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A General Palladium-Catalyzed Carbonylative Synthesis of Chromenones from Salicylic Aldehydes and Benzyl Chlorides

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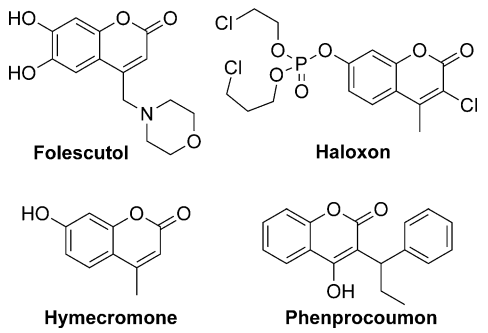
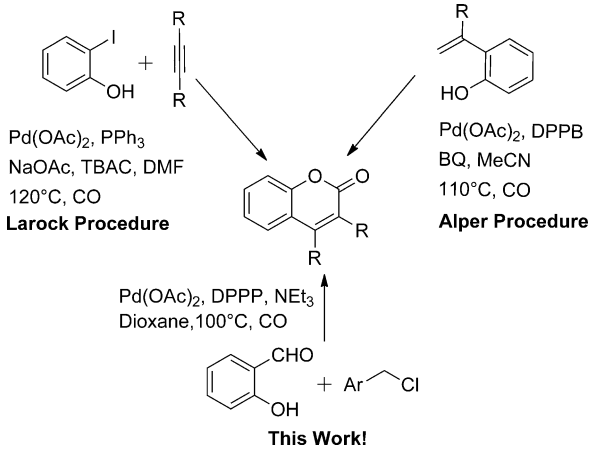
Chromenones (3-aryl-2*H*-chromen-2-one) is an important scaffold found in many natural products and synthetic drugs or drug candidates exhibiting a wide range of biological activities, including anticancer, antioxidant, and anti-HIV activities, as well as acting as enzymatic inhibitors (Scheme 1).[1] In addition, applications in the perfume industry and advanced materials have been described.[2] As a result, considerable synthetic effort has been aimed at their synthesis over the past few decades.[3] The most frequent routes to prepare chromenones include several named reactions, such as the Wittig, Perkin, Pechmann, and Knoevenagel-condensation reactions.[4]



Scheme 1. Selected examples of bioactive molecules.

Palladium-catalyzed carbonylative transformation of organohalides has already become a powerful tool in modern organic synthesis.[5] The advantages of carbonylation reactions are clear, and include 1) the fact that carbon monoxide (CO) can be used as a cheap C1 source; and 2) carbonyl-containing compounds can easily be prepared by introducing one or more CO molecules. Thus, the carbon chain of parent molecules can be readily lengthened, although the carbonylated compounds also have important applications in organic synthesis and advanced materials.

Heterocycle synthesis is one of the main branches in organic synthesis. Combining carbonylative transformations of organohalides with subsequent intramolecular cyclization reactions allows efficient access to interesting heterocycles.[6] Recently, we developed several methods for the carbonylative synthesis of heterocyclic compounds.[7] Furanones, benzoxazinones, flavones, and some other heterocycles were easily prepared from their parent molecules by installing one or even two molecules of carbon monoxide. Our interest in heterocycle synthesis prompted us to apply carbonylation to chromenone preparation. In the previous literature, Larock and Kadnikov reported a procedure starting from internal alkynes and 2-iodophenols[8] and Alper and co-workers developed the oxidative cyclocarbonylation of 2-vinylphenols (Scheme 2).[9] As our experience is with the carbonylation of benzyl chlorides and the study of coumarins,[10] we wish to report here a straightforward procedure for the carbonylation of salicylic aldehydes and benzyl chlorides to form coumarins. Notably, the substrates and chemicals applied herein are stable and commercially available, which highlights the synthetic importance of this method. Additionally, salicylic aldehydes are naturally occurring products



Scheme 2. Palladium-catalyzed carbonylative synthesis of coumarins (TBAC = tetrabutylammonium chloride, BQ = 1,4-benzoquinone).

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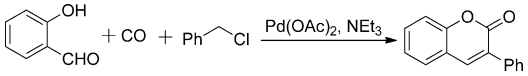
that can allow the avoidance of tedious pre-preparation in some cases.

Based on our experience of palladium-catalyzed carbonylation reactions, initial experiments were carried out with 2-hydroxybenzaldehyde and benzyl chloride as the model system. To our delight, by using $Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%), and NEt_3 (as the base) in DMSO (2 mL), under 10 bar of CO at 120°C, 61% of 3-phenyl-2*H*-chromen-2-one was produced after 16 h (Table 1, entry 1). The yield of the

Table 1. Palladium-catalyzed carbonylative reaction of salicylic aldehyde and benzyl chloride.[a]



Entry	Ligand ([mol%])	Solvent (2 mL)	*T* [°C]	Conversion [%][b]	Yield [%][b]
1	PPh_3 (4)	DMSO	120	100	61
2	DPPP (2)	DMSO	120	100	89
3	DPPP (2)	DMSO	100	100	85
4	DPPP (2)	dioxane	100	100	95 (86)[c]
5	DPPP (2)	DMF	100	100	79
6	DPPP (2)	toluene	100	100	88
7	DPPP (2)	dioxane	100	100	93[d]

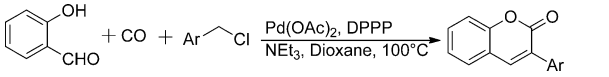
[a] Reaction conditions: salicylic aldehyde (1.0 mmol), benzyl chloride (1.1 mmol), $Pd(OAc)_2$ (2 mol%), ligand, solvent (2 mL), temperature, CO (10 bar), NEt_3 (2.0 mmol), 16 h. [b] Conversion and yield were determined by GC analysis based on salicylic aldehyde by using hexadecane as the internal standard. [c] Yield of the isolated product. [d] CO (5 bar). DPPP = 1,3-bis(diphenylphosphino)propane; DMSO = dimethyl sulfoxide; DMF = *N*,*N*-dimethylformamide.

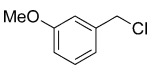
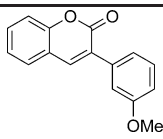
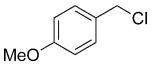
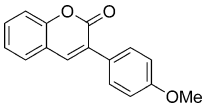
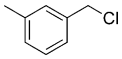
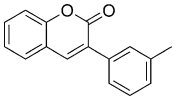
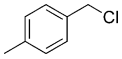
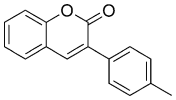
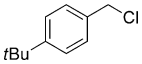
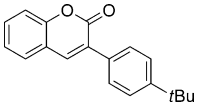
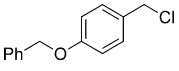
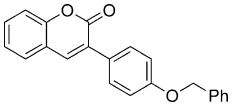
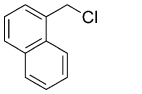
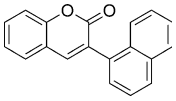
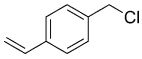
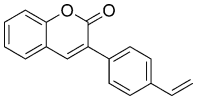
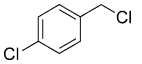
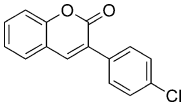
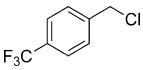
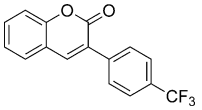
desired product can be further improved to 89% by using DPPP as the ligand (89% yield; Table 1, entry 2). Attempts to reduce the temperature were successful, and 85% yield of the coumarin was formed at 100°C (Table 1, entry 3). Of a variety of solvents, 1,4-dioxane was found to result in the best yield of 3-phenyl-2*H*-chromen-2-one, allowing the isolation of 86% yield of the product at 100°C (Table 1, entry 4). Remarkably, a good yield can also be achieved under a lower pressure (5 bar) of CO at 100°C.

With the best reaction conditions in hand (Table 1, entry 4), the generality and limitations of this palladium-catalyzed carbonylative synthesis of chromenones from salicylic aldehydes and benzyl chlorides was proven by use of 20 different substrates (Tables 2 and 3).

First, 2-hydroxybendaldehyde was used as the model substrate to test different types of benzyl chloride in the reaction. Good to excellent yields of the desired products were isolated for the reaction of benzyl chlorides substituted with electron-donating groups (69–99%; Table 2, entries 1–6). A 53% yield of 3-naphthyl-2*H*-chromen-2-one was produced from the corresponding starting materials (Table 2, entry 7). Interestingly, 4-vinyl substitution, which can cause problems due to self-polymerization, was tolerated and gave the desired product in a 30% yield under the same reaction conditions (Table 2, entry 8). Additionally, 71–76% yields of the corresponding chromenones were isolated when electron-

Table 2. Palladium-catalyzed carbonylative reaction of salicylic aldehyde with benzyl chlorides.[a]



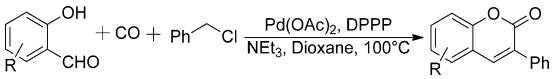
Entry	Benzyl chloride	Product	Yield [%][b]
1			87
2			71
3			83
4			99
5			79
6			69
7			53
8			30
9			76
10			71

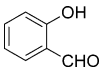
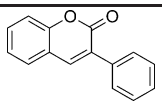
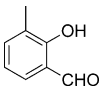
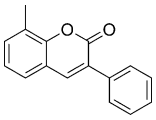
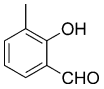
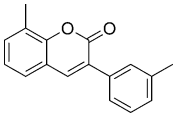
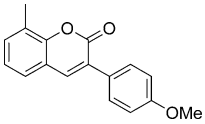
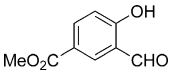
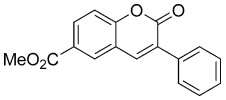
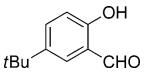
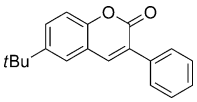
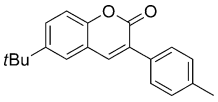
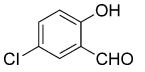
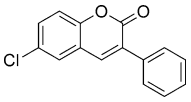
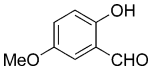
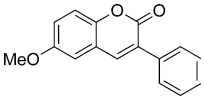
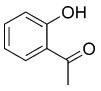
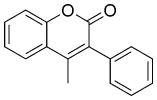
[a] Reaction conditions: salicylic aldehyde (1.0 mmol), benzyl chloride (1.1 mmol), $Pd(OAc)_2$ (2 mol%), DPPP (2 mol%), 1,4-dioxane (2 mL), 100°C, CO (10 bar), NEt_3 (2.0 mmol), 16 h. [b] Yields of the isolated product.

withdrawing substituents, such as 4-chloro, and 4-trifluoromethyl, were present in the benzyl chlorides (Table 2, entries 9 and 10).

Various substituted salicylic aldehydes were also tested in the reaction. In general, good to excellent yields of our target products were isolated without further optimization (44–95%; Table 3). Remarkably, 2-hydroxyacetophenone can be applied as a substrate and gave the desired product in a 44% yield without further optimization (Table 3, entry 10). In the case of nitro-substituted substrates (4-nitrobenzyl chloride and 5-nitrosalicylic aldehyde), none of the

Table 3. Palladium-catalyzed carbonylative reaction of salicylic aldehydes with benzyl chlorides.[a]

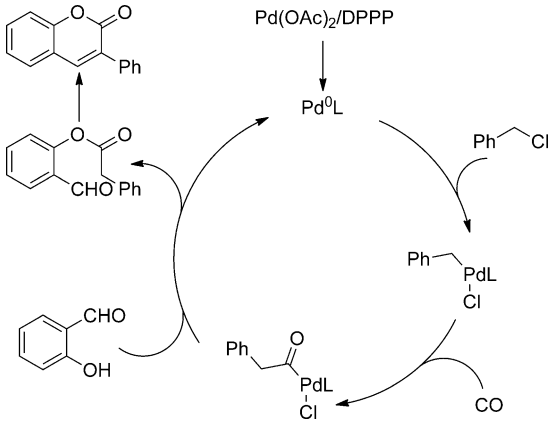


Entry	Salicylic aldehyde	Product	Yield [%][b]
1			86
2			75
3			80
4			75
5			66
6			70
7			69
8			95
9			54
10			44

[a] Reaction conditions: salicylic aldehyde (1.0 mmol), benzyl chloride (1.1 mmol), $Pd(OAc)_2$ (2 mol%), DPPP (2 mol%), 1,4-dioxane (2 mL), 100°C, CO (10 bar), NEt_3 (2.0 mmol), 16 h. [b] Yields of the isolated product.

desired products were produced; the reduction of the nitro functionality to the amine, followed by a self-polymerization reaction occurred instead.

Concerning the reaction pathway, we propose a probable reaction mechanism (Scheme 3). The reaction starts from Pd^0, which was reduced from Pd^{II} by the phosphine ligand. This was followed by the oxidative addition of benzyl chloride to Pd^0 to give the organopalladium species. After the coordination and insertion of CO, the key intermediate acylpalladium complex was formed. 2-Formylphenyl 2-phenylacetate was then eliminated after nucleophilic attack of the



Scheme 3. Proposed reaction mechanism.

salicylic aldehyde on the acylpalladium complex, which gave the terminal product after intramolecular condensation.[11] Pd^0 can be regenerated under the assistance of base and is then ready for the next catalytic cycle.

In conclusion, an interesting and straightforward procedure for the carbonylative synthesis of chromenones from readily available salicylic aldehydes and benzyl chlorides has been developed. Various coumarins were produced in good to excellent yields.

Experimental Section

Typical reaction procedure for the synthesis of 3-phenyl-2*H*-chromen-2-one: A vial (12 mL) was charged with $Pd(OAc)_2$ (2 mol%) and DPPP (2 mol%), and a stirring bar was added. Then, dioxane (2 mL), the salicylic aldehyde (1 mmol) and the benzyl chloride (1.1 mmol) were injected by syringe. The vial was placed in an alloy plate, which was transferred into an autoclave (300 mL) of the 4560 series from Parr Instruments under an argon atmosphere. After flushing the autoclave three times with CO, the pressure of CO was increased to 10 bar CO at ambient temperature. The reaction was performed for 16 h at 100°C. After the reaction finished, the autoclave was cooled to room temperature and the pressure was carefully released. The solution was extracted 3–5 times from an aqueous solution with ethyl acetate (2–3 mL). After evaporation of the organic solvent the residue was adsorbed on silica gel and the crude product was purified by column chromatography using *n*-heptane/AcOEt as the eluent.

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Keywords: benzyl chlorides · carbonylation · chromenones · palladium · salicylic aldehydes

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