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Photoinduced CO-releasing molecule (photoCORM) as *in situ* CO surrogate for palladium-catalysed aminocarbonylation

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Abstract

Herein, we show that a photoCORM behaves as a highly substrate-tolerant, photoactivable *in situ* CO surrogate, allowing the synthesis of variously functionalised amides including the biologically active compound Moclobemide by Pd-catalysed aminocarbonylation between aryl iodides and amines under mild conditions. This work should bring about a useful input to the field of carbonylative transformations.

Palladium-catalysed carbonylation has witnessed a remarkable rise during the last decades, enabling the synthesis of highly elaborate synthons. For this purpose, carbon monoxide (CO) gas remains the most important precursor for carbonyl incorporation.^{1,2} Despite its high synthetic potential, CO also presents several drawbacks. It is a colourless and odourless gas that exhibits acute toxicity. Its handling is tricky and imposes a series of constraints. For instance, pressurized cylinders, special equipment and CO detectors are required to prevent leakage and to ensure safe handling. As a result, efforts have been invested in developing more convenient and safer alternatives to CO gas.³ Especially, research has been focused on compounds that could stoichiometrically release CO for carbonylative transformations either via *ex situ* or *in situ* approaches.^{4–8} However, many CO surrogates present major shortcomings and notably their incompatibility with certain functional groups such as amines or alcohols. Furthermore, chemical activation is generally needed to ensure the generation of CO. In this scenario, acetic anhydride⁹, DCC¹⁰, alkaline base,¹¹ or Pd catalysts¹² are required for CO generation. Moreover, most of the previously reported reactions must be performed under thermal conditions and high temperatures are often applied to ensure completion and / or acceptable yields. As such, when applied as *in situ* CO sources, many CO surrogates are limited to transformations that are not affected by these reactive functional groups and activators. An important milestone has been achieved by Skrydstrup with the development of the two-chamber system (COware tube).¹³ This *ex situ* process physically separates the CO generation step from the carbonylation reaction step in two different chambers connected by a headspace. In the same vein, Wu recently developed the In-Ex tube for the production of CO.¹⁴ The two-chamber systems bypass the chemical incompatibilities but require specialized glassware and elaborate reaction setups. In addition, these protocols often need an excess of CO surrogates to reach acceptable reaction yields. The last decade has shown the development of new surrogates (Figure 1). For instance, in 2013, Manabe introduced *N*-formylsaccharin as stable and convenient CO source for the formylation of aryl bromide. In 2016, Wu introduced benzene-1,3,5-triyl triformate (TFBen) as an *in situ* inert CO source and applied it in several transformations.^{15,16}

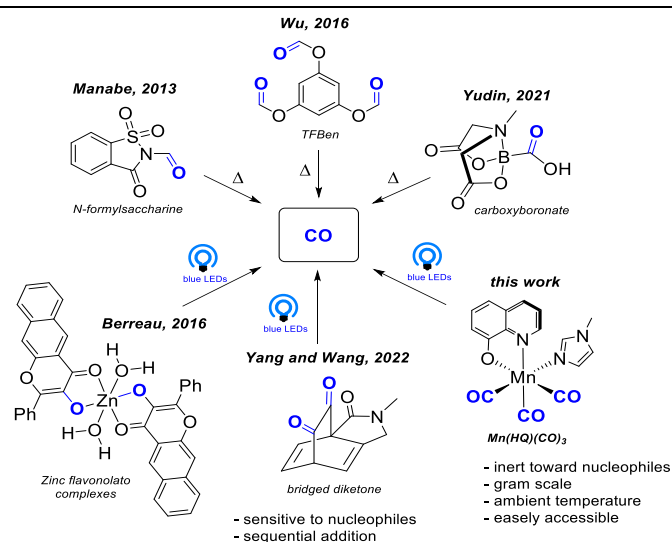
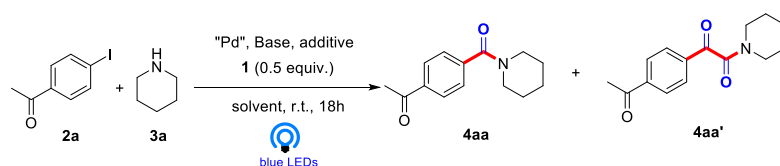


Figure 1: Representative CO surrogates for *in-situ* generation of CO.

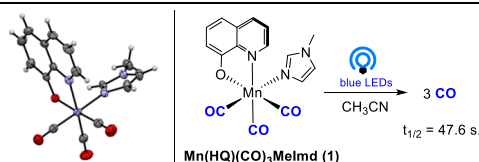
Table 1. Optimization of the reaction conditions for Pd-catalysed aminocarbonylation using **1** as photoactivable *in-situ* CO surrogate.^a



Entry	Solvent	Base	Pd source	Additive	Yield of 4aa ^b	Yield of 4aa' ^b	2a ^b
1	CH ₃ CN	Et ₃ N	Pd(PPh ₃) ₄ 5%	/	65%	22%	/
2	CH ₃ CN	Et ₃ N	Pd(PPh ₃) ₄ 5%	TEMPO	72%	13%	14%
3	CH ₃ CN	Et ₃ N	PdCl ₂ (PPh ₃) ₂ 5%	TEMPO	87%	11%	/
4	CH ₃ CN	Et ₃ N	PdCl ₂ (dppe) 5%	TEMPO	22%	/	75%
5	CH ₃ CN	Et ₃ N	PdCl ₂ (dppp) 5%	TEMPO	46%	8%	45%
6	CH ₃ CN	Et ₃ N	PdCl ₂ (dppf) 5%	TEMPO	72%	10%	11%
7	CH ₃ CN	DABCO	PdCl ₂ (PPh ₃) ₂ 5%	TEMPO	68%	/	27%
8	CH ₃ CN	K ₂ CO ₃	PdCl ₂ (PPh ₃) ₂ 5%	TEMPO	69%	/	18%
9	CH₃CN	DBU	PdCl₂(PPh₃)₂ 5%	TEMPO	92% (86%^c, 87%^{c,d})	/	4%
10	1,4-dioxane	DBU	PdCl ₂ (PPh ₃) ₂ 5%	TEMPO	86%	/	3%
11	THF	DBU	PdCl ₂ (PPh ₃) ₂ 5%	TEMPO	77%	/	4%
12	toluene	DBU	PdCl ₂ (PPh ₃) ₂ 5%	TEMPO	83%	/	12%
13	CH ₃ CN	DBU	PdCl ₂ (PPh ₃) ₂ 2%	TEMPO	40%	/	56%
14	CH ₃ CN	DBU	PdCl ₂ (PPh ₃) ₂ 1%	TEMPO	28%	/	53%
15	CH ₃ CN	DBU	PdCl ₂ (PPh ₃) ₂ 5%	/	43%	/	/
16 ^e	CH ₃ CN	DBU	PdCl ₂ (PPh ₃) ₂ 5%	TEMPO	/	/	98%
17 ^f	CH ₃ CN	DBU	PdCl ₂ (PPh ₃) ₂ 5%	TEMPO	16%	/	80%

^a reaction conditions: **2a** (0.5 mmol), **3a** (1 mmol) in 2 mL of solvent. ^b NMR yield, 1,3,5-trimethoxybenzene was used as standard. ^c isolated yield. ^d gram scale. ^e in the dark. ^f room light instead of blue LEDs irradiation

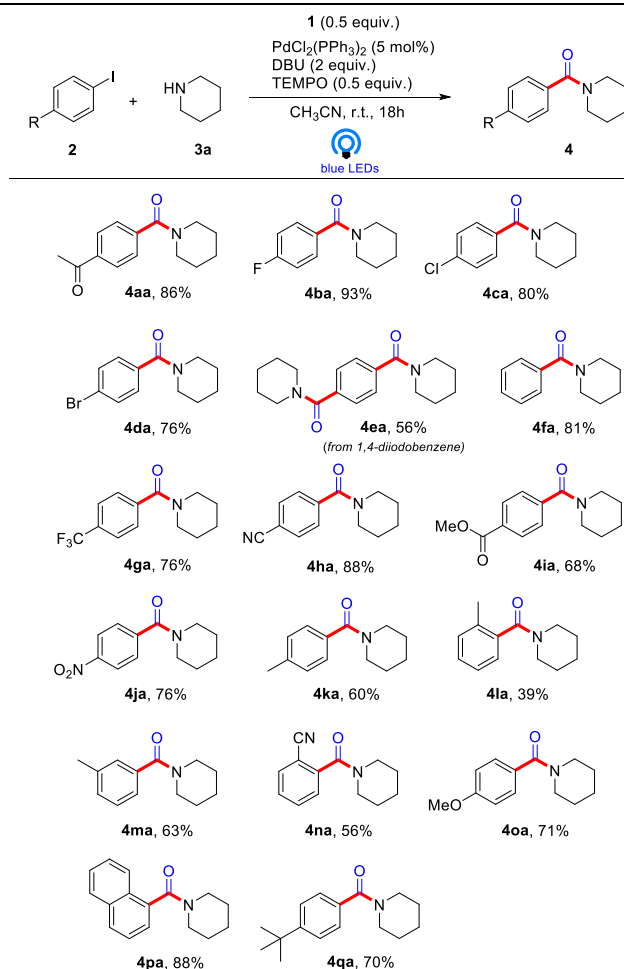
Another important milestone was achieved in 2021 with the work of Yudin, where he introduced carboxyboronate as an *ex situ* or *in situ* source of CO in Pd-catalysed carbonylative reactions.¹⁷ Even if these reagents are compatible with the *in situ* CO generation approach, they nonetheless require high thermal conditions. Therefore, a general CO surrogate and especially an *in situ* CO surrogate operating under mild conditions and compatible with a wide range of functional groups is still in demand. Surprisingly, photoinduced CO release strategies have remained largely underexplored to date. In 2016, Berreau introduced zinc flavonolato complexes as solid-state CO surrogates activated by blue light.¹⁸ Initial tests valed the compatibility of the complexes as an *in situ* CO generator in Pd-catalysed alkoxy carbonylation reaction. Another example has been disclosed in 2022 with the work of Yang and Wang that demonstrated the photoinduced CO-releasing capacity of bridged 1,2-diketone under blue light activation and successfully applied this CO surrogate in Pd-catalysed carbonylative reactions as a proof-of-concept.¹⁹ However, as the diketone reacts with nucleophiles such as amines and alcohols, CO production had to be run first in the absence of the nucleophile which was added sequentially after CO release, which strongly restricts its use. We recently introduced a series of Mn-based photoinduced CO-releasing molecules (photoCORMs) named Mn(HQ)(CO)₃(Imd) with HQ = 8-hydroxyquinoline and Imd = imidazole derivatives.²⁰ All complexes present a fast CO releasing profile with the production of 3 moles of CO per mole of complex upon blue LED irradiation, along with concomitant oxidation of the metal centre. In this series, the complex bearing a methyl imidazole ligand **1** was studied in more detail and presents many advantages. This complex is easily accessible from simple starting materials in one step, is soluble in all common organic solvents, and can release all its CO ligands under either aerobic or anaerobic conditions (Scheme 1).²⁰



Scheme 1: Structure and properties of Mn(HQ)(CO)₃Melmd (**1**).²⁰

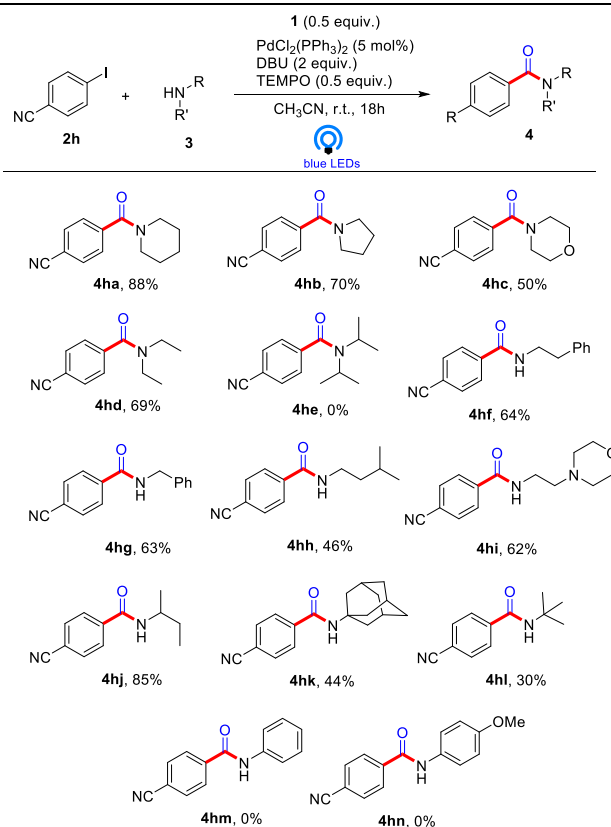
This fast liberation of 3 moles of CO per mole of complex prompted us to investigate their behaviour in visible light-mediated, Pd-catalysed reactions. Herein, we disclose that photoCORM **1** acts as an efficient and convenient source of CO in an operationally simple setup for the aminocarbonylation of aryl iodide with *in situ* generation of CO under blue LED irradiation in aerobic condition. We initiated our study by optimizing the parameters of the aminocarbonylation reaction with 4-iodoacetophenone **2a** and piperidine **3a** as model substrates in the presence of 0.5 eq. of **1** as CO surrogate (Table 1). We first explored the nature of the catalyst. Pleasingly, when the reaction was run with 5 mol% of tetrakis(triphenylphosphine) palladium(0) (Pd(PPh₃)₄) in the presence of triethylamine as the base in acetonitrile, a mixture of monocarbonylated and dicarbonylated products **4aa** and **4aa'** was obtained (entry 1) with **4aa** as the main reaction product. More surprisingly, acetophenone was also identified in the reaction mixture, resulting from dehalogenation of the starting aryl iodide. This side reaction could be explained by the high reductive property of Mn(I) after CO departure that elicited the reduction of the aryl iodide. To overcome this issue, TEMPO was

introduced as sacrificial electron acceptor to prevent the iodide reduction, giving rise to a slight increase in the reaction yield (entry 2). However, under these conditions, the reaction did not reach completion. Changing Pd(0) to PdCl₂(PPh₃)₂ allowed to reach full conversion but still afforded a mixture of mono- and dicarbonylated products (entry 3). The use of bidentate phosphines such as 1,2-bis(diphenylphosphino)ethane (dppe), 1,2-bis(diphenylphosphino)propane (dppp) or 1,1'-bis(diphenylphino)ferrocene (dppf) proved to be detrimental to catalysis (entries 3-6). Notably, a marked decrease in the reaction yield was observed with dppe but without double carbonylation product. The base appeared to be also a critical parameter to investigate. The use of DABCO or potassium carbonate (entries 7 and 8) abolished the formation of **4aa'** but without completion. The use of DBU as base improved the reaction yield and furnished exclusively the monocarbonylation adduct in excellent yield (entry 9). This result is fully in line with the work of Yamamoto where he demonstrated that DBU promoted single carbonylation products at the expense of double carbonylation ones.²¹ The role of the solvent was also investigated (entries 10-12). Common organic solvents suitable for carbonylation reactions were screened and all displayed good efficiency. Finally, decreasing the catalyst loading to 2 or 1 mol% afforded lower yields (Entries 13 and 14). As a control, no conversion was observed when the reaction was carried out in the dark, and the aryl iodide was fully recovered (entry 16). When room light was used instead of LED, very poor conversion was observed, suggesting a slow release of CO (entry 17). Noteworthy, the reaction could be achieved at the gram scale without any erosion of the yield (entry 9). From an experimental point of view, the reaction setup appears very simple. All reagents can be added at the time and the reaction could be run at different size scales. In addition, since complex **1** releases 3 CO upon irradiation, it can be used in a sub-stoichiometric amount with respect to reagents and the reaction by-product, i.e. the Mn^{II} complex generated after photo-release, can be readily removed by a simple acidic or basic work-up that greatly facilitates the purification step. With the optimized conditions in hand (Table 1, entry 9), the scope of aryl iodides was next investigated with piperidine **3a** as nucleophile (Scheme 2). A variety of functional group were engaged and well tolerated. *para*-Substituted aryl iodides with halogens afforded the corresponding amides **4ba**, **4ca** and **4da** in good yields. Good selectivity was observed for the iodide derivatives. Indeed, when bromo or chloro iodobenzene were used as electrophiles, the reaction only took place on the iodide part, allowing further functionalization by Pd cross-coupling reaction from the bromide or the chloride partner. Interestingly, when 1,4-diodobenzene was used as electrophile, a double reaction was observed leading to the di-functionalized arene **4ea** in good yield. Substrates having electron-withdrawing substituents such as trifluoromethyl, cyano, ester or nitro in *para* position reacted with piperidine to afford **4ja-ga** in good to excellent yields. *ortho*-Substituted aryl iodides reacted more slowly due to steric hindrance, resulting in a drop of reaction yield.



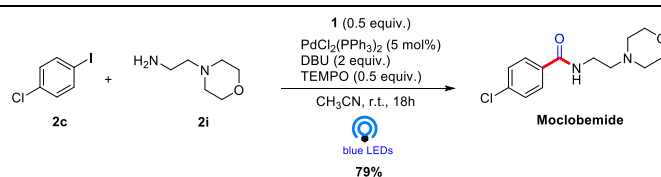
Scheme 2: Scope of Pd-catalysed aminocarbonylation of aryl iodides **2** with piperidine **3a** using **1** as photoactivable *in-situ* CO surrogate.

The scope of amines was then explored with 4-iodobenzonitrile **2h** as electrophile. In addition to piperidine, other cyclic amines such as pyrrolidine, morpholine were well-tolerated and gave the corresponding amides **4ha-hc** in good yields. Secondary acyclic amines also reacted albeit with a slight decrease in the reaction yield. However, when a bulky secondary amine was used such as diisopropylamine, no conversion was observed and only the aryl iodide was recovered. Primary amines reacted smoothly under these reaction conditions and afforded the corresponding primary amides **4hf-hl** and **4hk-hm** in moderate to good yields. When the steric hindrance of the primary amines increased, a decrease in the reaction yield was observed. Finally, as a limitation, when poor nucleophilic amines such as aniline derivatives were engaged, no reaction could be observed and all starting materials were recovered.



Scheme 3: Scope of Pd-catalysed aminocarbonylation of amines **3** with iodobenzonitrile **2h** using **1** as photoactivable *in-situ* CO surrogate.

To demonstrate the synthetic utility of our method, we applied our Pd-catalysed aminocarbonylation strategy to the synthesis of the pharmacologically active compound Moclobemide, a reversible selective inhibitor of monoamine oxidase (MAO) used to treat depression (Scheme 4). With this protocol, we were able to produce Moclobemide in one step from two commercially available precursors in 79% yield.



Scheme 4: Synthesis of biologically active compound (Moclobemide).

In conclusion, we disclosed a practical and operationally simple protocol for the palladium catalysed-aminocarbonylation of aryl iodides under blue LEDs irradiation at room temperature. The use of a photo-induced CO-releasing molecule (photoCORM) as a highly substrate-tolerant, *in situ* CO source has been achieved for the first time. The broad scope of the reaction and the excellent tolerance to a variety of functional groups were comprehensively demonstrated. Furthermore, the high synthetic potency of this reaction was shown by transposing it to the gram scale and for the one-step synthesis of a biologically active compound. Other palladium-catalysed reactions with photoCORM as *in situ* CO surrogate are currently under investigation in our laboratory and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

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