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Chloroform as a Carbon Monoxide Precursor: *In* or *Ex Situ* Generation of CO for Pd-Catalyzed Aminocarbonylations

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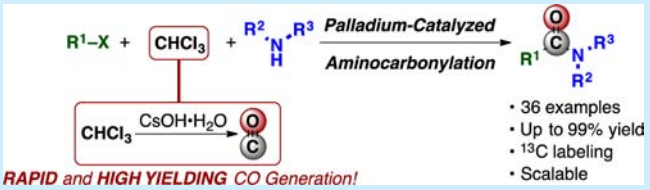
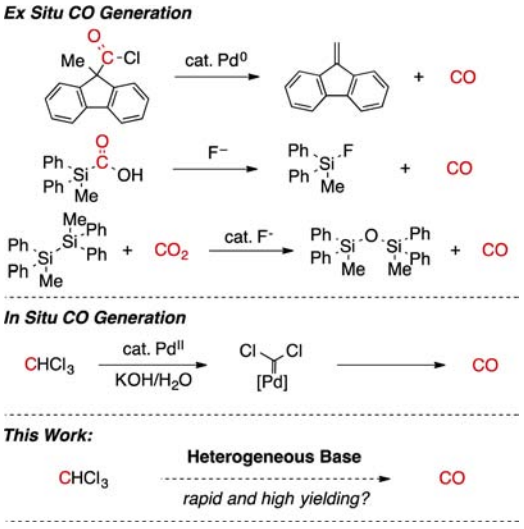
Supporting Information

ABSTRACT: Conditions for the rapid hydrolysis of chloroform to carbon monoxide (CO) using heterogeneous CsOH·H_2O are described. CO and ^{13}CO can be generated cleanly and rapidly under mild conditions and can be captured either *in* or *ex situ* in palladium-catalyzed aminocarbonylation reactions. Utilizing only 1−3 equiv of CO allows for the aminocarbonylation of aryl, vinyl, and benzyl halides with a wide variety of primary and secondary amines giving amide products in good to excellent yields.



Carbon monoxide (CO) represents an important C1 building block for organic synthesis. Its combination with transition metal catalysts allows for the facile installation of a carbonyl group into an organic molecule under mild conditions.[1−3] As CO is a highly toxic gas that is often required in excess, chemists have devised alternative methods that avoid its direct use.[4,5] A popular approach employs toxic transition metal carbonyl complexes.[4] However, it is important to identify CO sources that are inexpensive, easily implemented, and less toxic. Recent elegant approaches involve the *ex situ* generation of CO from an organic precursor, such as an acid chloride, silacarboxylic acid, or carbon dioxide (Scheme 1).[5a−d] While these precursors are general, they can require multistep synthesis and complex reaction setups and generate high molecular weight byproducts. It would be advantageous to identify a CO precursor that avoids these drawbacks.

Scheme 1. Previously Reported *in* and *ex Situ* CO Precursors[5a−d,9]



Chloroform ($CHCl_3$) is an inexpensive bulk chemical that has the potential to serve as a highly practical CO precursor for transition-metal-mediated carbonylation reactions. Further, as $^{13}CHCl_3$ and $^{14}CHCl_3$ are commercially available, such methodology would also allow for the facile incorporation of ^{13}CO and ^{14}CO into organic and organometallic compounds to give isotopically enriched products.

$CHCl_3$ has been known since 1862 to undergo hydrolysis in the presence of strongly basic aqueous hydroxide solutions to produce CO.[6] Unfortunately, this desirable transformation is constrained by slow reaction rates and low yields.[7] Further, side reactions of intermediate dichlorocarbene, such as disproportionation or cycloadditions to unsaturated linkages, often outcompete hydrolysis.[7,8]

The use of $CHCl_3$ as a CO source in the Pd-catalyzed synthesis of benzoic acids has been reported.[9] The reaction requires solvent quantities of both $CHCl_3$ and 60 wt % KOH in H_2O and only affords a 2.3% *in situ* yield of CO after 5 h. Mechanistic investigations suggest that the Pd-catalyst serves two purposes: to catalyze the hydrolysis of $CHCl_3$ and to catalyze the subsequent hydroxycarbonylation reaction.[9] Expansion of this approach to other carbonylation reactions is hindered due to the requirement for $CHCl_3$ as the organic reaction solvent, the low yield of CO, and the biphasic reaction conditions.[10] Due to these constraints, undesirable side reactions, such as hydroxycarbonylation, direct noncarbonylative coupling, or homocoupling can occur simultaneously. Thus, a new protocol for CO generation from $CHCl_3$ must be developed for this to become a practical and general method.

For $CHCl_3$ to serve as an effective and practical CO precursor, its hydrolysis must be rapid to allow the carbon-

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ylation reaction to outcompete noncarbonylative couplings. Additionally, the hydrolysis must be high yielding, so that a large excess of $CHCl_3$ is not required to achieve a high yield of the carbonyl product. Finally, the hydrolysis conditions must be relatively anhydrous, to allow the desired nucleocarbonylation to outcompete hydroxycarbonylation.

With these challenges in mind, we focused our initial efforts on developing conditions for facile and rapid $CHCl_3$ hydrolysis. We hypothesized that utilization of a heterogeneous hydroxide base in an organic solvent may allow for rapid hydrolysis at its surface. 1.0 equiv of $CHCl_3$ was heated at 80 °C in toluene in the presence of a variety of heterogeneous bases, and both the yield and rate of gas generation were determined. Indeed, employing heterogeneous bases leads to CO generation, with 3.3 equiv of $CsOH{\cdot}H_2O$ affording an approximate 50% yield after 15 min and 78% yield after 5 h (Figure 1).[10] The use of

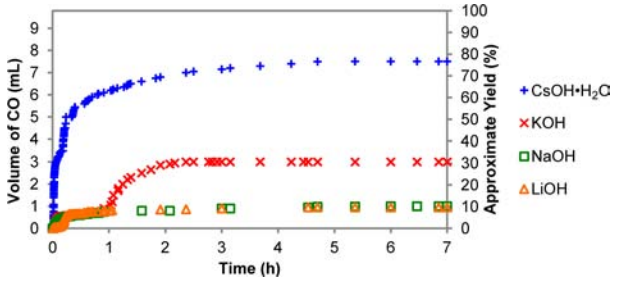


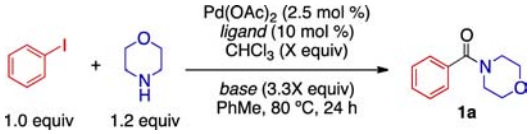
Figure 1. Heterogeneous $CHCl_3$ hydrolysis. Conditions: Base (1.33 mmol), $CHCl_3$ (0.40 mmol), PhMe (0.80 mL), 80 °C. See Supporting Information for more details.

the cesium salt is critical, as the analogous lithium, sodium, and potassium bases lead to a much slower evolution giving only a 6% yield of CO after 15 min. Not only were the reactions significantly slower with these bases, they were also drastically lower yielding, affording only 10%, 10%, and 30% yields, respectively, even after 24 h.[10] The identity of the gas generated was confirmed to be CO by a known chemical method.[10,11]

With an effective method for generating CO from $CHCl_3$ in hand, we next looked to incorporate it in a carbonylation reaction using an *in situ* CO generation protocol. We focused on the palladium-catalyzed aminocarbonylation of organic halides, as amides are a prominent functionality found in pharmaceuticals,[12] natural products,[13] and materials.[14] Initial efforts focused on the model reaction between iodobenzene, morpholine, and $CHCl_3$ (Table 1). As elaborated in Tables S1−S11, a variety of reaction conditions were explored to allow for an *in situ* CO generation and to optimize the yield of **1a**.[10] This included varying catalyst, ligand, $CHCl_3$ equivalencies, temperature, and solvent. In accordance with previous reports on Pd-catalyzed aminocarbonylation, bidentate phosphine ligands, such as DPEphos, provide high yields of **1a**.[15] Consistent with the CO generation studies, $CsOH{\cdot}H_2O$ is the superior base giving a 91% yield of **1a** whereas LiOH, NaOH, and KOH lead to yields of 0%, 20%, and 61%, respectively.

The optimized conditions are as follows (Table 1, entry 3): 1.0 equiv of iodobenzene, 1.2 equiv of morpholine, 2.5 mol % $Pd(OAc)_2$, 10 mol % DPEphos, 3.0 equiv of $CHCl_3$, and 10 equiv of $CsOH{\cdot}H_2O$ in toluene (0.2 M) under N_2 in a sealed vial at 80 °C. These conditions afford the benzamide **1a** in 91% isolated yield. Notably, neither the product resulting from *N*-arylation nor that of a double carbonylation are observed.[16]

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	base	$CHCl_3$ (equiv)	*in situ* yield (%)[b]
1	DPEphos	$CsOH{\cdot}H_2O$	1	40
2	DPEphos	$CsOH{\cdot}H_2O$	2	77
3	**DPEphos**	**$CsOH{\cdot}H_2O$**	**3**	**91**
4	PPh_3	$CsOH{\cdot}H_2O$	3	62
5	±-BINAP	$CsOH{\cdot}H_2O$	3	46
6	dppf	$CsOH{\cdot}H_2O$	3	72
7	dppp	$CsOH{\cdot}H_2O$	3	58
8	DPEphos	LiOH	3	0
9	DPEphos	NaOH	3	20
10	DPEphos	KOH	3	61
11	DPEphos	tBuOK	3	15
12	DPEphos	NaHMDS	3	0
13	DPEphos	Et_3N	3	0

[a] $Pd(OAc)_2$ (2.5 mol %), ligand (10 mol %), base (3−10 equiv), chloroform (1−3 equiv), PhMe, 80 °C, 24 h. [b] *In situ* yield determined by gas chromatography with comparison to undecane (10 μL) as an internal standard.

High isolated yields are obtained utilizing standard glovebox (91%) or air-free protocols (85%). Moreover, the reaction is easily scalable; an 89% yield was obtained on a 10 mmol scale. Finally, utilization of isotopically enriched $^{13}CHCl_3$ demonstrates a powerful application of this aminocarbonylation reaction, as **^{13}C-1a** was isolated in 96% yield; using only 1.0 equiv of $^{13}CHCl_3$ reduced the isolated yield to 56%.

Whereas previous reports suggest a transition metal catalyzed hydrolysis of $CHCl_3$,[9,17] CO formation under these new conditions is rapid and high yielding in both the presence or absence of the Pd catalyst. This implies a hydrolysis mechanism that is fundamentally different than what previous reports involving transition metals have suggested and that this protocol could be amenable to an *ex situ* CO generation protocol, where the CO-generating and CO-consuming reactions have been separated.[10] Indeed, employing *ex situ* CO generation affords **1a** in 85% isolated yield. To gain further mechanistic insight, the initial rates for the *in* and *ex situ* setups were determined and found to be nearly identical, 1.4×10^{-5} and 1.3×10^{-5} $M{\cdot}s^{-1}$, respectively.[10]

Having successfully incorporated this CO-generation method into the aminocarbonylation of iodobenzene with morpholine, the amine scope was next explored (Scheme 2). Cyclic and acyclic secondary amines are all incorporated in good to excellent yields (**1a−1e**) with 10 mol % DPEphos, while primary aliphatic amines (**1f−1l**) and anilines (**1m−1q**) both afford the corresponding amide using 3.75 mol % DPEphos.[10] Sterically hindered amines, such as di-*iso*-propylamine, *tert*-butylamine, and 2,6-dimethylaniline were all effective nucleophiles, affording the amides **1d**, **1h**, and **1p** in 62%, 87%, and 70% yields, respectively. Further, electron-rich anilines afford the product in higher yields than their less nucleophilic, electron-poor counterparts, as 4-methoxyaniline was incorporated in 96% yield while 4-trifluoromethylaniline only afforded a 59% yield.

Both aryl iodides and aryl bromides undergo the Pd-catalyzed aminocarbonylation reaction. The conditions are

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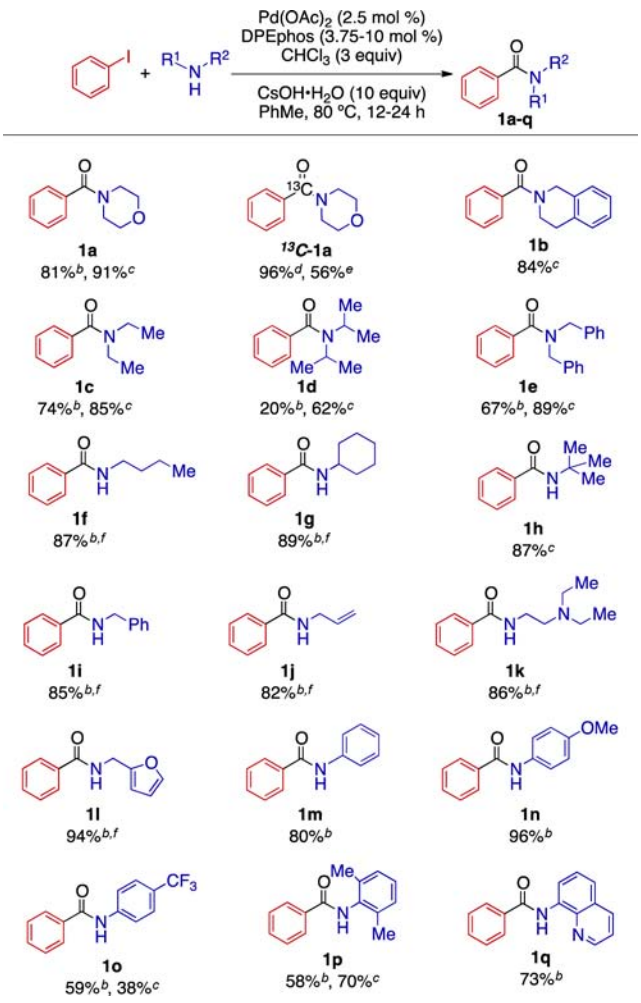
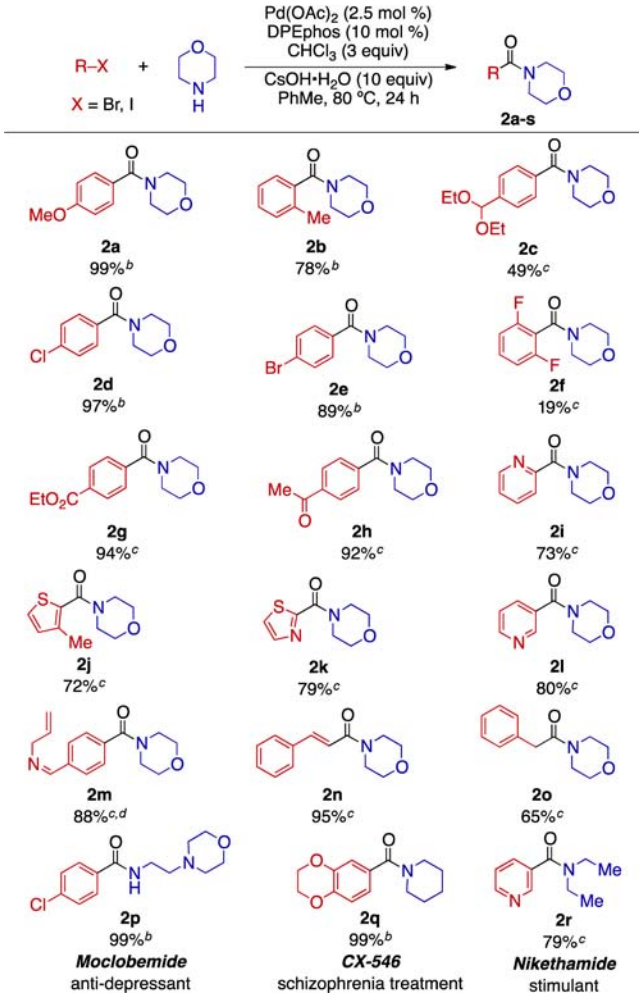
Scheme 2. Aminocarbonylation of Amines with Iodobenzene[a]



[a]General conditions: $Pd(OAc)_2$ (2.5 mol %), DPEphos (3.8−10 mol %), $CsOH·H_2O$ (10 equiv), iodobenzene (1.0 equiv), amine (1.2 equiv), chloroform (3 equiv), PhMe, 80 °C. Heated for 24 h unless otherwise specified. [b]With 3.75 mol % DPEphos. [c]With 10 mol % DPEphos. [d]With 3.0 equiv of $^{13}CHCl_3$. [e]With 1.0 equiv of $^{13}CHCl_3$. [f]Reaction conducted for 12 h.

Scheme 3. Aminocarbonylation of Halides with Morpholine[a]



[a]General conditions: $Pd(OAc)_2$ (2.5 mol %), DPEphos (10 mol %), $CsOH·H_2O$ (10 equiv), halide (1.0 equiv), amine (1.2 equiv), chloroform (3 equiv), PhMe, 80 °C. [b]Iodide used. [c]Bromide used. [d]Isolated after *in situ* reduction by $NaBH_4$.

tolerant of a wide variety of functionalities on the halides (Scheme 3), including ethers, acetals, halides, esters, and ketones (**2a**−**2h**). Importantly, as with other Pd-catalyzed coupling reactions, chemoselectivity was observed in the aminocarbonylation of 4-bromoiodobenzene, affording **2e** in 89% isolated yield.[18] Heterocyclic compounds are readily functionalized: pyridines (**2i** and **2l**), thiazoles (**2k**), and thiophenes (**2j**) readily undergo the aminocarbonylation reaction. The sterically hindered 2-iodotoluene and 2,6-difluoro-1-bromobenzene gave the desired product, in 78% and 19% yield, respectively. Further, the reaction is not limited to aromatic bromides and iodides, as vinyl and benzyl bromides afford the new amides **2n** and **2o** in 95% and 65% yields, respectively.

Dichlorocarbene is a known intermediate in the hydrolysis of $CHCl_3$ and has been shown to undergo [2 + 1]-cycloadditions with alkenes and imines to afford the corresponding cyclopropanes and aziridines.[7,8] To probe the lifetime of dichlorocarbene under these conditions, a competition experiment was carried out to afford the product **2m**. As demonstrated by the 88% isolated yield and inspection of crude reaction mixtures by GC-MS, aminocarbonylation occurs selectively, even in the presence of 1.0 equiv of *n*-Bu_4NBr, a phase transfer catalyst often employed to promote reactions with dichlorocarbene.[7] This indicates that dichlorocarbene is short-lived under the reaction conditions and that CO generation is faster than other pathways.

To show the utility of this aminocarbonylation protocol, it was applied to the synthesis of several pharmaceuticals (Scheme 3, **2p**−**2r**): Moclobemide[19] (**2p**), CX-546[20] (**2q**), and Nikethamide[21] (**2r**) were afforded in 99%, 99%, and 79% yields, respectively.

In conclusion, we have developed conditions for $CHCl_3$ hydrolysis that are clean, rapid, and high yielding. The generated CO and ^{13}CO can be efficiently incorporated into an aminocarbonylation reaction with excellent functional group tolerance and amine scope. Further it has been applied to the synthesis of several pharmaceuticals as well as an isotopically ^{13}C labeled amide. The work presented herein represents a major advance in the use of CO releasing molecules in transition metal mediated carbonylation reactions. Future work

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will focus on expanding the coupling partner scope and applying this protocol to other carbonylation reactions.

■ ASSOCIATED CONTENT

Supporting Information

Select optimization results, kinetic studies, experimental procedures, and spectroscopic data for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01385.

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Notes

The authors declare no competing financial interest.

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