SUPPORTING INFORMATION

The role of the milling environment on the copper-catalysed mechanochemical synthesis of Tolbutamide

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1. Chemicals and Hazards

Reagents are commercially available. For each substance, hazards are indicated according to Regulation (EC) No 1272/2008.

p-toulenesulfonamide: CAS [70-55-3], 98+% Alfa Aesar, Lot # 10233524 – non-hazardous

n-butyl isocyanate: CAS [111-36-4], 98% Sigma Aldrich, Lot #varies – H225, H302, H311, H314, H330, H334

- *n*-butyl isocyanate is a flammable lachrymator liquid causing acute toxicity if inhaled, swallowed, or adsorbed through skin or eyes. It is not considered by the IARC (International Agency for Research on Cancer) to persist or bioaccumulate at levels of 0.1% or higher.

Copper(I) chloride: CAS [7758-89-6], 99.999% Thermoscientific (metals basis), Lot # U20F173 – H302, H315, H318, H410

- Copper(I) chloride causes acute toxicity if inhaled. Contact can result in skin irritation and serious eye damage. At levels greater than 0.1% this compound has not been identified as a probable, possible, or confirmed human carcinogen by IARC.

Copper (II) chloride: CAS [7447-39-4], anhydrous, > 97% Aldrich Chemical, Lot # 18419PQ – H301, H302, H312, H315, H318, H335, H400, H410, H411, P233, P261, P264, P265, P270, P271, P273, P280, P301, P302, P304, P305, P316, P317, P319, P321, P330, P332, P338, P340, P351, P352, P354, P337, P362, P364, P391, P403, P405, P501.

- Copper(II) chloride is toxic if swallowed. Contact can result in skin irritation and serious eye damage and irritation. Respiratory irritation may result upon inhalation. This compound is also considered an environmental hazard being very toxic to aquatic life with long term effects. This compound has not been identified by the IARC as a probable, possible, or confirmed human carcinogen.

Ethylenediaminetetraacetic acid disodium salt dihydrate: CAS [6381-92-6], 99-100% Sigma-Aldrich, Batch # SLCK9139 – H332, H373

- Ethylenediaminetetraacetic acid disodium salt dihydrate is harmful if inhaled and may cause damage to the respiratory tract through prolonged repeated exposure.

Tolbutamide: CAS [64-77-7] – H303.

- Tolbutamide is not defined as a hazardous substance according to Regulation (EC) No 1272/2008 with [LD50 Oral – Rat: 2.490 mg/kg]

Dimethyl sulfoxide-d_6: CAS [2206-27-1] 99.9% Cambridge Isotope Laboratories Inc., Lot #varies – H227

Nitromethane: CAS [75-52-5], >95% Sigma-Aldrich, Batch # MKCM8091 – H226, H302, H351.

- Nitromethane is a flammable liquid that can cause harm if swallowed and is reported to be possibly carcinogenic by IARC and EPA (Environmental Protection Agency). If working with this chemical, ensure it is used in a fume hood and the amounts employed are small.

Phosphorus pentoxide: CAS [1314-56-3] 99.8% Fischer Chemical, Lot #191930 – H314, P280, P310, P351, P338, P310, EU014

Ethanol: CAS [64-17-5] 200 proof, Koptec – H225, P210, P233, P240, P241, P242, P243, P280, P303, P361, P353, P370, P378, P403, P235, and P501

Dry air: 99%, < 3ppm moisture – Nonhazardous

Dry nitrogen: – Nonhazardous

Silica Gel: CAS [63231-67-4] EM Science, Grade 922, 200 Mesh and Finer (Nominal), Batch #34363546 – H312, H319, H331, P261, P264+P265, P271, P280, P302, P352, P304, P340, P305, P351, P338, P316, P317, P321, P337, P317, P362, P364, P403, P233, P405, and P501

2. Custom Milling Jars

2.1. Milling Jars with Different Materials

Trials employed the following milling materials: 316 stainless steel (SS) milling jars (15 mm diameter SS balls or 12.7 mm diameter polytetrafluoroethylene (PTFE) balls), PTFE milling jars (15 mm diameter SS balls or 12.7 mm PTFE balls), PMMA milling jars (12.7 mm diameter polycarbonate balls), and multipurpose 6061 aluminium (Al) milling jars (12.7 mm diameter PTFE balls). All PTFE materials were Chemical-Resistant Slippery PTFE purchased from McMaster Carr. Aluminum for jars was also purchased from McMaster Carr while 316 Stainless steel was provided by the machine shop at TAMU. Stainless steel milling balls were sourced from Retsch. Milling jars made of different materials were machined in house with 25 mL internal volume. Attempts to run the reaction in PMMA worked poorly due to unwanted side reactions between the jars and the n-butyl isocyanate reagent which degraded the milling vessel and generated a large, sticky, and clumped crude mixture. This material was not explored further.

Figure S1. Ball milling jars made from different materials.

2.2. Milling Jars with KF Compression Seal

Attempts to use parafilm on SS with tight screwing of traditional 25 mL Retsch MM400 jars were unsuccessful at sealing out atmosphere reliably as threading was observed to loosen overtime. As such, specialized jars capable of sealing out atmosphere were developed and machined in house. Initially, KF wing nut clamps were explored for use with the designed jars. However, KF wing nut clamps unwound during the course of milling as with the previously threaded milling jars. Readers interested in manufacturing their own milling jars are advised to employ KF toggle clamps with a locking pin which endure well for prolonged milling. SolidWorks files are available upon request.

3. General Procedural Notes

3.1. Yield Determination by NMR spectrosocpy

When p-toluenesulfonamide (214 mg, 1.25 mmol), n-butyl isocyanate (140.8 μL, 1.25 mmol), and CuCl (6-7 mg, 5 mol%) are added directly to DMSO-d_6 and the NMR spectrum is recorded, the reaction will not proceed noticeably after mixing within the required time to obtain NMR. However,

this is not the case when CuCl$_2$ (6-8 mg, 5 mol %) is utilized, where the reaction is found to proceed to ~45% conversion over the course of ca. 24 hours at 298 K (Figure S2).
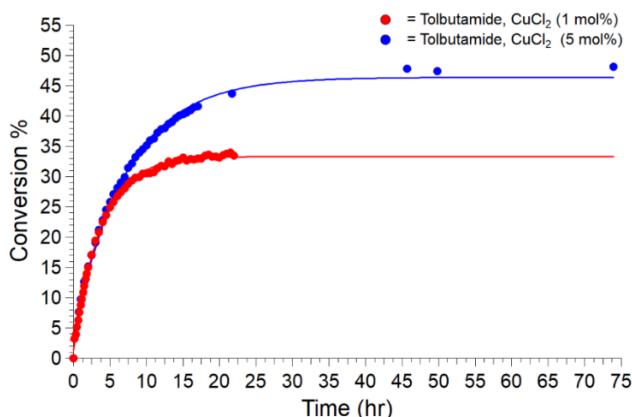

Figure S2. NMR tracking of solution reaction with CuCl$_2$ at room temperature (298 K).

For our reactions, NMR spectra were obtained on an autosampler device operating on a queue system, which means that sample sitting time before a spectrum is recorded could not be controlled. To obtain kinetics data to determine the extent of possible reactivity in the NMR tube, a solution was made with the same amounts of reagents as utilized in the mechanochemical experiments to ensure that the maximum possible concentration (and therefore the upper bound) of reactivity in the NMR tube would be observed; this bound was 50% yield. Care was taken to ensure reactions presented herein were characterized quickly or had yields by NMR sufficiently larger than 50%. As 50% is the largest yield that can be obtained by NMR after sitting in the tube longer than any of our samples utilizing the same ratio of reagents to product as would be present in the mechanochemical reaction mixtures (due to equimolar amounts of reactants being used, and the general lack of side products) and higher concentrations than most actual samples, we can be confident that yields higher than this value are representative of the mechanochemical reaction more generally. A similar control for trials with CuCl oxidizing to CuCl$_2$ (Figure 2, Table 1) cannot be run as the extent of Cu(I) oxidation is unknown, however the extent of reaction in solution with Cu(I) will be below the upper bound identified with the maximum possible true Cu(II) catalyst concentration in a tube. Therefore, caution should be taken when interpreting this data with NMR yield values below 50%.

3.2. Error Reporting

For the trials shown in Figure 2, error cannot be interpreted with a Gaussian distribution in mind because of the inconsistent mixing of the gas with the solid CuCl (specifically in neat conditions) to promote Cu(II) formation. Therefore, we have decided to present the range of yields observed at each oxygen concentration for these purposes with a box and whiskers distribution so each trial can be seen by readers. With trials for CuCl$_2$, a Gaussian distribution becomes more reasonable given the observation of consistent homogeneous mixing. Thus, error is shown as the more traditional standard deviation in Figure 4.

4. Summary of ^{1}H, ^{13}C and HRMS data

N-butylcarbamoyl)-4-methylbenzenesulfonamide CAS [64-77-7] – Tolbutamide White powder, m.p. 125.2-126.4 °C.[1] **^{1}HNMR** (400 MHz, DMSO-d$_6$) δ (ppm): 10.45 (s$_{broad}$, 1H, NHS), 7.78 (d, J =8.0 Hz, 2H, CH$_{Ar}$), 7.40 (d, J =8.0 Hz, 2H, CH$_{Ar}$), 6.42 (m, 1H, NHC=O), 2.94 (t, J = 6.4 Hz, 2H, CH$_2$), 2.39 (s, 3H, CH$_3$), 1.33-1.26 (m, 2H, CH$_2$), 1.19-1.14 (m, 2H, CH$_2$), 0.82 (t, J =

7.2 Hz, 3H, CH$_3$) ^{13}**C NMR** (500 MHz, DMSO-d_6) δ (ppm): 151.7, 143.3, 129.3, 127.1, 39.5, 31.3, 30.6, 20.9, 19.2, 13.5 **HRMS ESI (+):** calculated for C$_{12}$H$_{19}$O$_3$N$_2$S [M + H]$^+$: 271.1111; measured: 271.1104

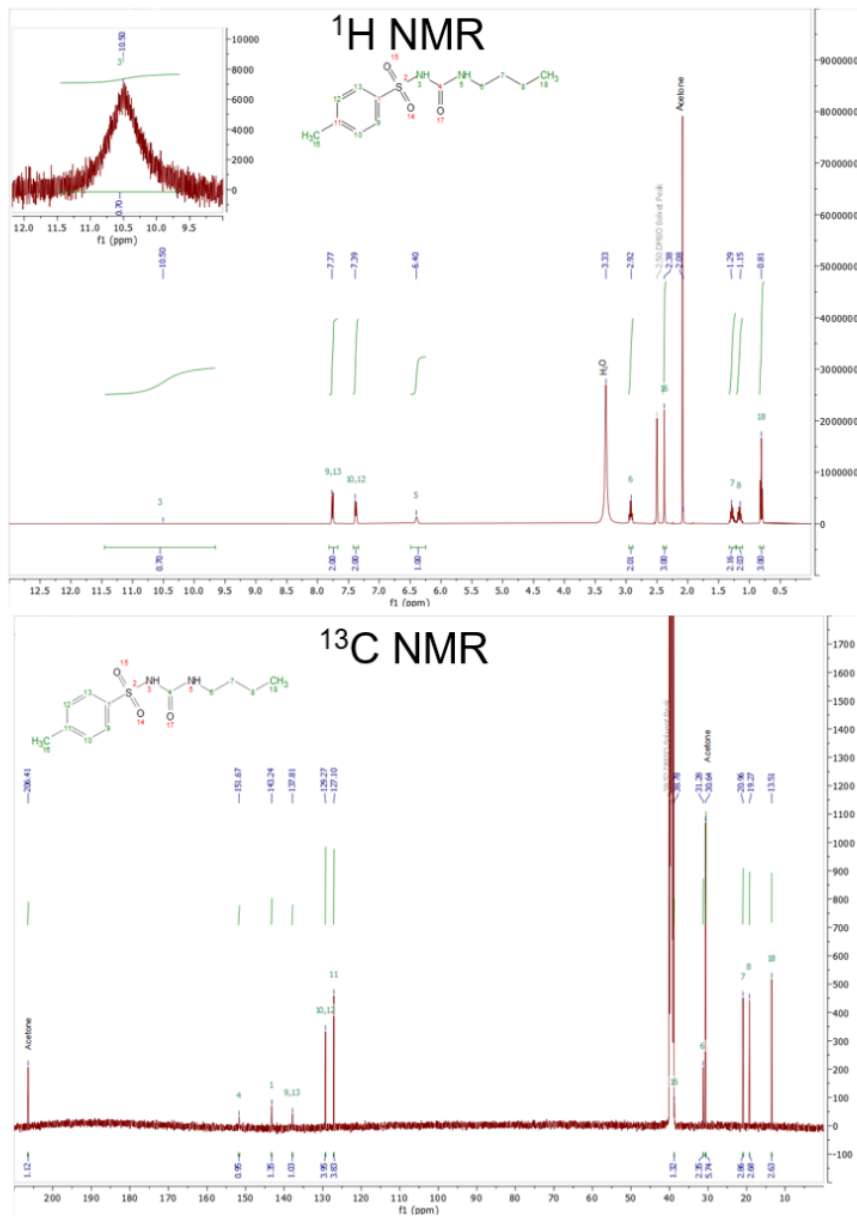## 5. ^{1}H and ^{13}C NMR Data for Isolated Tolbutamide

Figure S3. 1H and 13C NMR spectra of purified Tolbutamide.

6. Crude Product Color
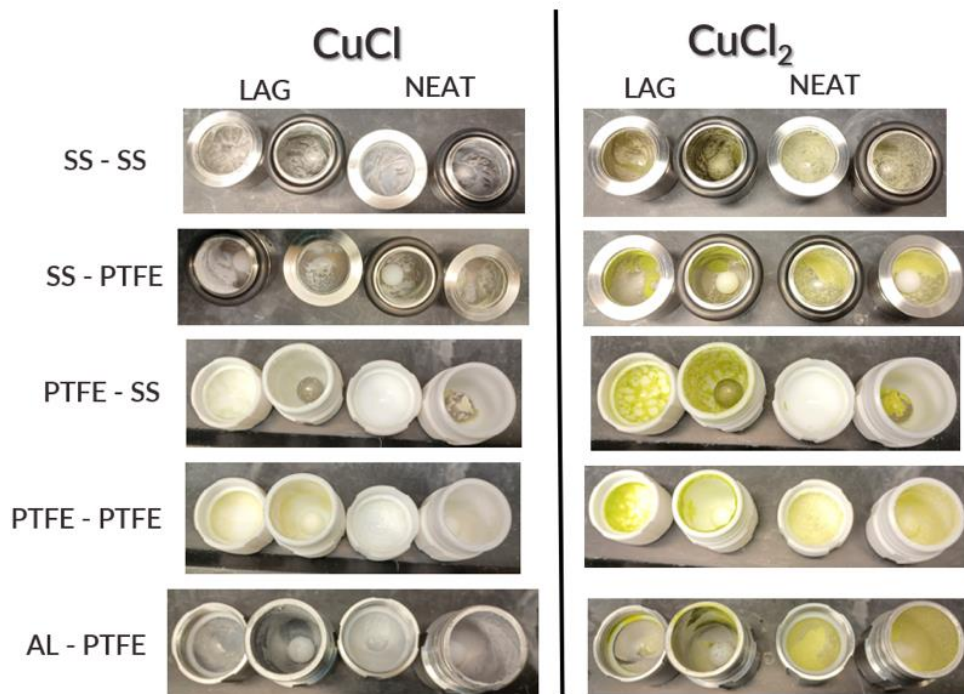
Figure S4. Pictures of the crude product after milling in different jar materials under dry air. Generally, the product appears brown/ orange or green after milling under LAG conditions and light brown/ green after neat milling. Note that product is white after milling in Al jars with CuCl, the trial in which reaction did not proceed at all.

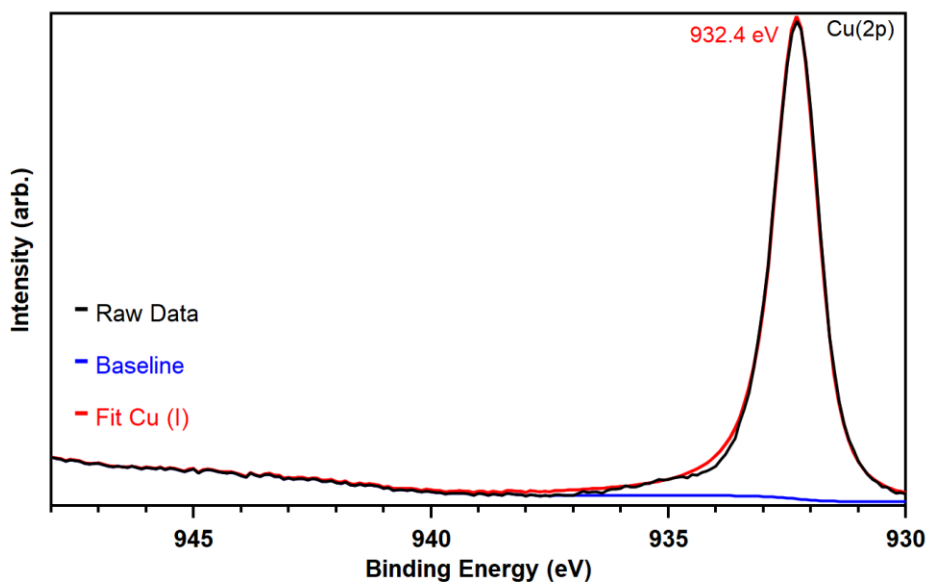## 7. XPS analysis of CuCl Catalyst

Figure S5. X-ray photoelectron spectrum of CuCl used in catalysis studies.

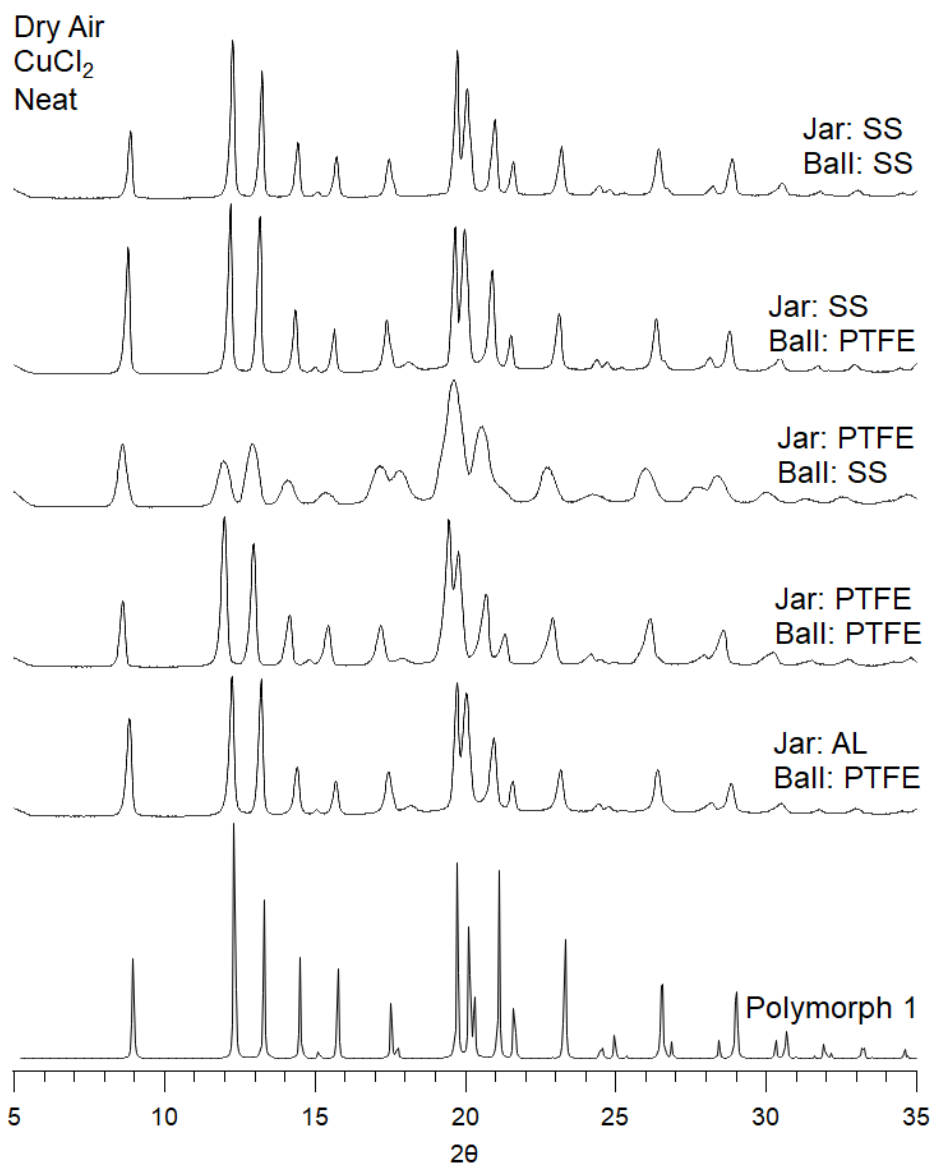## 8. PXRD Patterns of Tolbutamide by Milling Under Different Materials

Figure S6. PXRD patterns of Tolbutamide neat product obtained upon milling in different ball: jar materials with $CuCl_2$.
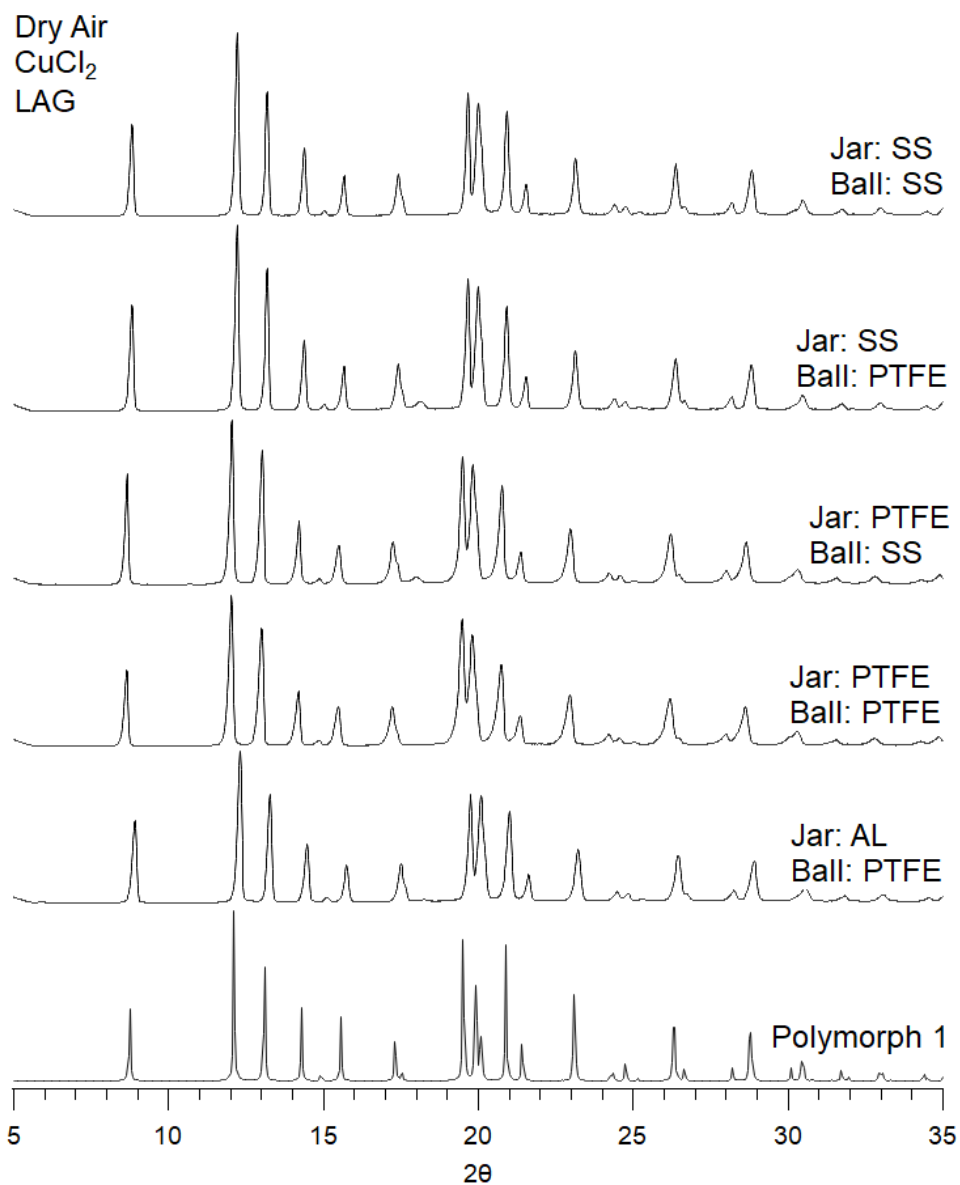
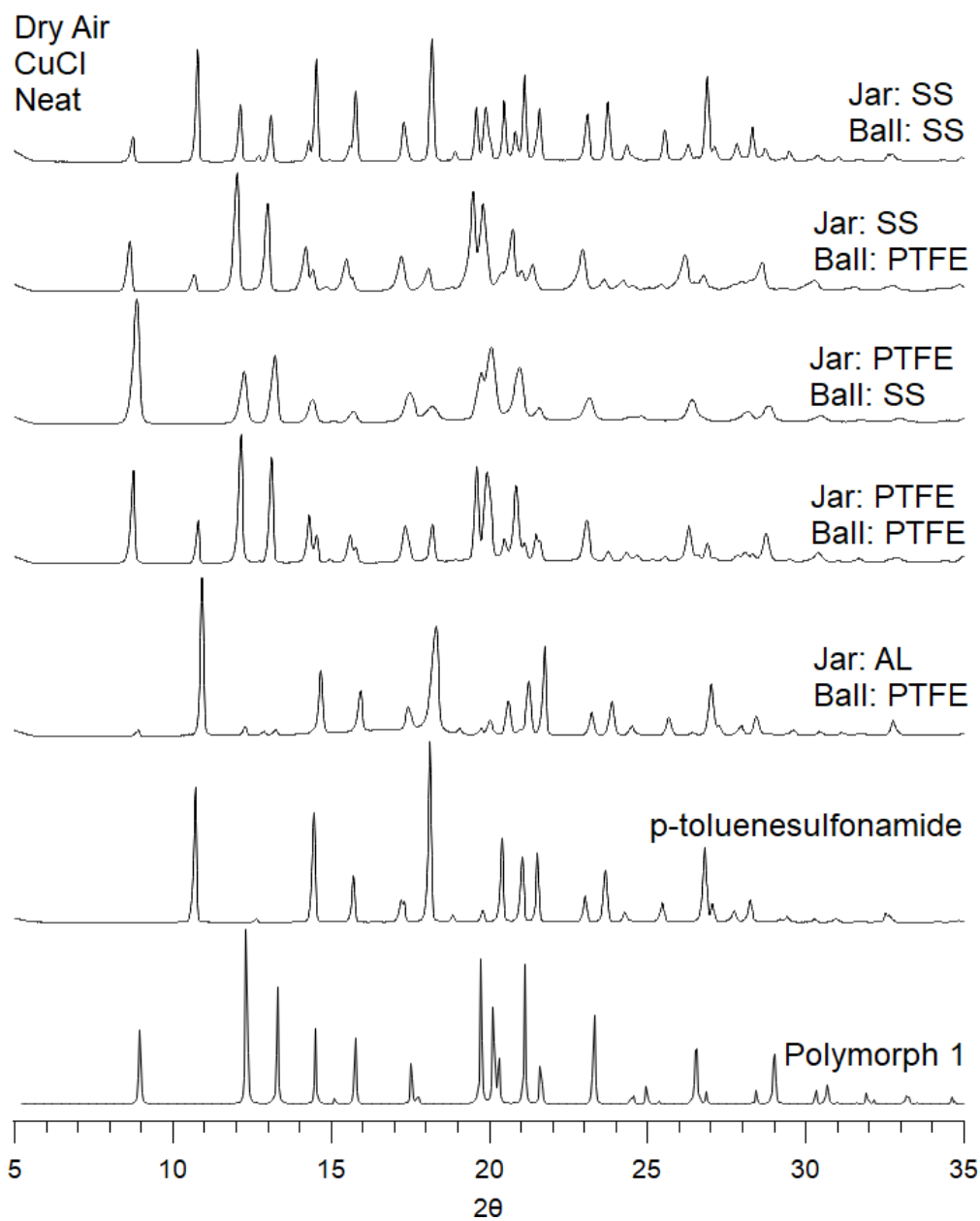**Figure S7.** PXRD patterns of Tolbutamide LAG product obtained upon milling in different ball: jar materials with $CuCl_2$.

Figure S8. PXRD patterns of Tolbutamide neat product obtained upon milling in different ball: jar materials with CuCl.
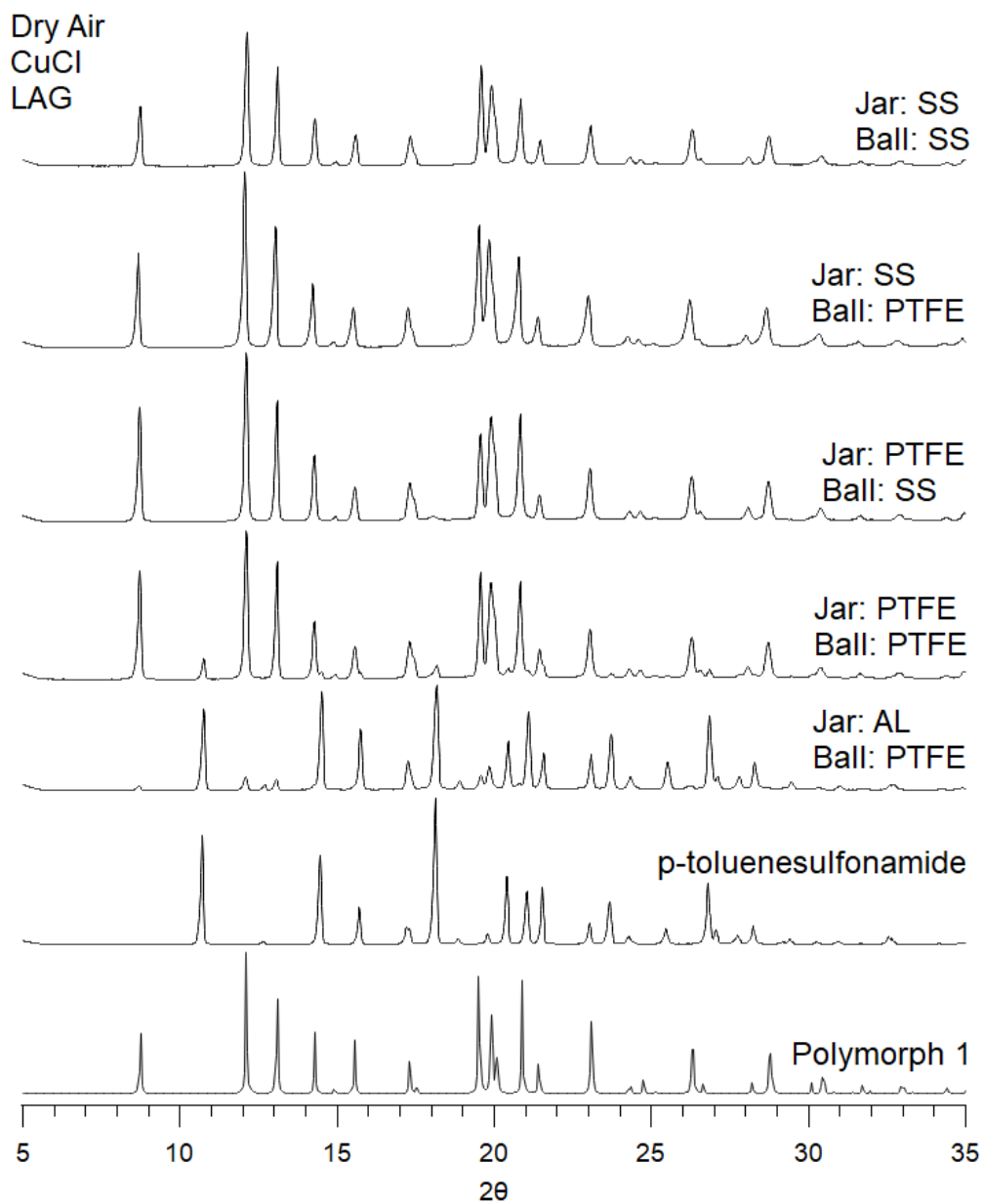
Figure S9. PXRD patterns of Tolbutamide LAG product obtained upon milling in different ball: jar materials with CuCl.

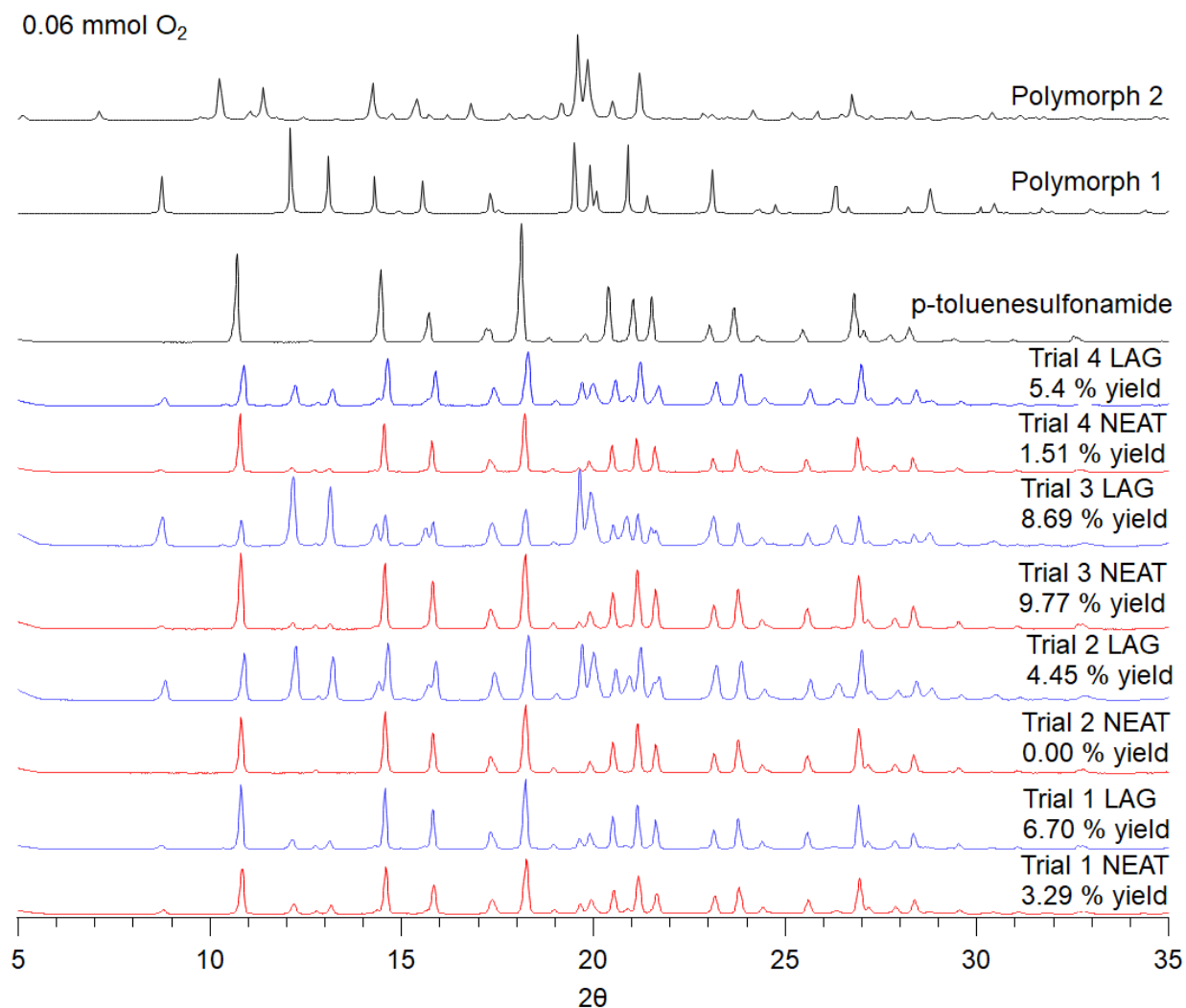## 9. PXRD Patterns of Tolbutamide by Milling Under Different O_2 Concentrations

Figure S10. PXRD patterns of Tolbutamide product obtained upon milling in atmospherically sealed SS jars with 0.06 mmol of O_2 gas
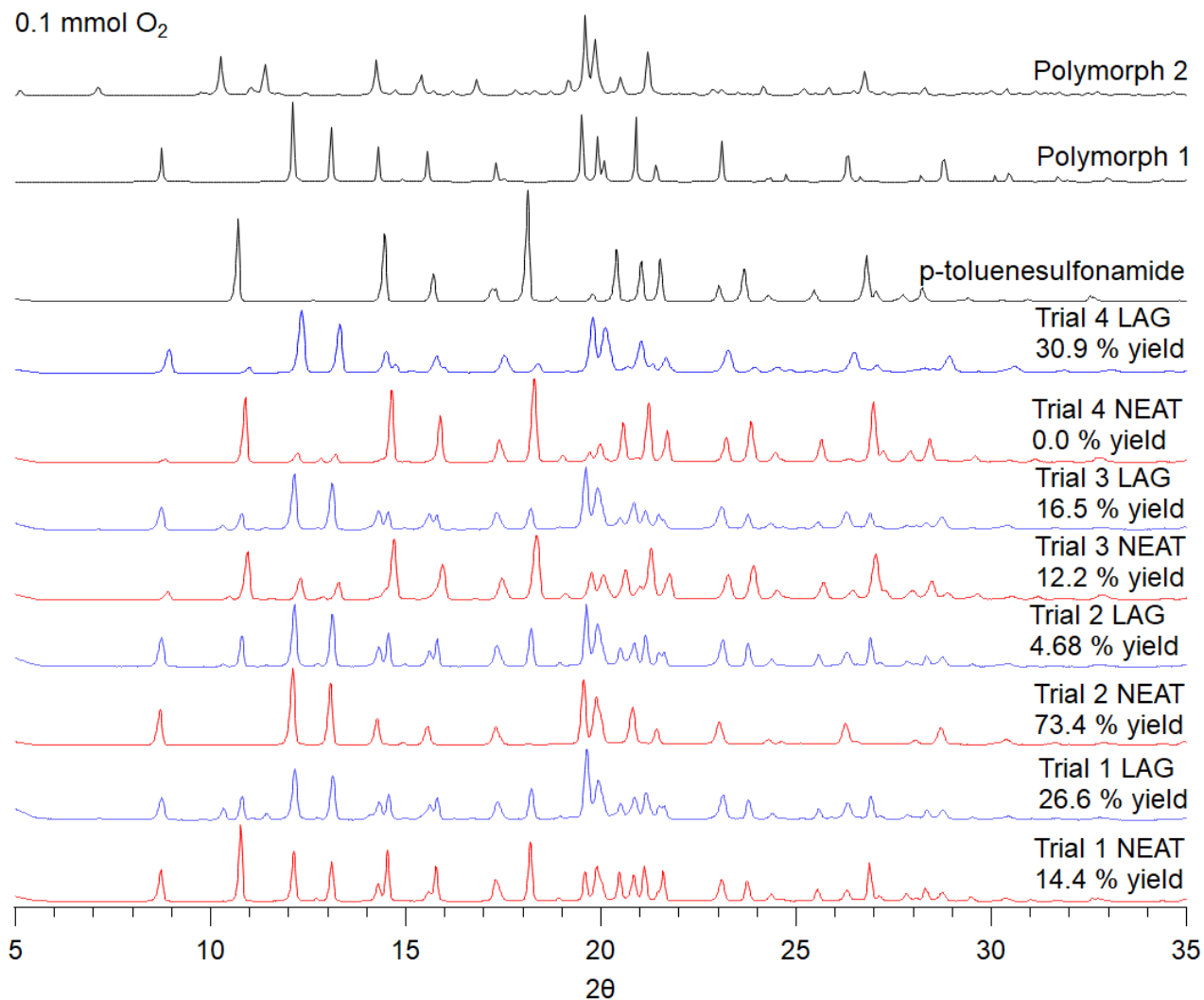
Figure S11. PXRD patterns of Tolbutamide product obtained upon milling in atmospherically sealed SS jars with 0.1 mmol of O_2 gas.

At 0.1 mmol of O_2, the majority of the sample was polymorph 1 while polymorph 2 was formed in trace amounts in Trial 1 LAG, Trial 2 LAG, Trial 3 NEAT, and Trial 3 LAG. Polymorph 1 dominates all other spectra and is uniquely formed in all other atmosphere and milling jar material conditions studied.
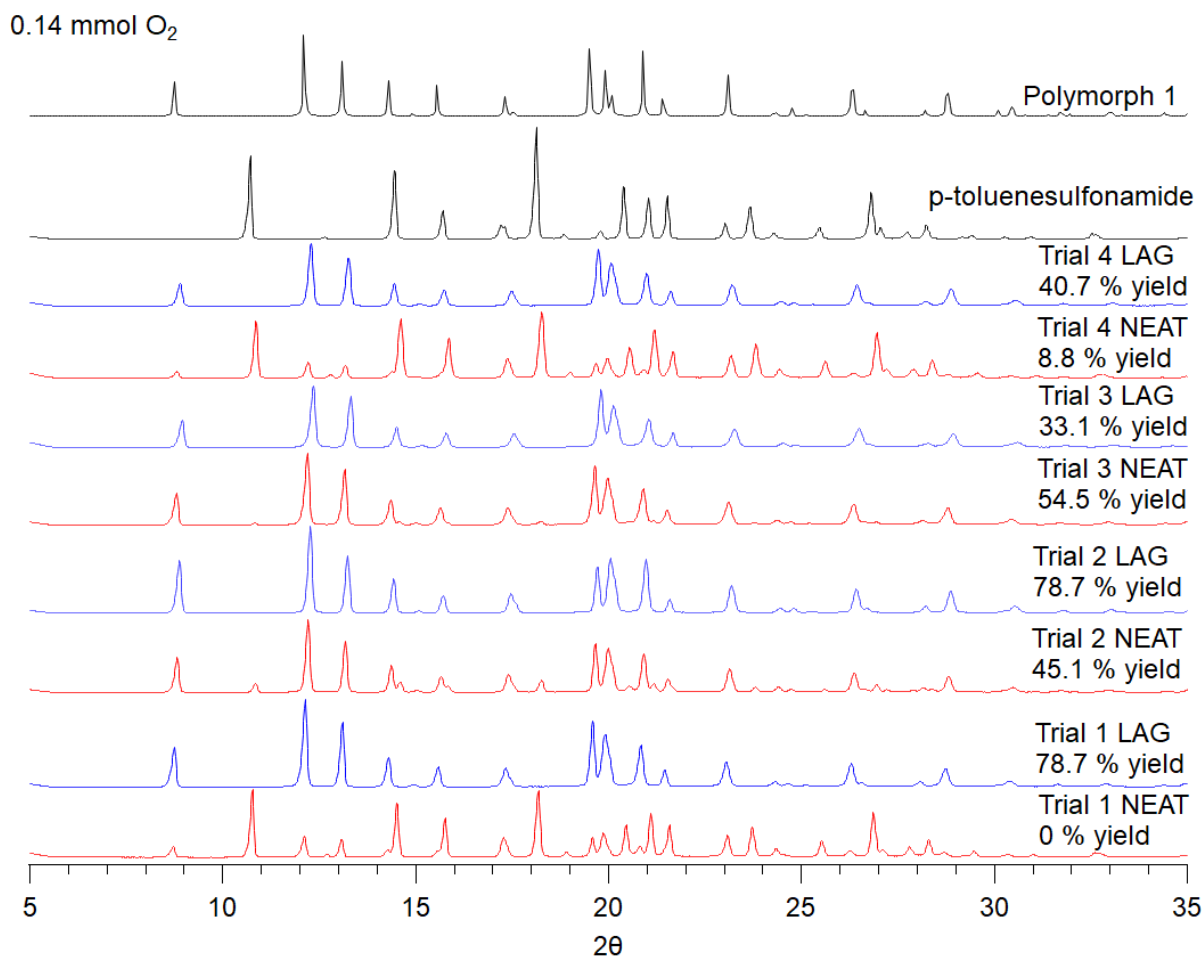
Figure S12. PXRD patterns of Tolbutamide product obtained upon milling in atmospherically sealed SS jars with 0.14 mmol of O_2 gas.

10. Catalyst Loading Under LAG Conditions and with Silica Grinding Additive
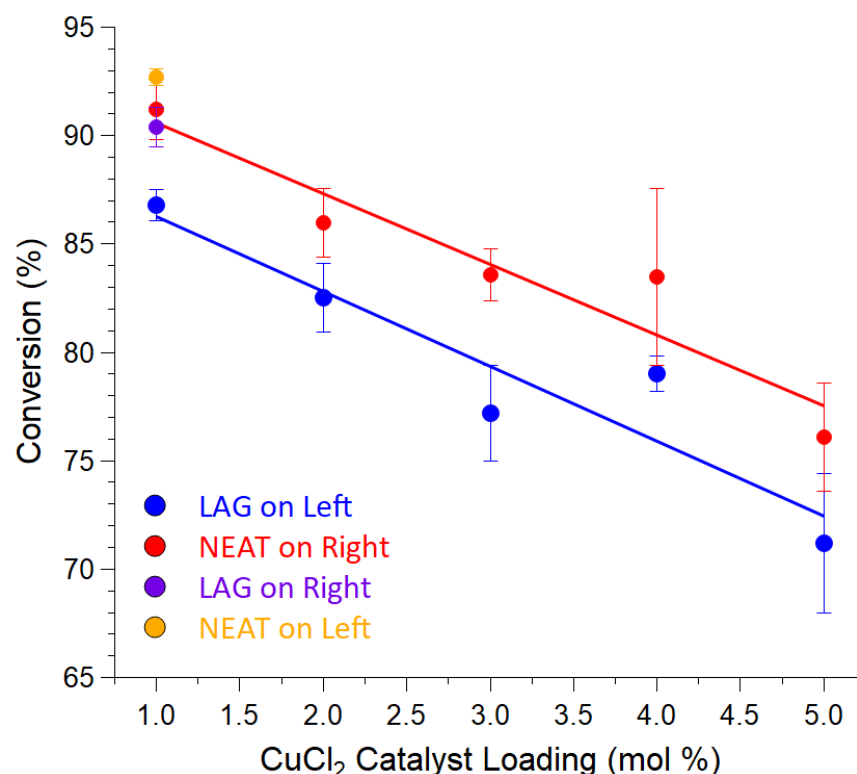

Figure S13. Conversion of the copper-catalyzed sulfonamide-isocyanate coupling to form Tolbutamide under dry air in SS jars with SS balls as a function of catalyst loading under LAG and neat conditions on different sides of the mill. Each data point is the average of three repeated experiments and error is shown as standard deviation. Lines are intended to guide the eye.

Catalyst loading in LAG follows a similar trend to that under neat conditions with yields on average ~4-5% lower than in neat systems (Figure S15). In Retsch MM 400 mills there are two jars, one on the left side of the mill and one on the right side. Applied forces may not be equivalent between sides of mills depending on the individual instrument (as slight variations between mills can be present even if a given instrument is within manufacturing specifications) and the degree to which the countertop is level. For consistency, LAG trials were all run on the left side of the mill while neat was run on the right side of the mill. Upon switching the LAG to the left side of the mill and neat to the right side of the mill at 1 mol% catalyst loading, LAG yield increased to 90.4% while neat yield remained unchanged. This suggests lower yield in LAG conditions may be contributed in part to a systematic error between the mill sides which is made evident in the presence of liquid which increases powder flowability and mixing, thus making the system more sensitive to mechanical factors. Similar trials at a $CuCl_2$ catalyst loading of 1 mol% with silica nanopowder (which may play a similar role as a LAG agent facilitating greater powder mixing and flowability) have not shown a statistical difference between left and right sides of the mill, but show yield reduction upon solid addition as observed when increasing catalyst loading (Figure S16). This indicates additional agents not directly participating in the reaction may generally impede reaction progress, thus yield reduction in LAG may not be fully accounted for by the side of the mill utilized. Further studies to clarify these results are underway.
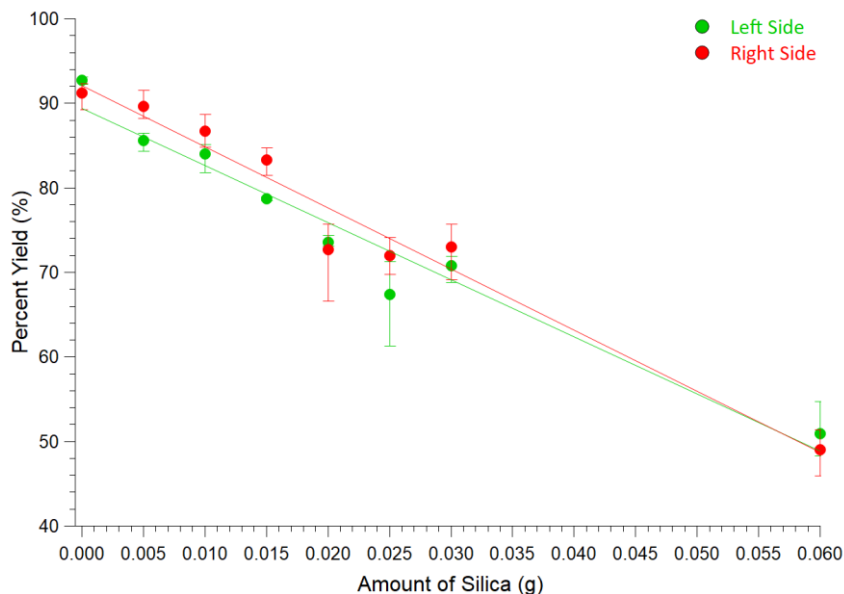
Figure S14. Conversion of the copper-catalysed sulfonamide-isocyanate coupling to form Tolbutamide under dry air in SS jars with SS balls as a function of silica nanopowder addition at 1 mol% catalyst loading. Each data point is the average of six repeated experiments and error is shown as standard deviation. Lines are intended to guide the eye.

11. Curve Fits

Table S1. Curve Fitting equations used in paper and SI figures.

Figure	Fitting Function	Fitting Coefficients*
S2 – 1 mol%	$y(t) = y_0 + Ae^{-kt}$	$y_0 = 33.325 \pm 0.095$ $A = -32.059 \pm 0.173$ $k = 0.26552 \pm 0.00388$
S2 – 5 mol%	$y(t) = y_0 + Ae^{-kt}$	$y_0 = 46.395 \pm 0.471$ $A = -42.452 \pm 0.589$ $k = 0.13683 \pm 0.00462$
4 & S13 – Neat	$y(x) = a + bx$	$a = 94.174 \pm 1.34$ $b = -3.3447 \pm 0.442$
S13 - LAG	$y(x) = a + bx$	$a = 89.75 \pm 2.44$ $b = -3.47 \pm 0.734$
S14 - Left	$y(x) = a + bx$	$a = 89.379 \pm 1.6$ $b = -674.72 \pm 58.9$
S14 -Right	$y(x) = a + bx$	$a = 92.102 \pm 1.49$ $b = -723.11 \pm 55$

* Coefficients are given as values ± one standard deviation

12. Abbreviations

Stainless steel = SS
Polytetrafluoroethylene = PTFE
Aluminium = Al

13. DOI Link to Raw Data Files

Raw data files for results presented herein are available at the following link: https://doi.org/10.6084/m9.figshare.25654194

14. References

1. E. Colacino, G. Dayaker, A. Morère and T. Friščić, *Journal of Chemical Education*, 2019, **96**, 766-771.