A Novel Double Carbonylation Reaction of Aryl Halides: Selective Synthesis of 5-Arylfuranones

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Catalytic coupling reactions of aryl halides and related compounds allow for the straightforward functionalization of arenes and heteroarenes.^[1] Palladium complexes particularly have proved to be versatile catalysts in numerous academic developments as well as in the production of intermediates for pharmaceuticals, agrochemicals, and fine chemicals on an industrial scale.^[2] The significant impact of palladium-catalyzed coupling reactions on organic chemistry was acknowledged by the awarding of the Nobel Prize to Heck, Negishi, and Suzuki in 2010.^[3]

Among the known coupling processes, in the past decade three-component carbonylative coupling reactions have become increasingly popular, extending the potential of common two-component C-C bond forming processes.[4] These carbonylation reactions permit for efficient synthesis of (hetero)aromatic ketones and alkynones in addition to the well-known esters, amides, and acids from commonly available (hetero)aryl (pseudo)halides.[5-7] Moreover, the application of in situ generated CO in carbonylative coupling reactions has been described.^[8] In recent years, our group has developed novel carbonylative Heck-type coupling reactions. More specifically, aryl triflates and aryl halides were reacted with styrenes in the presence of carbon monoxide to give substituted chalcones in high yields (Scheme 1).^[9] This approach was successfully extended to the carbonylative coupling of aryl bromides with vinylethers to yield the corresponding 3-alkoxy-alkenones.^[10]

Based on that work, we investigated the reactivity of nonfunctionalized terminal alkenes in that system. To our surprise, significant amounts of products incorporating two CO molecules were observed. Isolation and NMR investigations proved the formation of 5-arylfuranones.

Furanones, also referred to as α,β -unsaturated butenolides, constitute a structural motif shared by many biologically interesting natural compounds that show antileukemic,^[11] antimalarial,^[12] antitumor^[13] or anti-inflammatory^[14] properties. Although 4,5-dialkyl-substituted furanones are advanced intermediates on the way to naturally occurring



Scheme 1. (Double) carbonylative Heck reaction.

 γ -lactones with fragrance properties, like Whisky lactone and Cognac lactone,^[15] the synthesis of 4-alkyl-5-aryl-substituted furanones has barely been described.^[16] So far, selected 5-aryl furanones have been synthesized by selenium-catalyzed cyclization of styrylacetic acid^[17] or intramolecular metathesis procedures.^[18] Unfortunately, these methods are limited owing to their demand for very specific starting materials that have to be prepared through multistep procedures in most cases. Hence, no general protocol for the synthesis of 5-aryl furanones has been reported to date.

Considering the availability of both aryl halides as well as terminal alkenes, we believe that a direct synthesis of furanones from (hetero)aryl halides and alkenes in the presence of carbon monoxide would represent a valuable extension of the known procedures, especially if it is carried out in a regioselective manner. Thus, we set out to develop a general methodology for this type of reaction.

Initially, we reacted three different aryl (pseudo)halide compounds with 1-octene in the presence of CO, palladium catalyst, and base. In general, four different coupling products are observed in considerable amounts (Scheme 2 and Scheme 3). The use of phenyl triflate (PhOTf) as the starting material exclusively led to the formation of α,β -unsaturated ketones **1** and **2** with the linear *trans* product as the major product. Starting from iodobenzene, the mono- and dicarbonylated products were formed. Interestingly, concerning the formation of α,β -unsaturated ketones, the opposite selectivity compared to the use of PhOTf was observed: Branched product **2** was formed in excess of **1**. In addition, furanones **3** and **4** were formed by incorporating a second CO molecule. Notably, the 4-alkyl-5-aryl-substituted furanone **4** was formed preferentially compared to **3**. The use of



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Scheme 2. Carbonylative Heck coupling of PhOTf, PhI, and PhBr. General reaction conditions: PhX (1 mmol), 1-octene (6 mmol), $PdBr_2$ (3.3 mol%), ligand (8 mol%, 4 mol% in the case of DPPP), NEt₃ (2 mmol), MeCN (0.5 mL), CO (15 bar), N₂ (65 bar), 120 °C, 20 h. The ratios were determined by GC. Yield of **4** were determined by GC with hexadecane as an internal standard. DPPP=1,3-bis(diphenylphosphino)-propane, Tf=trifluoromethanesulfonyl.



Scheme 3. Proposed mechanism for the Pd-catalyzed double carbonylative coupling of bromobenzene with 1-octene. Cy=cyclohexyl.

bromobenzene as the starting material led to a remarkable selectivity towards the furanone 4, resulting in 59% yield. In the last case, only low amounts of the monocarbonylation product 2 were detected by GC, and only traces of compounds 1 and 3 were formed.

In most of the reactions, benzaldehyde and diethylbenzamide were detected as side products, which accounts for the differences between conversion and yield. Attempts to influence the selectivity of the carbonylative coupling of iodobenzene by adding bromide salts were not successful at this point. Owing to the good selectivity towards the formation of 4-*n*-hexyl-5-phenylfuran-2(5H)-one (4), we chose the carbonylative coupling of bromobenzene with 1-octene as a model system for further investigations.

As shown in Scheme 3, the unusual formation of 4 is explained by the following proposed mechanism: upon the well-known oxidative addition of the aryl halide and insertion of carbon monoxide, an acyl palladium species is formed. Then, coordination and insertion of 1-octene on the acyl palladium center would take place. Surprisingly, in the case of bromobenzene, the palladium intermediate with the branched alkyl chain is generated. Apparently, a second CO insertion is faster than the typical β -hydride elimination. We explain this fact by intramolecular coordination of the car-

bonyl group or the respective enolate, a binding mode that prevents β -hydride elimination. Finally, an intramolecular attack of the easily produced enolate leads to the product **4** with concomitant generation of the active palladium(0) complex, which finishes the catalytic cycle. Attempts to react the monocarbonylated α , β -unsaturated ketones **1** and **2** under the same reaction conditions showed no conversion. Thus a two-step reaction that includes the transient formation of **1** or **2** seems unlikely.

Using the reaction conditions optimized for the carbonylative coupling of vinylethers as a basis,^[10] the influence of the CO pressure was studied. Increasing the CO pressure from 5 to 20 bar led to an increase in the yield from 28 to 47% (Table 1, entries 1–3). According to previous observations of carbonylative Heck-type reactions, organic bases other than NEt₃ (for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazobicyclo[2.2.2]octane (DABCO), and 4-dimethylaminopyridine (DMAP)) promoted the reaction with significantly lower yields of **4**, while inorganic bases (such as, K_2CO_3 and NaOAc) did not enable any product

Table 1. Optimization of the model reaction.^[a]



[a] General reaction conditions: bromobenzene (1 mmol), 1-octene (6 mmol), PdBr₂ (3.3 mol%), ligand (8 mol%), NEt₃ (2 mmol), solvent (0.5 mL), 120 °C, 20 h. [b] Conversion and yield were determined by GC with hexadecane as the internal standard. [c] PdBr₂ (5 mol%), **L1** (10 mol%), NEt₃ (1.5 mmol), MeCN (1 mL), 140 °C, 20 h. Ad=1-ada-mantyl.

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formation. Changing the solvent did not give any improvement; indeed, using dioxane and 1,2-dimethoxyethane (DME) gave slightly worse yields of 31 and 38%, respectively (Table 1, entries 4, 8). Toluene, DMF, and N-methylpyrrolidone (NMP) decreased the selectivity; this resulted in low yields of the desired products (Table 1, entries 5-7). In the latter cases, significant amounts of N,N-diethylbenzamide, benzoic acid anhydride, and benzaldehyde were detected. With acetonitrile as the solvent, the influence of different phosphine ligands was tested in the model system. The use of simple triphenylphosphine did not generate an active catalyst, thus giving poor conversion and yield (Table 1, entry 9). As tricyclohexylphosphine enabled 54% conversion and 16% yield (Table 1, entry 10), we subsequently investigated the use of dicyclohexyl-substituted pyrrole-based cataCXium P ligands.

The observed result was a consistent increase in the yield with increasing steric demand of the ligand. When cataCXium PCy (L2) was used, a yield of 23 % was obtained, however, use of the more bulky cataCXium PInCy (L3) and the *ortho*-methoxy substituted cataCXium POMeCy (L1) gave yields of 42 % and 47 %, respectively (Table 1, entries 3, 11, 12). For comparison, the structurally similar cataCXium PIntB (L4) as well as the imidazole-based ligands L5 and L6 were applied in the model system, but they were not competitive (Table 1, entries 13–15).

However, using **L1** and further raising the CO pressure stepwise from 20 to 80 bar enhanced the yield of product to 72% (Table 1, entries 3, 16, 17). Several palladium precursors besides PdBr₂ promoted the reaction similarly well, even though the use of bases was limited to NEt₃ (for details, see the Supporting Information). Finally, the optimum reaction conditions of 5 mol% of PdBr₂, 10 mol% **L1**, 1 mL solvent, and 1.5 equivalents of base were found to form the product in 79% yield (Table 1, entry 18).

Having the optimal reaction conditions in hand, we turned our focus to the scope and limitations of the system (Table 2). Notably, even though the product was formed with high selectivity, distinct tailing during purification (flash chromatography) caused irregular difficulties in the

Table 2. Pd-catalyzed double carbonylative coupling of aryl bromides with 1-octene.^{[a]} \\



Entry	ArBr	Product	Yield [%] ^{[b}
3	Me Br	Me Me	76
4	Me Br	Me O-C nHex	60
5	tBu Br	Bu nHex	71
6	MeO	MeO	55
7	MeO OMe	MeO Hex	77
8	F	F Hex	83
9	Br	0-C nHex	78
10	S Br	S	45 ^[c]
11	Br S	SC	39 ^[c]
12	O Br	o - C - Hex	87
13	N Me	Ne O-C nHex	62

[a] General reaction conditions: bromobenzene (1 mmol), 1-octene (6 mmol), PdBr₂ (5 mol%), L1 (10 mol%), NEt₃ (1.5 mmol), MeCN (1 mL), 140 °C, 20 h. [b] Yield was determined by GC with hexadecane as the internal standard, average of two runs, for isolated yields see the Supporting Information. [c] Yields of isolated products.

quantitative isolation of the pure product. Thus, all compounds were also calibrated by GC after isolation (see the Supporting Information).

As in the model reaction with bromobenzene (79% yield), 2-, 3-, and 4-bromotoluene were converted into the

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corresponding 4-*n*-hexyl-5-tolylfuran-2(5*H*)-ones in good yields (60–76% Table 2, entries 1–4). Other bromobenzenes with electron-donating substituents, such as a *tert*-butyl group in the *para* position or a methoxy group in the *para* or *meta* positions, led to the desired products in 55–77% yield (Table 2, entries 5–7). The carbonylative coupling of 4-fluorobromobenzene also proceeded smoothly and gave the furanone in a good yield of 83% (Table 2, entry 8). Unfortunately, aryl bromides bearing stronger electron-withdrawing groups (4-bromoacetophenone, 4-bromoacetaldehyde, and 4-bromobenzonitrile) led only to traces of the corresponding products. Exemplarily for a bicyclic compound, 2-bromonaphthalene was transformed in 78% yield into the desired product (Table 2, entry 9).

To our delight also, heterocyclic compounds such as 3-bromothiophene and 3- bromothionaphthene can be applied on a preparative scale (Table 2, entries 10–11). In addition, benzodioxole and indole derivatives were tolerated, leading to synthetically interesting heterocyclic building blocks with up to 87 % yield (Table 2, entries 12 and 13).

Next, we examined the possibility of using different terminal alkenes as coupling partners. The slight decrease in yield that results from changing the alkene from 1-octene to the very similar 1-hexene is explained by the lower boiling point of 1-hexene, which causes a loss of substrate from the reaction vials in the parallel autoclave (Scheme 4). Use of the



Scheme 4. Pd-catalyzed double carbonylative coupling of bromobenzene with terminal alkenes. General reaction conditions: bromobenzene (1 mmol), alkene (6 mmol), $PdBr_2$ (5 mol%), **L1** (10 mol%), NEt_3 (1.5 mmol), MeCN (1 mL), 140°C, 20 h; yield was determined by GC with hexadecane as the internal standard, average of two runs, for isolated yields see the Supporting Information. [a] Yields of isolated products. [b] GC yield with iodobenzene as starting material, 100°C, 20 h.

more bulky vinylcyclohexane resulted in 54% yield. In the case of 4-phenyl-1-butene, the corresponding product was isolated in 28% yield and elevated amounts of the isomeric form (3-alkyl-5-aryl-substituted furanone) were observed. Moreover, triethylvinylsilane was converted into the corresponding furanone with a good yield of 73%.

Finally, we demonstrated that it is also possible to use aryl iodides for this novel transformation. By simply lowering the reaction temperature to 100 °C, iodobenzene can be converted into the corresponding furanone in 68% yield (Table 3, entry 1). In general, reactivity similar to the aryl Table 3. Pd-catalyzed double carbonylative coupling of aryl iodides with 1-octene. $^{\left[n\right] }$



[a] General reaction conditions: iodobenzene (1 mmol), 1-octene (6 mmol), PdBr₂ (5 mol%), L1 (10 mol%), NEt₃ (1.5 mmol), MeCN (1 mL), 100 °C, 20 h. [b] Yield was determined by GC with hexadecane as the internal standard, average of two runs, for yields of isolated products see the Supporting Information.

bromides was observed. Hence, the use of iodotoluenes resulted in 49–67% product yield, while use of 4-iodoanisole and 4-iodofluorobenzene gave enhanced yields of 72 and 87% (Table 3, entries 5–6).

In conclusion, we have developed a selective synthesis of 4-arylfuranones from aryl halides, CO, and terminal alkenes. Advantageously, when compared to previously known syntheses of this class of compounds, our procedure is based on the atom-efficient incorporation of two molecules of carbon monoxide into the desired products. A total of 18 different 4-arylfuranones were synthesized in up to 87% yield in a straightforward manner and with high regioselectivity.

Experimental Section

General procedure for the preparation of 4-hexyl-5-phenylfuran-2(5*H*)one: Six 4-mL glass vials were charged with $PdBr_2$ (5 mol%, 8.8 mg), CataCXium POMeCy (10 mol%, 37.0 mg), and a stirring bar. All vials were put into an alloy plate, equipped with a septum and an inlet needle and then flushed with argon. Acetonitrile (1 mL), NEt₃ (1.5 mmol, 208 µL), bromobenzene (1 mmol, 105 µL), and 1-octene (6 mmol, 943 μ L) were injected into each vial. The alloy plate with the six vials was then placed in a 300 mL autoclave (Parr Instruments, 4560 series). At RT the autoclave was flushed with CO and pressurized with CO to 80 bar. Afterwards the autoclave was heated to 140 °C for 20 h, then cooled to RT and the remaining CO was released slowly. After discharging, 2 mL of brine were added to the reaction mixture and the product was extracted with ethyl acetate. The aqueous phase was extracted another three times. After drying the combined organic phases over magnesium sulfate and evaporating the solvent, the crude product was purified by flash chromatography using *n*-heptane/ethyl acetate (6:1) to give 4*n*-hexyl-5-phenylfuran-2(5*H*)-one as a yellow oil.

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