

# The use of copper and vanadium mineral ores in catalyzed mechanochemical carbon–carbon bond formations

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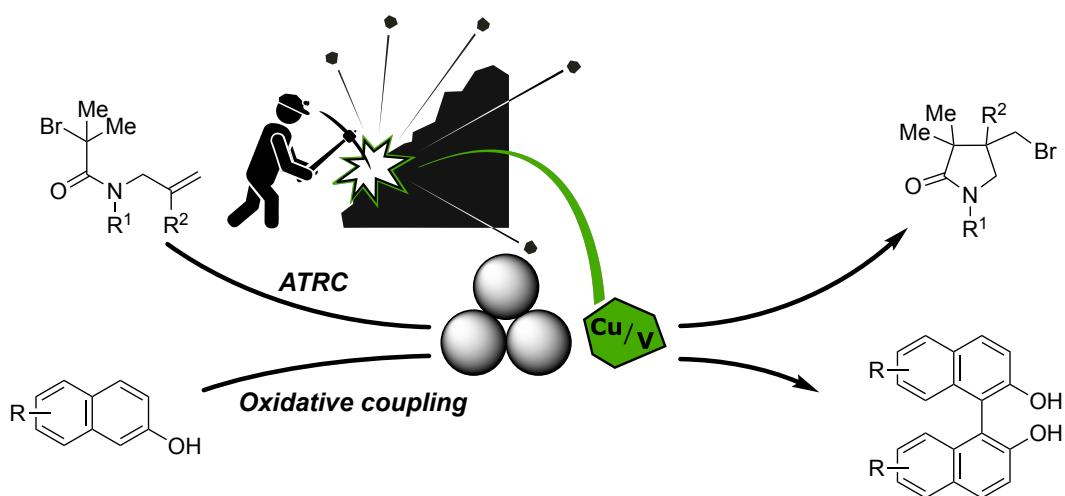
**Abstract:** Under mechanochemical conditions in ball mills, copper- and vanadium-containing minerals initiate atom transfer radical cyclizations and oxidative couplings, respectively. Only catalytic quantities of the minerals are required, and the reactions proceed either under neat conditions or in the presence of a minimal amount of solvent.

In nature, minerals play a fundamental role as mediators and catalysts during the complex set of chemical reactions leading to the formation of hydrocarbons.<sup>1,2</sup> This process generates structural complexity in light and heavier hydrocarbons, primarily through the formation and cleavage of carbon–carbon and carbon–hydrogen bonds. The ability of minerals to favor chemical reactions has been linked to their unique morphology and elemental composition, which consequently has inspired the design of materials resembling such structures. Recently, Fülöp and co-workers synthesized a Ag(I)Bi(III)-containing hybrid material mirroring naturally occurring layered double minerals.<sup>3</sup> The silver-containing hybrid exhibited outstanding catalytic properties in DMSO towards the synthesis of organic nitriles from terminal alkynes and trimethylsilyl azide. Complementarily, the direct use of minerals for catalysis has been reported as well. For instance, the earth-abundant mineral pyrite (FeS<sub>2</sub>) proved to be catalytically active for the selective hydrogenation of a broad class of functionalized nitroarenes to substituted anilines in a reaction medium composed of H<sub>2</sub>O-THF,<sup>4</sup> thus exemplifying the potential of minerals in catalysis research.<sup>5</sup>

As in the geochemical formation of hydrocarbons, organic chemists use metals to facilitate the formation of new C–C and C–H bonds. However, unlike in nature, the use of minerals as catalysts

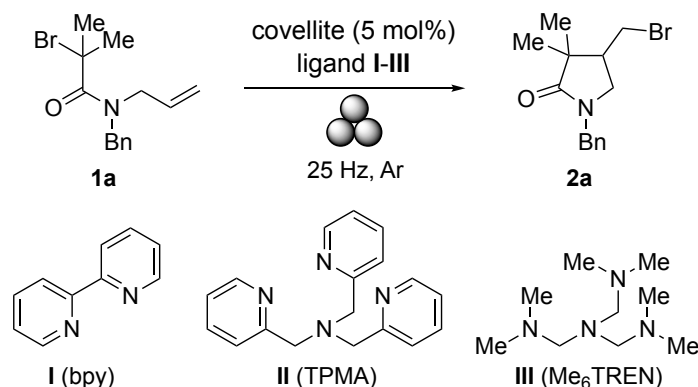
in organic chemistry laboratories is far from being the mainstream choice. Practical hurdles such as the scarce solubility of minerals in commonly used reaction media may be responsible for the slow adoption of mineral-catalyzed organic transformations. Seeing the potential and the opportunities of recently implemented mechanochemical techniques to synthesize minerals<sup>6-9</sup> and to facilitate the development of a myriad of reactions in organic chemistry,<sup>10-15</sup> we started wondering about developing mechanochemical mineral-catalyzed transformations.

If achievable, such merging could clearly elevate the sustainability of mechanochemical reactions<sup>16</sup> by harnessing the catalytic activity of bulk, readily available mineral ores, avoiding the need for the processing of the raw minerals into expensive metal catalysts.<sup>17-18</sup> In a proof-of-concept study, we have here focused on two mechanochemical carbon-carbon bond formation processes, namely, a copper-catalyzed atom transfer radical cyclization reaction and a vanadium-catalyzed oxidative coupling (Figure 1). As natural sources for the metals, a copper sulphide mineral named covellite and a vanadium-containing ore known as vanadinite were chosen for the mechanochemical reactions.



**Figure 1.** Use of raw mineral ores in copper-catalyzed atom transfer radical cyclization (ATRC) reactions and vanadium-catalyzed oxidative couplings under mechanochemical conditions.

As initial system, a copper-catalyzed atom transfer radical cyclization (ATRC) was selected. Commonly, this reaction is catalyzed by transition metals, being, in most cases, copper(I) salts and, particularly, copper(I) complexes bearing organic ligands.<sup>19</sup> Here, we chose the mineral covellite, which, despite its elemental formula of CuS suggesting the presence of copper(II) ions, predominantly consists of copper(I) species represented as  $(\text{Cu}^+)_3(\text{S}^{2-})(\text{S}_2^-)$  or  $(\text{Cu}^+)_4(\text{Cu}^{2+})_2(\text{S}_2)^{2-}_2(\text{S}^{2-})_2$ .<sup>20-22</sup>

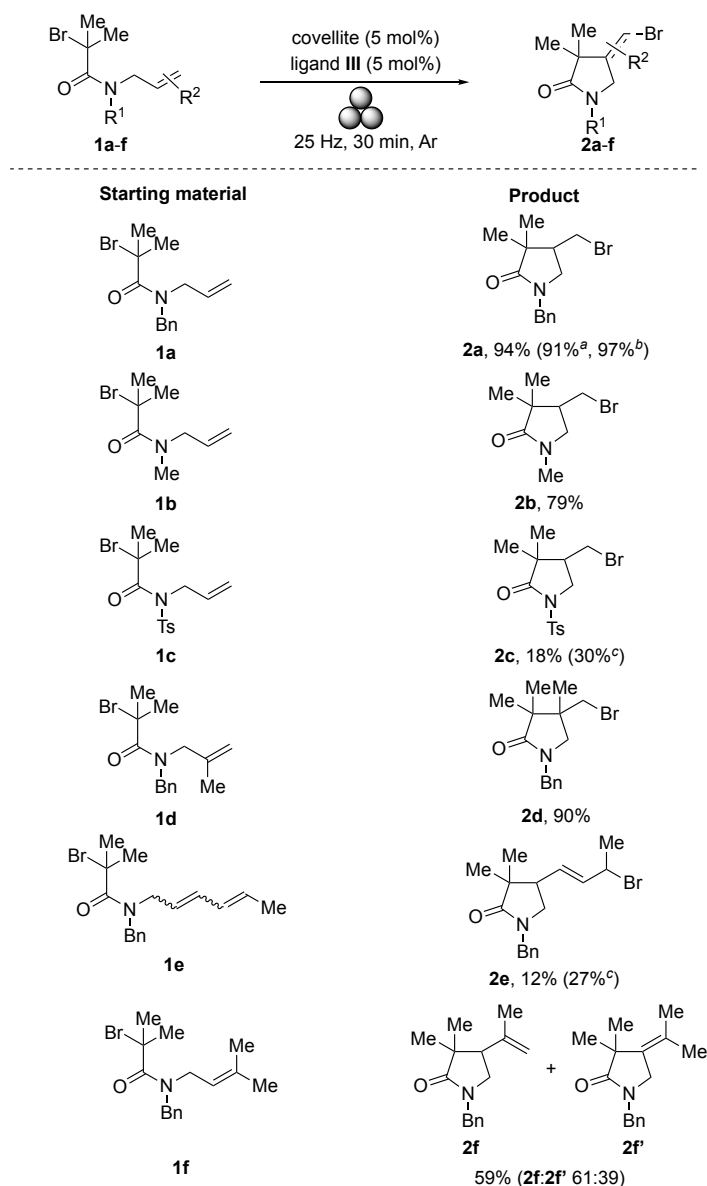
**Table 1.** Optimization of the reaction conditions: use of covellite in mechanochemical ATRC of **1a**.<sup>a</sup>

Entry	Ligand (mol%)	Reaction time (min)	<b>2a:1a</b> <sup>b</sup>
1	none	90	n.r.
2	<b>I</b> (20)	90	13:87
3	<b>II</b> (20)	90	80:20
4	<b>III</b> (20)	90	>99:1
5	<b>III</b> (15)	90	>99:1
6	<b>III</b> (10)	90	>99:1
7	<b>III</b> (5)	90	>99:1
8	<b>III</b> (2.5)	90	91:9
9	<b>III</b> (5)	60	>99:1
<b>10</b>	<b>III</b> (5)	<b>30</b>	<b>&gt;99:1</b>
11	<b>III</b> (5)	5	55:45
12 <sup>c</sup>	<b>III</b> (5)	90	n.r.

<sup>a</sup> Reaction conditions: **1a** (100.0 mg, 0.34 mmol), covellite (1.9 mg, 0.02 mmol, 5 mol%) and ligand **I-III** were milled in a mixer mill at 25 Hz under argon using a 10 mL ZrO<sub>2</sub>-Y milling jar with one 10 mm Ø milling ball of the same material. For calculations covellite was considered as pure CuS. For an elemental analysis of the mineral samples, see ESI. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy using signal integrals of **2a** and **1a**. <sup>c</sup> Under air.

The first evaluation of the catalytic activity of covellite in a mechanochemical ATRC reaction involved neat grinding of amide **1a** with the mineral under argon in a mixer mill for 90 min (Table 1, entry 1). To our disappointment, these conditions proved unsuitable, and none of the expected 5-*exo-trig* cyclization product **2a** was observed. The outcome changed, when the experiment was performed in the presence of commonly used ligands **I-III** (20 mol%),<sup>19</sup> which resulted in the formation of significant amounts of lactam **2a** identified by <sup>1</sup>H NMR spectroscopy of the crude mixture (Table 1, entries 2-4). In particular, tris[2-(dimethylamino)ethyl]amine (Me<sub>6</sub>TREN, **III**) proved effective leading to full conversion of **1a** and exclusive formation of pyrrolidone **2a**. Reducing the amount of ligand **III** from 20 mol% to 5 mol% had no effect on the final ratio of **2a:1a**, which remained >99:1 (Table 1, entries 4-7). Applying only 2.5 mol% of **III** lowered the product amount and the **2a:1a** ratio changed to 91:9 (Table 1, entry 8). Shortening the milling time from 90 min to 30 min was possible without affecting the product/educt ratio (>99:1), but milling for only 5 min changed the **2a:1a** ratio to 55:45 (Table 1, entries 9-11). Noteworthy, no product

was observed when the argon atmosphere was changed to air (Table 1, entry 12). Performing the ATRC reaction under the optimized reaction conditions (Table 1, entry 10) allowed isolating product **2a** in 94% yield after column chromatography (Scheme 1). Carrying out the ATRC reaction under the optimized reaction conditions using 1.0 mmol of **1a** (ca. 3-fold scaled up) led to lactam **2a** in 91% yield. The generality of the concept with respect to the mineral was shown by applying a combination of Me<sub>6</sub>TREN and bornite (Cu<sub>5</sub>FeS<sub>4</sub>)<sup>23</sup> instead of covellite, which provided lactam **2a** from amide **1a** in 97% yield.



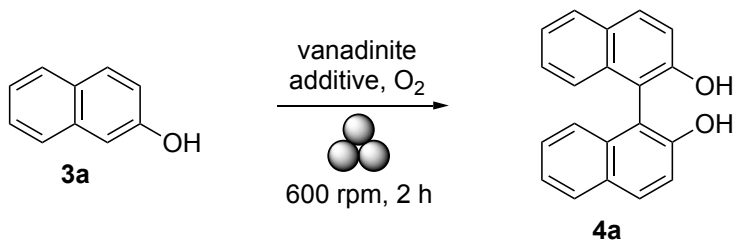
**Scheme 1.** Scope of the ATRC reaction. Reaction conditions: **1a-f** (0.3 mmol or 100.0 mg), covellite (0.02 mmol, 5 mol%) and ligand **III** (Me<sub>6</sub>TREN, 0.02 mmol, 5 mol%) were milled under argon in a 10 mL ZrO<sub>2</sub>-Y milling jar with one 10 mm Ø milling ball of the same material for 30 min at 25 Hz. For calculations covellite was considered as pure CuS. For an elemental analysis of the mineral samples, see ESI. <sup>a</sup> Reaction conducted on 1.0 mmol scale of **1a**. <sup>b</sup> Bornite mineral was used instead of covellite. <sup>c</sup> 90 min of milling.

To further test the applicability of the mechanochemical ATRC reaction, the study was extended to amides **1b-f**, which were subjected to millings with covellite and Me<sub>6</sub>TREN (Scheme 1). As *N*-benzyl derivative **1a**, also *N*-methyl- and *N*-tosyl-substituted amides **1b** and **1c**, respectively, underwent the cyclization reaction, although to a lesser extent compared to their *N*-benzyl analogue (Scheme 1). Probably, as shown in previous studies,<sup>24,25</sup> the steric and electronic effects of the *N*-substituent affected the population of the required anti-amide conformer, thereby lowering the overall reaction efficiency. As studied for the conversion of **1c**, extending the reaction time had a positive effect on the yield of **2c**, which increased from 18% to 30% when the reaction was performed for 90 min instead of the standard 30 min (Scheme 1). Next, three other *N*-benzyl amides (**1d-f**) were tested. The results were mixed. While **1d** exhibited a similar reactivity as **1a** providing **2d** in 90% yield, **1e** reacted sluggish, leading to lactam **2e** in only 12% yield under standard conditions. As observed before, extending the reaction time proved beneficial, and after 90 min of milling **2e** was isolated in 27% yield. The results for the latter substrate were attributed to the pronounced stability of the presumed allyl radical being formed as intermediate after the initial cyclization step of **1e** and its reduced rate in bromide transfer closing the catalytic cycle (see ESI).<sup>26</sup> Finally, applying amide **1f** in the mechanochemical ATRC reaction afforded bromine-free isomeric lactams **2f** and **2f'** in 59% overall yield. Most likely, both compounds resulted from the same cyclization product having a 2-bromo-2-propyl substituent. Subsequent HBr elimination gave olefinic products **2f** and **2f'** (in a ratio of 61:39).

With the goal to validate the concept of using minerals in mechanosynthesis by a second example, the vanadium-promoted oxidative coupling of  $\beta$ -naphthol (**3a**) was set into the focus.<sup>27,28</sup> The relatively high abundance of vanadium on earth compared to other transition metals has encouraged many studies on vanadium catalysis under homogeneous<sup>27</sup> and heterogeneous<sup>29</sup> reaction conditions. However, to the best of our knowledge, the direct use of a vanadium-containing mineral as catalyst for an organic reaction has remained unknown. For this part of the proof-of-concept study, we chose vanadinite [Pb<sub>5</sub>(VO<sub>4</sub>)<sub>3</sub>Cl] being one of the most abundant vanadium-based minerals and therefore a primary source of this metal at the industrial level.<sup>30</sup> By using vanadinite in combination with dioxygen under mechanical milling we envisaged promoting the oxidative coupling of **3a** to 1,1'-bi-2-naphthol (BINOL, **4a**) (Table 2), while expanding the applicability of ball milling techniques to mechanochemical reactions involving gaseous reactants.<sup>31-35</sup>

As in the case of the covellite-catalyzed ATRC reaction, the presence of an organic ligand proved critical here too. While in both the absence of vanadinite and the presence of the mineral alone the conversion of **3a** to **4a** was  $\leq 1\%$  (Table 2, entries 1 and 2), the product formation was triggered by the addition of an organic acid (entries 3-7). Testing a series of acidic additives showed that (at 1 atm of dioxygen pressure) multicarboxylic acids such as tartaric acid and citric acid were superior over, for example, simple amino acids (see ESI for details). Finally, the presence of 2,6-dipicolinic acid (DPA)<sup>36</sup> led to be best result giving a 24:76 mixture of **4a** and **3a** after 2 h of milling at 600

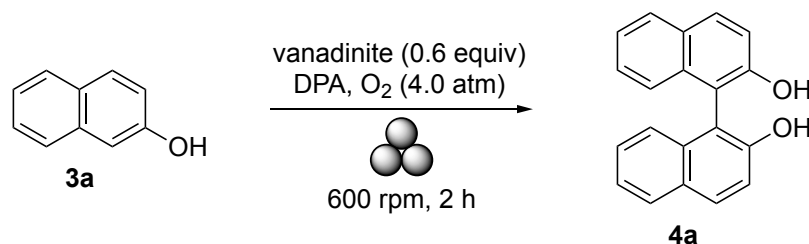
**Table 2.** Optimization of the reaction conditions: use of vanadinite in mechanochemical oxidative coupling of **3a**.<sup>a</sup>



Entry	O <sub>2</sub> (atm)	Additive <sup>b</sup>	<b>4a:3a</b> <sup>c</sup>
1 <sup>d</sup>	1.0	None	0:100
2	1.0	None	1:99
3	1.0	Glutamic acid	3:97
4	1.0	Aspartic acid	8:92
5	1.0	Tartaric acid	7:93
6	1.0	Citric acid	4:96
7	1.0	DPA	24:76
8	4.0	DPA	33:67
9	4.0	DPA, LAG (MeOH, $\eta = 0.5$ )	87:13
<b>10<sup>e</sup></b>	<b>4.0</b>	<b>DPA, LAG (MeOH, <math>\eta = 0.5</math>)</b>	<b>89:11</b>
11 <sup>f</sup>	4.0	DPA, LAG (MeOH, $\eta = 0.5$ )	68:32

<sup>a</sup> Reaction conditions: **3a** (100.0 mg, 0.69 mmol), vanadinite (1.0 g, equivalent to 1.70 mmol of vanadium) and additive (300.0 mg) were milled in a planetary ball mill under dioxygen in a 20 mL ZrO<sub>2</sub>-Mg milling jar with five 10 mm Ø balls of the same material for 2 h at 600 rpm (1 h × 2; 20 min pause after each milling cycle). For an elemental analysis of the mineral sample, see ESI. <sup>b</sup>  $\eta$  is the volume of solvent (in  $\mu$ L) divided by the total weight of the solid reactants (in mg). <sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy using signal integrals of **4a** and **3a**. <sup>d</sup> Without vanadinite. <sup>e</sup> Use of 500.0 mg of vanadinite (0.85 mmol of vanadium) and 150.0 mg of DPA (0.90 mmol). <sup>f</sup> Use of 250.0 mg of vanadinite (0.42 mmol of vanadium) and 75 mg of DPA (0.45 mmol).

rpm (Table 2, entry 7). Increasing the dioxygen pressure inside the milling vessel from 1 atm to 4 atm raised the product amount (**4a:3a** = 33:67; Table 2, entry 8). A further improvement was noted upon liquid-assisted grinding (LAG)<sup>37</sup> with methanol (Table 2, entry 9). The benefits of the LAG approach included reducing the vanadinite loading below stoichiometric amounts of vanadium, thereby achieving an oxidative coupling of  $\beta$ -naphthol (**3a**) in the ball mill under vanadinite catalysis (Table 2, entry 11). Intrigued by the remarkable effect of methanol on the mechanochemical reaction, LAG experiments with other liquid additives were carried out (Table 3). The screening revealed that the entire system was highly sensitive to even small changes. For example, adding MeOH-*d*<sub>4</sub> instead of MeOH changed the yield of **4a** (as determined by <sup>1</sup>H NMR spectroscopy with an internal standard) from 64% to 36% (Table 3, entries 2 and 3). Negative effects on the yield of **4a** were also noted when other common solvents were added (Table 3, entries 4-11). Finally, the amounts of methanol and DPA were fine-tuned to maximize the effects (Table 3, entries 12-15).

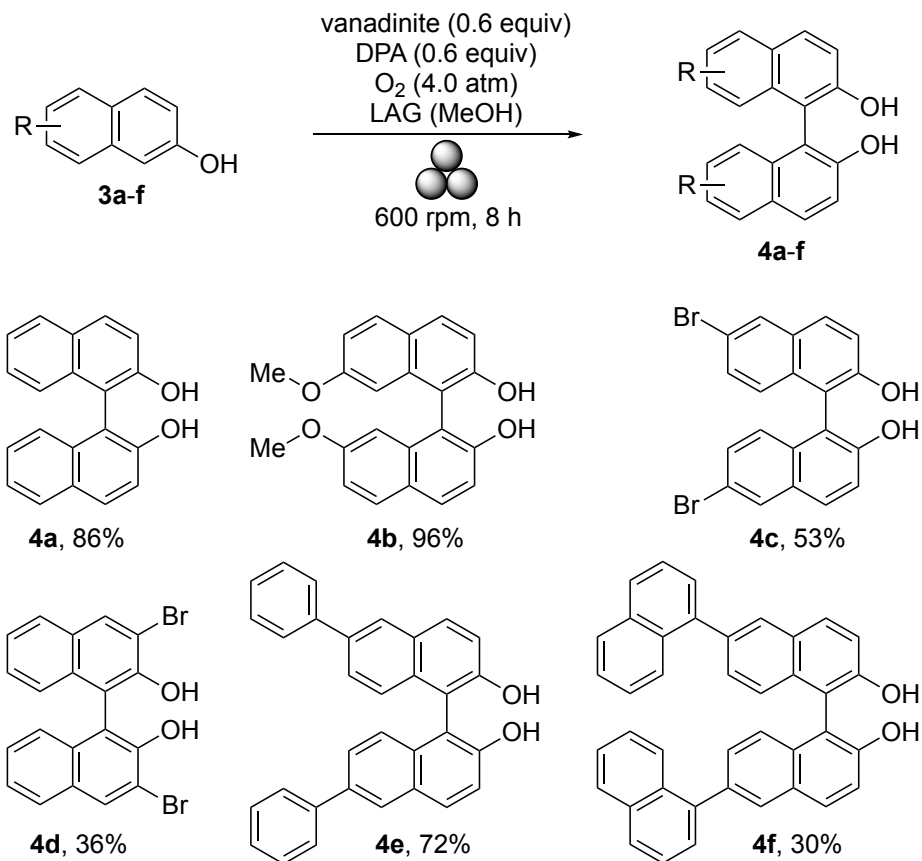
**Table 3.** LAG effects upon addition of liquids to the vanadinite-catalyzed oxidative coupling of **3a**.<sup>a</sup>

Entry	LAG additive ( $\eta$ )	Yield of <b>4a</b> (%) <sup>b</sup>
1	---	39%
2	MeOH (0.5)	64%
3	MeOH- <i>d</i> <sub>4</sub> (0.5)	36%
4	EtOH (0.5)	45%
5	CCl <sub>4</sub> (0.5)	42%
6	<i>i</i> -PrOH (0.5)	12%
7	HFIP (0.5)	10%
8	H <sub>2</sub> O (0.5)	12%
9	DMSO (0.5)	7%
10	DMF (0.5)	7%
11	MeCN (0.5)	11%
12 <sup>c</sup>	MeOH (0.5)	63%
13 <sup>c</sup>	MeOH (0.2)	50%
14 <sup>c</sup>	MeOH (0.1)	33%
15 <sup>c</sup>	<b>MeOH (0.05)</b>	<b>63%</b>

<sup>a</sup> Reaction conditions: **3a** (100.0 mg; 0.69 mmol), vanadinite (250.0 mg; 0.42 mmol of vanadium), DPA (75.0 mg; 0.45 mmol) and the LAG solvent were milled under O<sub>2</sub> (4.0 atm) in a planetary ball mill using a 20 mL ZrO<sub>2</sub>-Mg milling jar with five 10 mm  $\varnothing$  milling balls of the same material for 2 h at 600 rpm (1 h  $\times$  2; 20 min pause after each milling cycle). For an elemental analysis of the mineral sample, see ESI. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> Use of 0.42 mmol of DPA.

After having identified the best additive combination (DPA and MeOH), the vanadinite-catalyzed oxidative coupling of **3a** was carried out for 8 h of milling, which allowed to isolate of product **4a** in 86% yield (Scheme 2). Other naphthol derivatives showed a similar reactivity. For instance, the use of 7-methoxy 2-naphthol (**3b**) gave substituted BINOL **4b** in 96%. Bromo-substituted naphthols **3c** and **3d** proved less reactive affording the corresponding BINOLs **4c** and **4d** in yield of 53% and 36%, respectively (Scheme 2). Employing **3e** and **3f** with 6-aryl substituents led to yields of 72% for **4e** and 30% for **4f**. Overall, the results indicated that both electronic and steric

effects of the substrates have an impact of the coupling efficiency. In addition, solid-state properties (such as crystallinity) of both reactants and the products play a role.<sup>38</sup>



**Scheme 2.** Scope of the mechanochemical vanadium-catalyzed oxidative coupling. Reaction conditions: **3a-f** (0.70 mmol), vanadinite (252.5 mg; 0.43 mmol), DPA (71.5 mg, 0.43 mmol) and methanol ( $\eta = 0.05$ ) were milled under dioxygen in a planetary ball mill using a 20 mL ZrO<sub>2</sub>-Mg milling jar with five 10 mm  $\varnothing$  milling balls of the same material for 8 h at 600 rpm (1 h  $\times$  8; 20 min pause after each milling cycle). For an elemental analysis of the mineral sample, see ESI.

In summary, we have demonstrated the potential of using raw mineral ores as catalysts in copper-catalyzed atom transfer radical cyclizations and vanadium-catalyzed oxidative couplings. Both carbon-carbon bond forming processes occurred in mixer and planetary ball mills, which enabled the reactions to proceed mechanochemically. Moreover, the implementation of ball milling techniques permitted the poorly soluble copper and vanadium minerals (i.e., covellite, bornite and vanadinite) to promote the reactions under neat and LAG conditions. Such approach significantly reduced mineral processing operations typically required to access commercial metal salts, by directly using mineral ores as catalysts in ball mills. Key to harness the catalytic activity of the metals within the minerals was the use of readily available organic ligands such as Me<sub>6</sub>TREN and DPA. Thus, the approach avoided the need for highly engineered ligands or additive. Currently, this concept is further investigated in our laboratories applying it in other mechanochemical reactions, catalyzed by mineral ores.



**Supporting Information.** The following files are available free of charge. Experimental synthetic procedures and characterization (<sup>1</sup>H and <sup>13</sup>C NMR, IR, MS (EI,CI)) of compounds **1a-f**, **2a-f**, **3e-f** and **4a-f**; HRMS data for compounds **1b-f** and **2b-f**; extended version of Table 2; considerations on the mechanism for the formation of **2e**.

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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