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Palladium-Catalyzed Synthesis of Phthalazinones: Efficient Carbonylative Coupling of 2-Bromobenzaldehydes and Hydrazines

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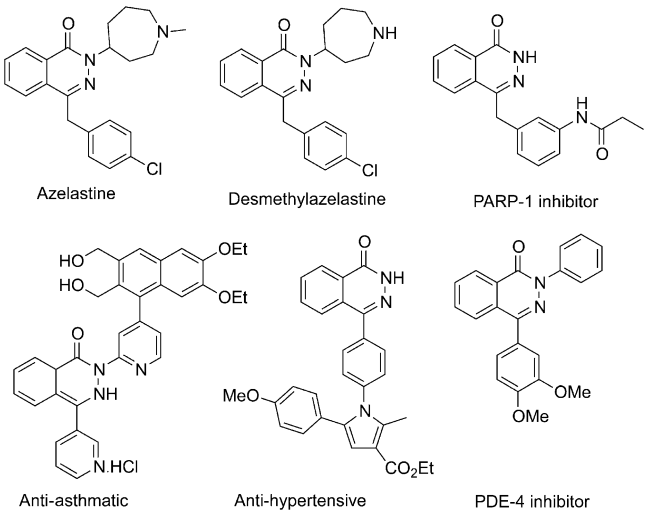
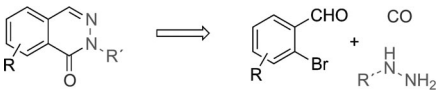
Phthalazinones constitute an interesting family of bioactive N-heterocycles.[1] Due to their diverse pharmacological activities, selected derivatives are used in the treatment of asthma, diabetes, hepatitis B, arrhythmia, and vascular hypertension. In addition, certain phthalazinones show antimicrobial activity and represent potent inhibitors of poly(-ADP-ribose)polymerase-1 (PARP-1). Selected examples of phthalazinone-based drugs and potential drug candidates are shown in Scheme 1.



Scheme 1. Selected examples of bioactive phthalazinones.

There is a continuing interest in the development of novel synthetic methodologies for the preparation of phthalazinones. More specifically, in the last decade various routes based on cyclocondensation reactions, cycloadditions, reductions, and even biotechnological approaches have been reported.[2] Despite these advances, there is still a need for original methodologies that avoid strongly basic or acidic reaction conditions and allow for an efficient assembly of the phthalazinone core from readily available starting materials. To fulfil this goal, we became interested in the idea of a domino sequence consisting of a palladium-catalyzed carbonylation of 2-halobenzaldehydes with hydrazines and a subsequent condensation reaction (Scheme 2). In such an approach, highly reactive *N*-(2-formylbenzoyl)hydrazones would be formed in situ.



Scheme 2. A new approach towards phthalazinones.

Clearly, palladium complexes have been shown to be powerful catalysts for many kinds of C–C coupling reaction.[3] Numerous applications have been reported for the synthesis of industrially relevant pharmaceuticals, agrochemicals, and advanced materials. Of the different kinds of palladium-catalyzed coupling reactions, carbonylation reactions allow for the straightforward synthesis of aromatic and heteroaromatic carboxylic acid derivatives.[4] By applying CO as an inexpensive C1 source with the assistance of a suitable palladium catalyst, one or even two molecules of CO can be introduced into the parent substrate. Interestingly, apart from common alkoxy-, hydroxyl-, and aminocarbonylation reactions, carbonylative coupling processes, such as Suzuki and Sonogashira carbonylations, are also possible. These methodologies give access to functionalized ketones that are ready for further synthetic modifications.

Based on our continuing interest in carbonylation reactions[5] and the importance of phthalazinones, we describe herein the first general and efficient palladium-catalyzed synthesis of phthalazinones from commercially available 2-bromobenzaldehydes, CO, and hydrazines.

The carbonylation of 2-bromobenzaldehyde with methylhydrazine was investigated as a model reaction in the presence of $Pd(OAc)_2$ and di-1-adamantyl-*n*-butylphosphine ($BuPAd_2$, CataCXium A). This catalyst system has proved to be generally useful for various carbonylations and related transformations. Initially, we reacted equimolar amounts of 2-bromobenzaldehyde with *N*-methylhydrazine in DMF under CO (5 bar) at 100 °C in the presence of different amines and inorganic bases (Table 1, entries 1–6). The best result (36 % of the desired product) was obtained by apply-

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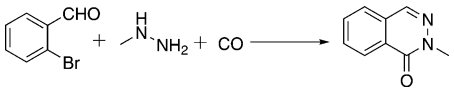
Table 1. Palladium-catalyzed carbonylative synthesis of *N*-methyl phthalazinone: Optimization of the model reaction.[a]



Entry	Ligand	Solvent	Base	Additive	Yield [%][b]
1	$BuPAd_2$	DMF	NEt_3[c]	–	0
2	$BuPAd_2$	DMF	TMEDA[d]	–	0
3	$BuPAd_2$	DMF	DiPEA[c]	–	2
4	$BuPAd_2$	DMF	DBU[d]	–	36
5	$BuPAd_2$	DMF	K_2CO_3[c]	–	7
6	$BuPAd_2$	DMF	K_3PO_4[d]	–	10
7	$BuPAd_2$	DMF	DBU[d]	–	21[e]
8	$BuPAd_2$	DMSO	DBU[d]	–	37[e]
9	$BuPAd_2$	NMP	DBU[d]	–	21[e]
10	$BuPAd_2$	dioxane	DBU[d]	–	18[e]
11	$BuPAd_2$	toluene	DBU[d]	–	24[e]
12	$BuPAd_2$	heptane	DBU[d]	–	9[e]
13	$BuPAd_2$	DMSO	DBU[d]	–	52
14	$BuPAd_2$	DMSO	DBU[d]	$MgSO_4$[d]	61
15	$BuPAd_2$	DMSO	DBU[d]	Na_2SO_4[d]	60
16	$BuPAd_2$	DMSO	DBU[d]	$MgSO_4$[c]	46
17	PPh_3	DMSO	DBU[d]	$MgSO_4$[d]	70
18	PCy_3	DMSO	DBU[d]	$MgSO_4$[d]	52
19	P(*o*-tolyl)$_3$	DMSO	DBU[d]	$MgSO_4$[d]	0
20	DPPF	DMSO	DBU[d]	$MgSO_4$[d]	82
21	D*t*BPF	DMSO	DBU[d]	$MgSO_4$[d]	48
22	XantPhos	DMSO	DBU[d]	$MgSO_4$[d]	74
23	DPEphos	DMSO	DBU[d]	$MgSO_4$[d]	76
24	BINAP	DMSO	DBU[d]	$MgSO_4$[d]	29
25	Diop	DMSO	DBU[d]	$MgSO_4$[d]	69
26	DPPB	DMSO	DBU[d]	$MgSO_4$[d]	63
27	DPPP	DMSO	DBU[d]	$MgSO_4$[d]	54
28	DPPE	DMSO	DBU[d]	$MgSO_4$[d]	66

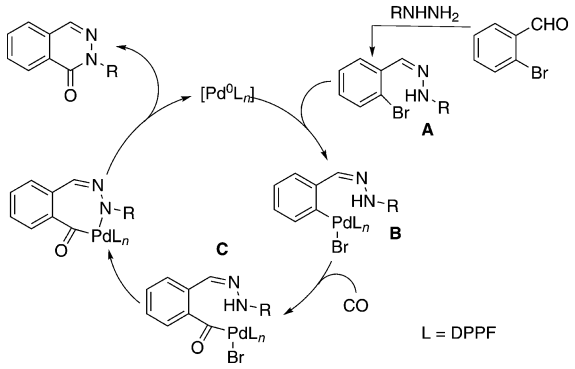
[a] $Pd(OAc)_2$ (2 mol%), ligand (6 mol% in the case of monodentate, and 2 mol% in the case of bidentate ligands), solvent (2 mL), base, 2-bromobenzaldehyde (1 mmol), methylhydrazine (1 mmol), CO (10 bar), 100°C, 16 h. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, DiPEA = *N*,*N*-diisopropylethylamine, NMP = *N*-methylpyrrolidinone, Cy = cyclohexyl, D*t*BPF = [1,1′-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II), BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, Diop = 2,3-*O*-isopropyliden-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, DPPB = 1,4-(diphenylphosphino)butane, DPPP = 1,3-bis(diphenylphosphino)propane, DPPE = 1,2-bis(diphenylphosphino)ethane. [b] GC yield, determined by GC using hexadecane as the internal standard, based on 2-bromobenzaldehyde. [c] 2 mmol of base or additive were added. [d] 1 mmol of base or additive was added. [e] 110°C.

ing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base (Table 1, entry 4). The investigation of six different solvents demonstrated that DMSO was optimal for this sequential carbonylation reaction and gave 52% of the product at 100°C (Table 1, entry 13).

To improve the condensation step in the domino sequence, $MgSO_4$ and Na_2SO_4 were tested as additives, and slightly improved yields of the corresponding phthalazinones were obtained (Table 1, entries 14 and 15; 60–61%). Notably, an excess of $MgSO_4$ decreased the product yield to only 46% (Table 1, entry 16).

Next, we explored the influence of 13 different mono- and bidentate phosphorus ligands (Table 1, entries 17–28). In general, electron-rich and bulky ligands resulted in low yields of the product. On the other hand, good yields between 74–82% of the *N*-methyl phthalazinone were observed by using 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos), bis(2-diphenylphosphinophenyl)ether (DPEphos), and 1,1-bis(diphenylphosphino)ferrocene (DPPF) as the ligand (Table 1, entries 20, 22–23). It should be noted that apart from the desired product, dehalogenation of 2-bromobenzaldehyde was observed in some cases, and resulted in the formation of 1-benzylidene-2-methylhydrazine.

Based on our experiments and other previously reported noncarbonylative cyclizations,[6] a possible reaction mechanism is proposed in Scheme 3. The reaction starts with the



Scheme 3. Proposed reaction mechanism.

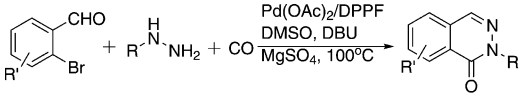
condensation of the hydrazine and the aldehyde group, at a lower temperature, to give **A**. Oxidative addition of the in situ generated active Pd^0 complex to **A** results in the arylpalladium complex **B**. After the coordination and insertion of carbon monoxide, the acylpalladium complex **C** is produced. Next, either nucleophilic substitution and reductive elimination or direct nucleophilic attack on the carbonyl group gives the terminal product and the active Pd^0 species for the next catalytic cycle.

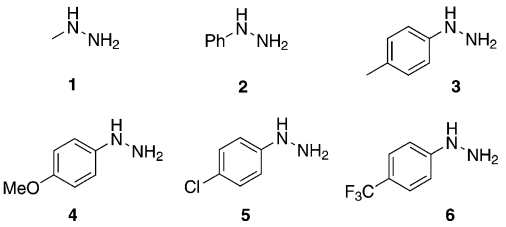
With suitable conditions for the model reaction in hand (Table 1, entry 20), a large variety of substrates was investigated for our protocol. As shown in Table 2, 20 examples of different phthalazinones were isolated in moderate to good yields (60–85%). In addition to simple alkylhydrazines (**1**), arylhydrazines with electron-donating and -withdrawing substituents (**2**–**6**) were successfully applied in the reaction with 2-bromobenzaldehyde to give 60–80% yields of the corresponding heterocycles (Table 2, entries 1–6).

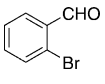
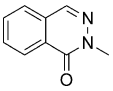
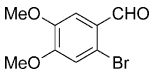
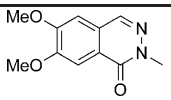
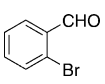
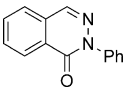
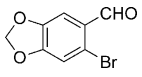
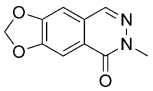
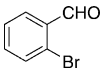
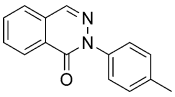
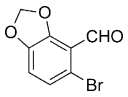
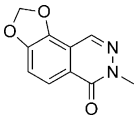
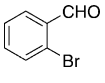
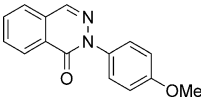
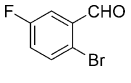
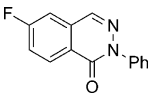
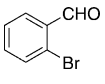
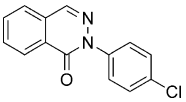
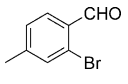
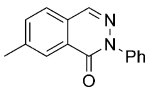
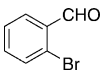
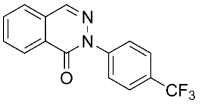
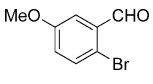
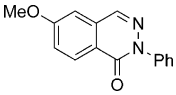
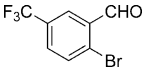
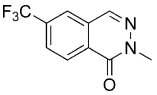
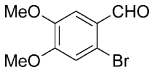
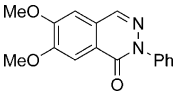
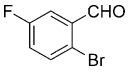
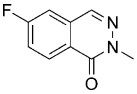
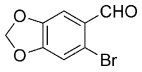
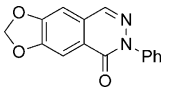
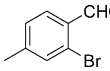
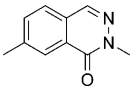
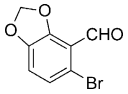
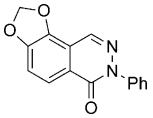
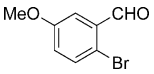
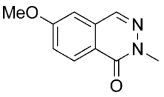
Moreover, the reaction tolerates 2-bromobenzaldehyde reagents with different electronic properties, and the corresponding phthalazinone products were isolated in good yields (Table 2, entries 7–19). Finally, we demonstrated that in addition to 2-bromobenzaldehydes, 2-bromoacetophenone can also be successfully applied in this methodology, and 2,4-dimethylphthalazinone was synthesized in 71% yield in a straightforward manner (Table 2, entry 20).

In conclusion, a general and straightforward methodology for the carbonylative synthesis of pharmacologically interesting phthalazinones has been established by using com-

Table 2. Palladium-catalyzed carbonylative synthesis of phthalazinones.[a]





Entry	Aryl halide	Hydrazine	Product	Yield [%][b]	Entry	Aryl halide	Hydrazine	Product	Yield [%][b]
1		**1**		80	11		**1**		80
2		**2**		67	12		**1**		82
3		**3**		65	13		**1**		85
4		**4**		60	14		**2**		75
5		**5**		71	15		**2**		79
6		**6**		73	16		**2**		81
7		**1**		69	17		**2**		82
8		**1**		74	18		**2**		78
9		**1**		70	19		**2**		85
10		**1**		75	20		**1**		71

[a] $Pd(OAc)_2$ (2 mol%), DPPF (2 mol%), DMSO (2 mL), DBU (1 mmol), 2-bromobenzaldehydes (1 mmol), hydrazine (1 mmol), CO (10 bar), $MgSO_4$ (1 mmol), 100 °C, 16 h. [b] Isolated yield.

mercially available palladium catalysts. Starting from readily accessible 2-bromobenzaldehydes or 2-bromoacetophenone and hydrazines, twenty different phthalazinones were synthesized in moderate to good isolated yields (60-85%).

Experimental Section

General procedure: A vial (12 mL) was charged with $Pd(OAc)_2$ (2 mol%), DPPF (2 mol%), $MgSO_4$ (1 mmol) and a stirring bar. Then DMSO (2 mL), 2-bromobenzaldehyde (1 mmol), methyl hydrazine (1 mmol), and DBU (1 mmol) were injected by syringe. The vial (or several vials) was (were) placed on an alloy plate and transferred into an autoclave (300 mL; 4560 series from Parr Instruments) under an argon atmosphere. After flushing the autoclave three times with CO and adjusting the pressure to 10 bar, the reaction was performed for 16 h at 100 °C. After this time, the autoclave was cooled to room temperature and the pressure was released carefully. The cooled mixture was partitioned between ethyl acetate and saturated NH_4Cl; the organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. After evaporation of the organic solvent, the residue was adsorbed on silica gel and purified by column chromatography using *n*-heptane/AcOEt (4:1) as the eluent.

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Keywords: carbonylation · heterocycles · hydrazines · palladium · phthalazinones

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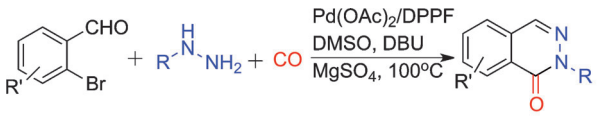

20 Examples
Up to 85% yield

Phthalazinones made easy! A new, straightforward methodology for the carbonylative synthesis of phthalazinones has been established. Starting from readily available 2-bromobenzaldehydes or 2-bromoacetophenone and hydrazines, a variety of phthalazinones have been produced in good isolated yields (see scheme).

Carbonylation