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Mechanochemical Iridium(III)-Catalyzed C–H Bond Amidation of Benzamides with Sulfonyl Azides under Solvent-Free Conditions in a Ball Mill

*Gary N. Hermann, Peter Becker, and Carsten Bolm**

Dedicated to Professor Dieter Enders on the occasion of his 70th birthday

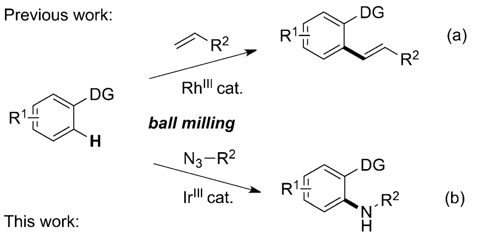
Abstract: *Mechanochemical conditions have been applied to an iridium(III)-catalyzed C–H bond amidation process for the first time. In the absence of solvent, the mechanochemical activation enables the formation of an iridium species that catalyzes the ortho-selective amidation of benzamides with sulfonyl azides as the nitrogen source. As the reaction proceeds in the absence of organic solvents without external heating and yields the desired products in excellent yields within short reaction times, this method constitutes a powerful, fast, and environmentally benign alternative to the common solvent-based standard approaches.*

The introduction of nitrogen-containing moieties into organic molecules is one of the key transformations of modern organic synthesis,[1] as various nitrogen functional groups are most common in natural products, agrochemicals, and pharmaceutically relevant compounds.[2] In recent years, direct transition-metal-catalyzed C–H functionalization processes of unactivated aromatic compounds were established as straightforward and elegant ways to form a great variety of new carbon–carbon or carbon–heteroatom bonds. In this context, Chang and others[3–6] have reported transition-metal-catalyzed C–N bond formation reactions using azides as the nitrogen source where dinitrogen is formed as the sole byproduct. For such transformations, Ir^{III} catalysts were particularly effective in activating aromatic compounds with weakly coordinating directing groups in the *ortho* position.[6] Unfortunately, however, most procedures involve the use of significant amounts of solvents, which reduces the overall sustainability of the processes.

In the past decade, advanced ball-milling applications have been established, enabling the mechanochemical activation of a large variety of organic transformations.[7] Compared to common solvent-based methods, mechanochemically induced processes often have various advantages, such as higher yields, shorter reaction times, lower catalyst loadings, and the possibility of performing reactions in the absence of organic solvents.[8] An illustrative example is the copper-catalyzed coupling of aryl boronic acids with amines under mechanochemical conditions that was recently developed by Su and co-workers, which yielded the corresponding products in a significantly shorter reaction times than the solvent-based standard procedure.[9,10] Our group reported the first catalytic mechanochemical C–H bond functionalization process under solvent-free conditions that proceeds via an active Rh^{III} intermediate catalyzing an oxidative Heck-type olefination process of acetanilides and olefins with dioxygen as terminal oxidant (Scheme 1 a).[11]

Inspired by the reports on Ir^{III}-catalyzed C–H bond functionalization[6] and encouraged by our previous work, we wondered whether adequately substituted aromatic compounds would undergo mechanochemically induced Ir^{III}-catalyzed amidation reactions in ball mills under solvent-free conditions. Herein, we report the implementation of this concept (Scheme 1 b).

For our investigations, Chang's method for the amidation of benzamides was chosen as the starting point.[6b] Thus, *N*-(*tert*-butyl)benzamide (**1a**) and phenylmethanesulfonyl azide (**2a**) were treated with a combination of $[\{Cp^*IrCl_2\}_2]$ (2.5 mol %) and $AgBF_4$ (10 mol %) as the catalyst and AgOAc (20 mol %) as an additive in a mixer mill. Confirming our hypothesis, after milling the reaction mixture with two milling balls (0.5 cm diameter) for 99 min at 30 Hz, the amidated product **3a** had been formed in 38 % yield (determined by ^1H NMR spectroscopy; Table 1, entry 1). Next, the influence of the number and size of the milling balls was investigated (entries 2–4). When only one large milling ball (1.5 cm) was used instead of two smaller ones (0.5 cm), the yield of **3a** increased to 80 % (entry 3). The use of an even larger ball (2.0 cm) did not improve the yield further (entry 4; 72 %). Next, the substrate amounts were varied. Using an excess of benzamide **1a** resulted in a slightly higher yield of **3a** (entry 5; 87 %). When the amount of **1a** was increased further, almost no change in yield was observed (entry 6;



Scheme 1. C–H bond functionalization under mechanochemical conditions (DG = directing group).

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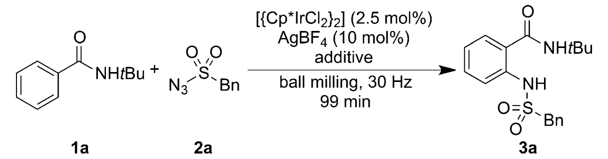
Table 1: Optimization of the Ir^{III}-catalyzed amidation of benzamides under mechanochemical conditions.[a]



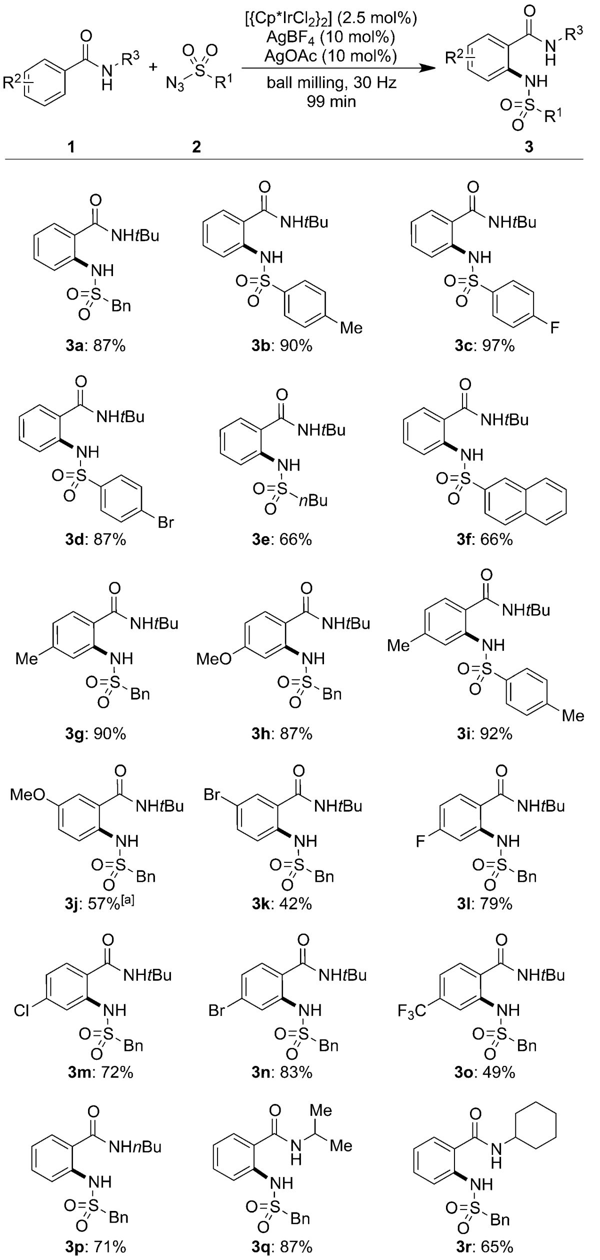
Entry	Additive (mol%)	**1a** [equiv]	**2a** [equiv]	Ball size [cm]	**3a**[b] [%]
1	AgOAc (20)	1.0	1.5	2×0.5	38
2	AgOAc (20)	1.0	1.5	2×1.5	77
3	AgOAc (20)	1.0	1.5	1.5	80
4	AgOAc (20)	1.0	1.5	2.0	72
5	AgOAc (20)	1.7	1.0	1.5	87
6	AgOAc (20)	1.8	1.0	1.5	83
7	–	1.7	1.0	1.5	24
8	AgOAc (10)	1.7	1.0	1.5	87
9	AgOAc (5)	1.7	1.0	1.5	60
10	NaOAc (10)	1.7	1.0	1.5	1
11	CsOAc (10)	1.7	1.0	1.5	3
12	$Cu(OAc)_2$ (10)	1.7	1.0	1.5	79

[a] Reaction conditions: $[\{Cp^*IrCl_2\}_2]$ (12.0 mg, 0.015 mmol, 2.5 mol%), $AgBF_4$ (12.0 mg, 0.06 mmol, 10 mol%), 30 Hz; the Retsch cryo mill, vessel (25 mL), and balls were made of ZrO_2. [b] Determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard. Bn = benzyl, Cp* = pentamethylcyclopentadienyl.

83%). Performing the reaction in the absence of AgOAc strongly affected the process, and **3a** was formed in only 24% yield (entry 7). However, decreasing the amount of AgOAc from 20 mol% to 10 mol% did not affected the reaction outcome, and **3a** was obtained in 87% yield (entry 8). However, with 5 mol% of AgOAc, the yield of **3a** decreased to 60% (entry 9). Replacing AgOAc with NaOAc or CsOAc was not possible (entries 10 and 11). In contrast, the use of $Cu(OAc)_2$ led to product **3a** in 79% yield (entry 12). These results confirm observations by Ackermann and others,[12] who found that the nature of the acetate plays an important role in directed C–H-bond functionalizations, and apparently, this effect is also relevant in mechanochemically activated processes performed under solvent-free conditions.

Three aspects of the Ir^{III}-catalyzed amidation process should be highlighted: First, because of the mechanochemical activation, the reaction could be performed under solvent-free conditions, generating the amidated products in high yields. Second, the reaction time for full conversion of the substrate was significantly shorter (99 min) than for the standard method in an organic solvent (12 h), and third, no external heating was required to form the desired products.[13]

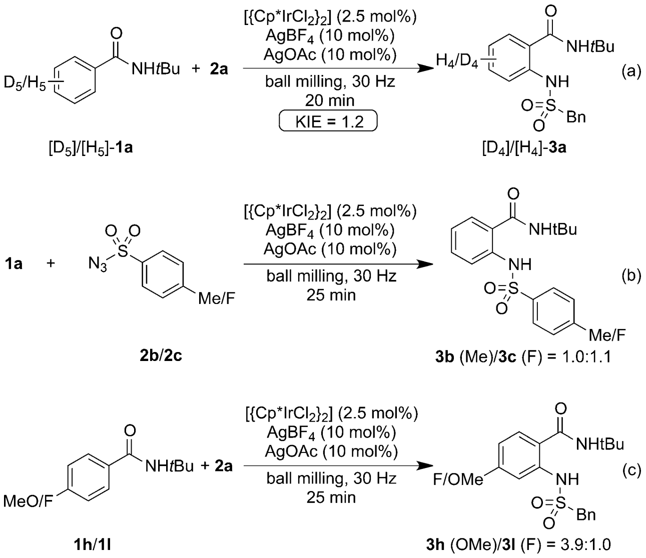
Next, the substrate scope of the Ir^{III}-catalyzed amidation under mechanochemical conditions was investigated (Scheme 2). Various sulfonyl azides performed well in the reaction with **1a**, affording the corresponding products **3a**–**3d** in yields ranging from 87% to 97%. Electronic effects played only a minor role. Furthermore, butane-1-sulfonyl azide (**2e**) and naphthalene-2-sulfonyl azide (**2f**) reacted satisfyingly, providing products **3e** and **3f**, respectively, in 66% yield each. To investigate the influence of substituents at the benzamide core, sulfonyl azide **2a** was reacted with substrates with an electron-donating methyl or methoxy group in the *para* position. Both transformations provided the corresponding products in high yields (**3g**: 90%; **3h**: 87%). The same was true when tosyl azide was used in the reaction with the 4-methyl-substituted benzamide. Again, the product was obtained in high yield (**3i**: 92%). A 1.28:1 regioisomeric mixture of **3j** was formed in 57% yield when 3-methoxy-substituted benzamide **1j** reacted with **2a**. The analogous transformation of a benzamide with a 3-bromo group provided **3k** as a single regioisomer in 42% yield. Starting from 4-halogen-bearing benzamides and **2a**, the corresponding products **3l**–**3n** were obtained in good yields of 79%, 72%, and 83%. In contrast, the reaction between 4-trifluoromethyl-substituted substrate **1o** and **2a** gave **3o** in only moderate yield (49%), which could be due to the strongly electron-withdrawing effect of the CF_3 substituent. Remark-



Scheme 2. Substrate scope of the mechanochemical Ir^{III}-catalyzed C–H amidation. [a] Obtained as a 1.28:1 regioisomeric mixture.

ably, the reaction remained efficient when the substituent at the amide nitrogen atom was changed from *tert*-butyl to *n*-butyl, isopropyl, or cyclohexyl. In each case, the desired product (**3p–3r**) was obtained in good yield (65–87 %).

To gain insight into the mechanochemically promoted reaction pathway, preliminary mechanistic studies were carried out. First, the kinetic isotopic effect (KIE) was determined in an intermolecular competition experiment with [D_5]-**1a**/[H_5]-**1a** and **2a** (Scheme 3 a).[14] For the solvent-free process presented here, a KIE of 1.2 was observed. This value differs significantly from the KIE of 3.4 that was determined for a similar reaction in solution.[6b,15] Apparently, a change in mechanism has occurred, leading to fast, non-turnover-limiting C−H bond cleavage under the applied (solvent-free) mechanochemical conditions. Analyzing the reasons for this unexpected behavior will be the focus of future work.

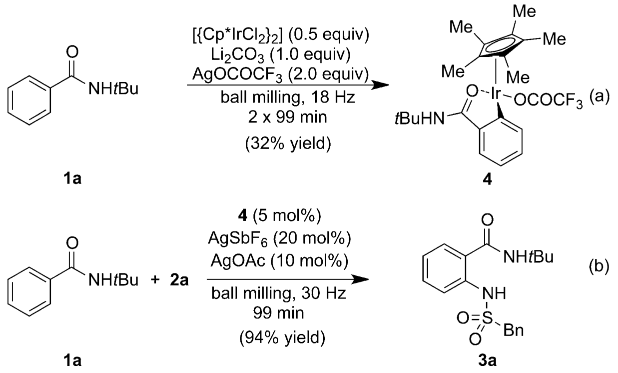


Scheme 3. Intermolecular competition experiments performed under mechanochemical conditions.

Intermolecular competition experiments with the differently substituted sulfonyl azides **2b**/**2c** (Scheme 3 b) and benzamides **1h**/**1l** (Scheme 3 c) revealed a slightly lower reactivity for electron-rich azide **2b** than for **2c** and a strong preference for the more electron-rich benzamide **1h** over **1l**, confirming that the cationic iridium species acts as an electrophile in the activation process.[5b]

Taking the solvent-based procedure as a guideline,[16] the stable cyclometalated iridium complex **4** was prepared in the absence of solvent using a mixer mill (Scheme 4 a). Complex **4** was then treated with $AgSbF_6$ (20 mol %) and AgOAc (10 mol %) and used as a catalyst (5 mol %) in the mechanochemical *ortho* amidation of **1a** with **2a**. After 99 min, product **3a** was obtained in 94 % yield, confirming the cyclometalated iridium species (complex **4**) to be an intermediate of the mechanochemically induced C−H amidation reaction (Scheme 4 b).

In summary, we have developed a mechanochemical iridium(III)-catalyzed process for the amidation of benzamides in a mixer mill. The active catalyst is formed in situ, and the amidated products were obtained in high yields and after shorter reaction times than in solution.



Scheme 4. Formation of iridacycle complex **4** and its catalytic reactivity.

Experimental Section

Representative procedure: Benzamide **1** (1.02 mmol, 1.7 equiv), sulfonyl azide **2** (0.6 mmol, 1.0 equiv), [{Cp^*IrCl_2}$_2$] (12.0 mg, 0.015 mmol, 2.5 mol %), $AgBF_4$ (12.0 mg, 0.06 mmol, 10 mol %), and AgOAc (10.0 mg, 0.016 mmol, 10 mol %) were transferred to a ball-milling vessel (ZrO_2, 25 mL) containing one grinding ball (ZrO_2, diameter: 1.5 cm). The ball-milling vessel was then transferred to a mixer mill (RETSCH cryo mill), and the reaction mixture was milled at 30 Hz for 99 min. The crude reaction mixture was extracted by washing the vessel and the ball with EtOAc (5 × 20 mL), and the resulting mixture was filtered through a thin layer of SiO_2 and concentrated. 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 sea sand (2 × 1 g) to the ball-milling vessel and milling the resulting mixture for 5 min (× 2). The amount of solvent utilized for the purification can thus be reduced, and **3a** was obtained in 83 % yield.[17]

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Keywords: ball mill · C−H amidations · iridium catalysis · mechanochemistry · solvent-free reactions

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[17] The reaction between **1a** and **2a** was repeated three times. The fact that **3a** was isolated in similar yields each time (81–85 %) show that the reaction is highly reproducible. Attempts to perform the reaction on 3.6 mmol scale (with the same-size ball-milling equipment) led to lower yields of **3a** (42 %) presumably owing to the altered reaction environment.

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