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Rapid Organocatalytic Formation of Carbon Monoxide: Application towards Carbonylative Cross Couplings

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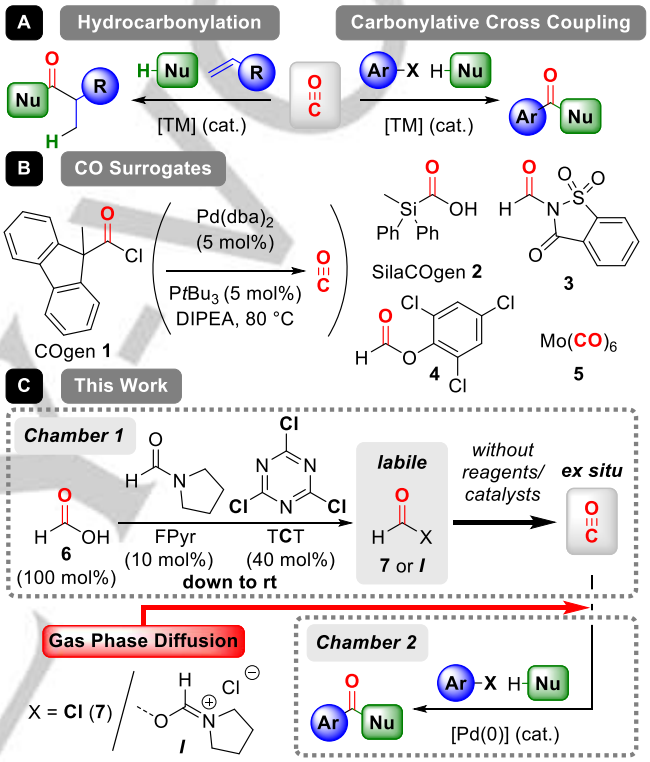
Abstract: Herein, the first organocatalytic method for the transformation of non-derivatized formic acid into carbon monoxide (CO) is introduced. Formylpyrrolidine (FPyr) and trichlorotriazine (TCT), which is a cost-efficient commodity chemical, enable this decarbonylation. Utilization of dimethylformamide (DMF) as solvent and catalyst even allows for a rapid CO generation at room temperature. Application towards four different carbonylative cross coupling protocols demonstrates the high synthetic utility and versatility of the new approach. Remarkably, this also comprehends a carbonylative Sonogashira reaction at room temperature employing intrinsically difficult electron-deficient aryl iodides. Commercial ^{13}C-enriched formic acid facilitates the production of radiolabeled compounds as exemplified by the pharmaceutical Moclobemide. Finally, comparative experiments verified that the present method is highly superior to other protocols for the activation of carboxylic acids.

Introduction

Carbon monoxide (CO) is one of the most important building blocks in chemistry in both, academia and industry.[1,2] Fundamental applications are, for example, carbonylative cross couplings and hydrocarbonylations of alkenes and alkynes (Scheme 1 **A**). Since CO is a highly toxic and flammable, odorless gas, its utilization is inevitably associated with severe safety hazards and risks. Therefore, compounds that liberate CO under controlled conditions in stoichiometric quantities have been developed (Scheme 1 **B**).[2] These so-called CO surrogates are either directly added to the reaction mixture for the *in situ* CO production, or CO is formed *ex situ* in a separate reaction vessel. In the latter case, the CO generating and consuming process are spatial separated, for which they do not need to be compatible. Beneficially, this facilitates the substitution of gaseous CO through a CO surrogate significantly. A gas exchange is secured by a connection of the two chambers. Several two chamber gas reactors have been constructed for the *ex situ* gas synthesis,[2,3a] whereby some devices are even commercially available.[4]

Examples of common commercial CO surrogates[2] are (1) carboxylic acid chlorides like COgen **1** and sila derivatives such as SilaCOgen **2**, which have been implemented by Skrydstrup and Lindhardt mainly for the *ex situ* CO preparation.[2c,e,f,4] (2) *N*-Formyl saccharin (**3**), the application of which has been pioneered by Manabe (*in situ*) and Fleischer (*ex situ*).[2b,5] (3) Aryl formates like **4**, which have been discovered by Manabe for the *in situ* CO production,[2b,g,6] and (4) metal carbonyl complexes like **5** as introduced by Larhed for the *in* and *ex situ* CO release.[2i,7]



Scheme 1. Previous and this work. [TM] = transition metal catalyst, dba = dibenzylidene acetone, DIPEA = di-*iso*-propyl ethyl amine, FPyr = *N*-formylpyrrolidine, TCT = 2,4,6-trichloro-1,3,5-triazine, rt = room temperature.

In fact, formic acid (**6**) is an even simpler and significantly cheaper source of CO, which has been initially applied *in situ* for hydrocarbonylations of alkenes and alkynes and carboxylations of aryl halides, respectively.[8,9] Furthermore, the group of Wu published a range of protocols for carbonylative cross couplings using the mixed anhydride of formic and acetic acid, which was synthesized from Ac_2O and HCO_2H in prior.[10] In addition, the same team discovered that carbodiimides promote the *in situ* development of CO directly from methanoic acid.[11]

Certain heterogeneous catalysts[12] and Brønsted acids like H_2SO_4[13] facilitate the *ex situ* decarbonylation of formic acid. Eventually, Cantat and co-workers recently described a chemical looping strategy for the decarbonylation of formic acid.[14] Therein, methyl formate was transformed *ex situ* to CO and MeOH by means of MeOK as transition metal-free catalyst.

So far, decarbonylation of methanoic acid typically requires high reaction temperatures of 75-190 °C.[8-14] Lower temperatures were only accomplished in rather specific cases.[10a,11b,12a] Under

consideration of the cost-efficiency of formic acid, the development of approaches for its *ex situ* decarbonylation under milder conditions (e.g. at room temperature) and with a broader applicability constitutes an indispensable task.

Lately, our group discovered that *Lewis* bases[15] like 1-formylpyrrolidine (FPyr) and dimethylformamide (DMF) catalyze the transformation of carboxylic acids into the respective acid chlorides by means of trichlorotriazine (TCT), which is also denoted as cyanuric chloride (see Scheme 1 **C** for structure).[16a,17b] Indeed, TCT is the most cost-efficient reagent for the activation of OH groups like in alcohols and acids besides phosgene ($COCl_2$).[16a] Since cyanuric chloride contains three Cl atoms, it can be applied in substoichiometric quantities down to 33 mol% with respect to the substrate (100 mol%). In fact, the beneficially low stoichiometry is facilitated by formamide catalysis. Against this background, we envisioned a novel *ex situ* CO formation approach based on formic acid (Scheme 1 **C**).

Activation of formic acid should either yield formyl chloride **7** or an intermediate like ***I***, which bears a similarly good leaving group as chloride. Actually, formic acid chloride is known to be labile towards decarbonylation, wherefore a rapid decomposition to CO was predicted.[18] Surprisingly, CO evolution from methanoic acid using common chlorination agents has not been reported in the realm of transition metal catalyzed transformations so far.[19] Actually, organocatalytic conversion of HCO_2H into CO is a challenging task, which has so far only been accomplished through preceding derivatization to methyl formate.[14,20] Herein, a novel operationally simple method for the transformation of formic acid into CO based on organocatalysis and *ex situ* application towards four different carbonylative cross couplings is disclosed.

Results and Discussion

At the outset, the reaction of methanoic acid with TCT was investigated by means of gas volumetry (Figure 1, see chp. 2 of the supporting information = SI for details). The use of DMF as solvent and catalyst enabled a rapid CO generation already at room temperature (Figure 1 **A**, see chp. 2.2 of the SI). Notably, DMF is a common and inexpensive organic solvent. When TCT was applied in excess (41 mol% = 1.2 equiv) with respect to methanoic acid (1.0 equiv), already after 4.5 min (= $t_{2/3}$) a gas yield $n(gas)/n_0(HCO_2H)$ of >67% was noted (green points). Since at room temperature solvent and HCl evaporation can be neglected, the gas yield is equivalent to the yield of CO and consequently also conversion of formic acid. In the present work, at most 1.5 equiv of HCO_2H were engaged in the carbonylative transformations (see Scheme 2 and 3). Hence, 67% conversion comply to 1 equiv of CO being generated. After 75 min 98% gas yield were reached, which substantiates an almost quantitative conversion of **6**. Such a fast CO generation was not expected, since under catalytic conditions a similarly rapid conversion of carboxylic acids into acid chlorides afforded heating to 80 °C.[16a] To the best of our knowledge, only SilaCOgen (**2**), which is more expensive than formic acid, allows a similarly fast gas development.[4b] Although very limited kinetic data is available, based on the reported reaction temperatures the current approach enables a considerably faster CO formation than other procedures using formic acid.[8-14] With an excess of formic acid (2 equiv) with regard to TCT (33 mol% = 1 equiv) the evolution of gas is slower (yellow points).

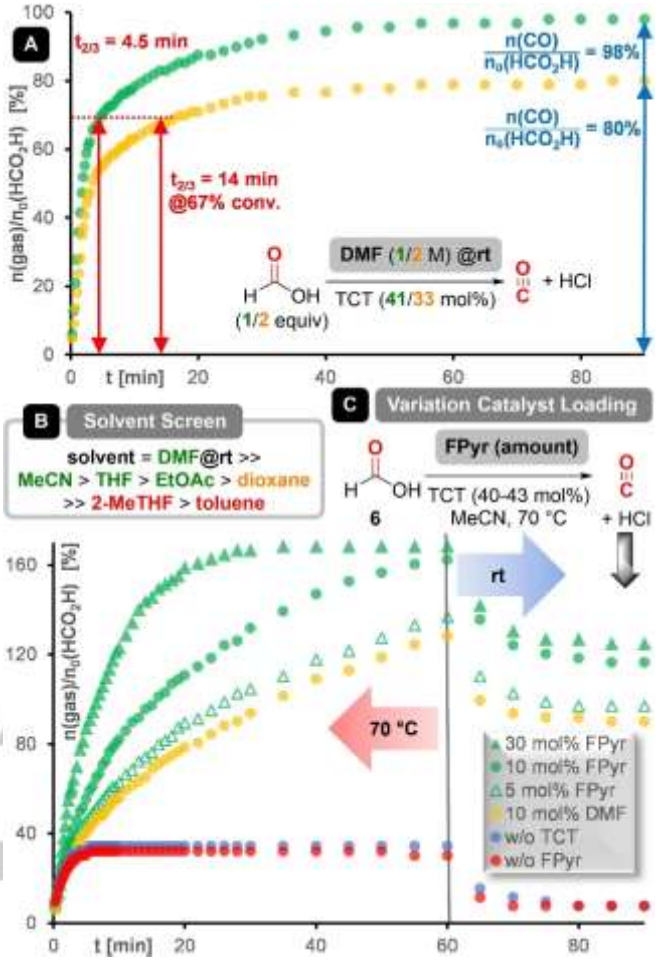


Figure 1. Gas volumetry to follow CO formation. n(gas) = amount of gas as determined by the ideal gas equation, $n_0(HCO_2H)$ = initial amount of formic acid, THF = tetrahydrofuran, EtOAc = ethyl acetate, 2-MeTHF = 2-methyltetrahydrofurane.

Nevertheless, after 90 min 80% yield in terms of CO had been accomplished. This verifies the partial substitution of the third Cl atom of TCT, as also observed in the cases of carboxylic acid and alcohol chlorinations (see mechanism in Scheme 4).[16a,17b] From a solvent screening using 10 mol% of FPyr at 70 °C MeCN and THF emerged as optimal (chp. 2.3 in the SI). Remarkably, the initial rate of gas formation in DMF at room temperature was four times faster than in MeCN at 70 °C.

Eventually, a variation of the catalyst loading in MeCN demonstrated the tremendous effect of FPyr (Figure 1 **C**, chp. 2.4 in the SI). In these measurements the reaction mixture was heated to 70 °C for 60 min. Both, the gas yield after cooling down to ambient temperature and the initial rate clearly increased from 5 over 10 to 30 mol% of FPyr (green points). Interestingly, a slower development of gas was observed using 10 mol% of DMF (yellow points) than with 5 mol% FPyr, which attests the latter as superior organocatalyst. The blue data points indicate the formation of gas in the absence of TCT, which was similar to heating MeCN to 70 °C (see chp. 2.4, SI). Therefore, the formed gas consists only of evaporated solvent. As an important aspect, the gas amount was even slightly lower in the absence of FPyr (red points). This highlights the importance of FPyr as catalyst: Without this formamide basically no CO is created at all.

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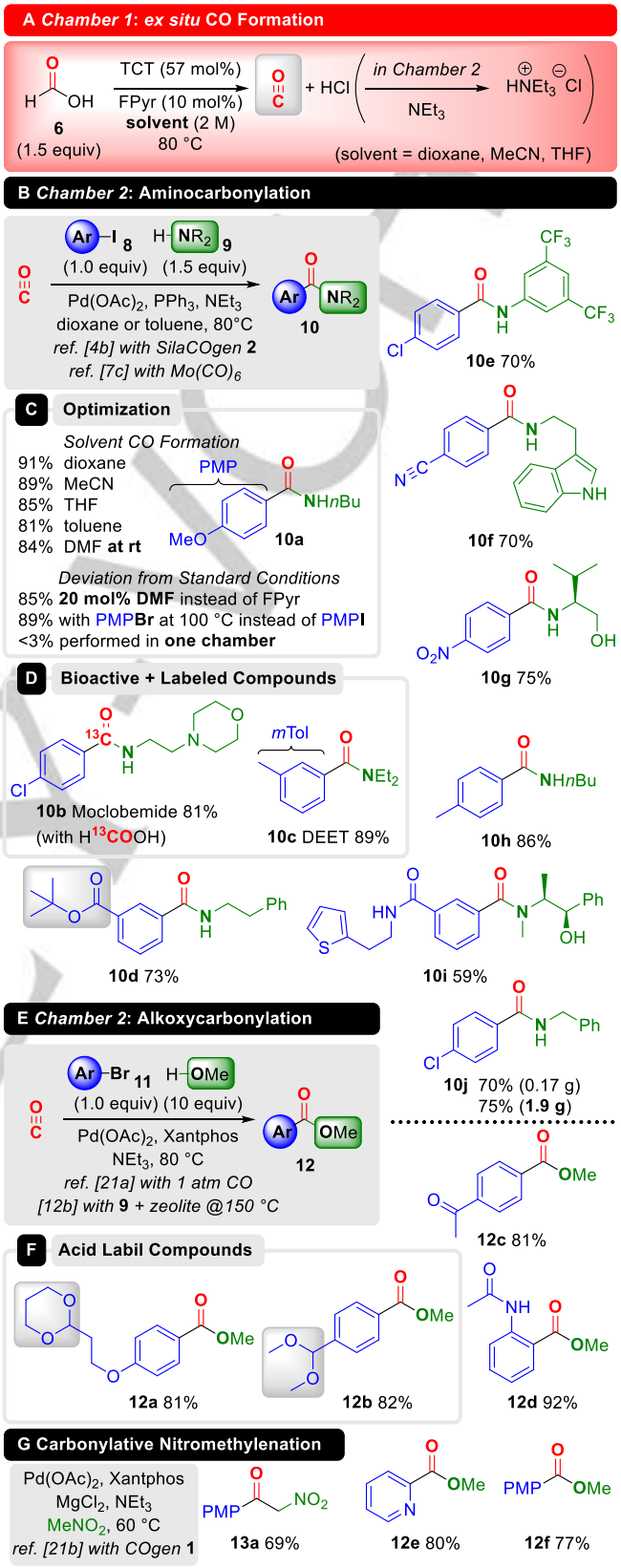
To probe the synthetic utility, in several carbonylative cross couplings either gaseous CO or another CO surrogate was substituted by the present approach (Scheme 2). These reactions were carried out in a commercial two chamber gas reactor named COware from Sytracks, which facilitates the spatially separated *ex situ* formation of CO (see Scheme 1 **C** and chp. 3.2 in the SI).[4] In carbonylative transformations at elevated temperatures CO was generated using 10 mol% of FPyr in reaction chamber 1 (Scheme 2 **A**). As a first example, SilaCOgen (**2**)[4b] and $Mo(CO)_6$,[7c] respectively, were replaced by the present method in the aminocarbonylation of aryl halides **8** (Scheme 2 **B**). An increase of the NEt_3 amount in the chamber 2, in which the amincarbonylation was carried out, by the amount of methanoic acid employed (1.5 equiv) facilitated the neutralization of HCl, which arose from the decarbonylation.

Importantly, production of CO using different solvents furnished amide **10a** in good yields of 81-91% at 80 °C, which was required for the C-N cross coupling (Scheme 2 **C**). Albeit the solvent has a significant impact on the rate of CO evolution (see above), the mitigated effect on the yield of **10a** may be explained by a rather sluggish direct coupling of butyl amine and aryl iodide **8a**. In addition, CO production at room temperature in DMF afforded **10a** in 84% yield (for conditions see Scheme 3 **A**). Thus, different solvents can be engaged in the CO generating and consuming process, cross diffusion causes no considerable difficulties. In general, CO formation in DMF is recommended for carbonylative transformations that are carried out at temperatures below 70 °C. At higher temperatures catalytic CO release preferably in MeCN, THF or dioxane is basically equally efficient.

In fact, FPyr could also be substituted by the twofold amount of simpler DMF, which furnished the amide **10a** in 85% yield. Also aryl bromides **11** could be engaged as starting materials, when the reaction temperature was increased to 100 °C. Worthy of note, *in situ* CO preparation is in general less suitable for aminocarbonylations, since CO surrogates are usually electrophilic and hence react with amines.[7c] Indeed, attempted *in situ* CO release in one reaction vessel furnished **10a** only in minor traces ≤3%, which testifies the crucial role of two chamber gas reactor. A high synthetic utility is witnessed by the preparation of the insecticide DEET (**10c**) and the pharmaceutical Moclobemide **10b** (Scheme 2 **D**). Actually, the use of commercial $H^{13}CO_2H$ as CO surrogate afforded isotopically labeled **10b**. This example also unambiguously accounts for formic acid as CO source and is, to the best of our knowledge, the first example for the application of ^{13}C enriched formic acid in a carbonylative transformation. Moreover, a reasonable scalability was demonstrated by the gram synthesis of amide **10j**.

Furthermore, in the alkoxycarbonylation of aryl bromides **11** an atmosphere of CO[21a] and formic acid decarbonylation at 150 °C using zeolite,[12b] respectively, were substituted by the current methodology (Scheme 2 **E**). This process and the aforementioned aminocarbonylation allowed the synthesis of the products **10d**, **12a** and **12b** with acid-labile functions (Scheme 2 **F**). These precedents evidence that the simultaneous HCl formation exerts no influence on the functional group compatibility. Thereby, particularly remarkable is example **12b**, which bears a highly acid susceptible acyclic acetal. Furthermore, formamide catalyzed CO release could replace COgen (**1**) in the preparation of α-nitro ketone **13a** from nitromethane and the respective iodide **8a** (Scheme 2 **G**).[21b]



Scheme 2. Application of the organocatalytic CO formation (**A**) towards various carbonylative cross couplings at elevated temperatures (**B**-**G**). Yields refer to isolated material after chromatographic purification. For detailed reaction conditions see SI. Bn = benzyl, PMP = *para*-methoxyphenyl.

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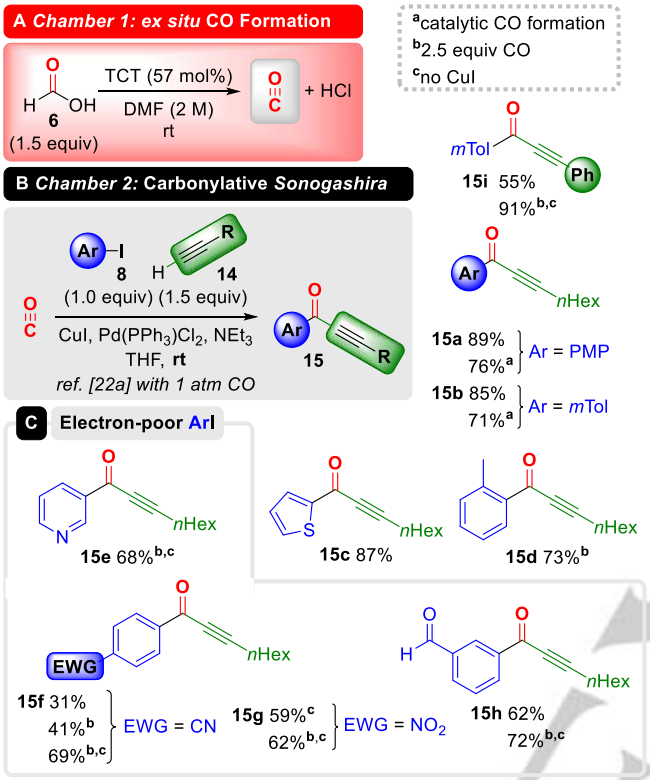
Ultimately, in a challenging carbonylative Sonogashira coupling at room temperature gaseous CO[22a] was substituted by the present approach using DMF as solvent (Scheme 3). Albeit in most cases CO was formed at room temperature in DMF as solvent (Scheme 3 **A**), examples **15a**+**b** show that catalytic CO release at 80 °C is also feasible. Especially in the case of electron deficient aryl iodides of type **8** the direct Sonogashira coupling without CO incorporation usually is predominant.[23]

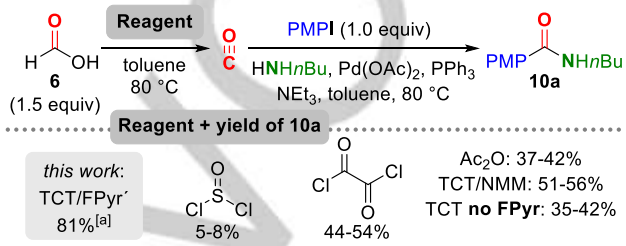


Scheme 3. A CO formation and **B** carbonylative Sonogashira coupling at room temperature. *m*Tol = *m*eta-tolyl, a. For conditions see Scheme 2 **A**. b. Prepared from 2.5 equiv of formic acid and 95 mol% TCT. EWG = electron withdrawing group, *m*Tol = *meta*-tolyl.

In the past, this problem has been circumvented by exploitation of the expensive and sensitive ligand P(*t*Bu)$_3$.[23b] In contrast, the present approach allows for the synthesis of the ynones **15e**-**h** even derived from highly electron poor aryl iodides containing nitro groups using plain PPh$_3$ (Scheme 3 **C**). Indeed, under standard conditions with 1.5 equiv CO ynone **15f**, which is deduced from electron-deficient *para*-cyanophenyl iodide, was formed as side-product in 31% yield besides the respective Sonogashira coupling product in 40% yield (Scheme 3 **C** and SI). An increase of the amount of CO to 2.5 equiv resulted in a minor improvement of the yield to 41%. However, when CuI was omitted, the desired ketone **15f** could be isolated in 69% yield. Moreover, even electron poorer 4-nitrophenyl iodide could be transformed into the corresponding carbonylated product **15g** in 59-62% yield. As an important aspect, also more reactive aryl alkynes, are suitable substrates, as confirmed by the synthesis of ynone **15i**. Again, without CuI the yield could be essential improved from 55 to 91%.

Moreover, the amide **10a** was formed in up to 88% yield when formic acid was engaged as yield-limiting starting material (1.0 equiv, see chp. 1.3 in the SI). This outcome proves high levels of CO incorporation. As an important feature, the present method is operationally simple and does not require a reaction setup in a glove box to exclude air like some other CO surrogates (see also graphical procedure in chp. 3.2.2 in the SI).

To the best of our knowledge, reactions of formic acid with ordinary chlorination agents like oxalyl and thionyl chloride have so far not been harnessed to access CO for carbonylative transformations. Against this background, a rigorous comparative assessment against other protocols for the activation of carboxylic acids was carried out (Scheme 4). Thereby, several experiments for each method were conducted under variation of the amount of base, which is why ranges of yields are stated (see also chp. 1.2 in the SI).



Scheme 4. Comparative aminocarbonylations. For detailed reaction conditions see SI, yield determined with internal standard. [a] isolated yield. NMM = *N*-methylmorpholine.

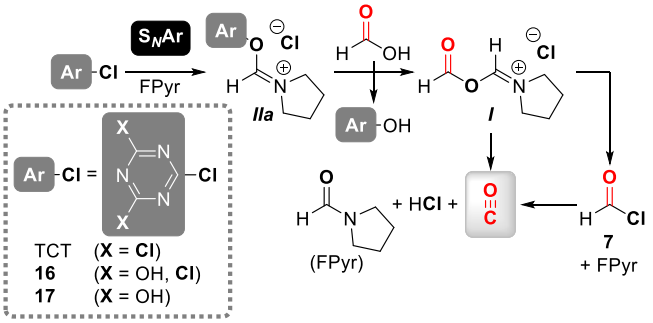
Indeed, reaction of formic acid with either thionyl or oxalyl chloride (SOCl$_2$ or C$_2$O$_2$Cl$_2$)[19] afforded the model amide **10a** in low yields of 5-8% and 44-54%, respectively, while the current method provides this amide in 81% yield. Despite *in situ* use of the mixed anhydride of formic and acetic acid allows carbonylative cross couplings,[10] *ex situ* preparation from Ac$_2$O and **6** delivered **10a** in synthetically non-useful yields of 37-42%. TCT and the amine base NMM have been engaged for the activation of carboxylic acids as mixed anhydrides with cyanuric acid.[24] When this protocol was applied to methanoic acid, amide **10a** arose in yields of 51-56%. Hence, the current organocatalytic approach is indeed superior to other carboxylic acid activation strategies.

The gas volumetric measurements confirmed that basically no decarbonylation takes place without FPyr (Figure 1 **C**). In contrast, the amide **10a** was still obtained in 35-42% yield, when FPyr was omitted. A likely explanation for this result is the diffusion of NEt$_3$ from the CO consuming chamber 1 into the CO producing chamber 2, which could effect mixed anhydride activation as in the case of TCT/NMM (see above).

In alignment to our previous work,[16a] the CO formation should be initiated by a nucleophilic aromatic substitution (S$_N$Ar) of a Cl atom of TCT through FPyr (Scheme 5). The emerging intermediate ***IIa*** shows structural similarities to the Vilsmeier Haack reagent. Next, substitution with formic acid would deliver salt ***I*** and dichlorohydroxytriazine (**16**). Intermediate ***I*** possesses a good leaving group and could undergo decarbonylation directly.

Alternatively, ***I*** could also proceed a nucleophilic substitution to yield formyl chloride (**7**), which is labile and would consequently decompose to CO and HCl.[18] As demonstrated through the gas volumetry with an excess of HCO$_2$H (Figure 1 **A**), **16** passes sequential transformation with FPyr and methanoic acid to generate intermediate ***I*** and chlorodihydroxytriazine (**17**). Finally, the remaining Cl atom of **17** is at least in part replaced by FPyr to again afford carboxy iminium salt ***I*** and cyanuric acid. This was

proven by gas volumetry (Figure 1 **A**) and in addition cyanuric acid was confirmed as by-product in our previous contributions.[16a,17b]



Scheme 5. Proposed mechanism.

Conclusion

The first organocatalytic method for the *ex situ* formation of CO from non-derivatized formic acid has been presented. Formamide catalysis enabled the transformation into CO by means of substoichiometric amounts of the bulk chemical TCT. As an important aspect, utilization of DMF as solvent and catalyst facilitates a rapid CO generation at room temperature. Implementation to four different carbonylative cross couplings, which also includes a carbonylative Sonogashira reaction at room temperature with challenging electron poor aryl iodides, proved high synthetic value. High levels of practical relevance were certified by the synthesis of the bioactive compounds, namely DEET and Moclobemide.

In addition, isotopically labeled molecules like the drug Moclobemide are amenable using commercial ^{13}C-enriched formic acid. Although HCl is generated simultaneously, even very acid sensitive functional groups are fully compatible. In order to exchange gaseous CO or other CO surrogates through the current methodology, the amount of base simply has to be adapted according to the amount of formic acid. Finally, comparison experiments witnessed that the present approach is superior to other common carboxylic acid activation procedures.

We are convinced that the high levels of synthetic utility and versatility and the low costs associated will pave the way for a rapid uptake of the current approach. Current efforts are dedicated towards the exploitation of CO and HCl for product incorporation.

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Keywords: carbon monoxide • C1 building blocks • carbonylation • homogenous catalysis • CO surrogates • organocatalysis

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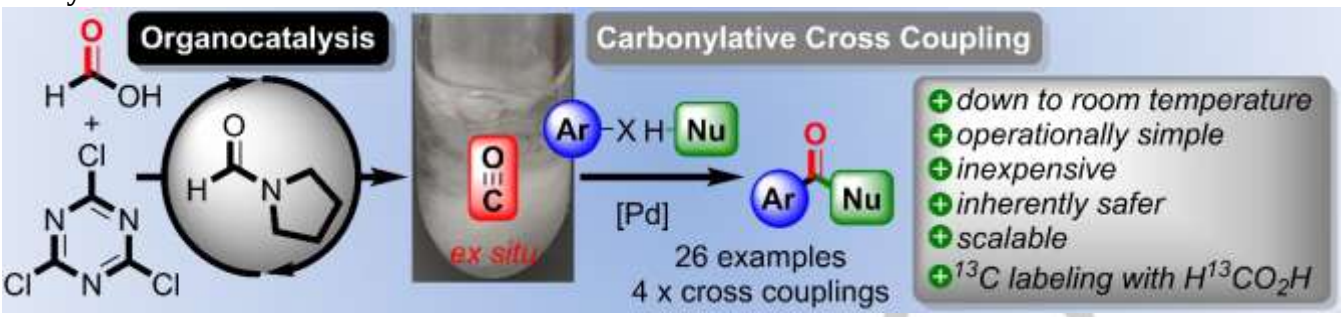

Double Formicable: A simple **form**amide catalyst enables the rapid transformation of **form**ic acid into carbon monoxide (CO) using inexpensive trichlorotriazine (TCT). Application towards four different carbonylative cross couplings down to room temperature showcases high levels of synthetic utility and versatility. The organocatalytic *ex situ* formation of CO using commercial $H^{13}CO_2H$ allows the synthesis of radiolabeled compounds such as the drug Moclobemide.

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