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Electrochemical bromofunctionalization of alkenes in a flow reactor†

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The bromination of organic molecules has been extensively studied to date, yet there is still a demand for safe and sustainable methodologies. Hazardous reagents, selectivity, low atom economy and waste production are the most persisting problems of brominating reagents. The electrochemical oxidation of bromide to bromine is a viable strategy to reduce waste by avoiding chemical oxidants. Furthermore, the *in situ* generation of reactive intermediates minimizes the risk of hazardous reagents. In this work, we investigate the electrochemical generation of bromine from hydrobromic acid in a flow electrochemical reactor. Various alkenes could be converted to their corresponding dibromides, bromohydrines, bromohydrin ethers and cyclized products in good to excellent yields.

Introduction

Despite a long history of bromination reactions, the search for safe and sustainable methods is continuously ongoing.^{1–3} A large number of different methods for the synthesis of bromohydrins have been reported as these are very useful building blocks in chemistry.^{4–8} Bromohydrins have been prepared by reacting alkenes in bromine/water^{9,10} or using *N*-bromo succinimide (NBS)/dimethyl sulfoxide (DMSO) systems.^{11–14} Masuda *et al.* (1994) generated hypohalous acids from the reduction of HBrO_3 and H_5IO_6 with sodium sulfite to synthesize halohydrins.¹⁵ NBS/[bmim] BF_4^- /water was also successfully utilised for this transformation.¹⁶ Bromodichloroisocyanuric acid in acetone/water mixtures is another example of a chemical brominating reagent which has been used in the bromination of alkenes.¹⁷ A particularly resourceful bromohydroxylation of alkenes with hydrobromic acid in DMSO was reported by Song *et al.* (2015).¹⁸ Halofunctionalizations of *gem*-difluoalkenes were demonstrated by Zhao and co-workers (2020).¹⁹

Over the past decade, several electrochemical strategies for the bromination of alkenes using anodically generated bromine have been reported. Early examples include the bromohydroxylation of alkenes which were limited to a small number of substrates.^{20–23} Other examples of electrochemical bromohydroxylation utilize the solvolysis of DMSO.^{24–26} Electrochemical bromoalkylation of alkenes was described

by Nikishin and co-workers (1988).²⁷ Electrochemical dibromination of alkenes and aromatic bromination has been reported by Yuan *et al.* (2019).²⁸ Kulangiappar *et al.* (2016) described the electrochemical dibromination of alkenes under biphasic conditions using $\text{NaBr}/\text{H}_2\text{SO}_4$ /water and alkene/chloroform mixtures.²⁹ Aromatic and benzylic electrochemical bromination reactions were performed with similar biphasic systems.³⁰ Hilt *et al.* (2021) employed paired electrolysis to drive the dibromination from the anodic oxidation of bromide and cathodic reduction of oxygen to hydrogen peroxide and subsequent mediation.³¹ Rueping and co-workers recently published electrochemical alkene oxybrominations for heterocycle synthesis.³²

The potential reduction of waste by electrochemical strategies, in comparison to chemical strategies, is an important driving force to their development. By implementing flow electrochemical methods, the scalability of processes can be facilitated while hazardous reagents such as bromine can be handled in a safe way.^{33–35} Despite the benefits of flow electrochemical methods, their use for electrochemical bromination reactions is still limited. Tan *et al.* reported the electrophilic aromatic bromination of late-stage intermediates and drug molecules in a divided micro-flow electrochemical cell with recirculation of the substrate solution from reservoirs.³⁶ The electrochemical bromination of fluorescein to eosin on a decagram scale was demonstrated by Vasudevan *et al.* (2000) by recirculating the substrate through a flow reactor.³⁷

Herein we describe the electrochemical bromination of activated and unactivated alkenes in a flow reactor under single-pass conditions (Fig. 1). These transformations include dibrominations, bromohydroxylations and bromoalkoxylations.

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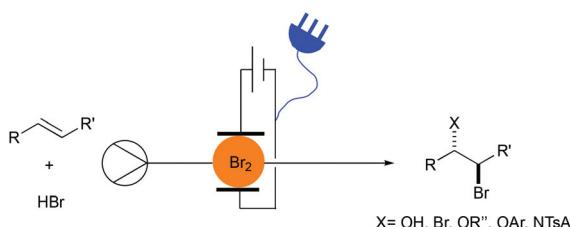


Fig. 1 Difunctionalization of alkenes with electrochemically generated bromine.

Results and discussion

The reaction conditions for the dibromination of alkenes were adapted from a batch electrochemical procedure from Lei and co-workers.²⁸ Flow experiments were carried out using an Ion Electrochemical Reactor from Vapourtec Ltd equipped with a platinum foil cathode and graphite anode.³⁸ The electrodes were separated by a 500 μm FEP spacer to provide a channel resulting in a reactor volume of 600 μL and an exposed surface area of 12 mA cm^{-2} for each electrode. The bromination of styrene (**1a**) was targeted in an effort to develop optimal electrochemical conditions (Table 1). Applying a flow rate of 0.1 mL min^{-1} , an applied current of 48 mA, a styrene concentration of 100 mM and charge of 3.0 F mol^{-1} gave the dibromide **2a** as the main product in 54% yield and the bromohydrin **3a** in 17% yield (Table 1, entry 1). In contrast to the batch experiment,²⁸ no additional water was needed and any

additional supporting electrolyte could be omitted due to the significantly smaller interelectrode gap. An increase in the concentration of HBr from 200 mM to 400 mM and 600 mM led to an increase in **2a** to 74% and 80% yield, respectively (Table 1, entries 2 and 3). Pleasingly, a decrease of the bromohydrin side product could be observed. The concentration of 600 mM of hydrobromic acid was used for the subsequent experiments. Changing the graphite anode material to glassy carbon gave the product **2a** in 73% yield while a platinum foil anode resulted in 79% yield (Table 1, entries 4 and 5). Meanwhile, increasing the applied charge resulted in 92% (3.5 F mol^{-1}), 86% (4 F mol^{-1}) and 80% (4.5 F mol^{-1}) yield (Table 1, entries 6–8). Increased flow rates at 4 F mol^{-1} , and thereby higher charge densities, led to a slight decrease in the yield (Table 1, entries 9 and 10).

By using a platinum coated titanium cathode and a graphite anode, 1,2-dibromo-1-phenylethane (**2a**) could be obtained in an 86% isolated yield under the optimized conditions of 100 mM styrene and 600 mM hydrobromic acid in acetonitrile, a flow rate of 0.4 mL min^{-1} and a charge of 4 F mol^{-1} (applied current: 257 mA) resulting in a productivity of 545 mg h^{-1} (Table 1, entry 11).

In order to demonstrate the scalability of the protocol, the optimized conditions were applied for 9.5 hours to afford 3.93 g of product **2a**, which corresponds to a yield of 65% and a productivity of 413 mg h^{-1} . Alkene and hydrobromic acid were mixed from two separate reservoirs before entering the reactor. When premixing the reaction mixture for a 9 hours experiment, the desired product **2a** was obtained with a significantly reduced yield of 47%. A control experiment confirmed a competing side reaction in the syringe, which led to the formation of 1-phenylethanol in the reservoir upon a prolonged reaction time.

The reaction with allyl benzene gave 64% yield of 1,2-dibromo-3-phenylpropane (**2b**) (Fig. 2). 2-(Pent-4-en-1-yl)isoindoline-1,3-dione was converted to **2c** in 84% yield. The reaction with 1,4-cyclohexadiene afforded the tetrabrominated product (**2d**) in 34% yield while the dibromination product was observed in trace amounts.

Table 1 Optimising reaction conditions for dibromination of styrene **1a**

Entry	HBr [mM]	Charge [F mol^{-1}] (current)	Flow rate [mL min^{-1}]	Yield 2a [%]	Yield 3a [%]
1	200	3 (48 mA)	0.1	54	17
2	400	3 (48 mA)	0.1	74	6
3	600	3 (48 mA)	0.1	80	3
4 ^b	600	3 (48 mA)	0.1	73	17
5 ^c	600	3 (48 mA)	0.1	79	13
6	600	3.5 (56 mA)	0.1	92	4
7	600	4 (64 mA)	0.1	86	3
8	600	4.5 (72 mA)	0.1	80	4
9	600	4 (129 mA)	0.2	78	8
10	600	4 (257 mA)	0.4	79	9
11 ^d	600	4 (257 mA)	0.4	86 ^e	

Reaction conditions: styrene (0.1 M), hydrobromic acid (48% w/w in water); acetonitrile (MeCN); constant current; undivided cell; graphite anode (surface area: 12 cm^2); Pt foil cathode; amount of water (HBr [mM]): 2% (200), 5% (400), 7% (600 mM). ^a Yields are determined by NMR with 1,3,5-trimethoxybenzene as internal standard. ^b Glassy carbon anode. ^c Pt foil anode. ^d Pt coated Ti cathode. ^e Isolated yield, **3a** not isolated.

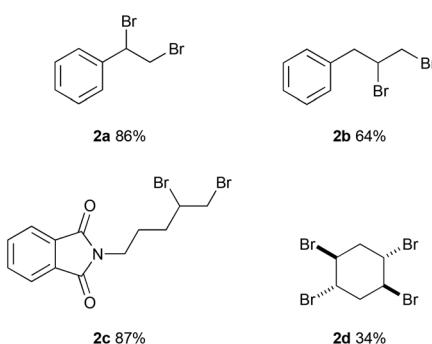


Fig. 2 Electrochemical dibromination of alkenes in flow. Reaction conditions: alkene (0.1 M, 0.7 mmol), hydrobromic acid (48% w/w in water, 0.6 M); MeCN; 0.4 mL min^{-1} , 4 F mol^{-1} (257 mA); constant current; undivided cell; graphite anode (surface area: 12 cm^2); Pt coated Ti cathode.



Following this, the optimization for the electrochemical bromohydrin formation in flow was targeted. The concentration of water, hydrobromic acid and styrene were considered as well as the electrode materials, charge density and flow rate. The initial conditions consisted of 100 mM styrene and 200 mM hydrobromic acid, a flow rate of 0.2 mL min⁻¹ and 3 F mol⁻¹ (97 mA) charge. At a water concentration of 5% in acetonitrile, the selectivity of the reaction could be switched and the bromohydrin was observed in 40% yield, while the dibromide was obtained in 29% yield (Table 2, entry 1). By increasing the water concentration, the formation of the dibromide was further suppressed while the yield of bromohydrin 3a peaked at 79% with a water concentration of 20% (Table 2, entry 2).

In the next optimization step, the influence of the hydrobromic acid concentration was investigated. The lowest concentration of 100 mM suppressed the dibromide formation to trace amounts, but the yield for bromohydrin was significantly decreased to 31% (Table 2, entry 4). The optimal concentration of hydrobromic acid was identified at 180 mM which resulted in a yield of 85% of the bromohydrin and 9% of the dibromide (Table 2, entries 5 and 6).

Next, different electrode materials were tested. Exchanging a graphite anode to materials such as Panasonic carbon (67%), glassy carbon (72%) or platinum foil (2%) had a negative effect on the bromohydrin formation. Also, varying the cathode material did not impact the yield significantly: platinum coated on titanium (85%), nickel (75%), graphite (82%) (see ESI, Table S3†).

Optimization of the applied charge had a positive influence on the yield. For instance, a yield of 86% for the bromohydrin was observed with an increased charge of 4 F mol⁻¹ at a flow rate of 0.2 mL min⁻¹ (Table 2, entry 8). Further increases (5 F mol⁻¹) or decreases (2 F mol⁻¹) of the charge decreased the yield to 68% and 63%, respectively (Table 2, entries 7 and 9).

Table 2 Optimising reaction conditions for the bromohydroxylation of styrene 1a

Entry	H ₂ O added[%]	HBr [mM]	Charge [F mol ⁻¹]	Flow rate [mL min ⁻¹]	Yield 2a ^a [%]	Yield 3a ^a [%]
1	5	200	3 (97 mA)	0.2	29	40
2	20	200	3 (97 mA)	0.2	14	79
3	30	200	3 (97 mA)	0.2	7	81
4	20	100	3 (97 mA)	0.2	1	31
5	20	180	3 (97 mA)	0.2	9	85
6	30	180	3 (97 mA)	0.2	8	85
7	30	180	2 (64 mA)	0.2	9	63
8	30	180	4 (129 mA)	0.2	4	86
9	30	180	5 (161 mA)	0.2	3	68
10	30	180	3 (193 mA)	0.4	7	81
11	30	180	4 (257 mA)	0.4	6	75
12	30	180	3 (290 mA)	0.6	6	72
13	30	180	4 (386 mA)	0.6	6	70

Reaction conditions: styrene (100 mM), hydrobromic acid (48% w/w in water); additional H₂O/MeCN; constant current; undivided cell; Pt foil cathode, graphite anode (surface area: 12 cm²). ^aYields are determined by NMR with 1,3,5-trimethoxybenzene as internal standard.

Increasing the flow rate to 0.4 mL min⁻¹ or 0.6 mL min⁻¹ resulted in decreased yields of 75% and 70%, respectively (Table 2, entries 11 and 13). Interestingly, a simultaneous decrease of current to 3 F mol⁻¹ at 0.4 mL min⁻¹ still afforded 81% of bromohydrin (Table 2, entry 10).

To demonstrate the versatility of the optimised reaction conditions, several aromatic and aliphatic alkenes were converted to the corresponding bromohydriins (Fig. 3). Since doubling the flow rate from the optimal conditions (Table 2, entries 8 and 10) did not significantly drop the yield, both conditions were investigated in an effort to maximize the productivity of the system (conditions A and B). The reaction with styrene and styrene derivatives afforded the bromohydriins 3a-f in good to excellent yields. Due to insolubility, 4-vinylbiphenyl (80 mM) was reacted in a solvent mixture of H₂O/MeCN/THF (3 : 3 : 4). The current and hydrobromic acid concentration were kept at 129 mA and 180 mM and 3g was obtained in a good yield of 65%. The reaction with 2-vinylnaphthalene resulted in 54% yield of 3h. The conversion of methyl cinna-

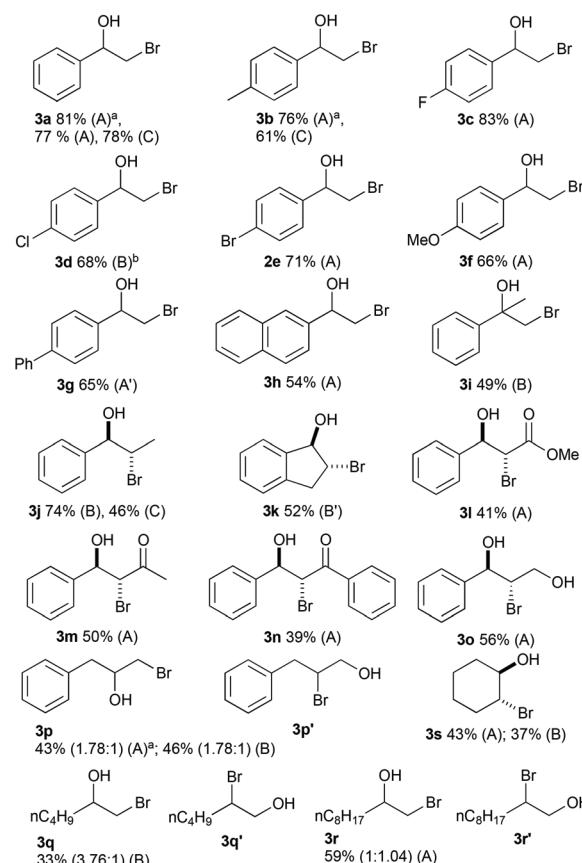


Fig. 3 Substrate scope for the electrochemical bromohydroxylation of alkenes in flow. Reaction conditions: alkene (100 mM, 0.7 mmol), hydrobromic acid (48% w/w in water, 180 mM), additional H₂O/MeCN 3 : 7; method A: 0.2 mL min⁻¹, 4 F mol⁻¹, constant current; Pt plated Nb cathode, graphite anode (surface area: 12 cm²), A': alkene (80 mM) in H₂O/MeCN/THF 3 : 3 : 4; method B: 0.4 mL min⁻¹, 3 F mol⁻¹, constant current 193 mA, Pt foil cathode, graphite anode (surface area: 12 cm²), B': THF instead of MeCN. (a) Pt foil cathode; (b) Pt plated Nb cathode.



mate furnished **3l** in a moderate yield. Two α,β -unsaturated ketones were converted in moderate yields to **3m** and **3n**. The reaction with allylbenzene gave mixtures of regioisomers **3p** and **3p'** (1.78 : 1) in 43% (method A) or 46% (method B) yield. The unactivated alkenes 1-hexene and 1-decene resulted in 33% yield with a 3.76 : 1 ratio of regioisomers (**3q/3q'**) and 59% yield with a 1 : 1.04 ratio of regioisomers (**3r/3r'**). The unsymmetrical internal alkene *trans*-2-hexene did not afford the bromohydrin. The bromohydrin **3s** was obtained in moderate yields from cyclohexene with method A and B. The use of graphite as a cathode material gave **3a** in 78% yield but for **3b** and **3j** yields dropped significantly compared to methods utilizing platinum cathodes.

Alcohols could be used as nucleophiles to trap the bromonium species, and internal nucleophiles would provide cyclized reaction products (Fig. 4). By changing from water to 30% of alcohol in acetonitrile, the bromoalkoxylated products were obtained. The reaction of styrene with 150 mM hydrobromic acid gave the corresponding methoxylated and ethoxylated products **4a** and **4b** in moderate yields at 0.4 mL min^{-1} and 4 F mol^{-1} . Alkenes containing internal nucleophiles were used with conditions adapted from method A. The substrates were electrolyzed in acetonitrile with 180 mM hydrobromic acid at a flow rate of 0.2 mL min^{-1} and charge of 4 F mol^{-1} . 4-Pentenoic acid was converted with a water concentration of 5% in acetonitrile to the corresponding lactone **4c** in 74% yield. The reaction of 2-vinyl benzoic acid with 30% water in

acetonitrile proceeded with a yield of 57% (0.4 mL min^{-1} , 3 F mol^{-1}) to afford an inseparable mixture of regioisomers. The 5-membered ring was obtained as the major isomer **4d** and the 6-membered ring as the minor one **4d'** in a ratio of 9 : 1. The reaction with *N*-(2-allylphenyl)-4-methylbenzenesulfonamide led to cyclization as well as subsequent bromination of the aromatic ring. The cyclized product **4e** was afforded in 22% yield. Cyclization and bromination of the aromatic ring gave product **4e'** in 21% yield. The electrochemical bromination of 2-allyl-6-methylphenol led to the bromination of the aromatic ring and the formation of 5- and 6-membered rings with the phenolic oxygen acting as nucleophile. The resulting complex mixture of products did not allow a conclusion about the selectivity of the reaction from the crude NMR spectrum. A mixture of regioisomers **4f** and **4f'** could be isolated in a ratio of 2.33 : 1 in 22% yield. Due to the challenging purification process, a conclusion on the regioselectivity of the reaction cannot be drawn.

Conclusions

In this work we provide a flow set-up to conduct various electrochemical brominations of alkenes by using hydrobromic acid as bromine source. The outcome of the reaction was easily controlled by switching the cosolvent. Bromohydrins, dibromides and vicinal bromo ethers were electrochemically synthesized in flow with moderate to excellent yields. The use of chemical oxidants, which are commonly used in bromination reactions, is completely avoided leading to a substantial reduction of waste. The flow set-up facilitated a safe handling of the intermediary generated bromine. The described methods have the potential of facile up-scaling. Furthermore, internal nucleophiles such as carboxylic acids, *N*-tosylaniline and phenol led to cyclized products.

Conflicts of interest

There are no conflicts to declare.

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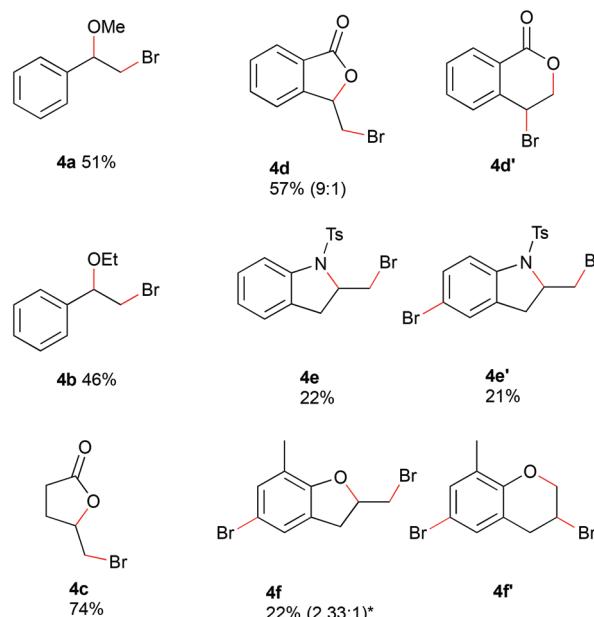


Fig. 4 Electrochemical bromoalkoxylation and cyclisation of alkenes in flow. Reaction conditions (alkoxylation): alkene (100 mM, 0.7 mmol), hydrobromic acid (48% w/w in water, 150 mM), 30% alcohol in acetonitrile; 0.4 mL min^{-1} , 4 F mol^{-1} , constant current 257 mA; Pt foil cathode, graphite anode (surface area: 12 cm^2); reaction conditions (cyclisation): alkene (100 mM), HBr (180 mM), $\text{H}_2\text{O}/\text{MeCN}$, 0.2 mL min^{-1} , 4 F mol^{-1} , constant current 129 mA. **4c** & **4f/f'**: 0% H_2O ; **5d/d'**: 30% H_2O , 0.4 mL min^{-1} , 3 F mol^{-1} ; **4e/e'**: 5% H_2O .



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