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COtab: Expedient and Safe Setup for Pd-Catalyzed Carbonylation Chemistry

Hugo P. Collin,[†,§,▽] Wallace J. Reis,[†,∥,▽] Dennis U. Nielsen,[*,†] Anders T. Lindhardt,[⊥] Marcelo S. Valle,[§] Rossimiriam P. Freitas,[∥] and Troels Skrydstrup[*,†]

[†]Department of Chemistry, Interdisciplinary Nanoscience Center (iNANO), Carbon Dioxide Activation Center (CADIAC), Aarhus University, Gustav Wieds Vej 14, 8000 Aarhus C, Denmark

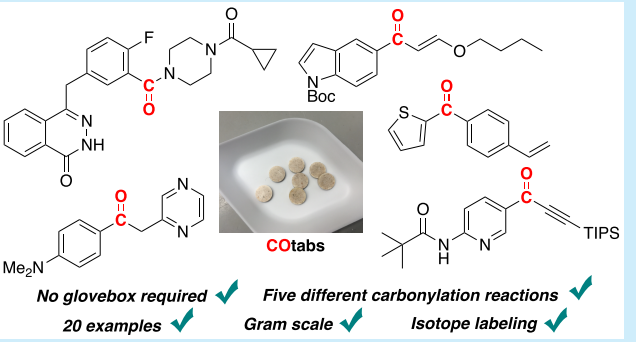
[§]Departamento de Ciências Naturais, Universidade Federal de São João del-Rei, São João del-Rei, MG 36301-160, Brazil

[∥]Departamento de Química, ICEx, UFMG, Av. Pres. Antônio Carlos, 6627, Pampulha, Belo Horizonte, MG 31270-901, Brazil

[⊥]Danish Technological Institute, Life Science Division, Kongsvang Allé 29, 8000 Aarhus C, Denmark

Supporting Information

ABSTRACT: Bench-stable tablets (COtabs) have been developed for the rapid and safe production of carbon monoxide. The tablets can be made in less than 5 min without the use of a glovebox and only require a stock solution of an amine base to liberate a specific quantity of CO in a two-chamber system. The COtabs were tested in five different carbonylation reactions and provided similar yields compared to literature procedures. Finally, a gram-scale reaction was conducted, as well as ^{13}C-isotope labeling of the anticancer drug, olaparib.

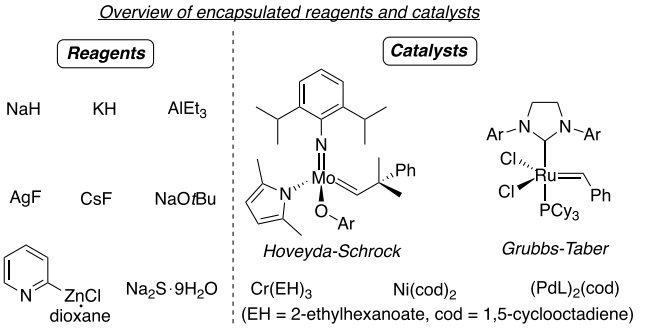


Transition-metal-catalyzed carbonylation chemistry is a powerful methodology for installing carbonyl groups into organic molecules.[1] Although carbon monoxide (CO) is a useful C1-building block, the inherent toxic properties of this gaseous molecule raise several safety concerns. To avoid potential gas leaks while handling pressurized cylinders, the utility of CO-releasing molecules has seen a tremendous increase during the past decade.[2] In 2011, we reported on the ex situ formation of CO from a crystalline acid chloride (COgen), which enabled the safe liberation of this diatomic molecule in a two-chamber system (COware).[3] Since then, we have reported on numerous carbonylative transformations utilizing this setup.[4] Although the safety concern can be eliminated by applying this strategy in small-scale reactions, it is still not without its drawbacks as the methodology requires an inert atmosphere, and therefore, reactions are set up in a glovebox. Furthermore, the ex situ formation of CO requires five components (COgen, Pd-source, phosphine ligand, base, and solvent), which makes it time-consuming to conduct several reactions at once. Since gloveboxes may not be standard equipment in all chemistry laboratories, and time is often an issue for compound synthesis in pharmaceutical companies, we became interested in finding solutions to increase the utility of COgen in order to make the CO release more user-friendly.

In this paper, we report on air-stable tablets (COtabs) that can be rapidly produced without special precautions and which release CO by merely adding a stock solution of base. We demonstrate the applicability of these tablets in five different carbonylative transformations using the double-chamber system, COware, as well as the possibility for its facile exploitation in ^{13}C-isotope labeling and a gram-scale reaction.

Handling of moisture-sensitive compounds can be simplified by submerging the reagent in a protective matrix (Scheme 1). A common example is sodium hydride, which is commercialized as a 60% mixture in mineral oil. Similar to this concept, pyrophoric reagents such as potassium hydride[5] or triethyla-

Scheme 1. Air- and Moisture-Sensitive Reagents/Catalysts Embedded in Paraffin/Mineral Oil



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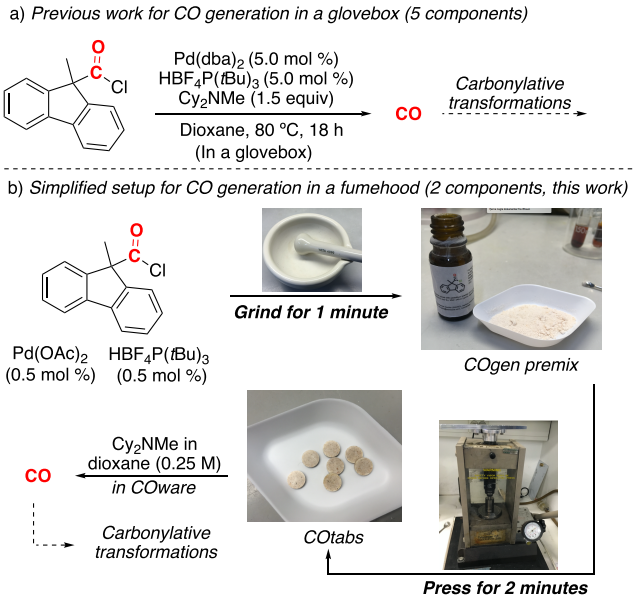
luminum[6a] can be handled in air by utilizing paraffin wax. Air-sensitive catalysts such as chromium(III) complexes for ethylene oligomerization[7] or metathesis-catalysts based on the work from Schrock and Hoveyda[6] or Grubbs[8] can also successfully be embedded in paraffin wax to avoid catalyst decomposition in air. In 2015, Buchwald and co-workers reported on the use of hollow paraffin wax capsules containing air-sensitive Pd catalysts and reagents for conducting coupling reactions without the need for a glovebox.[9] Following this report, Garg published on a similar strategy for handling the air-sensitive Ni(0) source, $Ni(cod)_2$.[10] Finally, Wu utilized the encapsulation method for performing multicomponent reactions with thiols, thereby avoiding catalyst poisoning and the foul smell often associated with these compounds.[11] These protocols point to the important feature that simple solutions can be employed to solve troublesome challenges in the laboratory. Although useful, and commercially available for most cases, the compounds depicted in Scheme 1 still require a glovebox for storage before being embedded in the protective matrix.

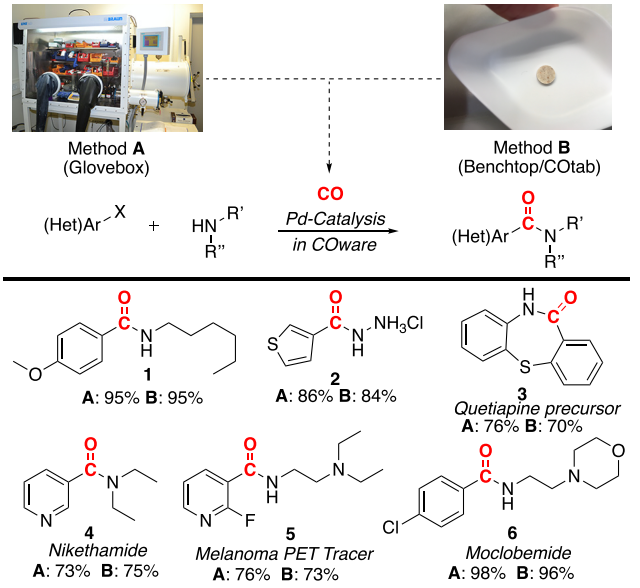
Inspired by these reports, we sought to develop a similar protocol for a glovebox-free and practical generation of CO in a two-chamber system. We initially chose the paraffin wax capsules designed by Buchwald as the delivery system. The goal was to include all reagents (Scheme 2a) into a single capsule to render the process more time-efficient. Since the active Pd(0) catalyst can be formed in situ from $Pd(OAc)_2$ and the HBF_4 salt of $P(tBu)_3$ as reported by Fu, a glovebox was not required.[12] Liquid tertiary amine bases such as DIPEA or Cy_2NMe are usually the best choice for the decarbonylation of COgen under the previously reported conditions, which in this setup would not be applicable. Screening of a range of solid bases revealed 1-cyclohexyl-4-tosylpiperazine to be a promising candidate (results not shown). However, fitting all reagents into a single hollow wax capsule proved to be challenging, and removal of the wax residues from the two-chamber system was likewise tedious. Discouraged by this, we decided to pursue the development of a more traditional approach. As the mass of the reagents was problematic for the paraffin capsule, we rationalized that pressing the reagents together under high pressure into a tablet might be an alternative but good solution. We therefore mixed COgen, $HBF_4P(tBu)_3$ (0.5 mol %), and $Pd(OAc)_2$ (0.5 mol %) in a mortar,[13] which provided a uniformly distributed powder (COgen premix)[14] upon grinding that could be compressed into a tablet (COtab) using a hydraulic press (Scheme 2b). The time efficiency of the process should be stressed as it takes less than 5 min to make a tablet.[15] The issue of the base was solved by preparing a 0.25 M solution of Cy_2NMe in dioxane.

With the COtabs in hand, we decided to test the efficiency of the tablets and compare them to carbonylation reactions set up in a glovebox with COgen. By using CO as the limiting reagent, amide **1** could be isolated in a nearly quantitative yield (95%) using either a glovebox procedure or COtabs set up in a fumehood (Scheme 3).[3,16]

Scheme 2. CO Generation from COgen



Scheme 3. Aminocarbonylations Performed in a Glovebox with COgen or with COtabs on a Benchtop[a]



[a]For specific reaction conditions, see the Supporting Information.

Excited by these results, we evaluated other aminocarbonylations as depicted in Scheme 3.[17] Boc-protected hydrazine could be employed as a potent nucleophile resulting in high isolated yields for **2**.[18] A precursor for the antipsychotic drug, quetiapine (**3**),[19] was synthesized through an intramolecular aminocarbonylation. Nikethamide (**4**, respiratory stimulant),[20] the melanoma PET tracer **5**,[21] and moclobemide (**6**, antidepressant)[22] could all be isolated in high yields. Importantly, COtabs provided a similar result compared to the reactions set up in a glovebox.

Aminocarbonylation reactions are among the most reliable carbonylation reactions due to the lack of a competing direct reaction, in this case the Buchwald–Hartwig amination.[23] In order to demonstrate the efficiency of the COtabs, we therefore turned our attention to more CO-sensitive reactions, whereby the direct coupling is challenging to suppress (Scheme 4). This was demonstrated by the synthesis of three alkynones (**7**–**9**) via a carbonylative Sonogashira reaction[24] whereby COtabs provided similar yields compared to the glovebox procedure. The carbonylative Mizoroki–Heck reaction was also achieved in the preparation of compounds

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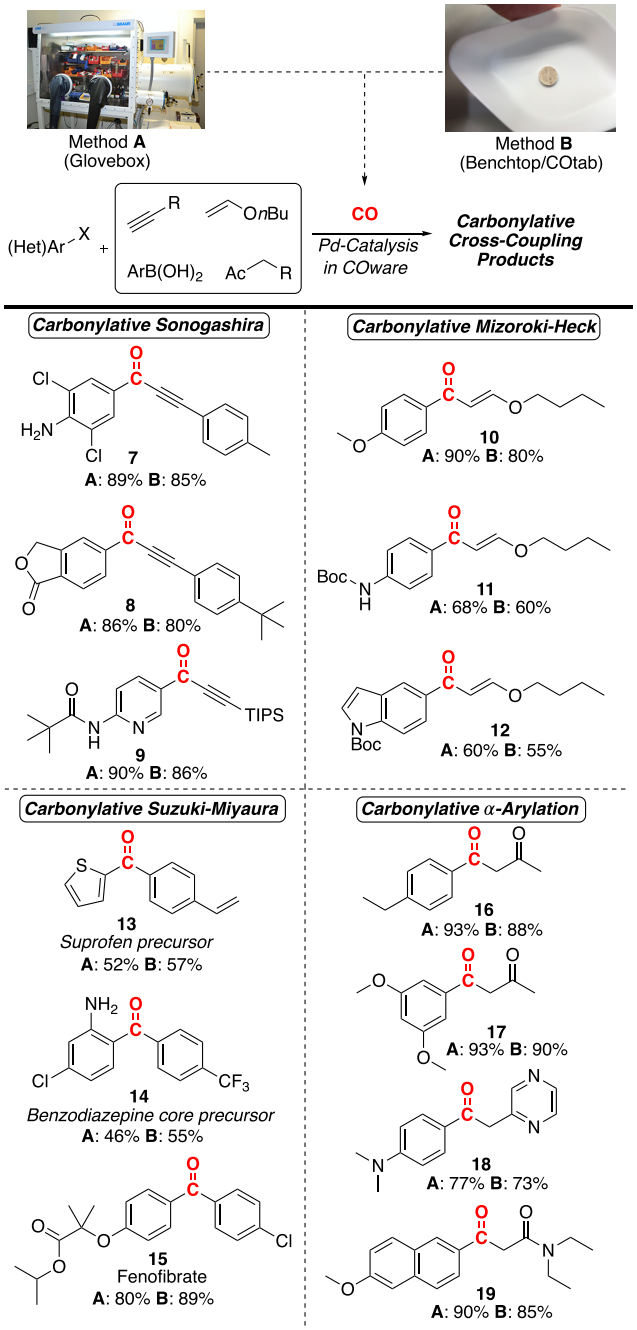
Scheme 4. Carbonylative C−C Bond-Forming Reactions Comparing Glovebox Conditions with COtab and BenchTop Conditions[a]

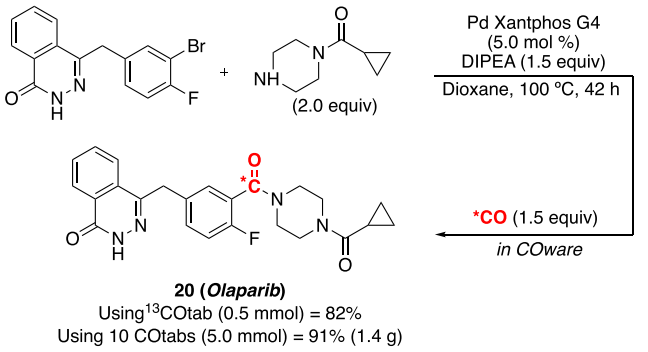


[a]For specific reaction conditions, see the Supporting Information.

10−**12** as demonstrated in Scheme 4.[25] Furthermore, by utilizing conditions favoring the carbonylative Suzuki−Miyaura reaction,[26] precursors for suprofen (NSAID)[27] and benzodiazepines[28] (compounds **13** and **14**) could be obtained, as well as the blood cholesterol lowering drug fenofibrate (**15**).[29] Finally, three different types of carbonylative α-arylation reactions were successfully demonstrated, resulting in the formation of 1,3-diketones **16** and **17**,[30] the pyrazine-containing ketone **18**,[31] and the 1,3-ketoamide **19**.[32] Gratifyingly, using COtabs for a glovebox-free alternative did not lead to a loss of efficiency compared to the original procedure.

As a final demonstration of the applicability of COtabs, the anticancer drug olaparib (**20**)[33] was prepared with a carbon-13 isotope label merely by employing a COtab composed of ^{13}C-labeled COgen (Scheme 5).[34] A gram-scale synthesis of the

Scheme 5. Scale-up and ^{13}C-Labeling of Olaparib



drug in a yield of 91% could be obtained by adding 10 COtabs (5 mmol of CO) to a larger COware system (see the Supporting Information for experimental details).

In conclusion, we have developed small tablets (COtabs) that can liberate CO in the presence of a stock solution of Cy_2NMe. The tablets can easily be prepared by mixing COgen, $Pd(OAc)_2$, and $HBF_4P(tBu)_3$ in a mortar and pressing the resulting powder in a hydraulic press. The formation of these tablets can be accomplished without precautions to exposure to air, and the tablets can be stored in a bottle without any trace of decomposition being observed.[35] The use of COtabs was demonstrated in five different carbonylation reactions, and the same efficiency for these transformations was obtained compared to the original literature. Furthermore, ^{13}C-isotope labeling, as well as gram-scale synthesis, was also demonstrated. We anticipate that this glovebox-free carbonylation protocol will be of great utility for chemists without access to specialized equipment, such as a glovebox or CO-containing cylinders, who wish to carry out Pd-catalyzed carbonylation reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01423.

Experimental procedures, product characterization and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: dun@chem.au.dk.
*E-mail: ts@chem.au.dk.

ORCID

Hugo P. Collin: 0000-0001-9483-7183
Dennis U. Nielsen: 0000-0002-4521-5991
Troels Skrydstrup: 0000-0001-8090-5050

Author Contributions

[▽]H.P.C. and W.J.R. contributed equally.

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Notes

The authors declare the following competing financial interest(s): A.T.L. and T.S. are co-owners of SyTracks A/S, which commercializes the two-chamber system (COware) and COgen premix.

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(13) A commercial miniblender was utilized for 100 g scale. See the Supporting Information for details.

(14) It should be noted that the COgen premix powder can also be used as an equally effective CO-surrogate compared to the COtabs, which might provide an alternative solution for laboratories that do not have access to a hydraulic press.

(15) The developed COtabs do not offer significant advantages regarding stability or reproducibility compared to adding the components individually. However, conducting several carbonylation reactions at once can be realized more rapidly using COtabs.

(16) Using $Pd(OAc)_2$ instead of $Pd(dba)_2$ as the precatalyst for CO-formation setup in a fumehood did not have an effect on the yield, as **1** was produced in an identical yield.

(17) For carbonylation reactions set up in a fumehood that rely on air-sensitive phosphine ligands, we employed the corresponding Buchwald generation 4 precatalyst. For examples, see: (a) Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161−4166. (b) Friis, S. D.; Skrydstrup, T.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 4296−4299.

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(35) COtabs tested after one month did not show any signs of degradation or lowered activity. For more stability studies, see the Supporting Information.

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