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Mechanochemical Rhodium(III)- and Gold(I)-Catalyzed C–H Bond Alkynylations of Indoles under Solventless Conditions in Mixer Mills

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Abstract: Mechanochemical activations in Rh^{III}- and Au^I-catalyzed C–H alkynylations lead selectively to C₂- and C₃-alkynylated indoles. The processes show excellent functional group tolerance, do not require additional heating and proceed under solventless conditions. Compared to solvent-based standard protocols, the reaction times are shorter and the catalyst quantities lower resulting in high product yields under ambient atmosphere in mixer mills.

As indoles are prevalent in a vast variety of natural products, agrochemicals and advanced materials they represent an important heterocyclic core structure. Consequently, the construction^[1] and selective functionalization^[2] of this motif remains an important goal for organic chemists. In the last decades. direct transition metal-catalyzed C-H bond functionalization^[3] has been established as a straightforward and elegant way for diversifying indoles.^[2] In this context, Waser, Li, and Shi introduced highly C2- and C3-selective transition metalcatalyzed C-H alkynylation reactions of indoles using reagents.[4-6] ethynylbenziodoxolone (EBX) Despite the effectiveness of these procedures, the use of significant amounts of organic and often harmful solvents, long reaction times and relatively high catalyst loadings are still limiting the overall sustainability of these transformations.

In recent years, ball milling^[7,8] has been developed into a valuable technique to conduct a wide range of organic transformations under mechanochemical conditions, including metalcatalyzed Sonogashira,^[9] Glaser,^[10] and cross-dehydrogenative coupling reactions.^[11] Besides the most striking advantage that nearly all of these processes can be performed in the absence of organic solvents, often lower quantities of the catalyst and shorter reaction times are needed to provide higher yields compared to solvent-based standard protocols.^[12]

The first mechanochemical C–H functionalization was reported by our group in 2015.^[13,14] Although this discovery was important, it is fair to state that the solventless process was limited in terms of catalyst efficiency, as the reaction in *t*-AmylOH at 120 °C required only a fraction of the rhodium catalyst to generate an even higher product yield.^[15] Since then, we and others have expanded the scope of mechanochemical C–H functionalizations to amidations, halogenations, and

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Scheme 1. Mechanochemical C-H bond alkynylations of indoles (TIPS = triisopropylsilyl).

arylation processes, among others.^[16,17] Although most of these reactions proceed within a shorter reaction time than in solvent, a reduction of the catalyst loading has remained a major challenge.

Herein, we report two mechanochemical C–H alkynylation processes of indoles that both employ EBX reagents as alkynyl sources under solvent-free conditions in mixer mills (Scheme 1). Gratifyingly, both the C₂-selective, directing group assisted Rh^{III}-catalysis as well as the C₃- (or C₂)-selective Au¹-catalyzed alkynylation process are not only operating in shorter reaction times than their solvent-based counterparts but more importantly also require significantly less catalyst. In addition, the two reactions represent, to the best of our knowledge, the first examples of mechanochemical transition metal-catalyzed sp² C– H alkynylation reactions that obviate the necessity of halogenated starting materials.

We began our studies by screening the reaction conditions for the Rh^{III}-catalyzed coupling between *N*-pyrimidyl indole (**1a**) 1-[(triisopropylsilyl)-ethynyl]-1,2-benziodoxol-3(1H)-one and (TIPS-EBX, 2a) under solvent-free conditions in a mixer mill. Using [{Cp*RhCl₂}₂] (5 mol %) in combination with AgBF₄ (20 mol %) as the catalyst and AgOAc (20 mol %) as an additive, 94% of the C2-alkynylated product 3a was isolated after just 99 minutes of milling at 30 Hz (Table 1, entry 1). Pleasingly, lowering the amount of catalyst to 0.5 mol % as well as the amount of AgBF₄ and AgOAc to 2 mol % had almost no effect, and 3a was obtained in 97% yield (Table 1, entries 2-4). Control experiments revealed that [{Cp*RhCl₂}2] and AgBF4 were essential for the outcome of this transformation, whereas AgOAc was not (Table 1, entries 5-7). A short screening of different silver salts revealed that AgNTf2 worked the best for this coupling (Table 1, entry 8, 99%). Furthermore, decreasing the

mechanochemical conditions.[a]

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К			catalyst additive 1 additive 2	
	Ŧ	29	30 Hz ball milling	N N

Table 1: Optimization of the Rh^{III}-catalyzed C-H alkynylation under

Entry	Catalyst (mol %)	Additive 1 (mol %)	Additive 2 (mol %)	Yield [%] ^b
1	[{Cp*RhCl ₂ } ₂] (5)	AgBF ₄ (20)	AgOAc (20)	94
2	[{Cp*RhCl ₂ } ₂] (2.5)	AgBF ₄ (10)	AgOAc (10)	98
3	[{Cp*RhCl ₂ } ₂] (1.0)	AgBF ₄ (4)	AgOAc (4)	97
4	[{Cp*RhCl ₂ } ₂] (0.5)	AgBF ₄ (2)	AgOAc (2)	97
5	-	AgBF₄ (10)	AgOAc (10)	-
6	[{Cp*RhCl ₂ } ₂] (0.5)	-	AgOAc (2)	-
7	[{Cp*RhCl ₂ } ₂] (0.5)	AgBF ₄ (10)	-	95
8	[{Cp*RhCl ₂ } ₂] (0.5)	AgNTf ₂ (2)	-	99
9 ^[c]	[{Cp*RhCl ₂ } ₂] (0.5)	AgNTf ₂ (2)	-	98
10 ^[d]	[{Cp*RhCl ₂ } ₂] (0.5)	AgNTf ₂ (2)	-	75

^[a] Reaction conditions: **1a** (0.6 mmol, 1.0 equiv.), **2a** (0.66 mmol, 1.1 equiv.), 30 Hz, 99 min., RETSCH mixer mill (MM 400), vessel (10 mL), and ball (diameter: 1 cm) are made of stainless steel ($Cp^* =$ pentamethylcyclopendadienyl, Tf = trifluoromethanesulfonyl);^[16] [^{15]} after chromatography; [^{c]} milling time: 60 min; ^[d] milling time: 30 min.

milling time to only 60 minutes had almost no influence on the product yield (Table 1 entry 9, 98%). The efficiency of this mechanochemical process is worth highlighting, since a similar reaction in DCE required 16 hours and a fourfold amount of the rhodium catalyst to achieve a slightly lower yield.^[5c,19] With the optimized reaction conditions in hand, the scope of the Rh^{III}catalyzed alkynylation process was investigated (Scheme 2). The use of unsubstituted N-pyrimidyl indole (1a) in the coupling with TIPS-EBX (2a) led to 98% of the alkynylated indole 3a on a 0.6 mmol scale. The process was highly reproducible [(three individual reactions between 1a and 2a gave 3a each time in a similar yield (98-99%)] and the robustness of the reaction was further highlighted by the excellent scalability, as demonstrated by a 2.0 mmol scale reaction in which 3a was again isolated in 98% yield (730 mg). Next, the influence of the functional group on the alkyne was investigated. Replacing the TIPS group by a TBDMS- (tert-butyldimethylsilyl), TBDPS- (tert-butyl-diphenylsilyl) or tBu-group was unproblematic and the corresponding products 3b-d were obtained in good to excellent yields (73-93%). Both, electron-donating and -withdrawing groups at the 5position of the indole, such as methyl (1e), methoxy (1f), fluoro (1h), bromo (1i), chloro (1j) or iodo (1k) were well tolerated in the mechanochemical coupling and the corresponding products were obtained in high yields (65-99%). Using a carboxyl functionality (1g) led to only 44% of the desired product 3g. Furthermore, N-pyrimidyl indoles containing substituents at various positions could be used in the mechanochemical process, and products 3I-p were isolated in good to essentially quantitative yields (71-97%).

To gain a closer insight into the Rh^{III}-catalyzed mechanochemical alkynylation process, preliminary mechanistic studies were conducted (Scheme 3).



Scheme 2. Substrate scope of the mechanochemical Rh^{II} -catalyzed C-H alkynylation.



Scheme 3. Preliminary mechanistic studies of the mechanochemical Rh^{III} -catalyzed C-H alkynylation.

To confirm the hypothesized intermediacy of a 5-membered rhodacycle in the mechanochemical process, rhodacycle 4 was prepared after milling a mixture of N-pyrimidyl indole (1a, 2.5

equiv.), [{Cp*RhCl₂}₂] (1.0 equiv.) and NaOAc (3.0 equiv.) under solvent-free conditions for 60 min at 30 Hz in a mixer mill [Scheme 3, eq. (1)].^[20] Then, rhodacycle **4** was utilized as a catalyst (1.0 mol %) together with AgNTf₂ (2.0 mol %) in the coupling of **1a** and **2a** [Scheme 3, eq. (2)]. After 60 min of milling, **3a** was obtained in 96% yield, confirming that rhodacycle **4** was most likely an intermediate (in its cationic form) in the mechanochemical alkynylation reaction.

Aiming at expanding the scope of the mechanochemical C–H alkynylations, a screening of conditions for a C₃-selective C–H alkynylation process was initiated. As a starting point, similar reaction conditions to those reported by Waser^[5a] for the gold-catalyzed C–H coupling of indole (**5a**) with TIPS-EBX **2a** were applied under mechanochemical conditions in a mixer mill. To our delight, after mixing the reactants together with AuCl (5.0 mol %) as the catalyst for only 99 min at 30 Hz, 72% of **6a** was obtained (Table 2, entry 1). Furthermore, it was possible to decrease the catalyst loading to only 2.0 mol % without impairing the product yield of **6a** (Table 2, entry 2).^[21] Shortening to reaction time had a negative effect on the coupling (Table 2, entries 3 and 4).

Again, the high effectiveness of the presented mechanochemical gold-catalyzed coupling is worth mentioning as **6a** was obtained in almost the same yield compared to the solventbased standard protocol (in diethyl ether) but with less than 50% of the catalyst and after a fraction of the reaction time.^[5a,19]

Table 2: Optimization of the Au^l-catalyzed C–H alkynylation under mechanochemical conditions.^[a]

H H + 5a	TIPS	-O AuCl 30 Hz ball milling	Ga	115
Entry	AuCl (mol %)	Time (min)	Yield [%] ^b	
1	5.0	99	72	
2	2.0	99	75	- 1
3	2.0	60	68	
4	2.0	30	47	

^[a] Reaction conditions: **5a** (0.6 mmol, 1.0 equiv.), **2a** (0.72 mmol, 1.2 equiv.), 30 Hz, RETSCH mixer mill (MM 400), vessel (10 mL), and ball (diameter: 1 cm) are made of stainless steel; ^[b] After chromatography.

Next, the substrate scope of the gold-catalyzed mechanochemical C–H alkynylation was examined (Scheme 4).^[22] The use of unsubstituted indole (**5a**) in the coupling with **2a** led to 75% of **6a**, along with ca. 6% of an undefined side-product. Again, the mechanochemical coupling exhibited high reproducibly, as demonstrated by three individual reactions between **5a** and **2a** in which **6a** was isolated each time in a similar yield (73–77%). Unfortunately, scaling up the reaction to 2.0 mmol led only to 42% of **6a** after 2 x 99 min of shaking. Changing the protecting group on the alkyne from a TIPS- to a TBDMS-group diminished the yield, and **6b** was obtained in only 31%.^[23] In contrast, using *N*-methyl indole (**5c**) as the reaction partner in the mechanochemical coupling proved unproblematic,

and 6c was isolated in 82% yield. Subsequently, the influence of substituents at the $C_{2}\text{-}$ and $C_{3}\text{-}\text{position}$ of the indole core was



Scheme 4. Substrate scope of the mechanochemical Au^l-catalyzed C-H alkynylation; ^[a] 2 x 99 min.; ^[b] AuCl (3.0 mol %).

evaluated. Using 2-methyl (**5d**) or 3-methyl indole (**5e**) in the coupling with **2a** led smoothly to products **6d** (80%) and **6e** (71%) in high yields, albeit under slightly modified conditions (for details, see footnotes in Scheme 4). Subsequently, the influence of substituents at the 5-position of the indole scaffold was investigated. Both electron-donating (**5f**: Me, **5g**: OMe)^[23] and - withdrawing groups (**5h**: I, **5i**: Br) were well tolerated, and the corresponding products were obtained in moderate to good yields (59–70%). In addition, applying 6-Cl (**5j**) or 7-Me indole (**5k**) in the mechanochemical coupling yielded **6j**^[23] and **6k** in 58 and 71%, respectively.

In summary, we developed two metal-catalyzed C–H alkynylation reactions in mixer mills. Both processes proceed under solventless conditions and do not require additional heating to produce the products in high yields. They are highly efficient as in both cases significantly smaller quantities of catalysts and shorter reaction times than in solvent were required.

Experimental Section

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Representative procedures: All reactants and catalysts were transferred to a ball-milling vessel (stainless steel, 10 mL) containing one grinding ball (stainless steel, diameter: 1.0 cm). The ball-milling vessel was then transferred to a mixer mill (RETSCH MM400), and the reaction mixture was milled at 30 Hz for the specified duration. In the case of the rhodiumcatalyzed coupling, the crude reaction mixture was extracted by washing the vessel and the ball with DCM or EtOAc (5 x 10 mL), and the resulting mixture was filtered through a thin layer of SiO2 and concentrated in vacuo. The product was then isolated by flash column chromatography on silica gel (n-pentane/EtOAc). To decrease the amount of solvent used for the extraction of the reaction mixture from the vessel, the crude product can alternatively be taken up by adding silica (2 x 1 g) to the ballmilling vessel and milling the resulting mixture for 5 min (x 2). In the case of the gold-catalyzed alkynylation, the crude was recovered by washing the vessel and the ball with Et₂O (5 x 10 mL). The organic layer was washed with 0.1 M NaOH (2 x 50 mL) and the combined aqueous layers were extracted with Et_2O (50 mL). The organic layers were combined, washed with saturated NaHCO $_3$ (50 mL), brine (50 mL), dried over MgSO₄, concentrated in vacuo and purified by flash chromatography (SiO₂, n-pentane/Et₂O).

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Under solventless mechanochemical conditions, C2- and C3-alkynylated indoles have selectively been prepared in mixer mills by Rh^{III}- and Au^Icatalyzed C-H alkynylations, respectively. Additional heating is not required, and both catalyses show an excellent functional group tolerance. Compared to their solventbased counterparts, shorter reaction times and lower catalysts loadings are needed to provide high product yields.



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Page No. – Page No.

Mechanochemical Rhodium(III)and Gold(I)-Catalyzed C–H Bond Alkynylations of Indoles under Solventless Conditions in Mixer Mills