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Oxalyl Chloride as a Practical Carbon Monoxide Source for Carbonylation Reactions

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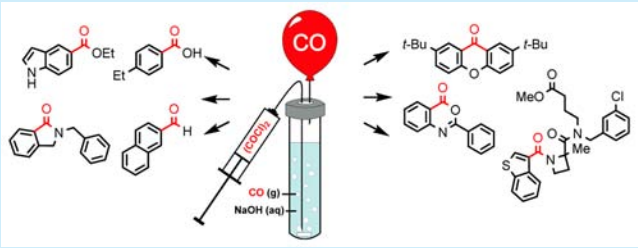
S *Supporting Information*

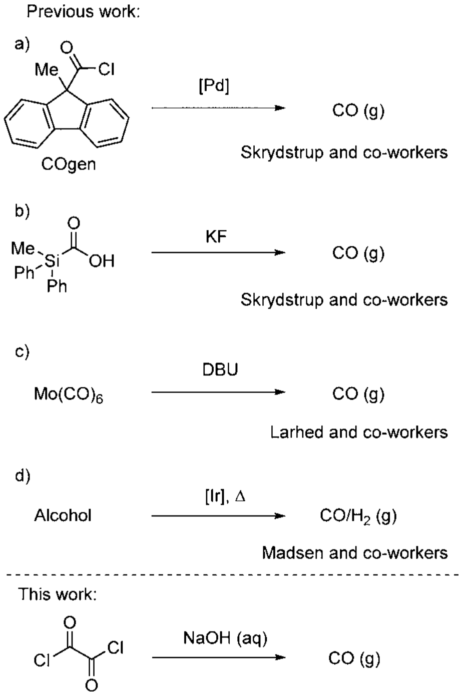
ABSTRACT: A method for generation of high-quality carbon monoxide by decomposition of oxalyl chloride in an aqueous hydroxide solution is described. The usefulness of the method is demonstrated in the synthesis of heterocycles and for hydroxy-, alkoxy-, amino-, and reductive carbonylation reactions, in several cases under milder conditions than previously reported.



Carbon monoxide (CO) is a carbonyl synthon of outstanding usefulness in organic synthesis. With ideal atom economy and low bulk price, the gas is extensively used in industrial production, e.g. in hydroformylation and the Monsanto and Cativa acetic acid processes.[1,2] A broad variety of metal-catalyzed carbonylation reactions have been developed, e.g. in heterocyclic synthesis, cross-coupling reactions, carbonylation of alkenes, alkynes and organometallic species, and carbonylative C−H activation, many of which are well suited for implementation with continuous flow synthesis.[3−14] Despite its established usefulness, synthetic use of CO is still relatively uncommon on laboratory-scale. The reason for this is no doubt related to its reputation as "the silent killer", since CO is a colorless, odorless, tasteless, and nonirritant gas that binds 210-fold more strongly to hemoglobin than oxygen.[15] For this reason, many laboratories, including ours, are reluctant to store and operate tanks of pressurized CO. Several methods have been developed to circumvent this safety issue, e.g. formation of CO gas by heat, acid, base, or metal catalyzed decomposition of formates or aldehydes, including *N*-formylsaccharin and paraformaldehyde, or release from metal carbonyl complexes such as $Mo(CO)_6$.[16−22] Most of these methods are based on in situ release of CO to avoid handling the gas. However, an inherent problem with this approach is compatibility issues with the chemicals and sometimes harsh conditions necessary to produce CO. To overcome these issues, Skrydstrup and co-workers developed a method for ex situ generation of CO using $Pd/P(tBu)_3$ catalyzed decomposition of 9-methylfluorene-9-carbonyl chloride (COgen) (Scheme 1a) in a two-chamber apparatus (COware).[23] An attractive feature of the method is accurate control of the amount of CO produced, and its usefulness has been demonstrated in a broad variation of applications.

Skrydstrup and co-workers have also described an alternative method for generating CO by reacting $MePh_2SiCO_2H$ with fluoride (Scheme 1b).[24] A two-chamber apparatus was used by Larhed and co-workers for carbonylation reactions using $Mo(CO)_6$ as the CO source (Scheme 1c).[25] A method for ex situ generation of syngas by dehydrogenative dehydroformylation of primary alcohols in a similar two-chamber system was recently described by Madsen and co-workers (Scheme 1d).[26] Although these technologies for ex situ CO generation represent considerable advantages for practical carbonylation

Scheme 1. Methods for ex Situ Generation of Carbon Monoxide or Syngas



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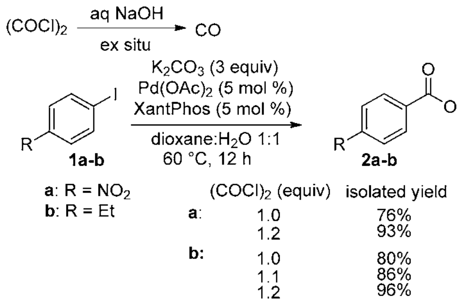
chemistry, drawbacks include high cost or laborious (re)-generation of CO precursors. It has long been known that oxalyl chloride reacts with water to produce CO, HCl, and CO_2.[27] We hypothesized that this reaction could serve as an inexpensive and convenient CO source in organic synthesis.[28] Herein, we demonstrate that decomposition of oxalyl chloride in an aqueous hydroxide solution at room temperature [eq 1] is a safe and convenient method for generation of stoichiometric amounts of high-quality CO gas for carbonylative reactions without the need for special equipment.

$$(COCl)_2 + 4NaOH \rightarrow Na_2CO_3 + 2NaCl + 2H_2O + CO(g) \qquad (1)$$

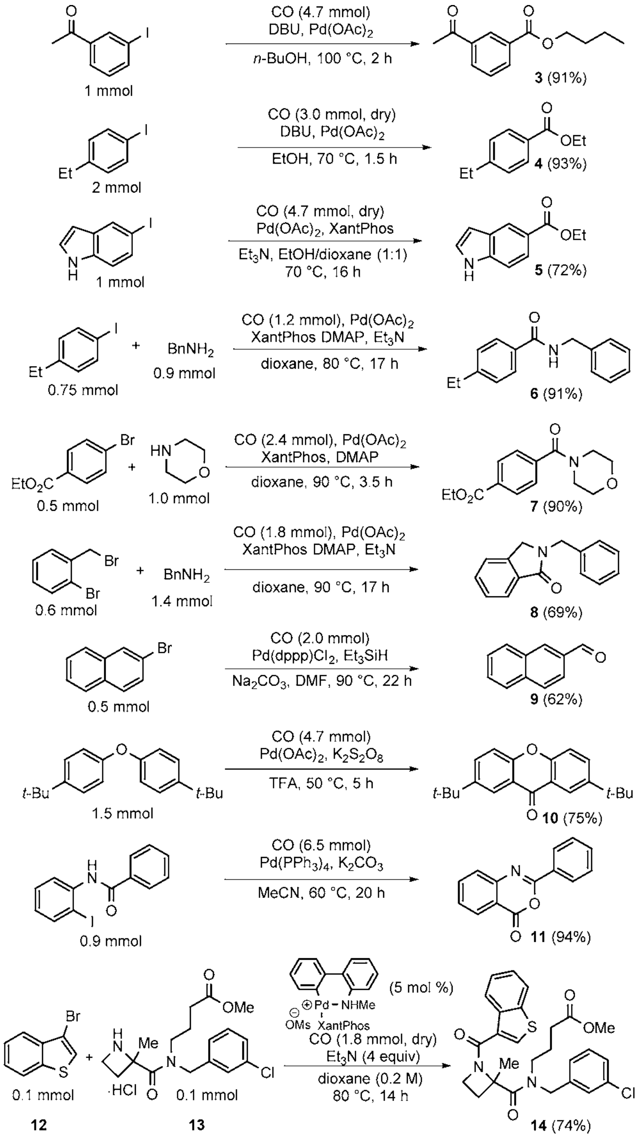
The HCl and CO_2 formed in stoichiometric amounts together with CO in the hydrolysis of oxalyl chloride can potentially interfere with many reactions. We assumed that reacting oxalyl chloride with an aqueous hydroxide solution would effectively quench both HCl and CO_2 but allow CO to escape due to its low aqueous solubility. To test this, capped vials containing aqueous NaOH (2 M) were equipped with deflated balloons and oxalyl chloride was either dripped to the top or slowly added at the bottom of the stirred solutions and the collected gas was tested with wet pH-indicator strips and lime solutions. Whereas gas from the first experiment was highly acidic, the gas collected after addition of oxalyl chloride to the bottom was free of both HCl and CO_2, suggesting efficient trapping of byproducts. The addition rate should be controlled, as the reaction is fast and exothermic. Although slow manual addition of oxalyl chloride is feasible, addition by syringe pump at a rate of 1 mL/h (producing 0.20 mmol CO per minute) is more convenient and results in gas formation at an appropriate rate.

Having established that HCl and CO_2 were effectively trapped in the NaOH solution, we next investigated if the evolved CO completely escaped into gas phase by determining the volume of the evolved gas. It was found that decomposition of 10.5 mmol oxalyl chloride led to evolution of 244.1 ± 1.5 mL gas, corresponding to 97% efficiency (see SI). To further probe the quality and stoichiometry of the CO gas, we set up carbonylation reactions in a gastight two-chamber system (COware[23]). Since CO is generated in aqueous solution and it is necessary to heat both chambers to the same temperature, a hydroxycarbonylation reaction was chosen, as vapor from the generation chamber was unlikely to influence the outcome. With 1.0−1.1 equiv of oxalyl chloride, small amounts of remaining starting materials were detected by HPLC analysis, while 1.2 equiv resulted in full conversion of the aryl iodides and isolation of **2a** and **2b** in 93% and 96% yields, respectively (Scheme 2). This indicates that CO generation is near-stoichiometric and that the efficiency is comparable to the best previous methods (Scheme 1).

Scheme 2. Efficiency of CO Release



Scheme 3. Carbonylation Reactions with CO (1 atm balloon) Generated Ex Situ from Oxalyl Chloride



Practical inconveniences with the two-chamber system, such as vapor from the generation chamber, the need to heat both chambers to the same temperature, and concerns related to operating a pressurized system, incited us to explore alternative reaction setups. We found collecting and transferring CO in balloons that did not have to leave the well-ventilated fume hood to be convenient and perfectly safe. CO gas generated by this method will be slightly wet due to the intrinsic vapor pressure of water. Whereas this did not appear to pose a significant problem in the reactions we tested (only three reactions in Scheme 3 were performed with dried CO), certain reactions may require dry gas. To investigate this and provide a solution, a specific amount of CO gas was collected in a balloon and bubbled through anhydrous THF. Using freshly prepared undried CO gas, the water content of the THF solution increased by almost 200 ppm (Table 1). We then investigated various drying agents. To keep the setup as simple as possible, these were packed between two layers of cotton in the syringe cylinder used as balloon socket (Figure S1, SI). Though

Table 1. Efficiency of Gas Drying Agents[a]

drying agent	water [ppm/mL THF][b]
none	196.4 (209.0)
Na_2SO_4	177.4 (193.2)
$MgSO_4$	170.8 (181.6)
KOH (pellets)	29.3 (40.8)
KOH (ground)	17.3 (26.8)
activated molecular sieves (MS) 3 Å	30.3 (39.8)
activated MS 3 Å (ground)	17.6 (28.6)
$CaCl_2$	12.6 (22.2)

[a] Water content in THF determined by Karl Fischer titration after bubbling 4.7 mmol of CO through 5 mL of anhydrous THF. [b] Corrected values, i.e. water content after letting CO through subtracted by water content before (measured values after CO are given in parentheses).

Na_2SO_4 and $MgSO_4$ proved unsuitable, KOH and activated molecular sieves were equally effective and their efficiency was improved further by grinding. Since $CaCl_2$ provided very dry gas and is easy to handle, this became the drying agent of choice and was used for the reactions performed with dry gas.

To explore the usefulness of the method, representative carbonylation reactions inspired by published chemistry were performed using balloons with CO generated ex situ from oxalyl chloride (Scheme 3). Several procedures for alkoxycarbonylation of aryl iodides using a Pd/DBU system have been reported, but all of these are conducted at high CO pressure (5−17 bar) and/or temperature (120−130 °C),[29−36] whereas $Pd(OAc)_2$ and dcpp have been demonstrated to be efficient with aryl chlorides at only 1 atm of CO.[37] We found that $Pd(OAc)_2$ and DBU in alcohol under 1 atm of CO at 70−100 °C gave the benzoate esters **3** and **4** in excellent yields. The ester **5** was obtained in good yield from the unprotected iodoindole using $Pd(OAc)_2$/XantPhos in dioxane/EtOH at 70 °C. Using similar catalytic systems,[38,39] aminocarbonylation of aryl bromides and iodides provided **6** and **7** in excellent yield. In the synthesis of **4** and **6**, CO from 1.5 equiv of oxalyl chloride was used and demonstrates excellent stoichiometric efficiency. For the other examples, a larger excess of CO was generated since this can be done at no extra cost and eliminates concerns regarding minor gas loss or complete emptying of the balloon. The direct synthesis of *N*-substituted isoindolinone **8** from *o*-bromobenzyl bromide has previously been conducted with $PdCl_2(PPh_3)_2$ in DMF at 100 °C under 13 atm of CO in 62% yield.[40] Using somewhat milder conditions, we obtained **8** in 69% yield. Using paraformaldehyde, $Pd(CH_3CN)_2Cl_2$, dppb, Et_3SiH, Na_2CO_3 in DMF at 100 °C under 20 bar of N_2, Beller and co-workers obtained **9** in 70% yield.[19] With 1 atm of CO and minor modifications of the conditions, we obtained **9** in 62% yield. Lei and co-workers described a double C−H activation of biaryl ethers to form xanthones, e.g. **10** in 92% yield, on a 0.2 mmol scale.[41] On a 7.5-fold larger scale, we obtained **10** in 75% yield. The synthesis of benzoxazin-4-one **11** proceeded in excellent yield using a published procedure and undried CO.[42] Being interested in a recently published FFA2 antagonist,[43] we decided to investigate aminocarbonylation with the inexpensive **12** using a balloon of CO and a recently described palladacycle precatalyst-based method.[44] Attempts to couple **12** with **13** at 45 °C for 14 h with 5 mol % of the precatalyst gave low conversion, in agreement with the reactivity reported for similar electron-rich heteroaryl bromides.[44] Gratifyingly, raising the temperature to 80 °C gave full conversion to **14** in an isolated yield of 74% without an excess of any reactant.

In conclusion, we have shown that oxalyl chloride is a practical ex situ CO source for carbonylation reactions. As decomposition is instantaneous, the rate of CO formation can be conveniently controlled by the addition rate of oxalyl chloride, a useful feature in reaction upscaling. For normal laboratory-scale synthesis, gas collection and transfer of the required amount by balloon is practical and safe, and a near-stoichiometric amount of high quality CO gas is obtained. Implementation of a $CaCl_2$ drying filter in the balloon socket produces completely dry gas. The method thus enables safe, facile, and inexpensive CO generation without the need for special equipment and should make the powerful carbonylation chemistry instantly accessible to any synthesis laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization, NMR spectra, and instructional video. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01252.

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Notes

The authors declare no competing financial interest.

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