Synthetic Methodology

Mechanophotocatalysis: A Generalizable Approach to Solvent-minimized Photocatalytic Reactions for Organic Synthesis

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Abstract: This proof-of-concept study cements the viability and generality of mechanophotocatalysis, merging mechanochemistry and photocatalysis to enable solvent-minimized photocatalytic reactions. We demonstrate the transmutation of four archetypal solution-state photocatalysis reactions to a solvent-minimized environment driven by the combined actions of milling, light, and photocatalysts. The chlorosulfonylation of alkenes and the pinacol coupling of aldehydes and ketones were conducted under solvent-free conditions with competitive or superior efficiencies to their solution-state analogues. Furthermore, decarboxylative alkylations are shown to function efficiently under solvent-minimized conditions, while the photoinduced energy transfer promoted [2+2] cycloaddition of chalcone experiences a significant initial rate enhancement over its solution-state variant. This work serves as a platform for future discoveries in an underexplored field: validating that solvent-minimized photocatalysis is not only generalizable and competitive with solution-state photocatalysis, but can also offer valuable advantages.

Introduction

Photocatalysis and mechanochemistry are each powerful tools for synthetic organic chemistry. Solution-state photocatalysis enables selective bond activation for the production of high-value products via photoinduced electron transfer (PET) or photoinduced energy transfer (PEnT) mechanisms.[1–3] Photocatalysts selectively absorb visible light to drive myriad photochemical reactions that would otherwise require direct photoexcitation of the substrates.[4–5] Due to the use of visible light energy, provided by low power light sources such as LEDs, photocatalysis is often presented as a "green" approach to synthesis. Yet despite the indisputable usefulness of photocatalysis, several facets

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limit its sustainability and potential value as a synthetic tool. Principal amongst these is the ubiquitous reliance on solution-state reaction environments. Although the use of solvents in photochemical reactions can offer important advantages, such as functioning as a heat sink and influencing reaction mechanisms, many of the most commonly employed polar aprotic solvents are associated with safety and sustainability concerns, and they typically become the single greatest source of waste from a reaction. Solution-state photocatalysis reactions are also frequently documented to proceed over long reaction times, which hints towards sluggish reaction kinetics. Furthermore, whilst photochemical reactions that are tolerant to or require the presence of oxygen do exist, many photocatalytic reactions can only proceed efficiently under an oxygen-free environment, in large part to mitigate undesired competitive quenching of the triplet excited state of the photocatalyst by molecular oxygen dissolved in solution, and the need to degas reactions increases the complexity of the reaction setup. Finally, akin to other solution-state approaches, the scope of transformations is often limited to reagents and catalysts that are soluble in the chosen solvent.

Mechanochemistry, by contrast, uses the mechanical grinding or milling of neat reagents together to induce chemical transformations under solvent-minimized conditions.[6–8] Mechanochemistry on a lab scale is typically conducted using planetary or shaker ball-mills. Neat reagents can be milled exclusively, or alternatively inert solid grinding auxiliaries or very small volumes of solvents as liquid-assisted grinding (LAG) agents can be included to improve reaction efficiencies. While some reactions proceed uniquely by mechanochemistry, significant attention is focused on transmuting conventional solution-state reactions to solvent-minimized conditions using mechanochemistry; examples include S_NAr reactions,[9] palladium catalysed cross-coupling reactions such as Buchwald–Hartwig amination,[10] Suzuki–Miyaura,[11–12] Sonogashira,[13–14] and nickel-catalysed cross-couplings,[15–16] and transformations using Grignard reagents.[17–18] Evidently, mechanochemistry offers improved sustainability and reduced waste generation compared to solution-state analogues of these reactions. Moreover, there are several other advantages these mechanochemical syntheses can offer, such as proceeding at significantly reduced reaction times,[19] being insensitive to oxygen, and unlocking the reactivity of insoluble substrates.[20]

Considering the previously mentioned factors that can limit the versatility of photocatalysis, and the identified advantages of mechanochemistry, it becomes evident a

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synergistic union of these synthetic approaches could be highly appealing. Within this dual *mechanophotocatalysis* approach, photochemical reactions are driven using visible light and a photocatalyst, while mechanical grinding mediates the rapid mixing of reagents (Figure 1). Despite the apparent potential of such a union, to date there is a paucity of documented examples of limited chemical scope.[21] Obst and König reported the solvent-free aerobic oxidation of benzylic alcohols to their corresponding carbonyl analogues (6 examples, 37–74 % yield in 24 hours),[22] while Štrukil and Sajko reported the solvent-free aerobic oxidation of diphenylacetylene to benzil in 43 % yield in 6 hours.[23] Hernández later reported the solvent-free borylation of aryldiazonium salts (5 examples, 41–68 % yield in 45–120 minutes).[24] Expanding beyond reactions involving a photocatalyst, Borchardt *et al.* recently reported the solvent-minimized synthesis of polycyclic aromatic compounds under mechanical milling and UV-light irradiation (7 examples, 18–92 % yield in 30 hours or more),[25] while the [2+2] cycloaddition

of acenaphthylene has also been demonstrated via simultaneous light irradiation and ball milling (up to 96 % in 20 hours).[26] These previous reports are typically limited to niche reactions like aerobic oxidations, or feature long reaction times. Notably, the typical benefits of mechanochemistry, aside from solvent reduction, including an increased tolerance to aerobic conditions and rate enhancements, have not been demonstrated in these examples.

Practically, mechanical milling of reagents under light irradiation is challenging. Conventional milling jars are made of opaque materials like stainless steel, zirconium oxide, tungsten carbide and PTFE, while glasses conventionally used for solution-state photocatalysis can lack the required strength to survive high-frequency milling. While transparent plastic milling jars made from materials such as PMMA have become commonplace in the mechanochemistry community, particularly for in situ monitoring applications,[27] their low chemical resistivity to liquid substrates curtails their effectivity. Obst and König used a low energy rod mill for their reaction,[22] while Štrukil and Sajko, Hernández, and Borchardt modified commercial shaker ball mills by removing the safety cover to install lights around transparent milling jars made of glass or PMMA.[23–25] While these ball mill approaches enabled the desired transformations, the safety of such designs evidently can be improved; in particular, the inclusion of a safety shield would limit high-energy light leakage and would provide a protective failsafe should mechanical failure occur during milling. Furthermore, the long reaction times required will incur a significant energy cost.

Clearly the field of mechanophotocatalysis is still in its infancy. Herein, we demonstrate mechanophotocatalysis to be a general tool to achieve solvent-minimized photocatalysis reactions (Figure 1). Furthermore, we demonstrate for the first time that reaction efficiency enhancements and an improved tolerance to oxygen can be realized for photocatalytic reactions under solvent-minimized conditions. The modified mill and reaction vessels used in this work (Figure 1 and SI) allow for efficient irradiation of photocatalysis reactions using commercial LED excitation sources while offering improved safety over previously reported reactors. The same excitation source was used for both solution-state and mechanophotocatalytic trials to facilitate comparisons of reaction outcomes. We demonstrate the generality of mechanophotocatalysis by investigating its application across four distinct photocatalysis reaction classes: the atom transfer radical addition (ATRA) of sulfonyl chlorides to alkenes, the pinacol coupling of carbonyl compounds, decarboxylative alkylations, and a [2+2] cycloaddition. This test suite showcases that mechanophotocatalysis can accomplish common oxidative and reductive quenching PET and PEnT reactions and is compatible with a range of organometallic and organic photocatalysts and with multiple substrates, paving the way for more synthetically useful reactions to be adapted to mechanophotocatalysis. We observe comparable or superior efficiencies with significantly reduced consumption of organic solvents compared to solution-state benchmark reactions. In some cases, reagent substitutions are required to achieve competitive efficien-
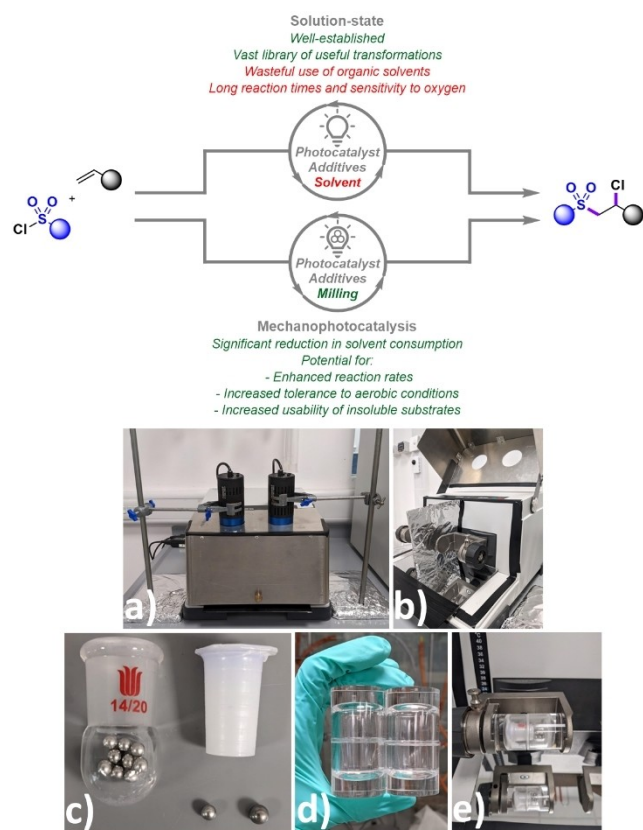

Figure 1. The design principle and motivation for realizing mechanochemically mediated photocatalysis reactions, and the mechanophotocatalysis reactor. a) Modified Retsch MM400 mill with a reflective safety shield allowing for the safe irradiation of reactions during milling. b) Interior view of reactor. c) Inner reaction vials that provide the required chemical resistivity, transparency, and robustness to withstand milling under visible light irradiation. d) Transparent PMMA encapsulation jars that facilitate clamping within the mill and provide additional protection. e) Reaction vessel clamped within the mill. The current design was found to maintain temperatures of 40–50 °C during a 2 hour reaction.

cies, providing insights into how other solution-state photocatalysis reactions could be adapted to mechanophotocatalysis.

Results and Discussion

ATRA

Our investigations began by exploring the ATRA of *p*-toluenesulfonyl chloride and styrene (Table 1). The reaction follows an oxidative quenching catalytic cycle, with the excited-state photocatalyst reducing the sulfonyl chloride (E_{red} of *p*-toluenesulfonyl chloride $= -1.37$ V vs SCE in MeCN)[28] to liberate a chloride anion and a sulfonyl radical. The sulfonyl radical undergoes addition to the alkene substrate, with the intermediate carbon-centred radical being oxidized by the radical cation photocatalyst to turnover the catalytic cycle. Nucleophilic attack by the chloride anion delivers the final product. [Ru(bpy)$_3$](PF$_6$)$_2$ was one of the first photocatalysts demonstrated to promote this reaction in solution efficiently;[29] however, a wide range copper complexes have become popular alternatives for these transformations.[30–31] Inspired by the use of similar

Table 1: The atom transfer radical addition of *p*-toluenesulfonyl chloride and styrene under solution-state photocatalysis and mechanophotocatalysis conditions.

Solution-state[a]					Mechanophotocatalysis[b]			
Entry	Reaction Time (h)	Modifications		Yield (%)[c]	Entry	Reaction Time (h)	Modifications	Yield (%)[c]
1a	24	(As in scheme)		98±2	**1b**	2	(As in scheme)	92±1
2a	2	(As in scheme)		87±0	**2b**	2	No light	0
3a	2	Aerobic		0	**3b**	2	No photocatalyst	0
4a	2	Aerobic, NaCl (4 equiv.)		0	**4b**	2	Na$_2$SO$_4$ as auxiliary[d]	91±4
5a	2	Aerobic, norbornene as alkene		0	**5b**	2	Norbornene as alkene	73±1
6a	2	Norbornene as alkene		8±0				

Reaction Yields [e]
Solution-state (anaerobic)
Solution-state (aerobic)
Mechanophotocatalysis (aerobic)

87% / 0% / 92% (Me)
8% / 0% / 73%
90% / 0% / 81% (I)
95% / 0% / 94% (CF$_3$)
16% / 0% / 89% [f] (F)
28% / 0% / 78% [f] (Br)
28% / 0% / 82% [f] (^{t}Bu)
13% / 0% / 70% [f] (F$_3$C)

[a] General procedure for solution-state photocatalysis experiments: *p*-toluenesulfonyl chloride (0.3 mmol), alkene (0.33 mmol), [Cu(dmp)(xantphos)]PF$_6$ (1 mol%), MeCN (1.2 mL), N$_2$ or ambient atmosphere, *Kessil* 456 nm LED, 2 or 24 h. [b] General procedure for mechanophotocatalysis experiments: *p*-toluenesulfonyl chloride (0.3 mmol), alkene (0.33 mmol), [Cu(dmp)(xantphos)]PF$_6$ (1 mol%), NaCl (1.2 mmol), ambient atmosphere, *Kessil* 456 nm LED, ball mill (20 Hz), milling ball (1×0.52 g), 2 h. [c] Yields determined via quantitative ^{1}H NMR spectroscopy utilizing an internal standard (1,3,5-trimethoxybenzene). Non-zero yields are the average of two experiments, with the standard deviation reported. [d] Equivalent mass of Na$_2$SO$_4$ (1.64 equivalents). [e] ^{1}H NMR yields are from single experiments of 2 hour reaction times in solution or by mechanophotocatalysis according to the general procedures outlined. [f] Modification from the general mechanophotocatalysis procedure: 2×0.52 g milling balls. Stainless steel milling balls were used throughout this study. We considered using PTFE as an alternative material to increase the light reflected within the reaction vessel. However, we were concerned that equivalently sized PTFE balls possessing lower masses and would become immobile within the typically "sticky" reaction mixtures.

heteroleptic copper complexes in chlorosulfonylation reactions, [Cu(dmp)(xantphos)]PF$_6$ was selected as a photocatalyst for the mechanophotocatalysis trials and solution-state benchmark reactions. Under anaerobic solution-state reaction conditions, [Cu(dmp)(xantphos)]PF$_6$ achieves NMR yields of 87 and 98% in 2 and 24 hours, respectively (Table 1, Entries 1a and 2a). However, under aerobic conditions this photocatalyst cannot perform the transformation in solution, with almost complete recovery of the starting material after 2 hours, showing that a deoxygenated environment is essential for this reaction to proceed in solution using this photocatalyst (Table 1, Entry 3a). The mechanophotocatalysis reaction was then explored. Using sodium chloride as an inert solid grinding auxiliary, and under aerobic and solvent-free conditions using the same light source as the solution-state reaction, a yield of 92% was achieved in just 2 hours (Table 1, Entry 1b). This result compares favourably with the equivalent time anaerobic solution-state reaction and shows a remarkably improved tolerance to aerobic conditions. Notably, to the best of our knowledge this is the first report of an increased tolerance to aerobic conditions being reported for a photocatalytic process under mechanochemical conditions. With efficient mechanophotocatalysis conditions identified, control reactions validated the dual activation protocol: milling in the absence of light failed to deliver the target product (Table 1, Entry 2b), while milling and light irradiation in the absence of a photocatalyst lead to no product formation (Table 1, Entry 3b), indicating that the combined actions of light, milling, and the presence of a photocatalyst are essential. To verify the grinding auxiliary does not contribute to the enhanced tolerance to aerobic conditions of the mechanophotocatalysis reaction, a solution-state trial was conducted in the presence of sodium chloride (Table 1, Entry 4a), with the reaction again failing to deliver the target product under aerobic conditions. We also assessed sodium sulfate as an alternative grinding auxiliary, which gave an equivalent yield of 91% in 2 hours (Table 1, Entry 4b). The relative efficiencies of the mechanophotocatalysis and solution-state photocatalysis reactions were then explored with an alternative solid alkene radical acceptor, norbornene. The mechanophotocatalysis reaction achieved a yield of 73% in 2 hours under aerobic, solvent-free conditions, in a reaction solely comprised of solid starting reagents (Table 1, Entry 5b). The same reaction in solution under aerobic conditions failed to deliver the target product, while the anaerobic solution-state reaction achieved a yield of only 8% in an equivalent time (Table 1, Entries 5a and 6a). In order to verify that the transmutation of the solution-state mechanism to mechanophotocatalysis does not limit the functional group tolerance of the reaction, a small substrate scope was investigated (Table 1). The mechanophotocatalysis protocol tolerated all functionalities employed, including iodo, bromo, fluoro, and trifluoromethyl groups, affording the products in high yields. Functionalized sulfonyl chlorides and both electron-poor and electron-rich styrenes were employed in high yielding reactions accomplished in short times. In all cases, the aerobic solution-state photocatalyzed reaction failed to deliver the target products,

whereas mechanophotocatalysis afforded products in high yields, demonstrating the generality and robustness of the solvent-free procedure. Within the 2-hour reaction time, while substituted sulfonyl chlorides are well tolerated and result in high product yields (90–95%) using anaerobic solution-state conditions, much lower yields (13–28%) were obtained when varying the styrene. By contrast, the mechanophotocatalysis procedure achieved high yields with all substrates evaluated (70–94%), demonstrating the generality of mechanophotocatalysis conditions towards this diversity of functional groups.

Pinacol Coupling

The ATRA reaction required minimal modifications from the solution-state conditions to be adapted to mechanophotocatalysis, as the major mass components of the reaction are solid substrates, which are more amenable to milling than liquids are. However, we noted that many photocatalysis reactions could potentially struggle with being transmuted to an environment operating via mechanochemical grinding, as common sacrificial reductants in photocatalysis are liquid amines. These reagents serve as proton and electron donors in many reactions, frequently in large excess. It was therefore important to showcase a mechanophotocatalysis reaction that was compatible with one of these transformations. The pinacol coupling of carbonyl-containing compounds was chosen as a model reaction (Table 2).[32] Classically, the reaction uses an excess of liquid amines such as tributylamine or DIPEA. While the reaction has been reported to follow a reductive quenching mechanism, it is also reasonable to postulate that an oxidative quenching mechanism may be operational depending upon the relative redox potentials of the chosen photocatalyst.[33] Regardless of the cycle, both will involve the photocatalyzed reduction of the aromatic carbonyl, which then undergoes radical-radical homocoupling to form a new C(sp^3)–C(sp^3) bond, while oxidation of a quencher (such as DIPEA) completes the photocatalytic cycle and provides a proton source for generating the final diol product. Using conditions from the literature,[33–34] the solution-state pinacol coupling of benzaldehyde in the presence of a large excess of DIPEA afforded the desired diol product in NMR yields of 62 and 81% in acetonitrile and tetrahydrofuran, respectively, in 2 hours (Table 2, Entries 1a and 2a). High yields were maintained when the 5-fold excess of quencher was decreased to 1.5 equivalents (Table 2, Entries 3a and 4a). A direct transmutation of the reaction to mechanophotocatalysis conditions using sodium chloride as an inert solid grinding auxiliary with either 5 or 1.5 equivalents of DIPEA as a quencher led to only moderate yields of 35 and 42%, respectively (Table 2, Entries 1b and 2b); likely a result of the high liquid content of the reaction. We identified that the Hantzsch ester could serve as an alternative and efficient solid quencher to adapt this reaction for mechanophotocatalysis. Its use under solution-state conditions afforded superior yields to those obtained using DIPEA (79 and 84% in acetonitrile and tetrahydrofuran, respectively,

Table 2: The pinacol coupling of benzaldehyde under solution-state photocatalysis and mechanophotocatalysis conditions.
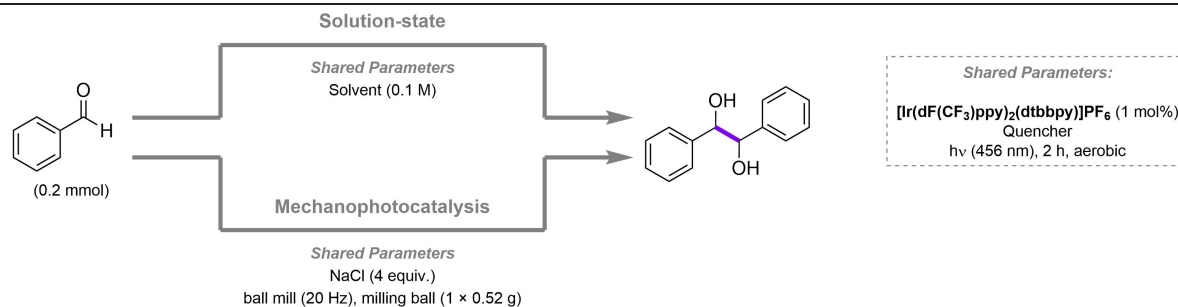
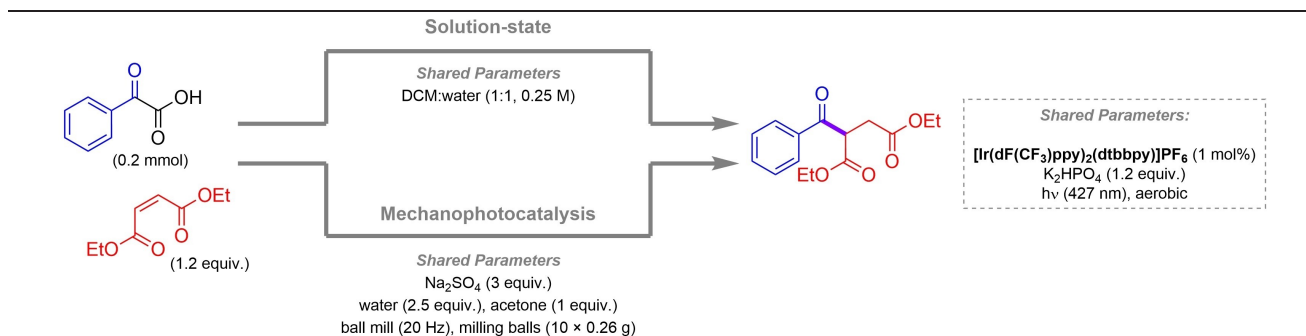| Solution-state[a]				Mechanophotocatalysis[b]			
Entry	Quencher (equivalents)	Solvent	Yield (%)[c]	Entry	Quencher (equivalents)	Other Modifications	Yield (%)[c]
1a	DIPEA (5)	MeCN	62±2	**1b**	DIPEA (5)	(As in scheme)	35±5
2a	DIPEA (5)	THF	81±6	**2b**	DIPEA (1.5)	(As in scheme)	42±3
3a	DIPEA (1.5)	MeCN	66±3	**3b**	Hantzsch ester (1.5)	(As in scheme)	81±2
4a	DIPEA (1.5)	THF	76±0	**4b**	Hantzsch ester (1.5)	4CzIPN as photocatalyst	72±3
5a	Hantzsch ester (1.5)	MeCN	79±0	**5b**	Hantzsch ester (1.5)	No light	0
6a	Hantzsch ester (1.5)	THF	84±0	**6b**	Hantzsch ester (1.5)	No photocatalyst	0
7a[d]	Hantzsch ester (1.5)	THF	91±2	**7b**[d]	Hantzsch ester (1.5)	Alternative substrate	93±0

[a] General procedure for solution-state photocatalysis experiments: benzaldehyde (0.2 mmol), quencher (0.3–1 mmol), [Ir(dF(CF$_3$)ppy)$_2$-(dtbbpy)]PF$_6$ (1 mol%), solvent (2 mL), ambient atmosphere, *Kessil* 456 nm LED, 2 h. [b] General procedure for mechanophotocatalysis experiments: benzaldehyde (0.2 mmol), Hantzsch ester (0.3 mmol), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%), NaCl (0.8 mmol), ambient atmosphere, *Kessil* 456 nm LED, ball mill (20 Hz), milling ball (1×0.52 g), 2 h. [c] Yields determined via quantitative ^{1}H NMR spectroscopy utilizing an internal standard (1,3,5-trimethoxybenzene). All non-zero yields presented are the average of two experiments, with the standard deviation reported. [d] 4-acetylbenzonitrile as substrate.

(Table 2, Entries 5a and 6a)). Under mechanophotocatalysis conditions, using sodium chloride as a solid grinding auxiliary and the Hantzsch ester as a solid quencher, the desired product was produced in a competitive yield of 81% under solvent-free conditions in the same reaction time of 2 hours (Table 2, Entry 3b). Notably, the same mechanophotocatalysis reaction could also proceed in a high yield of 72% with the organic photocatalyst 4CzIPN in lieu of the iridium complex (Table 2, Entry 4b). Control reactions without light (Table 2, Entry 5b) or photocatalyst (Table 2, Entry 6b) led to no product formation, evidencing the dual photocatalytic/mechanochemical reactivity. Using the solid ketone 4-acetylbenzonitrile as the substrate, the mechanophotocatalysis reaction proceeded with a 93% yield in 2 hours in a reaction comprised of only solid starting materials (Table 2, Entry 7b), while the solution-state reaction with this reagent in tetrahydrofuran achieved a comparable yield of 91% in 2 hours (Table 2, Entry 7a). It should be noted that the apparent necessity to employ a more expensive solid quencher to achieve competitive efficiencies might limit the scope for applying mechanophotocatalysis to reactions with a high liquid component, or necessitate the exploration of cheaper alternative reactants.

Decarboxylative Alkylation

Carboxylic acids are one of the most important classes of radical precursor substrates in photocatalysis due to their accessibility, typically low cost, and compatibility in a wide array of reactions.[35] Photocatalysis reactions utilizing carboxylic acids typically follow reductive quenching mechanisms: following deprotonation by a base, the carboxylate anion can be oxidized by an excited-state photocatalyst (E_{ox} of PhCOCO$_2$K = 1.03 V vs SCE in DMSO).[36] β-scission liberates carbon dioxide as a traceless gaseous by-product and generates a carbon-centred radical that can undergo addition to a suitable radical trap, such as an alkene. The photocatalyst radical anion then reduces the radical intermediate substrate to regenerate the ground-state photocatalyst and form an anionic species that is then protonated to afford the target compound. Carboxylic acids are also common substrates in other more synthetically useful photocatalytic applications, such as in metallaphotoredox catalysis,[4] and considering the significant importance of these versatile reagents, it was important their activation via mechanophotocatalysis be verified. Taking inspiration from Fu et al., the decarboxylative alkylation of electron-deficient alkenes, such as diethyl maleate, with the α-keto acid phenylglyoxylic acid was selected for such a showcase (Table 3).[37] Interestingly, the authors found that the inclusion of water was beneficial for improving the efficiency of the reaction; hence this was incorporated into the mechanophotocatalysis reaction. The solution-state reaction using [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ as the photocatalyst and a solvent system of a 1:1 mixture of dichloromethane and water achieved yields of 15 and 43% in 3 and 24 hours, respectively (Table 3, Entries 1a and 2a), while removal of

Table 3: The decarboxylative alkylation of diethyl maleate with phenylglyoxylic acid under solution-state photocatalysis and mechanophotocatalysis conditions.

Solution-state[a]				Mechanophotocatalysis[b]			
Entry	Reaction Time (h)	Modifications	Yield (%)[c]	Entry	Reaction Time (h)	Modifications	Yield (%)[c]
1a	24	(As in scheme)	43 ± 1	**1b**	3	No acetone	57 ± 5
2a	3	(As in scheme)	15 ± 0	**2b**	3	(As in scheme)	78 ± 0
3a	24	No organic solvent	20 ± 0	**3b**	3	No light	0
4a	3	Acetone instead of DCM	23 ± 5	**4b**	3	No photocatalyst	0
5a	3	Cbz-proline as substrate	51 ± 3	**5b**	3	Cbz-proline as substrate	88 ± 4
6a	24	Cbz-proline as substrate	92 ± 5				

[a] General procedure for solution-state photocatalysis experiments: phenylglyoxylic acid (0.2 mmol), diethyl maleate (0.24 mmol), K$_2$HPO$_4$ (0.24 mmol), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol %), water (0.4 mL), dichloromethane (0.4 mL), ambient atmosphere, *Kessil* 427 nm LED, 3–24 h. [b] General procedure for mechanophotocatalysis experiments: phenylglyoxylic acid (0.2 mmol), diethyl maleate (0.24 mmol), K$_2$HPO$_4$ (0.24 mmol), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol %), water (0.5 mmol), acetone (0.2 mmol), Na$_2$SO$_4$ (0.6 mmol), ambient atmosphere, *Kessil* 427 nm LED, ball mill (20 Hz), milling balls (10×0.26 g), 3 h. [c] Yields determined via quantitative ^{1}H NMR spectroscopy utilizing an internal standard (1,3,5-trimethoxybenzene). All non-zero yields presented are the average of two experiments, with the standard deviation reported.

the organic solvent led to a decreased yield of 20 % in 24 hours (Table 3, Entry 3a). The mechanophotocatalysis reaction using the same light source, sodium sulfate as an inert solid grinding auxiliary, and 2.5 equivalents of water afforded a superior yield of 57 % in only 3 hours under organic solvent-free conditions (Table 3, Entry 1b), notably more efficient than the solution-state trials. Considering the prevalence of LAG in the mechanochemistry literature, we questioned whether the inclusion of a small volume of an organic solvent in the mechanophotocatalysis reaction would further improve the reaction efficiency. While the original solution-state report used dichloromethane as an organic solvent, we instead turned our attention to the use of acetone as a 'greener' alternative.[38] Pleasingly, the yield of the mechanophotocatalysis reaction was improved to 78 % in just 3 hours with the inclusion of only 1 equivalent of acetone (Table 3, Entry 2b). Modifying the solution-state reaction conditions to use a 1:1 mixture of water and acetone to provide a more direct comparison with the mechanophotocatalysis reaction gave a yield of only 23 % (Table 3, Entry 4a); significantly less efficient than the mechanochemically mediated reaction. The exclusion of light (Table 3, Entry 3b) or the photocatalyst (Table 3, Entry 4b) resulted in no product formation, showing both are essential in the mechanophotocatalysis protocol. Finally, we explored the use of an alternative carboxylic acid to expand the substrate scope beyond α-keto acids. Inspired by

the pioneering work of MacMillan and co-workers, we selected the benzyl carbamate-protected proline derivative (Cbz-proline) as a second substrate for the reaction.[39] The mechanophotocatalysis reaction afforded a yield of 88 % in 3 hours (Table 3, Entry 5b), while the solution-state photocatalysis reaction gave yields of 51 and 92 % in 3 and 24 hours, respectively (Table 3, Entries 5a and 6a), again demonstrating the competitive efficiency of mechanophotocatalysis as a synthetic protocol.

[2+2] Cycloaddition

With three PET mechanophotocatalysis reactions demonstrated, we sought to explore the potential for PEnT reactions to be transmuted from the solution-state to a solvent-minimized environment. The [2+2] cycloaddition of *trans*-chalcone was selected for this initial validation. The cyclobutane motif is notable in a number of natural products and can be readily accessed via the [2+2] cycloaddition of a wide range of alkene substrates, including derivatised chalcones, cinnamates, cinnamamides, and styrenes,[40–43] promoted by either direct photoexcitation or by energy transfer photocatalysis. The cross-cycloaddition of such substrates is also possible, in addition to the classical symmetric cycloaddition.[43–44] We began our investigations using *trans*-chalcone as a substrate, *fac*-Ir(ppy)$_3$ as the

photocatalyst and 1,4-dioxane as the solvent (Table 4).[43] This reaction is notably sluggish in solution, providing yields of 51 and 64% in 24 and 48 hours, respectively (Table 4, Entries 2a and 1a), while in 3 hours the yield of the cyclobutane product was only 12% (Table 4, Entry 3a). A notable side reaction in this process, also occurring via Dexter energy transfer, is the *E/Z* isomerization of the alkene;[41] indeed, there was significant formation of *cis*-chalcone in 38% NMR yield in the 3 hour solution-state reaction. The mechanophotocatalysis reaction was then investigated. Under solvent-free conditions using sodium sulfate as a solid grinding auxiliary, a yield of 33% was obtained in just 3 hours (Table 4, Entry 1b), which is superior to the solution-state reaction at the same reaction time. The addition of 1 equivalent of dioxane as a LAG agent resulted in an improved yield of 44% (Table 4, Entry 2b). Increasing the amount of LAG agent to 3 equivalents gave a slightly increased yield of 47% (Table 4, Entry 3b), but a further increase led to a decrease in yield (Table 4, Entry 4b). The mechanophotocatalysis reactions were limited to 3 hours to minimize potential decomposition of the target product (see SI). Within this time, the mechanophotocatalysis reaction under both solvent-free and LAG conditions is significantly more efficient than the solution-state reaction; however, over longer time periods the solution-state yields are superior. Control reactions with no light led to no product formation (Table 4, Entry 5b), while the reaction without a photocatalyst gave 6 and 10%

yields of the desired cyclobutane product and *cis*-chalcone products, respectively (Table 4, Entry 6b), showing that the transformation can be promoted mechanophotochemically as well. A photochemical background rection also exists in the solution-state; however, within a 3 hour reaction time only the *cis*-chalcone by-product was detected and obtained in a 26% yield, while there was no observed formation of the desired cyclobutane product (Table 4, Entry 4a). We then explored the use of the organic photocatalyst 4CzIPN. Yields of 41 and 56% were obtained in 24 and 48 hours, respectively, under solution-state conditions (Table 4, Entries 6a and 5a). However, in 3 hours, only an 8% yield of the target cyclobutane was obtained, with 56% yield of the *cis*-chalcone by-product (Table 4, Entry 7a). Under mechanophotocatalysis conditions, the use of 4CzIPN afforded a yield of 38% of the cyclobutane adduct and a 12% yield of *cis*-chalcone (Table 4, Entry 7b), demonstrating that this initial rate enhancement in the mechanophotocatalysis experiment is not exclusive to the iridium photocatalyst.

Conclusion

Herein, we have showcased the simple combination of mechanochemistry and photocatalysis to achieve solvent-minimized photocatalysis reactions. A commercially available mixer ball mill was modified with a custom safety shield allowing for improved safety over similar examples in the

Table 4: The [2+2] cycloaddition of *trans*-chalcone under solution-state photocatalysis and mechanophotocatalysis conditions.

Solution-state[a]				Mechanophotocatalysis[b]			
Entry	Reaction Time (h)	Modifications	*cis*-chalcone:cyclobutane product yields (%)[c]	Entry	Reaction Time (h)[d]	Modifications	*cis*-chalcone:cyclobutane product yields (%)[c]
1a	48	(As in scheme)	4:64	1b	3	No dioxane	3:33
2a	24	(As in scheme)	13:51	2b	3	1,4-dioxane (1 equiv.)	5:44
3a	3	(As in scheme)	38:12	3b	3	(As in scheme)	6:47
4a	3	No photocatalyst	26:0	4b	3	1,4-dioxane (5 equiv.)	9:39
5a	48	4CzIPN as photocatalyst	13:56	5b	3	No light	1:0
6a	24	4CzIPN as photocatalyst	27:41	6b	3	No photocatalyst	10:6
7a	3	4CzIPN as photocatalyst	56:9	7b	3	4CzIPN as photocatalyst	12:38

[a] General procedure for solution-state photocatalysis experiments: *trans*-chalcone (0.3 mmol), photocatalyst (1 mol%), 1,4-dioxane (3 mL), N₂ atmosphere, *Kessil* 456 nm LED, 3–48 h. [b] General procedure for mechanophotocatalysis experiments: *trans*-chalcone (0.3 mmol), photocatalyst (1 mol%), Na₂SO₄ (1.23 mmol), 1,4-dioxane (0.9 mmol), ambient atmosphere, *Kessil* 456 nm LED, ball mill (20 Hz), milling balls (10×0.26 g), 3 h. [c] Yields determined via quantitative ¹H NMR spectroscopy utilizing an internal standard (1,3,5-trimethoxybenzene). All non-zero yields are the average of two experiments. [d] Mechanophotocatalysis reactions were limited to 3 hours to minimize product decomposition (see SI).

field while ensuring efficient irradiation of the reaction vessel. Milling vessels that combine the required transparency and robustness to withstand milling under light irradiation were developed to transmute four mechanistically distinct photocatalysis reactions from the solution-state to a mechanochemical environment. Unlike previous studies, the generality of a mechanophotocatalysis approach was highlighted across these four distinct reactions, with both energy and electron transfer reactions conducted. Such an approach was amenable to both solid and liquid substrates, and to a range of different photocatalysts, further demonstrating the generality of this synthetic methodology. The ATRA and pinacol coupling reactions were successfully conducted under completely solvent-free conditions, while the decarboxylative alkylations and [2+2] cycloaddition benefited from the inclusion of LAG agents to mediate more efficient mixing of reaction components. Furthermore, an enhanced reaction rate was observed for the ATRA, decarboxylative alkylation, and [2+2] cycloaddition reactions over their solution-state versions. Additionally, the ATRA reaction could be conducted under ambient conditions in the mechanophotocatalysis reaction, despite necessitating an oxygen-free environment in the solution-state reaction. This study is the first to systematically compare the results from solution-state photocatalysis reactions with those in a solvent-minimized environment. We show that there are tangible benefits of this approach across a mechanistically diverse range of reactions, demonstrating the value for further explorations into this field and setting the stage for more synthetically useful photocatalysis reactions to be transmuted to mechanophotocatalysis. However, researchers should be mindful that poor temperature control in mechanophotocatalysis reactors may adversely affect temperature-sensitive reactions, and further refinements to the reactor design may be needed to address this. Conceptually, mechanophotocatalysis attempts to achieve similar goals to mechanoredox catalysis, within which piezoelectric materials are milled with reagents under solvent-minimized conditions.[45] Mechanical grinding polarises the piezoelectric material to enable participation in electron transfer reactions that resemble the oxidative quenching pathway of photoredox catalysts. From a practical perspective, this approach is simpler than mechanically driven photocatalysis, as conventional milling jars and equipment can be used. However, the redox windows, and thereby the range of substrates that are feasibly activated by piezoelectric catalysts, are small. Contrasting, the use of photocatalysts should offer access to a much more diverse range of substrates and transformations via electron transfer as a function of the wider redox windows accessible by photoexcitation. Furthermore, photocatalysts can mediate reductive quenching electron transfer and energy transfer reactions unique to photochemistry, making mechanophotocatalysis a more versatile synthetic approach.

Naturally, the issue of scale up is of industrial importance. Both photocatalysis and mechanochemistry traditionally struggle with scale up: the former largely a result of the low penetration depth of incident light in batch reactors, and the latter being limited by the physical size of mixer and planetary ball mills. The current reactor and vessel setup detailed here is not amenable to reaction up-scaling, and we are currently working on modifying both to conduct mechanophotocatalysis reactions at a gram scale. The advent of continuous flow photocatalysis provides some potential for scaling up photocatalytic syntheses,[46] and in a conceptually similar approach extruder technologies have enabled the continuous mechanochemical synthesis of target products.[47–48] Perhaps mechanophotocatalysis could draw inspiration from both methodologies, allowing for industrially scalable continuous photocatalytic syntheses under solvent-minimized conditions. Alternatively, there is promise for lower energy drum or roller mills to be adapted for use in mechanophotocatalytic batch syntheses at scale.

This work is a necessary advance in the future development of mechanophotocatalysis, and we hope to inspire further explorations into this field as a new frontier for achieving solvent-minimized photocatalysis reactions.

Supporting Information

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

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Research Articles

Mechanophotocatalysis: A Generalizable
Approach to Solvent-minimized Photocata-
lytic Reactions for Organic Synthesis
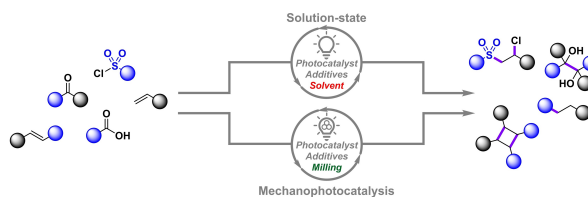
Via the synergistic union with mechano-
chemistry, four archetypal photocatalysis
reactions have been realized under sol-
vent-free or solvent-minimized condi-
tions. The mechanophotocatalytic ver-
sions feature competitive or superior
efficiencies to the solution-state reac-
tions, while also showcasing an en-
hanced tolerance to aerobic conditions.