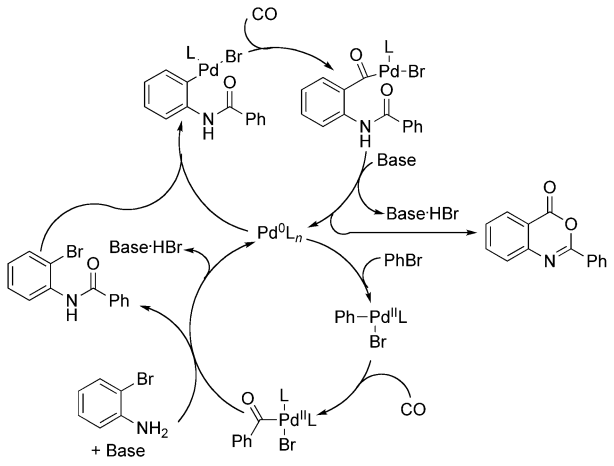


Entry	Ligand	Solvent	Base	T [°C]	Conv. [%][b]	Ratio **1**/**2**[b,c]
1	$BuPAd_2$	CH_3CN	K_2CO_3	100	66	33:67
2	$BuPAd_2$	dioxane	K_2CO_3	100	59	37:63
3	$BuPAd_2$	DMF	K_2CO_3	100	80	29:71
4	$BuPAd_2$	NMP	K_2CO_3	100	87	21:79
5	$BuPAd_2$	NMP	K_2CO_3	110	100	0:100 (69)
6	$BuPAd_2$	DMAc	K_2CO_3	110	100	25:75
7	$BuPAd_2$	DMSO	K_2CO_3	110	100	15:85
8	PPh_3	NMP	K_2CO_3	110	100	8:92
9	P(*o*-tol)$_3$	NMP	K_2CO_3	110	36	26:74
10	PCy_3	NMP	K_2CO_3	110	100	0:100 (63)
11	P(*t*Bu)$_3$	NMP	K_2CO_3	110	100	0:100 (55)
12	$BuPAd_2$	toluene	K_2CO_3	110	100	0:100 (75)
13	$BuPAd_2$	dioxane	K_2CO_3	110	68	18:82
14	$BuPAd_2$	toluene	NEt_3	110	100	0:100 (79)
15	$BuPAd_2$	toluene	DiPEA	110	100	0:100 (86)
16	$BuPAd_2$	toluene	TMEDA	110	100	0:100 (81)
17[d]	$BuPAd_2$	toluene	DiPEA	110	89	24:76

[a] $Pd(OAc)_2$ (6 mol%), ligand (12 mol%), solvent (2 mL), base (4 mmol), 2-bromoaniline (1.2 mmol), bromobenzene (1 mmol), CO (5 bar), 20 h (reaction time is not optimized). [b] Conversion and ratio of **1** and **2** were determined by GC using hexadecane as internal standard. [c] The data in parentheses shows isolated yields. [d] Use $Pd(OAc)_2$ (3 mol%), $BuPAd_2$ (6 mol%). DiPEA: *N*,*N*-diisopropylethylamine; TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.



Scheme 2. Palladium-catalyzed carbonylation of *N*-(2-bromophenyl)benzamide.

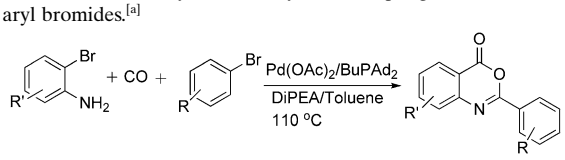


Scheme 3. Proposed mechanism for the carbonylative synthesis of 2-phenylbenzoxazinone.

acyl complex, which reacts immediately with the amino group of 2-bromoaniline to give *N*-(2-bromophenyl)benzamide. After this initial amino-carbonylation of bromobenzene, another oxidative addition of the active Pd^0 species to *N*-(2-bromophenyl)benzamide takes place, followed by CO insertion and intramolecular cyclization. Notably, the initial oxidative addition is highly chemoselective for bromobenzene due to the reactivity difference to the electron-rich 2-bromoaniline.

Next, other substrates were tested under the optimized reaction conditions. As shown in Table 2, *para*-, *meta*-, and *ortho*-bromotoluene as well as 2-bromonaphthalene did not differ significantly in reactivity and gave good yields of the corresponding products (Table 2, entries 2–5). *tert*-Butyl-, dimethylamino-, and methoxy-substituted electron-rich bromoarenes reacted smoothly with 2-bromoaniline under our standard conditions and resulted in 71–83% isolated yield (Table 2, entries 6–11). Besides, bromoarenes with electron-withdrawing substituents led to the corresponding 2-arylbenzoxazinones in 70–91% yield (Table 2, entries 12–14). Interestingly, *N*- and *S*-heterocyclic bromides gave the desired

Table 2. Palladium-catalyzed carbonylative coupling of 2-bromoanilines and aryl bromides.[a]



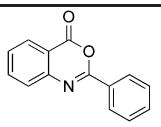
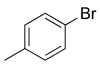
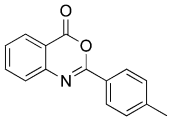
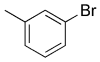
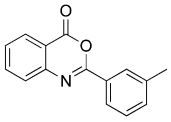
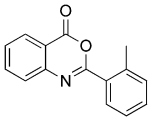
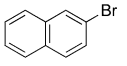
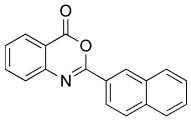
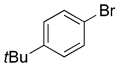
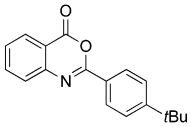
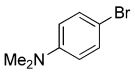
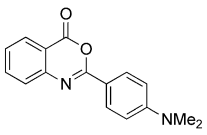
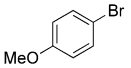
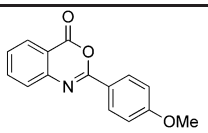
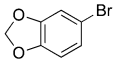
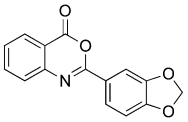
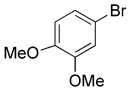
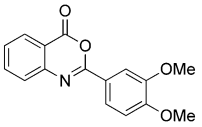
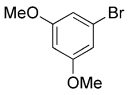
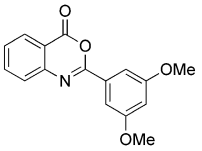
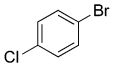
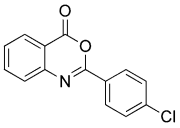
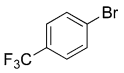
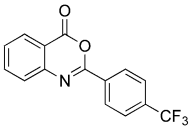
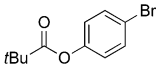
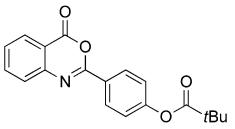
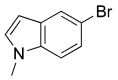
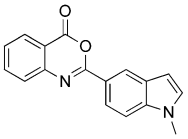
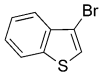
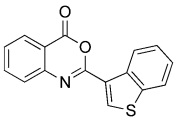
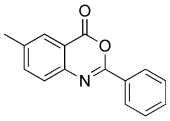
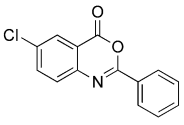
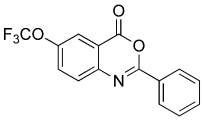
Entry	Aryl bromide	Product	Yield [%][b]
1			86
2			89
3			69
4			74
5			82
6			79
7			76

Table 2. (Continued)

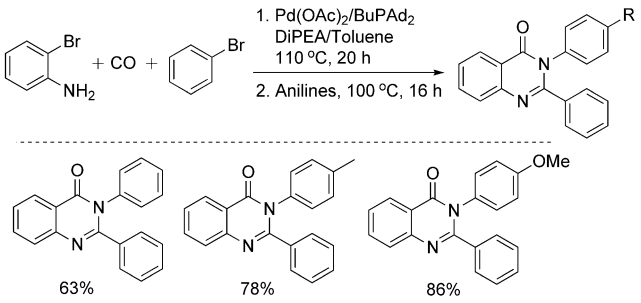
Entry	Aryl bromide	Product	Yield [%][b]
8			83
9			71
10			71
11			76
12			91
13			78
14			70
15			65
16			87
17			81
18			78
19			68

[a] $Pd(OAc)_2$ (6 mol%), $BuPAd_2$ (12 mol%), toluene (2 mL), DiPEA (4 mmol), 2-bromoanilines (1.2 mmol), aryl bromides (1 mmol), CO (5 bar), 110°C, 20 h (reaction time is not optimized). [b] Isolated yield.

products in good yields as well (Table 2, entries 15 and 16). Furthermore, three substituted 2-bromoanilines were used in this domino-transformation to also demonstrate the variability of this substrate (Table 2, entries 17–19). Unfortunately, using electron-deficient heterocyclic bromides and alkenyl bromides led to low selectivity and yields of the desired products (5–10%). In addition, we performed the reaction of phenyl triflate with 2-bromoaniline. In this case, under our standard conditions, decomposition of phenyl triflate occurred and carbonylative homocoupling of 2-bromoaniline to form dibenzo[*b*,*f*][1,5]diazocine-6,12(5*H*,11*H*)-dione was observed.

Finally, we demonstrated that our methodology can be easily extended to a one-pot synthesis of 2-arylquinazolinones (Scheme 4). It has been shown that arylquinazolines can be used as intermediates for the synthesis of other interesting heterocycles.[11] Indeed, completing our double carbonylation process and directly adding anilines under air gave 2-arylquinazolinones in good isolated yields after heating the reaction mixture for another 16 h at 100°C (63–86%).

In conclusion, a new domino synthesis of 2-arylbenzoxazinones has been developed. Starting from commercially available 2-bromoanilines and (hetero)aryl bromides 19 different benzoxazinones were produced in good yields (65–91%). Key step of this transformation is the chemoselective carbonylation of the aryl bromide. Moreover, a one-pot synthesis of 2,3-diarylquinazolinones was demonstrated exemplarily.



Scheme 4. A new one-pot synthesis of 2, 3-diarylquinazolinones.

Experimental Section

General procedure for the carbonylative synthesis of 2-arylbenzoxazinones: $Pd(OAc)_2$ (6 mol%) and $BuPAd_2$ (12 mol%) were transferred into a vial (12 mL reaction volume) equipped with a septum, a small cannula and a stirring bar. After the vial was purged with argon, bromobenzene (1 mmol), 2-bromoaniline (1.2 mmol), toluene (2 mL), DiPEA (4 mmol), and hexadecane (0.1 mL, internal GC standard) were injected into the vial by syringe. Then, the vial 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 5 bar was adjusted and the reaction was performed for 20 h at 110°C. After the reaction, the autoclave was cooled down to room temperature and the pressure was released carefully. Water (6 mL) was then added to the reaction mixture and the resulting solution was extracted with ethyl acetate 3–5×2–3 mL). The extracts

were evaporated adsorbed on silica gel and the crude product was purified by column chromatography using *n*-heptane and *n*-heptane/AcOEt (10:1) as eluent. The product was obtained as white solid (191 mg, 86% yield).

General procedure for the one-pot synthesis of 2,3-diarylquinazolinones: After the carbonylation reaction, the reaction mixture was cooled down to room temperature and the pressure was released carefully. Next, aniline (1 mmol) was added and the vial was moved to a 100 °C oil bath for another 16 h. After that time water (2 mL) was added to the reaction mixture and the organic layer was extracted with ethyl acetate (3–5×2 mL). The extracts were evaporated adsorbed on silica gel and the crude product was purified by column chromatography.

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