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Reductive Dehalogenation towards Olefins Mediated by Phase Transfer Electrocatalysis

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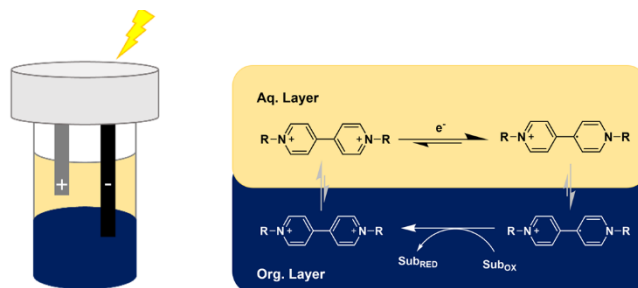
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Received:
 Accepted:
 Published online:
 DOI:

Abstract Mild, biphasic conditions enable dibutylviologen salts to act as both phase-transfer- and electro- catalysts for the electroreduction of vicinal dibromides. Optimized experimental reaction conditions permit the production of the corresponding alkene in competitive yields for a wide range of activated and unactivated substrates, demonstrating good functional group tolerance..

Key words electrocatalysis, electrocatalysis, phase transfer catalysis, viologen.

Organic electrosynthesis, electrocatalysis, and flow electrochemistry are increasingly popular as alternative or complimentary approaches to traditional synthetic redox reagents due to their: (i) selectivity; (ii) use of mild reaction conditions and; (iii) minimal waste generation.² Most importantly, these methods are no longer the domain of specialist electrochemists, due to the availability of commercial 'off the shelf' equipment.^{3–7}

To date, organic electrosynthetic and electrocatalytic approaches have been used for various reactions from conceptually simple electroreduction in the form of a Birch reaction,⁸ to complex transformations such as the electrosynthesis of vicinal diamines.⁹ However, these methods are not without limitation, with unpredictable side reactions and complex product separations often proving problematic. Common strategies to overcome these inherent limitations include the use of complex divided cells to prevent reactive intermediates from interacting, and/or the use of protic additives and sacrificial metal-based electrodes.⁸ However, these approaches introduce additional costs, and/or long-term stability issues.¹⁰

A further limitation to electrosynthesis is electrode fouling, where reaction products or by-products coat the electrodes,

leading to reduced active electrode surface, which changes the cell's electrical properties, leading to inefficient substrate conversion and additional complex side reactions.¹¹ One solution to this problem is mediated electrosynthesis wherein an electrochemically active homogeneous catalyst transfers electrons and/or proton equivalents between the electrode and target molecule, minimising activated substrate interactions with the electrode.^{12,13} However, the separation issue remains and indeed is compounded by both electrolyte and the (typically organic) mediator which require separation from the redox-processed product. This separation issue can be addressed using phase-transfer catalysis which has been extensively explored to utilize water-soluble reagents on hydrophobic substrates in organic synthesis.^{13,14} This approach facilitates the movement of reagents across an interface, aided by a catalyst such as an organic-soluble quaternary ammonium cation. In the context of electrosynthesis, this has been used for various reactions, including shuttling proton-electron reducing equivalents between immiscible phases.^{15,16}

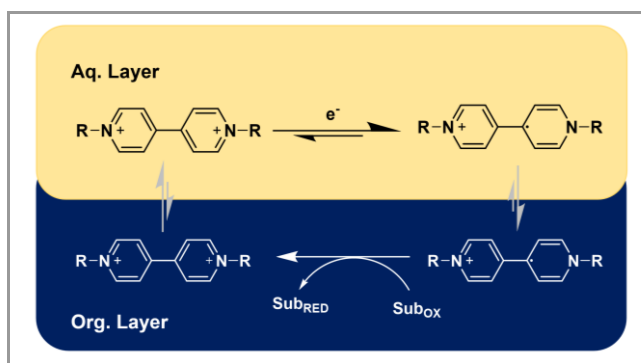


Figure 1 Viologen phase transfer electrocatalysis process.

Herein, we report the use of n-butyl viologen salts as phase-transfer electrocatalysts for the reductive dehalogenation of 1,2-dibromo moieties to produce alkenes, including styrenes.

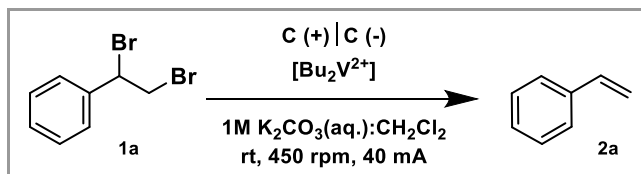
As a dication, alkyl viologens, $[R_2V]^{2+}$ are highly water soluble, but single electron reduction produces the radical cation, $[R_2V]^{\bullet+}$, which has high solubility in organic solvents. We hypothesized that this solubility switching would make viologens ideal candidates for phase transfer reactions. Dibutylviologen, $[Bu_2V]^{2+}$, was selected to validate our hypothesis due to a comparatively high solubility in water, and good chemical stability in mildly basic conditions.

Viologens possess multiple stable oxidation states which, coupled with their synthetically flexible structure to enable high solubility in both organic and aqueous phases, have led to their incorporation in electrochromic devices and their use as negolyte materials in redox flow batteries.^{17–19} These properties also make them ideal candidates to act as electrocatalysts and/or phase transfer catalysis. However, as they predominantly undergo simple outer-sphere electron transfer, their potential for catalysis has generally been considered relatively low.²⁰ Nevertheless, viologen-based reductive redox catalysis has been shown for examples including reductions of nitro compounds,²¹ azo compounds,²² and activated alkyl halides,¹⁷ using various chemical terminal reductants.

Initial experiments performed using N,N'-dibutylviologen iodide $[Bu_2V]I_2$ as both phase-transfer and electrocatalyst, showed successful reduction of (1,2-dibromoethyl)benzene, **1a**, to styrene, **2a**, at 96% conversion in a biphasic DCM/water system, Scheme 1, in an undivided cell in the widely available IKA Electrasyn® platform. (Table 1, Entry 1). A 450 rpm stirring speed was selected to maximise mixing as higher speeds led to "splashing" and breaking up of the interphase.

Cyclic voltammetry studies (see ESI) confirmed that both viologen redox events are observed in both organic and aqueous

conditions, and the consumption of reduced viologen in the presence of substrate. Subsequently, experimental conditions were optimized through the alteration of applied current and reaction time. Given the success of $[Bu_2V]^{2+}$, no other viologen substitution patterns were investigated. It was found that during attempted reductions, reactions with $[Bu_2V]I_2$ rapidly discoloured due to simultaneous oxidation of I^- to I_2 at the anode, rapidly fouling and decreasing the active surface area of the electrode which affected the rate of conversion, Figure S1. Even when electrode polarity was switched every 30 minutes to remove macro-deposits on the electrodes, the electrodes became increasingly ineffective.



Scheme 1 Initial biphasic electrocatalytic dehalogenation (Table 1, Entry 1).

To avoid iodide oxidation as a counter reaction, we tested $[Bu_2V]Br_2$ as an alternative catalyst. The initial conversion was comparable with that of $[Bu_2V]I_2$ (Entry 2) with no evident macro-deposits observed on the electrodes during the reaction process, thus improving the longevity of the electrodes, with oxygen evolution observed instead.

Monitoring the reaction over time showed that the rate of conversion increased as the reaction progressed. We therefore hypothesized that the system required an induction period to develop a sufficient concentration of the radical cation, $[Bu_2V]^{\bullet+}$, previously reported to be the catalytically active form for dehalogenation using chemical terminal reductants.^{21,23,24}

Table 1 Optimization of debromination reaction.^a

Entry	Electrodes			Catalyst	Solvent Ratio (Water: DCM)	Electrolyte	Current (mA)	Induction Time (h)	Reaction Time (h)	Conversion (%)
	Anode	Cathode	Anode Length							
1	Carbon	Carbon	Long	$[Bu_2V]I_2$	10 : 2	1M K_2CO_3	40	0	18	96
2	Carbon	Carbon	Long	$[Bu_2V]Br_2$	10 : 2	1M K_2CO_3	40	0	18	> 99
3	Carbon	Carbon	Long	$[Bu_2V]Br_2$	9 : 3	1M K_2CO_3	40	0	12	57
4	Carbon	Carbon	Long	$[Bu_2V]Br_2$	9 : 3	1M K_2CO_3	40	0	14	50
5	Carbon	Carbon	Long	$[Bu_2V]Br_2$	10 : 2	1M K_2CO_3	40	0	6	73
6	Carbon	Carbon	Long	$[Bu_2V]Br_2$	10 : 2	1M K_2CO_3	40	0	14	86
7 ^b	Carbon	Carbon	Long	$[Bu_2V]Br_2$	10 : 2	1M K_2CO_3	40	4	9 ^e	45
8 ^b	Carbon	Carbon	Long	$[Bu_2V]Br_2$	10 : 2	1M K_2CO_3	40	2	9 ^e	79
9 ^b	Carbon	Carbon	Long	$[Bu_2V]Br_2$	10 : 2	1M K_2CO_3	40	2	7 ^e	97
10 ^c	Carbon	Carbon	Long	$[Bu_2V]Br_2$	10 : 2	1M K_2CO_3	40	2	7 ^e	41
11	Carbon	Carbon	Long	$[Bu_2V]Br_2$	10 : 2	1M KCl	40	2	7 ^e	12
12	Carbon	Carbon	Long	$[Bu_2V]Br_2$	10 : 2	1M NaBr	40	2	7 ^e	0
13	Zinc	Carbon	Long	$[Bu_2V]Br_2$	10 : 2	1M K_2CO_3	30	0	7	16 ^f
14	Zinc	Carbon	Short	$[Bu_2V]Br_2$	10 : 1	1M NaCl	20	0	7	28
15	Zinc	Carbon	Short	$[Bu_2V]Br_2$	5 : 5	1M NaCl	30	0	7	72
16	Zinc	Carbon	Short	$[Bu_2V]Br_2$	5 : 5	1M HCl in NaCl	30	0	7	51
17	Nickel	Carbon	Short	$[Bu_2V]Br_2$	5 : 5	1M NaCl	10	0	7	32
18	Nickel	Carbon	Short	$[Bu_2V]Br_2$	5 : 5	1M K_2CO_3	10	0	7	42
19	Nickel	Carbon	Short	$[Bu_2V]Br_2$	5 : 5	1M K_2CO_3	30	0	7	30
20 ^d	Nickel	Carbon	Short	$[Bu_2V]Br_2$	5 : 5	1M K_2CO_3	10	0	16	> 99

^a Reactions were run at ambient temperature on 1.5 mmol scale using hexamethylbenzene as internal standard, at 450 rpm stirring speed. Percentages represent yield verified through ¹H NMR spectroscopy, with hexamethylbenzene employed internal standard. ^b Cyclohexene was used as Br scavenger. ^c No Br scavenger used. ^d 45 mol% catalyst loading ^e Purged solution of substrate & Br scavenger dissolved in DCM was added after specified induction period (I). ^f Reaction was stopped after 2.5% due to electrode fouling.

Visual monitoring of the system indicated that a two hour induction period, without substrate, gave a dark blue organic layer, consistent with bulk formation of $[\text{Bu}_2\text{V}]^+$, and injection of substrate at this point gave good rate of conversion. (Entries 7–12, Table 1). Monitoring conversion in these reactions revealed a new issue – anodic formation of Br_2 which, if left for an extended period (9 h), appeared to drive the reverse reaction (Entries 7 and 8, Table 1). This competitive counter reaction in part explained the low coulombic efficiencies observed.

Addition of cyclohexene as a competitive Br_2 scavenger was investigated, with reaction monitoring by ^1H NMR spectroscopy clearly showing the formation of 1,2-dibromocyclohexane and increased rate of conversion of the substrate to styrene. After optimization, we identified conditions which resulted in > 97% conversion after 7 h, inclusive of a 2 h induction period (Entry 9, Table 1).

Stoichiometric use of a Br_2 scavenger was found to significantly reduce the atom efficiency, and so alternative avenues for preventing this side reaction were explored. To this end, NaBr was explored as an electrolyte in the hope that NaBr_3 would be retained in the aqueous phase, preventing re-bromination, but this proved unsuccessful (Entry 12, Table 1). Instead, under these conditions significant Br_2 formation was seen upon the anode, and furthermore, visible gas formation at the cathode indicated water reduction as a further unwanted reaction. Use of KCl as the electrolyte (Entry 11, Table 1) gave sluggish conversion, forming only 12% of the product after 7 hours, albeit with no observed back reaction. However, significant H_2 formation was observed, indicating the need for a basic electrolyte.^{11,21,23,24}

As an alternative to an organic Br_2 scavenger, use of Zn sheet as a cheap sacrificial anode to provide an alternative counter reaction was explored.²⁵ Experimentation (Entry 13, Table 1) showed that this was incompatible with K_2CO_3 electrolyte due to deposition of ZnCO_3 at the anode. Use of 1M NaCl electrolyte was also unsuccessful as, despite the solubility of potential $\text{ZnCl}_2/\text{ZnBr}_2$, ZnO formed at the DCM-water interphase, substantially limiting the cycling of the catalyst between the phases (Entry 14, Table 1). Use of a shorter, half-length anode to avoid contact between organic phase and anode on stirring did not remove this problem. The use of a short anode did, however, lead to improved coulombic efficiency despite the formation of the solid deposits. We attribute this to anode intrusion into the organic phase allowing non-productive catalyst reoxidation and thus reduced coulombic efficiency. As such, we opted to retain this structure for future experiments.

Modification of the solvent ratios to reduce the volume of the aqueous phase, and thus increase the effective concentration of $[\text{Bu}_2\text{V}]^{2+}$ to facilitate activated catalyst transfer across the solvent interphase (Entry 15, Table 1) gave significantly improved conversion, indicating phase transfer as a rate limiting concern. Use of acidified NaCl electrolyte (Entry 16, Table 1) removed the issue of solid Zn salt formation at the interface, but conversion was accompanied by polymerisation of styrene which resulted in overall poorer yields.

The use of a sacrificial anode confirmed that control of the counter-reaction could afford high yields under mild conditions. Continuing in this vein, and in the interest of sustainability and

atom efficiency, Ni anodes were explored to exploit oxygen evolution as a counter-reaction^{5,8,26} reducing the required overpotential to make it more favourable than halide oxidation. An initial run in 1M NaCl showed good conversion without any competing Br_2 formation (Entry 17, Table 1), which was further improved using 1M K_2CO_3 (Entry 18, Table 1) to facilitate oxygen evolution. Despite good conversion observed at both 20 mA and 30 mA, Faradaic efficiency was moderate at best. Since catalyst concentration had proven important when considering solvent volumes, the concentration of the catalyst was again increased, and the reaction reached completion without any reverse reaction after 16 hours (Entry 20, Table 1) even at lower current. This high loading could be reduced by reducing the volume of the aqueous phase by using bespoke reaction vessel to maintain submerged electrode surface areas, though this was not investigated at this time.

Using these final conditions, we explored the electrocatalytic reduction of a series of substituted vicinal dibromo compounds;

Table 2 Debromination of substrate scope.

$\text{R}_1\text{CH}(\text{Br})\text{CH}(\text{Br})\text{R}_2 \xrightarrow[\text{1M K}_2\text{CO}_3(\text{aq}), \text{CH}_2\text{Cl}_2, 10 \text{ mA, 16 h, rt}]{\text{Ni (+) C (-) [Bu}_2\text{V}^{2+}]}$				
Entry	Substrate	Product	Conversion (Yield) [%] ^a	
1			100 (65)	
2			99 (85)	
3			100 (85)	
4			87 (31)	
5			99 (55)	
6			94 (31)	
7			92 (65)	
8			99 (75)	
9			85 (^b)	
10			19 (^b)	

Results are the average of 3 repeats. ^a Isolated yield provided in parenthesis. ^b Not isolated.

the results are summarised in Table 2. Simple styrene derivatives (Entries 1–4, Table 2) gave excellent conversion under these conditions, with moderate to excellent isolated yields, while benzylic and aryl halides are unaffected by these conditions. We also evaluated the use of this method on α,β -unsaturated substrates (Entries 6–8, Table 2), which were successfully dehalogenated in good yield. The low isolated yields reported are attributed to unoptimized purification methods, which often saw polymeric byproducts formed. Nevertheless, these are comparable with, or improved from, previously

reported yields.^{27,28} Finally, this method is also applicable to unactivated substrates (**Entries 9-10, Table 2**), giving good conversion for the reduction of **1j**, and even working, albeit poorly for the terminal vicinal dibromide, **1k**, though the volatility of **2j** and **2k** precluded easy isolation. Notably, the yield for compound **2j** is an improvement on that obtained by Endo,²³ using a chemical reductant, and here no catalyst degradation was observed, which we attribute to the milder and more controlled conditions. The nevertheless relatively low yields are attributed to lower reaction rates due the significantly higher energy barrier to forming an unstabilised radical as the rate determining step.

In conclusion, this work shows the untapped potential of biphasic electrocatalysis in adapting reduction chemistry from stoichiometric reductants to electro-reduction giving excellent conversion (>87%) and high purity products using cheap electrolytes and electrodes. This achieves increased yields, with less waste, under milder conditions than using traditional chemical reductants. The use of the IKA Electrasyn® 2.0 platform allowing easy exploration and modification the configuration of the electrochemical cell makes this approach accessible to non-specialists, and the high level of control afforded suggests this approach should be easily turned to other high-value organic substrates. The key limitation to this experimental method is the fixed size and geometry of reaction vessel currently commercially available for an IKA ElectraSyn. To remove this limitation, future work will focus on use of flow systems, as well as targeting other 1,2-di(pseudo)halide substrates.

Funding Information

OPE, JRH, ATM, and ERC would like to thank the University of Kent and the Royal Society of Chemistry for funding E21-0257561176. JRH would also like to thank the UKRI for her Future Leaders Fellowship, (MR/T020415/1).

Acknowledgment

We would like to thank Dr Mitchell R Anstey (Davidson College, USA) for productive conversations about anode materials and behaviours.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

No.

Conflict of Interest

The authors declare no conflict of interest.

References and Notes

- (1) Optimised vic-dibromide reduction conditions: [Bu₂V]²⁺ (0.629 mmol), potassium carbonate (5 mmol), hexamethylbenzene (0.36 mmol), and vic-dibromide (1.63 mmol) were dissolved in water (5 cm³) and dichloromethane (5 cm³). The mixture was stirred under inert environment for 5 minutes. Thereafter, reaction was started using the IKA Electrasyn with the following parameters: 10 mA constant current, 16 hour reaction time,

and 450 rpm stirring. The organic phase was filtered and concentrated under pressure, and the product was purified by flash column chromatography on silica gel.

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