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Mechanochemical Cobalt-Catalyzed C–H Bond Functionalizations by Ball Milling

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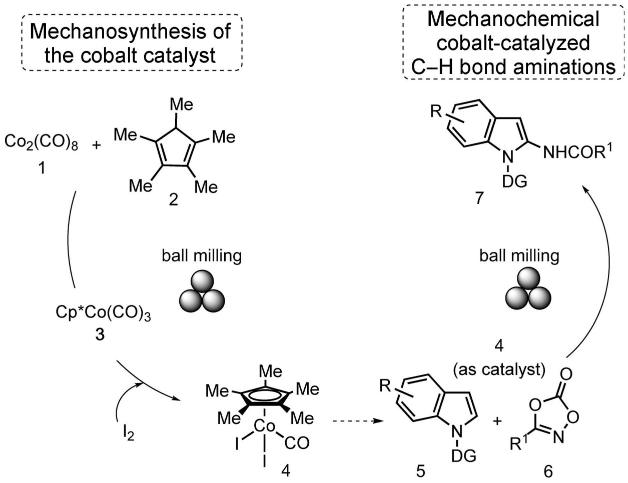
Abstract: Ball milling techniques have been applied in the development of a mechanosynthesis of [Cp*Co(CO)I_2], which proved highly efficient as catalyst in mechanochemical C–H bond amidations of indoles in a mixer ball mill. A wide range of amidated products is obtained in excellent yields. Compared to the solution-based methods, the procedure opens a more feasible and environmentally-friendly access to both the cobalt(III) catalyst and 2-amidated indoles.

Keywords: Amidation; ball mill; cobalt; C–H bond functionalization; mechanosynthesis

In the past decade, transition metal-catalyzed C–H bond activation has proven to be a powerful synthetic alternative for the functionalization of organic molecules,[1] for example, through the direct construction of C–N bonds.[2] It thereby complements classic methods for the C–N bond formation such as the Ullmann reaction,[3] the Buchwald-Hartwig amination approach,[4] and the Chan-Lam coupling[5] amongst others.

Traditionally, solution-based protocols for C–H bond functionalizations involve activations by transition metal complexes containing precious metals such as palladium, iridium, or rhodium. Recently, however, there has been a growing interest in achieving such transformations by using more abundant metals and in finding milder, benign reaction conditions.[6] Focusing on the latter aspect, we[7] and others[8] utilized mechanochemical techniques and developed C–H bond functionalizations under solvent-free conditions.[9] Compared with organic solvent-based protocols, the advantages of conducting chemical transformations by mechanochemistry include the reduction of harmful organic solvents and low E-factor synthesis,[10] shorter reaction times,[11] the absence of external heating,[7] and the possibility to access different product compositions,[9a,b] to name just a few.

With the goal to address the choice of metal we now investigated if mechanochemical C–H bond functionalizations could also be achieved by applying widely abundant and cheap first-row cobalt complexes, thereby substituting the previously used precious metal catalysts.[12] Clearly, the success of this approach required a high mechanical stress tolerance of the organocobalt complex.[13] Overall, we envisaged a two-step process: First, a solvent-free mechanosynthesis of pentamethylcyclopentadienyl cobalt complex Cp*Co(CO)I_2 (**4**) [Cp* = η^5-$C_5(CH_3)_5$], and, second, the use of this cobalt(III) complex as catalyst in solventless C–H bond functionalizations, specifically, indol amidations with dioxazolones (Scheme 1).



Scheme 1. Mechanosynthesis of [Cp*Co(CO)I_2] (**4**) and its use in C–H bond activation by milling.

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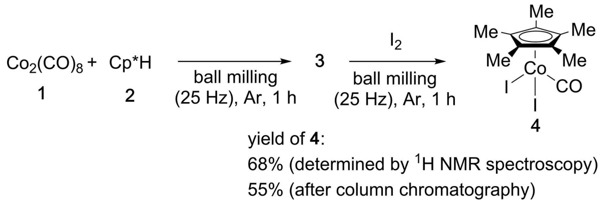
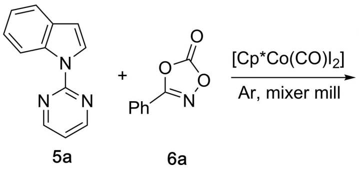
In solution chemistry, $[Cp^*Co(CO)I_2]$ (**4**) is typically prepared in a two-step approach starting from a mixture of $Co_2(CO)_8$ (**1**) and pentamethylcyclopentadiene (Cp*H, **2**) in dichloromethane. This reaction renders the intermediate $[Cp^*Co(CO)_3]$ (**3**), which is further reacted with iodine in diethyl ether to yield cobalt complex **4**.[14] Here, the mechanosynthesis of **4** was intended to be a one-pot two-step reaction sequence.[15] Thus, a mixture of dicobalt octacarbonyl (**1**) and Cp*H (**2**) was milled under argon for 60 min at 25 Hz to promote the formation of **3**. After this period of time, the milling jar was opened under argon and iodine was added. Then, the grinding was continued for 1 h. Gratifyingly, the analysis of the resulting reaction mixture by ^1H NMR spectroscopy confirmed the formation of **4**, which also revealed that the cobalt complex was stable under the ball milling conditions (Scheme 2; for details, see Supporting Information).



Scheme 2. Mechanosynthesis of $[Cp^*Co(CO)I_2]$ (4).

Motivated by the resilience of $[Cp^*Co(CO)I_2]$ (**4**) in the ball mill, the screening of the conditions for the mechanochemical cobalt-catalyzed C–H amidation reaction by milling was started. 1-(Pyrimidin-2-yl)-1*H*-indole (**5a**) and 3-phenyl-1,4,2-dioxazol-5-one (**6a**) were chosen as representative starting materials. First, a mixture of **5a** and **6a** (in a ratio of 1.0:1.2) was ball-milled in the presence of 10 mol% of $[Cp^*Co(CO)I_2]$ and 20 mol% of silver hexafluoroantimonate ($AgSbF_6$). To our delight, desired product **7aa** was obtained in 64% yield after only 99 min of milling at 30 Hz (Table 1, entry 1). Then, the effect of the substrate ratio was investigated. Applying 1.5 equiv. of **6a** led to a slightly increased yield (Table 1, entry 2). In contrast, when **6a** was the limiting reagent, the reaction gave **7aa** in only 48% yield (Table 1, entry 3). The presence of NaOAc (20 mol%) as additive,[16] exhibited a positive effect yielding indole **7aa** in 96% (Table 1, entry 4). Increasing the amount of NaOAc from 20 mol% to 1 equiv. inhibited the amidation reaction (Table 1, entry 5). This result suggested that NaOAc served as a carboxylic ligand for the Cp*Co(III) species and not as a base in the reaction.[17] Product **7aa** was also obtained (in 93% yield) when the experiment was conducted under an aerobic atmosphere showing that the catalytic system tolerated ambient conditions (Table 1, entry 6). Lowering the catalyst loading from 10 mol% to 2.5 mol% proved possible without significantly affecting the yield of **7aa** (Table 1, entry 7). Also the crude mixture of **4** after its mechanochemical preparation could be applied, but then, the yield of **7aa** was only 38% (Table 1, entry 8).

Table 1. Optimization of the mechanochemical amidation.[a]



Entry	Ratio of (**5a**:**6a**)	Co cat. (mol%)	$AgSbF_6$ (mol%)	NaOAc (mol%)	Yield of **7aa** [%][b]
1	1:1.2	10	20	–	64
2	1:1.5	10	20	–	68
3	1.5:1	10	20	–	48
4	1:1.5	10	20	20	96
5	1:1.5	10	20	100	trace
6[c]	1:1.5	10	20	20	93
7[c]	**1:1.5**	**2.5**	**5**	**5**	**95**
8[c]	1:1.5	–[d]	5	5	38

[a] All reactions were conducted on a 0.5 mmol scale (of **5a** or **6a**). A mixture of **5a** and **6a** was ball-milled under argon for 99 min at 30 Hz in a stainless steel milling jar of 10 mL in volume with one 10 mm milling ball made of the same material.

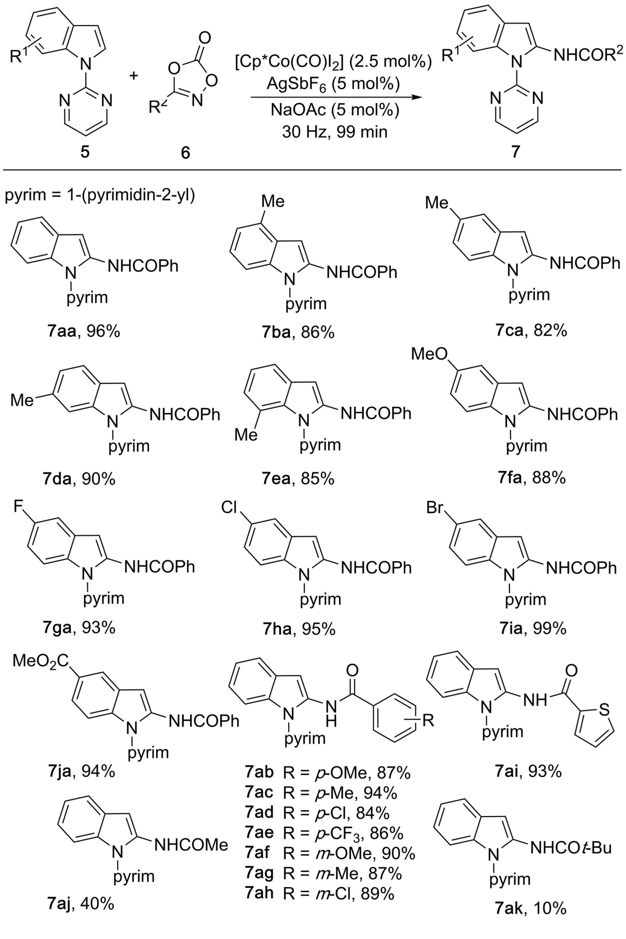
[b] After column chromatography.

[c] Air atmosphere.

[d] Use of 15 mg of the crude mixture of $[Cp^*Co(CO)I_2]$ (**4**) taken after its mechanochemical preparation, without purification.

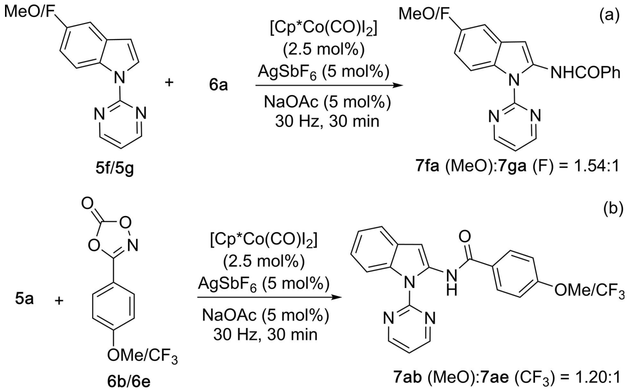
It is worth mentioning that even though the mechanochemical C–H amidation was carried out without external heating, high-speed ball milling of the sample can affect the temperature inside the milling container. Such temperature changes have been demonstrated to depend not only on milling parameters (type of ball mill, milling media's material, milling speed, time, etc.),[18] but also amorphization/crystallization events.[18a] Furthermore, changes in reaction mixture composition play significant roles on temperature fluctuation upon milling.[18d] Monitoring the changes in temperature on the outside wall of our milling vessel revealed a rise in temperature from 23 °C to 35 °C after 99 min of milling at 30 Hz (for details, see Supporting Information). It is reasonable to assume that this increase in temperature during the milling process facilitated the mechanochemical C–H bond functionalization reaction.

Having identified the optimal reaction conditions for the mechanochemical C–H bond amidation as 2.5 mol% of [Cp*Co(CO)I_2], 5 mol% of $AgSbF_6$, and 5 mol% of NaOAc for 99 min at 30 Hz, the substrate scope of indoles and dioxazolones was explored.[19] In general, 2-amidated indoles **7** were obtained with good tolerance of functional groups and with excellent yields, up to 99% (Scheme 3). First, a range of substituted 1-(pyrimidin-2-yl)-1*H*-indoles **5** was applied using dioxazolone **6a** as the reaction partner. In these cases, indole substrates substituted with electron-withdrawing groups exhibited a slightly better efficiency than those having electron-donating substitutes (Scheme 3). It is noteworthy that 5-halo-substituted indoles reacted smoothly giving the desired products in yields ranging from 93% to 99% (**7ga–ia**; Scheme 3). Next, the scope of the C–H amidation was expanded by using aryl substituted dioxazolones **6b–h**. With **5a** as coupling partner, such derivatives proved suitable for the amidation conditions as well, affording the corresponding products **7ab–ah** in excellent yields (up to 94%), regardless of the nature or substitution pattern (Scheme 3). Similarly, indole **5a** reacted with thienyl-substituted dioxazolone **2i** to effectively yield amidated product **7ai** (93% yield). Alkyl-substituted dioxazolones **7j** and **7k** bearing methyl and *t*-butyl groups, respectively, afforded products **7aj** and **7ak** in low yields (Scheme 3), probably due to a lower stability of these dioxazolones under high-energy mechanical forces in the ball mill. In amidations carried out in 1,2-dichloroethane at 80 °C alkyl-substituted dioxazolones proved less active for C–H bond amidations.[16b] In other cases, however, aryl- and alkyl-substituted dioxazolones have been reported to exhibit comparable reactivity.[16a]



Scheme 3. Substrate scope of indoles and dioxazolones.

Subsequently, an intermolecular competition experiment with dioxazolone **6a** and substituted indoles **5f**/**5g** was performed, which revealed that electron-rich indole **5f** exhibited a higher reactivity than **5g** [Scheme 4 (a)]. The mechanochemical amidation reaction of indole **5a** with a mixture of dioxazolones **6b** and **6e** showed a slight preference of the more electron-rich **6b** compared to **6e** [Scheme 4 (b)].



Scheme 4. Intermolecular competition experiments in ball mills.

An eight-fold scale-up experiment gave >1 g of **7aa** (83% yield) after 99 min of milling demonstrating the synthetic potential of the cobalt(III)-catalyzed C–H bond amidation (Scheme 5; top). Pleasingly, under these conditions the catalyst loading could be lowered to 1 mol% providing **7aa** in 65% yield. Attempts to remove the pyrimidin-2-yl directing group in **7aa** by ball milling remained unsuccessful.[20] Neither milling of a mixture of **7aa** in the presence of NaOEt under neat nor liquid-assisted grinding conditions (LAG; DMSO)[21] (99 min at 30 Hz) did afford the free indole. In solution, removal of the same directing group requires harsh reaction conditions (100–110 °C; 11 h to 24 h),[22] which apparently could not be matched by ball milling.

Then, with the goal to demonstrate the generality of the mechanochemical approach, cobalt(III)-catalyzed iodination reactions of 2-arylpyridines **8** were attempted (Scheme 5; bottom). Thus, grinding of **8** in

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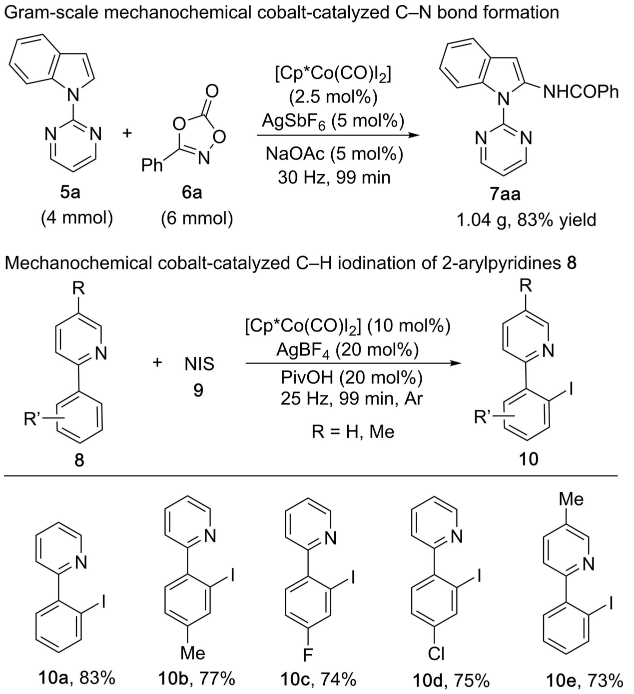

Scheme 5. Scale-up experiment and cobalt-catalyzed mechanochemical iodination reactions.

the presence 10 mol% of cobalt complex **4**, $AgBF_4$ (20 mol%), pivalic acid (20 mol%) and *N*-iodosuccinamide (NIS) as the limiting reagent, led to mono-iodinated products **10** in yields ranging from 73% to 83% (Scheme 5; bottom).

In conclusion, we demonstrated the use of mechanochemical techniques in facilitating the formation of the first-row metal complex [Cp*Co(CO)I_2] (**4**). Subsequently, **4** was applied in C–H bond amidations of indoles with 1,4,2-dioxazol-5-ones as amidating agents under neat grinding in a mixer ball mill. The resulting 2-amidated indoles were obtained in excellent yields without additional heating and in shorter reactions times than in solution.

Experimental Section

One-pot two-step reaction for the preparation of [Cp*Co(CO)I_2] (4): Under argon atmosphere, $Co_2(CO)_8$ (0.2 mmol, 68.4 mg), and pentamethylcyclopentadienyl (Cp*H, 0.50 mmol, 68.1 mg) were loaded in a 25 mL ZrO_2 milling jar together with one milling ball (ZrO_2, 1.5 cm in diameter). The milling jar was placed in the ball mill and milled at 25 Hz for 60 min. After this first cycle, iodine (0.5 mmol, 126.9 mg) was added to the mixture in the jar under argon atmosphere. Then, the jar was milled at 25 Hz for another 60 min. At last, the mixture was recovered from the milling jar with acetone (30 mL). The solvent was removed in vacuo and 1,3,5-trimethoxybenzene (30.0 mg) as internal standard was added to the mixture in the flask, followed by $CDCl_3$. 68% yield was determined by ^1H NMR spectroscopy. Isolation of **4** was done by flash column chromatography (for details, see Supporting Information).

General procedure for the preparation of 7: A mixture of indole (**5**, 0.5 mmol), dioxazolone (**6**, 0.75 mmol, 1.5 equiv.), [Cp*Co(CO)I_2] (6.0 mg, 0.0125 mmol, 2.5 mol%), $AgSbF_6$ (8.6 mg, 0.025 mmol, 5 mol%), and NaOAc (2.1 mg, 0.025 mmol, 5 mol%) was loaded in a milling jar (stainless steel, 10 mL) together with one milling ball (stainless steel, 1 cm in diameter). The milling jar was placed in the mixer mill and shaked at 30 Hz for 99 minutes. Then, the mixture in the jar was washed out with acetone (3×10 mL). The solvent was removed in vacuo, and the product was purified by flash column chromatography on silica gel (*n*-pentane/EtOAc) to afford **7**. To avoid the use of solvent during the removal of the reaction mixture from the milling jar, the mixture could alternatively be taken up by adding SiO_2 (2×0.5 g) to the jar, which was milled for another 2 min each time.

General procedure for the preparation of 10: Under argon atmosphere, the mixture of 2-phenylpyridine (**8**, 0.65 mmol), *N*-iodosuccinimide (0.5 mmol, 112.5 mg), [Cp*Co(CO)I_2] (23.8 mg, 0.05 mmol, 10 mol%), $AgBF_4$ (19.5 mg, 0.1 mmol, 20 mol%), and pivalic acid (10.2 mg, 0.1 mmol, 20 mol%) was loaded in a milling jar (stainless steel, 10 mL) together with one milling ball (stainless steel, 1 cm in diameter). The milling jar was placed in the mixer mill and shaked at 25 Hz for 99 minutes. Then, the mixture in the jar was washed out with acetone (3×10 mL). The solvent was removed in vacuo, and the product was purified by flash column chromatography on silica gel (*n*-pentane/EtOAc) to afford **10**. To avoid the use of solvent during the removal of the reaction mixture from the milling jar, the mixture could alternatively be taken up by adding SiO_2 (2×0.5 g) to the jar, which was milled for another 2 min each time.

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