

Electrophilic Bromination of Alkenes: Environmental, Health and Safety Aspects of New Alternative Methods

Marco Eissen*^[a] and Dieter Lenoir*^[b]

Abstract: More than twenty new alternative methods for bromination of alkenes have been evaluated taking into consideration their resource demands, waste production as well as environmental, health and safety aspects. The cost of bromine and the substances designated to circumvent the application of molecular bromine have also been taken into account. As bromine is only one of several problematic substances being used, its avoidance—by applying bromine supported on solid material or by performing the in situ generation of bromine—does not significantly reduce the technological requirements. On the contrary, the resource demands and amount of waste produced by most new methods are significantly higher compared to the standard methods, especially if the recycling of a carrying agent is not efficient. The method using hydrobromic acid and hydrogen peroxide can be regarded as a competitive alternative to the standard method. The application of certain carrying agents could be interesting, because solvents such as carbon tetrachloride or chloroform used during synthesis could be replaced with less problematic ones during work-up. However, problems associated with these alternatives are not resolved as yet.

Keywords: bromination • mass balances • oxidation • oxone • waste prevention

Introduction

Bromination of organic molecules is an important task in synthetic organic chemistry. Bromine can be added to alkenes and alkynes to yield vicinal dibromides. Alkynes and

prochiral alkenes are most often stereospecifically converted to *trans* adducts an important class of synthons.^[1] The relevant mechanisms of electrophilic additions have been studied intensively over the last two decades.^[2–4] Rather than adding bromine to multiple bonds, bromine reacts with aromatic systems by substitution.^[5] The importance of bromination reactions becomes evident by analysis of the large number of examples found in the Beilstein Database.^[6] Today there are reported to be about 1980 different 1,2-dibromoalkanes prepared from various alkenes and 270 1,2-dibromoalkenes prepared from alkynes. Previously, bromination has been primarily performed by using molecular bromine as reagent, mainly in chlorinated solvents. During the last ten years, several new bromination methods have been developed, which circumvent molecular bromine as reagent, mostly to avoid its hazardous potential. However, in the alternative protocols other problematic substances are often used. In addition, resource demands often seem to be significantly higher than in the traditional procedure.

Resource efficient syntheses and production processes of fine chemicals contribute significantly to sustainable development.^[7,8] This has also been pointed out in Agenda 21 of the United Nations plan for sustainable development: “Promote efficient use of materials and resources, taking into account the life cycles of products, to realise the economic and environmental benefits of using resources more efficiently and producing fewer wastes” (Agenda 21, Chapter 9.18).^[9]

We will compare different bromination methods to show and evaluate promising new approaches, and we will point out where improvements are necessary. Prior to a qualitative discussion of health and safety aspects, the different synthesis protocols are presented by using metrics regarding raw material demand and waste production. Besides yield and atom economy,^[10,11] mass balances are established to integrate solvents, catalytic systems and auxiliary materials for chemical reactions. The preparation of such mass balances can become very tedious. The Environmental Assessment Tool for Organic Syntheses (EATOS)^[12] is convenient software for mass balancing substrates, solvents, auxiliary materials, catalysts, etc. The following two parameters will be evaluated [Eqs. (1) and (2)]:

$$\text{Mass index } S^{-1} = \sum \frac{\text{raw materials [kg]}}{\text{product [kg]}} \quad (1)$$

$$\text{Environmental factor}^{[13]} E = \sum \frac{\text{waste [kg]}}{\text{product [kg]}} \quad (2)$$

[a] Dr. M. Eissen
Gymnasium Ganderkesee
Am Steinacker 12, 27777 Ganderkesee (Germany)
Fax: (+49) 4222-808868
E-mail: marco.eissen@web.de

[b] Prof. Dr. D. Lenoir
Helmholtz Zentrum München
Institut für Ökologische Chemie
Postfach 1129, 85758 Neuherberg (Germany)
Fax: (+49) 8931-873371
E-mail: lenoir@helmholtz-muenchen.de

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200800462>.

Regarding mass balances, the standard bromination method, the method using pyridinium perbromide, and the method that uses the oxidation of HBr with H_2O_2 have already been compared in literature.^[14] We have extended this approach with more detailed information. We also consider costs of bromine and of the substances that are designated to circumvent its application.

Results

The standard method for the generation of vicinal dibromides is the conversion of unsaturated compounds with molecular bromine (Method I). The use of supported bromine as an easy to handle carrying agent (summarised as Method II) is considered an appropriate measure to circumvent the hazardous potential of neat bromine. A third approach (Method III) is the generation of bromine in situ by using bromide compounds and oxidants. An overview of considered methods is schematically shown in Figure 1. These

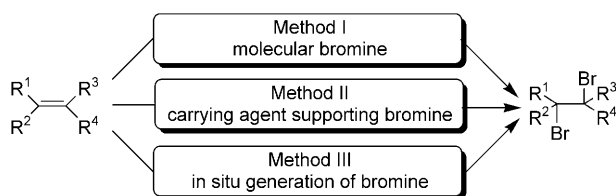


Figure 1. Considered methods for electrophilic bromination of alkenes.

methods are summarised in Table 1. Ideally, the comparison of different bromination methods should be based on the same alkene. The protocols chosen for this evaluation go through different alkenes, which are shown in Figure 2. The differences in reactivity and behaviour of these alkenes are not significant.

The standard method for bromination of an alkene is carried out in solvent; the alkene is dissolved in chloroform then bromine is added^[15,16] (entry 1, Table 1). Other protocols can be found in the literature.^[17–19] In special cases, bromination can be performed in boiling water as solvent, for example, in the bromination of fumaric acid^[15,18] (entry 2, Table 1). The synthesis in entry 3 makes use of a two-phase reaction of bromination with perfluorohexane as the second solvent.^[20] Bromination can also be performed in ionic liquids (entry 4, Table 1).^[21]

Employing carrying agents as a transport medium for bromine reduces the hazardous potential of molecular bromine, examples include; sol–gel-entrapped pyridinium hydrobromide perbromide (PHPB@s.g., entry 5, Table 1),^[22] poly(vinylpyrrolidone) (PVP, entry 6^[23]),^[23,24] pyridine hydrobromide (entries 7 and 8),^[25,26] pentylpyridinium bromide (entry 9),^[27] 1,2-dipyridiniumdibromide-ethane (entry 10),^[28] *N*-octylquinolinium bromide (entry 11),^[29] and tetrameric DABCO (TM)-bromine (DABCO = 1,4-diazabicyclo-

[2.2.2]octane, entry 12).^[30] The workshop script^[25] refers to the original procedure by Djerassi.^[31] Another protocol that uses polymer supported bromine was reported in 1996 by A. Kessat and A. Babadjamian.^[32]

The use of hydrogen bromide and bromide salts in the presence of oxidizing reagents liberates bromine in situ (Table 1). Oxidants used are sodium perborate (entry 13, Table 1),^[33] lead tetraacetate (entry 14),^[34] cerium(IV)ammonium nitrate (CAN, entry 15),^[35] sodium periodate (entry 16),^[36] Selectfluor[®] (entry 17),^[37] diacetoxyiodo benzene (DIB, entry 18)^[38] and hydrogen peroxide (entry 19).^[39] The latter was used to convert hydrobromic acid (entry 20),^[40,41] which can also be oxidised by using Oxone[®] ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$, entry 21).^[42] Oxone[®] is applied directly during the synthesis to convert the alkene into the dibromide (entry 21,^[42] entry 22^[43]), but also to regenerate the reagent, which is a carrying agent (entry 10b),^[29] an *N*-halo compound (entry 23),^[44,45] or another *N*-halo compound, *N*-bromosuccinimide (NBS, entry 24).^[46]

Overviews of applications of the oxidants sodium perborate,^[50–52] CAN,^[53–56] Selectfluor[®],^[57,58] and other *N*-halo reagents,^[59] sodium periodate,^[60] DIB as a polyvalent iodine compound^[61–64] and Oxone[®]^[65,66] can be found in the litera-

Marco Eissen received his PhD in organic chemistry in 2001 from the University of Oldenburg, Germany, under the direction of Prof. Jürgen O. Metzger. He was a post-doctoral fellow at the Swiss Federal Institute of Technology Zürich, Switzerland, under the direction of Prof. Konrad Hungerbühler and at the Saarland University with Prof. Elmar Heinzle, Germany. In 2003 Marco Eissen began teaching chemistry and mathematics in Göttingen and, since 2005, in Ganderkesee, Germany. The development of assessment methodologies in early stages of synthesis design is the main focus of his work. Since 2008 Marco Eissen cooperates with IFU Hamburg, Germany, which is a software company developing solutions in the fields of material flow management, life cycle assessment and environmental management.



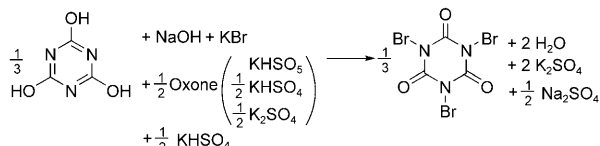
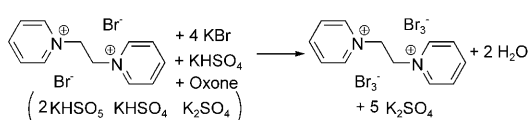
Dieter Lenoir graduated at Bonn University in 1967 and received there his PhD in 1969. After a postdoctoral stay at Princeton University with Paul Schleyer he moved to the Technical University of München for his habilitation in 1976. Afterwards he was appointed as group leader at Helmholtz Centre Muenchen associated with a professorship at the University of Bayreuth. He has published 192 papers on topics of Organic and Environmental Chemistry besides 48 contributions as books and book chapters. His main research topics are related to carbocations, chemistry of strained alkenes and stilbenes, halogenated micropollutants like polychlorinated dibenzodioxines and -furans, and sustainable oxidation reactions. Several times he has been a visiting professor at American Universities like Carnegie Mellon University in Pittsburgh and the University of Georgia.



Table 1. Bromination methods considered in Figure 1: Entries 1–4 (Method I, neat bromine), Entries 5–12 (Method II, carrying agent), and Entries 13–24 (Method III, in situ generation of bromine).^[47]

No.	Stoichiometric equation	Ref.	No.	Stoichiometric equation	Ref.
1	$2 + \text{Br}_2 \longrightarrow 10$	[15]	12	$1 + \frac{1}{4} \frac{[(\text{H}_2\text{DABCO})_2 (\text{HDABCO})_2 (\text{Br})_2(\text{Br}_3)_4]}{(\text{Br})_2(\text{Br}_3)_4} \longrightarrow 9 + \text{N} \begin{array}{c} \text{Br}^- \\ \\ \text{N}^+-\text{H} \end{array} + \frac{1}{2} \text{HBr}$	[30] ^[b]
2	$6 + \text{Br}_2 \longrightarrow 14$	[15]	13	$1 + 2 \text{NaBr} + \frac{1}{2} \text{Na}_2[\text{B}_2(\text{O}_2)_2(\text{OH})_4] \longrightarrow 9 + \text{Na}_3\text{BO}_3 + \text{H}_2\text{O}$	[33] ^[c]
3	$2 + \text{Br}_2 \longrightarrow 10$	[20]	14	$1 + \text{ZnBr}_2 + \text{Pb}(\text{CH}_3\text{COO})_4 \longrightarrow 9 + \text{Zn}(\text{CH}_3\text{COO})_2 + \text{Pb}(\text{CH}_3\text{COO})_2$	[34]
4	$3 + \text{Br}_2 \longrightarrow 11$	[21]	15	$2 + 2 \text{KBr} + 2 (\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6 \longrightarrow 10 + 2 \text{Ce}(\text{NO}_3)_3 + 4 \text{NH}_4\text{NO}_3 + 2 \text{KNO}_3$	[35] ^[d,e]
5	$1 + \text{Br}_2 \text{ (on sol-gel)} \longrightarrow 9$	[22] ^[b]	16	$2 + 2 \text{LiBr} + \frac{1}{4} \text{NaIO}_4 + 2 \text{CH}_3\text{COOH} \longrightarrow 10 + \frac{1}{4} \text{NaI} + \text{H}_2\text{O} + 2 \text{LiCH}_3\text{COO}$	[36]
6	$1 + \text{Br}_2 \text{ (on PVP)} \longrightarrow 9$	[23] ^[a]	17	$4 + 2 \text{KBr} + \text{F}^- \begin{array}{c} \text{N}^+ \\ \\ \text{N}^+ \end{array} \begin{array}{c} \text{Cl} \\ \\ \text{Cl} \end{array} \longrightarrow 12 + \text{KF} + \text{KBF}_4 + \begin{array}{c} \text{N}^+ \\ \\ \text{N}^+ \end{array} \text{BF}_4^-$	[37]
7	$3 + \text{C}_6\text{H}_5\text{NH}^+ \text{Br}_3^- \longrightarrow 11 + \text{C}_6\text{H}_5\text{NH}^+ \text{Br}^-$	[25]	18	$5 + 2 \text{LiBr} + \text{C}_6\text{H}_5\text{I} \longrightarrow 13 + 2 \text{LiCH}_3\text{COO} + \text{C}_6\text{H}_5\text{I}$	[38]
8		[26]	19	$2 + 2 \text{NaBr} + \text{H}_2\text{O}_2 + \text{H}_2\text{SO}_4 \longrightarrow 10 + 2 \text{H}_2\text{O} + \text{Na}_2\text{SO}_4$	[39]
9a	$1 + \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^- \longrightarrow 9 + \text{C}_6\text{H}_5\text{N}^+ \text{Br}^-$	[27]	20	$4 + 2 \text{HBr} + \text{H}_2\text{O}_2 \longrightarrow 12 + 2 \text{H}_2\text{O}$	[40]
9b	$\text{C}_6\text{H}_5\text{N}^+ \text{Br}^- + \text{Br}_2 \longrightarrow \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^-$	[27]	21	$8 + 2 \text{H}^+ + 2 \text{Br}^- + \frac{1}{2} \text{Oxone} \longrightarrow 16 + \text{H}_2\text{O} + \frac{3}{2} \text{KHSO}_4 + \frac{1}{2} \text{K}_2\text{SO}_4$	[42] ^[b]
10a	$2 + \frac{1}{2} \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^- \longrightarrow 10 + \frac{1}{2} \text{C}_6\text{H}_5\text{N}^+ \text{Br}^-$	[28]	22	$1 + 2 \text{NaBr} + \text{Oxone} \longrightarrow 9 + \text{H}_2\text{O} + 2 \text{K}_2\text{SO}_4$	[43] ^[f]
10b	$\text{C}_6\text{H}_5\text{N}^+ \text{Br}^- + \frac{4}{3} \text{Oxone} \longrightarrow \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^- + 2 \text{H}_2\text{O}$	[28] ^[h]	23a	$2 + \text{NaBr} + \frac{1}{3} \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^- \longrightarrow 10 + \frac{1}{3} \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^-$	[44]
11a	$7 + \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^- \longrightarrow 15 + \text{C}_6\text{H}_5\text{N}^+ \text{Br}^-$	[29]	23b	$\frac{1}{3} \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^- + \text{NaOH} + \text{KBr} \longrightarrow \frac{1}{3} \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^- + 2 \text{H}_2\text{O} + \text{NaHSO}_5 + 3 \text{K}_2\text{SO}_4$	[45]
11b	$\text{C}_6\text{H}_5\text{N}^+ \text{Br}^- + \text{Br}_2 \longrightarrow \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^-$	[29]	24	$1 + \text{LiBr} + \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^- \longrightarrow 9 + \text{C}_6\text{H}_5\text{N}^+ \text{Br}_3^- + \text{Li}^+$	[46]

[a] poly(vinylpyrrolidone)-bromine complex. [b] Sol-gel, pyridinium hydrobromide perbromide (PHPB@s.g.). [c] Na_2BO_3 is assumed to be the coupled product if sodium perborate is used as the oxidizing agent. [d] $[(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6]$, cerium(IV) ammonium nitrate (CAN). [e] Personal communication with V. Nair enabled us to conjecture that the inorganic by-products of the reaction are cerium(III) nitrate, ammonium nitrate and potassium nitrate. Although this has not been verified experimentally the stoichiometry is plausible. [f] Cyclohexene (2 mmol), sodium bromide (6 mmol), Oxone[®] (4 mmol), water (1 mL), and carbon tetrachloride (5 mL). Personal communication with R. Karl Dieter allowed us to identify that no triethyl amine was used in this reaction, contrary to the table published in Ref. [43]. [g] K. M. Kim does not agree with the stoichiometry noted here. In a personal communication he suggests an alternative to applying an equimolar amount of Oxone[®]. He prefers the following: but-2-en-1,4-diol + 2 HBr + 1-Oxone[®] \rightarrow 2,3-dibromobutan-1,4-diol. The reason for us to deviate from this reaction equation is that the preparation of a mass balance requires a correct stoichiometry in which the number of input-atoms has to equal the number of output-atoms. [h] Discussions with B. K. Patel lead us to hypothesise that this is plausible if an additional H^+ source is used, such as extra KHSO_4 . A stoichiometry is conceivable that uses potassium hydrogen peroxysulphate more efficiently (left scheme below).^[48] Regarding the stoichiometry in entry 23b, we suggest that extra KHSO_4 would result in a more efficient application of Oxone[®] (right below) similar to entry 10b.



[j] In ref. [30] one sixth of the 1,4-diazabicyclo[2.2.2]octane (DABCO) was used in relation to the alkene (1 mmol). However, considering the molecular formula we see that, stoichiometrically, one quarter of the amount of DABCO is necessary for the equation. We would like to suggest that a hydrogen source is missing in the protocol of the DABCO synthesis.^[49]

ture. Special protocols such as enantioselective bromination reactions,^[67] the application of a CuBr₂/LiBr-system^[68] or

special polymer supports^[32] have not been considered here. The alkenes considered in this paper are listed in Figure 2.

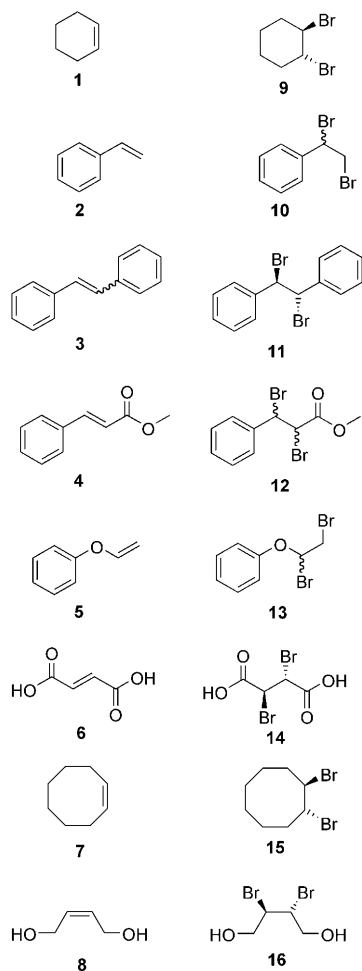


Figure 2. Alkenes used for bromination in this study (1–8) and their trans adducts (9–16).

In general, work-up procedures and methodologies (Table S2 in the Supporting Information), such as washing with brine, drying over sodium sulphate and chromatography were not considered for various reasons, including that details of these standard laboratory procedures are generally not fully described in the literature considered. Furthermore, the work-up procedures can be very similar for a number of syntheses, therefore this part of each protocol is assumed to be alike. Lastly, work-up methodologies in the laboratory will be different to those used in potential industrial processes and, therefore, not particularly comparable.

Mass Balances

By using the software EATOS, mass balances were calculated for all syntheses, see Figure 3. The mass balances show a huge disparity in resource demand and waste generation and give a rough overview of which syntheses are most resource intensive. The higher a column the larger the amount of raw material used and waste produced.

First, we will look at the protocols applying molecular bromine. The amounts of substrate used in the Method I syntheses are very similar (Figure 4) and there was no substrate excess of bromine. Waste production for each of the protocols aggregates to about 4.1 kg of waste per kg of product except for protocol entry 4, 37 kg kg⁻¹ (for details, see Table S3 in the Supporting Information). In contrast, the approaches that use a carrying agent have a much higher resource demand (Figure 4). Even if 95 % of the carrying agent is assumed to be recyclable, and this is the reason to use such reagents, a large amount of solvent is necessary for reaction (Solvents) and extraction purposes (Auxiliaries (isolation)). Since the “Recycling” segment of column entries 5 and 6 in Figure 4 is very small and not identifiable, we refer to the details given in Table S3 in the Supporting Information. Interestingly, the dimension of solvent utilization is similar in two references (Figure 4 and Table 2, entries 5 and 6). Apparently, there is a need for a large quantity of solvent in these systems. The segment “Substrates” demonstrates the necessity to apply bromine in excess for these reactions (Figure 4b).

The carrying materials of entries 5 to 12 (Method II) are potentially recyclable. The quantities are shown in Table 2 and the extent of their disposal depends on the recyclability, the costs of which (Table 2) will diminish correspondingly.

In contrast to the procedures of methods I and II, the generation of bromine in situ is strictly linked to a high production volume of coupled products (Figure 5). When hydrobromic acid reacts with hydrogen peroxide (see entry 20, Table 2) the lowest amount of coupled product, water (about 0.15 kg kg⁻¹) is produced. All other syntheses give salts such as sodium borate, zinc acetate, lead diacetate, or lithium acetate in amounts up to 4.45 kg kg⁻¹. For entry 18 D. C. Braddock et al. suggest that there is the possibility of a recycling system for iodobenzene (0.72 kg kg⁻¹). Regarding the coupled product formation, the substrate quantities already indicate that the amounts of waste to be disposed of are not low (Table S4 in the Supporting Information). Solvent utilization of Method III is generally from 2.5 to 60 kg kg⁻¹. Entry 17 in Table S4 uses 418 kg solvent per kg⁻¹ synthesised product. This appears to be an exception and the high potential for savings can easily be conceived. However, the solvent demand of Method III is relatively high compared to Method I. Some reaction conditions and metrics are summarised in Table 2.

Substance Properties and Safety Aspects

Many of the chemicals used in these bromination methods carry additional risk and require particular care. *n*-Hexane is highly flammable and harmful, bears the risk of impairing fertility and is an irritant (entries 3, 5, Table S3 in the Supporting Information). Diethyl ether (entries 4, 11, 19), tetrahydrofuran (entry 18) or 1,4-diazabicyclo[2.2.2]octane (DABCO) (entry 12) are extremely or highly flammable and may form explosive peroxides. For dichloromethane,

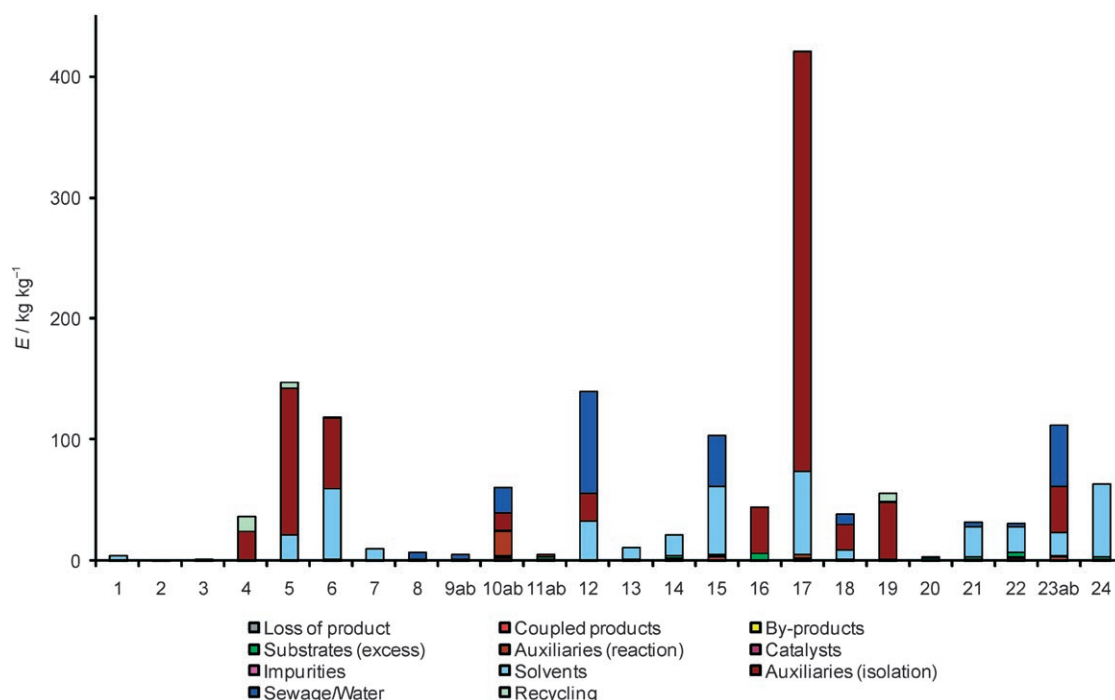


Figure 3. Environmental factor E of syntheses shown for different bromination methods of Table 1. More detailed information is given in Figures 4 and 5.

chloroform and carbon tetrachloride there is evidence that they might have carcinogenic effects (entries 1, 5, 6, 14–18, 20, 22). Concerning carcinogenic potential, pyridine (animal carcinogen A3), quinoline (suspicion of carcinogenic effects) and other aromatic amines are problematic substances, which were used indirectly or directly in entries 5 to 11. Generally, one should consider that non-polar alkyl chains such as pentyl in pentylpyridinium bromide or octyl in octylquinolinium bromide have negative toxicological effects,^[69,70] also valid for [bmim][Br] (bmim: 1-butyl-3-methylimidazolium) used in entry 4.^[71] Acetic acid causes severe burns and is flammable. Hydrogen peroxide (entries 19, 20) causes burns and may react spontaneously in certain situations.^[72,73] These and other adverse effects are summarised in Table S1 in the Supporting Information. These reports are a formal consideration, and may be important when applied to industrial processes. Chemicals with harmful properties can be handled by trained chemists by using appropriate measures in the laboratory.

Costs

The availability of starting materials and the costs of the overall process technology plays a dominant role in the final costs assessment. To obtain a rough overview of economy, the raw material costs of bromine or bromine compound and carrying agent or oxidant have been calculated for the conversion of one mole alkene (Table 2), regardless of the costs for the alkene, solvent, auxiliary material, substrate excess etc. The costs for Method II entries will depend on

the recyclability of the carrying agents (Table 2, right column).

Discussion

All results obtained are based on the protocols given in literature. They allow a comparison of raw material consumption and potential waste production, regardless of recycling options, down stream processing etc. It is clear that the protocols given in literature, in which only milligrams of the alkene had been converted (see scale in Table 2), are not optimised. If these procedures were scaled up to kilogram and ton scale for industrial purposes the amounts of solvents and other auxiliary materials would be optimised. This would also improve the mass balance of the procedures to a certain extent. However, the relative amounts of coupled products will remain unchanged during scaling up. Regarding characteristic materials of the bromination methodology, such as polymer support, we believe that a significant optimization cannot be expected, because the effectiveness of the bromination methodology is generally a major concern for synthetic chemists, that is to say that the protocols potential yield and ease of use is more important to them than the amount of consumables used. Though no data exists, we assume a general recyclability of 95 % for some substances as a first approach. Ideally this amount should be even higher, ionic liquids, for example, should be recyclable to an extent of 99 % or more. As no modelling of technological solutions has been conducted, this examination cannot be an in-depth eco-efficiency or life cycle analysis. Instead of con-

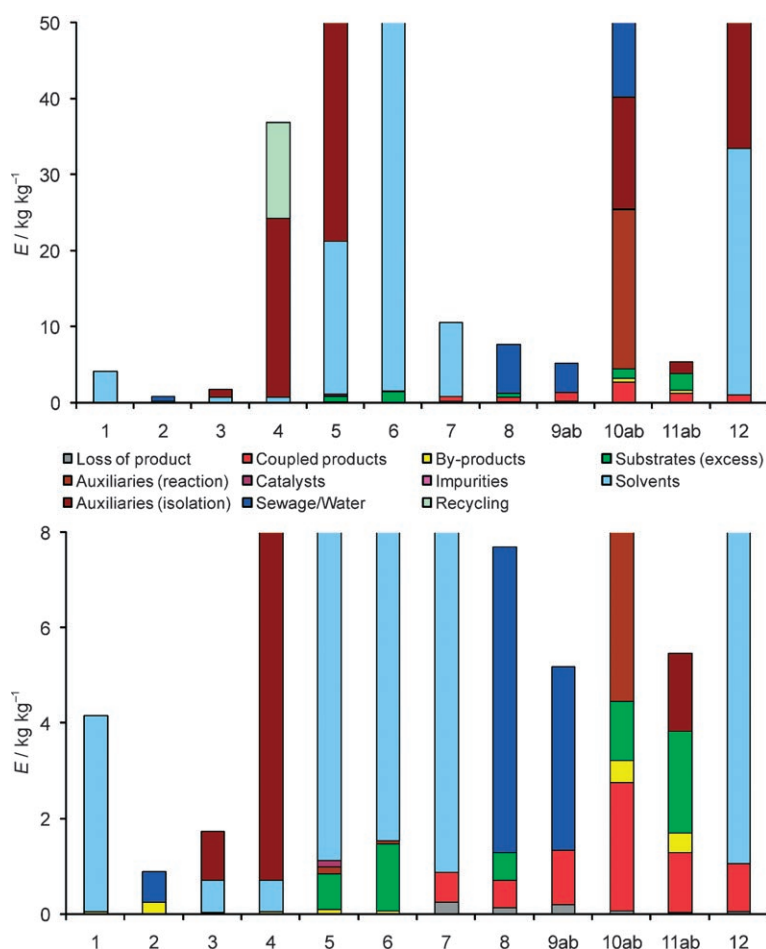


Figure 4. a) Environmental factor E of Method I (entries 1 to 4) and Method II (entries 5 to 12) syntheses (Table 1). Slightly magnified cutout of Figure 2. For details see Table S3 in the Supporting Information. b) Environmental factor E of Method I (entries 1 to 4) and Method II (entries 5 to 12) syntheses (Table 1). Magnified cutout of Figure 2. For details see Table S3 in the Supporting Information.

sidering real or at least calculated emissions, substances are discussed regarding their properties and resulting dangers. Regarding the energy issue, there is insufficient data. This is why we refer to reaction times and temperature (see Table 2) as well as solvent demand, which becomes relevant for the work-up procedures.

Health/safety requirements: The initial efforts in the literature focused on circumventing the use of molecular bromine to reduce the hazard potential. Method II and the use of a carrying agent merely causes a forward displacement of the problem into an earlier reaction step. The overall hazard potential remains because the inherent safety risk is connected to the specific properties of a problematic substance. Exposure to hazards is also dependent on technology so introducing a carrying agent only makes sense if the technological equipment used for loading this agent with bromine increases safety in the overall synthesis route. This means that an appropriate production unit must exist at least for loading the carrying agent. Multi-purpose equipment, which is not

particularly constructed for the application of molecular bromine, could then be used for the electrophilic bromination reaction. The loaded bromine reagent could then be used flexibly in various synthetic applications requiring different technologies. However, during the bromination step, a range of technological equipment is required to handle certain substances such as solvents that have toxicological (*n*-hexane, chloroform and carbon tetrachloride in entries 1, 3, 5, 12, 14, 20, 22, Table S1 in the Supporting Information) and chronic effects on health (*n*-hexane, dichloromethane, chloroform, carbon tetrachloride, entries 1, 3, 5, 6, 12, 14–18, 20, 22, Table S1). A number of the solvents used in Methods I–III are flammable (3–5, 7, 10–13, 16, 17, 19, 23, 24) and may form explosive peroxides (entries 4, 11, 18, 19, 24). Owing to these hazardous substances, the safety standard of the available technological equipment is possibly already safe enough for the application of molecular bromine. Consequently, the question arises as to whether the indirect way of using a carrying system is justified.

Instead of bromine, other substances such as acetic acid, hydrogen peroxide and hydrobromic acid, which also causes burns, are introduced (Table S1 in the Supporting Information). In addition, aromatic amines such as pyridine and quinoline show carcinogenic effects. They are used to produce pyridinium hydrobromide perbromide (entries 7, 8), pentylpyridinium tribromide (entry 9), 1,2-dipyridinium-dibromide-ethane (entry 10) and *N*-octylquinolinium tribromide (entry 11). The negative effect of alkylchains concerning toxicology has been reported in literature.^[69,70] It is questionable whether the overall hazard potential is reduced to a significant extent in these protocols. One has to keep in mind that bromine is used regardless in the production line of Method III (Figure 6). However, as bromine appears very early on in the synthesis sequence concept, the technology should already be adjusted appropriately.

Environmental issues: The protocols of Method I are normally relatively resource efficient, although there are exceptions (entry 4 in Table S3 represents a protocol that has a

Table 2. Overview of reaction conditions and metrics of bromination methods shown in Table 1.



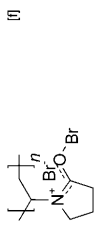
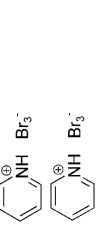
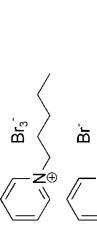
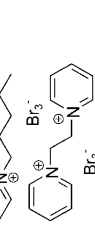
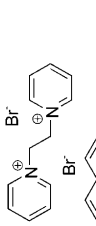
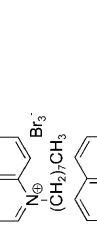
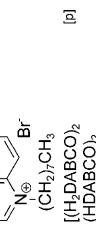
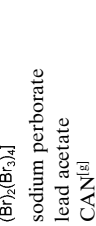

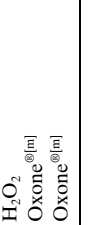
No.	Carrying agent or oxidant	Costs ^[k] [Euro]	Scale [mmol]	T [°C]	t [h]	Yield [%]	AE ^[j] [%]	Alkene ^[m]	E ^[j] ^[n]	Water ^[o]	Org. Solvents ^[p]	Carrier ^[q]
1		5.03	[b]	0–5	[b]	95	100	0.4153	4.2		4.1	
2		5.03	[b]	100	[b]	80	100	0.5259	0.25	0.64		
3		5.03	2	RT	48	97	100	0.4068	1.7		1.7	
4		5.03	0.6	RT	[b]	95	100	0.5204	24.3 ^[s]		23.6 ^[t]	
5		?	3	65	6	90	100	0.3772	142.8 ^[u]		141.7	
6		25.47	1	RT	0.5	94	100	0.3612	118 ^[v]		116.5	
7		72.32	12.8	heating	0.1	[b,c]	66.4	0.6179	10.6		9.7	0.63
8		72.32	2.8	RT	15	88	66.4	0.5617	1.3	6.4		0.58
9a		29.23	12.8	RT	2.5	84	51.3	0.4042	1.3	3.8		1.13
9ab		29.23	404.4 + 12.8	RT	≈2.5	84	51.3	0.4042	1.3	3.8		1.13
10a		27.42	5	RT	0.5	93	60.4	0.4243	15.4	20.4	14.7 ^[o]	0.70
10ab		27.42	0.343	RT	[b]	93	28.5	0.4243	40	20.4	35.8	0.70
11a		45.40	25	RT	4	95	60.4	0.4251	4.8		1.6	1.24
11ab		45.40	60	RT (cooling)	2.5	95	45.6	0.4251	5.5		1.6	1.24
12		12.23	1	RT	≈0.5	95	50.9	0.3574	55.8	84.2	51.9	0.84
13	sodium perborate	12.66	13.5	RT	2	87	54.8	0.3902	10.7	0.075	9.2	
14	lead acetate	136.86	2	RT	0.1	88	32.2	0.3858	22.2		17.5	
15	CAN ^[g]	834.57	1	RT	[b,d]	91	18.3	0.4336	61.6	42.1	55.8	
16	sodium periodate	39.88	10	10–15	[b]	98	58.5	0.4026	44.9	0.07	38.4	
17	Selectfluor ^{®[h]}	2571.85	1	RT	2	89	42.7	0.5659	421		418.1	
18	DIB ^[i]	137.44	5	RT	0.5	87	45.6	0.4980	30.6	8.15	28.9	
19	H ₂ O ₂	10.30	2	RT	4	85	59.7	0.4642	49.6 ^[w]	0.9	47.3 ^[v]	
20	H ₂ O ₂	13.59	10	ambient	2	99	89.9	0.5088	2.6	1.16	2.5	
21	Oxone ^{®[m]}	31.18	5	RT	1/12	87	44.5	0.4085	28.2	4.4	24.6	
22	Oxone ^{®[n]}	45.55	2	0	[b]	79	26.8	0.4298	28.3	2.7	20.8	

Table 2. (Continued)

No.	Carrying agent or oxidant	Costs ^[k] [Euro]	Scale [mmol]	T [°C]	t [h]	Yield [%]	AE ^[j] [%]	Alkene ^[i]	E ^[l] ^[a]	Water ^[a]	Org. Solvents ^[a]	Carrier ^[a]
23a		48.23	5	RT	2	79	80.2	0.4995	58.1	1.9	57	
23ab	Oxone [®] ^[m]	51.58	12.5	0	24	68	25.8	0.4995	61.9	50.7	57	
24	NBS ^[q]	27.42	0.2	RT	1/30	61	69.7	0.5566	63.4		60.2	

[a] kg per kg of dibromide produced. [b] No data given. [c] Arbitrary assumption: 80%. [d] Reaction times for other styrene derivatives are 0.3–0.75 h. [e] PVPB@sg. [f] PVP-bromine complex. [g] Cerium(IV) ammonium nitrate (Table 1). [h] 1-Chloromethyl-4-fluoro-1 and 4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) (Table 1). [i] (Diacytotoxyd)benzene (Table 1). [j] Atom economy. [k] The costs of bromine or bromine compound and carrying agent or oxidant [Euros] to convert 1 mole of alkene according to the Aldrich catalogue (for more details see Table S6 in the Supporting Information). [l] The environmental factor *E* includes solvents and comprises no water. As the carrying materials are not supposed to end up as by-product, a quantitative (100%) conversion is assumed in entries 7 to 12. Therefore, the discrepancy to 100% yield is understood as “Loss of product” being part of the E-factor. [m] 2 KHSO₅·KHSO₄·K₂SO₄. [n] *N*-Bromosuccinimide. [o] Similar syntheses have been conducted without solvent for extraction. [p] The precise structure is given in the literature^[49] [q] *N*-Bromosuccinimide. [r] Assumption: 95% of ionic liquid (12.65 g) are recyclable and are missing here. [s] Includes 0.67 g ionic liquid, which is 5% of the used amount of 13.322 g. [t] Providing that 95% of silica gel (≈3 g) and PH@sg. (≈2.3 g) are recyclable. [u] Providing that 95% (≈1.4 g) of PVP are recyclable. [v] Assumption: 95% of ionic liquid (6.4 g) are recyclable and are missing here. [w] Includes 0.3 g ionic liquid, which is 5% of the used amount of 6.7 g.

high solvent demand). This is possibly owed to the very small scale of the experiment, which does not allow handling substance quantities in an optimised manner. Surprisingly, no purification step for separation from by-products is reported in literature. It is not clear how the ionic liquid is treated and how large its overall loss is after several runs. Even if 95% recyclability is assumed, waste production resulting from the ionic liquid has to be reduced. Thus, recyclability must be even higher. However, stereoselectivity observed for alkynes is better compared to that of normal solvents. The applicability of Method II, among other things, depends on the recyclability of the carrying agents. Nonetheless, even if 95% recyclability is guaranteed, there will be solid waste of up to 0.6 kg per kg of product, which needs to be disposed of (Table S3 in the Supporting Information). The use of large volumes of solvent is the second issue, however in industry solvents are often recycled to a high degree, although this environmental performance is offset by the significant energy demand of recovery. This has been shown to be the case in a biochemical procedure in which the solvent demand is high compared to the chemical and extraction procedures that were necessary.^[80] Even without conducting an eco balance, mass balancing can provide valuable corresponding clues.^[81] In this regard, the application of pentylpyridinium tribromide (entry 9, Table S3) and of *N*-octylquinolinium tribromide (entry 11) seem to be two of the best variants of Method II, because no or only few non-toxic solvents are used and recyclability is claimed to be efficient. Unfortunately, the yield of entry 9, Table S3, is not as high as in Method I protocols. Additionally, the scale-up of the work-up procedure does not seem to be possible without significant changes, including the introduction of a solvent for extraction and washing procedures. Therefore, the potential ecotoxicological effects and biodegradability^[82] of the carrier have to be taken into account.

Most Method III protocols suffer from a high coupled-product formation, and furthermore, indirect processes cause high levels of pollution. For example, propylene oxide was investigated and described in detail by the Enquete Commission of the German Bundestag as an example of a chlorine-free end product produced by using chlorine.^[83] Since additional process steps are required, a compulsory formation of coupled products is always less advantageous than a direct process, as has been pointed out previously in the literature.^[7] Salts produced in Method III protocols represent a significant problem (spotlighted in Table S1 in the Supporting Information). Moreover, the production of these alkali metal salts already produces quite a large amount of coupled products (Figure 6).

Other environmental problems such as ozone-depletion potential or stress to the aquatic environment are indicated in Table S1 in the Supporting Information. Emissions from potential industrial processes will have to be minimised. Corresponding technological equipment will also have a positive impact on safety, and vice versa, safety concepts addressing chronic adverse effects on a company employee's health or the fire and explosion hazard will reduce emissions

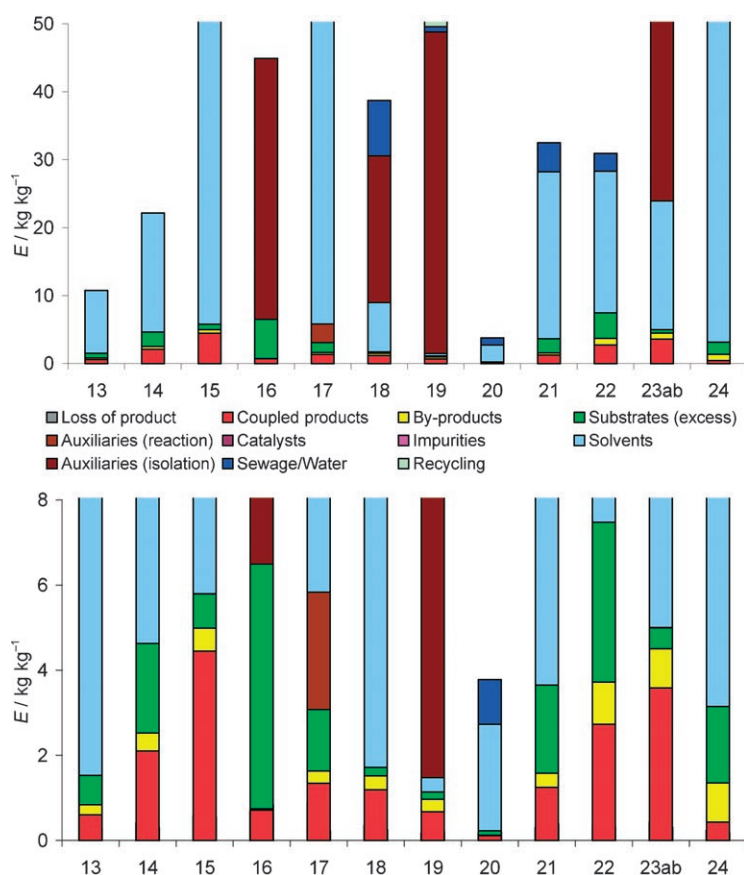


Figure 5. a) Environmental factor E of Method III syntheses (Table 1). Slightly magnified cut-out of Figure 2. For details see Table S4 in the Supporting Information. b) Environmental factor E of Method III syntheses (Table 1). Magnified cutout of Figure 2. For details see Table S4 in the Supporting Information.

to the environment. In our opinion, all efforts will have to be comprehensive in the sense that handling negative effects of bromine will already be met to the greatest possible extent. Especially when considering the significant waste

production (Table S1 in the Supporting Information and Figures 3–5), which is cost intensive on the raw material and the disposal side, the aim to eliminate molecular bromine is not justified.

The in situ oxidation of hydrobromic acid by using hydrogen peroxide seems to be an alternative to the traditional procedure that uses molecular bromine. However, as hydrobromic acid and hydrogen peroxide, though not as volatile as bromine, are also dangerous substances, the safety aspect is less of a motivation than the sensible utilization of the coupled product hydrogen bromide resulting from the bromination of hydrocarbons (Figure 6). Regarding the conditions listed in the conclusion section, some Method II protocols have to be considered as well.

Costs: The protocols for bromination of one mole of alkene by standard procedures (entries 1 to 4 in Table 2) show

the lowest costs at 5.03 Euros mol⁻¹, followed by the costs when using sodium perborate and sodium bromide (entry 13, 12.66 Euros mol⁻¹), HBr and H₂O₂ (entry 20, 13.59 Euros mol⁻¹), and NaBr and H₂O₂ as reagent

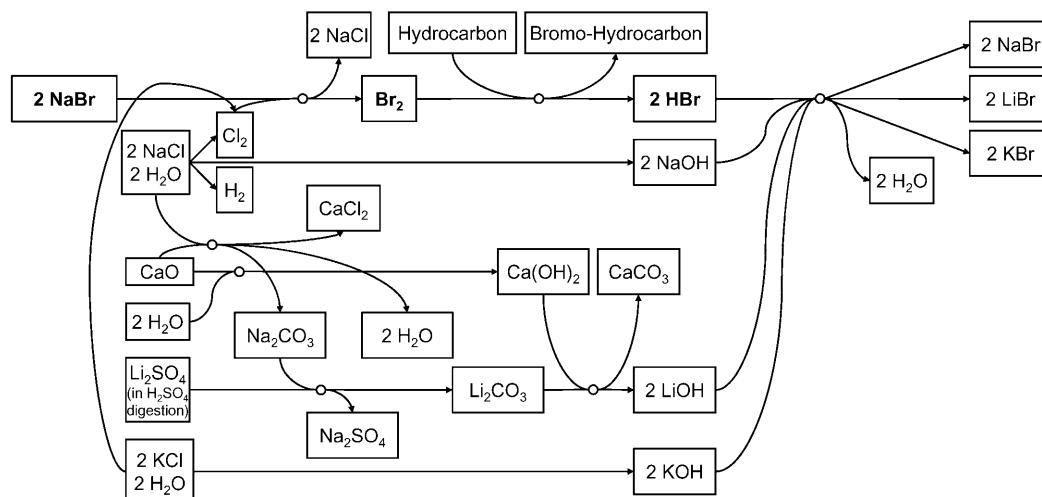


Figure 6. Bromine and hydrobromic acid in the production of alkali metal bromides from sodium bromide out of sea water. Sodium chloride is used by means of electrolysis^[74] to produce molecular chlorine and, by way of the Solvay process,^[75] to produce sodium carbonate. Calcium carbonate is produced from calcium hydroxide, that is, calcium oxide.^[76] Sodium carbonate and calcium hydroxide are necessary to produce lithium carbonate^[77] and lithium hydroxide.^[78] Potassium hydroxide is produced by electrolysis.^[79]

(entry 19, 10.30 Euros mol⁻¹, without ionic liquid). All other protocols show significantly higher costs. In the cases in which the carrying agents (Table 2, right column) are recyclable the extent of costs diminishes correspondingly and, in ideal conditions, might be almost as low as the standard procedure. The oxidants and bromides used in protocols entry 15 and entry 17 are very cost intensive with 834.57 and 2571.85 Euros mol⁻¹, respectively. Obviously, Selectfluor® displays its potential as a fluorinating agent rather than as an oxidant. Solvents etc. were not even considered and costs frequently reflect, at least partially, the conditions under which a substance has been produced. The synthesis of an expensive starting material is supposed to be more elaborate (e.g. more steps or expensive technology design etc.). Therefore, in this preliminary examination, which only considers the key substances for bromination, the traditional Method I appears to be most cost efficient. If hydrogen bromide results from a synthesis as a coupled product (Method III, entry 20), it can be reintroduced in another bromination reaction in combination with hydrogen peroxide, which is relatively low-priced (Table S6 in the Supporting Information). However, the more expensive the alkene, the less important the costs for bromine or bromine compounds and carrying agent or oxidant become and the significance of the yield increases (Table 2).

Aside from all bromination reactions considered in this examination, it should at least be mentioned that bromination of the double bond of *E*-cinnamic acid has recently been described by using a method without any solvent. Bromine is transferred as gas, which flows on the surface of the crystals of this compound. The reaction is clean, without formation of side products, but the reaction has to be performed on a very small scale in a desiccator under special experimental conditions. In addition, the reaction needs about one week to be complete for the amount of 100 mg; it is an example of a very special case of a bromination reaction.^[84]

Several organic reactions have been performed recently as solid/solid phase reactions, which avoid the use of solvents.^[85–88] However, their so-called process-intensity is low,^[89] meaning that the reaction conditions require long performance times and upscaling may be difficult. It would also be difficult to control the temperature for exothermic reactions, such as the bromination of alkenes.

Conclusion

Most of the new bromination methods, which circumvent the use of molecular bromine have severe disadvantages, owing to waste production. Additionally, solvent demand is significantly higher than in the traditional procedures and necessitates energy intensive recycling operations. As safety equipment has to allow for a range of toxic or dangerous substances regardless, we do not consider the avoidance of molecular bromine to be a significant improvement.

The application of hydrobromic acid with hydrogen peroxide (entry 20) might be an interesting alternative to sensibly use the coupled product hydrogen bromide, which results from the production of bromohydrocarbons (Figure 6). However, the problematic solvents used in the traditional procedure (e.g. entries 1, 3, 20 in Tables S1, S3 and S4) could potentially be avoided by application of a carrying agent (see for example, entries 9, 11 in Tables 1, S1 and S3) if this agent was proven to be the following:

- Non-toxic^[69,70] or created no emissions during the work-up procedure (i.e. no solubility in any solvents that are applied during or after synthesis, or if the work-up was by distillation).
- Recyclable to a degree much higher than 95 % (for relevant aspects concerning recycling see ref. [82]).
- Prepared and worked-up in an agreeable manner. Presently, preparation and work-up of ionic liquids are not environmentally benign.^[90]

In our opinion, these prerequisites are currently not being met, because thorough examinations have not been described in literature. Nonetheless, the approach can be judged as promising and in this regard more scientific work is needed. In addition, the problematic substances pyridine and quinoline still precede these concepts. Furthermore, the argumentation concerning the technological equipment is now valid, considering bromine on the one hand and solvents such as chloroform on the other. However, the replacement of such solvents during reaction by less toxic ones in the work-up procedure is progress and could orientate itself by the literature.^[91] In this regard, the bromination through the oxidation of hydrobromic acid with oxygen in acetonitrile in the presence of sodium nitrite as catalyst could be an interesting alternative.^[92] As some protocols are similarly resource efficient, further examinations should consider work-up procedures in more detail.

The method using a solid alkene and bromine vapour^[84] is favourable according to the mass balance, but the very low space-time yield renders this method unattractive on preparative scale. For liquid alkenes micro reactors^[93] could overcome the problem of heat transport and, thus, make carrying agents and solvents redundant. The applicability of micro reactors for halogenation reactions and specifically for the bromination of thiophene was demonstrated by P. Löb.^[94,95]

Acknowledgement

We are grateful to Dr. Stojan Stavber who shared his experience concerning Selectfluor® with us.

- [1] G. H. Schmid, *The Chemistry of Double Bonded Functional Groups*, Vol. 2, Suppl. A, Part 1 (Ed.: S. Patai), Wiley, New York, **1989**, 699.
- [2] M.-F. Ruasse, *Adv. Phys. Org. Chem.* **1993**, 28, 207–291.
- [3] R. S. Brown, *Acc. Chem. Res.* **1997**, 30, 131–137.
- [4] D. Lenoir, C. Chiappe, *Chem. Eur. J.* **2003**, 9, 1037–1044.

- [5] For bromination of aromatic structures see: M. B. Smith and J. March, *Advanced Organic Chemistry, Reactions, Mechanisms, and Structure*, 5th ed., Wiley Interscience, New York, **2001**, chapter 12.
- [6] Elsevier MDL, *CrossFire Beilstein*, Elsevier, **2007**, www.mdl.com/products/knowledge/crossfire_beilstein/index.jsp.
- [7] M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind, *Angew. Chem.* **2002**, *114*, 402–425; *Angew. Chem. Int. Ed.* **2002**, *41*, 414–436.
- [8] S. Bösch, D. Lenoir, M. Scheringer, *Naturwissenschaften* **2003**, *90*, 93–102.
- [9] Agenda 21, Report of the United Nations Conference on Environment and Development, Rio de Janeiro, 3–14 June **1992**, www.un.org/esa/sustdev/documents/agenda21/english/agenda21toc.htm; www.un.org/esa/sustdev/documents/agenda21/index.htm; www.un.org/esa/sustdev.
- [10] B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.
- [11] M. Eissen, R. Mazur, H.-G. Quebbemann, K.-H. Pennemann, *Helv. Chim. Acta* **2004**, *87*, 524–535.
- [12] M. Eissen, J. O. Metzger, *Chem. Eur. J.* **2002**, *8*, 3580–3585.
- [13] R. A. Sheldon, *CHEMTECH* **1994**, *3*, 38–47.
- [14] L. C. McKenzie, L. M. Huffman, J. E. Hutchison, *J. Chem. Educ.* **2005**, *82*, 306–310.
- [15] H. G. O. Becker, *Organikum: Organisch-chemisches Grundpraktikum*, 21st ed., 3–527–29985–8, Wiley-VCH, Weinheim, **2001**, 299.
- [16] Translation of the literature (Organikum, 22nd edition): General protocol for the conversion of hex-1-en, oct-1-en, cyclohexene, styrene, fumaric acid: in a three-necked flask with stirrer, dropping funnel and inside thermometer, the unsaturated compound is cooled to 0°C in the two- to three-fold quantity of carbon tetrachloride or chloroform. At 0 to 5°C an equimolar amount of bromine solved in about the two-fold volume of the same solvent is added dropwise while stirring steadily in such a way that the temperature remains within the given limit. No large concentration of unconsumed bromine should appear (colour!). The addition product precipitates and is suctioned. Otherwise, the solvent is distilled and the residue is purified by distillation or recrystallization. The yields for these examples are 90%, 90%, 95%, 95% and 80%, respectively. Additional remarks: 1) Fumaric acid is suspended in a two-fold volume of boiling water. Bromine is added dropwise at boiling heat. The addition product precipitates during cooling to 10°C and the remaining bromine is washed out with water. 2) Converting cyclohexene, 10% less bromine should be applied because the yield is reduced due to substitution products in side reactions. Additional purification could be achieved by shaking the crude product with 1/3 of its volume with a 20% solution of potassium hydroxide in alcohol for five minutes, subsequent dilution with the same amount of water, alkali-free washing, drying with sodium sulphate and distillation. This procedure diminishes the yield by about 10%. 3) Styrene should be used freshly distilled.
- [17] H. R. Snyder, L. A. Brooks, *Org. Synth.* **1943**, *2*, 171.
- [18] H. S. Rhinesmith, *Org. Synth.* **1943**, *2*, 177.
- [19] T. W. Abbott, D. Althousen, *Org. Synth.* **1943**, *2*, 270.
- [20] I. Ryu, H. Mathsubara, S. Yasuda, H. Nakamura, D. P. Curran, *J. Am. Chem. Soc.* **2002**, *124*, 12946–12947.
- [21] C. Chiappe, D. Capraro, V. Conte, D. Pieraccini, *Org. Lett.* **2001**, *3*, 1061–1063.
- [22] Y. Levin, K. Hamza, R. Abu-Reziq, J. Blum, *Eur. J. Org. Chem.* **2006**, 1396–1399.
- [23] M. M. Lakouraj, M. Tajbakhsh, M. Mokhtary, *J. Chem. Res.* **2005**, 481.
- [24] E. P. Koshy, J. Zacharias, V. N. R. Pillai, *React. Funct. Polym.* **2006**, *66*, 845–850.
- [25] J. E. Hutchison, S. M. Reed in *Green Chemistry in Education Workshop*, **2001**, p. 11.
- [26] K. Tanaka, R. Shiraishi, F. Toda, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3069–3070.
- [27] J. Salazar, R. Dorta, *Synlett* **2004**, 1318–1320.
- [28] V. Kavala, S. Naik, B. K. Patel, *J. Org. Chem.* **2005**, *70*, 4267–4271.
- [29] M. P. Kaushik, V. Polshettiwar, *Indian J. Chem., Sect. B* **2006**, *45*, 2542–2545.
- [30] M. M. Heravi, F. Derikvand, M. Ghassemzadeh, *S. Afr. J. Chem.* **2006**, *59*, 125–128.
- [31] C. Djerassi, C. R. Scholz, *J. Am. Chem. Soc.* **1948**, *70*, 417–418.
- [32] A. Kessat, A. Babadjamian, *Eur. Polym. J.* **1996**, *32*, 193–199.
- [33] G. W. Kabalka, K. Yang, N. K. Reddy, C. Narayana, *Synth. Commun.* **1998**, *28*, 925–929.
- [34] H. A. Muathen, *Synth. Commun.* **2004**, *34*, 3545–3552.
- [35] V. Nair, S. P. Panicker, A. Augustine, T. G. George, S. Thomas, M. Vairami, *Tetrahedron Lett.* **2001**, *42*, 7417–7422.
- [36] G. K. Dewkar, S. V. Narina, A. Sudalai, *Org. Lett.* **2003**, *5*, 4501–4504.
- [37] C. Ye, J. M. Shreeve, *J. Org. Chem.* **2004**, *69*, 8561–8563.
- [38] D. C. Braddock, G. Cansell, S. A. Hermitage, *Synlett* **2004**, *3*, 461–464.
- [39] T. K. Ying, W. L. Bao, Y. M. Zhang, *J. Chromatogr. B J. Chem. Res. Synop.* **2004**, 806–807.
- [40] N. B. Barhate, A. S. Gajare, R. D. Wakharkar, A. V. Bedekar, *Tetrahedron* **1999**, *55*, 11127–11142.
- [41] T.-L. Ho, B. G. Balaram Gupta, G. A. Olah, *Synthesis* **1977**, 676–677.
- [42] K. M. Kim, I. H. Park, *Synthesis* **2004**, 2641–2644.
- [43] R. K. Dieter, L. E. Nice, S. E. Velu, *Tetrahedron Lett.* **1996**, *37*, 2377–2380.
- [44] S. D. F. Tozetti, L. S. de Almeida, P. M. Esteves, M. C. S. de Mattos, *J. Braz. Chem. Soc.* **2007**, *18*, 675–677.
- [45] L. S. de Almeida, P. M. Esteves, M. C. S. de Mattos, *Synlett* **2006**, *10*, 1515–1518.
- [46] L. X. Shao, M. Shi, *Synlett* **2006**, 1269–1271.
- [47] To clarify the full stoichiometric equations, it was necessary to contact several authors. We would like to recommend including the precise presentation of the full stoichiometric equations of a chemical synthesis including all coupled products (if possible). Additionally, we would like to suggest that chemists take a more thorough look at alternative methodologies in the introduction of an article. The consideration of the respective mass balances (see N. Winterton, *Green Chem.* **2001**, *3*, G73–G75.) and the characteristics of used substances could improve the value of a scientific work, see for example, S. Protti, D. Dondi, M. Fagnoni, A. Albini, *Pure Appl. Chem.* **2007**, *79*, 1929–1938; M. Selva, A. Perosa, *Green Chem.* **2008**, *10*, 457–464; A. Rybak, M. A. R. Meier, *Green Chem.* **2008**, *10*, 1099–1104; M. A. Kuzemko, S. D. Van Arnum, H. J. Niemczyk, *Org. Process Res. Dev.* **2007**, *11*, 470–476. There is a course for students to learn about mass balances given by NOP (Sustainability in the organic chemistry lab course), which is a laboratory course available via internet (www.oc-praktikum.de/en-entry). Two protocols (experiment no. 5004 and no. 2003) and their environmental performance metrics exist for the acetalisation of 3-nitrobenzaldehyde. See J. Ranke, M. Bahadir, M. Eissen, B. König, *J. Chem. Educ.* **2008**, *85*, 1000–1005. Additional information regarding reaction metrics can be found in the literature, for examples see: D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.* **2002**, *4*, 521–527; J. Andraos, *Org. Process Res. Dev.* **2005**, *9*, 149–163; J. Andraos, *Org. Process Res. Dev.* **2005**, *9*, 404–431; J. Andraos, M. Sayed, *J. Chem. Educ.* **2007**, *84*, 1004–1010; J. Augé, *Green Chem.* **2008**, *10*, 225–231.
- [48] We would like to mention a correction that B. K. Patel indicated to us relating to Ref. [28] page 4271. The weight of KBr corresponding to 225 mmol should be 26.7 mg and not 267 mg and the weight of Oxone® corresponding to 100 mmol should be 61.4 mg and not 122.8 mg.
- [49] M. M. Heravi, F. Derikvand, M. Ghassemzadeh, B. Neumüller, *Tetrahedron Lett.* **2005**, *46*, 6243–6245.
- [50] A. McKillop, W. R. Sanderson, *Tetrahedron* **1995**, *51*, 6145–6166.
- [51] M. Safaie, *Synlett* **2006**, *15*, 2513–2514.
- [52] A. McKillop, W. R. Sanderson, *J. Chem. Soc. Perkin Trans. 1* **2000**, 471–476.
- [53] V. Nair, A. Deepthi, *Chem. Rev.* **2007**, *107*, 1862–1891.

- [54] R. H. Jih, K. Y. King, *Curr. Sci.* **2001**, 70, 1043–1053.
- [55] V. Nair, L. Balagopal, R. Rajan, J. Mathew, *Acc. Chem. Res.* **2004**, 37, 21–30.
- [56] A. Dhakshinamoorthy, *Synlett* **2005**, 3014–3015.
- [57] S. Stavber, M. Zupan, *Acta Chim. Slov.* **2005**, 52, 13–26.
- [58] L. Manral, *Synlett* **2006**, 807–808.
- [59] E. Kolvari, A. Ghorbani-Choghamarani, P. Salehi, F. Shirini, M. A. Zolfigol, *J. Iraqi Chem. Soc.* **2007**, 4, 126–174.
- [60] M. Rezaeivalla, *Synlett* **2006**, 3550–3551.
- [61] A. Kirschning, *J. Prakt. Chem.* **1998**, 340, 184–186.
- [62] P. J. Stang, *J. Org. Chem.* **2003**, 68, 2997–3008.
- [63] E. D. Matveeva, M. V. Proskurnina, N. S. Zefirov, *Heteroat. Chem.* **2006**, 17, 595–617.
- [64] U. Ladziata, V. V. Zhdankin, *Arkivoc* **2006**, 26–58.
- [65] W. He, *Synlett* **2006**, 3548–3549.
- [66] A. V. Narsaiah, *Synlett* **2002**, 1178–1179.
- [67] A. K. El-Qisairi, H. A. Qaseer, G. Katsigras, P. Lorenzi, U. Trivedi, S. Tracz, A. Hartman, J. A. Miller, P. M. Henry, *Org. Lett.* **2003**, 5, 439–441.
- [68] R. Rodebaugh, J. S. Debenham, B. Fraser-Reid, J. P. Snyder, *J. Org. Chem.* **1999**, 64, 1758–1761.
- [69] S. Stolte, M. Matzke, J. Arning, A. Boschen, W. R. Pitner, U. Welz-Biermann, B. Jastorff, J. Ranke, *Green Chem.* **2007**, 9, 1170–1179.
- [70] J. Arning, S. Stolte, A. Böschen, F. Stock, W. R. Pitner, U. Welz-Biermann, B. Jastorff, J. Ranke, *Green Chem.* **2008**, 10, 47–58.
- [71] P. Wasserscheid, R. van Hal, A. Bosmann, *Green Chem.* **2002**, 4, 400–404.
- [72] M. Eissen, A. Zogg, K. Hungerbühler, *J. Loss Prev. Process Ind.* **2003**, 16, 289–296.
- [73] I. Eto, M. Akiyoshi, T. Matsunaga, A. Miyake, T. Ogawa, *J. Therm. Anal. Calorim.* **2006**, 85, 623–627.
- [74] *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A6, Wiley-VCH, Weinheim, **1986**, p. 399 ff.
- [75] *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A24, Wiley-VCH, Weinheim, **1993**, p. 301, 308.
- [76] *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. 20, Wiley-VCH, Weinheim, **1992**, p. 494.
- [77] *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A-15, Wiley-VCH, Weinheim, **1992**, p. 407 ff.
- [78] *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A 15, Wiley-VCH, Weinheim, **1990**, p. 409 ff.
- [79] *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A 22, Wiley-VCH, Weinheim, **1993**, p. 94 ff.
- [80] G. Jödicke, O. Zenklusen, A. Weidenhaupt, K. Hungerbühler, *J. Clean. Prod.* **1999**, 7, 159–166.
- [81] M. Eissen, B. Bühler, G. Geisler, C. Fischer, K. Hungerbühler, A. Schmid, E. M. Carreira, *Mass balances and Life Cycle Assessment in Green Chemistry Metrics, Measuring and Monitoring Sustainable Processes* (Eds: A. Lapkin and D. J. C. Constable) Blackwell Publishing, **2008**.
- [82] P. J. Scammells, J. L. Scott, R. D. Singer, *Aust. J. Chem.* **2005**, 58, 155–169.
- [83] Enquete-Kommission "Schutz des Menschen und der Umwelt" des Deutschen Bundestages, *Die Industriegesellschaft gestalten Perspektiven für einen nachhaltigen Umgang mit Stoff- und Materialströmen*, 3-87081-364-4, Economica Verlag, Bonn, **1994**.
- [84] S. L. Jenkins, M. J. Almond, P. Hollins, *Phys. Chem. Chem. Phys.* **2005**, 7, 1966.
- [85] K. Tanaka, F. Toda, *Chem. Rev.* **2000**, 100, 1025–1074.
- [86] G. Kaupp, *Top. Curr. Chem.* **2005**, 254, 95–183.
- [87] F. Toda, *Top. Curr. Chem.* **2005**, 254, 1–40.
- [88] K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem.* **2004**, 116, 410–451; *Angew. Chem. Int. Ed.* **2004**, 43, 406–446.
- [89] W. Himmelsbach, W. Keller, K. Gezork, R. Krebs, *Chem. Ing. Tech.* **2007**, 79, 967.
- [90] D. Kralisch, D. Reinhardt, G. Kreisel, *Green Chem.* **2007**, 9, 1308–1318.
- [91] C. Capello, U. Fischer, K. Hungerbühler, *Green Chem.* **2007**, 9, 927–934.
- [92] A. Podgoršek, M. Eissen, J. Fleckenstein, S. Stavber, M. Zupan, J. Iskra, *Green Chem.* **2008**, DOI:10.1039/B814989E.
- [93] B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, 107, 2300–2318.
- [94] P. Löb, H. Löwe, V. Hessel, *J. Fluorine Chem.* **2004**, 125, 1677–1694.
- [95] P. Löb, V. Hessel, H. Klefenz, H. Löwe, K. Mazanek, *Lett. Org. Chem.* **2005**, 2, 767–779.

Published online: October 16, 2008