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Environmentally benign electrophilic and radical bromination 'on water': H_2O_2–HBr system versus *N*-bromosuccinimide

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ABSTRACT

A H_2O_2–HBr system and *N*-bromosuccinimide in an aqueous medium were used as a 'green' approach to electrophilic and radical bromination. Several activated and less activated aromatic molecules, phenyl-substituted ketones and styrene were efficiently brominated 'on water' using both systems at ambient temperature and without an added metal or acid catalyst, whereas various non-activated toluenes were functionalized at the benzyl position in the presence of visible light as a radical activator. A comparison of reactivity and selectivity of both brominating systems reveals the H_2O_2–HBr system to be more reactive than NBS for benzyl bromination and for the bromination of ketones, while for electrophilic aromatic substitution of methoxy-substituted tetralone it was higher for NBS. Also, higher yields of brominated aromatics were observed when using H_2O_2–HBr 'on water'. Bromination of styrene reveals that not just the structure of the brominating reagent but the reaction conditions: amount of water, organic solvent, stirring rate and interface structure, play a key role in defining the outcome of bromination (dibromination vs bromohydroxylation). In addition, mild reaction conditions, a straightforward isolation procedure, inexpensive reagents and a lower environment impact make aqueous brominating methods a possible alternative to other reported brominating protocols.

1. Introduction

Brominated aromatic compounds are important synthetic intermediates and products in organic chemistry. For example, they are found in C–C coupling reactions, as precursors to organometallic *species*, and in nucleophilic substitutions. They are also used for the synthesis of materials, pharmaceuticals, agrochemicals and other chemicals.[1] All of which has encouraged chemists to develop a variety of bromination protocols in order to gain access to this important class of compounds.[2]

The use of molecular bromine, as a basic electrophilic brominating reagent, has several drawbacks arising out of its toxic and corrosive nature, difficult handling and its high reactivity, which results in highly exothermic and non-selective reactions. Additional problems arise from using chlorinated solvents and the release of corrosive HBr as a by-product. Alternative brominating reagents such as *N*-bromosuccinimide[3] and pyridinium or tetraalkylammonium tribromides[4] make for easier handling and result in improved selectivity, but are unfortunately limited by their low atom efficiency and the need to remove the reagent's residue. Also, molecular bromine is required for their preparation.[5]

Oxidative bromination has potential in developing a sustainable and ecologically more acceptable procedure by the in situ preparation of an active brominating species via the oxidation of bromide using a suitable oxidant.[6a] A diluted aqueous solution of hydrogen peroxide is a convenient, safe and environmentally favourable oxidizing agent that yields water as the effluent.[6b] Moreover, the molar mass of the H_2O_2–HBr couple is lower than that of bromine and other brominating agents, which means that bromination in the presence of H_2O_2 allows for the complete utilization of bromine atoms resulting in a higher atom economy. To date, oxidative bromination with H_2O_2 has been studied mainly on activated aromatic substrates either in the presence or absence of a metal catalyst.[7,8]

The concept of oxidative halogenation was inspired by the *haloperoxidase* enzymes.[9] While enzymatic reactions in biological systems proceed in an aqueous medium, analogous reactions in chemistry are performed in organic solvents (i.e., chlorinated solvents, dioxane, toluene, acetic acid and methanol); the use of water was avoided in organic chemistry owing to the low solubility of the organic substrates. Despite this, over the last 20 years many working in the field have recognized that water can have a beneficial effect on the reactivity of insoluble substrates for which the term 'on water' reactions was coined.[10] With growing concern over the impact that using volatile organic solvents has on the environment, water is increasingly becoming an important choice of

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reaction medium when designing 'green' chemical processes. This is on account of its environmentally favourable properties that include being abundant, non-toxic, non-flammable.[11]

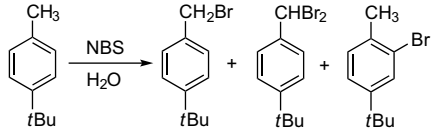
Published research on oxidative halogenation in water is scarce and limited to iodination.[12] However, we have shown that water is an excellent medium for the bromination of ketones with H_2O_2–HBr, where it acts as an activator making the addition of an acid catalyst superfluous.[13] Preliminary results of the bromination of methyl substituted aromatic molecules 'on water' have shown that water can be a medium for radical benzyl bromination using either *N*-bromosuccinimide[14] or a H_2O_2–HBr combination[15] at ambient temperature and with visible light as an activator. The observed difference in reactivity between these two reagents in aqueous media has prompted us to make a thorough examination of the effect that water has on the bromination of aromatic molecules: benzene and toluene derivatives, aromatic ketones and styrene, with H_2O_2–HBr and NBS 'on water'.

2. Results and discussion

A radical reaction in an aqueous/organic biphasic system can be initiated in either the aqueous or the organic phase depending on where the reaction occurs. In a preliminary study[14] of the benzylic bromination of 4-*tert*-butyltoluene (**1**), as a model substrate (Table 1), with *N*-bromosuccinimide 'on water', various modes of activation of the radical chain mechanism were investigated. Activation by heat led to the formation of benzyl bromide **2a** accompanied by a small amount of ring-brominated product **3** (entry 2). Alternatively, using AIBN as the radical initiator meant that benzyl bromination was selective albeit a dibrominated product **2b** was formed (entry 3). Selectivity was lost when DBP was the radical initiator (entry 4). Interestingly, in reactions with water soluble radical initiators (ACVA and AMPA, entries 5 and 6) selectivity was poorer and a greater amount of the ring-brominated product **3** was formed. Importantly, we found that light also induces the radical reaction and that irradiation from a 40 W incandescent light bulb is superior in terms of yield and selectivity than the other modes of activation that we have investigated (entry 8).

Based on this result, various *para*-substituted toluenes were subjected to NBS in water in the presence of light (40 W, Table 2).

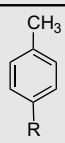
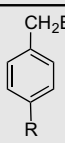
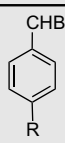
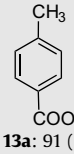
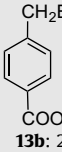
Table 1
Effect of mode of activation of a radical reaction on the bromination of 4-*tert*-butyltoluene (**1**) with NBS 'on water'



Entry	Reaction conditions[a]	Product distribution[b]		
		2a	**2b**	**3**
1	24 °C, 22 h, dark	25%	—	—
2	80 °C, 5 h, dark	76%	—	8%
3	5% AIBN, 80 °C, 1.5 h	77%	10%	—
4	5% DBP, 80 °C, 2.5 h	73%	6%	5%
5	5% ACVA, 80 °C, 2 h	43%	1%	15%
6	5% AMPA, 80 °C, 2 h	38%	1%	23%
7	Ambient light, 24 °C, 22 h	78%	4%	—
8	40 W bulb, 27 °C, 22 h	86%	6%	—
9	'Sunlight',[c] 30 °C, 3.5 h	83%	6%	—

[a] 4-*tert*-Butyltoluene (**1**, 1.0 mmol), NBS (1.0 mmol), H_2O (5 mL). Radical initiators: AIBN (2,2′-azobis(2-methylpropionitrile)), DBP (dibenzoyl peroxide), ACVA (4,4′-azobis(4-cyanovaleric acid)), AMPA (2,2′-azobis(2-methylpropionamidine)-dihydrochloride).
[b] Determined by ^{1}H NMR spectroscopy.
[c] High-pressure mercury lamp, OSRAM HQL 125 W.

Table 2
Visible-light induced free-radical bromination of *para*-substituted toluenes with NBS 'on water'

Entry	Substrate[a]	Time	Yield[b] (%)	
				
1	**1** R=^{t}Bu	22 h	**2a**: 86 (70)	**2b**: 6 (4)
2	**4** R=H	25 h	**5a**: 84 (77)[c]	**5b**: 5 (3)
3	**6** R=COOEt	23 h	**7a**: 81 (72)	**7b**: 5 (3)
4	**8** R=$COCH_3$	25 h	**9a**: 81 (76)	**9b**: 8 (6)
5	**10** R=NO_2	24 h	**11a**: 6	—
6	**12** R=CHO	25 h	 **13a**: 91 (80)	 **13b**: 2

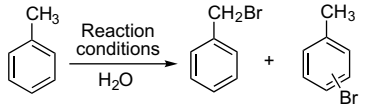
[a] Substrate (1.0 mmol), NBS (1.0 mmol), H_2O (5 mL), 40 W incandescent light bulb, react. temp=27 °C.
[b] Distribution of products was determined by ^{1}H NMR spectroscopy of the isolated reaction mixture, yields in parentheses refer to isolated yields.
[c] Larger scale experiment (5.0 mmol **4**, 5.0 mmol NBS, 25 mL water).

Generally, the benzyl bromides were formed in good yields accompanied by small amounts of the dibrominated products. What is interesting to note is the selectivity of benzylic bromination in the presence of ketone functionality, given that 4-methylacetophenone (**8**) was exclusively brominated by a free-radical process at the benzyl position leading to benzyl bromide **9a**. On the contrary, oxidative bromination of 4-methylacetophenone (**8**) in an aqueous H_2O_2–HBr system shows different regioselectivity by forming 2-bromo-1-*p*-tolylethanone through enolization.[13] Under these reaction conditions bromination of a strongly deactivated 4-nitrotoluene (**10**) gave only a 6% yield of 1-(bromomethyl)-4-nitrobenzene (**11a**). Interestingly, 4-methylbenzaldehyde (**12**) was almost completely oxidized to 4-methylbenzoic acid **13a** with NBS in water. A similar result was reported for the photooxygenation of benzyl alcohol with catalytic amounts of NBS in organic solvents.[16a] Alternatively, oxidation of benzyl alcohol with 1 equiv of NBS in the aqueous phase and in the presence of cyclodextrin selectively yielded benzaldehyde.[16b]

A further advantage of benzylic bromination using NBS in water is the simple isolation protocol. This is made straightforward because the only reaction residue succinimide is soluble in water, unlike hydrophobic organic products. This means that any solid product work up consists of filtration, albeit if an oily product is formed in a small-scale experiment then liquid–liquid extraction is necessary. In the case of the bromination of toluene (**4**) on a larger scale (Table 2, entry 2), a clear phase separation occurs at the end of the reaction. The organic and aqueous phases could then be separated and the organic phase further washed with water and transferred directly to the chromatographic column. Column chromatography (SiO_2, hexane/EtOAc) gave 77% of the pure oily benzyl bromide (**5a**).

A 'greener' protocol for free-radical bromination would involve oxidative bromination in an aqueous solution of H_2O_2 and HBr, given that bromine is generated in situ and the use of H_2O_2 as an oxidant means that water is the only by-product. This then obviates the formation of a reagent residue and the need for its separation, as well as increasing the overall atom economy. In order to make a comparison of the effect of the mode of initiation of radical chain process for H_2O_2–HBr benzyl bromination of toluene (**4**) we applied the optimum reaction conditions that were determined from our

Table 3
The effect of the mode of activation of radical chain on the selectivity of bromination of toluene (**4**) with H_2O_2–HBr 'on water'



4 **5a** **6**

Entry	Reaction conditions[a]	Conv (%)[b]	Product ratio[b] (%)	
			Benzyl br. (**5a**)	Ring br. (**6**) (*p*-/*o*-)
1	H_2O_2–HBr, dark, 24 h, rt.	90	1	3.00 (69:31)
2	H_2O_2–HBr, 5% DBP, 2 h, 80 °C	94	1	0.33 (65:35)
3	H_2O_2–HBr, 5% HMPA, 2 h, 80 °C	95	1	0.88 (66:34)
4	H_2O_2–HBr, 40 W, 24 h	96	1 (81%)[c]	—

[a] A 0.8 mL suspension of 1.0 mmol of **4**, 2.0 mmol of H_2O_2 and 1.1 mmol of HBr.
[b] Determined by ^{1}H NMR spectroscopy. Numbers in parentheses refer to the ratio of *para*- versus *ortho*- bromotoluene.
[c] Yield of isolated product, 7% of dibromobenzylbromide (**5b**) was also formed.

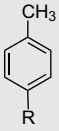
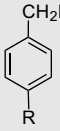
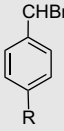
initial investigation of visible-light induced oxidative benzyl bromination of **1** (Table 3).[15] For this we added 1.0 mmol of **4** to a 0.8 mL solution of 2.0 mmol of H_2O_2 (overall 9% H_2O_2 solution) and 1.1 mmol of HBr (overall 11% HBr solution). When performing the reaction in the dark at room temperature for 24 h, ring-bromination was the main reaction channel, while benzyl bromide (**5a**) was formed in only a yield of 15% (entry 1). Next the radical chain process was activated by adding either 5 mol% of hydrophobic DBP or hydrophilic AMPA radical initiator and performing the reaction at 80 °C for 2 h (entries 2 and 3). In both cases the yield of benzyl bromide (**5a**) increased, but selectivity was poor and ring-brominated products together with some products of further bromination were formed. Finally, we tested the third mode of activation of the radical process, i.e., visible light (entry 4). Similar to the reaction with NBS, oxidative bromination using aqueous H_2O_2–HBr induced by visible light from a 40 W incandescent light bulb gave selectively benzyl bromide (**5a**) with an 81% isolated yield.

Next, various methylbenzene derivatives were brominated by a visible-light induced reaction with an H_2O_2–HBr couple in an aqueous medium. Table 4 shows how the benzyl brominated products were formed selectively in high yields without any significant amount of dibrominated products being formed. In the above-mentioned small-scale experiments, at the end of the reaction, the crude reaction mixture was diluted by adding a small amount of organic solvent (hexane/EtOAc) and a drying agent (Na_2SO_4), this was followed by filtering the insoluble material and removing the solvent. However, when performing bromination of toluene (**4**) on a larger scale (5.0 mmol), benzyl bromide **5a** was the only reaction product and a clear phase separation occurred. After the upper aqueous phase had been removed, and the organic phase had been dried under vacuum, **5a** was obtained as pure oil with a 79% yield (Table 4). In this case, we avoided the use of an organic solvent throughout the entire benzylic bromination procedure. In contrast to using NBS, an aqueous H_2O_2–HBr system also allows the benzyl bromination of the toluene derivative bearing electron-withdrawing groups in good yields. To increase radical formation, we performed the reactions illuminated by a 125 W 'solar' lamp and by adding a 30% aqueous solution of H_2O_2 gradually to the reaction mixture. By slow addition of H_2O_2 the decomposition of H_2O_2 during the reaction, owing to the presence of HBr and Br_2, was reduced. We anticipate that this is the main reason for the lower yields that we obtain with deactivated methylbenzenes.

To understand the difference in the reactivity of both aqueous brominating systems, we studied a reaction involving *para*-xylene (**19**), since it has a mildly activated aromatic ring and two equivalent methyl substituents. Table 5 shows that using either the H_2O_2–HBr system or NBS in water at ambient temperature and in the dark gives the ring-brominated derivative **21** as the main product. Nevertheless the radical pathway is still operative. The reactivity of the oxidative bromination system without light activation (entry 1) was much higher since the conversion was 80%, while bromination with NBS (entry 2) yielded only 31% of brominated products. In the bromination activated by light the side chain bromination was the sole reaction pathway, producing 1-(bromomethyl)-4-methylbenzene (**20a**) and 1,4-bis(bromomethyl)benzene (**20b**) with similar conversion. Improved selectivity is observable for bromination with NBS, since **20a** and **20b** are in a ratio 6.5:1 (entry 4), while in an aqueous H_2O_2–HBr these products are in a 3.5:1 ratio (entry 3).

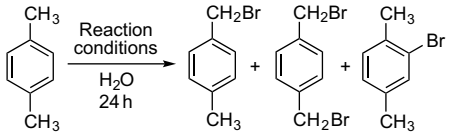
Based on the outcome of the bromination of alkylbenzenes using either NBS or a H_2O_2–HBr couple in water, which produced ring-brominated products, we became interested in exploring the feasibility of both bromination systems for electrophilic aromatic bromination in aqueous media. The difference in reactivity and selectivity of both brominating systems led us to investigate the bromination of selected aromatic molecules 'on water' using the H_2O_2–HBr system and NBS (Table 6). First, we tested the mesitylene

Table 4
Visible-light induced free-radical bromination of *para*-substituted toluenes with H_2O_2–HBr 'on water'

Entry	Substrate[a]	Time	Yield[b] (%)	
				
1	**1** R=^{t}Bu	24 h	**2a**: 91 (80)	—
2	**4** R=H[c]	10 h	**5a**: (79)	—
3[d]	**15** R=Br	28 h	**16a**: 85 (77)	—
4[d]	**6** R=COOEt	32 h	**7a**: 84 (71)	**7b**: 6 (4)
5[d]	**17** R=COPh	66 h	**18a**: 93 (90)	—
6[d]	**10** R=NO_2	66 h	**11**: 91 (90)	—

[a] A 0.8 mL suspension of 1.0 mmol of substrate, 2.0 mmol of H_2O_2 and 1.1 mmol of HBr, 40 W incandescent light bulb, react. temp=27 °C.
[b] Distribution of products were determined by ^{1}H NMR spectroscopy of the isolated reaction mixture, yields in parentheses refer to isolated yields.
[c] Experiment on a larger scale (5.0 mmol **4**, 10.0 mmol H_2O_2, 5.5 mmol HBr, 4 mL water).
[d] 30% Aqueous solution of H_2O_2 was added slowly and the reaction mixture was irradiated with a 125 W high-pressure mercury lamp.

Table 5
Effect of reaction conditions on regioselectivity of bromination of *para*-xylene (**19**) in water

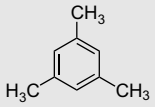
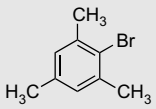
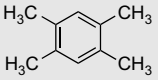
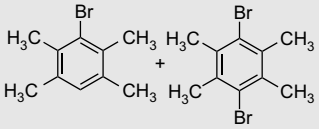
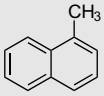
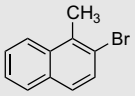
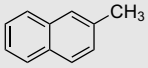
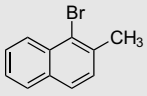
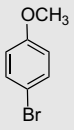
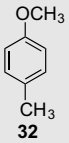
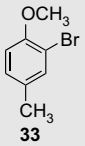
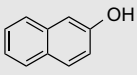
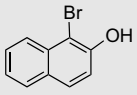
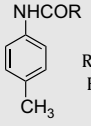
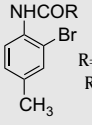
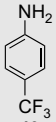
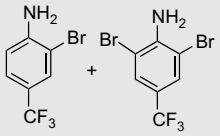


19 **20a** **20b** **21**

Entry	Reaction conditions[a]	Yield (%)[b]	
		Benzyl br. (**20a**/**20b**)	Ring br. (**21**)
1	$2H_2O_2$–HBr, dark	14 (100:0)	66
2	NBS, dark	4 (100:0)	27
3	$2H_2O_2$–HBr, hν (40 W)[c]	84 (77:23)	—
4	NBS, hν (40 W)[c]	82 (87:13)	—

[a] Reactions with H_2O_2–HBr: 1.0 mmol of **19** in 0.8 mL of water. Bromination with NBS: 1.0 mmol of **19** in 5 mL of water.
[b] Yields of products were determined by ^{1}H NMR spectroscopy of the isolated reaction mixture and are based on starting compound, numbers in parentheses refer to ratio of **20a**/**20b**.
[c] 40 W incandescent light bulb.

Table 6
Bromination of various aromatic compounds using H_2O_2–HBr system or NBS 'on water'

Entry	Substrate	Reaction conditions[a]	Product	Yield (%)[b]
1	 **22**	$2H_2O_2$–1HBr, 24 h	 **23**	100 (98)
2		1NBS, 24 h		94 (85)[14]
3	 **24**	$2H_2O_2$–1HBr, 24 h	 **25a** **25b**	**25a**, 47 (46), **25b**, 26 (25)
4		1NBS, 24 h		Mixture of products
5	 **26**	$2H_2O_2$–1HBr, 24 h	 **27**	100 (94)
6		1NBS, 24 h		82 (75)
7	 **28**	$2H_2O_2$–1HBr, 24 h	 **29**	100 (95)
8		1NBS, 24 h		93 (89)
9	 **30**	$2H_2O_2$–1HBr, 8 h	 **31**	100 (90)
10		1NBS, 8 h		94 (87)
11	 **32**	$2H_2O_2$–1HBr, 8 h	 **33**	100 (95)
12		1NBS, 8 h		93 (82)[14]
13	 **34**	$2H_2O_2$–1HBr, 8 h	 **35**	97 (90)
14	 R=CH_3 **36**	$2H_2O_2$–1.1HBr, 24 h	 R=CH_3 **37**	100 (95)
15	R=Ph **38**	$2H_2O_2$–1.1HBr, 24 h	R=Ph **39**	94 (89)
16	 **40**	$2H_2O_2$–1HBr, 8 h	 **41a** **41b**	**41a**, 94 (88), **41b**, 3
17		$3H_2O_2$–2HBr, 8 h		**41a**, —, **41b**, 100 (91)
18	 **42**	$2H_2O_2$–1HBr, 24 h	 **43**	100 (90)
19	 **44**	$3H_2O_2$–1.5HBr–$2H_2SO_4$, 24 h at 55 °C	 **45**	(20)

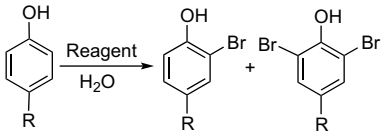
[a] Bromination with H_2O_2–HBr: a suspension of 1 mmol of substrate in 0.8 mL of water. Bromination with NBS: a suspension of 1 mmol of substrate in 5 mL of water. Room temperature unless otherwise noted.
[b] Yields were determined by ^{1}H NMR spectroscopy and are based on starting compound; yields in parentheses refer to isolated yields.

(**22**)/durene (**24**) couple (Table 6, entries 1–4). Both methods, produced after 24 h at room temperature in an aqueous medium bromomesitylene (**23**) in high yields, however, only the oxidative bromination was quantitative (entry 1). Oxybromination of durene (**24**) produced only the ring-brominated products monobromo- and dibromodurene **25a** and **25b**, obtained in 46% and 25% yields, respectively (entry 3). The reaction with NBS gave a complex mixture of side chain and ring-brominated derivatives (entry 4). Both methyl substituted naphthalenes **26** and **28** reacted only at the aromatic ring to give the monobrominated products **27** and **29** with H_2O_2–HBr (entries 5 and 7), while bromination with NBS gave lower yields of **27** and **29**, respectively, nevertheless no radical bromination products were noted (entries 6 and 8). A similar reactivity can be seen with activated aromates. Anisole (**30**) and 4-methylanisole (**32**) were transformed with quantitative conversion in the H_2O_2–HBr system, while lower yields of brominated products were formed with NBS. Again no radical chain bromination was observed in the reaction of **32** (entries 9–12). Next, oxidative bromination 'on water' was tested on different aromatic molecules. 2-Naphthol (**34**) and *p*-tolylacetamides **36** and **38** were selectively transformed to the brominated products that were isolated in very good yields (entries 13–15). There was no further bromination although a 10% excess of HBr was used for brominating the acetamides. In the bromination of the aniline derivative **40** a monobrominated product **41a** was formed in a 94% yield, in addition 3% of the dibrominated product **41b** was also formed. Increasing the amount of reagent (H_2O_2 and HBr were used in ratio 3:2) resulted in a complete conversion to 2,6-dibromo-4-(trifluoromethyl)benzenamine (**41b**). A combination of aqueous H_2O_2–HBr as the brominating agent with water as a reaction medium is applicable to less activated aromatics. The bromination of naphthalene (**42**) proved highly selective resulting in a 90% isolated yield of 1-bromonaphthalene (**43**). When benzene (**44**) was submitted to 2 equiv of H_2O_2 and 1 equiv of HBr at room temperature for 24 h, only the starting compound was recovered. Using higher amounts of reagents in the presence of 2 equiv of H_2SO_4 and by increasing the reaction temperature to 55 °C resulted in a 20% yield of bromobenzene (**45**).

para-Substituted phenols and anilines usually give mono- and di-brominated products in bromination reactions. This makes them interesting substrates on which to study the effect of our brominating system on the selectivity of the reaction. Surprisingly, 2 equiv of H_2O_2 and 1 equiv of HBr in 5 mL of water were sufficient to convert 1.0 mmol of 4-*tert*-butylphenol (**46**) both regioselectively and quantitatively into 2-bromo-4-*tert*-butylphenol (**47a**, Table 7). Under the same reaction conditions the bromination of **46** with NBS gave 32% of 2-bromo-4-*tert*-buthylphenol (**47a**) and 29% of 2,6-dibromo-4-*tert*-buthylphenol (**47b**). Increasing the amount of the reagent used to 2 equiv resulted in the complete conversion of **46** to the dibrominated product **47b**, regardless of the brominating reagent used. Our results of oxybromination are in accordance with the reported selective monobromination of 4-methylphenol using H_2O_2–HBr[8c] in ethylenedichloride at 45 °C and using ^{t}BuOOH–HBr[8a] in boiling methanol. Photochemical bromination with NBS in acetonitrile gave 2-bromo-4-methylphenol accompanied by only small amounts of the dibrominated product.[17a]

The less reactive 4-nitrophenol (**48**) shows a similar reactivity pattern for both brominating systems; the dibrominated product **49b** predominates during bromination with 1 equiv of reagent (**49a**/**49b**=1:4.4 and 1:3.2, respectively), while with 2 equiv of reagent 2,6-dibromo-4-nitro-phenol (**49b**) is formed exclusively (Table 7). Similar selectivity is observed in the reaction with NBS in MeCN, however, when the reaction was promoted by $HBF_4 \cdot Et_2O$, selective monobromination of 4-nitrophenol (**48**) with NBS in CH_3CN was observed.[3b] On the contrary, photochemical

Table 7
Bromination of *para*-substituted phenols using the H_2O_2–HBr system or NBS in water as a reaction medium



46 R=*t*Bu **47a** **47b**
48 R=NO_2 **49a** **49b**

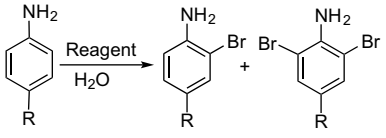
Entry	Sub.	Reaction conditions[a]	Distribution[b] (%)		
			46/48	**47a/49a**	**47b/49b**
1	**46**	$2H_2O_2$–1HBr, 8 h	—	100 (90)	—
2		$4H_2O_2$–2HBr, 32 h	—	—	100 (98)
3		1NBS, 8 h	39	32	29
4		2NBS, 24 h	—	—	100 (95)
5	**48**	$2H_2O_2$–1HBr, 8 h	46	10	44 (40)
6		$3H_2O_2$–2HBr, 24 h	—	—	100 (95)
7		1NBS, 8 h	45	13	42
8		2NBS, 24 h	—	—	100 (90)

[a] Bromination with H_2O_2–HBr: a suspension of 1 mmol of substrate in 5 mL of water. Bromination with NBS: a suspension of 1 mmol of substrate in 5 mL of water. Room temperature.
[b] Yields were determined by ^{1}H NMR spectroscopy; yields in parentheses refer to isolated yields.

bromination of **48** with NBS in acetonitrile, gave an inverse ratio of mono and dibrominated products (3.5:1).[17a] Solid state bromination with NBS at 30 °C of 4-nitrophenol gave only the dibrominated product in a yield of 50%.[17b]

Brominations of the aniline analogues **50** and **52** revealed different behaviour to the phenol ones. The reaction of 4-*tert*-butylaniline (**50**) with 2 equiv of H_2O_2 and 1 equiv of HBr produced over a period of 24 h a mixture of products, where the mono- and dibrominated products **51a** and **51b** were formed in the ratio 1.8:1 (Table 8). Bromination of the same substrate with NBS, however, gave predominantly the dibrominated product, **51a** and **51b** were formed in an inverse ratio. Complete formation of 2,6-dibromo-4-*tert*-butylaniline (**51b**) was achieved by using 4 equiv of H_2O_2 and

Table 8
Bromination of *para*-substituted anilines using H_2O_2–HBr system or NBS in water as a reaction medium



50 R=*t*Bu **51a** **51b**
52 R=NO_2 **53a** **53b**

Entry	Sub.	Reaction conditions[a]	Distribution[b] (%)		
			50/52	**51a/53a**	**51b/53b**
1	**50**	$2H_2O_2$–1HBr, 24 h	35	42	23
2		$4H_2O_2$–2HBr, 28 h	—	—	100 (95)
3		1NBS, 8 h	46	18	36
4		2.5NBS, 24 h	—	—	100 (93)
5	**52**	$2H_2O_2$–1HBr, 24 h	12	88	—
6		$3H_2O_2$–2.5HBr, 28 h	—	—	100 (95)
7		1NBS, 8 h	38	33	29
8		2.5NBS, 24 h	—	—	100 (93)

[a] Bromination with H_2O_2–HBr: a suspension of 1 mmol of substrate in 5 mL of water. Bromination with NBS: a suspension of 1 mmol of substrate in 5 mL of water, room temperature.
[b] Yields were determined by ^{1}H NMR spectroscopy; yields in parentheses refer to isolated yields.

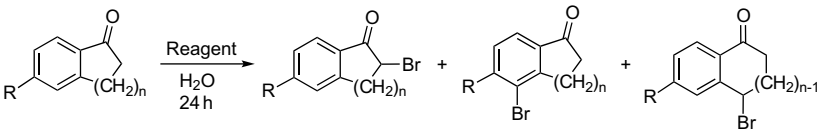
2 equiv of HBr or 2.5 equiv of NBS in 28 h and 24 h, respectively. In this case, bromination of the less activated 4-nitroaniline (**52**) in aqueous H_2O_2–HBr gave selectively the monobrominated product **53a** with 88% conversion within 24 h. No further attempt was made to improve the yield. Similarly, oxidative bromination using a sodium perborate–KBr system in the presence of molybdate in AcOH afforded 2-bromo-4-nitroaniline (**53a**) selectively.[18] Again, over the same period of time bromination with 1 equiv of NBS gave **53a** and **53b** in almost equal amounts. These results contrast with those from the bromination of **52** with NBS, either in MeCN[17a] or under solvent-free conditions.[3d] In that case the monobromo derivative **53a** is formed selectively. The introduction of two bromine atoms was successfully accomplished when higher amounts of reagent and longer reaction times were applied.

Our previous study of the oxidative bromination of carbonyl compounds in an aqueous H_2O_2–HBr system demonstrated that water plays a key role in the activation of the ketone group through enolization.[13] However, water does not have this effect when NBS is used as a brominating reagent.[14,19] To obtain some additional information about this interesting phenomena, we investigated the selectivity of bromination with H_2O_2–HBr and NBS in water both under dark and illuminated conditions. Indanone (**54**), α-tetralone (**58**) and both methoxy-substituted analogues **56** and **60** are promising substrates for such studies since they posses all three reactive sites—at the benzyl position, the α-position to the ketone group and at the aromatic ring.

Indanone (**54**) is an interesting example for highlighting the difference in the reactivity of both aqueous brominating systems. With H_2O_2–HBr the reaction occurs only at the α-position to the carbonyl group, while the reaction with NBS under similar conditions does not proceed (Table 9, entries 1 and 3). Irradiation by light induces the benzyl bromination of **54**, however, oxidative bromination results only in a 18% yield, while the NBS radical chain process was the only reaction pathway (entries 2 and 4). A lesser effect was observed during the bromination of tetralone (**58**), where NBS under conditions of darkness converted only 8% of **58**. In the presence of light, the main reaction pathway was α-bromination. The introduction of a methoxy substituent on the aromatic ring in **54** and **58** altered the reactivity. The aromatic ring became the most important reaction site in **56** and **60**. There are two interesting features concerning the bromination of both the methoxy-substituted derivatives **56** and **60**. First, light does not trigger the benzyl bromination but instead, a small amount of the α-brominated ketones **57a** and **61a** can be detected during the reaction with H_2O_2–HBr. Alternatively, there is no such effect during bromination with NBS. Second, the reactivity of the methoxy-substituted ketone **60** at the aromatic ring is slightly higher with NBS than in the H_2O_2–HBr system (entries 14 and 17). The reactivity at the ketone functional group was much higher for H_2O_2–HBr than that for NBS.

Styrene (**62**) is a useful substrate for investigating the nature of the active halogenating agents and is used often in biomimetic studies of haloperoxidation,[20a] mainly with a metal catalyst.[7b,20b,c] Research has focused on the selectivity of bromohydrin and dibromide formation in a vanadium(V) or molybdenium(VI) catalyzed oxybromination of **62** using potassium bromide and hydrogen peroxide. Performing these reactions in water gives bromohydrin as the main product, despite a large excess of bromide ions.[7f] In a two-phase system using either H_2O–$CHCl_3$[7b,20b,c] or H_2O–CH_2Cl_2[20b,d] more of the dibrominated product forms. This makes styrene a good substrate for which to study the phase behaviour of 'on water' reactions by observing the difference in

Table 9
The effect of brominating system on the regioselectivity of bromofunctionalization of benzocycloalkanones in water

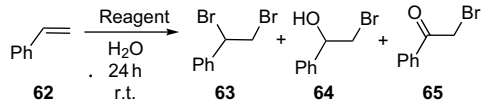


54 R=H, n=1 — **55a** — **55b** — **55c**
56 R=OCH_3, n=1 — **57a** — **57b** — **57c**
58 R=H, n=2 — **59a** — **59b** — **59c**
60 R=OCH_3, n=2 — **61a** — **61b** — **61c**

	Sub.	Reaction conditions[a]	Conv. (%)	Distribution (%)[b]		
				a	**b**	**c**
1	**54**	H_2O_2–HBr, dark[13]	94	100	—	—
2		H_2O_2–HBr, hν	94	82	—	18
3		NBS, dark	0	—	—	—
4		NBS hν (40 W)[14]	70	—	—	100
5	**56**	H_2O_2–HBr, dark[13]	76	—	100	—
6		H_2O_2–HBr, hν	88	14	86	—
7		NBS, dark	82	—	100	—
8		NBS, hν (40 W)	94	—	100	—
9	**58**	H_2O_2–HBr, dark[13]	95	100	—	—
10		H_2O_2–HBr, hν	91	95	—	5
11		NBS, dark	8	87	—	13
12		NBS, hν	32	91	—	9
13	**60**	H_2O_2–HBr, dark[13]	80	—	100	—
14		H_2O_2–HBr, dark[c]	43	—	100	—
15		H_2O_2–HBr, hν	93	8	92	—
16		NBS, dark	85	—	100	—
17		NBS, dark[c]	78	—	100	—
18		NBS, hν	79	—	100	—

[a] Bromination with 2 mmol of H_2O_2, 1 mmol of HBr: 1 mmol of substrate in a 0.5 mL of water suspension. Bromination with NBS: 1 mmol of NBS and 1 mmol of substrate in a 0.5 mL of water suspension. Reactions were performed at room temperature.
[b] Yields were determined by ^{1}H NMR spectroscopy are based on starting compound; yields in parentheses refer to isolated yields.
[c] Time: 3 h.

Table 10
Bromination of styrene (**62**) using H_2O_2–HBr system or NBS in water as a reaction medium



Entry	Reaction conditions[a]	Conv. (%)	Distribution[b] (%)		
			63	**64**	**65**
1	H_2O_2–2HBr	100	35	53	12
2	H_2O_2–2HBr[c]	100	50	50	—
3	H_2O_2–2HBr, CH_2Cl_2	100	56	22	22
4	H_2O_2–2HBr, CH_2Cl_2[c]	100	70	30	—
5	H_2O_2–2HBr, 2NaOH, 48 h	100	—	40[d]	—
6	1NBS	100	—	100	—
7	2NBS	100	—	19	81

[a] Bromination with H_2O_2–HBr: 1.0 mmol of **62** in 0.8 mL of water. Bromination with NBS: 1.0 mmol of **62** in 0.5 mL of water.
[b] Yields were determined by ^{1}H NMR spectroscopy and are based on starting compound.
[c] Without stirring.
[d] 2-Phenyloxirane (60%) was formed.

bromination in a two-phase system (dibromination) and an aqueous system (bromohydrine formation).

When the 'on water' bromination with H_2O_2–HBr system was performed under vigorously stirred conditions, the ratio of dibromination (**63**) to bromohydroxylation (**64** and **65**) was 35:65 (Table 10, entry 1). The main product was bromohydrin **64**, which was further oxidized under reaction conditions to α-bromoacetophenone **65**. Performing the same reaction without stirring, so as not to disturb the interface increases the amount of dibromination and the dibromide **63** and the bromohydrin **64** were formed in a 50:50 ratio (entry 2). Next, an analogous study with a solution of **62** in CH_2Cl_2 was performed. In this case a further increase in dibromination was noted with **63** being the main product (dibromination/bromohydroxylation=56:44, entry 3). An analogous experiment without stirring resulted in 70% of the dibromide **63** and only 30% of the bromohydrin **64** (entry 4). This indicates that not only the nature of the brominating reagent defines the outcome of bromination but also the way in which the reaction under two-phase conditions is performed. Penetration of Br_2 into the organic phase could lead to the formation of dibromide **63**, while increasing the interfacial area bromohydroxylation becomes the more important process. It is a challenge to direct the reaction towards the selective formation of bromohydrin **64** in oxidative bromination because increasing the basicity of the aqueous phase leads to the rapid decomposition of H_2O_2, while the addition of NaOH immediately after bromination to perform nucleophilic substitution leads to an intramolecular nucleophilic attack resulting in 2-phenyloxirane (entry 5). Expectedly, 'on water' bromination with NBS produced 2-bromo-1-phenylethanol **64** both selectively and quantitatively (entry 6). Increasing the amount of NBS to 2 equiv results in further oxidation to produce 2-bromo-1-phenylethanone **65** (entry 7).

3. Conclusion

We have studied 'on water' electrophilic and radical bromination using two types of reagent: NBS and oxidative bromination with H_2O_2–HBr. Both brominating systems in the aqueous phase allow for a straightforward isolation of the brominated product since it is the only non-soluble compound remaining after the reaction. The H_2O_2–HBr system in water was more reactive than NBS for benzyl bromination and for the bromination of ketones, while the opposite was observed in the bromination of the aromatic ring in the case of a methoxy-substituted tetralone derivative **60**. Although water activates the bromination of ketones in the aqueous H_2O_2–HBr system the use of NBS for the bromination of ketones 'on water' was unsuccessful and 1-indanone **54** reacted only through the benzyl bromination process. The reactivity of both brominating systems for electrophilic aromatic substitution is very similar, albeit oxidative bromination results in better yields and is more selective. As was shown in the bromination of styrene **62**, that the outcome of bromination (dibromination vs bromohydroxylation) is not solely defined by the structure of reagent but also by reaction conditions, such as the amount of water used, the organic solvent, stirring rate, and the structure of the interface. In conclusion, mild reaction conditions, a simple isolation procedure, inexpensive reagents and an overall reduced impact on the environment make this aqueous brominating method a promising alternative to other reported brominating methods.

4. Experimental

4.1. General

All chemicals were obtained from commercial sources and were used without further purification. Column chromatography was carried out using silica gel 60 (0.063–0.200 mm). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Varian Inova 300 MHz spectrometer. The chemical shifts (δ) are reported in parts per million relative to TMS as the internal standard for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR. Melting points were determined using a Büchi 535 melting point apparatus and were uncorrected. Mass spectra were obtained using an Autospec Q mass spectrometer with electron impact ionization (EI, 70 eV).

4.2. Typical reaction procedure for visible-light induced benzylic bromination with *N*-bromosuccinimide in water

Methylbenzene (1.0 mmol) was suspended in 5 mL of water. To this was added *N*-bromosuccinimide (178 mg, 1.0 mmol) and the mixture stirred at 500 rpm at room temperature under irradiation from a 40 W incandescent light bulb. The progress of the reaction was monitored by either TLC or GC. At the end of reaction (22–25 h) the mixture was transferred into a separating funnel and 10 mL of 0.002 M $NaHSO_3$ added. The crude product was then extracted using 3×5 mL of a hexane/ethyl acetate mixture and the combined organic phases were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture was analyzed by ^{1}H NMR spectroscopy. Finally the products were isolated by column chromatography (SiO_2, hexane/EtOAc) and identified by comparison with literature data.

*4.2.1. 4-tert-Butylbenzyl bromide (**2a**)*[21]

Yield: 159 mg (70%), oily product. ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 9H), 4.46 (s, 2H), 7.30 (d, J=8.6 Hz, 1H), 7.32 (d, J=8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 31.25, 33.56, 34.34, 125.76, 128.76, 134.76, 151.56. MS (EI): m/z 228 and 226 (M^+, 1:1 ratio), 147 (100%), 132 (38%), 117 (20%), 91 (13%).

*4.2.2. 1,1-Dibromomethyl-4-tert-butylbenzene (**2b**)*

Yield: 12 mg (4%), white crystals; mp 41–43 °C (lit.[22] 41–42 °C). ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 9H), 6.61 (s, 1H), 7.33 (d, J=8.6 Hz, 2H), 7.45 (d, J=8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 31.21, 34.78, 41.03, 125.57, 126.18, 139.13, 153.06.

*4.2.3. 2-Bromo-4-tert-butyltoluene (**3**)*[23]

Reaction in the presence of 5% AMPA at 80 °C (Table 1), 43 mg (19%) of oily product. ^{1}H NMR ($CDCl_3$): δ 1.23 (s, 9H), 2.35 (s, 3H), 7.14 (d, J=8.0 Hz, 1H), 7.21 (dd, J=8.0, 2.0 Hz, 1H), 7.53 (d, J=2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 22.2, 31.2, 34.4, 124.3, 124.8, 129.3, 130.4,

134.7, 150.8. MS (EI): *m*/*z* 228 and 226 (M^+, 1:1 ratio), 213 (100%), 211 (98%), 185 (18%), 183 (18), 132 (58), 115 (20%), 91 (16%).

*4.2.4. Ethyl 4-(bromomethyl)benzoate (**7a**)*[24]

Yield: 175 mg (72%), oily product. ^{1}H NMR ($CDCl_3$): δ 1.39 (t, *J*=7.1 Hz, 3H), 4.37 (q, *J*=7.1 Hz, 2H), 7.45 (d, *J*=8.4 Hz, 2H), 8.02 (d, *J*=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.25, 32.19, 61.02, 126.51, 128.91, 129.88, 142.43, 165.96. MS (EI): *m*/*z* 244 and 242 (M^+, 1:1 ratio), 199 (9%), 197 (9%), 163 (100%), 135 (16%), 119 (21%), 90 (15%).

*4.2.5. Ethyl 4-(dibromomethyl)benzoate (**7b**)*

Yield: 10 mg (3%), white crystals; mp 98–99 °C (lit.[25] 97–99 °C). ^{1}H NMR (DMSO-d_6): δ 1.40 (t, *J*=7.1 Hz, 3H), 4.38 (q, *J*=7.1 Hz, 2H), 6.66 (s. 1H), 7.61 (d, *J*=8.4 Hz, 2H), 7.91 (d, *J*=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.3, 40.0, 61.1, 126.5, 129.5, 131.4, 145.6, 165.8.

*4.2.6. 1-(4-(Bromomethyl)phenyl)ethanone (**9a**)*

Yield: 162 mg (76%), white crystals; mp 38.5–40.0 °C (lit.[26] 42–43 °C). ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H), 4.50 (s, 2H), 7.48 (d, *J*=8.5 Hz, 2H), 7.93 (d, *J*=8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 26.6, 32.1, 128.8, 129.2, 136.9, 142.8, 197.3. MS (EI): *m*/*z* 214 and 212 (M^+, 1:1 ratio), 199 (9%), 197 (9%), 171 (4%), 169 (4%), 133 (100%), 118 (42%), 105 (25%).

*4.2.7. 4-Methylbenzoic acid (**13a**)*

Yield: 109 mg (80%), white crystals; mp 178–180 °C (lit.[27] 182–183 °C). ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H), 7.27 (d, *J*=8.2 Hz, 2H), 8.00 (d, *J*=8.2 Hz).

4.3. Large scale visible-light induced benzylic bromination with *N*-bromosuccinimide in water

Toluene (**4**, 460 mg, 5.0 mmol) was combined together with water (25 mL) and NBS (900 mg, 5.05 mmol) in a conical flask. The reaction mixture was stirred at 500 rpm at room temperature under irradiation from a 40 W incandescent light bulb for 24 h. At the end of the reaction the lower organic and upper aqueous phases were separated and the organic phase washed with 2×10 mL of water. The organic phase was then transferred to the column. Column chromatography (SiO_2, hexane/EtOAc) gave 658 mg (77%) of 1-bromomethylbenzene (**5a**)[28] oily product. ^{1}H NMR ($CDCl_3$): δ 4.51 (s, 2H), 7.30–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 33.50, 128.79, 129.02, 137.80. MS (EI): *m*/*z* 172 and 170 (M^+, 1:1 ratio), 91 (100%), 65 (15%).

4.4. Typical reaction procedure for visible-light induced benzylic bromination with aqueous H_2O_2–HBr system

Methyl benzene (1.0 mmol) was added to 0.8 mL aqueous solution of 2.0 mmol of H_2O_2 and 1.1 mmol of HBr. The reaction mixture was then stirred at 500 rpm at room temperature under irradiation from a 40 W incandescent light bulb for 10–24 h. For deactivated substrates, like **6**, **10** and **17**, the substrate (1.0 mmol) was added to 0.6 mL of an aqueous solution of 1.1 mmol of HBr to which 2.0 mmol of 30% aqueous H_2O_2 was added gradually (0.5 mmol per 3 h). The reaction mixture was stirred at 500 rpm at room temperature while under irradiation from a 125 W high-pressure mercury lamp. On completion the work up procedure was the same as that for bromination with NBS. The crude reaction product was analyzed by ^{1}H NMR spectroscopy, isolated by column chromatography and identified by comparison with literature data.

*4.4.1. 1-(Bromomethyl)-4-nitrobenzene (**11a**)*

Yield: 194 mg (90%), white crystals; mp 98–99 °C (lit.[29] 98–99 °C). ^{1}H NMR ($CDCl_3$): δ 4.52 (s, 2H), 7.57 (d, *J*=8.7 Hz, 2H), 8.21 (d, *J*=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 30.8, 124.0, 129.9, 144.7, 147.6. MS (EI): *m*/*z* 217 and 215 (M^+, 1:1 ratio), 136 (100%), 106 (23%), 90 (34%), 78 (31%).

*4.4.2. 1-Bromo-4-(bromomethyl)benzene (**16a**)*

Yield: 193 mg (77%), white crystals; mp 52–54 °C (lit.[30] 62–63 °C). ^{1}H NMR ($CDCl_3$): δ 4.43 (s, 2H), 7.26 (d, *J*=8.3 Hz, 2H), 7.47 (d, *J*=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 32.3, 122.4, 130.6, 131.9, 136.8. MS (EI): *m*/*z* 252, 250 and 249 (M^+, 1:2:1 ratio), 171 (100%), 169 (100%), 90 (80%), 63 (58%).

*4.4.3. 4-(Bromomethyl)benzophenone (**18a**)*

Yield: 248 mg (90%), white crystals; mp 113–114 °C (lit.[31] 110–111 °C). ^{1}H NMR ($CDCl_3$): δ 4.53 (s, 2H), 7.46–7.52 (m, 4H), 7.57–7.63 (m, 1H), 7.77–7.81 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 32.2, 128.3, 128.9, 130.0, 130.6, 132.5, 136.4, 137.4, 142.1, 196.0. MS (EI): *m*/*z* 276 and 274 (M^+, 1:1 ratio), 195 (100%), 167 (52%), 77 (14%).

*4.4.4. 1-Bromomethyl-4-methylbenzene (**20a**)*

Yield: 115 mg (62%), white crystals; mp 32.6–33.1 °C (lit.[32] 38.0–39.7 °C). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 4.47 (s, 2H), 7.15 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=8.0 Hz, 2H). MS (EI): *m*/*z* 186 and 184 (M^+, 1:1 ratio), 105 (100%), 77 (12%).

*4.4.5. 1,4-Bis-bromomethylbenzene (**20b**)*

Yield: 50 mg (19%), white crystals; mp 144.3–145.4 °C (lit.[33] 144.8–145.4 °C). ^{1}H NMR ($CDCl_3$): δ 4.46 (s, 4H), 7.36 (s, 4H). MS (EI): *m*/*z* 266, 264 and 262 (M^+, 1:2:1 ratio), 185 (81%), 183 (83%), 104 (100%), 77 (17%).

4.5. Large scale visible-light induced benzylic bromination with aqueous H_2O_2–HBr system

Toluene (**4**, 460 mg, 5.0 mmol) was combined together with 4.2 mL of an aqueous solution of 10.0 mmol of H_2O_2 and 5.5 mmol of HBr in a conical flask. The reaction mixture was stirred at 500 rpm at room temperature under irradiation from a 40 W incandescent light bulb for 24 h. At the end of reaction the lower organic and the upper aqueous phases were separated and the organic phase dried under vacuum to give 675 mg (79%) benzyl bromide (**5a**) as pure oil.

4.6. Typical reaction procedure for bromination of aromatic molecules with *N*-bromosuccinimide in water

The substrate (1.0 mmol) was initially suspended in 5 mL of water. To this *N*-bromosuccinimide (178 mg, 1 mmol) was added and the reaction mixture stirred at 500 rpm at room temperature for 5–32 h. The progress of the reaction was monitored by either TLC or GC. At the end of reaction, the work up procedure depended on the aggregate state of the products. In the case of solid products, the reaction mixture was filtered off and rinsed with water (10 mL). If the product was oily, in the case of the small-scale experiment, the mixture was transferred into a separating funnel, to which 10 mL of water and 2 mL of 0.01 M $NaHSO_3$ were added. The crude product was extracted using 3×5 mL of a mixture of hexane and ethyl acetate and the combined organic phase dried over anhydrous Na_2SO_4. The solvent was then evaporated off and the crude reaction product analyzed by ^{1}H NMR spectroscopy. Finally the products were isolated by column chromatography and identified by comparison with literature data.

4.7. Typical reaction procedure for bromination of aromatic molecules in aqueous H_2O_2–HBr system

The substrate (1.0 mmol) was suspended in 0.5 mL of water in a flask and the contents covered with aluminium foil to create

a dark environment. To this a 48% aqueous solution of HBr (0.114 mL, 1.0 mmol) and a 30% aqueous solution of H_2O_2 (0.204 mL, 2 mmol) were added. The reaction mixture was stirred at 500 rpm at room for 5–32 h. The progress of the reaction was monitored by either TLC or GC. At the end of reaction, the work up procedure depended on the aggregate state of the products.

4.8. Work up procedure for liquid products

The reaction mixture was dissolved in 5 mL of hexane/ethyl-acetate (20:1 or 10:1) and solid $NaHSO_3$ added to reduce any unreacted Br_2 or H_2O_2. The solution was then dried over anhydrous Na_2SO_4. The insoluble material was filtered off and the organic solvent evaporated under reduced pressure. The crude reaction mixture was then analyzed by ^{1}H NMR spectroscopy. Where necessary, the product was isolated by column chromatography (SiO_2, hexane–EtOAc), and its structure determined by comparison with literature data.

4.9. Work up procedure for solid products

The reaction mixture was filtered off and rinsed with water (10 mL). The crude mixture was then analyzed by ^{1}H NMR spectroscopy. The product was isolated by either column chromatography (SiO_2, hexane–EtOAc) or purified by crystallization and its structure determined by comparison with literature data.

*4.9.1. 2-Bromo-1,3,5-trimethylbenzene (**23**)*[28]

Yield: 195 mg (98%), oily product. ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H), 2.36 (s, 6H), 6.88 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 20.6, 23.7, 124.2, 129.0, 136.2, 137.8. MS (EI): *m*/*z* 200 and 198 (M^+, 1:1 ratio), 119 (100%), 103 (13%), 91 (28%), 77 (13%).

*4.9.2. 3-Bromo-1,2,4,5-tetramethylbenzene (**25a**)*

Yield: 98 mg (46%), white crystals; mp 60–61 °C (lit.[34] 60.5 °C). ^{1}H NMR ($CDCl_3$): δ 2.27 (s, 6H), 2.35 (s, 6H), 6.88 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.2, 21.0, 129.0, 130.3, 133.9, 134.7. MS (EI): *m*/*z* 214 and 212 (M^+, 1:1 ratio), 133 (100%), 119 (32%), 73 (25%).

*4.9.3. 1,4-Dibromo-2,3,5,6-tetramethylbenzene (**25b**)*

Yield: 73 mg (25%), white crystals; mp 200 °C (lit.[34] 198–199 °C). ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 22.3, 128.1, 135.0. MS (EI): *m*/*z* 294, 292 and 290 (M^+, 1:2:1 ratio), 213 (60%), 211 (60%).

*4.9.4. 2-Bromo-1-methylnaphthalene (**27**)*

Yield: 208 mg (94%), pale brown crystals; 36–37 °C (lit.[35] 31 °C). ^{1}H NMR ($CDCl_3$): δ 2.64 (s, 3H), 7.14 (dd, *J*=7.6, 0.7 Hz, 1H), 7.56 (m, 2H), 7.65 (d, *J*=7.6 Hz, 1H), 7.96 (dd, *J*=7.3, 2.3 Hz, 1H), 8.23 (dd, *J*=7.8, 2.0 Hz, 1H). ^{13}C NMR (76 MHz, $CDCl_3$, Me_4Si): δ 19.3, 119.6, 120.7, 124.6, 126.5, 127.0, 127.7, 129.5, 131.8, 133.8, 134.4. MS (EI): *m*/*z* 222 and 220 (M^+, 1:1 ratio), 141 (100%).

*4.9.5. 1-Bromo-2-methylnaphthalene (**29**)*[36]

Yield: 210 mg (95%), oily product. ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 3H), 7.32 (d, *J*=8.3 Hz, 1H), 7.44 (ddd, *J*=8.0, 6.9, 1.0 Hz, 1H), 7.55 (ddd, *J*=8.4, 6.9, 1.3 Hz, 1H), 7.68 (d, *J*=8.3 Hz, 1H), 7.76 (d, *J*=8.00 Hz, 1H), 8.28 (d, *J*=8.48 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 24.14, 124.0, 125.6, 126.8, 127.2, 128.0, 128.7, 132.5, 132.9, 135.9. MS (EI): *m*/*z* 222 and 220 (M^+, 1:1 ratio), 141 (100%).

*4.9.6. 1-Bromo-4-methoxybenzene (**31**)*[8a]

Yield: 168 mg (90%), oily product. ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3H), 6.78 (d, *J*=9.0 Hz, 2H), 7.37 (d, *J*=9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 55.4, 115.7, 119.7, 122.2, 132.2. MS (EI): *m*/*z* 188 and 186 (M^+, 1:1 ratio), 173 (51%), 171 (51%), 145 (34%), 143 (34%), 77 (15%).

*4.9.7. 2-Bromo-1-methoxy-4-methylbenzene (**33**)*[37]

Yield: 191 mg (95%), oily product. ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H), 3.85 (s, 3H), 6.78 (d, *J*=8.4 Hz, 1H), 7.05 (dd, *J*=8.4, 2.2 Hz, 1H), 7.35 (d, *J*=2.2 Hz). MS (EI): *m*/*z* 202 and 200 (M^+, 1:1 ratio), 187 (39%), 185 (39%), 121 (32%), 78 (71%).

*4.9.8. 1-Bromonaphthalene-2-ol (**35**)*

Yield: 201 mg (90%), brown crystals; mp 78–80 °C (lit.[38] 78 °C). ^{1}H NMR ($CDCl_3$): δ 7.25 (d, *J*=8.9 Hz, 1H), 7.37 (ddd, *J*=8.1, 6.9, 1.2 Hz, 1H), 7.56 (m, 2H), 7.71 (d, *J*=8.9 Hz, 1H), 8.00 (d, *J*=8.5 Hz, 1H). MS (EI): *m*/*z* 224 and 222 (M^+, 1:1 ratio), 143 (5%), 114 (89%), 87 (21%), 63 (35%).

*4.9.9. N-(2-Bromo-4-methylphenyl)acetamide (**37**)*

Yield: 217 mg (95%), white crystals; mp 119.4–120.4 °C (lit.[39] 117 °C). ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H), 2.29 (s, 3H), 7.10 (d, *J*=8.3 Hz, 1H), 7.34 (s, 1H), 7.53 (s, 1H, NH), 8.15 (d, *J*=8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 20.5, 24.7, 113.2, 121.9, 128.9, 132.4, 133.1, 135.2, 168.1. MS (EI): *m*/*z* 229 and 227 (M^+, 1:1 ratio), 187 (100%), 185 (100%), 148 (97%), 106 (90%), 77 (40%).

*4.9.10. N-(2-Bromo-4-methylphenyl)benzamide (**39**)*

Yield: 258 mg (89%), white crystals; mp 146–148 °C (lit.[40] 148 °C). ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H), 4.76 (br s, 1H, NH), 7.18 (dd, *J*=8.4, 1.4 Hz, 1H), 7.41 (d, *J*=1.4 Hz, 1H), 7.48–7.69 (m, 2H), 7.93 (dd, *J*=8.0, 1.3 Hz, 2H), 8.39 (d, *J*=8.4 Hz, 2H). ^{13}C NMR (76 MHz, $CDCl_3$, Me_4Si): δ 20.5, 113.7, 120.28, 121.6, 127.0, 128.9, 129.1, 129.5, 132.0, 132.5, 135.4, 165.1. MS (EI): *m*/*z* 291 and 289 (M^+, 1:1 ratio), 210 (62%), 105 (100%), 77 (40%).

*4.9.11. 2-Bromo-4-(trifluoromethyl)aniline (**41a**)*[41]

Yield: 211 mg (88%), oily product. ^{1}H NMR ($CDCl_3$): δ 4.38 (br s, 2H, NH_2), 6.74 (d, *J*=8.4 Hz, 1H), 7.32 (dd, *J*=8.4, 1.7 Hz, 1H), 7.65 (d, *J*=1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 108.0, 114.7, 120.9 (q, CF_3), 125.6, 129.9, 147.0. MS (EI): *m*/*z* 241 and 239 (M^+, 1:1 ratio), 222 (18%), 220 (18%), 160 (20%), 140 (17%), 107 (27%).

*4.9.12. 2,6-Dibromo-4-(trifluoromethyl)aniline (**41b**)*[42]

Yield: 290 mg (91%), oily product. ^{1}H NMR ($CDCl_3$): δ 4.88 (br s, 2H, NH_2), 7.62 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 107.7, 121.2 (q, CF_3), 128.9, 129.0, 144.8. MS (EI): *m*/*z* 321, 319 and 317 (M^+, 1:2:3 ratio), 302 (4%), 300 (12%), 298 (4%), 158 (25%).

*4.9.13. 1-Bromonaphthalene (**43**)*[43]

Yield: 186 mg (90%), oily product. ^{1}H NMR ($CDCl_3$): δ 7.27 (t, *J*=7.9 Hz, 1H), 7.52 (m, 2H), 7.78 (m, 3H), 8.21 (d, *J*=8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 122.8, 125.8, 126.1, 126.6, 127.01, 127.2, 128.2, 129.8, 131.9, 134.5. MS (EI): *m*/*z* 208 and 206 (M^+, 1:1 ratio), 127 (70%), 84 (100%).

*4.9.14. Bromobenzene (**45**)*

Yield: 31 mg (20%), oily product. ^{1}H NMR ($CDCl_3$): δ 7.21–7.31 (m, 3H), 7.48–7.51 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 122.5, 126.8, 130.0, 131.6.

*4.9.15. 2-Bromo-4-tert-butylphenol (**47a**)*[44]

Yield: 206 mg (90%), oily product. ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 9H), 5.36 (s, 1H, OH), 6.95 (d, *J*=8.5 Hz, 1H), 7.23 (dd, *J*=8.5, 2.3 Hz, 1H), 7.44 (d, *J*=2.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 31.3, 34.1, 109.8, 115.42, 126.1, 128.7, 145.0, 149.7. MS (EI): *m*/*z* 230 and 228 (M^+, 1:1 ratio), 215 (100%), 213 (100%), 187 (14%), 185 (14%), 134 (78%).

*4.9.16. 2,6-Dibromo-4-tert-butylphenol (**47b**)*

Yield: 302 mg (98%), white crystals; mp 70–71 °C (lit.[45] 70–71 °C). ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 9H), 5.71 (s, 1H, OH), 7.41 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 31.2, 34.3, 109.4, 129.1, 146.0, 147.0. MS (EI): *m*/*z*

310, 308 and 306 (M^+, 1:2:1 ratio), 295 (60%), 293 (100%), 291 (60%), 214 (31%), 212 (31%).

*4.9.17. 2,6-Dibromo-4-nitrophenol (**49b**)*

Yield: 282 mg (95%), yellow crystals; mp 148–150 °C (lit.[46] 141 °C). ^{1}H NMR ($CDCl_3$): δ 6.55 (br s, 1H, OH), 8.41 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 109.6, 128.0, 150.0, 155.0. MS (EI): *m*/*z* 299, 297 and 295 (M^+, 1:2:1 ratio), 269 (32%), 267 (63%), 265 (32%), 187 (25%), 185 (25%), 172 (41%), 170 (41%).

*4.9.18. 2,6-Dibromo-4-tert-butylaniline (**51b**)*[47]

Yield: 292 mg (95%), oily product. ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 9H), 4.40 (br s, 2H, NH_2), 7.37 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 31.3, 34.1, 108.7, 128.9, 139.5, 143.1. MS (EI): *m*/*z* 309, 307 and 305 (M^+, 1:2:1 ratio), 294 (60%), 292 (100%), 290 (60%), 213 (35%), 211 (35%).

*4.9.19. 2-Bromo-4-nitroaniline (**53a**)*

Yield: 163 mg (75%), yellow crystals; mp 103–104 °C (lit.[48] 102–104 °C). ^{1}H NMR ($CDCl_3$): δ 4.90 (br s, 2H, NH_2), 6.75 (d, *J*=9.0 Hz, 1H), 8.02 (dd, *J*=9.0, 2.5 Hz, 1H), 8.36 (d, *J*=2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 107.0, 113.4, 124.9, 129.1, 150.0. MS (EI): *m*/*z* 218 and 216 (M^+, 1:1 ratio), 172 (25%), 170 (25%), 90 (100%).

*4.9.20. 2,6-Dibromo-4-nitroaniline (**53b**)*

Yield: 281 mg (95%), yellow crystals; mp 202–203 °C (lit.[49] 203 °C). ^{1}H NMR ($CDCl_3$): δ 5.30 (br s, 2H, NH_2), 8.34 (s, 2H). MS (EI): *m*/*z* δ 298, 296 and 294 (M^+, 1:2:1 ratio), 252 (15%), 250 (36%), 248 (15%).

4.10. Typical reaction procedure for bromination of ketones with *N*-bromosuccinimide in water

Substrate (1.0 mmol), 0.5 mL of water and *N*-bromosuccinimide (178 mg, 1.0 mmol) were combined in a procedure analogous to the bromination of aromates with NBS. The reaction mixture was stirred at room temperature in either the dark or under irradiation from a 40 W incandescent light bulb, as noted in Table 9. After 24 h, an identical work up procedure as in the case of the bromination of aromates with NBS was applied. First, the crude reaction product was analyzed by ^{1}H NMR spectroscopy and then the products were isolated by column chromatography and identified by comparison with literature data.

*4.10.1. 3-Bromoindan-1-one (**55c**)*

Yield: 110 mg (52%), crystals; mp 50–52 °C (lit.[50] 54.5–55.0 °C). ^{1}H NMR ($CDCl_3$): δ 3.05 (dd, *J*=19.8, 2.7 Hz, 1H), 3.36 (dd, *J*=19.8, 7.2 Hz, 1H), 5.6 (dd, *J*=7.2, 2.7 Hz, 1H), 7.46–7.51 (m, 1H), 7.70–7.76 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 40.6, 48.0, 123.3, 127.5, 129.6, 135.5, 135.9, 154.2, 201.4. MS (EI): *m*/*z* 212 and 210 (M^+, 1:1 ratio), 131 (100%), 103 (54%).

4.11. Typical reaction procedure for bromination of ketones in aqueous H_2O_2–HBr system

The substrate (1.0 mmol), 0.5 mL of water, a 48% aqueous solution of HBr (0.114 mL, 1.0 mmol or 0.125 mL, 1.1 mmol) and a 30% aqueous solution of H_2O_2 (0.204 mL, 2.0 mmol) were combined in a procedure analogous to the bromination of aromates with H_2O_2–HBr. The reaction mixture was stirred at room temperature either in the dark or under irradiation from a 40 W incandescent light bulb, as noted in Table 9. After 24 h, an identical work up procedure followed as for the bromination of aromates with H_2O_2–HBr. The crude reaction product was analyzed by ^{1}H NMR spectroscopy. The products were isolated by column chromatography and identified by comparison with literature data.

*4.11.1. 2-Bromoindan-1-one (**55a**)*

Yield: 169 mg (80%), crystals, mp 37–38 °C (lit.[13] 37–38 °C). ^{1}H NMR ($CDCl_3$): δ 3.42 (dd, *J*=18.1, 3.2 Hz, 1H), 3.84 (dd, *J*=18.1, 7.5 Hz, 1H), 4.65 (dd, *J*=7.5, 3.2 Hz, 1H), 7.40–7.46 (m, 2H), 7.64–7.69 (m, 1H), 7.81–7.84 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 37.9, 44.0, 125.0, 126.4, 128.2, 133.5, 135.9, 151.1, 199.5. MS (EI): *m*/*z* 212 and 210 (M^+, 1:1 ratio), 131 (100%), 103 (46%), 77 (28%).

*4.11.2. 4-Bromo-5-methoxy-indan-1-one (**57b**)*

Yield: 137 mg (57%), white crystals; mp 120–121 °C (lit.[19] 120 °C). ^{1}H NMR ($CDCl_3$): δ 2.67–2.73 (m, 2H), 3.02–3.09 (m, 2H), 4.00 (s, 3H), 6.94 (d, *J*=8.4 Hz, 1H), 7.70 (d, *J*=8.4 Hz). ^{13}C NMR ($CDCl_3$): δ 27.1, 36.3, 56.8, 110.0, 111.2, 124.0, 131.8, 156.9, 160.9, 204.9. MS (EI): *m*/*z* 242 and 240 (M^+, 1:1 ratio), 214 (17%), 212 (17%), 199 (12%), 197 (12%), 171 (11%), 169 (11%), 161 (10%).

*4.11.3. 2-Bromo-1-tetralone (**59a**)*

Yield: 198 mg (88%), crystals; mp 40–42 °C (lit.[13] 38–39 °C). ^{1}H NMR ($CDCl_3$): δ 2.41–2.60 (m, 2H), 2.90 (dt, *J*=17.2, 4.5 Hz, 1H), 3.26–3.37 (m, 1H), 4.73 (t, *J*=4.5 Hz, 1H), 7.25 (d, *J*=7.9 Hz, 1H), 7.34 (t, *J*=7.9 Hz, 1H), 7.51 (td, *J*=7.9, 1.5 Hz, 1H), 8.09 (dd, *J*=7.9, 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 26.1, 31.9, 50.4, 127.1, 128.6, 128.7, 129.9, 134.1, 142.9, 190.5. MS (EI): *m*/*z* 226 and 224 (M^+, 1:1 ratio), 144 (33%), 118 (100%), 115 (32%), 90 (42%).

*4.11.4. 5-Bromo-6-methoxy-1-tetralone (**61b**)*

Yield: 182 mg (60%), crystals; mp 119–120 °C (lit.[51] 119–122 °C). ^{1}H NMR ($CDCl_3$): δ 2.09–2.18 (m, 2H), 2.60 (t, *J*=6.6 Hz, 2H), 3.02 (t, *J*=6.2 Hz, 2H), 4.00 (s, 3H), 6.87 (d, *J*=8.7 Hz, 1H), 8.04 (d, *J*=8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 22.4, 30.4, 38.0, 56.4, 109.5, 113.0, 127.5, 128.3, 145.4, 159.7, 196.7. MS (EI): *m*/*z* 256 and 254 (M^+, 1:1 ratio), 228 (100%), 226 (100%), 200 (11%), 198 (11%), 119 (27%).

4.12. Reaction procedure for bromination of styrene with *N*-bromosuccinimide in water

Styrene (**62**, 104 mg, 1.0 mmol), 0.5 mL of water and *N*-bromosuccinimide (178 mg, 1.0 mmol or 356 mg, 2.0 mmol) were combined in a procedure analogous to the bromination of aromates with NBS. The reaction mixture was vigorously stirred at room temperature in the dark. After 24 h, an identical work up procedure to that of the bromination of aromates with NBS was followed. The crude reaction product was analyzed by ^{1}H NMR spectroscopy and the products isolated by column chromatography and identified by comparison with literature data.

*4.12.1. 2-Bromo-1-phenylethanol (**63**)*[52]

Yield: 191 mg (95%), white crystals; mp 114–115 °C. ^{1}H NMR ($CDCl_3$): δ 2.75 (br s, 1H, OH), 3.54 (dd, 1H, *J*=10.4, 8.2 Hz), 3.60 (dd, 1H, *J*=10.4, 4.0 Hz), 4.90 (dd, 1H, *J*=8.2, 4.0 Hz), 7.34–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 40.1, 73.8, 125.9, 128.4, 128.6, 140.2. MS (EI): *m*/*z* 202 and 200 (M^+, 1:1 ratio), 121 (2%), 107 (100%).

4.13. Reaction procedure for bromination of styrene in aqueous H_2O_2–HBr system

Styrene (**62**, 104 mg, 1.0 mmol), 0.5 mL of water (or 0.25 mL of water and 0.25 mL of CH_2Cl_2), a 48% aqueous solution of HBr (0.228 mL, 1.0 mmol) and a 30% aqueous solution of H_2O_2 (0.102 mL, 1.0 mmol) were combined in a procedure analogous to the bromination of aromates with H_2O_2–HBr. The reaction mixture was vigorously stirred at room temperature in the dark for 24 h. For the reaction with NaOH, after bromination NaOH (80 mg, 2.0 mmol, dissolved in 3 mL of water) was added. An identical work up procedure followed as in the case of the bromination of aromates with H_2O_2–HBr. The crude reaction mixture was then analyzed by ^{1}H NMR spectroscopy and the

reaction products were isolated by column chromatography and identified by comparison with literature data.

*4.13.1. 1,2-Dibromoethylbenzene (**64**)*

Yield: 74 mg (28%), white crystals; mp 70–72 °C (lit.[53] 70–72 °C). ^{1}H NMR ($CDCl_3$): δ 4.06 (t, J=10.4 Hz, 1H), 4.08 (dd, J=10.4, 5.7 Hz, 1H), 5.14 (dd, J=10.4, 5.7 Hz, 1H), 7.32–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 35.0, 50.9, 127.6, 128.8, 129.2, 138.6. MS (EI): m/z 185 (60%), 183 (60%), 104 (100%).

*4.13.2. α-Bromoacetophenone (**65**)*

Yield: 10 mg (5%), crystals; mp 48.8–49.3 °C (lit.[13] 49–51 °C). ^{1}H NMR ($CDCl_3$): δ 4.46 (s, 2H), 7.49 (t, J=7.4 Hz, 2H), 7.61 (tt, J=7.4, 1.5 Hz, 1H), 7.98 (dd, J=7.4, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 30.9, 128.8, 128.9, 133.9, 133.9, 191.2. MS (EI): m/z 200 and 198 (M^+, ratio 1:1), 105 (100%), 77 (22%), 69 (12%), 57 (19%).

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