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Mechanochemical Palladium-Catalyzed Carbonylative Reactions Using $Mo(CO)_6$

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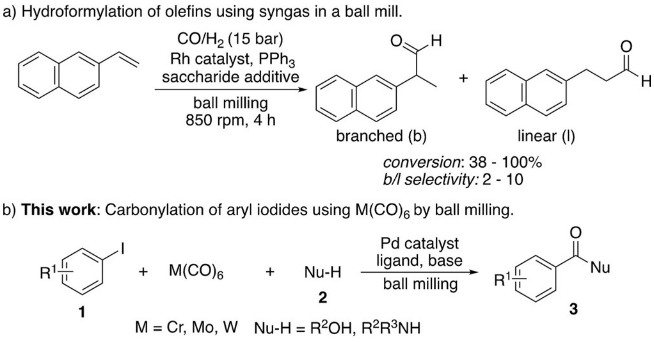
Abstract: Esters and amides were mechanochemically prepared by palladium-catalyzed carbonylative reactions of aryl iodides by using molybdenum hexacarbonyl as a convenient solid carbonyl source and avoiding a direct handling of gaseous carbon monoxide. Real-time monitoring of the mechanochemical reaction by in situ pressure sensing revealed that CO is rapidly transferred from $Mo(CO)_6$ to the active catalytic system without significant release of molecular carbon monoxide.



Scheme 1. Mechanochemical carbonylation reactions by ball milling.

Ball milling techniques are largely used in academia and in industry for advanced comminution and mixing of solids.[1] Due to the operational simplicity and especially to the effectiveness of ball milling to transduce mechanical loads to the sample being milled, a significant growth in the use of ball mills to mechanically induce chemical reactions has recently been experienced.[2] Intuitively, mechanochemical activation by ball milling appears more appropriate for solid samples. However, mechanical treatment of soft organic materials, liquids and even gaseous reactants has proven equally effective.[3]

In the case of mechanochemical reactions involving gaseous components, gases such as H_2,[4] O_2,[5] CO,[6] CO_2,[7] HCN,[8] C_3H_6,[9] CH_4,[10] among others,[11] have been reported to undergo clean chemical transformations inside ball mills in various areas of synthetic chemistry. For example, in 2017 Hapiot and coworkers reported a rhodium-catalyzed mechanochemical hydroformylation of styrene derivatives in a planetary ball mill using a mixture of CO/H_2 (Scheme 1 a).[12] Although the reactions led to high conversions of substrates such as 2-vinylnaphthalene without the need for external heating, they required a 15 bar pressure of carbon monoxide and hydrogen inside a pressurized milling vessel.[12] Notably, such a high pressure is however not an intrinsic requirement of the mechanochemical approach. In general, most carbonylation reactions rely on the use of special high-pressure laboratory equipment and involve the handling of odorless, toxic, and flammable CO gas. To mitigate this problem, carbonylation procedures were developed that improved both reaction performance and overall safety. Recent examples include the introduction of flow chemistry protocols to react gaseous CO,[13a] and the use of reagents with the ability to release or to form carbon monoxide in situ during the reaction.[13b,c] Among the latter, metal carbonyls, such as $M(CO)_6$ (M=Cr, Mo, W) and $Co_2(CO)_8$, have received large attention as convenient carbonyl sources avoiding the need for directly handling gaseous carbon monoxide.[13b,14] Although, the toxicity of metal carbonyls always depends on their stability, volatility and on the harmfulness of the given metal.

These precedents made us wondering if solid metal carbonyl complexes such as $M(CO)_6$ (M=Cr, Mo, W) could be activated by ball milling allowing for mechanochemical carbonylations. Specifically, the use of metal carbonyls as one-carbon building blocks in palladium-catalyzed carbonylation reactions, such as alkoxycarbonylations and aminocarbonylations, was envisaged (Scheme 1 b).[15] Herein, we report the findings on our investigation, which include the development of a solvent-free protocol for the palladium-catalyzed carbonylation by ball milling, the in situ pressure monitoring of the reaction, and the application of the mechanochemical approach to the synthesis of series of esters and amides.

Initially, the carbonylation reaction between iodobenzene (**1 a**), *n*-butanol (**2 a**), $M(CO)_6$ (M=Cr, Mo, W), K_3PO_4, and a catalytic system composed by $Pd(OAc)_2$/triphenylphosphine in a mixer mill was tested.[16] After 90 min of milling the crude mixtures of these experiments were directly analyzed by ^{1}H NMR spectroscopy. In all experiments, formation of butyl benzoate (**3 aa**) was confirmed, and out of the three metal carbonyl

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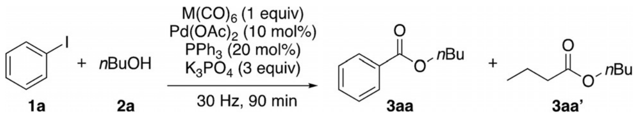
Table 1. Screening of metal carbonyls $M(CO)_6$ (M=Cr, Mo, W) in the mechanochemical carbonylation of **1a** with *n*-butanol **2a**.[a]



Entry	$M(CO)_6$	Yield **3aa** [%][b]	Yield **3aa'** [%][b]
1	$Cr(CO)_6$	13	26
2	**$Mo(CO)_6$**	**99**	**<1**
3	$W(CO)_6$	22	26

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $M(CO)_6$ (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), PPh_3 (0.04 mmol), and K_3PO_4 (0.6 mmol) were milled in a 5 mL stainless steel milling jar with one 10 mm milling ball of the same material. [b] Determined by ^1H NMR spectroscopy using ethylbenzene as the internal standard.

complexes tested molybdenum hexacarbonyl proved to be the most active one for the carbonylation reaction (Table 1, entry 2). In the reactions with $Cr(CO)_6$ and $W(CO)_6$, a competitive oxidative homocoupling reaction of **2a** led to the formation of butyl butyrate (**3aa'**).

Having observed chemical reactivity towards the carbonylative pathway for all the group 6 hexacarbonyl complexes, we wondered if the mechanical treatment of these complexes had promoted the release of molecular carbon monoxide inside the ball mill. To test this hypothesis, $M(CO)_6$ (M=Cr, Mo, W) were milled under air by using a planetary ball mill suitable for sensing changes in pressure and temperature during milling (for details see Supporting Information). The experiments showed that, other than the calculated rise in pressure due to the expansion of the air inside the milling jar by frictional heating, the pressure inside the milling container stayed essentially constant (Figure 1a, inset). Alternatively, repeating the milling experiments with $M(CO)_6$ in the presence of K_3PO_4 (1 equiv) produced almost immediately gaseous carbon monoxide as indicated by the corresponding pressure increase (Figure 1a).[17] This indicated that the K_3PO_4 used in the carbonylation reactions could have two roles: First, as base for the deprotonation of **2a**, and second, as a promoter for the release of carbon monoxide from the metal hexacarbonyl sources. The mechanism by which K_3PO_4 facilitates the release of CO is not completely elucidated, but ^{31}P NMR analysis of the milled samples revealed the presence of new peaks in the ^{31}P NMR spectrum (Figure S5, Supporting Information), suggesting that K_3PO_4 might have participated in a ligand displacement with $M(CO)_6$. After 4 h of milling, $Cr(CO)_6$ had produce the highest CO pressure inside the milling vessel. However, as noted before, the carbonylation of **1a** with $Cr(CO)_6$ and **2a** had been sluggish (Table 1), and this result led us doubt that the carbonylation really involved gaseous carbon monoxide formed from the reaction of $M(CO)_6$ and K_3PO_4. Hence, subsequent experiments were performed to evaluate if an alternative mechanism was operational by ball milling.

First, the most active $M(CO)_6$ (M=Mo) in the carbonylation reaction was milled for 4 h with various amounts of K_3PO_4 (1–3 equiv), and the reaction was followed by sensing changes in pressure (Figure 1b). Clearly, the extent of the gas evolution depended on the amount of K_3PO_4 used. For example, 1.05 equiv of CO were released after milling of a mixture of $Mo(CO)_6$ and K_3PO_4 (1 equiv) for 4 h. Whereas the same experiment with 2 equiv of K_3PO_4 afforded 1.66 equiv of CO.[18] Moreover, the use of 3 equiv of K_3PO_4 promoted a fast buildup of pressure upon milling, which after 110 min of milling gradually dropped (Figure 1b). Such a drop in pressure was detected to occur earlier and to reduce the CO pressure more rapidly when 4 equiv of K_3PO_4 were used (see Figure S4 in the Supporting Information). A similar feedback mechanochemical reaction has been recently reported in experiments between CO_2 and zeolitic imidazolate frameworks.[19] However, repeating our experiments under argon was observed to offer a protective effect leading to higher pressure values while avoiding the drop in pressure upon milling (see Figure S6 in the Supporting Information).

Even more surprising was the pressure monitoring profile of the palladium-catalyzed carbonylation between **1a**, **2a**,

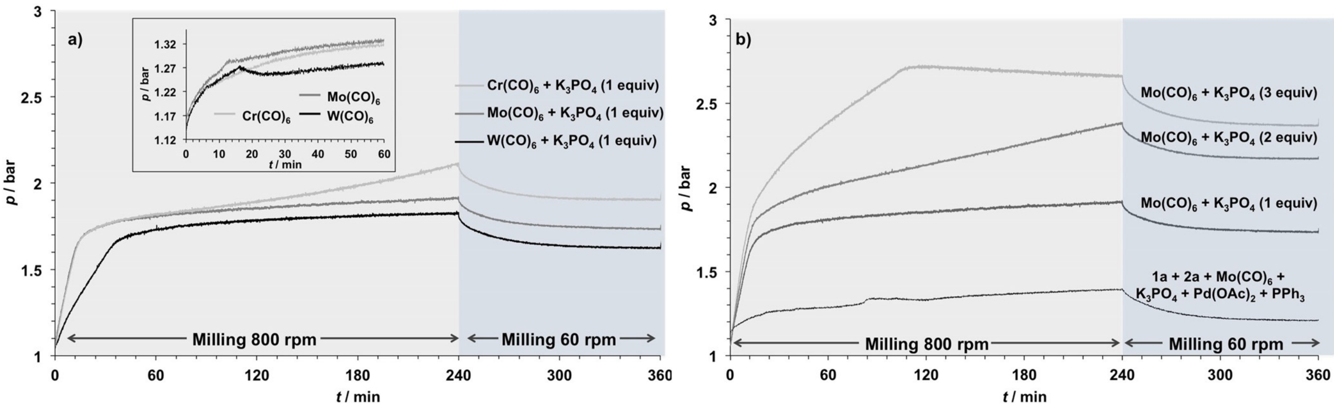
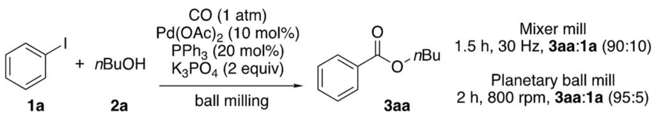


Figure 1. a) Pressure monitoring of milling experiments of $M(CO)_6$ and K_3PO_4 (1 equiv). The inset shows the control experiments in the absence of K_3PO_4. For pressure and temperature monitoring profiles, see Figure S2 (Supporting Information). b) Pressure monitoring of milling experiments between $Mo(CO)_6$ and K_3PO_4 (1–3 equiv) and of the mechanochemical palladium-catalyzed carbonylation reaction between **1a**, **2a** (2 equiv), $Mo(CO)_6$ (1 equiv), and K_3PO_4 (2 equiv). Milling parameters: planetary ball mill operated at 800 rpm using a ZrO_2 milling vessel charged with five milling balls (10 mm in diameter), for additional experimental details, see Supporting Information.

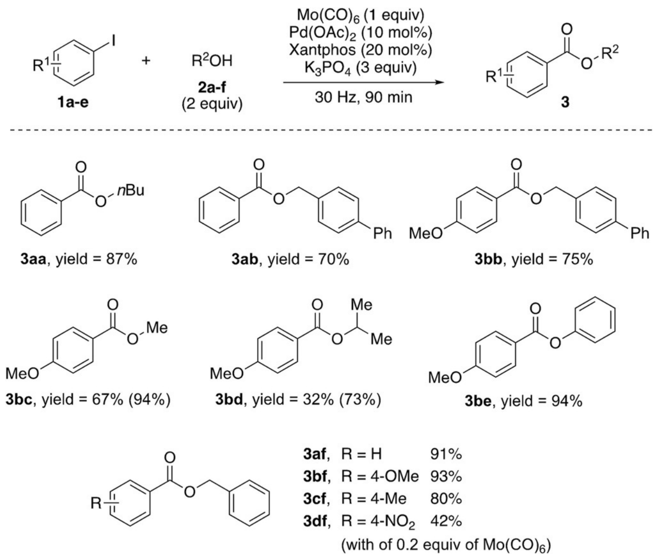
$Mo(CO)_6$ and K_3PO_4 (2 equiv), which did not reveal any significant buildup of pressure upon milling (Figure 1 b). This result hinted at the possibility for the carbonylation reaction to involve a fast CO transfer from $Mo(CO)_6$ to the active palladium species during the catalytic cycle, rather than the release of molecular CO followed by its consumption during the reaction. This hypothesis was further tested after carrying out the reaction by using 3 equiv of K_3PO_4. This time, an increase in pressure was detected after the carbonylation had finished (after 90 min of milling), which can be interpreted as resulting from a reaction between the remaining $Mo(CO)_6$ and K_3PO_4 (see Figure S7 in the Supporting Information). Similar gas-free carbonylative reactions using metal carbonyls complexes have precedence. For instance, recent palladium-catalyzed carbonylative Suzuki reactions using $Mo(CO)_6$,[20a] and carbonylation reactions using $Co_2(CO)_8$ under palladium catalysis[20b] were proposed to involve cooperative rapid CO insertion into the catalytic cycle directly from the metal carbonyl source. Despite this likely scenario, it was important to evaluate if the mechanochemical carbonylation could also take place using gaseous carbon monoxide. Thus, the palladium catalysis was repeated by ball milling **1 a**, **2 a** and K_3PO_4 (2 equiv) in the absence of $Mo(CO)_6$ but under a CO atmosphere (1 atm), and experiments in both a mixer mill and a planetary ball mill confirmed the formation of butyl benzoate (**3 aa**) (Scheme 2).



Scheme 2. Mechanochemical carbonylation reaction using gaseous CO by ball milling.

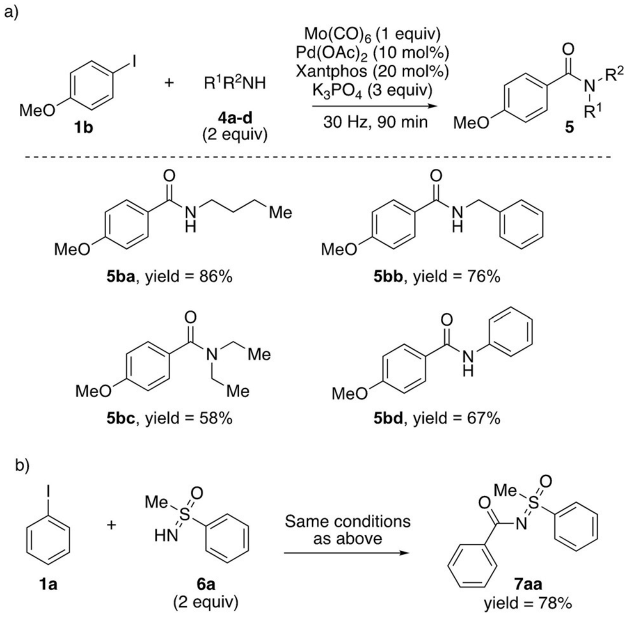
These results reveal that in ball mills both mechanistic alternatives are feasible: First, a gas-free carbonylation pathway for which the CO is rapidly transferred from $Mo(CO)_6$ to the active catalytic system as demonstrated by in situ pressure monitoring of the mechanochemical alkoxycarbonylation reaction and, second, a direct uptake of gaseous CO by the palladium catalyst during the ball milling reaction.

After having studied the mechanochemical alkoxycarbonylation by ball milling between **1 a** and **2 a** using $Mo(CO)_6/K_3PO_4$, we set to evaluate the applicability of the protocol to other substrates. For this, the standard conditions were applied with the exception of using Xantphos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene] instead of triphenylphosphine to facilitate the isolation by column chromatography. First, iodobenzene (**1 a**) was reacted with solid biphenyl-4-methanol (**2 b**) (m.p. 96–100 °C). After purification by column chromatography, ester **3 ab** was isolated in 70 % yield (Scheme 3). Then, solid 4-iodoanisole (**1 b**) (m.p. 50–53 °C) and solid biphenyl-4-methanol (**2 b**) were milled under the optimized reaction conditions affording the corresponding product **3 bb** in 75 % yield (Scheme 3). Also methanol (**2 c**), isopropanol (**2 d**), phenol (**2 e**) and benzyl alcohol (**2 f**) were tested as nucleophiles in the mechanochemical carbonylation reactions. The results with 4-iodoanisole (**1 b**) as reaction partner showed that all alkoxycarbonylations leading to **3 bc**–**3 bf** proceeded smoothly within 90 min of milling. However, the high volatility of some of the products during post-processing vacuum drying prevented the isolation of the esters in higher yields after separation by column chromatography (Scheme 3). Reacting iodobenzene (**1 a**) and 4-iodotoluene (**1 c**) with benzyl alcohol (**2 f**) led to esters **3 af** and **3 cf** in 91 % yield and 80 % yield, respectively (Scheme 3). To our surprise, the reaction of *p*-iodonitrobenzene (**1 d**) under the standard reaction conditions [i.e., $Mo(CO)_6$ (1 equiv)] gave ester **3 df** in only 23 % yield. Having realized that $Mo(CO)_6$ has the capability of reducing nitro groups,[21] the reaction was repeated with only 0.2 equiv of $Mo(CO)_6$. This small change led to an increase in the yield of ester **3 df** to 42 % yield after the same milling time. Using such substoichiometric amounts of $Mo(CO)_6$ for other substrates produced lower yields, indicating that the initially applied quantity (1 equiv) was preferable.



Scheme 3. Mechanochemical alkoxycarbonylation reactions using $Mo(CO)_6$ by ball milling (yields after column chromatography; in parentheses, yields as determined by ^1H NMR spectroscopy).

Attempts to carry out the mechanochemical alkoxycarbonylation of benzyl alcohol (**2 f**) with 4-bromoanisole or phenyl triflate instead of iodobenzene (**1 a**) showed that the latter substrate (**1 a**) was superior over the formed two. Thus, with 4-bromoanisole product **3 bf** was obtained in only 15 % yield, and the use of phenyl triflate gave ester **3 af** in 86 % yield.[22] For comparison, with substrates **1 b** and **1 a**, **3 bf** had been obtained in 93 % yield and **3 af** in 91 % yield (Scheme 3). Then, it was examined if the mechanochemical carbonylation procedure using molybdenum hexacarbonyl could be extended to palladium-catalyzed aminocarbonylation reactions. For this, 4-iodoanisole (**1 b**) was reacted with primary and secondary amines under the standard milling conditions (Scheme 4 a). Among them, *n*-butylamine (**4 a**), benzyl amine (**4 b**), diethyl amine (**4 c**) and aniline (**4 d**) proved to be suitable as nucleophiles leading to amides **5 ba**–**5 bd** in yields ranging from 58 % to 86 % (Scheme 4 a). Finally, the mechanochemical carbonyl-



Scheme 4. (a) Mechanochemical aminocarbonylation reactions and (b) sulfoximinocarbonylation of **1a** using $Mo(CO)_6$ by ball milling. Yields after column chromatography.

ation protocol was applied to the sulfoximinocarbonylation of iodobenzene (**1a**) with *S*-methyl-*S*-phenyl-sulfoximine (**6aa**), which gave the corresponding *N*-aroyl sulfoximine **7aa** in 78% yield (Scheme 4b).

In summary, we have developed a mechanochemical protocol to carry out palladium-catalyzed carbonylative reactions (alkoxycarbonylations and aminocarbonylations) in ball mills using molybdenum hexacarbonyl as a one-carbon building block. The model alkoxycarbonylation reaction was found to proceed mostly through a gas-free mechanism as evidenced by the real-time monitoring of the mechanochemical reaction by using in-situ pressure sensing during ball milling. This result suggests that CO is rapidly transferred from $Mo(CO)_6$ to the active catalytic system without significant release of molecular carbon monoxide. However, if preferred, gaseous CO can be applied in the mechanochemical alkoxycarbonylation reaction as well. From a more general perspective, this study reinforces the concept of in situ generation and consumption of gaseous reactants by mechanochemistry, which reduces the direct handling and exposition to toxic or highly reactive gaseous substances.[3]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: ball milling · carbonylation · mechanochemistry · molybdenum hexacarbonyl · real-time monitoring

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[22] Aryl bromides are known to undergo aminocarbonylation reactions in toluene at 80 – 120 °C for 5 – 22 h by using $Pd(OAc)_2$, Xantphos CO (1 atm) and Na_2CO_3, see: J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7102 – 7107. The lower reactivity of aryl bromides observed in this work could be a consequence of the substantially different reaction conditions by milling, that is, 90 min without external heating. For in situ temperature monitoring of the reaction, see Figure S7 (Supporting Information).

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