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Solid-state molecular oxygen activation using ball milling and a piezoelectric material for aerobic oxidation of thiols†

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The agitation of $BaTiO_3$ *via* ball milling converts mechanical energy into electrical energy, leading to the reduction of molecular oxygen *via* a single electron transfer pathway analogous to the photocatalytic reaction. This mechanoredox strategy for the oxidative coupling of thiols could eliminate waste and develop a recyclable methodology to accomplish organic transformations in a greener fashion, exhibiting promising potential for large-scale chemical manufacturing.

Mechanochemical synthesis using ball milling has become an emerging field of research in organic synthesis as reactions under ball milling could be performed more sustainably and practically.[1–8] The mechanochemical organic transformations exhibit many advantages over liquid-phase reactions in terms of the elimination of environmentally harmful organic solvents, ambient reaction temperatures, milder reaction conditions, shorter reaction times, and simpler work-up procedures.

$BaTiO_3$ as one of the most typical piezoelectric perovskite oxides has a dipole moment and produces a polarized electric field to drive the separation and migration of bulk charges to the surface under stress.[9,10] Li's group applied the piezoelectrochemical effect (conversion of mechanical energy to chemical energy) of $BaTiO_3$ for water splitting under ultrasonic vibration.[11] $BaTiO_3$ was also used to realize the decolorization of Rhodamine B in a vibration-catalytic process.[12] $BaTiO_3$ nanoparticles could reduce Cu(II) catalyst with ultrasound as an external stimulus and thereby generated an ATPR activator to initiate radical polymerization.[13,14] Although effective, those strategies are limited to the use of acoustic cavitation by ultrasonication in solution. Recently, Ito's group developed a mechanoredox system to activate small organic molecules, in which the agitation of piezoelectric materials in response to ball milling generates temporarily highly polarized particles and thus serves as a charge-transfer catalyst. The electrons could be transferred from the distorted piezoelectric materials to substrates, generating radical intermediates. They applied this mechanoredox system to arylation or borylation reactions of aryl diazonium salts (Fig. 1A),[15] and C–H trifluoromethylation of aryl compounds.[16] In a more recent example, mechanical ball milling could be harnessed to induce electrical polarization of $BaTiO_3$, leading to reduction of Cu(II) catalyst precursor into the active ligand-stabilized Cu(I) species for atom transfer radical cyclizations.[17] Mechanically ball milling of $BaTiO_3$ could merge electric and mechanical activation modes, extending the applicability of $BaTiO_3$ not only as additives but also as a charge-transfer catalyst. Although the mechanical stimulation of piezoelectric $BaTiO_3$ represents an attractive strategy to reduce the environmental impact of organic synthesis and leads to practical applications in industrial manufacturing, the studies in this realm are still highly limited.[18]

Organodisulfides possessing S–S bonds are commonly encountered moieties of great significance and synthetic interest.[19] Applications of organic disulfides range from synthetic tools, anti-oxidants, pharmaceuticals, agricultural chemicals, and rubber vulcanization reagents. S–S bonds are

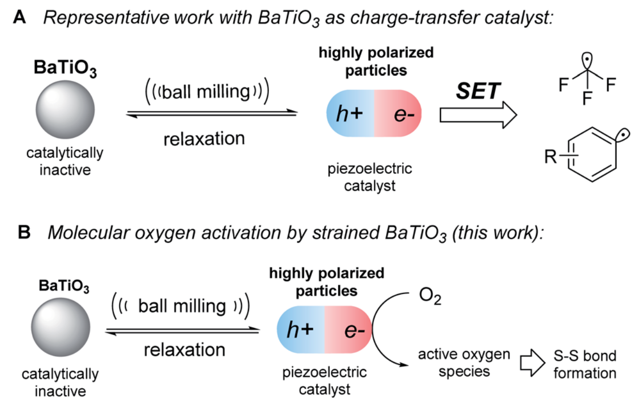

Fig. 1 Radical generation using ball milling and piezoelectric catalyst in the solid-state for organic synthesis.

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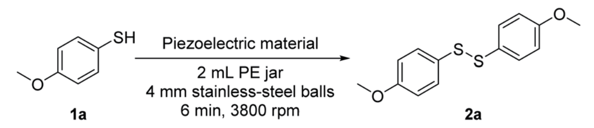
widely found in naturally bioactive products and protein structures. The formation of disulfide units is essential for protein folding and the stability of secondary structures. Considering the great importance of disulfide compounds, extensive efforts have been made to assess the oxidative coupling of thiols with oxidants, such as molecular oxygen, peroxides, metal oxidants, halogens, halogenating agents, and so on. Among those, the aerobic oxidation of thiols to produce disulfides is preferred since molecular oxygen is much cheaper and more environmentally benign. The aerobic oxidative coupling of S–H bonds has been realized in a solvent by transition metal catalysts[20–23] and metal-free catalysts.[24–26]

Inspired by piezoelectricity of $BaTiO_3$ under ball milling for the generation of radical intermediates, we set to investigate whether this piezoelectric charge-transfer catalyst could be able to activate molecular oxygen and generate thiyl radical (Fig. 1B). If achievable, the agitated $BaTiO_3$ under ball milling could enable the development of a mechanoredox system for oxidative coupling reaction with milder reaction conditions, shorter reaction times, solvent-free system, operational simplicity, recyclability of piezoelectric charge-transfer catalyst. While we were preparing our manuscript, Cao's group reported the mechanochemical synthesis of 1,2-diketoindolizines from indolizines and epoxides using $BaTiO_3$ as a piezoelectric catalyst.[27] In the reaction mechanism, they proposed that the highly polarized piezoelectric particles led to radical intermediate and superoxide radical anion, which could be supportive evidence for our hypothesis.

Table 1 Reaction condition screening[a,b]

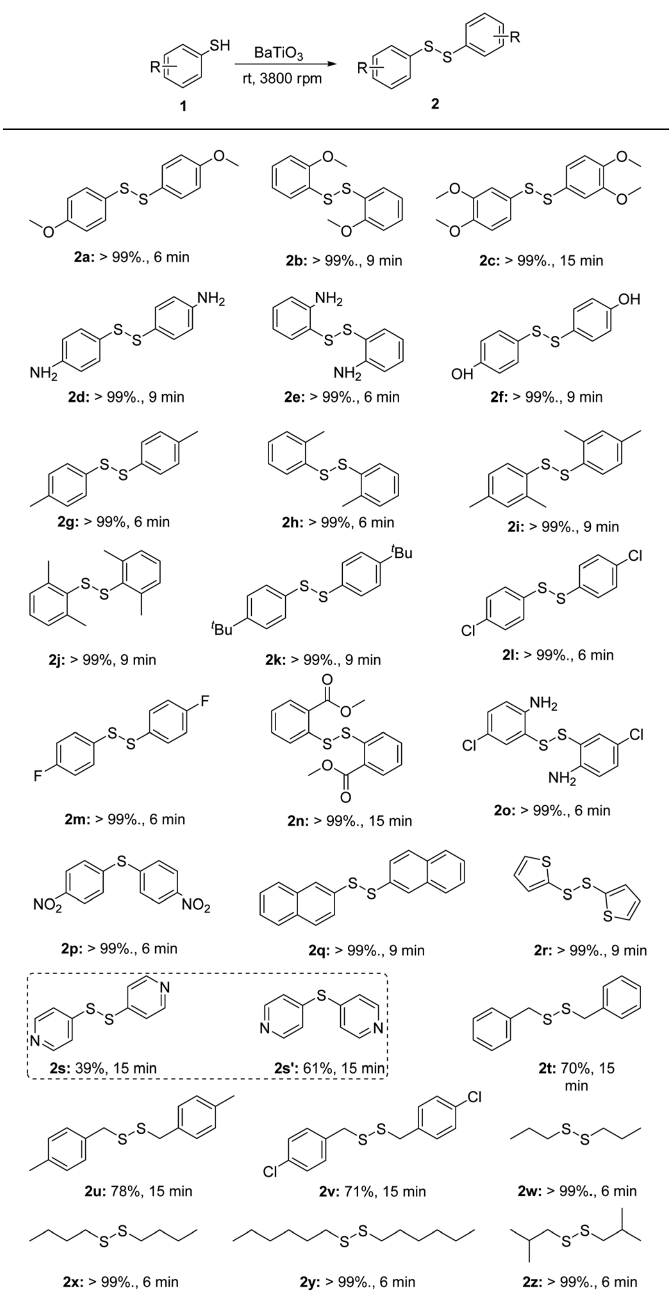


Entry	Piezoelectric material	Milling ball	Yield [%]
1[c]	$BaTiO_3$ (<3 μm)	ZrO_2	15
2	$BaTiO_3$ (<3 μm)	Steel	>99
3	PZT	Steel	95
4[d]	None (Na_2SO_4)	Steel	22
5[e]	None (NaCl)	Steel	16
6	None	Steel	12
7[f]	$BaTiO_3$ (<3 μm)	Steel	Trace
8	$BaTiO_3$ (0.6–1 μm)	Steel	99
9	$BaTiO_3$ (200 nm)	Steel	99
10[g]	$BaTiO_3$ (<3 μm)	Steel	Trace
11[h]	$BaTiO_3$ (<3 μm)	Steel	20

[a] **1a** (0.2 mmol) and $BaTiO_3$ (<3 μm, 0.2 mmol) in a 2 mL PE milling jar, five 4 mm stainless-steel balls, 3800 rmp. [b] Isolated yields. [c] Five 4 mm ZrO_2 balls, 3800 rpm. [d] Anhydrous Na_2SO_4 (1.9 mmol) as solid grinding aid in the absence of $BaTiO_3$. [e] NaCl (1.9 mmol) as solid grinding aid in the absence of $BaTiO_3$. [f] The reaction was performed under N_2 in a glovebox. [g] The reaction was carried out in CH_3CN (0.1 M) with a stirring bar at room temperature for 20 min with an air balloon. [h] The reaction was carried out in acetone (0.1 M) under ultrasonic agitation at room temperature for 20 min with an air balloon.

To explore this hypothesis, we applied the mechanoredox system to the aerobic oxidative homocoupling of thiols to synthesize disulfides under ball milling. 4-Methoxybenzenethiol was used as the model substrate, and the model reaction was carried out in an MSK-SFM-12M mixer mill (2 mL PE milling jar with 4 mm stainless-steel balls) in the presence of commercially available $BaTiO_3$ under air. Initially, we used zirconia balls as milling media, unfortunately, only 15% product was observed (Table 1, entry 1). We speculated that the lightweight of zirconia balls subjected $BaTiO_3$ to lower-impact mechanical collisions thus failed to provide sufficient mechanical impact to activate the $BaTiO_3$. This result also suggests ball milling is not only mixing reactants but also agitating the piezoelectric material. Next, we switched the milling media to 4 mm stainless-steel balls. To our delight, the desired disulfide **2a** was produced in quantitative yield in 6 min (entry 2). This result demonstrated that a piezoelectric potential to initiate the oxidative coupling reaction was generated by the mechanical agitation under suitable ball milling conditions. Other typical piezoelectric materials, such as Pb(Zr, Ti)O_3 (PZT) ceramic powder, could also convert the starting thiol into the target product in 95% yield (entry 3). Considering its low cost, high efficiency, and environmental benignity, $BaTiO_3$ was used as the optimal charge-transfer catalyst for further exploration. In addition, when anhydrous Na_2SO_4 was used as solid grinding aid while no $BaTiO_3$ was added, the product yield dropped substantially (entry 4). Once we change the solid grinding aid to NaCl, the product yield decreased to 16% (entry 5). When the reaction was performed in the absence of piezoelectric material, product **3a** was formed in low yield (entry 6). These results illustrate that the piezoelectric material is necessary for the transformation of thiols into the corresponding disulfides. The higher yield resulting from anhydrous Na_2SO_4 compare to that from NaCl should be caused by its water absorptivity, since anhydrous Na_2SO_4 is a typical drying agent and the byproduct of this oxidative disulfide formation is water. To test and verify the effect of molecular oxygen on the disulfide formation, we performed the model reaction under a nitrogen atmosphere as a control experiment (entry 7). The only trace amount of disulfide was observed by GCMS, which might be the impurity in the commercially purchased starting material or result from the presence of traces of air. We tried commercially available $BaTiO_3$ with different particle sizes (0.6–1 μm, 200 nm). All particle sizes led to product **2a** in quantitative yields with 6 min, showing no considerable size effect on the reaction performance (entries 8, 9). Even though there was no big difference in their prices, $BaTiO_3$ (<3 μm) is the cheapest. Thus, we choose $BaTiO_3$ (<3 μm) for the following experiments. When the reaction was carried out in CH_3CN (0.1 M) with an air balloon under stirring for 20 min, only a trace amount of product **2a** was observed (entry 10). This result states that mechanical agitation of $BaTiO_3$ induced by ball milling is essential for the piezoelectric potential that is sufficient to activate molecular oxygen and thiol. The acoustic cavitation by ultrasonication in solution has been used to activate piezoelectric materials for catalysis.[28–31] When the reaction was performed in acetone (0.1 M) with an air ballon and ultrasonication, the target product **2a** was obtained in 20% yield (entry 11). This result illustrates that the piezoelectric potential generated by ball milling has a different reactivity profile compared to the solution version using ultrasonic agitation. Conclusively, these experimental results are consistent with our theory that the agitation of $BaTiO_3$ under mechanochemical ball milling conditions could activate molecular oxygen for a successful oxidative transformation of thiols into disulfides.

Table 2 The substrate scope of thiols[a,b]



2a: > 99%., 6 min
2b: > 99%., 9 min
2c: > 99%., 15 min
2d: > 99%., 9 min
2e: > 99%., 6 min
2f: > 99%., 9 min
2g: > 99%, 6 min
2h: > 99%, 6 min
2i: > 99%., 9 min
2j: > 99%, 9 min
2k: > 99%., 9 min
2l: > 99%., 6 min
2m: > 99%., 6 min
2n: > 99%., 15 min
2o: > 99%., 6 min
2p: > 99%., 6 min
2q: > 99%., 9 min
2r: > 99%., 9 min
2s: 39%, 15 min
2s': 61%, 15 min
2t: 70%, 15 min
2u: 78%, 15 min
2v: 71%, 15 min
2w: > 99%., 6 min
2x: > 99%., 6 min
2y: > 99%., 6 min
2z: > 99%., 6 min

[a] **1a** (0.2 mmol) and $BaTiO_3$ (<3 μm, 1.9 mmol) in a 2 mL PE milling jar, 4 mm stainless-steel balls, 3800 rpm. [b] Isolated yields.

With the optimal reaction condition in hand, we started to explore the substrate scope of this mechanochemically aerobic oxidation with a wide range of aryl- and alkyl thiols (Table 2). With regard to arylthiols, a large variety of electron-donating groups on the phenyl ring, such as methoxyl groups at the *para*-, *meta*-, or *ortho*-position (**2a–c**), amino groups at the *para*- or *ortho*-position (**2d**, **2e**), hydroxy (**2f**), methyl groups at the *para*-, *meta*-, or *ortho*-position (**2g–j**), *t*-butyl (**2k**), and electron-withdrawing groups, including chloro (**2l**, **2o**), fluoro (**2m**), carboxymethyl (**2n**), could be converted into the target disulfides in quantitative yields in 6–15 min. Interestingly, when 4-nitrobenzenethiol was used as the substrate, diarylsulfide **2p** was produced in quantitative yield in 6 min instead of the corresponding disulfide. 2-Naphthalenethiol with extended π-framework furnished the desired disulfide **2q** in 6 min. In the case of heteroaryl thiols, the reaction of thiophene-2-thiol also underwent mechanochemical oxidative coupling to afford pure product **2r** successfully in a very short reaction time. However, when we used 4-pyridinethiol as substrate, a mixture of the corresponding disulfide **2s** and diarylsulfide **2s′** were produced in a ratio of 4 : 6 while the starting material conversion was complete. Benzyl mercaptan and derivatives could be wholly converted in 15 min resulting in good yields as well (**2t–v**). We also obtained successful results with alkyl thiols as substrates in 6 min.

To be highlighted in most cases, the reactions were clean, fast, and quantitatively yielding with no byproduct. Once the reaction was accomplished (monitored by TLC/GCMS), the reaction mixture was washed by CH_2Cl_2, followed by evaporation of the solvent under vacuum. Such a simple work-up procedure was able to afford pure products (purity identified by NMR) without further purification by column chromatography on silica gel. Since the piezocatalyst $BaTiO_3$ could be easily recovered by filtration, we tried the reuse of $BaTiO_3$ for the aerobic oxidative coupling of 4-methoxybenzenethiol **1a**. The piezoelectric $BaTiO_3$ could be reused 20 times with no decrease in product yield or increase in reaction time (Fig. 2), indicating the catalytic activity of $BaTiO_3$ was not attenuated at all. It is

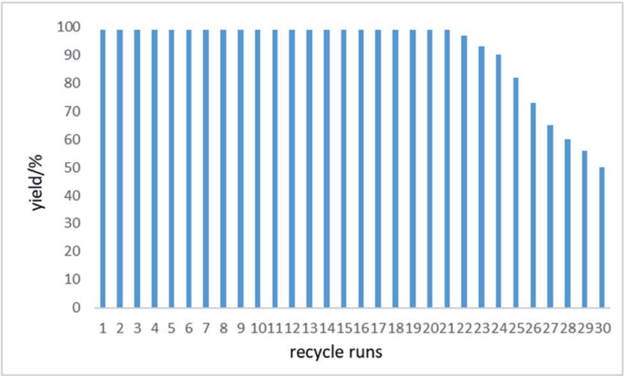
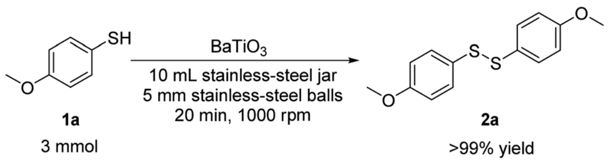


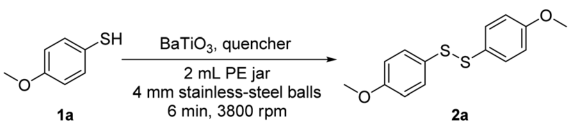
Fig. 2 Recycling efficiency of piezocatalyst $BaTiO_3$ for the oxidative coupling of 4-methoxybenzenethiol **1a** as measured by yields of the corresponding disulfide **2a**. Each run was conducted with 0.2 mmol **1a** under the optimal reaction condition (entry 2, Table 1).

reasonable to assume that the piezoelectric material could be recycled more times before the recovery loss of $BaTiO_3$ sets a limit to the recycling times. However, we found that the product yield started to drop rapidly after the 21st run. We did an SEM analysis of the piezoelectric catalyst to find out if the ball milling process would affect the size and morphology of $BaTiO_3$ (Fig. S1–S4,† see the ESI), which might affect the reaction performance as well. Compared to the commercially available $BaTiO_3$ (<3 μm) before use (Fig. S1†), the SEM image of recycled $BaTiO_3$ from the 15th run showed that the particle size distribution got narrower along with the milling process. Most amorphous particles presented in the commercially available $BaTiO_3$ disappeared during the milling process, which might be a result of agglomeration and recrystallization under the current ball milling conditions. The SEM image of recycled $BaTiO_3$ from the 24th run showed that the $BaTiO_3$ particles started to agglomerate into bigger particle sizes, which might cause the product yield reduction (the product yield of the 24th run is 90%). After 30th recycle run, the size and morphology of $BaTiO_3$ showed a big difference, demonstrating the occurrence of $BaTiO_3$ recrystallization during the milling process. Thus, the recovery loss and morphology change caused by the milling process of $BaTiO_3$ would both affect the recycle limit of the piezoelectric material. Besides, we performed a gram-scale aerobic oxidative coupling of **1a** in an AM100S mixer mill (10 mL stainless-steel milling jar with five 5 mm stainless-steel milling balls). During the reaction, we opened the mill jar every five minutes to ensure there was enough molecular oxygen for the reaction. To our delight, this gram-scale synthesis successfully afforded the desired product **2a** in quantitative yield in 20 min (Scheme 1). The reaction is as clean and efficient as the 0.2 mmol-scale. Hence, we have developed a highly sufficient and recyclable strategy to eliminate waste and simplify the workup procedure, which is an essential aspect for performing the reaction in a green fashion.



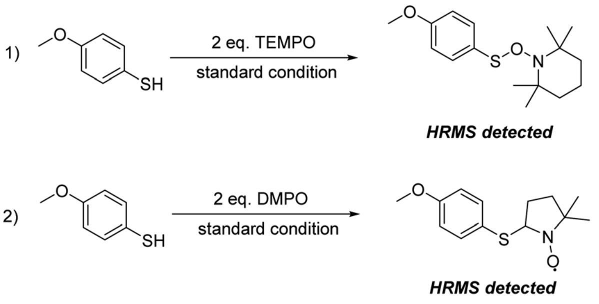
Scheme 1 Gram-scale synthesis of **2a**.

Table 3 Mechanistic studies on the mechanochemical oxidation of **1a** with $BaTiO_3$ as piezocatalyst[a,b]



Entry	Quencher	Notes	Yield/[%]
1	TEMPO	Radical scavenger	27
2	DMPO	Radical scavenger	25
3	Benzoquinone	Superoxide radical anion scavenger	10

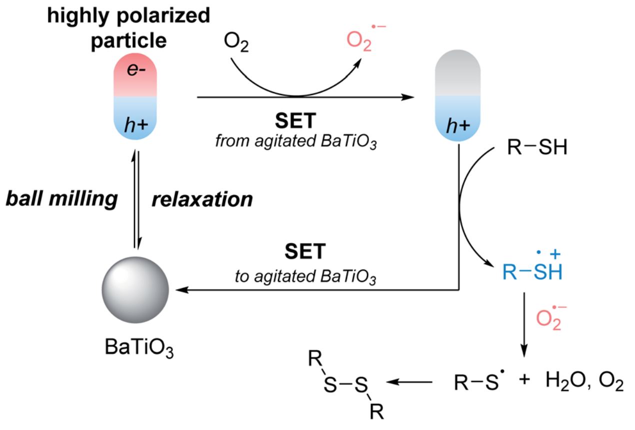
[a] **1a** (0.2 mmol), $BaTiO_3$ (<3 μm, 1.9 mmol), and quencher (2 equiv.) in a 2 mL PE milling jar, 4 mm stainless-steel balls, 3800 rpm, 6 min. [b] Isolated yield.



Scheme 2 HRMS analysis of the radical scavenger experiments with **1a**.

To probe the reaction mechanism, several mechanistic experiments were conducted with various scavengers (Table 3). When the reaction was performed in the presence of (2,2,6,6-tetramethyl piperidine-1-yl)oxidanyl (TEMPO) or 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) as a radical scavenger (entries 1 and 2), the product yields were sufficiently suppressed, indicating radical intermediates were involved in the reaction pathway. Then, we analyzed both reaction mixtures *via* HRMS (Scheme 2). The corresponding adducts of the thiyl radical with TEMPO or DMPO were identified respectively, illustrating that thiyl radical was produced during the reaction process. These results demonstrate our hypothesis that the piezoelectric material $BaTiO_3$ under ball milling is able to generate a thiyl radical. When the reaction of benzoquinone as superoxide radical anion scavenger with **1a** was conducted under the standard reaction condition, the product yield decreased to 10% (entry 3), suggesting superoxide radical anion takes part in the reaction.

Based on previous reports[15,16,27] and mechanistic studies, a plausible reaction mechanism is proposed in Scheme 3. When subjected to ball milling, the $BaTiO_3$ particles generate



Scheme 3 Proposed mechanism for aerobic oxidative coupling of thiols.

a temporary electrochemical potential that would be suitably persistent for the piezoelectric reduction of molecular oxygen to produce a superoxide radical anion *via* a single electron transfer (SET) mechanism analogous to the photoredox system. Subsequently, the thiol substrate could be oxidized by the hole in the agitated $BaTiO_3$, generating a cationic-radical-type intermediate. Then, the superoxide radical anion abstracts a proton from the cationic-radical intermediate to form the corresponding thiyl radical. The homocoupling of thiyl radical resulted in the corresponding disulfide as the final product.

Conclusions

In conclusion, we described here the application of piezoelectric-effect for the activation of molecular oxygen and generation of thiyl radicals. This piezochemically oxidative coupling of thiyl radicals led to the quantitative production of the corresponding disulfides in 6 min. Mechanistic experiments on the mechanochemically oxidative coupling with $BaTiO_3$ as piezocatalyst showed that superoxide radical anion and thiyl radicals were involved in the reaction process. This solid-state mechanoredox oxidative coupling of thiols with air as the sole oxidant avoids the usage of any solvents or catalysts. In most cases, the pure product could be collected *via* simple operation, while no further purification by gel chromatography on silica gel is needed. The piezocatalyst $BaTiO_3$ could be recycled 20 times with no loss in reactivity or product yields. Compared to solution methods, the operational simplicity, wide substrate tolerance, and short reaction time of this mechanochemical technique offer promising potential in industrial manufacturing.

Conflicts of interest

There are no conflicts to declare.

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