Bronze Age of Direct Mechanocatalysis: How Alloyed Milling Materials Advance Coupling in Ball Mills

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The copper-catalyzed Glaser coupling is conducted mechanochemically, with the milling balls and vessels being the catalyst. Thus, neither catalyst powders nor soluble catalyst salts are required. Substituting Cu⁰ milling tools by copper alloys not only increases the yield of the reaction, but also greatly reduces abrasion, and in turn increases catalyst long-term stability and reusability. Tracking the reaction by Raman spectroscopy allows to identify the active intermediate directly on the milling ball surface and propose a reaction mechanism.

1. Introduction

Copper is known to mankind for millennia. However, one of the most impactful events in the evolution of civilization was when copper was mixed with tin to yield bronze roughly 5000 years ago. Alloying the metal made it far more durable and harder and enabled our civilization to progress. In the same spirit, we elaborate how copper alloys are more potent in direct mechanocatalytic applications compared with pure copper metal.

Copper is cheap and non-toxic but beyond that a highly potent alternative to commonly used catalysts such as palladium.¹ It is applied in palladium-free versions of Heck,³ Negishi,⁴ Sonogashira,⁵ Stille,⁶ or Suzuki coupling reactions.⁵ Most of these reactions are conducted in solution in a homogeneous manner.²,⁹ One main requirement toward these homogeneous catalyst complexes is their solubility in the reaction medium.¹⁰ However, the recycling of the expensive and meticulously designed catalysts is difficult and costly.¹¹ A technique that proved to evade solubility requirements entirely and therefore offers a highly sustainable alternative is the solvent-free synthesis using ball mills.¹² Without the requirement of solubility in mechanochemical syntheses, simple, cheap, and air-stable metal salts without ligands have been used in many reactions such as cross-coupling reactions,¹³ homocouplings of boronic acids,¹³ and phenols,¹⁵ or click reactions.¹⁶ However, recyclability is still a drawback in this approach as the catalyst is usually discarded after the reaction.

A concept to overcome this issue is “direct mechanocatalysis.” It uses the metallic milling material itself, i.e., the milling ball or vessel as catalyst inside the vibrating ball mill.¹⁷ Thereby, the catalyst separation is strongly simplified and process steps are reduced.¹¹,¹⁸ Pioneer work on this concept was done by the Mack group, who used it for Sonogashira coupling, azide–alkyne-type click reaction, and the cycloaddition of alkynes toward cyclo-octetraenenes.¹⁹,²⁰ Sawarna et al. later showed the capability of stainless steel materials to catalyze hydrogen generation¹¹,²² and reduction of organic molecules.²³,²⁴ Recently, we expanded on this idea by palladium-catalyzed Suzuki cross coupling facilitated by solid palladium milling balls.²⁴ However, all these examples suffer from high abrasion of the soft palladium, copper, or nickel milling media and therefore limit the catalysts’ recyclability and impede the separation of insoluble compounds.²⁴ Solving this issue is a fundamental challenge in direct mechanocatalysis, where the milling balls have to be both hard enough to withstand the milling conditions as well as catalytically active.

In this contribution, we advance the concept of “direct mechanocatalysis” toward alloyed milling materials. This broadens the scope of possible materials tremendously and transforms it from a mere curiosity toward a powerful tool for synthetic chemists. In here we show that, although the concentration of the catalytically active metal is reduced, a considerably increase in activity, reduced abrasion, and enhanced cyclability can be achieved utilizing alloys. We showcase this concept using the copper-catalyzed Glaser coupling of terminal alkynes toward 1,3-butadiynes. This particular reaction is an important tool in the synthesis of natural products⁵,¹³ and polymer materials⁵,²⁶ and is usually conducted with Cu⁺ salts as catalyst.²⁵,²⁷ It can also be conducted on metal surfaces²⁸ or in a ball mill.²⁹,³⁰ In this study, we demonstrate the advancement and evolution of this reaction from a mechanochemical approach that used Cu⁺ salts²⁰ to copper milling balls and beyond toward alloy milling balls and vessels as catalyst (Figure 1).
Nevertheless, in an attempt to transfer this reaction into “direct mechanocatalysis,” we replaced the ZrO2 milling balls by two 10 mm copper balls and observed 1,4-diphenylbuta-1, 3-diyne (2a) in a 47% yield (Table 1, Entry 2). Thereby, we enable direct mechanocatalytic Glaser coupling with Cu9 applied as milling ball catalyst, although typically Cu1 and Cu11 salts are used. However, Cu balls, expectedly, proved too soft to be considered suitable catalysts for this reaction and consequently produced enormous abrasion (302.7 mg) over the course of the 90 min reaction. To mitigate this drawback while keeping the “direct mechanocatalytic” approach, we, thus, turned to milling balls out of harder and readily available copper alloys. We started this screening with milling balls made of bronze (CuSn8). This approach led to a higher yield of 52%, while reducing the abrasion by a factor of 100 (Table 1, Entry 3). To verify the reproducibility, we repeated this experiment five times with comparable results. We also conducted a cycling study with the same milling balls (see ESI Section 1 and Table S1, Supporting Information). Satisfied with the performance of bronze, other alloys were studied. Brass (CuZn36) balls with a copper content of only 64 wt.% showed little abrasion (8.0 mg) as well as comparable yields of 53% (Table 1, Entry 4). To further reduce the copper content, Monel K–500 (NiCu30Al, 30 wt% Cu) balls were used but the yield decreased to 17% and the abrasion was also slightly higher (Table 1, Entry 5). As the effect of the alloying metals cannot be ruled out at this point and nickel is known to catalyze these reactions in solution[30,31] we also purchased Ni balls. These balls merely yielded 3% of 2a (Table 1, Entry 6) and also caused high abrasion. Therefore, nickel catalysts turned out inappropriate in our direct mechanocatalytic protocol (interestingly, for both Monel and pure Ni balls, no side reactions known from Ni catalysis occurred, such as cyclotrimerization.[32]

### Table 1. Direct mechanocatalytic Glaser coupling using catalytic milling balls.

| Entry | Reagent/substituent | Ball material (copper content [wt. %]) | Vickers hardness of milling balls | Weight per ball [g] | Milling time [min] | Base | Total abrasion of balls [mg] [%] | Yield [%] |
|-------|---------------------|----------------------------------------|---------------------------------|---------------------|------------------|------|------------------------------|----------|
| 1      | 1a/H                | ZrO2 (0)                               | ≈ 1200 [34]                     | 3.19                | 90               | K2CO3 | 0.2/−0.01                     | 0        |
| 2      | 1a/H                | Copper (100)                           | 70–110 [39,40]                  | 4.08                | 90               | K2CO3 | 302.7/3.70                    | 47       |
| 3      | 1a/H                | Bronze (92)                            | 120–175 [41]                    | 4.04                | 90               | K2CO3 | 2.3/0.035                     | 52 [6]   |
| 4      | 1a/H                | Brass (64)                             | 120–155 [42]                   | 4.42                | 90               | K2CO3 | 8.0/0.09                      | 53       |
| 5      | 1a/H                | Monel (30)                             | 210–336 [39]                   | 3.83                | 90               | K2CO3 | 15.6/0.21                     | 17       |
| 6      | 1a/H                | Nickel (0)                             | 90–130 [39,41]                 | 4.67                | 90               | K2CO3 | 41.6/0.49                     | 3        |
| 7      | 1a/H                | Bronze (92)                            | 120–175                       | 4.04                | 20               | K2CO3 | 0.7/0.01                      | 33       |
| 8      | 1a/H                | Bronze (92)                            | 120–175                       | 4.04                | 180              | K2CO3 | 8.9/0.08                      | 61       |
| 9      | 1a/H                | Bronze (92)                            | 120–175                       | 4.04                | 90               | Rb2CO3 | 3.2/0.04                     | 52       |
| 10     | 1a/H                | Bronze (92)                            | 120–175                       | 4.04                | 90               | Cs2CO3 | 2.1/0.03                     | 52       |
| 11     | 1a/H                | Bronze (92)                            | 120–175                       | 4.04                | 90               | KOH/Br | 8.5/0.11                     | 46       |
| 12     | 1b/Br               | Bronze (92)                            | 120–175                       | 4.04                | 90               | KOH/Br | 2.6/0.03                     | 30       |
| 13     | 1c/C6H5              | Bronze (92)                            | 120–175                       | 4.04                | 90               | K2CO3 | 6.0/0.07                     | 42       |

55 µL (0.5 mmol) 1a were milled together with 3.0 g K2CO3 and two 10 mm milling balls in a 25 mL ZrO2 milling vessel in MM 400 at 30 Hz. The products were extracted on a frit with dichloromethane6 and the solution dried under vacuum to obtain the product 2a.7 About 3.2 mg (10 mol%) copper powder was added as catalyst.8 It was reproduced five times with yields of 52% ± 1.3% and abrasions of 2.3 ± 0.3 mg and 0.03 ± 0.003%.9 The utilized dichloromethane was recovered from the evaporator and reused consistently during the project.

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2. Results

In a typical synthesis, two milling balls (diameter ≈10 mm) were placed together with 55 µL (0.5 mmol, 1a) phenylacetylene and 3.0 g (21.7 mmol) K2CO3 as base and bulking material in a 25 mL ZrO2 milling vessel and milled at 30 Hz in an MM400 (for detailed procedure and characterization, see ESI). As a starting point, we reproduced the experiments of Schmidt et al. with our ball mills.10 Most importantly we confirmed that copper powder (Table 1, Entry 1) is not capable of replacing the Cu1 salts in this reaction. This was expected but disheartening nonetheless, as in our prior study of the Suzuki reaction, we found that the metal powders could indeed act as catalysts.11
cycloctetramerization,[20,33] or hydrogenation[21–23] and copper appears to be the active component.

After establishing the feasibility, several reaction parameters were screened for the bronze system (see ESI Section 1 and Table S1, Supporting Information). For example, the milling time was varied, and after 20 min milling, 2a was isolated in 33% yield (Table 1, Entry 7), and with 180 min of milling 61% of (2a) could be isolated (Table 1, Entry 8). However, no quantitative yield could be reached only by extending the reaction time, whereas longer milling time inadvertently also caused higher abrasions (see Table S1, Supporting Information, Entries 4 and 5). The investigation of different bases (Table 1, Entries 9-11) showed reactivity solely for Rb₂CO₃ (52%), Cs₂CO₃ (52%), and KOtBu (46%) with almost identical output. Application of the standard protocol to other para-substituted phenylacetylene reagents (Table 1, Entries 12 1b and 13 1c) yielded 30% of 2b and 42% of 2c. This alteration between the reagents is in line with the reactivity reported in the literature.[34] Altogether, the screening experiments proved the robustness of the direct mechanocatalytic Glaser coupling toward the examined influencing parameters.

The established system can now be investigated further to answer several key questions relating to direct mechanochemical reactions with alloys as catalysts and in general.

2.1. What Needs to be Made Out of the Catalytically Active Material, the Vessel, the Ball, or Both?

To tackle this, we combined bronze milling balls with a bronze milling vessel (see Figure S2, Supporting Information, only one milling ball was used, due to the smaller vessel size) and obtained 2a in 61% yield (Table 2, Entry 1). The equal hardness of milling ball and vessel resulted in a low abrasion of 3.8 mg (combined vessel+balls). If only the vessel is made out of the active material and the balls out of the inert ZrO₂, the yield reaches 71% (Table 2, Entry 2). The total abrasion was also rather low at 5.0 mg. Consequently, we followed testing milling vessels made of a harder aluminum–bronze alloy (CuAl10Ni5Fe4, Al-bronze, Figure S2, Supporting Information). The yield and abrasion of the Al–bronze vessel with a bronze ball of 63% (Table 2, Entry 3) are comparable with the bronze–bronze system, whereas, finally, milling with a ZrO₂ ball in the Al–bronze vessel resulted in the second-best yield of 67% (Table 2, Entry 4) with strongly reduced abrasion (1 mg-combined vessel and balls). These results prove that an increase in catalytic surface is beneficial for the reaction, while a harder material leads to a higher energy transfer and is desirable especially for the ball (see Table S3, Supporting Information, for comparison with conventional and mechanochemical reactions). If feasible, a catalytically active milling vessel with inert balls seems to be preferable. Furthermore, the strong influence of milling material known from mechanocatalysis holds true for direct mechanocatalysis.[35]

In addition, we compared our approaches from standard conditions (Table 1, Entry 3) and in the Al–bronze vessel (Table 2, Entry 4) with conventional and former mechanocatalytic procedures regarding environmental aspects (ESI Section 4). While the conventional and mechanochemical procedures show low energy consumption due to room-temperature conditions (conventional) and short reaction time (mechanochemical), our direct mechanocatalytic procedure reaches a high EcoScale[36] (up to 77.5 vs ≤65.5), thanks to the entire avoidance of hazardous chemicals. The mass productivity of conventional syntheses differs strongly within the ball-milling procedures. Thus, for the latter, workup procedures and catalyst recyclability are not taken into account, which would strengthen the direct mechanocatalytic Glaser coupling further.

2.2. Where Is the Reaction Happening?

To verify the catalytic nature, we conducted experiments with the bronze milling material replaced by ZrO₂, base substituted by KCl, or under an inert argon atmosphere. In all cases no product was formed (see ESI Section 3.3), confirming the need of a copper-containing catalyst, a base, and oxygen in this reaction. However, the oxygen can also be replaced by a solid oxidant (see ESI Section 3.4).

While we already established that copper powder is not catalytically active, we also checked the abrasion from the bronze milling balls. We recycled the base with incorporated abrasion (700 nm bronze particles according to scanning transmission electron microscopy (STEM)/energy dispersive X-ray spectroscopy (EDS), Figure S9, Supporting Information) from our reference experiment (Table 1, Entry 3), added 0.5 mmol of 1a, and milled for 90 min with two 10 mm ZrO₂ balls. In this second cycle, the yield of 2a was only 3% (Table 2, Entry 5), which might be caused by insufficient washing of the base. We can thus exclude the abrasion as the cause of the reaction. The only possible catalytically active site is thus the ball/vessel surface. To verify this further, we took a bronze ball of the standard approach directly after the stopped reaction and measured Raman spectra at several spots. On several occasions, we could observe a shifted acetylene signal at 1930 cm⁻¹, which is in line with the literature reference of copper phenylacetylide (1a-Cu).[37]

Table 2. Catalytic activity of milling balls versus vessels.

| Entry | Ball material | Vessel material | Total abrasion vessel and balls [mg%] | Yield [%] |
|-------|---------------|----------------|--------------------------------------|----------|
| 1a    | 1x Bronze     | Bronze         | 3.8/0.021                             | 61       |
| 1b    | 1x ZrO₂       | Bronze         | 5.0/0.002                             | 71       |
| 2a    | 1x Bronze     | Al–bronze      | 4.8/0.32                             | 63       |
| 3a    | 1x ZrO₂       | Al–bronze      | 1.0/0.001                            | 67       |
| 4a    | 2x ZrO₂       | ZrO₂           | 0.2/0.01                             | 3        |
| 5a    | 1x Bronze     | PFA            | 0.6/0.01                             | 39       |
| 6a    | 2x Bronze     | PFA            | 4.7/0.06                             | 42       |
| 7a    | 1x Bronze     | PFA            | 0.8/0.02                             | 31       |

[a] About 0.28 mmol of 1a were milled together with 1.68 g K₂CO₃ and one milling ball in a 14 mL milling vessel for 90 min at 30 Hz in the MM. Vickers Hardness for milling materials: ZrO₂: ≈1200 HV; bronze: 120–175 HV; Al–bronze milling vessels: 170–220 HV.[44] [b]Because of the smaller volume, the amounts of 1a and base were reduced proportional and only one milling ball instead of two could be used. [c] Base recycled from standard approach, Table 1, Entry 3, with incorporated abrasion of the bronze milling balls; [d] Milled for 60 min for Raman measurement; [e] 1a-Cu was used instead of 1a.
confirm the formation of 1a-Cu on the surface of the bronze ball as intermediate species in the mechanochemical reaction protocol (see Figure S11, Supporting Information).

2.3. What Is the Reaction Mechanism?

To elucidate the mechanism, we monitored the reaction in situ via Raman spectroscopy. Therefore, we transferred the reaction into a transparent 20 mL perfluoroalkoxy alkane polymer (PFA) milling vessel with one bronze milling ball (Table 2, Entry 6). The reaction could be followed by monitoring the /C≡C/ vibrations. In 1a, they appear at 2110 cm⁻¹ and in 2a at 2215 cm⁻¹ (Figure 2a). While 1a was consumed constantly but not completely, 2a was formed after an incubation time of 10 min. This could be reduced to 6 min utilizing two bronze balls (Table 2, Entry 7, Figure S15, Supporting Information). Interestingly, no vibrations of 1a-Cu at 1930 cm⁻¹ were detected in the in situ experiment. Together with the incubation time, these two findings point toward a heterogeneous formation of the intermediate on the ball surface, which is then converted to 2a in a second step. To confirm this theory, we replaced 1a by 1a–Cu. For these experiments, no incubation time was detected (Table 2, Entry 8; Figure S15, Supporting Information). As catalyst, intermediate and energy impact coincide on the surface of the catalyst milling ball; the direct mechanocatalytic approach provides a high effectivity of possibly reactive ball-wall hits and thus enables the Glaser coupling that is impossible with Cu powder as catalyst. We thus propose that the catalytic cycle starts from Cu⁰, which forms Cu¹ phenylacetylide under oxidation by air. Further, this couples with 1a or a second equivalent of 1a-Cu to form the desired product 2a under oxidation of the terminal acetylenic carbon whereas Cu¹ is reduced back to Cu⁰ (see Figure 2b). Therefore, the observed incubation time from in situ Raman is inevitable to saturate the milling ball surface with 1a-Cu.

3. Conclusion

In a nutshell, we developed a direct mechanocatalytic Glaser coupling of phenylacetylenes using elemental copper and copper alloy as milling balls and vessels in as little as 90 min with a yield of up to 71% and no side products. The use of common alloys like bronze increased the yield and reduced the abrasion by a factor of 100 compared with the pure copper. We could establish that a vessel made out of the catalytically active metal in combination with inert milling balls yields the best result. Furthermore, we found intermediate directly on the milling balls and thus established the milling tools as the active site. This also explained the observed induction period and the lack of intermediate in situ Raman measurements. Finally, we used these experiments to propose a mechanism for the direct mechanocatalytic Glaser coupling. The use of alloys significantly broadens the scope of direct mechanocatalysis and opens up a concept of utilizing specifically tailored catalytic alloys in cascade reactions.

4. Experimental Section

Representative Procedure for the Direct Mechanocatalytic Glaser Coupling: Phenylacetylene 1a (55 μL, 0.5 mmol) and potassium carbonate (3.0 g, 21.7 mmol) were placed together with two milling balls (about 10 mm diameter) in a 25 mL milling vessel. The mixture was milled for 90 min at 30 Hz in a Retsch MM400 mixer mill (MM). After milling, remaining starting material 1a was removed by evaporation. Afterward, the product was washed out of the reaction mixture with dichloromethane (DCM; the solvent was recovered from the evaporator and reused consistently during the project), the solution was dried under vacuum, and the yield was calculated from the dry sample weight. Product purity was confirmed by NMR spectroscopy. Especially, regarding the sustainability of the direct mechanocatalytic protocol, no chromatography was needed for purification. The milling balls were cleaned, dried, and weighed to determine the abrasion from weight loss after every single reaction.

In situ Raman Measurements: In situ Raman spectra were obtained using a RENISHAW inVia Qontor Raman microscope with fiber optic and 4x objective (NA = 0.13, 40 mm free working distance). The wavelength for the measurement was 785 nm with 100% laser power. The spectra were collected with 10 s exposure time, each without an interval between the measurements. Data processing included cosmic ray removal using WiRe 5.1 software, followed by smoothing with Savitzky-Golay algorithm and baseline correction with asymmetric least squares using MATLAB 9.9 (see Figure S13–S17, Supporting Information, for details and results).

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interests
The authors declare no conflict of interest.

Author Contributions
C.G.V., M.O., and W.P. fabricated and characterized the samples. C.G.V., M.O., and S.G. analyzed the experimental data. S.G. and L.B. directed and supervised the project. C.G.V., S.G., and L.B. cowrote the manuscript. All authors discussed the results and commented on the article.

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