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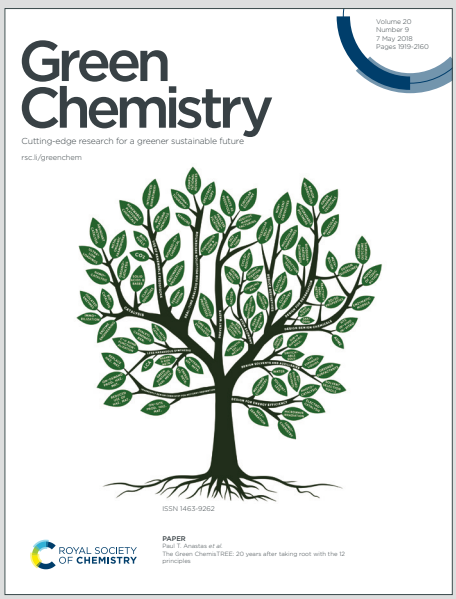

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ARTICLE

Enantiospecific on-water bromination: a mild and efficient protocol for the preparation of alkyl bromides†

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Herein we report the first example of an on-water enantiospecific synthesis of alkyl bromides. This procedure allowed the conversion of secondary activated alkyl sulphides to benzylic alkyl bromides, which were obtained in 80-99% yields. The reaction carried out on enantio-pure sulphides provided the corresponding bromides in high yields and enantioselectivity (up to 92% ee; 94% es) at room temperature. The on-water condition reduced significantly the reaction times compared to similar procedures run in organic medias. The condition identified made use of no solvent, required no temperature control and produced a smooth organic phase easily separated for further synthetic use on a multigram-scale without the need for any organic extraction. Therefore, the present constitutes the most operationally simple and environmentally benign approach to a class of much sought organic intermediates.

Introduction

Compounds bearing the C–Br moiety are of great synthetic value as they easily form carbon–carbon or carbon–heteroatom bonds and they are ubiquitous in natural bioactive compounds.[1–3] Given the vast number of alkyl bromides used in the manufacture of active pharmaceutical ingredients (API) and fine chemicals, the literature presents many procedures to insert bromine into organic molecules, with the Appel reaction being the most commonly applied procedure.[4] However, the Appel procedure often give rises to unwanted side products especially when carried out on compounds prone to elimination;[5] in addition, the atom efficiency of the Appel is heavily impaired by the stochiometric production of phosphine oxides, difficult to separate from the desired products.[6] Although catalytic Appel has been developed to improve the atom efficiency,[6–8] challenges remain such as: (i) requirement of multiple reagents, (ii) adoption of strictly anhydrous conditions, (iii) limited functional group tolerance.[5,9]

We have recently reported a new protocol that provides alkyl bromides in high yield and enantiospecificity.[10] This new reaction that we named *desulphurative bromination* converted phenyl alkyl sulphides to bromides using reagents as simple as molecular bromine. Mechanistic studies showed that key to the observed reactivity was the formation of a di-bromo sulphurane which via an equilibrium with its corresponding sulphonium bromide provided the final product through a bromide-lead S_N2 reaction. This procedure required strictly anhydrous conditions and to be operated at -40 °C to ensure high enantiospecificity.

In an attempt to study a range of electrophilic brominating reagents, we have noted that the reaction of (*S*)-**1** (Table 1) was significantly accelerated when run in the presence of water. The bromination of compound (*S*)-**1** using *N*-bromosuccinamide (NBS) required 60 hours to achieve 80% conversion when run in dichloromethane (0.2M). However, the same reaction run neat and in the presence of water reached full conversion in just 2 hours. It should be noted that reaction of organic products in the presence of water could take place in two different modalities, namely *in-water* or *on-water*.[11] In the in-water processes, water is the actual solvent and the reaction happens in the water bulk.[11] On the other hand, the term on-water is used to label the chemical transformations where the transition state occurs at the organic side of the organic–water interface. This term was first introduced by Sharpless, Fokin and co-workers upon observation of the acceleration that water provided to Lewis acid catalysed reactions.[12] When compared to the respective reaction in organic solution, the on-water effect is capable of accelerate a reaction rate up to 200-fold.[13] In addition, setting-up a reaction as on-water presents other returns such as efficiency, safety and cost-reduction. Despite the technical advantage and cost-efficiency associated with the concept of reactions on-water, the number of reports on enantioselective on-water syntheses is limited to those reported by Mukherjee.[14] Brominations in a water environment (both *in* and *on*) includes bromination of alkenes via Br_2/H_2O in which the water is also a reagent required to add the hydroxy-group. Further examples includes transformations at an sp^2 carbon, such as Katta's catalyst-free bromination on (hetero)aromatics[15] and Li's oxidative bromination of aryls.[16] The bromination at sp^3 carbon is limited to the report of Iskra[17] on the reactivity of H_2O_2–HBr system versus NBS in electrophilic and radical reactions. Hence, the development of on-water reactions that provides enantio-enriched material is still in its infancy.

We now like to report an improved set of conditions for the desulphurative bromination that proceeded (i) at room temperature

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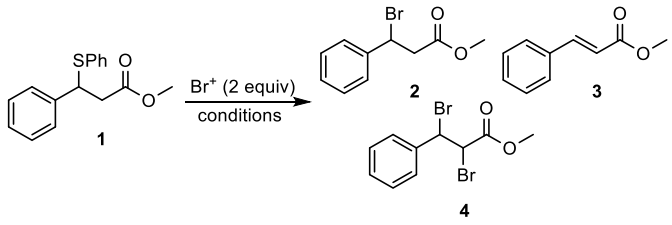
(ii) without solvent, i.e. on-water, and (iii) in significantly shorter reaction times. This procedure avoids using large quantities of chlorinated solvents; therefore, this protocol qualifies as the first and green enantioselective methodology to access title compounds.

Results and discussion

With the aim of assessing the efficiency of reagents other than Br_2 in the desulphurative bromination, we have screened a number of commercially available electrophilic brominating reagents, under reaction conditions previously identified.[10] Therefore, racemic **1** was selected as the standard substrate and its conversion to bromide **2** recorded (Table 1). Aim of this study was the selection of the reagent that ensured the highest yield of desired **2** in the shortest reaction time. For this reason, a sample was collected at 15 min, 30 min and 120 min and the yield of compounds **2**, alkene **3** and di-brominated **4** was obtained via ^{1}H NMR analysis. Throughout this study we identified a number of potential brominating reagents with (Table 1, entry 1a) dibromoisocyanuric acid (DBI) being effectively comparable to molecular bromine (Table 1, entries 8a, 8b and 8c) and superior to other *N*-brominating reagents in terms of reaction times and yields of **2**. Reaction of **1** and DBI provided desired **2** in comparable yields even when the reaction times were prolonged up to 120 minutes (Table 1, entries 1a, 1b and 1c). This can be explained with the low basicity of the debrominated heterocycle arising from reaction of DBI. Dibromantin (DBDMH) provided compound **2** (Table 1, entry 5a, 5b and 5c) in a slightly decreased, although comparable, yield and selectivity *vs* **3** and **4** than DBI and Br_2. The observed erosion of yield might be associated with the longer reaction times required to achieve full conversion, during which a small portion of **2** was degraded to **3** and consecutively to **4**. Other brominating reagents, such as NBS, *N*-bromophthalimide (NBP), 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO), $PyrBr_3$ and trimethylphenylammonium tribromide ($TMPAB_3$) gave compound **2** in low yields and in long reaction times. Therefore, this study identified in DBI the best alternative reagent to molecular bromine, which may provide some technical advantage in large scale reactions on the consideration of being a non-volatile solid.

Table 1 Brominating agent selection via ^{1}H NMR analysis [a]. NBP = N-Bromophthalimide, $TMPAB_3$ = Trimethylphenylammonium tribromide.



Entry	Oxidant	Time	Conversion [b]	**2** : **3** : **4** [b]
1a	DBI (1.0 equiv)	15 min	100% (91%) [c]	97 : 1 : 2
2a	NBS (2.0 equiv)	15 min	0%	0 : 0 : 0
3a	NBP (2.0 equiv)	15 min	0%	0 : 0 : 0
4a	TBCO (1.0 equiv)	15 min	12%	10 : 2 : 0
5a	DBDMH (1.0 equiv)	15 min	33%	28 : 5 : 0
6a	$PyrBr_3$ (1.0 equiv)	15 min	4%	4 : 0 : 0
7a	$TMPABr_3$ (1.0 equiv)	15 min	1%	1 : 0 : 0
8a	Br_2 (1.0 equiv)	15 min	100%	98 : 1 : 1
1b	DBI (1.0 equiv)	30 min	100%	97 : 0 : 3
2b	NBS (2.0 equiv)	30 min	0%	0 : 0 : 0
3b	NBP (2.0 equiv)	30 min	0%	0 : 0 : 0
4b	TBCO (1.0 equiv)	30 min	17%	15 : 2 : 0
5b	DBDMH (1.0 equiv)	30 min	80%	75 : 3 : 2
6b	$PyrBr_3$ (1.0 equiv)	30 min	20%	19 : 1 : 0
7b	$TMPABr_3$ (1.0 equiv)	30 min	3%	3 : 0 : 0
8b	Br_2 (1.0 equiv)	30 min	100%	98 : 0 : 2
1c	DBI (1.0 equiv)	120 min	100%	97 : 0 : 3
2c	NBS (2.0 equiv)	120 min	5%	4 : 1 : 0
3c	NBP (2.0 equiv)	120 min	1%	1 : 0 : 0
4c	TBCO (1.0 equiv)	120 min	20%	18 : 2 : 0
5c	DBDMH (1.0 equiv)	120 min	98%	95 : 0 : 5
6c	$PyrBr_3$ (1.0 equiv)	120 min	42%	41 : 1 : 0
7c	$TMPABr_3$ (1.0 equiv)	120 min	4%	4 : 0 : 0
8c	Br_2 (1.0 equiv)	120 min	100%	98 : 0 : 2

[a] Conditions: **1** (0.20 mmol), oxidant, CH_2Cl_2 (0.2 M), rt. [b] Conversion and relative ratios of products **2**, **3**, **4** were obtained by evaporation of the reaction mixture, dilution with $CDCl_3$ and ^{1}H NMR analysis. [c] isolated yield of **2** after column chromatography on silica gel (PE : EtOAc = 98 : 2).

The reaction of **1** and DBI was briefly studied by: (*i*) increasing DBI equivalents, (*ii*) change of temperature and (*iii*) variation of concentration (Table 2). This study showed that DBI should be limited to 1.0 equivalent to prevent formation of undesired dibromide **4** (Table 2, entry 2). On the other hand, when only 0.5 equivalents of DBI were employed, the reaction proceeded to 80% conversion in 10 minutes but then stopped (Table 2, entry 3). Temperatures over rt promoted elimination (Table, entry 5), meanwhile no significant effect was observed upon carrying out the conversion of **1** to **2** at 0 °C (Table 2, entry 4). This is remarkable as desulphurative bromination conducted with Br_2 showed a notable dependence of the reaction time on temperature within the same temperature ranges.[10]

In conclusion, this study confirmed that bromination of compound **1** to desired **2** is best achieved using 1.0 equivalent of DBI in methylene chloride at rt (Table 2, entry 1).

A significant breakthrough was obtained when the reaction of **1** and DBI was studied in a variety of media (Table 3). The use of solvents containing Lewis bases, such as acetone, MeCN and THF (Table 3, entry 1-3), provided a complex mixture (CM) of products, which could not be analysed. The reaction carried out in DMF provided a substantial amount of desired **2** accompanied by a significant proportion of elimination product **3** (Table 3, entry 4). The use of toluene (Table 3, entry 5) provided **2** in only 10% yield after 10 min. The reaction carried

Table 2 Initial optimization: changes of major conditions [a].

Entry	Oxidant equiv	Conc	Temp	Conversion [c]	**2** : **3** : **4** [c]
1	1.0	0.2M	rt	100%	96 : 2 : 2
2	2.0	0.2M	rt	100%	95 : 0 : 5
3	0.5	0.2M	rt	80%	76 : 4 : 0
4	1.0	0.2M	0 °C	100%	96 : 2 : 2
5	1.0	0.2M	50 °C [b]	100%	88 : 0 : 12
6	1.0	0.1M	rt	95%	86 : 4 : 5

[a] Conditions: **1** (0.20 mmol), DBI, CH_2Cl_2, 10 min. [b] Reaction performed in DCE. [c] Conversion and relative ratios of products **2**, **3**, **4** were obtained by evaporation of the reaction mixture, dilution with $CDCl_3$ and ^{1}H NMR analysis.

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Table 3 Secondary optimization: solvent effect [a].

Entry	Oxidant	Solvent	Temp	Conversion [b]	**2** : **3** : **4** [b]
1	DBI (1.0 equiv)	Acetone	RT	100%	complex mixture
2	DBI (1.0 equiv)	MeCN	RT	100%	complex mixture
3	DBI (1.0 equiv)	THF	RT	100%	complex mixture
4	DBI (1.0 equiv)	DMF	RT	89%	48 : 41 : 0
5	DBI (1.0 equiv)	Toluene	RT	10%	10 : 2 : 0
6	DBI (1.0 equiv)	H_2O	RT	100%	100 : 0 : 0

[a] Conditions: **1** (0.20 mmol), DBI (0.20 mmol), solvent (0.2 M), 10 min, rt. [b] Conversion and relative ratios of products **2**, **3**, **4** were obtained by evaporation of the reaction mixture, dilution with $CDCl_3$ and ^1H NMR analysis.

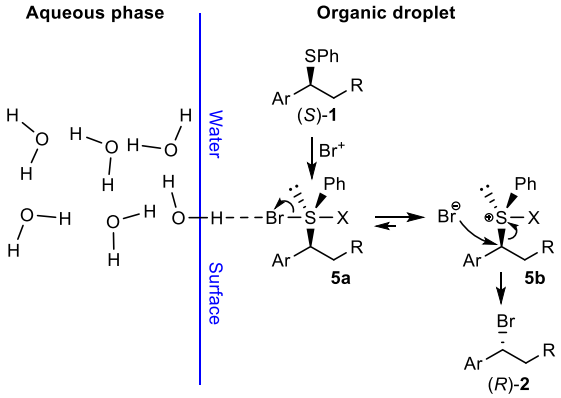
out in water provided full conversion of **1**, quantitative yield of desired **2** uncontaminated by side products (Table 3, entry 6) as evidenced in the crude ^1H NMR. Noteworthy, the reaction rates were comparable to the ones obtained in methylene chloride (Table 2, entry 1). It was noted that neither substrate **1** nor DBI were soluble in water: addition of substrate **1** to water produced a two-phase system in which solid **1** was in suspension. Treatment of biphasic water-**1** with DBI gave rise to an orange oil with concomitant disappearance of solid **1**. This observation, in conjunction with the acceleration previously noted, led to the assignment of the observed transformation as an on-water process. Water is the cheapest and greenest solvent to be used in organic transformations and, with this in mind, we underwent a subsequent round of screening of brominating reagents (Table 4).

As illustrated above, the number of enantioselective and enantiospecific transformations that occur on-water is still limited.[14] Therefore, we found intriguing that a transformation involving water sensitive intermediates and reacting via an S_N2 mechanism, hence potentially enantiospecific, could equally take place in the presence of large quantities of H_2O nucleophile as it happens under on-water conditions. With this in mind, we have reacted enantiopure (*S*)-**1** with a selection of brominating reagents. Delightfully, these experiments demonstrated that compound (*R*)-**2** could be obtained with significant enantioenrichment (Table 4), showing an S_N2 mechanism operative under the on-water conditions. The experiments were conducted as follows: 1.0 equiv of (*S*)-**1** (98% ee) were premixed with 2 mL of water in a vial; an oxidant, as specified (Table 4), was then loaded and the resulting biphasic system was stirred vigorously. The progression of the reaction could be followed by visual observation, considering that a colour change from an initial orange to final colourless could be observed upon consumption of the brominating reagent. The organic phase was then extracted with 0.4 mL of $CDCl_3$ and the crude analysed via ^1H NMR. In order to demonstrate that the reaction occurred before extraction, we repeated the on-water reaction of (*S*)-**1** and DBI using d_8-toluene as the extracting solvent, which we showed before being an un-ideal solvent for this transformation (Table 3, entry 5). This experiment provided identical results showing therefore that the transformation of (*S*)-**1** to (*R*)-**2** occurred prior to work-up. It was also verified that extraction could be avoided and crude (*S*)-**1** obtained by evaporation of water. (*S*)-**1** was obtained pure enough to be reacted in a following step when obtained from a larger scale experiment, however for small scale characterisation chromatography was used. All the reaction of (*S*)-**1** and the oxidants employed occurred in an on-water modality. With the exception of TBCO and NBP (Table 4, entries 3 and 4) all the others experiment provided a full conversion of (*S*)-**1**, with DBI, DBDMH and Br_2 providing the shortest reaction times (Table 4, entries 1, 5 and 6). Reaction of (*S*)-**1** and DBI, NBS, DBDMH and Br_2 gave desired (*R*)-**2** in enantiopurity comprised between 63% and 67% ee. In all of these experiments it was observed that addition of the oxidant to a suspension of solid (*S*)-**1** in water generated an orange oil. Hence, the formation of two different non-miscible phases was evident, which is in line with the description of on-water processes as reported by Butler and Coyne.[18] The reaction of NBS or DBI and (*S*)-**1** performed in the absence of water, *i.e.* neat, did not form a biphasic system, but a semisolid aggregate that could not be stirred. In analogy with other reported on-water reactions, [18] it is plausible that in this example water plays the role as the polar media favouring the formation of a biphasic system and also alters the equilibrium between sulphurane **5a** and sulphonium **5b** (Scheme 1), therefore acting as a Lewis acid. Hence, the acceleration observed for the desulphurative bromination could be explained considering that a larger proportion of sulphonium **5b** is formed in the presence of water. We noted that the stirring rate had an effect on the reaction time, which can be explained considering the larger surface contact achieved between the organics and the water at vigorous stirring (*i.e.* 1500 rpm: maximum rotation of the magnetic stirrer). This latter observation supports the role of water as the Lewis acid and the

Table 4 Brominating agent selection in water environment [a].

Entry	Oxidant	Ox equiv	Time	Conv [b]	ee of **2** [c]	er of **2**
1	DBI	1.0	10 min	100%	63	82 : 18
2	NBS	2.0	120 min	100%	67	84 : 16
3	NBP	2.0	360 min	80%	46	73 : 27
4	TBCO	1.0	240 min	2%	NA	NA
5	DBDMH	1.0	15 min	100%	64	82 : 18
6	Br_2	1.0	15 min	100%	67	84 : 16

[a] Conditions: (S)-**1** (0.20 mmol), oxidant, 2 mL water, rt. [b] Conversion was obtained by evaporation of the reaction mixture, dilution with $CDCl_3$ and ^1H NMR analysis. [c] Desired **2** was isolated by column chromatography on silica gel (PE : EtOAc = 98 : 2) and ees were determined by HPLC analysis on chiral stationary phase.



Scheme 1 proposed role of water in the acceleration of desulfurative bromination.

acceleration observed on-water (Scheme 1). The absence of side-products arising from elimination is a secondary yet important effect provided by the aqueous environment, that diluted the bases originating from the de-bromination of reagents. It also should be mentioned that no alcohol arising from substitution at C–S or C–Br bonds could be detected, proving unambiguously that the reaction took place at the interface between the two phases, *i.e.* on-water.

This new procedure performed at lower levels of enantiospecificity when compared with the one previously reported by us run in 0.2 M methylene chloride solution.[10] In order to address the origin of the drop of enantiospecificity, *i.e.* S_N2 *vs* S_N1, we ran the reaction of (*S*)-**1** and Br_2 at different concentrations (Table 5). This study showed a significant effect of the concentration on the enantiomeric excess of (*R*)-**2**. When the desulphurative bromination was performed neat without any water environment compound **2** was obtained in 54% ee (Table 5, entry 1). It should be highlighted that the addition of Br_2 to pure (*S*)-**1** generated a dense oily orange phase that could be stirred. Dilution of the organic phase with increasing amounts of methylene chloride restored the high ees to the same levels as seen in previous studies (Table 5, entries 2, 3 and 4). The results of the neat experiment and the one carried out at 10M gave comparable yields, ees and reaction times. However, Br_2 the reaction of (*S*)-**1** and Br_2 at 1 M, gave (*R*)-**2** in 84% ee. This set of experiments pointed out at the concentration as the most important variable to achieve high ees. Hence, we demonstrated that the erosion of ees was entirely depending upon the concentration of reactants, rather than the effect a polar aqueous ambient may have on the S_N2 *vs* S_N1 competitive mechanisms.

The organic phase dispersed in the water layer appeared non-homogeneous and dense, consequently the stirring of the reaction was unideal. In order to ease the formation of a smooth oily phase and increase the area of interface we therefore tried to add an organic thinner. We have selected NBS, Br_2 and DBI as the oxidants and studied the reaction in the presence of 1.0 equiv of methylene chloride, chlorobenzene, dibutyl ether or ethyl acetate (Table 6, entry 4-11). The reaction carried out using Br_2 and PhCl provided the best results in terms of reaction rates, which we have linked to the formation of larger quantities of smaller droplets of organics in the reaction, leading to a visibly improved area of interface (Figure 1). The use of PhCl over DCM produced a marginal yet measurable increase in the ee of compound **2** (Table 6, entries 4 and 6). The use of less hazardous thinners, such as dibutyl ether (Table 6, entry 7) and ethyl acetate (Table 6, entry 8), is a feasible greener alternative to chlorobenzene, granting similar yields but a slight lower enantiomeric excess which went from 72% ee (er 86:14) to 64% ee (er 82:18). Reduction of the temperature from rt to 0 °C (Table 6, entry 10) and then to -20 °C (Table 6, entry 11) had no effect on the reaction ees, but increased the reaction times required to achieve full conversion.

We have noted that although effective the use of 2.0 equiv of NBS formed a gummy phase instead of a smooth oil, even with the aid of a thinner. This may be un-ideal in an industrial scale-up and may impose the aid of an organic extraction. On the other hand, combination of DBI or Br_2 and a thinner produced a smooth organic phase easily separated for further purification on a gram-scale setup

Table 5 Effect of concentration on reaction times and ees of desulfurative bromination [a].

Entry	Solvent	Conc	Time	Conv [b]	ee of **2** [c]	er of **2**
1	Neat	NA	10 min	100%	54	77 : 23
2	DCM	10 M	10 min	100%	60	80 : 20
3	DCM	1 M	25 min	100%	84	92 : 8
4	DCM	0.2 M	25 min	100%	82	91 : 9

[a] Conditions: (S)-**1** (0.20 mmol), Br_2 (0.2 mmol), rt, inert atmosphere. [b] Conversion was obtained by evaporation of the reaction mixture, dilution with $CDCl_3$ and ^1H NMR analysis. [c] Desired **2** was isolated by column chromatography on silica gel (PE : EtOAc = 98 : 2) and ees were determined by HPLC analysis on chiral stationary phase.

Table 6 On-water reaction optimization [a].

Entry	Ox	Ox equiv	Thinner	Temp	Time	ee of **2** [d]	er of **2**
1	NBS	2.0	Neat	rt	2 hrs	67	84 : 16
2	Br_2	1.0	Neat	rt	10 min	67	84 : 16
3	DBI	1.0	Neat	rt	10 min	63	82 : 19
4	Br_2	1.0	DCM [b]	rt	15 min	67	84 : 16
5	DBI	1.0	PhCl [b]	rt	15 min	65	83 : 17
6	Br_2	1.0	PhCl [b]	rt	15 min	72	86 : 14
7	Br_2	1.0	Bu_2O [b]	rt	15 min	64	82 : 18
8	Br_2	1.0	EtOAc [b]	rt	15 min	62	81 : 19
9	NBS	2.0	PhCl [b]	rt	2 hrs	71	86 : 14
10	Br_2	1.0	PhCl [b]	0 °C	6 hrs	73	87 : 13
11	Br_2	1.0	PhCl [b]	-20 °C [c]	18 hrs	73	87 : 13

[a] Conditions: (S)-**1** (0.20 mmol), oxidant, 2 mL water. [b] 1.0 equiv of thinner added to (S)-**1**. [c] Reaction performed in 2 mL satd. aqueous NaBr instead of water. [d] Desired **2** was isolated by column chromatography on silica gel (PE : EtOAc = 98 : 2) and ees were determined by HPLC analysis on chiral stationary phase.

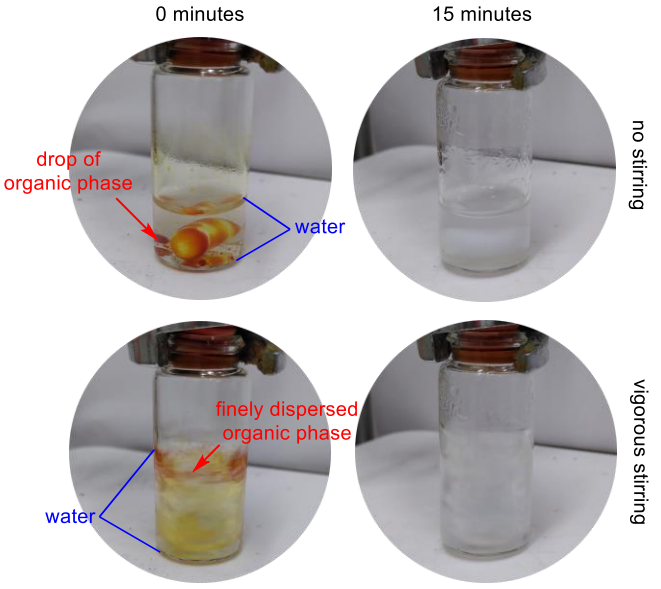
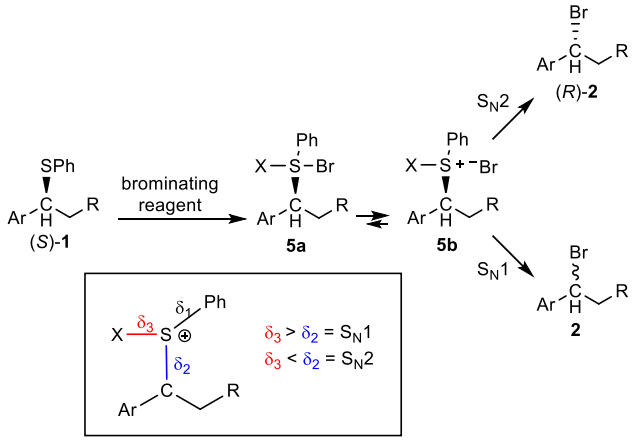


Figure 1 Picture of the on-water reaction of (*S*)-**1** and Br_2 in the presence of a thinner (Table 6, entry 6). At 0 rpm denser drops of organic phase deposited at the bottom of the vial. At maximum rotation of the magnetic stirrer (1500 rpm) the drops were finely dispersed in the aqueous phase, greatly increasing the surface of interaction. After 15 minutes the organic phase appeared colourless marking the complete consumption of Br_2.

without the need for any organic extraction. However, Br_2 was deemed as superior to DBI based upon the density of the organic droplet formed. In addition, Br_2 produced compound **2** in a slight



Scheme 2 Proposed mechanistic pathways: S_N1 against S_N2 and the rationale that favours one or the other.

increased ees and with a considerably purer crude of reaction (see ESI). In conclusion, this study identified in Br_2 and 1.0 equiv of PhCl as the best set of conditions to run the desulphurative bromination on-water (Table 6, entry 6; Figure 1).

Analysis of the mechanistic pathways arising from sulphurane 5a

Considering our previously published data[10] and the additional information collected into this work (Table 7), a mechanistic analysis can be proposed that explains the variation of the enantioselectivity with the electronic properties of the substrates (Scheme 2). Initial reaction between sulphide (*S*)-**1** and the oxidating agent (*i.e.* Br_2, DBI, NBS or NBP) generated a sulphurane of structure **5a**. It is established that sulphuranes and sulphoniums are in equilibrium,[19] therefore species **5a** can evolve to sulphonium **5b** which further reaction is irreversible. Species **5b** can undergo two possible reactive pathways, namely S_N1 or S_N2. The factors directing the evolution of **5b** towards (*R*)-**2** (S_N2 pathway) or racemic-**2** (S_N1 pathway) could be influenced by the relative bond polarities of X–S (δ_3) and S–C_{sp3} (δ_2) bonds. The driving force behind evolution of **5b** towards their product lays in the inclination of sulphur to gain back its neutrality. Therefore, when X–S is considerably more polarized towards X compared to the polarization of S–C_{sp3} ($\delta_3 > \delta_2$) intermediate **5b** will break preferentially giving rise to an S_N1 pathway. On the contrary, when S–C_{sp3} is considerably more polarized towards C_{sp3} compared to the polarization of X–S ($\delta_3 < \delta_2$) then intermediate **5b** would be sufficiently stable to undertake an S_N2 pathway. Based upon the reasoning outlined above, it would be expected that when the polarity of the S–C_{sp3} bond is shifted toward C_{sp3} via introduction of electron-withdrawing moieties, the enantioselectivity of the bromination would be enhanced, as an S_N2 mechanism of reaction is favoured.

Scope of reaction

Table 7 Scope of the on-water desulfurative bromination.

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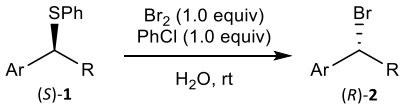

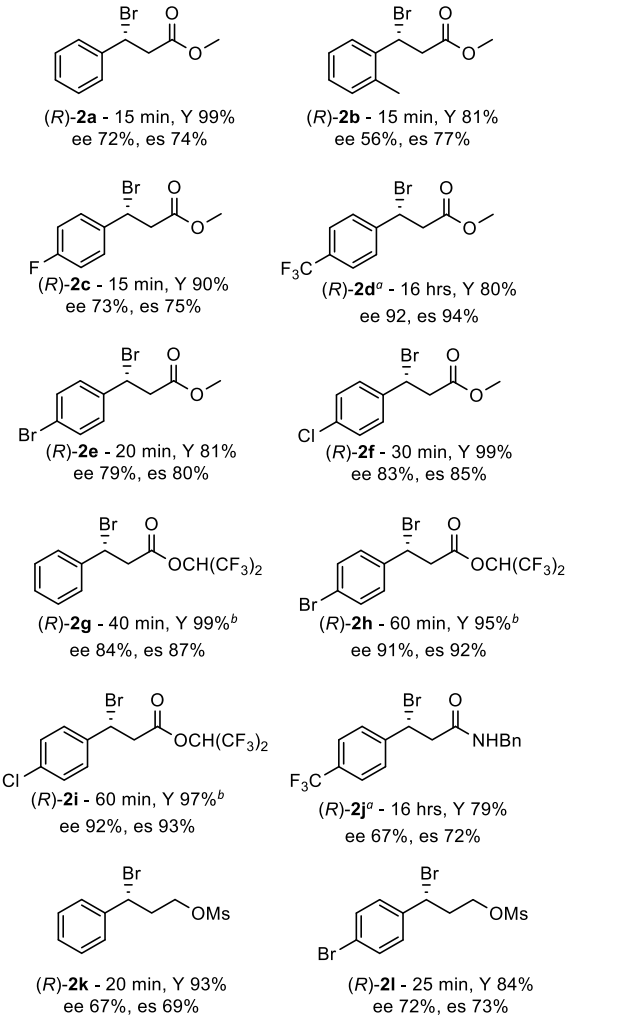

[a] 2.0 equiv of Br_2 used. [b] Product isolated as an inseparable mixture with 5-14% alkene. Ee's were determined by HPLC analysis on chiral stationary phase.

The scope of reaction was planned on secondary benzylic phenyl sulphides bearing both electron-donating and electron-withdrawing groups on the aromatic portion. The rationale of selecting this motif laid in the availability of compounds **1** in enantiopure form from the addition of thiophenol to cinnamates.[20] In addition, the effect of various functional groups such as esters, amides and mesylates on the reaction enantiospecificity was also explored. The optimized conditions involved reacting a suitable sulphide (*S*)-**1a-l** and Br_2 in water with 1.0 equiv of PhCl at rt. This reaction provided corresponding (*R*)-**2a-i** in high yields and in up to 94% es. The introduction of electron-donating group, such as *o*-CH_3 on the phenyl had no detrimental effect: compound (*R*)-**2b** was obtained in a similar 77% es in spite of the presence of a sterically encumbering group on the *ortho* position. As might be expected, the presence of

p-F on the aromatic ring in (*R*)-**2c** resulted in a similar ee as when no substituents are present, in line with the observation proposed by Schuster.[21] The introduction of electron-withdrawing groups on the aromatic ring produced a sharp increase in the observed enantiospecificity. Hence, compound (*R*)-**2d** bearing a *p*-CF_3 was obtained in 94% es, meanwhile less strong EW substituents such as Br or Cl yielded (*R*)-**2e** and (*R*)-**2f** in 80% es and 85% es respectively. It was noted that to obtain (*R*)-**2d** the reaction required additional amounts of oxidant due to an operative electrophilic bromination of the thiophenyl group as previously observed by us.[10] We reported that the reaction between (*S*)-**1d** and Br_2 in dichloromethane provided an intermediate that was visible in the ^{1}H NMR and that was assigned to be a sulphide Br_2 adduct, precursor to sulphurane **5a**.[10] Conversely, when the reaction between (*S*)-**1d** and Br_2 was carried out as on-water mode, no intermediate could be detected via ^{1}H NMR analysis of the reaction mixture. The fast decay of adduct, sulphurane and sulphonium species under the on-water condition could be explained again by the Lewis acid catalysis provided by water, which favour **5b** over **5a** (Schemes 1 and 2). The introduction of electron-withdrawing groups on the ester produced a sharp increase in the enantiospecificity. For example, compound (*R*)-**2a**, bearing a methyl ester, was obtained in 74% es, meanwhile (*R*)-**2g**, bearing a *bis*-trifluoromethyl ester, was formed in significantly higher 87% es. This trend was proven to be general and compounds (*R*)-**2h** and (*R*)-**2i** were similarly obtained in 92% es and 93% es respectively. Less electron-withdrawing substrates provided lower level of enantiospecificity such as (*R*)-**2j**, (*R*)-**2k** and (*R*)-**2l** which were obtained in *ca* 70% es. It was therefore proven that pivotal to the obtainment of high enantiospecificity is the introduction of a distal electron-withdrawing group which was a success. However, it should be considered that meanwhile compound (*R*)-**2g**-**i** were stable both in solution and as isolates, their chromatographic purification was accompanied by limited amounts of products of decomposition, *i.e.* the alkene. One last consideration involves a discussion on the stability of mesylates present in products (*R*)-**2k** and (*R*)-**2l** under the on-water conditions which did not provide compounds of substitution.

Recycling of residual waters and large scale reaction

To further define the green impact of our on-water bromination, we run a test to verify if the residual water, contaminated by HBr, could be used in following bromination cycles. Hence, **1a** was reacted with 1.0 equiv of Br_2, crude **2a** extracted with Et_2O, and analysed via ^{1}H NMR to determine conversion of **1a** and yield of **2a**. The residual water was used for a subsequent cycle by adding fresh **1a** and Br_2. However feasible, we noted that the recycling of water containing incremental amounts of HBr negatively impacted on the reaction rate, effectively requiring greater amounts of Br_2 to achieve full conversion (see ESI). The decrease of the reaction rate is most probably caused by the extraction of Br_2 from the organic phase into the aqueous phase due to the formation of Br_3^-, which could be avoided by electrolytic removal of bromide from water layer and regeneration of 0.5 equivalents of Br_2 reagent.[22]

We have also demonstrated that the conversion of (*S*)-**1a** to (*R*)-**2a** could be run at 3-gram scale (10 mmol) with small detriment of yields and no loss of enantiospecificity. In this regard, the boiling point of PhCl provided the additional advantage of simplifying the isolation of (*R*)-**2a**. Indeed, upon completion of the reaction the water layer was selectively eliminated by vacuum-evaporation, leaving behind an organic phase that was thinned by the high boiling (132 °C) PhCl residue. The lower viscosity of crude (*R*)-**2a** allowed an easier collection and purification without the need of liquid-liquid extraction. This is very relevant bearing in mind scaling-up this reaction further. In summary, this method, employed 1 equiv of thinner rather than the 100-150 mL of solvent typically required for an extraction, that is standard to purify 10 mmol of organics.

Conclusions

Herein we have described a highly enantiospecific green on-water methodology for the preparation of highly enantioenriched (up to 92% ee) alkyl bromides. The reaction is mechanistically remarkable and synthetically useful many folds. Firstly, its unobvious that S_N2 reactions of highly reactive intermediates, such as sulphoniums, may still be preferred over S_N1 pathways at rt and in the presence of large excess of water. Secondly, no other reaction of sulphoniums with nucleophiles different from bromides was observed which is surprising considering the amount of water being present and the strength of nucleophiles being generated when DBI, NBS and similar *N*-based brominating reagents are used. Thirdly, it was established a strict relationship between the presence of substituents capable of strong -*I* effects and the extent of a stereo conservative mechanism of reaction. Fourthly, water has been identified as a good enough Lewis acid to perturb the equilibrium existing between sulphuranes and sulphoniums providing a steep acceleration to desulphurative bromination. In addition, this protocol provides a synthetically useful method of preparation of alkyl bromides that does not require low temperatures, controlled atmosphere and solvents. The E-factor for the procedure carried out in a DCM solution[10] was 34.6; meanwhile, the E-factor for this new on-water protocol is 1.5, hence this latter is significantly greener. Hence, this method is effectively green, expands the range of brominating reagents that could be employed, is simple to execute and constitutes one of the very few reports of enantioselective synthesis that is carried out on-water. We believe this report to be of interest to whoever is concerned with the preparation of enantiopure alkyl bromides and their use for the preparation of fine chemicals and APIs at scale.[23]

Conflicts of interest

There are no conflicts to declare.

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