

# Mechanochemical Rhodium(III)-Catalyzed C–H Bond Amidation of Arenes with Dioxazolones under Solventless Conditions in a Ball Mill

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#### Supporting Information

**ABSTRACT:** A procedure for the direct mechanochemical rhodium(III)-catalyzed C–H bond amidation of arenes with 1,4,2-dioxazol-5-ones as the nitrogen source has been developed. The transformation proceeds under solventless conditions and does not require additional heating. The corresponding *ortho* amidated products are formed in high yields and in shorter reaction times than in solution.





itrogen-containing molecules are important for natural products, agrochemicals, and pharmaceuticals.<sup>1</sup> Consequently, in the past decades, the development of efficient C-N bond formation processes<sup>2</sup> has been extensively explored. In recent years, transition-metal-catalyzed C-H bond functionalization of traditionally unreactive C-H bonds have been established as a potent tool to generate a wide range of new carbon-carbon and carbon-heteroatom bonds. Along these lines, Chang and others<sup>3-5</sup> reported transition-metal-catalyzed C-H amidation reactions using dioxazolones<sup>6,7</sup> as the amidation reagents where carbon dioxide is formed as the sole byproduct. For such transformations, [Cp\*Rh(III)] catalysts<sup>3</sup> have been proven to be highly efficient. Commonly significant amounts of solvents are used, and in most of the cases, relatively harsh reaction conditions are required, still limiting the overall sustainability of the processes.

In the past decades, ball-milling has been established as a useful tool for the implementation of a wide range of organic transformation by means of mechanochemical activation.<sup>8</sup> Such mechanochemically promoted processes often provide advantages compared to common solvent-based methods, including higher yields, shorter reaction times, lower catalyst loadings, and mostly the avoidance of organic solvents and elevated reaction temperatures.<sup>9</sup> Also altered reactivity profiles have been observed.<sup>10</sup> In this context, our group reported the first catalytic mechanochemical C-H bond functionalization.<sup>11,12</sup> Under solvent-free conditions, the active Rh(III) species were formed in situ allowing to couple acetanilides with olefins in an oxidative Heck-type olefination with dioxygen as the terminal oxidant. In addition, we applied mechanochemical conditions to an Ir(III)-catalyzed C-H bond amidation process.<sup>13</sup> There, the mechanochemical activation led to the formation of an active iridium species, thus enabling an ortho-selective C-N bond formation process in the absence of solvent. Organic azides served as nitrogen sources (Scheme 1a). Inspired by the reports on Rh(III)-catalyzed C-H bond amidation processes<sup>3</sup>

Scheme 1. C–H Bond Amidation Processes under Mechanochemical Conditions (DG = Directing Group)





and encouraged by our previous work,<sup>12,13</sup> we wondered whether dioxazolones could be employed as nitrogen sources in mechanochemically induced catalytic amidation processes. Herein, we report on the realization of this concept (Scheme 1b).

As a starting point, we used similar reaction conditions to those reported by Chang.<sup>3a</sup> For this, *N*-(*tert*-butyl)benzamide (1a) and methyl-1,4,2-dioxazol-5-one (2a) were treated with a combination of  $[{Cp*RhCl_2}_2]$  (2.5 mol %) and AgSbF<sub>6</sub> (10 mol %) as the catalyst and AgOAc (10 mol %) as an additive in a mixer mill. To our delight, after milling the reaction mixture for only 99 min at 30 Hz, the amidated product 3a was formed in 76% yield (Table 1, entry 1). Substituting  $[{Cp*RhCl_2}_2]$  by

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Table 1. Optimization of the Rh(III)-Catalyzed C–H Amidation under Mechanochemical Conditions<sup>*a*</sup>



<sup>*a*</sup>Reaction conditions: **1a** (1.7 equiv), **2a** (0.5–0.8 mmol),<sup>15</sup> catalysts, and additives (10 mol %) were milled in a mixer-mill at 30 Hz, using a 25 mL ZrO<sub>2</sub> milling jar with one ZrO<sub>2</sub> ball of 15 mm diameter. The crude reaction mixture was extracted by adding sea sand (2 × 2 g) to the milling jar and milling the resulting mixture for 5 min (× 2). <sup>*b*</sup>Determined by <sup>1</sup>H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard. Cp<sup>\*</sup> = pentamethylcyclopentadienyl. <sup>c</sup>Use of AgSbF<sub>6</sub> (16 mol %), AgOAc (16 mol %). <sup>*d*</sup>Use of AgSbF<sub>6</sub> (20 mol %), AgOAc (20 mol %).

 $[{Cp*IrCl_2}_2]$  or  $[{Ru(p-cymen)Cl_2}_2]$  did not lead to the formation of **3a** (Table 1, entries 2 and 3). Next, the influence of additives was investigated<sup>14</sup> (Table 1, entries 4–7). In the absence of AgOAc, **3a** was formed in 66% (Table 1, entry 4). A negative effect was observed, when AgOAc was replaced by NaOAc or CsOAc (Table 1, entries 5 and 6). In contrast, the use of Cu(OAc)<sub>2</sub> led to product **3a** in 69% yield (Table 1, entry 7). Increasing the amount of  $[{Cp*RhCl_2}_2]$ , AgSbF<sub>6</sub> and AgOAc enhanced significantly the yield of the reaction (Table 1, entry 8 and 9). In particular, the use of 5 mol % of the Rh(III) catalyst afforded the amidated product **3a** in 97% yield (Table 1, entry 9).

Next, the substrate scope was investigated (Scheme 2). The use of unsubstituted benzamide 1a in the coupling with methyl-1,4,2-dioxazol-5-one (2a) afforded 3a in 90% yield (after column chromatography).<sup>16</sup> The use of benzamide 1a as limiting reagent (1a/2a: 1.0/1.7) afforded product 3a in a slightly lower yield (64%).<sup>17</sup> To study the influence of substituents on the benzamide core, various substrates bearing electron-donating groups in para or meta position of the arene were applied. Using *p*-methoxy benzamide 1b in the coupling with 2a provided 3b in a quantitative yield (>99%). In contrast, the reaction between *m*-methoxy-substituted benzamide 1c and 2a yielded 3c in only 45% and as a 1 1.1:1 regioisomeric mixture.<sup>18</sup> An analogous transformation of 1d bearing a chloro group in meta position of the benzamide afforded the corresponding product 3d as a single regioisomer in 88% yield. Treating 2a with benzamides containing halogens in para position, provided the corresponding products in quantitative yields (3e: > 99%, 3f: > 99% and 3g: 98%).<sup>19</sup> A moderate yield (45%) was observed when 2a was reacted with p-CF<sub>3</sub>substituted benzamide 1h, which could be due to the strong electron-withdrawing effect of the CF<sub>3</sub> group.<sup>20</sup> Replacing the tert-butyl group on the amide nitrogen atom by an adamantyl, isopropyl, cyclohexyl, or n-butyl group gave the corresponding

### Scheme 2. Mechanochemical Rh(III)-Catalyzed C-H Bond Amidation of Benzamides



<sup>*a*</sup>Obtained as 1.1:1 regioisomeric mixture. <sup>*b*</sup>Use of  $[{Cp*RhCl_2}_2]$  (10 mol %), AgSbF<sub>6</sub> (40 mol %), AgOAc (40 mol %).

products 3i-3l in very good to moderate yields (3i: 83%, 3j: 93%, 3k: 69%, and 3l: 38%).

Subsequently, the amidating reagent was varied. Replacing the methyl substituent on 1,4,2-dioxozol-5-one **2a** by an ethyl,<sup>18</sup> *tert*-butyl<sup>18</sup> or phenyl group gave the corresponding amidated products 3m-3o in yields ranging from 50% to 58%.

Performing the mechanochemical C–H amidation on a gram scale using 10 mmol of **1a** and 6 mmol of **2a** as substrates and a catalyst/additive combination of 2.5 mol % of  $[{Cp*RhCl_2}_2]$ , 20 mol % of AgBF<sub>4</sub>, and 10 mol % of AgOAc in a mixer mill for 99 min gave **3a** in 84% yield.

Three points of these results are particularly noteworthy: First, the mechanochemical activation allowed performing the reaction in the absence of any solvents, yielding the *ortho* amidated products in high yields by using similar catalysts loading as in solvent.<sup>3a</sup> Second, the desired products were formed in significant shorter reaction times (99 min) compared to the solvent-based standard protocol (12 h), and third, no additional heating was required.

To broaden the scope of the mechanochemical C-H amidation, the directing moiety was modified (Scheme 3).

Scheme 3. Mechanochemical Rh(III)-Catalyzed C–H Bond Amidation with Different Directing Groups



<sup>*a*</sup>Use of [{Cp\*RhCl<sub>2</sub>}<sub>2</sub>] (10 mol %) AgSbF<sub>6</sub> (40 mol %), AgOAc (40 mol %). <sup>*b*</sup>2 × 99 min at 30 Hz.

Pleasingly, a wide variety of directing groups could be applied.<sup>21</sup> For example, the coupling of 2a with ketoxime 4a or benzo[h]quinoline (4b) worked well, providing the corresponding products in good yields (5a: 78% and 5b: 81%). In addition, 2-phenylpyridine (4c), 2-phenyl pyrimidine (4d) and oxazoline 4e were suitable substrates forming the products in good to moderate yields, albeit under slightly more demanding conditions (5c: 70%, 5d: 24% and 5e: 34%). For some substrates (e.g., 5b and 5c), higher catalyst loadings were required compared with those in solution.<sup>3a</sup> Most interesting, isobutyrophenone, a very challenging weakly coordinating directing group<sup>3a</sup> was also effective under ball-milling conditions smoothly, generating product 5f in 49% yield by using 2a as the amidation reagent. Changing the substituent on the amidation reagent 2 from a methyl to a phenyl group led to product 5g in 49% yield together with a small amount (10%) of diamidation product 5g'.

For gaining insight into the reaction mechanism a kinetic isotopic effect (KIE)<sup>22</sup> was determined by performing intermolecular competition reactions between  $[D_5]$ **1**a and  $[H_5]$ **1**a with **2**a as the coupling partner (Scheme 4). Under mechanochemical conditions, the KIE value was 4.8. As this number was close to the one (4.4) determined in an analogous experiment under the previously reported reaction conditions

# Scheme 4. KIE Experiment of the Mechanochemical Rh(III)-Catalyzed C-H Bond Amidation



(with DCE as the solvent at 40 °C),  $^{3a,23}$  both processes appear to follow similar reaction pathways with the C–H bond cleavage being turnover-limiting.

Finally, we intended to confirm the competence of a rhodacyle to undergo amidation under the reported mechanochemical reaction conditions (Scheme 5). Following our





previously reported protocol,<sup>12b</sup> rhodacycle **6** was prepared by milling of **4c** with [{Cp\*RhCl<sub>2</sub>}<sub>2</sub>] (1.0 equiv) and NaOAc (6.0 equiv) for 2 × 99 min in a mixer mill. Then, a catalytic quantity of **6** (10 mol %) was combined with AgBF<sub>4</sub> (20 mol %) and AgOAc (20 mol %) and applied in the coupling between **4c** and **2a**. After 99 min of milling, product **5c** was isolated in 67% yield, confirming our hypothesis that rhodacycle **6** (in its cationic form) was a likely intermediate in the catalytic cycle of the mechanochemically induced C–H bond amidation process.<sup>24</sup>

In summary, we developed a mechanochemical rhodium-(III)-catalyzed C–H bond amidation of arenes with 1,4,2dioxazol-5-ones as amidating reagents. Under solventless conditions, the amidated products are formed in high yields, without additionally heating and in shorter reactions times than in solution. Preliminary investigations revealed mechanistic analogies to the solvent-mediated protocol.

# ASSOCIATED CONTENT

#### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b00582.

Experimental procedures, characterization data, and <sup>1</sup>H and <sup>13</sup>NMR spectra for the synthesized compounds (PDF)

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#### Notes

The authors declare no competing financial interest.

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(15) Because compound 2a was a viscous liquid, it was directly weight in the ball milling jar, and the amounts of the other reaction components were calculated on the basis of the exact weighted-in quantity of 2a. Consequently, the reaction scale varied between 0.5 and 0.8 mmol, and the ratio of all reactants remained the same.

(16) Attempts to recover the catalyst and additives remained unsuccessful.

(17) Using a large excess (6.1 equiv) of 2a in the coupling of 1a exclusively led to 3a (53%). For an interesting example of an iterative C-H amidation, see: Park, J.; Lee, J.; Chang, S. Angew. Chem., Int. Ed. 2017, 56, 4256–4260.

(18) Performing the reaction with a higher amount of catalyst or/and a longer reaction time did not lead to a higher yield.

(19) The reaction between 1g and 2a was performed three times. Each time, 3g was isolated in about the same yield (93–98%) showing that the transformation is highly reproducible.

(20) In some cases, low yields could be improved by using more catalysts or/and a longer reaction time as illustrated by the data given in parentheses in Schemes 2 and 3.

(21) No C-H amidation was observed with methyl benzoate, benzoic acid, N-phenylacetamide or 2-phenoxypyridine as substrates.

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