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Three low-cost standard lab chemicals; formic acid, mesyl chloride and triethylamine, were used for instant carbon monoxide (CO) generation at room temperature. Subsequently this gas was implemented in palladium-catalysed aminocarbonylation chemistry. Moreover, ^{13}C-enriched formic acid was used as one of the most economical CO precursors for ^{13}C-carbonyl labelling.

Carbon monoxide is beyond doubt one of the most important C1 building blocks for organic synthesis.[1] In addition, CO can also act as an excellent ligand in transition metal chemistry.[2-4] Although carbonylation chemistry is very mild and versatile, safety issues constrain the direct utility of this highly toxic gas. Especially on lab scale in a typical research lab, storage and use of pure, pressurised carbon monoxide gas raises serious safety concerns. In order to improve the applicability of this gas, an alternative carbon monoxide source is highly desired.

Different CO sources have successfully been used: examples are metal carbonyl derivates,[5] aldehydes,[6,7] formamides,[8,9] *N*-formyl saccharin[10,11] and aryl formates.[12,13] Unfortunately, these precursors are either very toxic themselves, require high temperatures for carbon monoxide liberation and/or generate a nucleophilic byproduct that can participate in the carbonylation reaction.

The Skrydstrup group developed three efficient carbon monoxide generating systems: methyldiphenylsilacarboxylic acid,[14] 9-methyl-9*H*-fluorene-9-carbonyl chloride[15] and tetraphenyldimethyldisilane in combination with carbon dioxide.[16] These CO-precursors however are non-trivial specialty chemicals with an associated higher cost. It would be advantageous if inexpensive commodities could be used to release carbon monoxide at ambient temperature in a robust manner. Different groups are working towards optimising such precursor systems.

In 2015, rapid hydrolysis of chloroform to carbon monoxide by caesiumhydroxide hydrate was described.[17] As chloroform is an inexpensive bulk chemical, it is an interesting CO precursor with the possibility of ^{13}C labelling since ^{13}C-$CHCl_3$ is commercially available. On the other hand, the heterogeneous hydroxide ($CsOH.H_2O$) base is an expensive chemical and must be used in excess to ensure rapid hydrolysis of chloroform. Replacement of this caesium salt by a more cost efficient one leads to a drastic decrease in carbon monoxide production.

Generation of carbon monoxide by dehydration of formic acid[18] in presence of sulfuric acid is known as the Morgan reaction.[19] The utility of this reaction was improved by adapting this CO-generating system to a continuous microflow system by using a tube-in-tube reactor or by making use of a two-chamber system.[20] However, this system still requires corrosive concentrated sulfuric acid. Zeolites are known to be safe alternatives to strong and corrosive liquid acids.[21] Although replacement of sulfuric acid by zeolites seems promising, only a few specific zeolites can adequately decompose formic acid at elevated temperature (150 °C), hampering robustness of the method.[22]

Recently, the Wu group discovered that formic acid releases carbon monoxide in the presence of acetic anhydride under basic conditions.[23-25] Moderate to excellent yields were obtained when using this CO precursor in Pd-catalysed alkoxycarbonylation, carbonylative Suzuki and Sonogashira coupling of aryl halides. Unfortunately, the decomposition of the mixed anhydride is slow, while instant carbon monoxide generation is desired as it directly stabilises the catalytic system and shortens the reaction time.[26] Furthermore, this method is not suitable for Pd-catalysed aminocarbonylation chemistry as the *in situ* formed acetic formic anhydride is known to be a formylating agent for amines.[27]

In this paper we report a state-of-the-art low-cost CO generating system based on the instant decomposition of formic acid by addition of mesyl chloride (MsCl) and triethylamine (Et_3N) at room temperature (Scheme 1). This system is 30 to 140 times more cost efficient than non formic acid precursors (see Supporting Information), since all the

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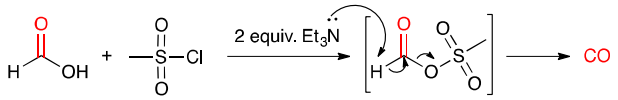
Electronic Supplementary Information (ESI) available: ^{13}C-NMR study of the CO generating system, influence of MsCl and Ac_2O on the decomposition rate of HCOOH, price comparison of recently published CO and ^{13}CO generating systems, detailed experimental procedures and copies of ^{1}H-NMR and ^{13}C-NMR data. See DOI: 10.1039/x0xx00000x

Scheme 1 Proposed decomposition mechanism of formic acid in presence of 1 equiv. mesyl chloride and 2 equiv. triethylamine leading to instant CO generation.



1 equiv. **1 equiv.** **Instant CO generation due to highly unstable intermediate**

required starting products are inexpensive commodity chemicals. The replacement of acetic anhydride by mesyl chloride was necessary to ensure instant CO generation at room temperature (See Supporting Information). This replacement also contributes to the general safety aspects of the procedure, since mesyl chloride is a non-flammable chemical compared to acetic anhydride. As ^{13}C-formic acid is also commercially available, this procedure provides an obvious source of ^{13}CO. Comparing the costs of commercially available ^{13}CO precursors, this system is probably one of the least expensive ^{13}C-carbonylation methods (see Supporting Information).

To gain more insight in the steps involved in the decomposition of formic acid to carbon monoxide in presence of mesyl chloride and triethylamine, a ^{13}C-NMR study was conducted at room temperature (Scheme 2). First, 0.5 mmol HCOOH was added to 600 µL CD_3CN (Scheme 2[A]). Then, 0.5 mmol MsCl was added to this solution (Scheme 2[B]). At this point no changes seemed to occur in the NMR spectrum of the mixture, indicating that base is needed to start the reaction. Subsequent dropwise addition of 1.0 mmol Et_3N resulted in vigorous gas development for several seconds. Afterwards a ^{13}C-NMR spectrum was recorded (Scheme 2[C]) and complete decomposition of HCOOH was observed as the corresponding peak disappeared. MsCl also disappeared in the spectrum and a new peak at lower ppm-value appeared (39.6 ppm), indicating the formation of methanesulfonate anion and triethylammonium cation (see Supporting Information).

These results indicate that once the formic acid is deprotonated, it most probably reacts with mesyl chloride and forms a highly unstable mixed anhydride intermediate. A second deprotonation leads to instant CO formation, as the methanesulfonate is an excellent leaving group (Scheme 1). At this point it is not known whether the elimination of the sulfonate happens concerted with the deprotonation or not.

We also found that other sulfonyl chlorides are equally able to decompose formic acid to carbon monoxide in the presence of triethylamine: tosyl chloride, triflyl chloride, nosyl chloride, *etc*. However, for reasons of atom economy, mesyl chloride was our reagent of choice.

Palladium-catalysed aminocarbonylation of aryl bromides was chosen as test case to prove the utility of this CO precursor. As already mentioned, *in situ* formation of CO by *e.g.* acetic formic anhydride will lead to formylation of the amine. More general, decomposition of any precursor will lead to the formation of by-products which could potentially cause side reactions. In our case, the amine moiety (needed to form

Scheme 2 ^{13}C-NMR study of the CO precursor at room temperature. [A] 0.5 mmol HCOOH in 600 µL CD_3CN. [B] 0.5 mmol HCOOH and 0.5 mmol MsCl in 600 µL CD_3CN. [C] 0.5 mmol HCOOH, 0.5 mmol MsCl and 1.0 mmol Et_3N in 600 µL CD_3CN.

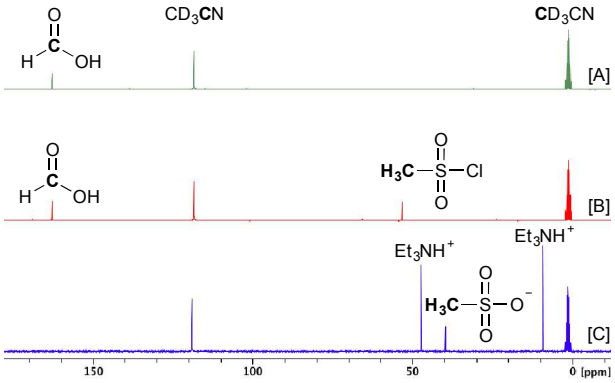
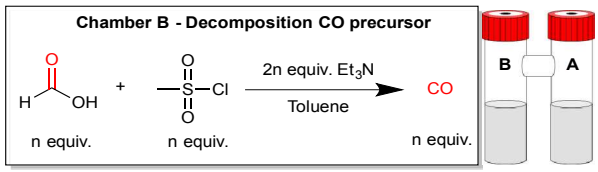
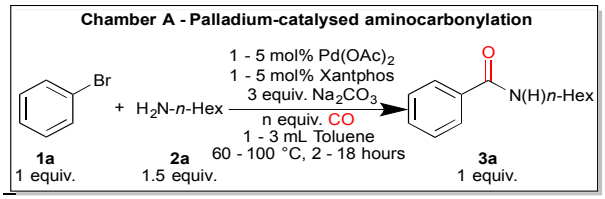


Table 1 Optimisation of the reaction conditions[a]





Entry	T (°C)	t (h)	CO eq.	Catalyst/Ligand	Conc. (M)	Yield[b] (%)
1	60	18	3.0	5 mol% $Pd(OAc)_2$/Xantphos	0.167	41
2	80	18	3.0	5 mol% $Pd(OAc)_2$/Xantphos	0.167	80
3	**100**	18	3.0	5 mol% $Pd(OAc)_2$/Xantphos	0.167	96
4	100	18	2.0	5 mol% $Pd(OAc)_2$/Xantphos	0.167	95
5	100	18	**1.3**	5 mol% $Pd(OAc)_2$/Xantphos	0.167	93
6	100	18	1.3	2 mol% $Pd(OAc)_2$/Xantphos	0.167	96
7	100	18	1.3	**1 mol% $Pd(OAc)_2$/Xantphos**	0.167	94
8	100	18	1.3	1 mol% $Pd(P(Ph_3))_4$	0.167	19
9	100	**2**	1.3	1 mol% $Pd(OAc)_2$/Xantphos	0.167	95
10	100	2	1.3	1 mol% $Pd(OAc)_2$/Xantphos	0.250	96
11	100	2	1.3	1 mol% $Pd(OAc)_2$/Xantphos	**0.500**	98

[a]Reaction conditions: Chamber A – Bromobenzene (0.5 mmol), *n*-hexylamine (0.75 mmol, 1.5 equiv.), Na_2CO_3 (1.5 mmol, 3.0 equiv.), $Pd(OAc)_2$ (0.005 mmol), Xantphos (0.005 mmol) and 1 mL dry degassed toluene. Chamber B – Formic acid (0.65 mmol, 1.3 equiv.), methanesulfonyl chloride (0.65 mmol, 1.3 equiv.) in 2 mL dry degassed toluene. Finally, Et_3N (1.3 mmol, 2.6 equiv.) was added by injection through the septum in chamber B at room temperature. After 2 minutes the reactor was placed in an oil-bath at 100 °C. [b]Isolated yield.

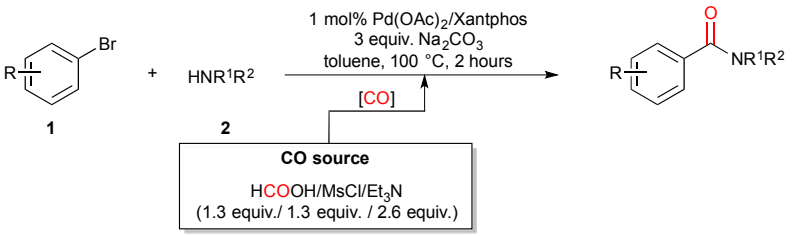
an amide) could react with mesyl chloride and a mixture of compounds might be expected. Inspired by the elegant two-chamber setup of the Skrydstrup group, *ex situ* CO generation was implemented to address these difficulties.[28]

We began our optimisation by using the conditions reported by Buchwald *et al.* as a benchmark for the Pd-catalysed aminocarbonylation chemistry.[29] Initially, chamber A was filled with 5 mol% $Pd(OAc)_2$/Xantphos, Na_2CO_3 (3 equiv.), 3 mL dry degassed toluene (0.167 M), bromobenzene (1 equiv.) and *n*-hexylamine (1.5 equiv.). Chamber B was loaded with 3 equiv. of formic acid and mesyl chloride. Finally, Et_3N (6 equiv.) was added by injection through the septum in chamber B at room temperature (Table 1). Performing the reaction at 60 °C resulted in 41% of the desired amide **3a** after 18 hours (Entry 1). To our delight an increased yield was observed at higher temperature (Entries 2 and 3). In contrast to our results at 100 °C, Buchwald reported an incomplete conversion of the starting material at this temperature. This unusual result was ascribed to decreased catalyst stability at higher temperature.[29] However, in our system, CO pressure builds up in the closed system. We assume that the generated pressure stabilises the catalytic system and therefore higher temperatures and lower catalyst loadings can be applied.

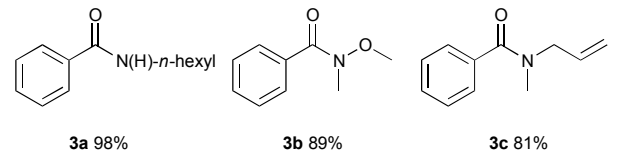
In order to increase the cost efficiency of this system, a reduction of CO and catalyst loading was investigated (Entries 4-7). Performing the reaction with only 1 mol% $Pd(OAc)_2$/Xantphos in presence of 1.3 equiv. of CO (assuming full conversion of the precursor) affords the amide in 94%. Further improvements were made by reducing the reaction time and increasing the concentration to respectively 2 hours (Entry 9) and 0.5 M (Entry 11).

The *ex situ* generated CO was successfully implemented in

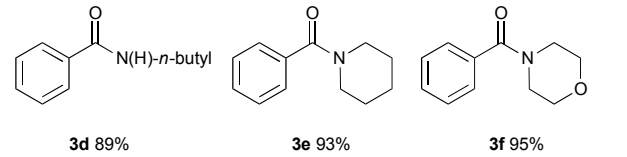
Scheme 3 Palladium-catalysed aminocarbonylation by using formic acid, mesyl chloride and triethylamine as CO source[a]



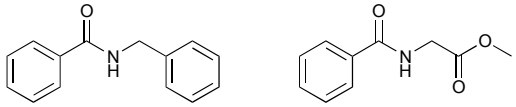
Synthesis of Benzamides



3a 98% **3b** 89% **3c** 81%

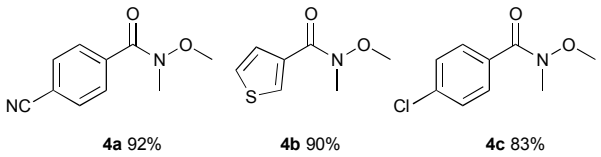


3d 89% **3e** 93% **3f** 95%

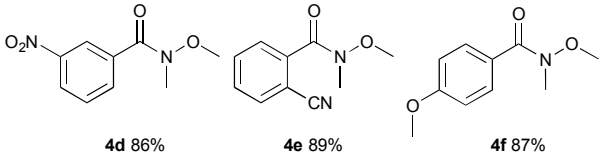


3g 91% **3h** 96%

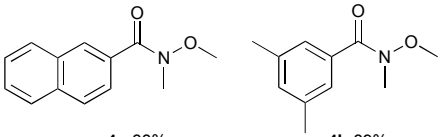
Synthesis of Weinreb Amides



4a 92% **4b** 90% **4c** 83%

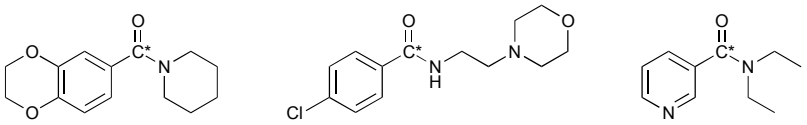


4d 86% **4e** 89% **4f** 87%



4g 88% **4h** 89%

Synthesis of Pharmaceutical Compounds



CX-546
5a 90% (^{12}C)
5b 93% (^{13}C)

Moclobemide
6a 97% (^{12}C)
6b 94% (^{13}C)

Nikethamide
7a 76% (^{12}C)
7b 82% (^{13}C)

[a]Reaction conditions: Chamber A – Bromobenzene (0.5 mmol), amine (0.75 mmol, 1.5 equiv.), Na_2CO_3 (1.5 mmol, 3.0 equiv.), $Pd(OAc)_2$ (0.005 mmol), Xantphos (0.005 mmol) in 1 mL dry degassed toluene. Chamber B – HCOOH (0.65 mmol, 1.3 equiv.) and MsCl (0.65 mmol, 1.3 equiv.) in 2 mL dry degassed toluene. Finally, Et_3N (1.3 mmol, 2.6 equiv.) was added by injection through the septum in chamber B at room temperature. After 2 minutes the reactor was immersed in an oil-bath at 100 °C.

the system comprising bromobenzene and *n*-hexylamine yielding **3a** in 98%. With the optimised conditions in hand, the scope of the Pd-catalysed aminocarbonylation chemistry was further explored. As shown in Scheme 3, different benzamides and Weinreb amides were synthesised in good to excellent yields.

The reaction conditions tolerate a wide variety of functional groups on both the aryl bromide and the amines, including allyl (**3c**), nitrile (**4a** and **4e**), nitro (**4d**), aryl chlorides (**4c** and **6a**) and esters (**3h**). In addition, also heteroaryl bromides (thiophene **4b** and pyridine **7a**) gave good to excellent yields.

This work was finalised with the synthesis of three relevant ^{13}C-labelled pharmaceuticals: CX-546[30] (**5a** and **5b**), Moclobemide[31] (**6a** and **6b**), and Nikethamide[32] (**7a** and **7b**). These compounds were labelled using ^{13}C-formic acid. Notably, this enriched precursor is at least 9 times less expensive per mmol of ^{13}CO generated than any other reported commercial ^{13}CO precursor (see Supporting Information).

In conclusion, we report a state-of-the-art low-cost system to instantly generate CO at room temperature: formic acid, mesyl chloride and triethylamine. Since these reagents are inexpensive commodity chemicals, which are available in research labs, it belongs to one of the most economical and readily available CO precursor systems. The *ex situ* generated CO is successfully applied in Pd-catalysed aminocarbonylation chemistry resulting in high yielding amide formation. Remarkably, this is the first report on ^{13}C-carbonylation labelling in a Pd-catalysed reaction by decomposition of ^{13}C-HCOOH into ^{13}CO.

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A simple and robust method for instant carbon monoxide generation at room temperature using easily accessible standard lab chemicals: Formic Acid, Mesyl Chloride and Triethylamine.