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Concept
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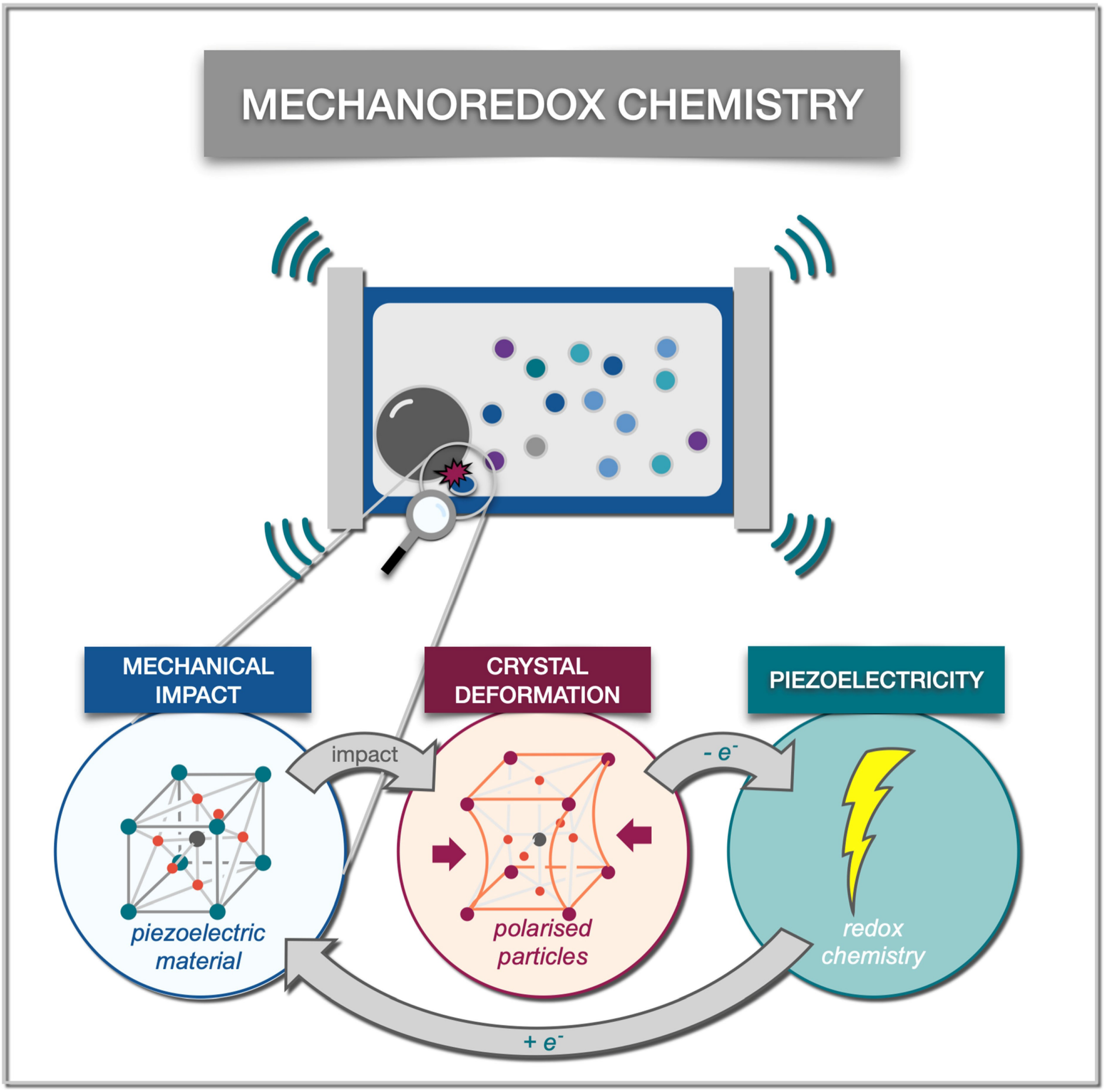
Mechanoredox Chemistry as an Emerging Strategy in Synthesis

Jamie A. Leitch*[a] and Duncan L. Browne*[a]



Abstract: Recent research endeavors have established that the mechanochemical activation of piezoelectric materials can open new avenues in redox chemistry. Impact forces, such as those imparted by a ball mill, have been shown to transform piezoelectric materials such as barium titanate ($BaTiO_3$) into a highly polarized state, which can then donate an electron to a suitable oxidant and receive an electron from a suitable reductant, mimicking established photoredox catalytic cycles. Proof-of-concept studies have elucidated that mechanoredox chemistry holds great potential in sustainable and efficient radical-based synthesis.

The use of mechanochemical force is well-known in the fields of crystal engineering and materials chemistry, and has become a vital tool in the investigation of solid-state phenomena such as polymorphism.[1] However, due to increased recent interest from synthetic organic communities, mechanochemistry has emerged as a powerful technology in contemporary synthetic methodology development. This strategy has been coveted as a sustainable alternative to solution phase chemistry, showcasing complementary solvent-free systems, often coupled with dramatically reduced reaction times (Scheme 1A).[2] Importantly, the use of mechanochemistry introduces new reaction design vectors such as milling frequency, ball size/material, jar size/material, and grinding agents (both solid and liquid). Furthermore, recent developments have established that mechanochemical transformations can provide improved and/or complementary selectivity to their solution-based counterparts, highlighting that mechanochemistry serves not just as a sustainable substitute but also as an influential avenue in reaction discovery.[3]

Parallel to the expanding developments in two-electron chemistry, and through elegant exploitation of piezoelectric materials,[4] ground-breaking advances in mechanochemical redox (mechanoredox) chemistry have opened the door to radical-based one-electron reaction manifolds. Under mechanochemical impact/agitation (using a ball mill for example), piezoelectric materials have been shown to generate temporarily polarized particles that can participate in redox events. Barium titanate ($BaTiO_3$, in either its cubic or tetragonal forms) has emerged as the initial piezoelectric material of choice in mechanoredox chemistry, where highly polarized particles can facilitate the single electron reduction of a suitable substrate. Such a reduction leaves a "hole" which then returns to the unpolarized ground state upon single electron oxidation (Scheme 1B).

This net redox-neutral cycle mimics the well-established oxidative quenching cycle of a photoredox catalyst (e.g. $Ru(bpy)_3^{2+}$), where photoexcitation of a suitable catalyst leads to the formation of an excited triplet state capable of carrying out the same single electron reduction/oxidation events (Scheme 1C).[5] Since the renaissance of photoredox chemistry, an abundance of methods have been developed with direct impact in the construction of building blocks and complex molecules alike. Despite this, due to complex and bespoke equipment required for photoredox manifolds, especially on scale, coupled with the necessity of often-expensive photocatalysts, analogous mechanoredox strategies can offer potent alternatives for industry, through the re-purposing of mixer mills and large-scale mixing equipment, routinely used in formulation and crystallisation studies.

Pioneering studies on the mechanically-induced redox properties of tetragonal $BaTiO_3$ and hexagonal ZnO materials were originally reported by Xu and co-workers in 2010.[6] Here they demonstrated that solution-phase ultrasonic activation of these piezoelectric materials could generate polarized particles capable of overcoming the water splitting potential ($E^{red} = -1.23$ V). Further elegant investigations by Esser-Kahn and co-workers in 2017 into the ultrasonic activation of $BaTiO_3$ elucidated that atom transfer radical polymerization (ATRP) manifolds could be triggered by the mechanoredox reduction of inactive Cu(II) salts to catalytically active Cu(I).[7]

However, in December 2019 Kubota and Ito were the first to apply these early proof-of-concept studies on ultrasonic mechanoredox chemistry to small-molecule organic synthesis, where notably the polarized particles were generated through mechanochemical agitation transduced by ball-milling. Here they reported the mechanochemical generation of aryl radicals from diazonium salts using commercially available, inexpensive, and easy-to-handle cubic $BaTiO_3$ nanoparticles as the piezoelectric material.[8] The authors demonstrated that the resulting aryl radicals could engage in two coupling mechanisms. The first, through interception with electron rich heteroarenes such as furans, thiophenes and one example of a protected pyrrole.[9] Single electron oxidation of the addition adducts reforms the ground state piezoelectric material, balancing the redox cycle, and enables rearomatization to the C–C coupled product after proton loss. This transformation was shown to be applicable to a range of aryl diazonium salts with electron-poor diazonium salts providing higher reaction efficiency. In a second transformation, the reductively-generated aryl radicals were capable of coupling to B_2Pin_2 to give the C-borylated product.

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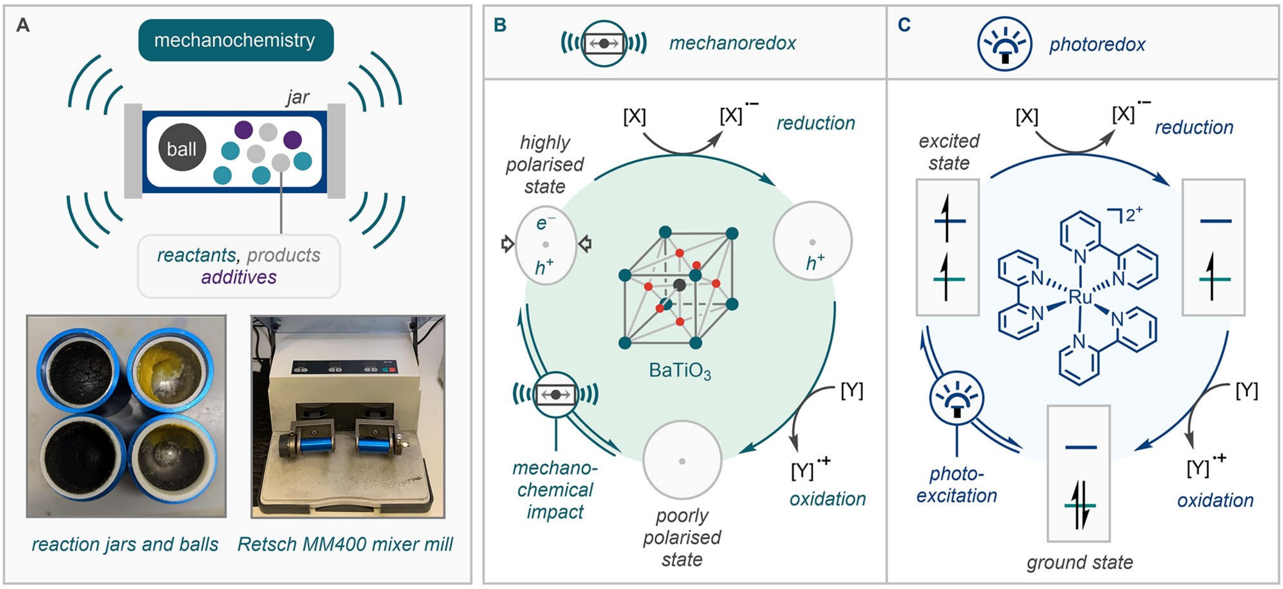
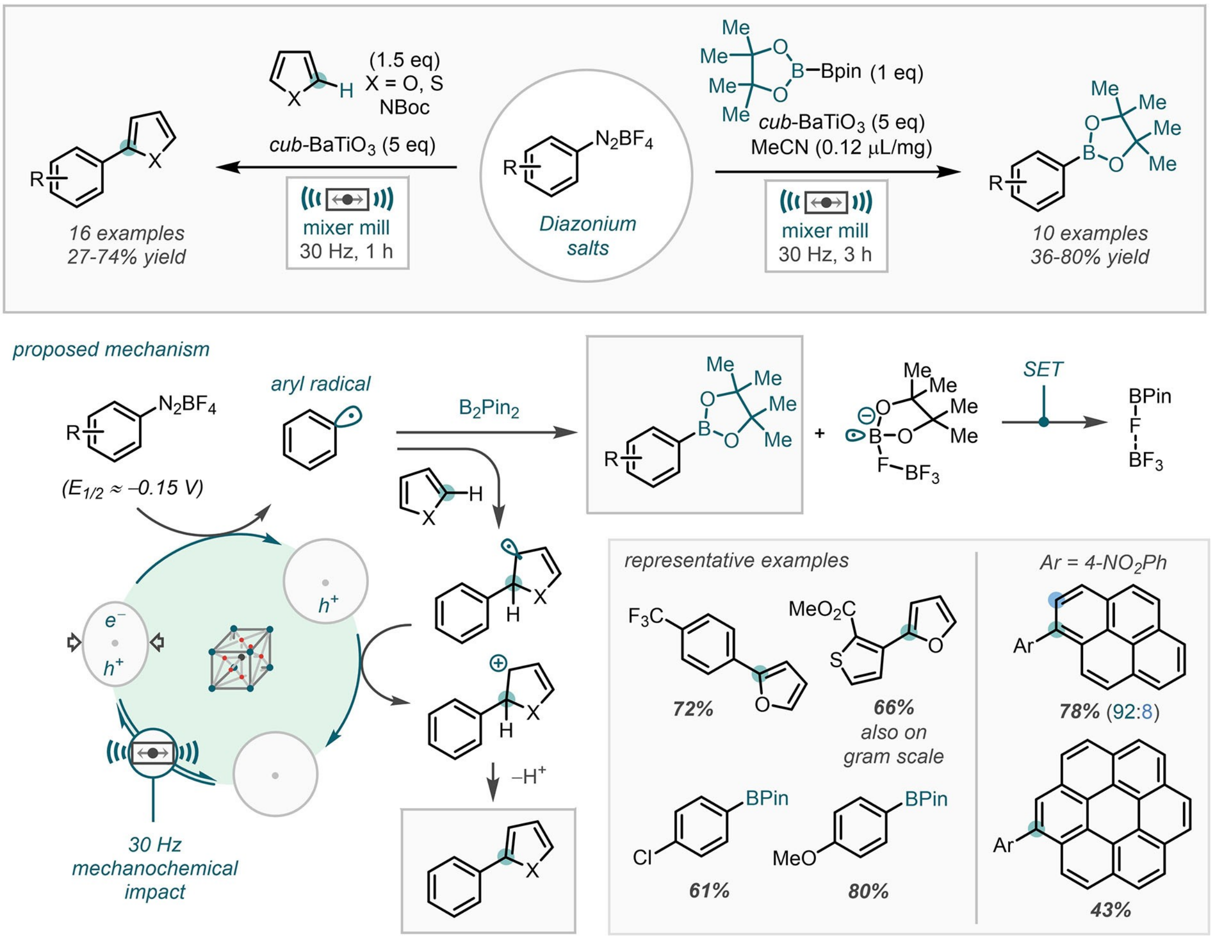


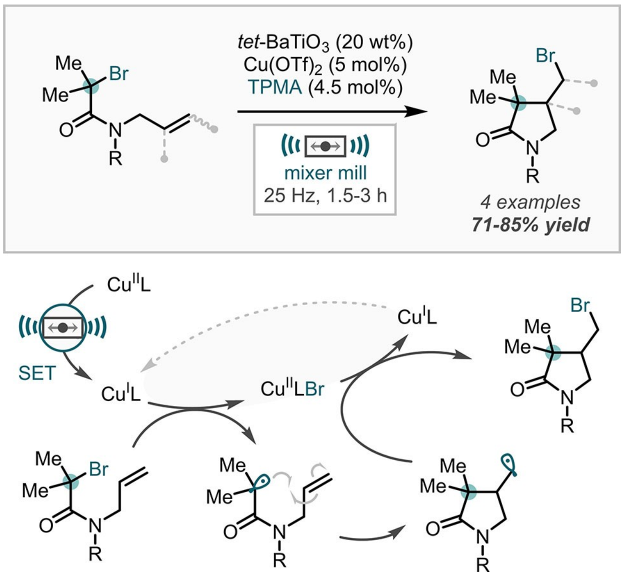
Scheme 1. Mechanochemistry and redox cycles in the context of photoredox and mechanoredox manifolds. Cubic $BaTiO_3$ shown as a representative piezoelectric material.



Scheme 2. Mechanoredox formation of aryl radicals using piezoelectric materials.

In this case the redox cycle is balanced by the boron-based radical anion addition by-product donating an electron to the “hole” of the piezoelectric material.[10] This second transformation required longer milling times (3 h versus 1 h previously) and was shown to be improved by the addition of acetonitrile as a liquid-assisted grinding (LAG) agent, a common feature of “all-solid” mechanochemical transformations.[11] Moreover a small library of aryl-BPin substrates were prepared using this method in moderate to good yield, where interestingly in this case, electron-rich diazonium salts performed more favorably. Notably these mechanoredox systems were shown to function effectively without precautions to exclude air or moisture from the reaction set-ups,[12] a common necessity in photoredox manifolds. The heteroarene arylation reaction was also performed on scale using a 25 mL ball-milling jar, enabling the synthesis of 1.1 grams of the C–C coupled structure. Due to the high quantities of the piezoelectric material required for reaction efficiency, the authors demonstrated that the BaTiO$_3$ could be recovered from the reaction mixture ($>95\%$) and reused in the reaction methodology in up to 5 runs with only a modest drop in reaction efficiency. One unique opportunity that mechanochemistry holds over complementary solution-based chemistry is the incorporation of traditionally highly-insoluble materials. This has led to the development of an array of methods that enable the functionalization of high-value polyaromatic hydrocarbons (PAHs).[2] In this report, pyrene and coronene were employed in the mechanoredox system as the electron-rich arene partner and both led to C–C coupled product in good yields. Importantly, thermography and radical scavenger studies were used to illuminate a redox-based mechanism, rather than a pathway resulting from the thermal activation of the diazonium salts.

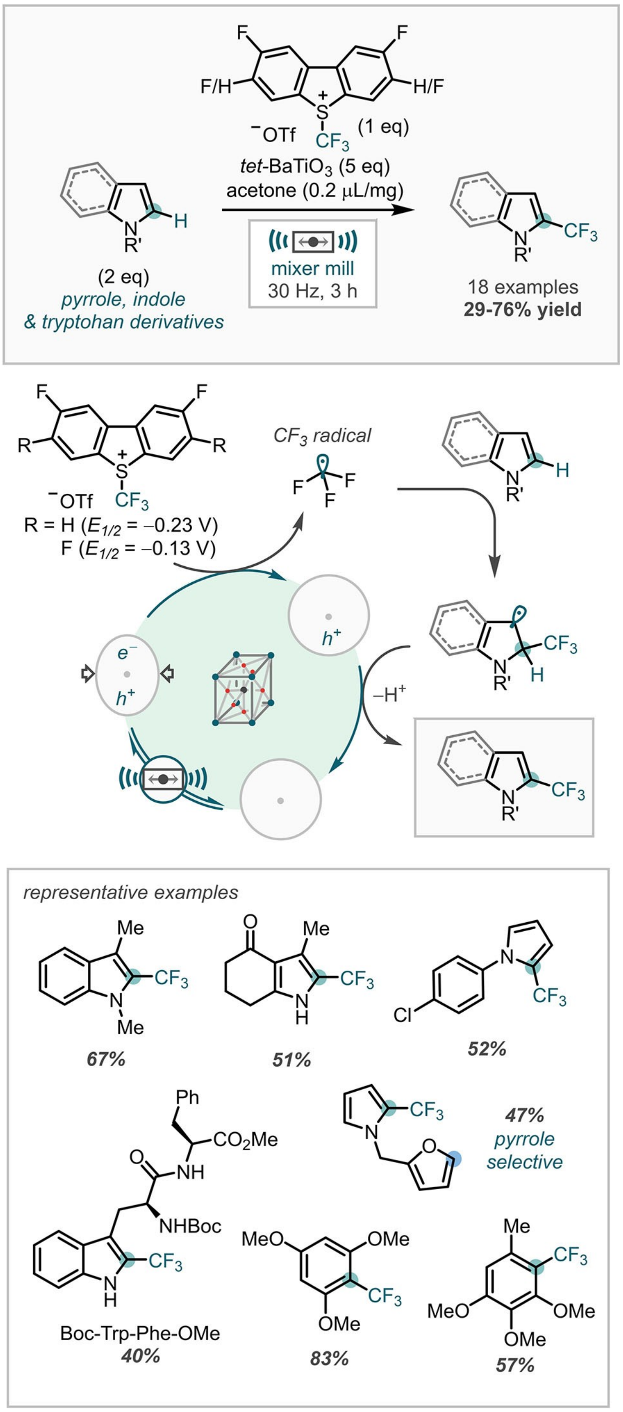
In June 2020, and inspired by the above ultrasonic polymerization work, Schumacher, Hernández and Bolm disclosed the mechanoredox atom transfer radical cyclization (ATRC)[13] of alkene-tethered α-bromoamides using tetragonal barium titanate as the piezoelectric material.[14] In this report, they identified that ATRC reactions – catalyzed by Cu(I) complexes – are often hindered through the accumulation of deactivator Cu(II) species, afforded by off-cycle radical-radical coupling mechanisms, or aerobic oxidation. Due to this “on-off” dichotomy between the copper species, the authors believed this would be a perfect opportunity to study piezoelectric materials in a mechanoredox ball-milling environment (Scheme 3). In this report, it is proposed that highly polarized BaTiO$_3$ particles produced by mechanochemical impact, are capable of reducing the Cu(II) pre-catalyst to the catalytically competent Cu(I) species. Intramolecular cyclization and halide abstraction affords the ATRC product and reforms the catalytically active Cu(I) species. The authors suggest that small quantities of the tris(2-pyridylmethyl)amine (TMPA) ligand could be responsible for balancing the redox cycle, donating an electron to the hole formed upon reduction of the copper species.



Scheme 3. Mechanoredox-triggered ATRC of alkene-tethered α-bromoamides. TMPA = tris(2-pyridylmethyl)amine.

The concept was applied to a small subset of ATRC substrates with good efficiency maintained when substituted alkene substrates were employed in the reaction mixture. This report paves the way for further exploration into mechanoredox-triggered catalytic manifolds and highlights the potential utility of piezoelectric materials as redox mediators in transition-metal catalyzed cross coupling reactions.

Following their seminal report on the mechanoredox arylation of hetereoarenes, in September 2020, Kubota, Ito and co-workers reported the application of piezoelectric materials to the mechanochemical generation of high-value trifluoromethyl radicals, which were then coupled to a variety of electron-rich heteroaromatics.[15] Here, the authors employed tetragonal barium titanate ($<3\ \mu$m) as the mechanoredox-active material, and Umemoto-type reagents were used as the trifluoromethyl radical source (Scheme 4).[16] Polar solvents as LAG agents were found to be crucial to increased reaction efficiency and acetone proved to be most optimal. Furthermore this reaction system benefitted from the use of larger jar sizes (5 mL) and larger and more numerous balls (2×7.5 mm). The mechanoredox strategy was applied to the trifluoromethylation of a library of indoles (either protected or free NH), substituted pyrroles, and tryptophan derivatives – including application to a number of dipeptide architectures. In addition, the C–H trifluoromethylation of a small subset of electron-rich methoxyarene derivates was demonstrated with modest to good efficiency. Throughout the scope the difluorinated Umemoto-type reagent was the radical precursor of choice, however with some examples the tetrafluorinated derivative (which is easier to reduce) was found to be more efficient. The authors also showcased the side-by-side reactivity of a mechanoredox and photoredox reaction of a furan-tethered pyrrole structure. In this case, the mechanochemical strategy showed absolute selectivity for the pyrrole fragment whereas the photoredox manifold led to a mixture of mono- and di-trifluoromethylated structures. TEMPO-trapping studies were used to probe the intermediacy of the key trifluoromethyl radical species, and



Scheme 4. Mechanoredox generation of trifluoromethyl radicals using piezoelectric materials.

remarkably the reaction was shown to take place (albeit in low yields) by using mechanochemical impact derived from striking the reaction mixture repeatedly with a hammer.

The recent use of piezoelectric materials, notably barium titanate, under mechanochemical ball-milling conditions has revealed that there is synthetic potential in mechanoredox chemistry. Furthermore, the ability to generate high-value radical species without the need for air- and moisture-free reaction environments, an expensive photocatalyst, complicated light set-ups, and also in a solvent-free environment renders these transformations highly industrially applicable.

To date, the pioneering redox transformations that have been adapted to a mechanochemical setting have taken place using radical precursors with close-to-zero reduction potentials, in redox-neutral cycles, and often requiring large quantities of the piezoelectric material. Despite this, the stage is now set for the exploration into more challenging radical precursors, increased incorporation into dual catalytic cycles, and also into the investigation of new piezoelectric materials.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: mechanochemistry · mechanoredox · radicals · redox · synthesis

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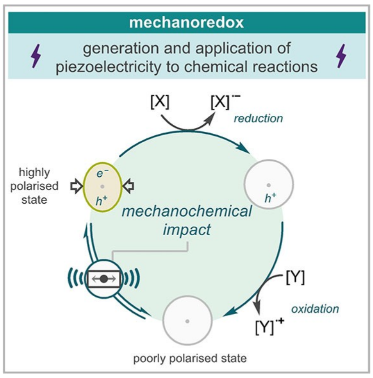
CONCEPT

The application of mechanical force to a material can lead to the generation of electric charge; piezoelectricity. For the first time, this effect has been harnessed and applied to radical reactions under ball-milling conditions, this Concept briefly describes the first appearances of this ground-breaking technique in the literature.



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