Novel applications of light, electricity, mechanical force and flow in synthesis

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Abstract |

The input of energy is often required to promote chemical reactions. While heat is commonly applied to overcome activation barriers in such processes, it is well established that other forms of energy can be utilised to unlock chemical potential. For example, it has been demonstrated that light, electric current, mechanical force, and flow can also facilitate chemical transformations. Although many of these synthetic approaches have been the subject of considerable investigation since the 19th century, recently, various associated research areas have enjoyed resurgences or, in some cases, significantly emerged for the first time. These developments have generally coincided with seminal conceptual and technological advancements. With this in mind, this review showcases a selection of recent advances aligned with these themes spanning photoredox catalysis, mechanochemistry, electrosynthesis, and synthesis in static electric fields and in flow.

[H1] Introduction

An ongoing challenge in chemical synthesis relates to the creation of complex molecules by combining simpler, readily accessible reactants and reagents via a series of chemical reactions that proceed with high efficiency and precise control over the products formed. Traditionally, such reactions have been carried out in batch processes, often with isolation and purification between steps. To overcome the often-significant activation barriers for such reactions, thermal energy is usually utilised, along with barrier-lowering chemical catalysts or additives. However, in recent years, there has been a growing emphasis and/ or realisation that other forms of energy can be used instead.

This review focuses on discussing original applications of external stimuli (light, voltage, mechanical force, and flow) in enhancing and enabling various aspects of chemical synthesis. By design, this is not intended as an all-encompassing and exhaustive account of progress in these highly active fields. Rather, a selection of vignettes showcasing important recent developments aligned with these four key themes are presented.

We aim to draw attention to fundamental research exploring original ideas and approaches or work that investigates intriguing applications of new concepts and technologies, which offer exciting opportunities to extend, augment, and better understand chemical synthesis. Specifically, we highlight recent conceptual or technological advances in the areas of photoredox catalysis,¹⁻⁹ organic electrosynthesis,¹⁰⁻¹³ electrostatic chemistry and synthesis in static electric fields,^{14,15} mechanochemistry,¹⁶⁻²² and synthesis in flow that have appeared within the preceding five years.^{23,24}

[H1] Visible-light-mediated photocatalysis

Over the past decade, photoredox catalysis has enjoyed a renaissance, emerging as an important and active area of research.¹⁻⁹ The intrinsic properties of photoredox catalysts allow them to create chemical potential by harvesting energy from sources of low-intensity visible light, which can be utilised to facilitate an array of valuable synthetic reactions.¹⁻⁹ Many of these transformations proceed under mild conditions and are amenable to flow processes. Because many organic molecules do not absorb visible light, these processes often minimise unwanted

side-reactions that may arise from the direct photoexcitation of these compounds via more traditional (and less practical) ultraviolet irradiation.

This section highlights creative synthetic approaches that have evolved to harness and exploit the inherently reactive species that can arise from the innate interaction of light and matter.

[H2] Photocatalysts capable of asymmetric induction

The majority of photoredox-catalysed reactions are understood to operate via outer-sphere mechanisms in which these catalysts are not involved in pivotal bond-forming steps.¹⁻⁹ For this reason, dual catalysis strategies where asymmetric induction is controlled by separate chiral cocatalysts or additives are typically utilised to effect stereoselective variants of these processes.²⁻

⁴ In contrast, the two examples specifically discussed below represent particularly elegant and original strategies that have defined exciting new approaches for controlling the stereoselectivity of photoredox-catalysed reactions.

A pioneering report disclosed by Meggers and coworkers illustrated that a single photoactive, chiral-at-metal iridium catalyst system could mediate an efficient and highly selective asymmetric α -alkylation (Figure 1a).²⁵ This work profited from the group's earlier studies concerning the preparation of enantiopure second and third row transition metal complexes.²⁶ It is proposed that this reaction proceeds via the two-point binding of the planar enolate derived from ketone **1** to complex **3** to activate this Lewis basic substrate. In parallel, the photoexcited complex reduces bromide **2** while the approach of the ensuing radical is controlled very effectively by the inherent steric bias associated with the coordination environment of the metal. All of this is possible because the absolute (and relative) configuration of the photo-active chiral iridium complex is retained throughout the transformation. Meggers' research group has since exploited this strategy to great effect in establishing other stereoselective processes.²⁷ In complementary work, Yoon and coworkers recently utilised a chiral hydrogen-bonding iridium triplet sensitiser to effect enantioselective intramolecular [2 + 2]-photocycloadditions.²⁸

In 2016, a team led by Fu and Peters proved that a three-component, first row transition metal-based photoactive catalyst system (generated *in situ*) could be utilised to establish unprecedented enantioconvergent C–N couplings of indoles/carbazoles **7** and racemic alkyl chlorides **6** (Figure 1b).²⁹ This impressive report followed on from Fu and Peters' earlier work that identified and exploited the fundamental properties of photoactive copper(I) carbazolidines to effect C–N couplings of alkyl and aryl halides for the first time.^{30,31} Specifically, in the asymmetric transformation shown in Figure 1b, the authors illustrated that the copper catalyst effectively differentiates between the three carbon-substituents of tertiary electrophile **6** to very efficiently control the absolute configuration of product **10**. It is proposed that a photoexcited copper(I) carbazolidine species reduces chloride **6** to generate a putative alkyl radical, which leads to observed compound **10** in an enantioconvergent fashion.^{29,32}

[H2] Consecutive photoinduced electron-transfer (PET) in photoredox catalysis

A significant challenge in photoredox catalysis relates to designing and engineering catalysts with the requisite intrinsic electrochemical properties to overcome the relatively high redox potentials of many accessible bulk chemical substrates, such as aryl chlorides. With this in mind, identifying and exploiting novel strategies that facilitate these types of non-trivial photoinduced, electron-transfer processes is valuable.

König and coworkers reported hydrodehalogenation, arylation, and cyclisation reactions of activated aryl halides **11** employing perylene-based organic dye PDI (**12**) (Figure 1c).³³ The proposed mechanism underpinning these processes (and its implications) are particularly fascinating, more so than the general chemical transformations themselves.¹ This is because the electrochemical properties of PDI^{*} and PDI^{•-} reflect that these compounds are not capable of reducing aryl halides **11**. Instead, the authors suggest that PDI has the capacity to harvest the

energy of two photons, which ultimately leads to the formation of strongly reducing $\text{PDI}^{\bullet-}$. This intermediate is the only species present in the reaction mixture that can facilitate electron-transfer to substrate **11** and, thus, mediating the reduction or functionalisation of these aryl halides. The proposed mechanism contrasts with more conventional single-photon excitation which is typically invoked in photoredox catalysis and has some similarities to the Z-scheme in photosynthesis.

[H2] Photoredox-catalysed generation of hydrated electrons

Hydrated electrons ($e_{\text{aq}}^{\bullet-}$) represent powerful reducing agents ($E_{\text{red}} = -2.6 \text{ V vs SCE}$),³⁴ with potential applications in chemical synthesis.^{35,36} In 2017, Goez and coworkers disclosed an unprecedented photoredox-catalysed approach for generating hydrated electrons under mild conditions and then exploited this chemistry to facilitate the reduction of chloroacetate (Figure 1d).³⁷ This reaction employed an aqueous mixture containing $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ (**16**) as the sensitizer and vitamin C as the sacrificial oxidant. The latter oxidises the photoexcited $[\text{Ru}(\text{bpy})_3]^{2+*}$ (**16***) to afford the one-electron reduced form of catalyst **16**, $[\text{Ru}(\text{bpy})_3]^+$. Notably, it is proposed that this intermediate is capable of absorbing a second photon, which allows for the generation a hydrated electron that mediates the challenging hydrodechlorination transformation.

Although an expensive Nd:YAG laser (~€25,000) was required to facilitate this reaction,³⁷ in a subsequent study, the authors demonstrated that green LED-irradiation can be utilised to effect the above-mentioned transformation.³⁸ Furthermore, the authors have used this strategy to promote other photoredox-catalysed processes, including the hydrodefluorination of *p*-fluorobenzoate ($E_{\text{red}} = -2.0 \text{ V vs SCE}$), carbonyl reduction of α,α,α -trimethylacetone ($E_{\text{red}} = -2.3 \text{ V vs SCE}$), and the hydrogenation of cinnamate ($E_{\text{red}} = -2.2 \text{ V vs SCE}$).³⁸

[H2] Application of pulsed irradiation in photoredox catalysis

A wide body of research has focused on catalyst development and the use of co-catalysts and additives to provide enhanced reactivity and broaden reaction scope in photoredox catalysis.^{1-5,8} However, beyond utilising high intensity light sources and light-emitting diodes (LEDs), which emit defined wavelengths of light (particularly the venerable blue LED), the investigation of more novel irradiation strategies in synthesis has arguably received much less attention.

Interestingly, pulsed LED irradiation is known to enhance photosynthetic activity, phytochemical production and facilitate superior plant growth.^{39,40} This prompted Bissember and coworkers to postulate that pulsed irradiation strategies may find important applications in organic synthesis.⁴¹ In 2018, these researchers demonstrated for the first time that pulsed LED irradiation enhances the efficiency of photoredox-catalysed reactions (Figure 1e).⁴¹ An inexpensive multiphase circuit was constructed and employed to deliver pulsed visible light (100 kHz, 25% duty cycle) (Figure 1f), which facilitated the development of an efficient dual α -amino C–H/ C–F functionalisation process.

Lowering the pulse frequency by orders of magnitude (10 kHz or 1 kHz) provided a lower rate of product formation and incomplete conversion. In comparison, conventional (continuous) blue LED irradiation provided inferior results and incomplete conversion was observed even after extended reaction times (i.e., 61% yield after 65 h). When the scope of this methodology was investigated, pulsed LED irradiation led to enhanced reaction efficiency in the majority of cases. The reasons for the reaction enhancements provided by pulsed irradiation in this process are yet to be unravelled and the wider applications of this strategy must also be explored. Interestingly, in related work reported in 2018, pulsed infrared irradiation was recently shown to accelerate a ground-state reaction for the first time.⁴²

[H1] Organic Electrosynthesis

The direct conversion of electrical energy into chemical potential offers a variety of possible advantages over more standard reagent-based strategies. In electrochemistry, redox processes

occur at the interface of solid surfaces and solutions. Preparative electrolysis has featured in industrial processes since the turn of 19th century and is particularly important for the synthesis of bulk chemicals.⁴³ In contrast, the development and uptake of laboratory-scale organic electrosynthesis has lagged significantly behind, particularly in academia.^{10,43,44} However, more recently, electrosynthesis has enjoyed a notable resurgence in interest amongst synthetic organic chemists.^{10–13} This may derive from growing pressures to prepare complex targets with increasing efficiency, selectivity and atom economy from readily available inexpensive precursors as safely as possible. In addition, the former issues have also coincided with the recent development of new technologies and more user-friendly instrumentation to facilitate organic electrochemistry.⁴³ These factors have aligned to transport electrosynthesis firmly into the realm and consciousness of organic chemists. By doing so, it appears that this fundamental mode of innate reactivity is poised to be restored at the vanguard of new reaction development.^{10–13}

A selection of noteworthy examples and significant advances in the area of organic electrosynthesis are examined with a focus on transformations that complement and augment more traditional reagent-based approaches, in addition to noteworthy developments in reactor design.

[H2] Accessing vicinal diamines via metal-catalysed electrosynthesis

The oxidative functionalisation of olefins to afford vicinal diols or their precursors is well established.⁴⁵ In comparison, general methods for efficiently accessing equivalent 1,2-diamines or their analogues are not as well developed, although elegant stereoselective 1,2-diazidation reactions have been reported more recently.⁴⁶

In 2017, Lin and coworkers exploited electrochemistry to develop a novel 1,2-diazidation of alkenes that provided 1,2-diazides in generally high yields, which could be easily reduced to the give the corresponding vicinal diamines (Figure 2a).^{47,48} The merger of transition metal catalysis with electrosynthesis was crucial to identifying mild reaction conditions that provided broad scope across sterically-varied and substituted olefins. Indeed, 1,1-disubstituted, 1,2-disubstituted, trisubstituted, and tetrasubstituted substrates were compatible with this chemistry. This methodology also featured excellent chemoselectivity, functional group compatibility, and atom economy. In this process, putative azidyl radicals were generated after oxidation at the anode, which then added to the olefin **22**. The authors suggest that the redox-active magnesium catalyst mediates the reaction of ensuing radical **25** to furnish vicinal diazide **23**. The impressive chemoselectivity observed in this transformation derived from precise potentiostatic control during the reaction, which ensured that the anode delivered only the minimum potential required to effect the key oxidation step. In subsequent studies, the same research group has extended this strategy to electrochemical dichlorination and chlorotrifluoromethylation.⁴⁹

[H2] Anodic unsymmetrical biaryl cross-couplings of phenol and aniline derivatives

The creation of versatile and efficient approaches for direct functionalisation of unactivated C–H bonds has enhanced the arsenal of powerful reactions available to synthetic chemists and significant progress has been made in electrochemical C–H activation chemistry.^{10–13,50,51}

In 2016, Waldvogel and coworkers reported an electrochemical method allowing for one-step unsymmetrical biaryl C–C couplings of phenols **26** with silyl-protected phenol derivatives **27** (Figure 2b).⁵² This phenol–arene coupling chemistry extended the scope and synthetic utility of anodic phenol–phenol cross-couplings that the authors had established in 2014.⁵³ The application of a boron-doped diamond (BDD) anode and the use of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as a stabilising solvent were crucial to favouring *ortho,ortho*-coupled products **28** and optimal results were obtained when electrolysis was performed at slightly elevated temperatures (50 °C). Importantly, these conditions, circumvented previous issues that had complicated electrochemical biaryl coupling chemistry, which included poor selectivity and oligomerisation of unprotected

phenols.^{10,11,13} This methodology compares favourably to reagent-based aromatic coupling transformations, which require stoichiometric quantities of chemical oxidants.⁵⁴

In the presence of additives, such as water or methanol, HFIP has also been shown to enable the “decoupling” of nucleophilicity and redox potential.⁵⁵ This interesting property has been exploited to effect other biaryl cross-couplings.^{10,11,13} In 2017, Waldvogel and coworkers extended this strategy to enable the cross-couplings of amide- or carbamate-protected anilines **29** and **30** affording 2,2'-diaminobiaryl products **31** in moderate to excellent yields (Figure 2b).⁵⁶ This research group has also employed this approach to effect cross-couplings of phenols with various aromatic heterocycles, including thiophenes, furans, and benzofurans.¹³

[H2] Stabilised “cation pool” strategies in electrosynthesis

Anodic oxidation is often harnessed to electrochemically generate carbocations which can be captured by various nucleophiles.^{10–13} However, in an undivided cell, many cationic intermediates are sensitive to cathodic reduction, while nucleophiles (particularly carbon nucleophiles) can be preferentially oxidised, which complicates reaction development and restricts reaction scope. Yoshida conceived and pioneered the elegant and powerful “cation pool” strategy which ameliorated many of these issues.^{57,58} In this approach, cation generation and nucleophilic trapping are separated both temporally and spatially by employing divided cells and a two-stage process. The carbocations are typically generated and accumulated after low temperature electrolysis in the anode chamber then nucleophiles are added into the mixture under non-oxidative conditions to trap these reactive intermediates.

In 2016, Yoshida and coworkers demonstrated that through the use of additives, such as sulfilimine **33**, anodically-generated carbocations **40** could be stabilised as the corresponding benzylaminosulfonium species **34** (Figure 2c).⁵⁹ Importantly, this stabilised “cation pool” strategy, allowed for efficient cation generation and stabilisation of rather unstable benzylic cations at ambient temperatures.⁵⁸ The array of benzylaminosulfonium derivatives **34** that were prepared in this manner could be captured by a variety of carbon nucleophiles, including benzene derivatives, aromatic heterocycles, an enol ether, and allyltrimethylsilane, to enable simple downstream functionalisation. In a separate study, the authors also demonstrated that treatment of benzylaminosulfonium species **34** with tetrabutylammonium iodide furnished N-tosylbenzylamines **35**.⁶⁰

[H2] Advances in reactor design

It has been suggested that general reticence of synthetic chemists to embrace electrosynthesis originates, at least in part, from the relative inaccessibility of user-friendly technology, standard equipment, and materials that have traditionally not allowed for the efficient development of readily reproducible electrosynthetic methodology.^{43,12} In the past, equipment for electrosynthesis has been available and resourceful scientists have ingeniously repurposed household equipment to effect electroorganic transformations.⁶¹ However, access to simple, purpose-made instruments that remove barriers to adoption are valuable and can aid in demystifying electrochemistry to synthetic chemists who are non-specialists.⁴³

In 2017, after a three-year collaboration between engineers at IKA and Baran’s research group, the ElectraSyn 2.0 was developed (Figure 3).⁴³ Depending on the customer’s location, this commercially available device retails for ~US\$2,100–4,200 (excluding accessories).⁶² The developers suggest that this system can ameliorate a number of issues that have presented obstacles to the emergence of laboratory-scale electrosynthesis. This stand-alone equipment has the footprint of a standard stirrer plate and features a user-friendly interface and, importantly uses standardised sets of electrodes and cells that are also commercially available. The unit is modular by design, features analytical capabilities, and offers built-in data analysis and data transferability. In 2017, IKA also released the Electrasyn flow, which enables continuous flow

electrosynthesis and was developed as part of a collaboration with Waldvogel and his coworkers.⁶³

It is possible that the ElectraSyn may come to represent defining technological advancement in this area the generally acknowledged benchmark instrument employed for electrosynthesis. This can only be borne out by time. Whether or not this is the case, the promotion and availability of this device has aided in redirecting and refocusing the attention of the general organic chemistry community on a somewhat dormant area of organic synthesis that is arguably yet to realise its full potential. This has already prompted many groups to initiate programs in electrosynthesis and this is beneficial for the field advancing in the future.

[H1] Electrostatic chemistry and chemistry in static electric fields

Not to be confused with the electric currents associated with electrochemical reactions, static electric fields are also increasingly being recognised as a potential tool for manipulating chemical synthesis.¹⁵ Because most molecules and transition structures have some degree of polarity, the prospect of stabilising them with carefully aligned electric fields has long been recognised by theoreticians.^{15,64} However, it is only recently that experimental strategies for harnessing them have been developed.¹⁴ These methods – spanning the nano- to the macro-scale – can be loosely grouped into single-molecule experiments, interfacial experiments, and the use of charged functional groups to deliver internal electric fields.

[H2] Single molecule experiments

The first unambiguous demonstration that an external electric field could be used to catalyse a simple carbon–carbon bond-forming reaction was provided by Aragonès et al.⁶⁵ in 2016 using scanning tunnelling microscopy (STM) experiments. A norbornene derivative was tethered via gold–sulfur bond to the plate of an STM while a furan derivative was tethered to the tip. The STM was operated in what is known as “blinking” mode: a known potential difference is set between the tip and plate, and the tip is scanned at a constant rate, a fixed distance above the plate. In this way, the reagents are exposed to a known field strength and their orientation in the field is both controlled and known. When a reaction occurs between the diene and dienophile, the covalent bond linkage (or “junction”) between the tip and plate causes a tunnelling current, which is then lost as continued scanning causes rupture of the junction. By counting these current “blinks” per unit time, one obtains a measure of the single molecule reaction rate. By measuring the reaction rate as a function of field strength, it was shown that when the bias was negative, the rate of the Diels–Alder reaction increased steadily with increasing field strength up to a factor 5 within the limits of the experiment; for positive bias, the rate remained constant. Quantum-chemical calculations of the same system confirmed that these trends were due to the effects of electric field.

Follow-up studies have also demonstrated that appropriately aligned external electric fields can be used to trigger bond cleavage of an alkoxyamine into a nitroxide and carbon-centred radical.⁶⁶ Single molecule experiments provide an excellent platform for studying the effects of electric fields on chemical reactions, and could conceivably provide a means of harnessing such effects in nanotechnology applications such as micropatterning, but are not suitable for bulk chemical synthesis.

[H2] Interfacial experiments

To scale up electric field effects, attention has drawn to electrodes and charged insulating surfaces. In electrochemical cells, substantial electric fields (ca. 0.5 V/nm) are generated near the electrode surface as a result of the electrical double layer. These fields are similar in strength to those generated in STM experiments, and hence could be used to catalyse chemical reactions on a larger scale. As a proof-of-concept, Zhang et al.⁶⁶ studied the electrochemical oxidation of an alkoxyamine, finding that the species undergoes an $EC_{\text{irrev}}E$ mechanism in which alkoxyamine

oxidation is followed by rapid irreversible cleavage to a nitroxide radical and carbocation, followed in turn by reversible oxidation of the nitroxide product. While this is primarily an electrochemical, rather than electrostatic, process, it was shown that the bond cleavage reaction was actually intrinsically disfavoured (by ca. 35 kJ/mol) and only made possible as a result of the electrical double layer. The reaction, which occurs both in surface-tethered and diffusive conditions, has since been harnessed as a means of generating carbocations on a surface,⁶⁷ and applications in synthesis are currently being explored. In another demonstration of electrostatic catalysis, Matille and co-workers tethered an anion- π catalyst on an indium tin oxide electrode and explored the addition reaction of malonic acid half thioesters to enolates.⁶⁸ They showed that, in the presence of an electric field, there is increase in activity (by more than 100-fold) of the otherwise disfavoured enolate addition reaction.

An alternative approach to harnessing electrostatic fields has been pioneered by Kanan and co-workers,^{69,70} who used a parallel plate cell in which an insulating film is placed on the top of the standard electrodes. When voltage is applied charge develops on the insulating surface, and Kanan has shown that this charge can catalyse and/ or alter the selectivity of chemical reactions. In an initial study, they showed that the rearrangement of *cis*-stilbene oxide could be catalysed by surface charges, with the aldehyde to ketone product ratio of the rearrangement increasing by up to a factor of 63 in the presence of the electric field. In a follow-up study, these researchers showed that the product ratio of the Rh-porphyrin-catalysed intramolecular rearrangement of 1-diazo-3,3-dimethyl-5-phenylhex-5-en-2-one could be likewise altered from 10:1 in favour of the cyclopropanation product over the insertion product in the absence of voltage to values varying from 100:1 to 1:2, depending on the voltage and nature of the insulating film. This ability of surface charges to catalyse chemical processes raises the possibility of scale-up, particularly if combined with flow chemistry and other forms of surface charging, such as tribocharging.

[H2] Charged functional groups

An alternative approach to harnessing electric fields, and one that is truly scalable in chemical synthesis, is to make use of the internal electric fields generated by charged functional groups such as Brønsted acids or bases, or metal ions and their clusters. When Brønsted acids or bases are used the electrostatic effects are switchable via simple pH changes. Electric field effects from charged groups are short range, decaying at $1/r^2$ for a charge-dipole interaction, and hence affect only the molecule or supramolecular assembly to which they are attached. As a result, careful placement of the charged group allows for precise control of the field orientation without the need for surface chemistry techniques. Field effects are progressively quenched by polar solvents, and hence reactions need to be carried either in the gas phase, or in non-polar media where solubility becomes an increasing constraint. Nonetheless experiments have shown that sizable electrostatic effects in solution are nonetheless possible.⁷¹ Alternatively, the polarity versus solubility trade-off can be solved through the use of heterogeneous catalysis, as is the case in enzymes.⁷² An example of how charged-groups can be harnessed to catalyse a Diels–Alder reaction, and alter its regioselectivity and diastereoselectivity, is provided in Figure 4.⁷³

Electrostatic effects almost certainly play a contributing role in many chemical systems, and indeed, one of the earliest experimental demonstrations of electrostatic catalysis was the observation that bond heterolysis reactions were catalysed by ionic aggregates in concentrated LiClO_4 solutions.⁷⁴ Nonetheless, it is only relatively recently that there has been an appreciation that they can be systematically introduced to catalyse and/ or alter chemical processes. One area that is receiving particular attention is gas-phase CH_4 and H_2 activation, where charged ligands such as $[\text{TaO}_2]^+$ have been shown to act as electrostatic catalysts.⁷⁵ Another area is radical chemistry, where it has been shown that a wide-range of distonic radical anions are significantly stabilised by the presence of the negative charge when compared with the corresponding neutral species.^{76,77} These stabilising effects have been harnessed to develop pH-switchable control agents for radical polymerisation,⁷⁸ and are likely to have implications for our understanding of

radical biochemistry. Electrostatic effects also underpin the ability of Lewis acids to catalyse radical addition reactions,^{79–81} and may help to explain the catalytic effects of ionic liquids in many chemical reactions.

[H1] Mechanochemistry

IUPAC defines a mechanochemical reaction as a, “*chemical reaction that is induced by the direct absorption of mechanical energy*”.⁸² Although there has been renewed interest in research exploring the applications of mechanochemistry in synthesis more recently,^{16–22} this field enjoys a rich and storied history. Indeed, the ancient Greeks reported the mechanochemical synthesis of elemental mercury from cinnabar as early as 315 BC.⁸³ While mechanochemical processes have traditionally remained at the margins of ‘mainstream’ synthesis, these transformations offer tremendous potential to augment and extend our capacity to prepare molecules and effect challenging transformations.^{16–22} Indeed, mechanochemical strategies are increasingly being utilised by synthetic chemists to guide reaction development rather than being deployed as an afterthought or last resort.^{18,19} Fundamental understanding of the principles that underpin the mechanisms of mechanochemical processes continues to improve and evolve, which has stemmed from advances in reactor design and in situ reaction monitoring using more sophisticated analytical technologies.¹⁹

This section showcases a selection of interesting recent applications of mechanical force to enable chemical synthesis and generally focuses on examples in which mechanochemical strategies have provided complementary or divergent reactivity relative to more conventional approaches.

[H2] Synthesis of elusive molecules and activation of ‘inert’ molecules

An interesting and particularly valuable feature of mechanochemistry is the capacity to activate molecules that are unreactive under more traditional synthetic approaches or to prepare and/or isolate compounds that are perhaps thought to be inaccessible or too reactive in solution.

[H3] Synthesis of challenging molecules

Prior to 2016, although a number of *N*-alkyl substituted adamantoid P₄N₆-cyclophosphazenes had been synthesised, *N*-*t*-butyl phosphazene **42** remained inaccessible via conventional approaches (Figure 5a).⁸⁴ It had previously been demonstrated that employing forcing conditions and extended reaction times (24 days) could not facilitate the conversion of substrate **41** to target **42**.⁸⁵ On this basis, it was proposed that this sterically encumbered molecule could not be prepared.⁸⁴ However, García and coworkers circumvented this obstacle by simply grinding substrate **41**, in the presence of LiCl (20%), in a ball mill for 90 minutes to facilitate the challenging isodesmic isomerisation.⁸⁶ This inspired, solvent-free mechanochemical approach afforded phosphazene **42** for the first time in quantitative yield and the structure of the product was secured by X-ray crystallography. Interestingly, employing a lower loading of LiCl (10%) gave no reaction under the same conditions, while LiCl (33%) provided only 30% conversion.

[H3] Isolation of reactive molecules

It is well established that the reaction of anilines with bis-benzotriazole **43** in solution leads to aryl isothiocyanate **46** (Figure 5b). It is proposed that this transformation leading to product **46** proceeds via key intermediate **44**.⁸⁷ However, due to the intrinsic reactivity of aryl *N*-thiocarbamoylbenzotriazoles **44** in solution, these particular species could not be isolated by traditional approaches. In contrast, a team led by Štrukil and Friščić isolated and extensively characterised this elusive family of molecules in near quantitative yields after only ten minutes of liquid-assisted grinding.⁸⁸ Following a subsequent milling step, these aryl *N*-thiocarbamoylbenzotriazoles **44** provided simple and efficient access to mixed *N,N'*-diaryl

thioureas **7**. The authors illustrated that although molecules **4** were stable in the solid-state for over a year, they immediately reacted when dissolved in solution.

[H3] Activation of unreactive molecules

Noble metals, represent a class of important elements. The valuable properties associated with their derivatives underpin an array of important industrial processes and have found widespread applications in science, more generally. These metals are defined by their characteristic chemical inertness and resistance to oxidation and corrosion processes. This necessitates that harsh conditions, such as heating at high temperatures, exposure to strong acids/ halogen gases, are typically required to process these elements and convert them into more useful, soluble complexes and valued-added derivatives. These processes, which are often performed on large-scales, are typically not well aligned with the principles of green chemistry.

In 2018, Friščić and coworkers reported a remarkable procedure that utilised ball milling to activate elemental palladium in the presence of inexpensive salts and oxone[®] (Figure 5c).⁸⁹ This particularly elegant and utilitarian oxidative mechanochemical approach, enabled the efficient conversion of these noble metals into more soluble derivatives in a single step under solvent-free conditions at ambient temperature after short milling times. Specifically, (NH₄)₂[PdCl₄] could be prepared from elemental palladium in excellent yield. The authors also demonstrated that analogous bromide and iodide complexes could be prepared in this manner and this strategy could also be applied to activate elemental gold and platinum. Furthermore, the subsequent milling of (NH₄)₂[PdCl₄] in the presence of various ligands allowed for a number of common phosphine-ligated palladium(II) complexes, [Pd(NCMe)₂Cl₂], and palladium(II) acetylacetonate to be readily synthesised. The authors noted that this protocol could also be exploited to recycle up to 89% of palladium from palladium black waste.

[H2] Influence on catalyst efficiency and stereoselectivity by intramolecular mechanical forces

Although the external application of mechanical force is typically utilised to induce chemical reactions, intramolecular mechanical forces can also alter the outcomes of synthetic processes. For example, this principle is relevant when considering the applications of dynamic responsive, so-called “switchable”, molecular systems in synthetic catalysis.^{90,91}

In 2014, a team led by Craig and Boulatov reported a palladium-catalysed asymmetric Mizoroki–Heck coupling by utilising macrocyclic, axially chiral bidentate phosphine ligand **48**, which featured a photoswitchable stilbene (1,1'-biindane) unit (Figure 5d).⁹² It was demonstrated that MeOBiphep (**49**) analogue phosphine *Z*-**48** undergoes a photoinduced isomerisation to afford a photostable state mixture of stereoisomers featuring vastly different dihedral angles (ϕ). Phosphine *Z*-**48** ($\phi = 83^\circ$) represents a compressed analogue of MeOBiphep (equivalent to 130 pN *compressive* force applied to MeOBiphep), while *E*-**48** ($\phi = 106^\circ$) corresponds to a stretched derivative of the latter (equivalent to 140 pN *tensile* force applied to MeOBiphep).

The influence of these ligands on the outcome of palladium-catalysed couplings was then investigated. It was determined that, MeOBiphep provided 23% conversion and high enantioselectivity (90% ee), phosphine *Z*-**48** gave 55% conversion and very high enantioselectivity (96% ee), while ligand *E*-**48** allowed for high conversion (95%) and significantly lower enantioselectivity (79% ee). When ligand *E*-**48** was employed in the presence of 365 nm light, product **51** was efficiently formed in 90% ee. The authors also explored the applications of this photomechanical actuation strategy employing ligand **48** in palladium-catalysed asymmetric Trost allylic alkylations.⁹²

[H2] Mechanochemically promoted electron-transfer processes

In addition to work focusing on the capacity of mechanical force to effect ‘bulk’ synthetic reactions, the properties of this stimulus have also been explored within the context of fundamental single molecule experiments utilising scanning tunnelling and atomic force

microscopy.^{20,93} For example, seminal work disclosed by Fernandez and coworkers employed single-molecule force-clamp spectroscopy to identify the key role that strain plays in the reduction of a disulfide bond with a thiol nucleophile.⁹⁴ This research group also specifically investigated the implications of this type of mechanical activation in biology by studying the reduction of a single disulfide bond within the active site of the enzyme thioredoxin.⁹⁵ However, quantifying the relationship between mechanical force and changes in the redox potentials of individual molecules remains challenging.

In 2017, a team led by Ciampi, Coote, and Tao demonstrated that mechanical strain could facilitate electron-transfer processes leading to changes in the redox states of intact single molecules.⁹⁶ Specifically, their work utilised density functional theory (DFT) studies and single molecule conductance experiments to probe the effects that the mechanical stretching of a metal–ligand bond within a single ferrocene-containing molecule had on this species switching between oxidised and reduced forms (Figure 5e). In this way the authors, unambiguously determined that the distortion of a metal–ligand bond induces changes in the redox potential of the molecule. This observation suggests that the interplay of these variables could be harnessed to modulate molecular conductance and, thus, aid in the development of mechanically controllable dynamic responsive “switchable” systems.⁹⁶

[H1] Synthesis in flow

Synthetic chemistry has been traditionally undertaken in batch and it was not until relatively recently that flow synthesis enjoyed widespread uptake by organic chemists.^{23,24} In batch processes, the mixing of reactants and reagents is typically performed via magnetic stirring, while in flow systems mixing occurs at the location in which these species are allowed to converge. For various reasons, controlling the nature and quality of this mixing can be particularly significant and this is notable advantage that flow chemistry offers. Other virtues of flow, include enabling continuous processing, ease of handling, rapid heating/ cooling, while minimising concerns relating to scalability and safety, and providing opportunities to better align contemporary chemical practices with the principles of green chemistry.^{23,24,97}

This section highlights two interesting recent applications in which aspects of synthesis have been enabled by intrinsic features of continuous flow processes.

[H2] Chemoselective synthesis via microfluidic rapid mixing

Flow processes can offer alternative strategies for directing the outcome of synthetic transformations and overcoming intrinsic reactivity principles and issues associated with particularly unstable intermediates that can complicate traditional batch chemistry.⁹⁸ In this regard, microfluidic reactors offer interesting opportunities.⁹⁹ An impressive and relevant example was reported by a team led by Kim and Yoshida in 2016.¹⁰⁰ These researchers exploited the powerful temporal control afforded by microfluidic devices to facilitate the chemoselective *ortho*-functionalisation of iodophenyl carbamates **53** via a two-stage halogen–lithium exchange/ electrophilic trapping sequence, which delivered products **55** (Figure 6). By employing a rapid mixing strategy, the competing intramolecular anionic Fries rearrangement, which predominates under classical batch conditions at ambient temperature, could be completely suppressed. This reaction was performed in a polymer-based chip microreactor (CMR) that provided sub-millisecond residence times, which enabled the less favourable bimolecular reaction of aryllithium **54** with various electrophiles to occur exclusively. Product **57**, derived from the unimolecular rearrangement of intermediate **54**, was not formed. In comparison, the authors demonstrated that amide **57** could be efficiently prepared when longer residence times (628 ms) were utilised.

ortho-Lithiophenyl esters **54**, which are even more susceptible to anionic Fries rearrangements than carbamates, were also smoothly converted to compounds **55**. In these cases, cryogenic temperatures were required and the CMR device still allowed rapid mixing and high

flow rates despite the significant increase in the viscosity of the solution at these low temperatures. The utility of this work was further reinforced by employing this approach to prepare biologically active amide, afesal (**60**) from iodide **58** and isocyanate **59**. These results suggest that this easily scalable continuous process maybe well-suited to industrial chemical synthesis.¹⁰⁰

[H2] Rapid protein purification and surface tethering in flow enabled by vortex fluidics

Raston and co-workers have developed a vortex fluidics device (VFD) that has enhanced the synthetic utility of dynamic thin films and also allows for continuous flow processes to be incorporated within this reaction manifold.¹⁰¹ Dynamic thin films enable effects including micromixing and shear stress to be investigated and harnessed in synthesis.¹⁰¹ Employing this technology, a team led by Weiss and Raston, revealed that the rapid spatial segregation of enzymes could be achieved in a thin film using a continuous flow VFD and immobilised affinity metal chromatography (IMAC).¹⁰² Specifically, it was demonstrated that six different proteins could be immobilised (in near quantitative attachment yields) and efficiently purified and separated from a cell lysate in ten minutes. The authors could also regulate the concentrations of proteins within each zone to allow different enzymes to feature similar $k_{\text{cat}}/K_{\text{m}}$ values. These aforementioned properties can be employed to facilitate multi-step biocatalysis in flow and, notably, the ability to spatially control enzyme concentrations in these systems offers exciting prospects regarding the development of more sophisticated and complex biocatalytic reactions.

[H1] Conclusion and perspectives

Chemical synthesis will always be necessary and important to enabling science, technology, and progress. But, even if this was not the case, our intrinsic curiosity would ensure that it remains so. As Woodward affirmed with characteristic eloquence and aplomb, “*The unique challenge which chemical synthesis provides for the creative imagination and the skilled hand ensures that it will endure as long as men write books, paint pictures, and fashion things which are beautiful, or practical, or both.*”.¹⁰³ Chemical synthesis continues to evolve. Our capacity to develop, utilise, and control sophisticated processes enabling the cleavage and formation of chemical bonds continues to improve. Within this context, aspects of reactivity and selectivity remain constant and unmistakeable themes.¹⁰⁴

Extending the scope of earth abundant, first row transition metals and the applications of quantum dots in photoredox catalysts are developing areas,^{105–107} and notable cooperative strategies that pair photoredox catalysis with biocatalysis or electrocatalysis are emerging.¹⁰⁸ This is in addition to more established approaches that have elegantly combined photoredox catalysis with transition metal, Lewis and Brønsted acid co-catalysis.^{2–4}

With ongoing advances in technology and instrumentation, the scope, utility, and versatility of direct and indirect electrosynthesis will continue to grow.^{43,63,109–111} The application of electrochemistry in flow and dual catalysis strategies, such as the combination of electroorganic chemistry with established modes of organocatalysis and transition metal catalysis, are notable.^{10–12} Furthermore, interesting opportunities exist in bioelectrochemistry,¹² and exploring asymmetric electroorganic synthesis by employing chiral electrodes for example.¹¹²

While techniques are still developing, the use of static electric fields also shows great promise in chemical synthesis, both in isolation and in conjunction with electrochemical techniques. Such electrostatic effects can also be directly harnessed through charged functional groups, ionic ligands and potentially ionic solvents. Recent work also suggests interesting applications of magnetic fields to chiral resolution.¹¹³

Recently, the development of more sophisticated analytical tools enabling in situ monitoring of mechanochemical reactions and advances in theoretical methods that aid in the elucidation of the physical principles underpinning these processes have emerged.^{18,19} The fields of quantum and single-bond mechanochemistry continue to grow.^{20,93,114} In addition to extending

mechanochemical synthesis, these areas can contribute to improving our understanding of the fundamental mechanisms that are responsible for enzymatic processes.^{20,93}

Advances in flow chemistry continue to progress at a fast pace. This includes the evolution of automated reaction optimisation flow systems,¹¹⁵ more sophisticated miniaturised reactors,^{98,116} and the role of 3D printing in facilitating enhanced design and engineering.¹¹⁷ The increasing benefits associated with machine-assisted flow synthesis and its capacity to expedite and/or augment chemical synthesis will continue to extend the scope and widespread applications of this important area of chemistry in the future.¹¹⁸

Creative applications of light, voltage, mechanical force, or flow will continue to play a role in improving our capacity to access and discover new and unexplored chemical space. However, in order to develop powerful new methods that utilise the innate and distinctive properties of these external stimuli to generate and unlock chemical potential, better communication and greater interaction with people who can contribute complementary knowledge, expertise, and perspective is critical. In this regard, the need for synthetic chemists to better engage with their peers in other areas of chemistry and specialists in adjacent fields, such as biologists, physicists, mathematicians, engineers, and computer scientists and programmers, is particularly important.^{43,119,120}

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[H1] Author contributions

J.C.R. researched data for the article and contributed to writing and preparation of figures. M.L.C. and A.C.B. researched data for the article and contributed to the discussion of content, preparation of figures, writing, and reviewing/ editing the manuscript prior to submission.

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Figure 1 | Synthetic applications of visible-light-mediated photocatalysis. **a** | Asymmetric α -alkylation reaction mediated by a chiral-at-metal iridium photoredox-catalyst²⁵. **b** | Photoinduced, copper-catalysed enantioconvergent C–N couplings of indoles/ carbazoles and racemic 3° alkyl chlorides²⁹. **c** | Organic photoredox-catalysed hydrodehalogenation and arylation reactions employing a “two-photon” strategy³³. **d** | Photoredox-catalysed generation of hydrated electrons³⁷. **e** | Time course experiments monitoring the effects of modulating pulsed blue LED irradiation on the progress on a copper photoredox-catalysed dual α -amino C–H/ C–F functionalisation process²⁹. **f** | Schematic representation of the original multiphase circuit constructed to control LED pulse frequency in the experiments shown in Part **e**⁴¹. Part **e** was adapted from REF. 41 by permission of The Royal Society of Chemistry.

Figure 2 | **Applications of electrochemistry in organic synthesis.** **a** | Accessing vicinal diamines via metal-catalysed electrochemical diazidation of alkenes⁴⁸. **b** | Metal- and reagent-free anodic C–C couplings for the preparation of unsymmetrical biaryl molecules^{52,56}. **c** | Employing stabilised “cation pool” strategies in electrosynthesis^{59,60}.

Figure 3 | New enabling device for electrosynthesis. The IKA Electrasyn 2.0⁴³.

Figure 4 | Applications of static electric fields in organic synthesis. Harnessing the electric fields of acidic or basic groups to catalyse a Diels–Alder reaction and alter regio- and diastereoselectivity^{14,73}. Figure 4: was adapted from REF. 14 and 73 by permission of the *Phys. Chem. Chem. Phys.* Owner Societies and The Royal Society of Chemistry, respectively.

Figure 5 | Applications of mechanochemical force in synthesis. **a** | Synthesis of elusive sterically encumbered phosphazene via ion-assisted grinding⁸⁶. **b** | Mechanochemistry-enabled isolation of reactive *N*-thiocarbamoylbenzotriazoles⁸⁸. **c** | More practical and efficient strategies for activating unreactive noble metals via oxidative mechanochemistry under mild conditions⁸⁹. **d** | Influencing the enantioselectivity of a palladium-catalysed coupling via modulation of ligand geometry via photomechanical actuation⁹². **e** | Electron-transfer processes and conductance switching induced by mechanical stretching⁹⁶. Part **e**: adapted with permission from REF. 96. Copyright 2017 American Chemical Society.

Figure 6 | **Microfluidic-controlled chemoselectivity in synthesis.** Employing microfluidic rapid mixing to outpace Fries rearrangements¹⁰⁰.

[H1] Subject categories

[H1] ToC blurb

This review highlights a selection of conceptual and/ or technological advances that have appeared recently in the areas of photoredox catalysis, organic electrochemistry, electrostatic chemistry and synthesis in static electric fields, mechanochemistry, and synthesis in flow.