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Zn-Mediated Reduction of Oxalyl Chloride Forming CO and Its Application in Carbonylation Reactions

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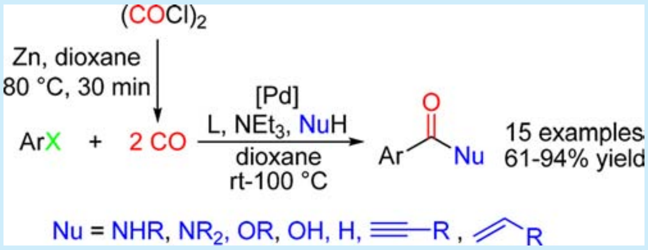
Ⓢ *Supporting Information*

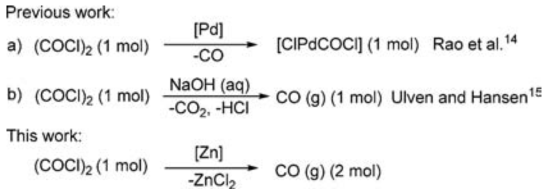
ABSTRACT: An efficient protocol for the generation of carbon monoxide by Zn-mediated reduction of oxalyl chloride has been developed. Oxalyl chloride was applied as an extremely effective substitute for toxic gaseous CO in the palladium-catalyzed alkoxy-/amino-/hydrogen-/hydroxycarbonylation processes providing industrially interesting esters, amides, aldehydes, and carboxylic acids in good to excellent yields. This new procedure can be applied to various carbonylation reactions in the presence of a transition metal catalyst under mild conditions and with a stoichiometric amount of CO source.



Chemistry for a sustainable future has become an important concept in contemporary organic chemistry. The development of modern synthetic methods focusing on reaction efficiency and the avoidance of waste generation are of particular relevance. Specifically, those methods commonly used in an industrial manner are at the center of systematic research. With regard to sustainability, methodologies based on domino reactions, including multicomponent reactions, belong to highly efficient strategies in synthetic organic chemistry.[1] Among them, carbonylation of aryl halides providing carboxylic acid derivatives are of relevant interest in the pharmaceutical and agrochemical industry.[2] In recent decades, increased attention has been paid to carbonylation reactions in which the toxic carbon monoxide gas is replaced by safer sources of CO.[3] Among new carbonylating reagents, the use of metal carbonyls such as $[Mo(CO)_6]$,[4] $[Cr(CO)_6]$,[5] $[W(CO)_5]$,[5,6] and $[Fe(CO)_5]$,[7] was reported. Further, several CO surrogates have been successfully introduced to carbonylation processes, namely tertiary acid chlorides[8] (9-methylfluorene-9-carbonyl chloride),[8a,b] pivaloyl chloride,[8a] silacarboxylic acids,[9] formic acid,[10] formates,[11] formamides,[12] and formaldehyde.[13] Each of these synthetic methods has its merits and offers exceptional and useful alternatives for the preparation of carbonyl compounds.

In 2010 Rao et al.[14] described the application of oxalyl chloride as a C1 synthon in Pd-catalyzed carbonylation of triarylbizmuth/indium species (Scheme 1a). Very recently, Hansen and Ulven[15] published the generation of carbon monoxide by the reaction of oxalyl chloride with an aqueous solution of NaOH (Scheme 1b). However, both methods utilize only 1 mol of carbon monoxide generated from oxalyl chloride and they usually require an excess of reagent/carbon monoxide (3.2–18 equiv) in carbonylation reactions.

Scheme 1. Methods for Generation of Carbon Monoxide from Oxalyl Chloride



In the course of our long-term program directed toward domino carbonylation transformations, we have recently developed a new protocol for Heck-type carbonylations based on the use of iron pentacarbonyl.[7] In this procedure, 25 mol % of $[Fe(CO)_5]$ represents an affordable and safe liquid supply of the carbonyl unit, fully replacing gaseous carbon monoxide. Continuing with the development of new processes, we herein report a new reaction system for Pd-catalyzed carbonylation of aryl halides. The highly reactive CO gas is generated by Zn-mediated reduction of the oxalyl chloride. This easily accessible CO surrogate can provide 2 mol of CO in an efficient manner. Moreover, *ex situ* generated carbon monoxide has been successfully applied in a number of Pd-promoted carbonylative reactions under mild reaction conditions in a newly developed two-chamber system. The carbonylation reactions using such a reagent are safe, easily feasible, and more efficient.

Inspired by the work of Rao,[14] we examined the reaction of a dioxane solution of oxalyl chloride with an electropositive metal such as Zn and Mg. In both cases, gas formation at temperatures above 60 °C was observed. To confirm the formation of carbon

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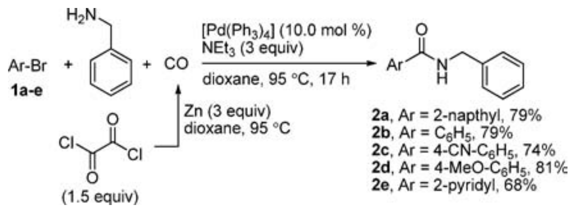
monoxide gas, we combined this experiment with Pd-catalyzed aminocarbonalytion of various aryl bromides (Scheme 2). The reactions were carried out under standard conditions[4g] with $Pd(PPh_3)_4$ (10.0 mol %), benzylamine (1.5 equiv), and NEt_3 (3 equiv) in dioxane at 95 °C. Thus, carbonylation using CO gas released from $(COCl)_2$ (1.5 equiv, 3 equiv of CO) and Zn powder (3 equiv) provided corresponding benzyl amides in good yields. These reactions were performed in two vials (screw top with solid green Melamine cap with PTFE liner) attached to each other with an HPLC tube (PTFE, 1/16 in. O.D. × 1/32 in. I.D.).

Scheme 2. Palladium-Catalyzed Aminocarbonylation of Aryl Bromides in Two-Vial System



With these promising initial results, we decided to perform extensive screening of the reaction conditions ($COCl_2$/Zn ratio, temperature, pressure, and required amount of CO for carbonylation reaction). First, we examined the influence of the ratio between the oxalyl chloride and activated Zn powder on the rate of the CO gas evolution. These experiments were carried out in an Ace pressure tube capped with a Michel–Miller Swagelok adapter connected to a pressure sensor. We monitored the time dependence of pressure in the reaction system at 80 °C until the pressure stabilized (Figure 1).

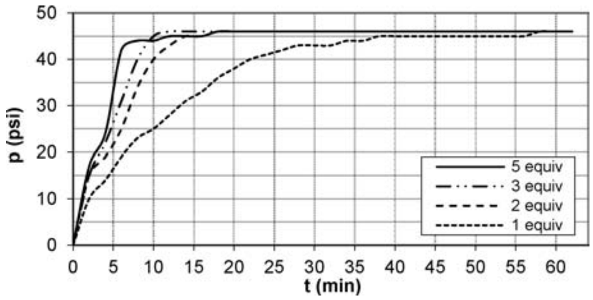


Figure 1. CO formation as a function of time using 1–5 equiv of Zn at 80 °C.

As shown in Figure 1, the optimal results were obtained by using 2 equiv of Zn powder with complete decomposition of $(COCl)_2$ in 15 min. Evidently, larger amounts of zinc supported faster evolution of carbon monoxide; however, the time difference was not so remarkable. Furthermore, we decided to examine the influence of reaction temperature on CO evolution. It has been found that the fastest decomposition (15 min) of oxalyl chloride using 2 equiv of Zn was achieved at 80 °C. Clearly, lower temperatures remarkably slowed down the development of CO gas (Figure 2). Having the optimal parameters for Zn-mediated decomposition of oxalyl chloride in hand, we then examined the amount of carbon monoxide required for the carbonylation reaction in terms of conversion.

For this purpose, we designed a new reaction system consisting of two vials (reaction and development chamber). This new system was constructed from two Ace pressure tubes capped with the Michel–Miller Swagelok adapters connected through a three-way valve (Figure 3; see Supporting Information).

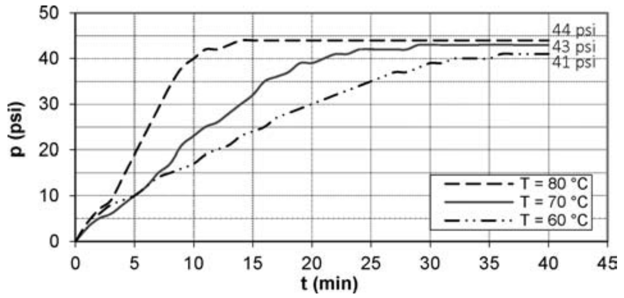


Figure 2. CO formation as a function of temperature using 2 equiv of Zn.

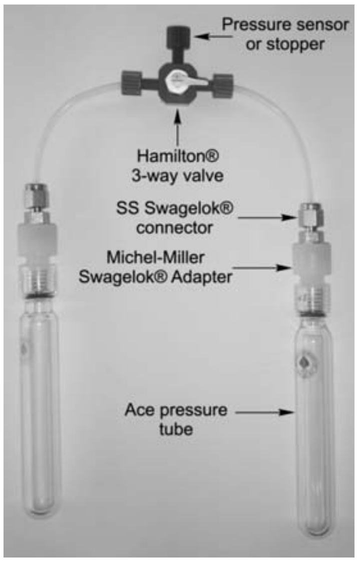
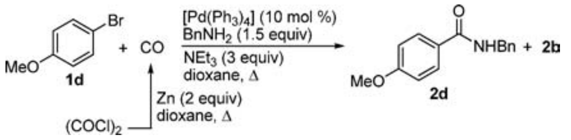


Figure 3. Two-chamber apparatus.

Thus, the model reaction of 4-bromoanisole and benzyl amine proceeded with good yields using 3 equiv of CO (1.5 equiv of oxalyl chloride) at 80 °C in 16 h (Table 1, entry 1). Unfortunately, reducing the quantity of the CO source to 2 or 1.5 equiv respectively (Table 1, entries 2, 3) led to decreased conversion of substrate, even after extended reaction time (Table 1, entry 4). Since common carbonylation reactions often require higher pressures of CO gas and higher reaction temperatures, we also explored the reactions at 100 °C (Table 1, entries 5 and 6). Although, the conversion of reaction has increased, the desired product **2d** was obtained in lower yield along with byproduct **2b**. Similar formation of this side product as a result of P–Ar/P–Ar′ exchange has also been reported in the literature.[16] In order to increase the pressure in the reaction chamber, we performed the reaction in the same apparatus at higher dilution, thereby reducing the dead volume (Table 1, entries 7–10). The best results were obtained at 100 °C and at higher pressures (Table 1, entries 9, 10). With such an experimental arrangement, we achieved full conversion to the desired product using only 2 equiv of CO in good yield (77%, Table 1, entry 10).

In the next stage of the process optimization, we looked at the effectiveness of the decomposition of the CO surrogate. The volume of CO gas during the decomposition of oxalyl chloride

Table 1. Palladium-Catalyzed Aminocarbonylation of 4-Bromoanisole[a]



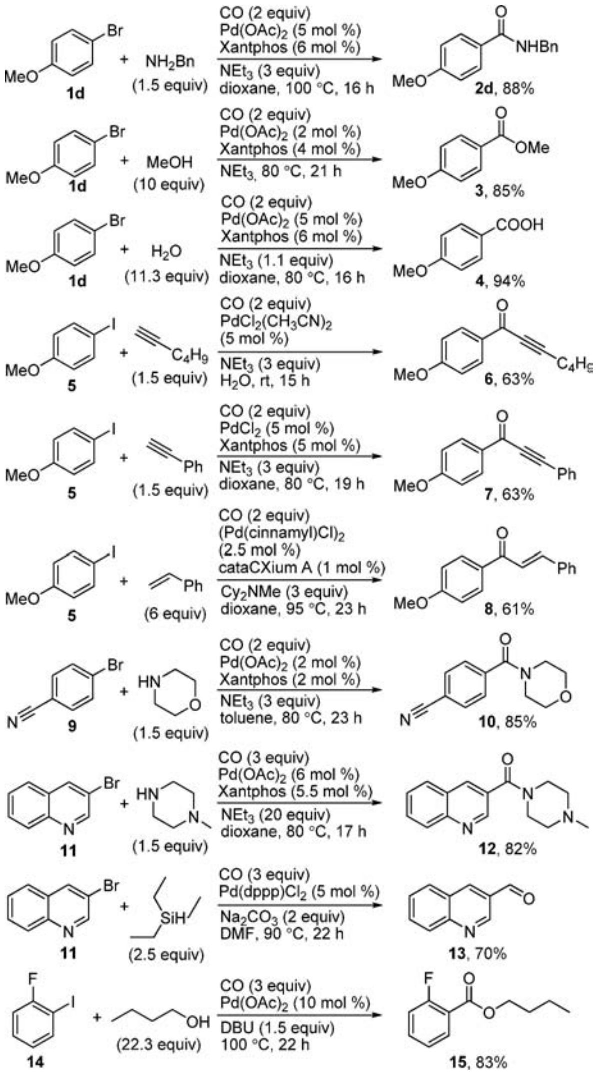
entry	CO (equiv)	dioxane[b] (mL)	conv[c] (%)	yield **2d**/**2b** (%)	react. time (h)/ temp (°C)
1	3	3.9/3.9	100	90/–	16/80
2	2	3.9/3.9	85	63/–	18/80
3	1.5	3.9/3.9	60	42/–	18/80
4	1.5	3.9/3.9	90	51/–	42/80
5	2	3.9/3.9	100	62/24	120/100
6	1.5	3.9/3.9	76	55/13	120/100
7	1.5	7.5/3.9	62	57/–	20/80
8	2	7.5/6.4	79	67/–	20/80
9	1.5	7.5/6.4	100	72/8	84/100
10	2	7.5/6.4	100	77/20	46/100

[a]Reactions were performed using 2 mmol of 4-bromoanisole, 10 mol % of $Pd(PPh_3)_4$, 1.5 equiv of $BnNH_2$, and 3 equiv of NEt_3. [b]Solvent in the development/reaction chamber. [c]Conversions were determined on the basis of isolated substrates.

was measured in a single vial connected to a measuring cylinder filled with water. Thus, the decomposition of $(COCl)_2$ (2 and 1.5 mmol) provided CO gas (62 and 42 mL) corresponding to 69% and 62% of theoretical volume, respectively. It should be noted that, in all previous experiments, the oxalyl chloride was applied directly from the cold bottle stored in a refrigerator using a micropipette. To avoid possible hydrolysis of the oxalyl chloride while handling, we decided to prepare a stock solution of distilled $(COCl)_2$ in dry dioxane (1:11).[17] The measured volume of evolved gas using the stock solution amounted to 86% efficiency, even when the reaction time of the decomposition was extended to 30 min. In addition to the greater efficiency of CO development, yet another advantage was the later start of $(COCl)_2$ decomposition, thereby preventing loss of CO gas in the application itself.

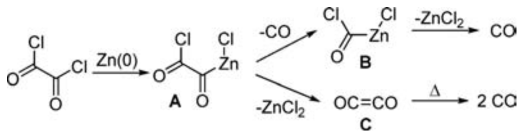
Having the optimized reaction conditions in hand,[18] we explored the scope of Pd-catalyzed reactions (Scheme 3). Accordingly, several carbonylation transformations of 4-haloanisole producing interesting pharmaceuticals were performed. All of the products were prepared using 2–3 equiv of CO evolved from the stock dioxane solution of $(COCl)_2$ (0.5–1 M) and Zn powder in a separated development chamber. In the first example, the reaction of 4-bromoanisole and benzyl-amine provided an inhibitor of stromelysin (MMP-3)[19] **2d** (88%, lit.[7a] 51%) and **2b** (9%). Methoxycarbonylation of **1d** very cleanly afforded methyl ester **3** in 85% isolated yield, using only 2 equiv of CO in contrast to the use of a large excess of CO described in the literature.[20] Similarly, 4-methoxycarboxylic acid **4**[21] was obtained in 94% yield using slightly modified literature conditions.[22] However, the first carbonylative Sonogashira coupling using bromo derivative **1d** with hex-1-yne and phenylacetylene provided corresponding products **6** and **7** only in poor 23% and 36% yield, respectively. Ketones **6** and **7**, intermediates of meridianins,[23] were then prepared from more reactive 4-iodoanisole **5** according to Skrydstrup's reaction conditions[9] in 63% yields. Heck carbonylative coupling of **5** with styrene afforded chalcone **8**[24] in 61% yield. Additionally, we tested the capability of the reaction system using less reactive aryl halides. As can be seen in Scheme 3, also substrates containing electron-withdrawing substituents (**9** and **14**) were capable of undergoing the reaction providing corresponding carboxylic acid derivatives **10** (85%) and **15** (83%, lit.[25] 76%), respectively. Next, the heterocyclic amide **12** was obtained in excellent yield from the 3-bromoquinoline. As the last example, the formylation of **11** with the tested CO surrogate in the presence of triethylsilane afforded aldehyde **13** in 70% yield (lit.[12a] 70%).

Scheme 3. Carbonylative Couplings Using $(COCl)_2$ as the CO Source



Based on these results, we proposed the mechanism of CO gas formation (Scheme 4). Initially, an intermediate **A** is formed by the oxidative addition of Zn(0) into the C–Cl bond of $(COCl)_2$. In the first pathway, intermediate **A** undergoes decarbonylation forming carbonyl species **B** which decomposes into $ZnCl_2$ and a CO molecule. In the second possible pathway, the elimination of $ZnCl_2$ forms heat-labile CO dimer **C**. According to the

Scheme 4. Mechanism of Zn-Mediated Reduction of $(COCl)_2$



literature,[26] LiCl could efficiently promote the insertion of Zn into the C−Cl bond and enhance the CO formation under milder conditions. Indeed, the evolution of gas using the suggested Zn/LiCl combination started at room temperature. However, the efficiency of gas evolution was greatly reduced even when the mixture was gradually heated to 95 °C.

In summary, we have developed a novel procedure for domino reactions including Pd-catalyzed carbonylation with *ex situ* generation of gaseous CO. The reported reactions proceeded in a simple two-chamber system with 1 equiv of CO surrogate. Reduction of oxalyl chloride with zinc powder resulted in 2 equiv of carbon monoxide being released. Moreover, a simple apparatus constructed from two pressure Ace tubes (rated to 150 psi, connected to each other and to a pressure sensor via a three-way valve) permitted flexible application with *ex situ* released CO gas under the specified pressure. Furthermore, the commercially available parts of this reaction apparatus can be easily modified to meet appropriate requirements for different reaction conditions. The applicability of the reported protocol was illustrated on a set of Pd-catalyzed carbonylative couplings of aryl halides providing industrially interesting products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02840.

Experimental procedures and characterization for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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