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Oxidative Halogenation with "Green" Oxidants: Oxygen and Hydrogen Peroxide

*Ajda Podgoršek, Marko Zupan, and Jernej Iskra**

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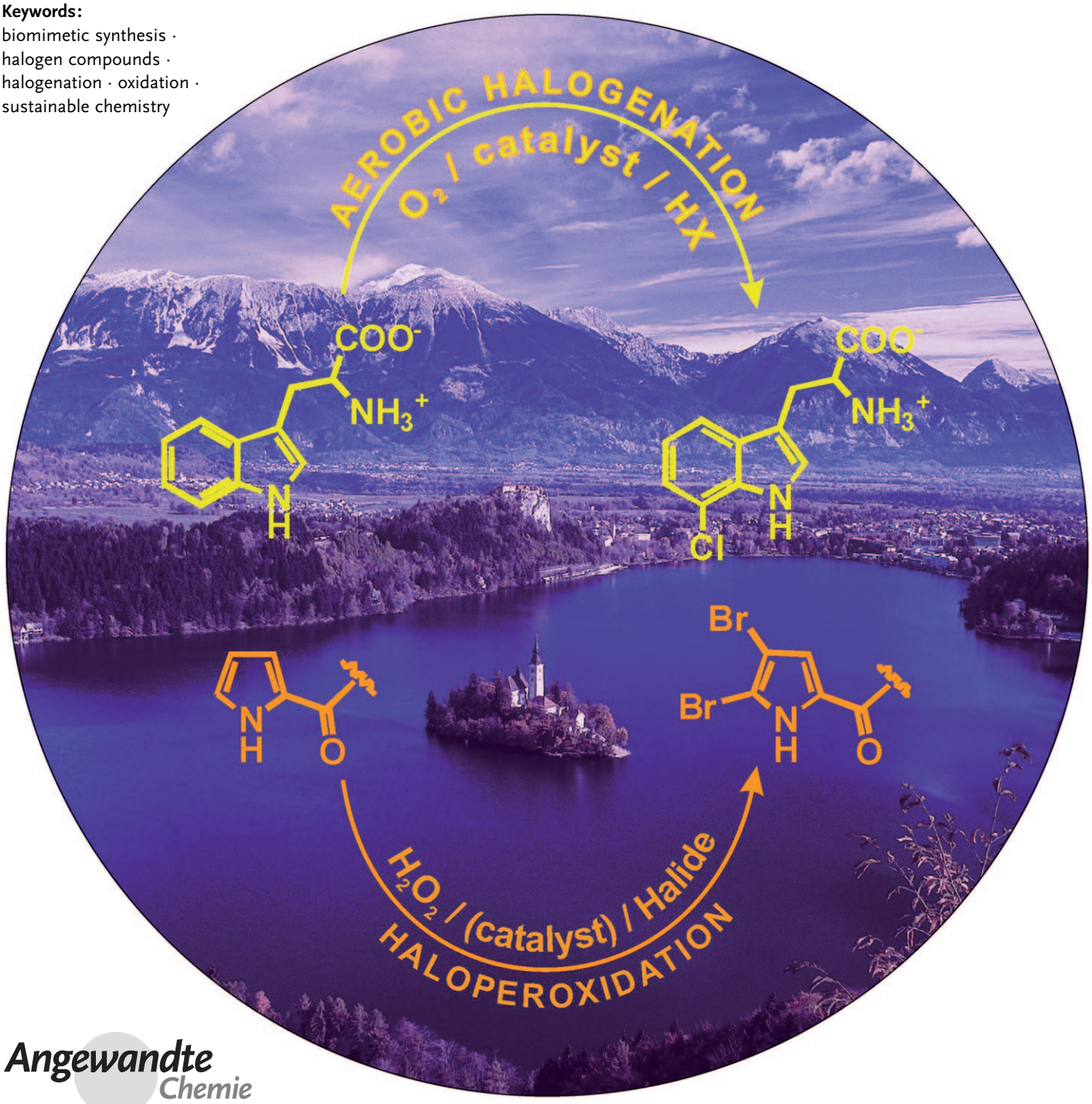
biomimetic synthesis · halogen compounds · halogenation · oxidation · sustainable chemistry



It is difficult to imagine organic chemistry without organo-halogen compounds and the molecular halogens needed for their preparation. The halogens have very different reactivity, with iodine usually requiring some form of activation, while others are reactive and hazardous chemicals. To avoid their use, various modified reagents have been discovered (N-bromo- and N-chlorosuccinimide, Select-fluor…), but halogens are used to prepare these reagents and when they are used the atom economy is poor. A better approach, which is based on biomimetric research on oxidative halogenation in nature, consists of generating the halogenating reagent in situ under acidic conditions from a halide salt. The result of such a reaction has been halogenation with 100% halogen atom economy. Suitable oxidants for the oxidation of halides are hydrogen peroxide and oxygen.

From the Contents

1. Introduction

Nature has always served as a source of inspiration for those working in diverse areas—from creating intelligent systems to discovering new building blocks. In this respect, organic chemistry is no exception, although chemists have yet to match the efficiency by which nature synthesizes complex and chiral molecules. A good example is halogenation: Halogenated organic compounds play a very important role in chemistry, they are essential in organic synthesis as starting compounds and synthetic intermediates, as designer molecules for material science, industrial chemicals, and bioactive compounds.[1–3] Electrophilic halogenation in nature mainly occurs by oxidative halogenation through the catalyzed oxidation of the halide ion to form a halogenating reagent. (An exception is fluorination, since it is too difficult to oxidize fluoride.) In the laboratory, however, halogenation is usually carried out with hazardous, toxic, and corrosive molecular halogens, and furthermore often performed in chlorinated solvents. A growing ecological awareness among chemists has coincided with an increased understanding of oxidative halogenation in biological systems, which has boosted research in the field of oxidative halogenation.

From a "green" chemistry perspective[4,5] the best candidates for oxidants would be either hydrogen peroxide or oxygen since water would be the only side product (Scheme 1). This reaction is widely used in industry during the preparation of vinyl chloride, where waste HCl generated during the production of isocyanate is regenerated by passing it together with oxygen and ethylene in the gas phase over a Cu^{II} catalyst at a temperature of over 200 °C.[6] On the other hand, various oxidative halogenation methods are reported in the literature, where residual HX is regenerated by various oxidants such as metals, persulfates, and hypervalent iodine oxidants. Recently, the environmental, health, and safety aspects of various methods for the dibromination of alkenes—modified reagents (NBS), carrying agents (mainly derivatives of pyridinium perbromides), and oxidative halogenation—have been compared against dibromination with Br_2 in $CHCl_3$ (Figure 1).[7] Based simply on the amount of waste produced, it is difficult to match dibromination with bromine, although oxidative halogenation could be competitive if either H_2O_2 or air is used as the oxidant. To obtain the complete picture, other factors should be taken into consideration, for example,

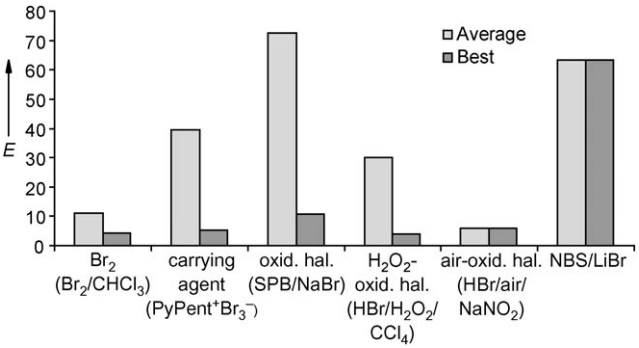
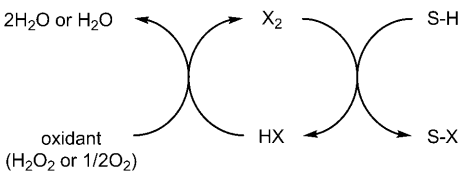


Figure 1. Comparison of environmental factor *E* (kg of waste per kg of product) for the dibromination of alkenes, as calculated by EATOS software. The method with the lowest *E* factor is presented in brackets.[7–12] (A list of abbreviations can be found at the end of the Review.)



Scheme 1. Oxidative halogenation with H_2O_2 or O_2.

[*] Dr. A. Podgoršek, M. Zupan, Prof. J. Iskra
Laboratory of Organic and Bioorganic Chemistry
Department of Physical and Organic Chemistry
"Jožef Stefan" Institute
Jamova 39, 1000 Ljubljana (Slovenia)
Fax: (+386) 1-4773-822
http://www.ijs.si/ijsw/Physical_and_Organic_Chemistry_K3/Iskra
E-mail: jernej.iskra@ijs.si

origin of the starting material, waste and its disposal, toxicity, and safety issues. Moreover, oxidative halogenation has the potential to be used in reactions where only one halogen atom is incorporated into the molecule and the residual HBr is regenerated by oxidation (Scheme 1).

This Review focuses on the current status of oxidative halogenation reactions with hydrogen peroxide and oxygen as the oxidants, with emphasis on the development of new catalysts and new reaction systems in noncatalyzed reactions.

2. Metal-Catalyzed Oxidative Halogenation with Hydrogen Peroxide

2.1. Biological Halogenation and Biomimetics

The number of known naturally occurring organohalogen compounds has increased tremendously during the last few decades. Fifty years ago there were less than 30 known examples, whereas today there are more than 4500 documented examples of naturally occurring organohalogen compounds (ca. 120 iodinated, 2100 brominated, 2300 chlorinated, and 30 fluorinated compounds).[13–15] Our understanding of biological halogenation also evolved concurrently, and haloperoxidases with various cofactors (heme-containing, vanadium-containing, metal-free, etc.) were discovered.[14,15] The first halogenating agent to be discovered in biological systems was the heme-dependent enzyme chloroperoxidase (isolated from the fungus *Caldariomyces fumago*) which uses hydrogen peroxide and chloride anions for "electrophilic" chlorination.[16,17] To date, chloroperoxidase from *Caldariomyces fumago* remains the most studied halogenating enzyme. The use of enzymes for halogenation is still potentially the most effective and environmentally friendly route, but so far large-scale enzymatic halogenation has not been commercialized because of the low operational stability of the haloperoxidase enzymes (resulting from either inactivation with H_2O_2 or the organic solvent).[18] Consequently, these reactions need to be performed in mixtures of dilute aqueous buffer and organic solvents, thus rendering them economically unattractive. There have been several efforts to enhance its stability, including maintaining a low H_2O_2 concentration during the reaction by the continuous addition of peroxide[19] or by in situ generation of H_2O_2.[20] The use of *tert*-butylhydroperoxide (TBHP) in the place of H_2O_2 has proven successful in some cases.[21] In other strategies, polymers[22] and antioxidants[23] were added, or co-solvents such as an ionic liquid[24,25] or ternary systems[26] were employed. Immobilization of haloperoxidases on solid supports did increase the stability of the enzyme and facilitated its recovery.[27] A promising alternative is biological halogenation with $FADH_2$-dependent halogenases, which use oxygen as the oxidant. Although other routes for halogenation in natural systems have also been discovered, this strategy remains prevalent (excluding fluorination because of the higher oxidation potential of F^-).[15,28–31]

One especially intriguing question is what is the active halogenating species at the active site of the enzyme? Despite extensive mechanistic studies involving haloperoxidase enzymes, the exact active halogenating intermediate remains unknown. Various hypotheses have been made, including the formation of molecular halogen, hypohalous acid, or species with a halogen bound via oxygen to a metal center (metal-OX). Nevertheless, as pointed out by Rothenberg and Clark, it is very difficult to mimic actual reaction conditions of the enzymatic action to obtain reliable data.[32] Furthermore, metal centers, such as iron, vanadium, and molybdenum interact with hydrogen peroxide to give numerous reaction outcomes that are dependent on the initial reaction conditions, for example concentration, pH, ligand types, etc.

Nevertheless, research on biological halogenation has boosted the interest in oxidative halogenation, and has resulted in the development of several environmentally friendly methods with various catalysts, oxidants, and reaction media.

2.2. Vanadium and Molybdenum Complexes as Functional Mimics of Vanadium Bromoperoxidase

In addition to heme-dependent haloperoxidases, vanadium-dependent haloperoxidases are another very important group of halogenating enzymes and their action was intensively investigated in enzymatic reactions and in biomimetic studies. Interestingly, vanadium does not change its oxidation state during the reaction, but is transformed by H_2O_2 into various peroxo complexes. Although the nature of the halogenating species remains unknown, research suggests that either HOBr or even V-OBr compounds are involved.[33–37] Besides leading to a better understanding of the role of vanadium in biological systems, biomimetic

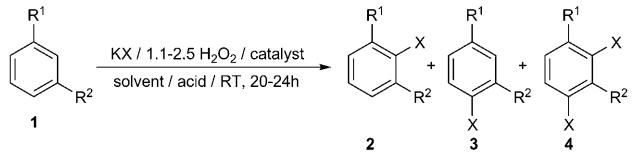
Ajda Podgoršek studied chemistry at the University of Ljubljana and received her PhD in organic chemistry in 2009 under the supervision of Dr. Jernej Iskra. Her research interest is the halogenation of organic molecules, with emphasis on green and sustainable mehods. She is currently working as a postdoctoral fellow with Prof. A. A. H. Pádua and Dr. M. F. Costa-Gomes at the University Blaise Pascal in Clermont-Ferrand.

Marko Zupan was born in 1947 in Ljubljana, received his PhD in 1974 from the University of Ljubljana, and is Professor of organic chemistry at the Faculty of Chemistry and Chemical Technology of the University of Ljubljana. He is one of the pioneers of modern organohalogen chemistry, which remains his main scientific interest, along with research in the fields of polymer-supported reagents and catalysts, photochemistry, and organic "green" chemistry.

research has led to the use of vanadium catalysts for the oxidative halogenation with H_2O_2. The two main catalysts are NH_4VO_3 and V_2O_5.

Ammonium vanadate(V) has proved to be an effective catalyst for oxidative halogenation when the reaction is performed with 30% aqueous H_2O_2 and potassium halides in a CH_3CN/H_2O mixture, with the pH value maintained at 5 by the addition of dilute perchloric acid (Table 1).[38] Most of the

Table 1: Vanadium(V)-catalyzed oxidative halogenation of arenes.



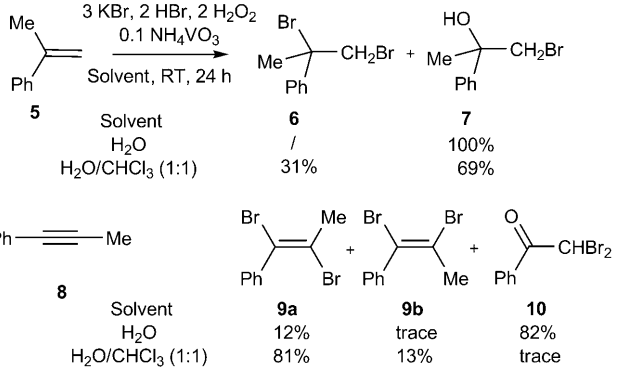
	R^1	R^2	KX	Cat. [mol%]	Acid	Solvent[a]	Yield [%] 2	3	4
				NH_4VO_3					
1a	OMe	OMe	2 KCl	10	$HClO_4$[b]	A	45		
1a	OMe	OMe	2 KBr	5	$HClO_4$[b]	A	65		
1b	OH	OH	2 KBr	10	$HClO_4$[b]	A	37		
1c	*sec*Bu	H	2 KBr	10	$HClO_4$[b]	A	15		
1d	OMe	H	3 KBr	10	2 HBr	B	94		
1d	OMe	H	3 KBr	10	2 HBr	H_2O	48		48
				V_2O_5					
1d	OMe	H	1 KBr	1	1 HBr	H_2O		68	
1d	OMe	H	1 KBr	2.5	8.4 AcOH	H_2O		30	
1d	OMe	H	1 KBr	1.5	0.5 H_2SO_4	H_2O		79	6
1e	OH	H	1 KBr	3	0.5 H_2SO_4	H_2O		62	28
1f	Me	H	1 KBr	2	0.5 H_2SO_4	H_2O		58	2
1g	Et	H	1 KBr	2	0.5 H_2SO_4	H_2O		21	2

[a] A = $MeCN/H_2O$ (2:1), B = $CHCl_3/H_2O$ (1:1). [b] pH 5.

examples given in the literature concern the bromination of various electron-rich aromatic molecules to give the corresponding brominated compounds in moderate yields. In addition, the reaction shows a remarkable *ortho* selectivity. Only one chlorination reaction has so far been reported. The use of either $VO(SO_4)$ or V_2O_5 under identical conditions failed to halogenate these substrates. Bromination of 1,3,5-trimethoxybenzene in water gave only 10% of the monobrominated product, while 90% was formed in CH_3CN/H_2O.[38] An alternative possibility for obtaining acidic conditions, instead of by using an acidic solvent or buffer, is to add an equivalent of acid. This has been shown to be the case by adding HBr, although the authors also decided to add a bromide salt as the source of the bromine atoms. When water is used as the solvent (0.24 wt% H_2O_2) anisole (**1d**) is transformed into monobromoanisole (**3d**) and dibromoanisole (**4d**) in equal amounts, while the former derivative is obtained selectively in a biphasic $H_2O/CHCl_3$ system (Table 1).[39]

When a sufficiently large amount of vanadium(V) oxide is used (50 mol%), no additional acid is required to ensure complete halogenation, since V_2O_5 itself ensures an acidic media (pH 2.1).[40,41] Similar results were obtained when flavone and aurone derivatives were brominated. The bromination of ketones in the presence of V_2O_5 leads to enolization through chelation of a 1,3-dicarbonyl compound.[42,43] Although this protocol has proven effective, it does not meet the criteria for a "green" reaction because of the use of a noncatalytic amount of V_2O_5 and a large excess of H_2O_2. However, catalytic amounts of V_2O_5 (1.5–3%) are sufficient if diluted mineral acid (1M aqueous solution) is used as the reaction phase.[44] Therefore, a combination of KBr and an aqueous solution of H_2O_2 (4–8%) in the presence of mineral acid and a catalytic amount of V_2O_5 has been adopted for the oxidative bromination of various aromatic compounds (Table 1).[44] The reaction is less effective in a weaker acid, for example, AcOH. The method also has the advantages of low risks in handling the reagents and employs relatively safe 35% H_2O_2. The drawbacks are the higher associated costs and low productivity when compared to the use of bromine and the concurrent unwanted decomposition of the peroxide.

Vanadium catalysts have also been investigated for the oxidative bromination of alkenes and alkynes. A distinct difference was noticeable when performing the same reaction in either an aqueous or a biphasic medium. While α-methylstyrene (**5**) in water produces bromohydrin (**7**) selectively and quantitatively, the biphasic reaction produces dibromide **6** and bromohydrin (**7**) in a ratio of 31:69 (Scheme 2).[39] The difference was even more pronounced when brominating alkyne **8**: α,α-dibromoketone **10** is the major product in water, while dibromides **9a** and **9b** are formed selectively in a biphasic system. Similar results were observed when a stoichiometric amount of NH_4VO_3 was used.



Scheme 2. Effect of the reaction media on the selectivity of the V^V-catalyzed oxidative bromination of unsaturated C–C bonds.

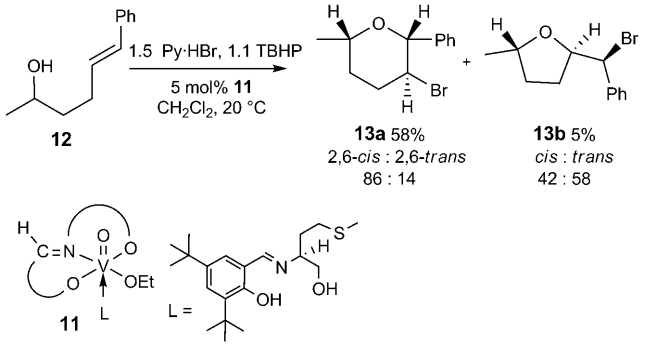
Jernej Iskra received his PhD in organic chemistry from the University of Ljubljana in 1998 ubder the supervision of Prof. M. Zupan, and then joined the Laboratory of organic and bioorganic chemistry at the Jožef Stefan Institute in Ljubljana. From 2000 to 2002 he carried out postdoctoral research (Marie Curie Individual Fellowship) with Dr. J. P. Bégué at the University Paris XI. After returning to the Jožef Stefan Institute in Ljubljana, he has continued with his research on halogenation and oxidation reactions, with an emphasis on the chemistry of organic peroxides.

The study showed that the stirring rate and reagent concentration determined the product distribution, which suggests that phase transfer affects the course of the bromination and that different halogenating species are responsible for each product.[33,45] An analogous study was performed in hydrophilic (one phase) and hydrophobic (biphasic) ionic liquids (ILs), where the selectivity in the biphasic IL/H_2O system was reversed, and bromohydrin was formed as the main product because of the higher polarity of the IL.[46] Although bromination in an IL is fast and efficient, the required concentration (0.02 mol L^{-1}) makes this particular reaction uneconomical.

In contrast to the numerous published examples on the oxidative halogenation of unsaturated compounds, it is clear that bromination of the sp^3-hybridized C atom is more challenging. Amavidine, a natural octacoordinated vanadium(IV) complex $[V(hidpa)_2]^{2-}$, present in species of the Amanita fungi, can act either as a peroxidase or as a catalase. Reis et al. observed that salts of synthetic amavidine compounds, such as $Ca[V(hidpa)_2]$ and $Ca[V(hida)_2]$ catalyze the bromination of cyclohexane and benzene in an acidic CH_3CN/H_2O medium containing H_2O_2, KBr, and an excess of HNO_3 at room temperature to give the corresponding brominated product with a turnover number (TON) of up to 17.[47]

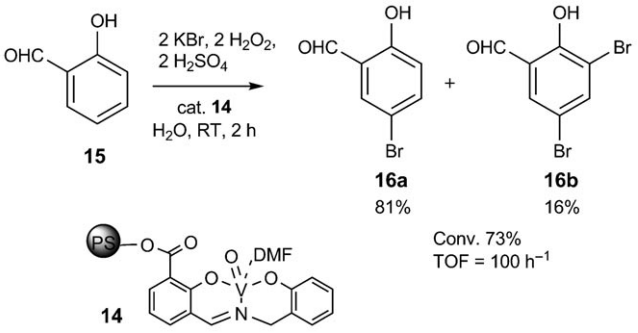
During a study of the functional mimics of vanadium peroxidases, Butler and co-workers prepared vanadium(V) complexes with Schiff bases as catalysts for oxidative bromination. On the basis of the UV/Vis, ^{51}V NMR spectroscopy, and kinetic data they proposed a mechanism whereby the active catalyst is LVO(OH). The binding of LVO(OH) to the peroxide releases H_3O^+, which then oxidizes the bromide before binding with another equivalent of peroxide to generate $LVO(O_2)^-$.[48] In another study, vanadium(V)–Schiff base complexes **11** served as catalysts for the oxidative bromination of substituted 4-penten-1-ol (**12**) into β-brominated cyclic ethers **13a** and **13b** in the presence of pyridinium hydrobromide and *t*BuOOH (Scheme 3).[49]

Immobilizing the Schiff base enabled recovery of the catalyst. Two variations of this principal have been used. In the first case, the catalyst is covalently attached to a polymer support. Polystyrene-bound vanadium (**14**) and molybdenum complexes have been prepared and the catalytic potential of these complexes for the oxidation of styrene, ethyl benzene,



Scheme 3. Oxidative bromination using Schiff base complexes of vandium(V) as catalysts.

phenol, and the oxidative bromination of salicylic aldehyde **15** studied (Scheme 4).[50] The bound V^V and Mo^{VI} complexes had a comparable catalytic activity as the corresponding free complexes. Moreover, the higher stability and easier recycling



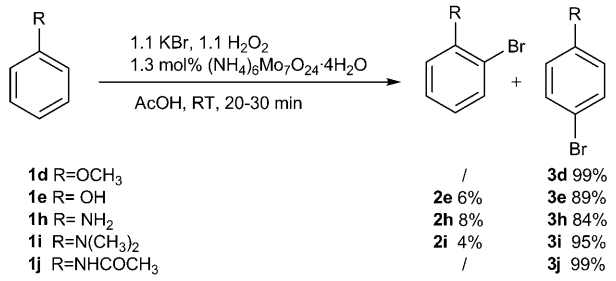
Scheme 4. Oxidative bromination using a polymer-bound Schiff base complex of vanadium(V) as catalyst.

and separation of the catalysts make the use of polymer-supported complexes a promising method. In the second possibility, vanadium(V)–Schiff base complexes were encapsulated in zeolite-Y. In this case no leaching or decomposition was observed during the catalytic reaction, and an almost identical result was achieved using either fresh or recovered catalyst.[51]

Molybdenum(VI) complexes are a further class of catalysts for oxidative halogenation with H_2O_2. The main difference between them and vanadium(V) complexes is their activity under slightly acidic to neutral pH conditions. In fact, $K_2[Mo_2O_3(O_2)_4]\cdot H_2O$ can catalyze the oxidation of bromide to give brominated products at pH 5. This difference may be explained by the higher reduction potential of the molybdenum-bound peroxide even at a higher pH value (5–7), which in turn is attributable to the higher oxidation state of the metal.[52] At higher pH values, however, molybdate(VI) catalyzes the disproportionation of alkaline aqueous H_2O_2; the reaction is known as a "dark" generation of singlet oxygen.[53] Most studies were performed under controlled pH conditions to prevent this disproportionation of H_2O_2 as a side reaction in molybdenum(VI)-catalyzed oxidative halogenation. One option is to use AcOH as a reaction medium, as demonstrated by an ammonium molybdate catalyzed oxidative bromination of phenols, anilines, and their derivatives in high yields (Scheme 5).[54] In another example, 0.2 equivalents of $HClO_4$ was sufficient for oxidative bromination in the presence of $H_2MoO_4\cdot H_2O$ in CH_3CN/H_2O.[41]

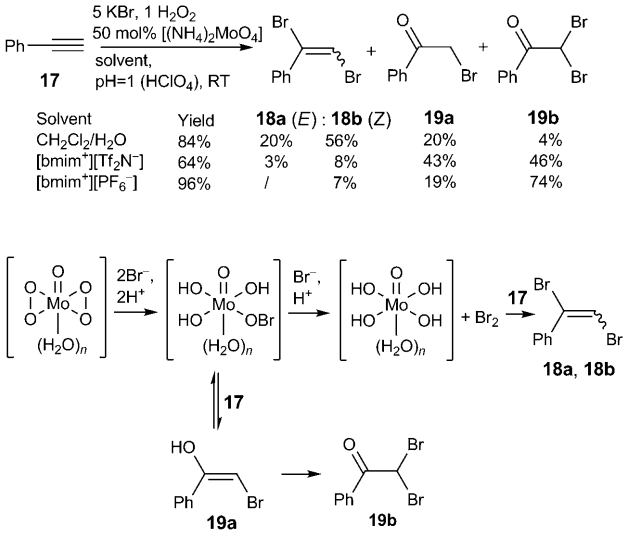
In a similar way, phenylacetylene (**17**) was transformed under biphasic CH_2Cl_2/H_2O conditions into mainly 1,2-dibromostyrene (**18a** and **18b**), while the formation of α,α-dibromoacetophenone (**19b**) was preferred in ionic liquids (Scheme 6).[55] The authors of the study claim that products **18** and **19** arise from different reaction pathways and it is the polarity of the solvent used to extract the Br_2 from the inorganic phase that governs the product ratio.

This oxidative bromination strategy was also applied in a version of the Hunsdiecker reaction, where α,β-unsaturated aromatic carboxylic acids resulted in β-bromoalkenes in high



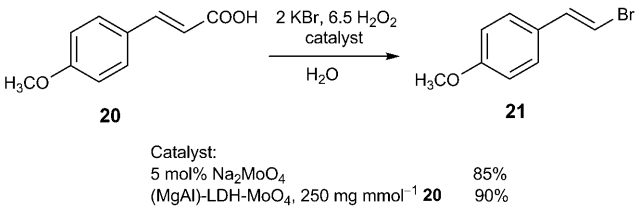
1d R=OCH_3	/	**3d** 99%
1e R= OH	**2e** 6%	**3e** 89%
1h R= NH_2	**2h** 8%	**3h** 84%
1i R=$N(CH_3)_2$	**2i** 4%	**3i** 95%
1j R=$NHCOCH_3$	/	**3j** 99%

Scheme 5. Mo^{VI}-catalyzed oxidative bromination of arenes.



Solvent	Yield	**18a** (*E*) : **18b** (*Z*)	**19a**	**19b**
CH_2Cl_2/H_2O	84%	20% 56%	20%	4%
$[bmim^+][Tf_2N^-]$	64%	3% 8%	43%	46%
$[bmim^+][PF_6^-]$	96%	/ 7%	19%	74%

Scheme 6. Possible active species in the metal-catalyzed oxidative halogenation and the role of the reaction media in this process.



Catalyst:

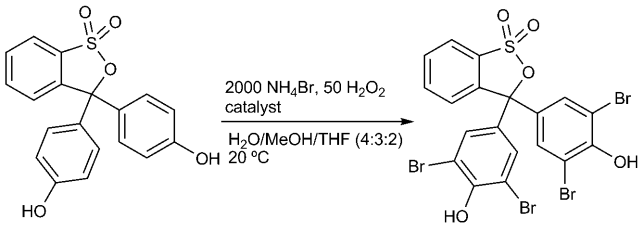
5 mol% Na_2MoO_4	85%
(MgAl)-LDH-MoO_4, 250 mg $mmol^{-1}$ **20**	90%

Scheme 7. Homogeneous and heterogeneous Mo^{VI}-catalyzed Hunsdiecker reactions in aqueous media.

yields when $Na_2MoO_4\cdot H_2O$ was used in an aqueous medium (Scheme 7).[56] The addition of an external proton source was not necessary,[32] since the acid **20** itself acts as the proton source. An analogous reaction without the Mo catalyst (such as Br_2 in aqueous KOH (HOBr-OBr^-) and Br_2 in aqueous KBr (Br_3^-)) proved unsuccessful; however, it shows the important role of the molybdenum(VI) center, probably in coordinating to the substrate. The same reaction was accomplished using recyclable molybdate-functionalized layered double hydroxide (MgAl)LDH-MoO_4 as a heterogeneous catalyst, which led to somewhat higher yields.[57]

2.3. Tungsten and Layered Double Hydroxides

Tungsten(VI) catalysts are another widely studied group of catalysts that are more effective in oxidative halogenation than either molybdenum(VI) or vanadium(V) compounds.[58–60] Tungsten(VI) was used with $KI/H_2O_2/H_2SO_4$ for the oxidative iodination of aromatic amides in AcOH.[61] Acidic conditions are necessary for efficient H_2O_2-mediated halogenation to minimize the catalase-type degradation of H_2O_2 by halides and halogens. One of the main challenges in oxidative halogenation is to create a catalytic system that shows high activity under mild pH conditions. Vanadium bromoperoxidases meet these requirements, and tungstate-functionalized layered double hydroxides (LDHs) were studied as a model of these enzymes.[62–64] LDHs consist of alternating cationic $M^{II}_{1-x}M^{III}_x(OH)_2^{x+}$ and anionic $A^{n-}\cdot z\,H_2O$ layers. The cationic layers contain edge-shared octahedra comprised of M^{II} and M^{III} hydroxides, with the charges neutralized by A^{n-} ions that are located either in the interlayer spacing or at the edges of the lamellae. The tungsten-functionalized LDHs (for example, (NiAl)LDH-WO_4^{2-} or (MgAl)LDH-WO_4^{2-}) were prepared by exchanging either the chloride or nitrate ions in (NiAl)LDH or (MgAl)LDH, respectively, with WO_4^{2-} ions. The bromination of phenol red (**22**) to bromophenol blue (**23**) was used as a test reaction to compare the effectiveness of the synthetic LDH catalyst with several homogeneous ones (Scheme 8). The



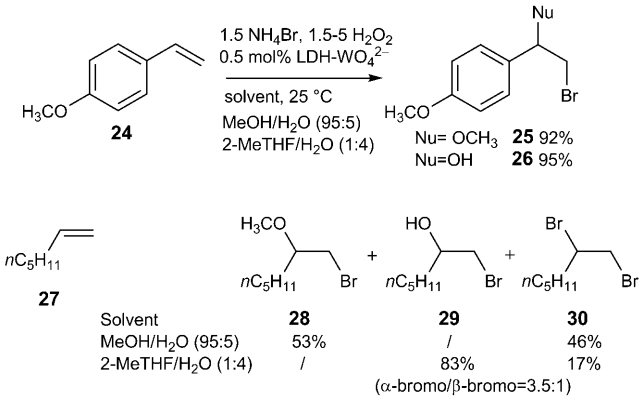
Catalyst	TOF [h^{-1}]
NH_4VO_3	0.001
Na_2MO_4	0.050
Na_2WO_4	0.280
(MgAl)-LDH	/
(MgAl)-LDH-VO_3^-	0.1
(MgAl-LDH-MoO_4^{2-}	20.1
(MgAl)-LDH-WO_4^{2-}	21.6

Scheme 8. Incorporation of the catalyst into a layered double hydroxide enhances its activity for oxidative halogenation.

results show that VO_3^-, MoO_4^{2-}, and WO_4^{2-} catalysts exhibit a much higher activity in an LDH environment than in solution.[62,63] The activation could be attributed to a unique spatial organization and shielding of the surface charge on the catalyst. The bromination occurs under mild pH conditions (pH 6–8), while a similar efficiency is possible with an homogeneous catalyst at $pH < 2.5$.[62] Additionally, LDH-WO_4^{2-} is relatively stable toward high H_2O_2 concentration and leaching, which makes the catalyst suitable for recovery and reuse.[63] Furthermore, the use of the (MgAl)LDH-WO_4^{2-} catalyst in the presence of Br_2/H_2O_2 (0.6 equiv each) in a

biphasic dichloroethane/water system led to the bromination of several aromatic compounds in good yields.[65]

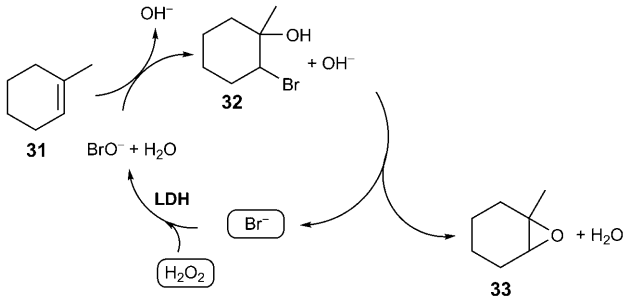
The (NiAl)LDH-WO_4^{2-} catalyst has also been used to brominate various alkenes in the presence of NH_4Br and H_2O_2.[64] The bromination of styrene derivatives in MeOH or in an aqueous biphasic system produces methoxybromides or hydroxybromides, respectively, as the major products, despite the excess of bromide ions (Scheme 9). Moreover, the bromination is *anti* steroselective and proceeds with Markovnikov regioselectivity, while the large negative Hammett parameter ($\rho(\sigma^+) = -3.91$) suggests the development of a positively charged transition state followed by the formation of an asymmetrically bridged bromonium ion.



Scheme 9. Tungstate-functionalized LDH is an effective catalyst for selective oxidative bromination under neutral conditions.

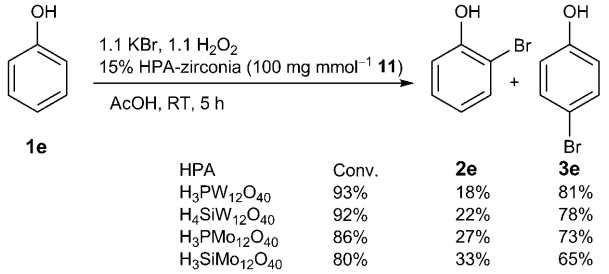
The bromination of aliphatic linear and cyclic alkenes appears to be less chemoselective and regioselective, and bromomethoxylation is accompanied by dibromination in MeOH. Dibromination (formation of **30**) is less pronounced in the biphasic MeTHF/H_2O system and the reaction does not completely follow the Markovnikov rule (formation of a small amount of an *anti*-Markovnikov product; Scheme 9). Furthermore, the mild pH conditions of the H_2O_2/NH_4Br/LDH-WO_4^{2-} system offers the possibility of a one-pot epoxidation of alkenes via the formation of bromohydrins as intermediates. Kinetic studies and labeling experiments indicate that the alkene is not epoxidized directly, and hydroxide ions generated in each oxidative bromination cycle promote the cyclization of the intermediate bromohydrin.[62,64] The proposed reaction cycle for the NH_4Br-catalyzed epoxidation of alkenes is depicted in Scheme 10. Epoxides were formed in 86–94% yield under monophasic aqueous (H_2O/CH_3CN, 3:7) conditions. The LDH-WO_4^{2-} catalyst was also used to generate halohydrins and β-haloethers from cyclic enol ethers in the presence of NH_4Br or NH_4I and H_2O_2 in aqueous CH_3CN or THF as the solvent.[66]

Heteropolyacids (HPAs) are strong acids and have a significantly higher catalytic activity than the corresponding homogeneous systems. Additionally, they can be recovered and reused. As an example, $H_4SiW_{12}O_{40}$ has been used as a catalyst for the oxidative α-iodination of ketones with 0.5 equivalents of iodine and 0.6 equivalents of H_2O_2 in



Scheme 10. The LDH catalyst enables oxidative bromination under neutral conditions, thus making possible the direct epoxidation of alkenes through the formation of bromohydrines.

MeOH at 65 °C.[67] The main disadvantages are their relatively low stability and surface area. To overcome this, HPAs are usually supported on a suitable carrier, which not only increases the available surface area, but also increases the catalytic performance. The catalyst prepared with 15% HPA impregnated on a zirconia support has been used for the bromination of phenol (**1e**) by using KBr and H_2O_2 at room temperature in acetic acid (Scheme 11). The highest catalytic



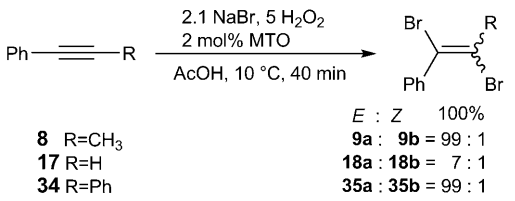
Scheme 11. Heteropolyacids act as heterogeneous catalysts in oxidative halogenation reactions in organic solvents.

activity was found with zirconia-supported phosphotungstic acid (93% conversion and 81% *para* selectivity).[68,69] A similar trend was also reported when heteropolyacids were bound on either ZrP (zirconium phosphate)[70] or titanium phosphate (TiP).[71]

Another possibility for heterogeneous catalysis is titanium(IV)-grafted mesoporous silicate materials (Ti/MCM-48), where reactions proceed efficiently in an aqueous solution at neutral pH and in organic solvents.[72] Alternatively, titania-modified zirconium phosphate and titanium phosphate can also be used.[73]

2.4. Other Metal Catalysts

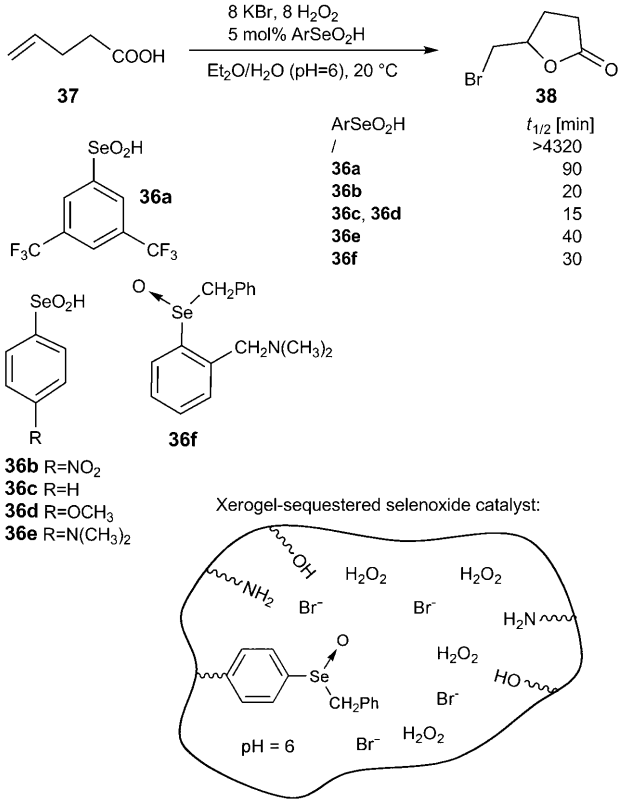
Methyltrioxorhenium (MTO), a catalyst with a broad spectrum of application, has been used for bromination with $NaBr/H_2O_2$ in AcOH.[74] The bromination proceeds rapidly and various methyl-substituted phenols and phenyl acetylenes are quantitatively brominated within minutes (Scheme 12). This is one of the rare examples of the use of NaBr insead of



Scheme 12. An example of MTO-catalyzed oxidative bromination.

the more expansive KBr or NH_4Br. The cation should not play any role in the reaction, and the most probable reason why sodium salts are not used is their hygroscopic properties. The investigation reveals that the peroxo form of MTO is the active catalyst, while binding of BrO^- to a metal center (as one of the possibilities in V^V-catalyzed reactions) is excluded. It is suggested that either Br_2 or H_2OBr^+ can act as a brominating species (relative electrophilicities $HOBr/Br_2/H_2OBr^+ = 1:10^{3.8}:10^6$), with the former being the most likely.

A study of the oxychlorination of manganese(IV)–salen complexes showed that $[Mn^{IV}OCl(salen)]$ is the active form of the catalyst.[75] This finding provides an important clue to the mechanism of heme-dependent chloroperoxidase. A different type of action was reported for the $CuCl_2$-catalyzed chlorination of aliphatic aldehydes. In this case, the substrate is activated by Cu^{II}-catalyzed enolization followed by transfer of chlorine to generate the enol form. An equimolar mount of $CuCl_2$ was used in the reaction, although the authors state that Cu^0 is regenerated into Cu^{II} by H_2O_2.[76]



Scheme 13. Aryl selenium catalysts, whose reactivity can be tuned by substituents on the aromatic ring. Sequestration of the aryl selenium catalysts into xerogels enhances the performance and enables recovery.

2.5. Nonmetal Catalysts

Selenium compounds are also of interest for haloperoxidation because of their role in peroxide activation in biological processes. Various substituted aryl selenic acids **55** were found to be appropriate catalysts for bromolactonization and aromatic bromination with KBr and H_2O_2 in the presence of a buffer (pH 6) that provides the protons.[77] In the bromolactonization of **37**, the catalytic activity of aryl selenic acids increases as the electron-donating properties of substituents on the aromatic ring of **36** increases (Scheme 13). In a later study, it was demonstrated that selenoxide **36 f** gives the same activity as the selenic acid.[78] PhSeCl can also be used as a catalyst, although this possibility is less appealing from a "green" chemistry standpoint, as NCS or NBS are used as halogen sources. Nevertheless, one example shows the possibility of using $NaCl/H_2O_2$ in the allylic chlorination of 2-methyl-2-hexene in CH_2Cl_2/H_2O; however, only 33% of the corresponding chlorinated product was obtained.[79]

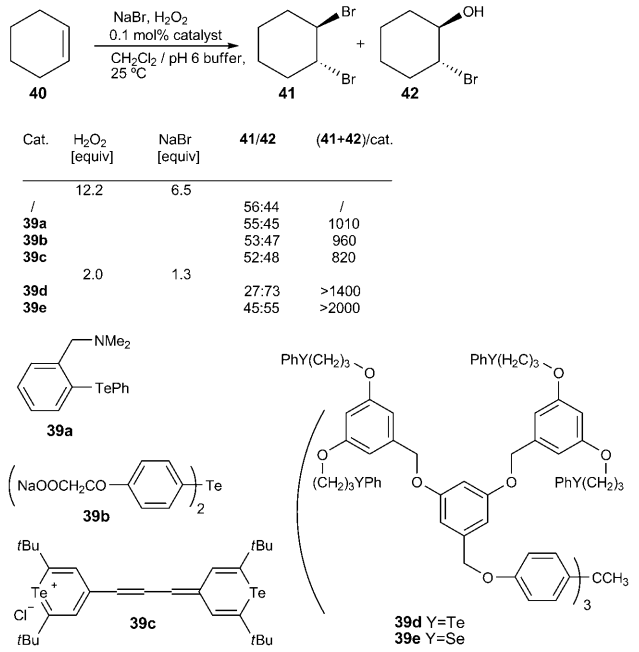
More recently, a reusable selenium catalyst, 4-(hydroxymethyl)phenylbenzyl selenoxide, was reported which is sequestered within halide-permeable xerogels (Scheme 13).[80] It was observed in the bromolactonization of **37** that sequestration not only makes the catalyst 23-times more active than a xerogel-free catalyst in solution, but it also makes for an easy separation of it from the reaction mixture.

Organotellurium compounds **39** act very similarly to organoselenium ones. Species such as ArTeR are able to catalyze the oxidation of NaI, NaBr, and NaCl with 50% H_2O_2 in a phosphate buffer at pH 6, although harsher conditions are required for NaCl and the TON was smaller (1010 for NaBr and 100 for NaCl).[81] Examples of oxidative halogenation include halolactonization, addition to alkenes, and aromatic halogenation.[81,82] A water-soluble derivative was used for iodination in the absence of an organic solvent.[83] Scheme 14 shows how the catalysts **39 a–c** give almost the same ratios of **41** and **42** as the uncatalyzed reactions. This finding suggests that it is the same oxidizing species in all cases. Catalysts bound into dendrimers with either phenyltelluro (**39 d**) or phenylseleno end groups (**39 e**) have been prepared.[84] A much higher TON per PhSe group was observed for the PhSe dendrimers, and the enhanced catalytic activity was attributed to the cooperative effect of the multiple reactive groups present in its structure, no such enhancement was observed for the tellurium analogues.

3. Noncatalyzed Oxidative Halogenation with Hydrogen Peroxide

3.1. Oxidative Halogenation in Organic Solvents

Biomimetic halogenation has fueled research into oxidative halogenation, and the most usual approach makes use of metal catalysts for the oxidation of halides with hydrogen



Cat.	H_2O_2 [equiv]	NaBr [equiv]	41/42	(41+42)/cat.
	12.2	6.5		
/			56:44	/
39a			55:45	1010
39b			53:47	960
39c			52:48	820
	2.0	1.3		
39d			27:73	>1400
39e			45:55	>2000

Scheme 14. Selenium catalysts show enhanced activity when bound into a dendrimer structure, while tellurium ones do not show such an effect.

peroxide. The use of a metal catalyst is necessary because dilute solutions (< 0.01 M H_2O_2) are required to mimic these biological conditions. Alternatively, performing reactions on a laboratory scale generally demands higher concentrations of reagents (> 0.1 M), and in this case the use of a metal catalyst is superfluous. This was already known in the 1920s, when Leulier and Speyer and Rosenfeld published the first examples of the oxidative halogenation of activated arenes.[85,86] Around the same time, Bray and Livingston discovered that an acidic solution of hydrogen peroxide oxidizes bromide to bromine [Eq. (1)] and also reduces bromine to bromide [Eq. (2)]; the net result of these two compensating reactions is the catalytic decomposition of hydrogen peroxide [Eq. (3)].[87,88] The decomposition of H_2O_2 [Eq. (3)] is pH dependent and faster at higher pH values.[89] Both reactions [Eqs. (1) and (2)] are faster than in the case of iodine/iodide. Although molecular halogen is stated as the product of oxidation in Equation (1), it does not mean that it is also the active halogenating speices. The most probable reagent is hypohalous acid (HOX), at least in chlorination and bromination. In iodination, the chemistry of hypervalent iodine compounds is very complex and it is difficult to define the nature of the halogenating species. Furthermore, interconversion of various halogen compounds is pH dependent.[90]

$$H_2O_2 + 2X^- + 2H^+ \rightarrow X_2 + 2H_2O \quad (1)$$

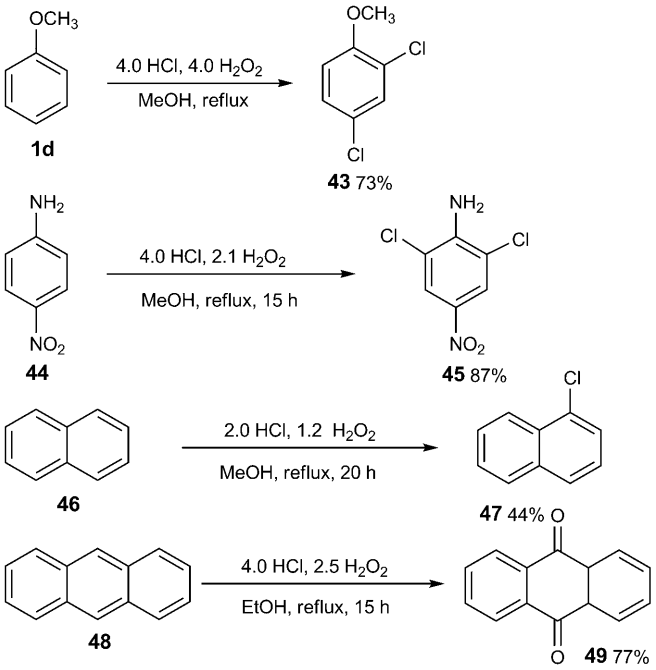
$$H_2O_2 + X_2 \rightarrow O_2 + 2X^- + 2H^+ \quad (2)$$

$$2H_2O_2 + X_2 \rightarrow 2H_2O + O_2 \quad (3)$$

Oxidative halogenation of this type offers extremely interesting perspectives, as there are no reagent residues apart from water and the reaction occurs with 100% halogen atom economy.

3.1.1. Chlorination

Hydrochloric acid is difficult to oxidize with dilute H_2O_2, and oxidative chlorination is achieved by using an excess of HCl at higher temperatures. Consequently, selective chlorination is difficult to accomplish. An example is shown in Scheme 15, where the chlorination of **1d** and **44** was achieved



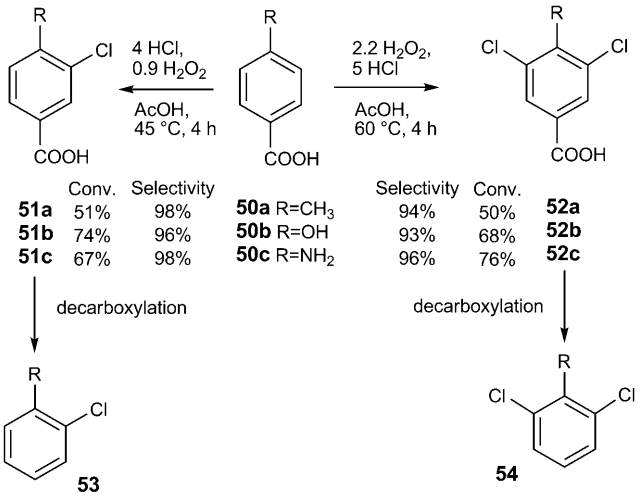
Scheme 15. Uncatalyzed oxidative chlorination requires higher reaction temperatures, and a selective reaction is difficult to achieve.

using a fourfold excess of HCl in boiling MeOH. Under these conditions, only the dichlorination to **43** and **45** was observed. Monochlorination of **1d** was achieved only by using *t*BuOOH as the oxidant.[10] A combination of HCl and H_2O_2 has been used for the chlorination of less-activated substrates such as naphthalene (**46**), while anthracene (**48**) was oxidized to **49**.[91]

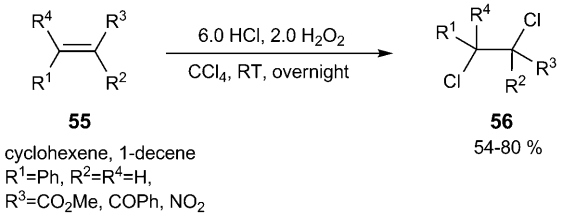
The HCl/H_2O_2 method has also been used to prepare *ortho*-chloro-substituted arenes **53** and **54** by a two-step oxidative chlorination/decarboxylation reaction of derivatives of benzoic acid **50** (Scheme 16).[92,93] The selectivity toward the desired mono- or dichlorinated *ortho* products **51** or **52**, respectively, was regulated by dropwise addition of an appropriate amount of H_2O_2.

The oxychlorination of alkenes to vicinal *trans*-dichloroalkanes was performed in the nonpolar solvent CCl_4 with a sixfold excess of HCl and a twofold excess of H_2O_2 (Scheme 17).[10]

Another example of the application of the HCl/H_2O_2 system is the chlorination of cyclic and linear ketone oximes



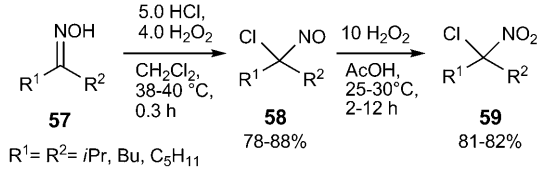
Scheme 16. Formation of *ortho*-chloroarenes by oxidative chlorination/decarboxylation.



Scheme 17. An example of a H_2O_2-mediated oxidative dichlorination of alkenes.

57 in a two-phase CH_2Cl_2/H_2O system to form *gem*-chloronitroso compounds **58** (Scheme 18).[94] These compounds are further oxidized to *gem*-chloronitro alkanes **59** with peracetic acid prepared in situ from acetic acid and a tenfold excess of H_2O_2. The nature of the solvent system is the key factor in determining the yield of nitroso compound **58**. Only heterogeneous systems (H_2O with benzene or CH_2Cl_2) furnished **58** in satisfactory yield, while under homogeneous conditions (H_2O with MeOH, THF, dioxane, or AcOH) the conversion into the target compound was lower because of the deoximination of oximes followed by chlorination of the resulting ketones.

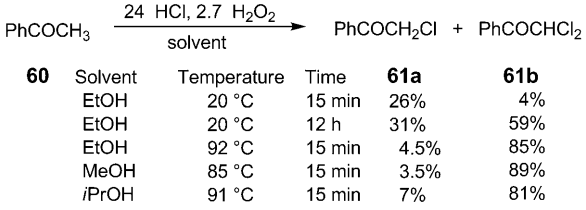
The problem of the selectivity of oxidative chlorination is evident in the reaction involving ketones. For example, the oxidative chlorination of acetophenone (**60**) in a boiling 1:1 mixture of concentrated hydrochloric acid and alcohol affords



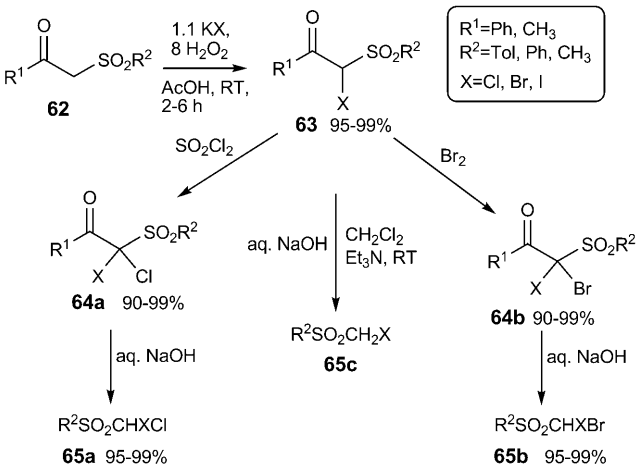
Scheme 18. Ketone oximes are converted into *gem*-chloronitro alkanes by oxidative chlorination oxidation.

only α,α-dichloroacetophenone derivatives (**61b**; Scheme 19).[95]

Another example of the chlorination of active methylene compounds includes the oxychlorination of β-ketosulfones **62** with KCl (or KBr, KI) and a large excess of H_2O_2 in an aqueous acetic acid medium to yield the α-halo-β-ketosulfones **63**, which after hydrolysis give the α-halomethylsulfones **65c** or α,α-dihalo-β-ketosulfones **65a**,**b** by a second halogenation step (Scheme 20).[96,97]



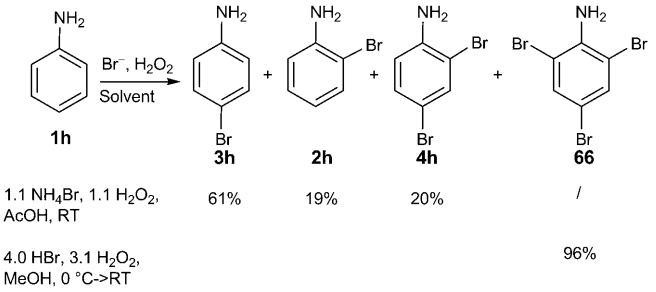
Scheme 19. Oxidative chlorination in boiling methanol leads to the dichlorination of acetophenone.



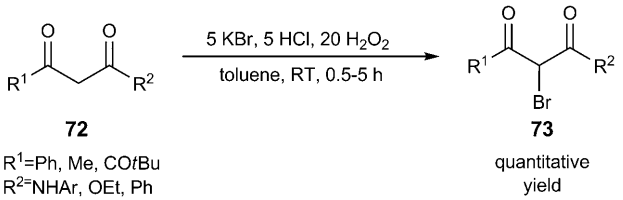
Scheme 20. Strategies for the synthesis of α-halomethylsulfones.

3.1.2. Bromination

Oxidation of HBr with H_2O_2 is faster than the oxidation of HCl because of the lower oxidation potential of HBr, which enables the oxidative bromination of organic molecules under milder conditions and with a smaller excess of reagents. Nevertheless, the selective monobromination of reactive aromatic compounds remains problematic. For example, the bromination of 1,4-dimethoxybenzene with HBr/H_2O_2 (4 equiv each) in boiling methanol yielded 2,5-dibromo-1,4-dimethoxybenzene selectively.[10] Similarly, aniline (**1h**) could be selectively brominated only to the tribromo derivative **66** (Scheme 21), while less-reactive substrates such as naphthalene and anthracene were selectively monobrominated.[91] When using more reactive substrates, such as *para*-substituted phenol, the selectivity could be controlled by the portionwise addition of H_2O_2. For example, 4-methylphenol was brominated with a combination of 4 equivalents of HBr and 0.89 equivalents of H_2O_2 in EDC at 45 °C, with 89 %



Scheme 21. Uncatalyzed oxidative bromination of aniline in acetic acid leads to a mixture of products.

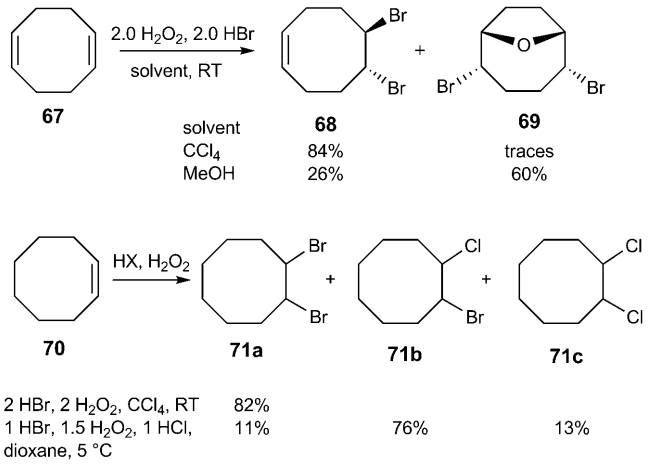


Scheme 23. Bromination of 1,3-diketones with HBr/HCl in toluene occurs quantitatively.

conversion and 99.6% selectivity for the monobrominated product. Increasing the quantity of H_2O_2 to 2.1 equivalents produced a dibrominated product with 99.2% selectively.[98] In a similar manner, various anilines and anisoles were oxybrominated using the NH_4Br/H_2O_2/AcOH system at room temperature.[99] The presence of an acid is no longer required when the bromide salt is substituted by bromine since the H_2O_2 regenerates all the residual HBr. An example of this strategy is the preparation of 4,4′-isopropylidenebis(2,6-dibromophenol) and other analogous brominated di- and tripolyols for fire-resistant epoxy resins. The bromination with 2 equivalents of Br_2 and 2.1 equivalents of H_2O_2 in the biphasic H_2O/CH_2Cl_2 system afforded the tetrabromobisphenol in 92% yield.[100]

A solution of HBr and H_2O_2 in a biphasic H_2O/CCl_4 system was used for the dibromination of various alkenes and alkynes (an example is shown in Scheme 22).[10] Cyclooctadiene (**67**) was transformed mainly to the 1,2-dibrominated **68**, while in a one-phase reaction in MeOH an intermediate bromohydrin was formed, which transformed into **69** (Scheme 22). In contrast, a mixed dihalide **71b** was formed together with the dihalides **71a** and **71c** when HCl was added to the reaction mixture (Scheme 22).[10]

A combination of KBr, HCl (5 equiv of each), and an excess of H_2O_2 have been applied to the chemoselective bromination of the active methylene group of 1,3-dicarbonyl

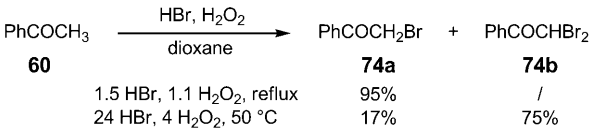


Scheme 22. Effect of the reaction medium on the course of the oxidative bromination of alkenes.

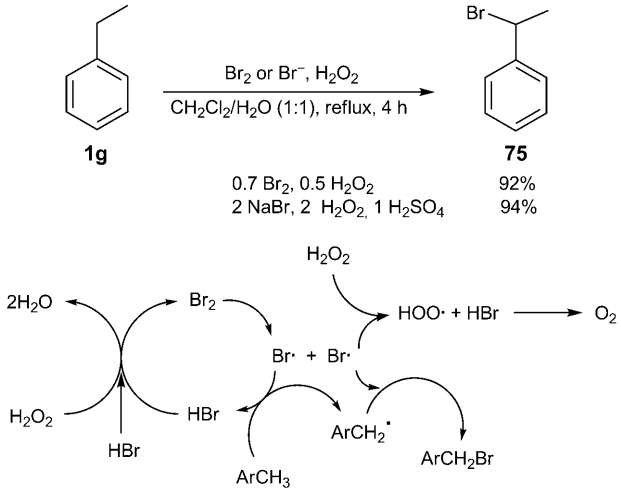
compounds in toluene at room temperature (Scheme 23).[101] Interestingly, it was observed that the use of a mechanical stirrer instead of a magnetic one was more effective in driving the reaction, and that only 1 equivalent of KBr and HCl and 1.2 equivalents of H_2O_2 were sufficient to obtain quantitative yields of brominated products.

Depending on the quantity of reagents used, various 1-aryl ethanones were brominated in dioxane to give either monobromo or dibromo products. The reaction of acetophenone (**60**) with HBr/H_2O_2 in a ratio of 1.5:1.1 afforded **74a** in 95% yield, while increasing this ratio to 24:4 gave **74b** as the main product (accompanied by 17% of **74a**; Scheme 24).[102,103] Under similar conditions, indanone was selectively transformed into the dibrominated α,α-derivative in 89% yield. Electrophilic aromatic bromination becomes a competitive process when electron-donating groups are present in the aromatic ring.

This oxidative bromination strategy has also been applied in a radical reaction. Amati et al. reported that it is possible to achieve benzylic bromination using either bromine or hydrobromic acid in a two-phase H_2O/CH_2Cl_2 system. An example is the reaction of ethylbenzene (**1g**) shown in Scheme 25.[104]



Scheme 24. Mono- and dibromination of acetophenone.

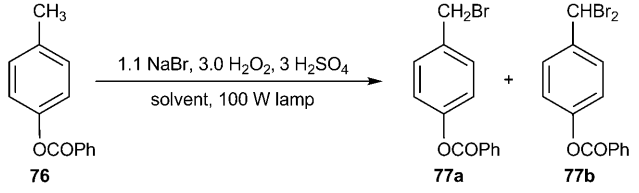


Scheme 25. Oxidative bromination strategies can be used for the radical bromination of alkyl benzenes.

Substrates with electron-withdrawing groups (NO_2, CN, Cl) usually give lower yields because of the reversible benzyl radical abstraction of the hydrogen atom from HBr. In a biphasic system, HBr is extracted from the organic phase into the aqueous one, thus minimizing the reversibility, and under these conditions even deactivated alkyl benzenes may be brominated in yields of 88–98%. It was observed that an excess of H_2O_2 inhibits the reaction, as the bromine radical abstracts a hydrogen atom from H_2O_2 and thereby results in its decomposition (Scheme 25). Tertiary sp^3 carbon atoms do not afford brominated products, because HBr elimination takes place under the applied reaction conditions, thereby producing the α-methylstyrene and the *cis*- and *trans*-α-methyl-β-bromostyrenes.

It is possible to avoid the use of chlorinated solvents by using more environmentally benign ones. The best results are obtained with various esters and ethers, with methyl pivalate being the most potent solvent for benzylic oxidative bromination (Table 2).[105] The presence of aqueous H_2O_2 was

Table 2: Benzylic bromination of toluene derivatives in chlorinated and nonchlorinated solvents.



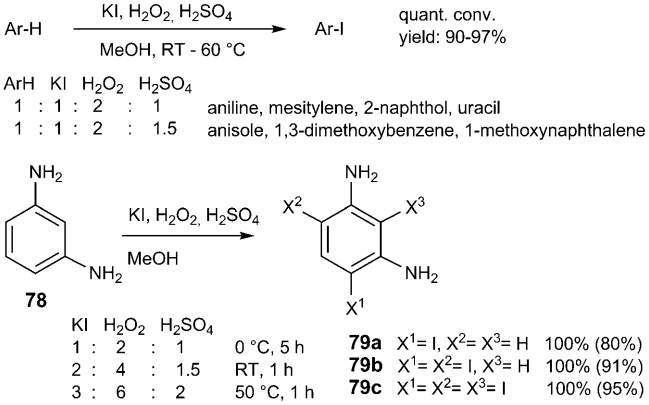
Solvent	Product distribution		
	76 [%]	**77a** [%]	**77b** [%]
CCl_4	6	84	10
MeCOOEt	66.5	33.5	–
MeCOO*i*Pr	20.4	79.6	trace
*i*PrCOOMe	67	33	–
*t*BuCOOMe	11	84	5

beneficial for the conversion of alkyl-substituted benzenes into acetophenone derivatives (by benzyl bromination, subsequent hydroxylation with water, and oxidation with H_2O_2 to the corresponding ketones).[106]

3.1.3. *Iodination*

Iodine has three distinct properties from the other halogens: 1) iodide (I^-) has the lowest oxidation potential among all the halides so it is most readily oxidized; 2) HI is unstable and seldom used; and 3) iodine is the least reactive halogen, and activation of the iodination reaction is usually needed.

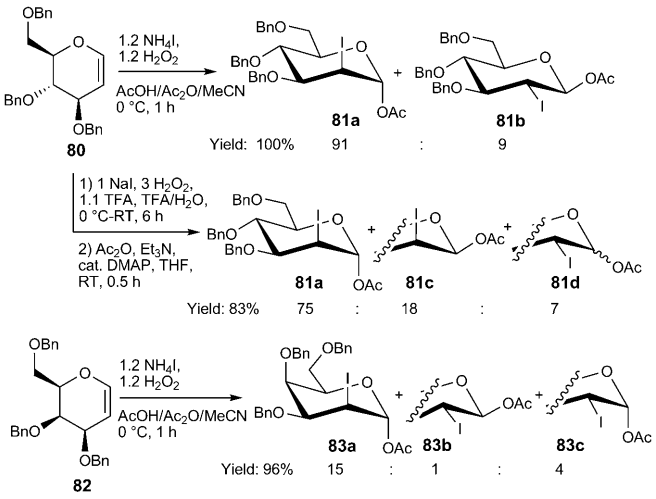
In the case of oxidative iodination, HI is generated from iodide and an acid, while an additional amount of acid is used for the activation of the iodination. If no acid is present, only decomposition of the H_2O_2 is observed with the vigorous release of oxygen. The oxidative iodination of various arenes was performed using 1 equivalent of KI and 2 equivalents of 30% H_2O_2 in methanol, with the reactivity tuned by varying the quantity of H_2SO_4 used. Under these conditions, representative aromatic molecules were quantitatively and regioselectively transformed into their corresponding iodinated compounds (Scheme 26).[107] Amino groups on the aromatic



Scheme 26. The reactivity in the oxidative iodination can be tuned by the amount of acid.

ring were compatible with this method, and anilines could be iodinated in quantitative yields without the need to protect the amino group. Interestingly, *m*-phenylenediamine (**78**) was converted selectively into the mono-, di-, and triiodinated products **79a**, **79b**, and **79c**, respectively, in good yields by using various ratios of reagents (Scheme 26).[107]

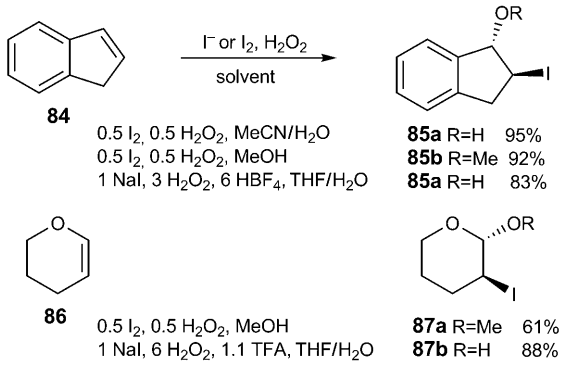
The use of NH_4I in the presence of H_2O_2 in an acetic acid medium resulted in the iodination of highly activated arenes.[108] The same iodination system was used for the haloacetoxylation of protected glycals, such as glucal **80** and galactal **82** (Scheme 27).[109] The combined use of Ac_2O and AcOH as a reaction medium intercepted the water present in the system and ensured selective conversion into iodoacetates **81** and **83** without the formation of any iodohydrines as by-products. The addition of acetonitrile allowed the reaction temperature to be lowered so as to favor stereoselectivity.



Scheme 27. Glycals as starting compounds for the synthesis of iodinated sugars by oxidative iodination.

Under these conditions, only the 1,2-*trans* addition products were detected, with the α-manno product **81a** predominating over the α-gluco isomer **81b**. Some *cis*-addition product **83c** was formed in the reaction of galactal **82**. The corresponding 2-deoxy-2-bromoglycosyl acetates were obtained using NH_4Br, although increased reaction times were required and the selectivity was inferior.[109] Glucal **80** was also iodohydroxylated with NaI/H_2O_2 in the presence of TFA in a THF/H_2O mixture (Scheme 27). In this case, the crude mixture isolated from the iodination reaction was rapidly treated with Ac_2O in Et_3N, thereby resulting in the mixture of compounds shown in Scheme 27. Again, the manno isomer **81a** predominated, although the reaction was less selective.[110]

The H_2O_2-mediated iodination of alkenes can be achieved by using either I_2 or NaI and an acid. The use of I_2 appears more economical, since only 0.5 equivalents (or a slight excess) of H_2O_2 and 0.5 equivalents of I_2 is sufficient for a good conversion of various alkenes without the need for an acid (Scheme 28).[111] Alternatively, various alkenes have

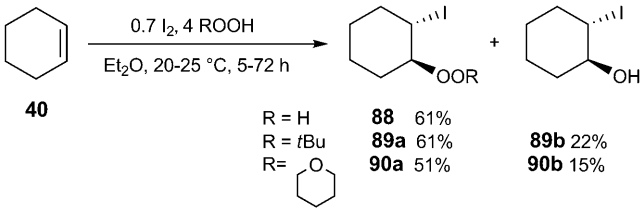


Scheme 28. Strategies for the oxidative iodination of alkenes.

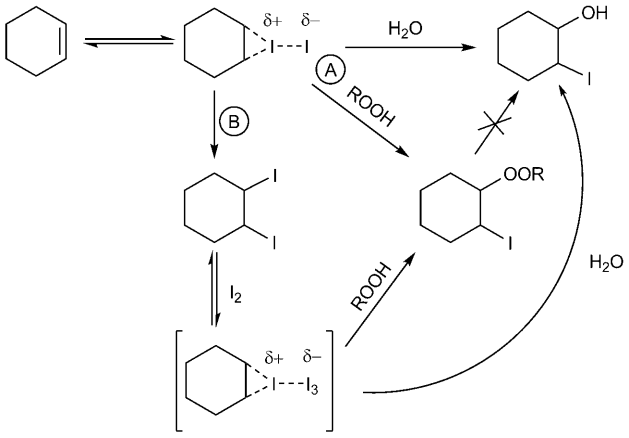
been iodinated using NaI/H_2O_2 combined with acid in a THF/H_2O system to give the corresponding iodohydrines in high yields (Scheme 28).[110] A wide range of acids have been tested, such as HBF_4, H_2SO_4, oxalic acid, TFA, H_3PO_4, and Amberlyst 15, with the best results obtained using HBF_4. It was not possible to promote the reaction in such a way as to provide a satisfactory conversion with a weaker acid. Both systems gave similar results in terms of stereoselectivity and regioselectivity.

The nucleophile in the oxidative iodination of alkenes is usually a solvent (MeOH, AcOH, or H_2O). H_2O_2 can also act as a nucleophile, and it was reported that peroxides are formed together with iodohydrines in the iodination of cyclohexene (**40**).[110] Vicinal iodoperoxyalkanes were isolated together with some iodohydrines when different alkyl hydroperoxides—and even H_2O_2—were used for the oxidative iodination (Scheme 29).[112] Interestingly, it was found that an excess of iodine led to an increase in the formation of the peroxide product.

Scheme 30 shows two possible pathways for this reaction.[112] According to path A, iodoperoxyalkane is formed by the classical addition of the electrophilic iodine and the



Scheme 29. Peroxides as oxidants and nucleophiles in the oxidative iodination of alkenes.

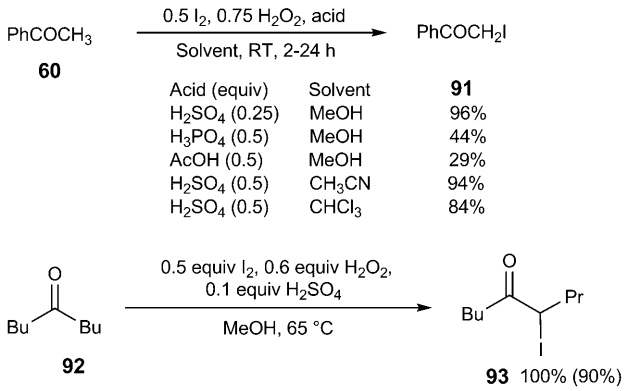


Scheme 30. Mechanism of the I_2-catalyzed iodoperoxidation of alkenes.

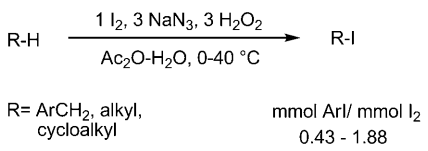
nucleophilic hydroperoxide to the double bond. A new proposition (path B) includes the formation of 1,2-diiodocyclohexane followed by its transformation under the action of another molecule of iodine to form an intermediate containing a partial positive charge on the carbon atoms. This intermediate then further reacts with hydroperoxide and explains why an excess of iodine promotes peroxidation. Furthermore, the 1,2-diiodocyclohexane is transformed into the peroxide product when I_2 is present in the reaction mixture. The selective activation and departure of an OH group by iodine in the presence of an OOH group had already been observed during the peroxidation of carbonyl compounds.[113,114]

The effect of acid has also been studied in the iodination of carbonyl compounds. Such reactions require a strong acid, and the best yields for the iodination of acetophenone to **91** were obtained using H_2SO_4 in CH_3CN. In a similar manner, cyclic and linear dialkyl ketones (for example, **92**) were iodinated at the α position selectively and quantitatively in the presence of 0.1 equivalents of H_2SO_4 in MeOH (Scheme 31).[67]

For the iodination of various types of sp^3-hybridized carbon atoms (alkanes, benzylic positions), which is a difficult reaction to perform, Barluenga et al. proposed a new method involving a combination of iodine, sodium azide, and hydrogen peroxide (Scheme 32). The reactions were performed in the presence of acetic anhydride, and small amounts of water were added to adjust the concentration of H_2O_2 and so minimize the formation of by-products. The authors suggest



Scheme 31. Effect of acid on the oxidative iodination of ketones.



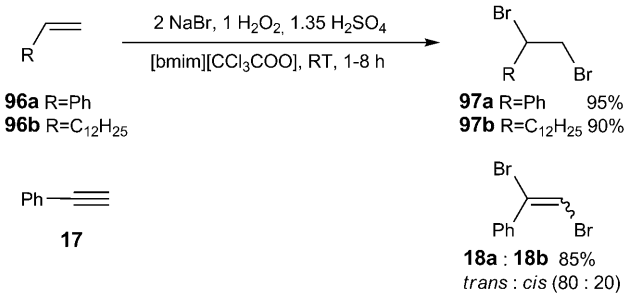
Scheme 32. NaN_3-mediated oxidative iodination of sp^3-hybridized C atoms.

that the reaction proceeds through a radical pathway, with H_2O_2 acting as the oxidant in the formation of IN_3. Although azide is not used in catalytic amounts, this reaction is an efficient procedure for the incorporation of iodine at the sp^3-hybridized C atom in **94**.[115]

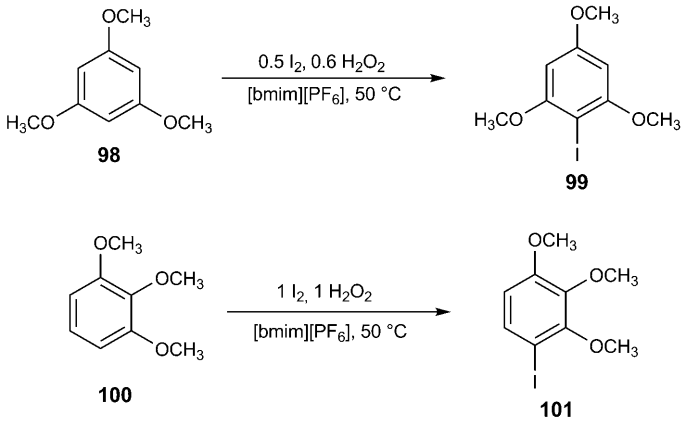
3.2. Ionic Liquids

Room-temperature ionic liquids (RTILs) have become important constituents in novel reaction media as a replacement for volatile organic solvents.[116] Although RTILs have received some attention in halogenation reactions,[117] their use in noncatalyzed oxidative halogenation reactions remains scarce. In 2004, the oxidative dibromination of phenylacetylene (**17**) and several alkenes with $NaBr/H_2O_2$ in 1-butyl 3-metylimidazolium trichloroacetate ([bmim][CCl_3COO]) was reported. The reaction was initiated and controlled by the slow addition of H_2SO_4 (Scheme 33). Cyclic, acyclic, and styrene derivatives gave the corresponding dibromides **97** (70–95%). The dibromination occured with very similar stereoselectivity as conventional bromination with Br_2.[118]

Oxidative iodination in ionic liquids has only recently been investigated. The iodination of trimethoxybenzenes with I_2 and 30% H_2O_2 or UHP was studied in two hydrophilic RTILs: water-miscible [bmim][BF_4] and water-immiscible [bmim][PF_6]. Interestingly, for all the investigated substrates, the iodination occurred more rapidly in an immiscible system than in a homogeneous one (Scheme 34).[119] The more-reactive arenes (for example, **98**) were iodinated efficiently using a $0.5\,I_2/0.6\,H_2O_2$ system, while the less-reactive ones (for example, **100**) required greater amounts of reagents. Ketones (acetophenone, indanone, tetralone, and methoxy derivatives) were iodinated at the α position relative to the ketone group, although in lower yield. Again, the reaction was faster in a biphasic system.



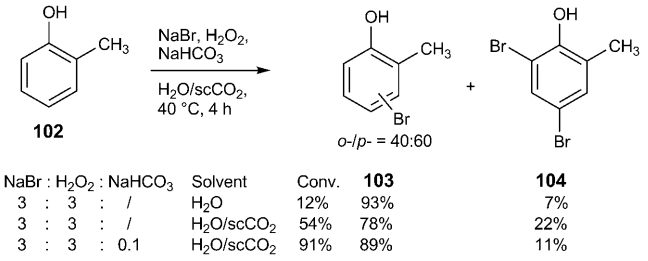
Scheme 33. Ionic liquids as reaction media for the oxidative dibromination of unsaturated C–C bonds.



Scheme 34. The reactivity of the substrate determines the amount of reagents needed in the oxidative iodination of arenes in ionic liquids.

3.3. Supercritical CO_2

Supercritical solvents and in particular $scCO_2$ are promising alternative to organic solvents, since these are nontoxic, nonflammable, cheap, readily available, and reusable.[120,121] In addition to the benign character of both $scCO_2$ and water, the use of an $H_2O/scCO_2$ biphasic system has several potential advantages. For example, the pH value is "switchable": the coexistence of water with $scCO_2$ results in an intrinsic pH value of the water phase of about 3, but after depressurization of the CO_2 the pH value of the water phase returns to neutral. This property was ingeniously applied to the oxidative bromination with $NaBr/H_2O_2$ without the need for an external acid, since the intrinsic acidity of the $H_2O/scCO_2$ couple was used as an "on-demand" proton source.[122] Treatment of *o*-cresol (**102**) with $NaBr/H_2O$ in water at 40 °C resulted in only a 12% conversion, while the conversion increased to 54% in a biphasic $H_2O/scCO_2$ system and to 89% when $NaHCO_3$ was added. The last observation suggests an in situ generation of the percarbonic acid (Scheme 35). The system was successfully applied to the bromination of several alkyl-substituted phenols and anilines.



$NaBr : H_2O_2 : NaHCO_3$	Solvent	Conv.	**103**	**104**
3 : 3 : /	H_2O	12%	93%	7%
3 : 3 : /	$H_2O/scCO_2$	54%	78%	22%
3 : 3 : 0.1	$H_2O/scCO_2$	91%	89%	11%

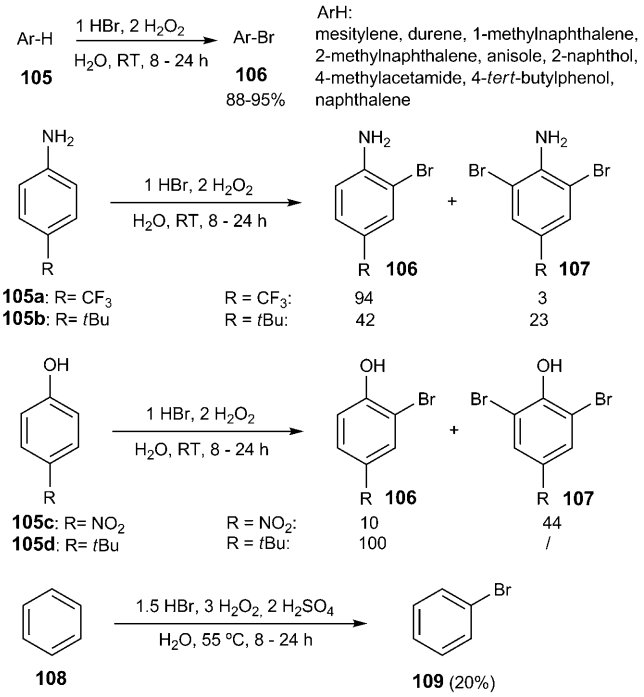
Scheme 35. Water/$scCO_2$ as a reaction medium and proton source in oxidative bromination with NaBr.

3.4. Oxidative Halogenation "On Water"

The use of water as a solvent has been greatly underestimated over the last century, but it is now receiving a lot of attention.[120,123,124] For a long time it was believed that solubility of the substrates and reagents in water was crucial for a reaction to be run in water. This led to the development of phase-transfer catalysts (PTCs) for systems where one reaction component is soluble and the other insoluble. Tetraalkylammonium halides, for example, were used as PTCs, for halogenation in a biphasic system consisting of water and a chlorinated solvent, where besides acting as transfer agents they could also act as halogenating agents.[125–127] In the presence of Bu_4NBr, oxybromination of non-activated aromatic molecules occurred, and a 50–70 times rate acceleration was determined in the bromination of benzene.[128] The catalytic activity of different $R_4N^+Br^-$ compounds in the bromination step decreases in the order: Et > Pr > Bu > Hex > Oct > Me. The anions (Cl^-, HSO_4^- instead of Br^-) had no effect on the reaction rate. An increasing number of reactions are now being performed "on water" and in the presence of water.[129–131] One such example is the oxidative halogenation of organic molecules with HX/H_2O_2 but without any organic solvent. The substrate in this case is insoluble, and the aqueous phase is a solution of H_2O_2 and HX or X_2.

A higher amount of concentrated HCl must be used for efficient chlorination reactions, which makes it difficult to control the selectivity of the reaction. Oxidative chlorination can be used without problem when polychlorinated compounds are the desired products.[132,133] However, mono- and dichlorinated products can be obtained by controlling the amount of H_2O_2 (4 HCl/0.9 H_2O_2 gives monochlorination, 5 HCl/2.2 H_2O_2 gives dichlorination). One example of this is the chlorination/decarboxylation of benzoic acids for the preparation of *ortho*-substituted phenols, anilines, and toluenes (Scheme 16 in Section 3.1.1).[92,93]

In the case of bromination, one equivalent of HBr is sufficient for the reaction to be completed; however, an excess of H_2O_2 should be used to compensate for its HBr-catalyzed decomposition. Alternatively, H_2O_2 can be added slowly. Scheme 36 shows some examples of the efficient and selective bromination of aromatic molecules in aqueous solution with 3% H_2O_2 and 7% HBr.[134] As there is no organic residue or by-products and the only organic product after the reaction is the desired brominated compound,

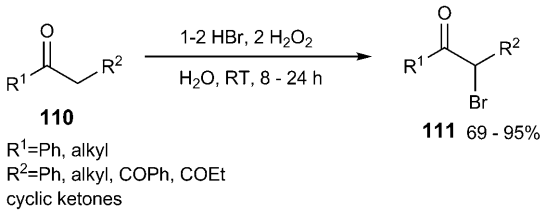


Scheme 36. Examples of oxidative bromination of aromatic molecules in water.

isolation is simple and only phase separation and washing with water is necessary. The "on-water" bromination of 4-trifluoromethylaniline (**105a**) with one equivalent of HBr and two equivalents of H_2O_2 afforded 2-bromo-4-trifluromethylaniline (**106a**), with 94% conversion and contaminated with only 3% of the corresponding dibrominated product **107a**. When an electron-donating group, such as 4-*tert*-butyl, is present in the aromatic ring of the aniline (**105b**), a mixture of mono- (**106b**) and dibrominated (**107b**) products are formed; complete conversion into **107b** is achieved by using an excess of reagents. A different behavior was observed in the oxidative bromination of 4-*tert*-butylphenol (**105d**), where a monobrominated product **106d** was formed selectively and quantitatively, while the presence of an electron-withdrawing group (NO_2) at the *para* position in **105c** produced a mixture of **106c** and **107c**. An additional activation using acid was needed to brominate benzene (**108**) in aqueous HBr/H_2O_2, and only 20% of **109** was isolated (Scheme 36).[134]

A series of 1,3-diketones, β-ketoesters, cyclic ketones, and aryl alkyl and dialkyl ketones were efficiently brominated by aqueous HBr/H_2O_2 at room temperature. The resultant brominated ketones **111** were isolated in yields of 69–95%, with high selectivity for monobromination over dibromination (Scheme 37).[135] The reactivity was tuned by using a more dilute aqueous solution of H_2O_2/HBr or by the use of excess HBr. Besides being a good reaction medium for the α-bromination of carbonyl compounds, water also activates the ketone group for α-bromination through generation of the enol form.

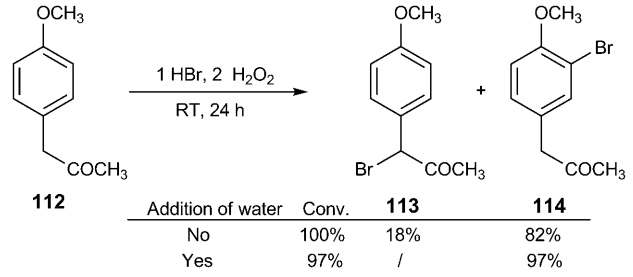
Furthermore, the aqueous H_2O_2/HBr system has also been used for tandem oxidation/bromination in the preparation of α-bromoketones directly from alcohols. The authors found



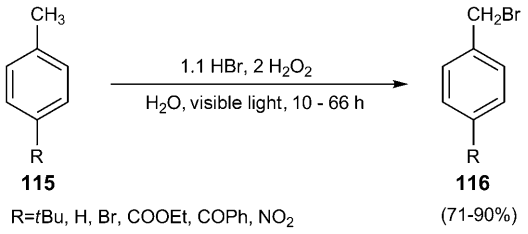
Scheme 37. The oxidative bromination of carbonyl compounds in aqueous medium occurs selectively.

that the use of a more dilute HBr/H_2O_2 system increases the selectivity toward ring bromination over α-bromination for aryl ketones with an activated phenyl ring, such as **112** (Scheme 38).[135]

Water is also a promising solvent for radical reactions because the OH bond is strong and does not interfere with the radical chain mechanism.[136,137] Oxidative bromination in aqueous media was applied to benzyl bromination. Of the different ways of activating the radical chain process in water, visible light (a 40 W lamp) gave the best results.[135,138] Benzyl bromides **116** were formed in good yields and with high selectivity, while a stronger light source was necessary with alkyl benzenes bearing electron-withdrawing groups, and H_2O_2 needed to be added slowly to reduce decomposition (Scheme 39).



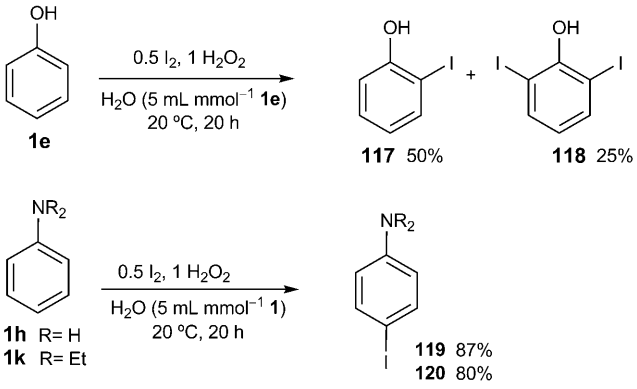
Scheme 38. The amount of water influences the selectivity of the oxidative bromination.



Scheme 39. Radical oxidative bromination in an aqueous medium.

Iodination in the aqueous phase is problematic because of the solubility of iodine, while HI is much easier to regenerate. Aqueous-phase iodination with I_2/H_2O_2 without any cosolvent or activator was effective only for reactive arenes, such as phenols, anilines, and anisoles. Interestingly, phenol (**1e**) was iodinated only at the *ortho* position (Scheme 40).[139]

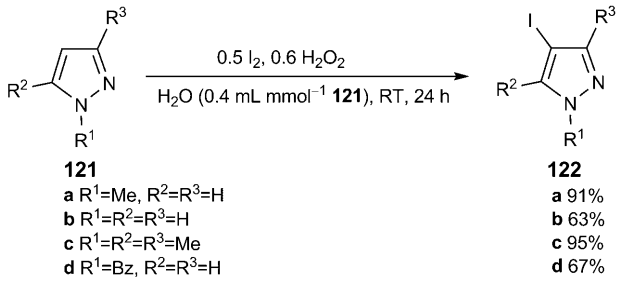
Oxidative iodination in water has also been applied for the 4-iodination of various substituted pyrazoles **121**. Under



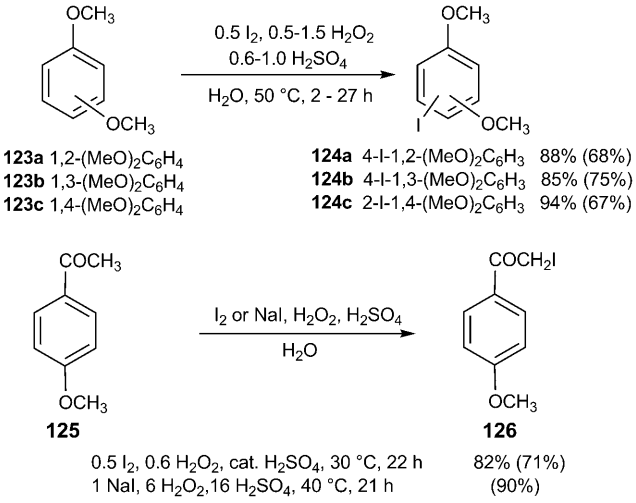
Scheme 40. Iodination of reactive arenes with I_2/H_2O_2 in water.

these conditions, the reaction proceeds well for unsubstituted as well as *N*-alkyl- and *N*-aryl-substituted pyrazole derivatives (Scheme 41).[140]

Similar results to the ones obtained in ionic liquids were observed in aqueous media except that a catalytic amount of sulfuric acid was needed for the iodination of **123** (Scheme 42).[141,142] The acetophenone derivative **125** was selectively iodinated by I_2/H_2O_2 in water at the α position to the carbonyl group (Scheme 42);[141,142] when sodium iodide was used as the iodine source, the addition of sulfuric acid



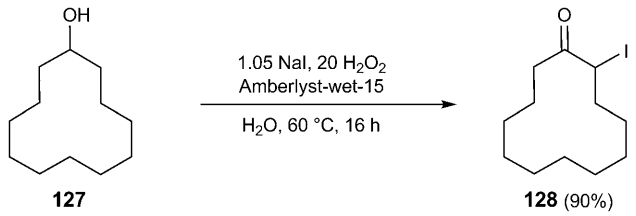
Scheme 41. Iodination of pyrazoles with I_2/H_2O_2 in water.



Scheme 42. The reaction medium determines the selectivity of the iodination.

became necessary.[143] A combination of $0.5\,I_2/0.5\,H_2O_2$ in water at 50 °C efficiently transformed various ketones, including cyclic, dialkyl, and alkyl aryl ketones, to the corresponding α-iodinated products in yields of up to 86%, even without the addition of an acid.[139]

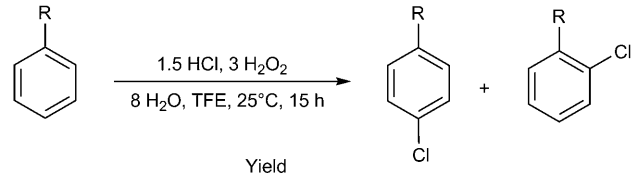
The comination of oxidative iodination with the oxidation of alcohols leads to a tandem system for the transformation of alcohols such as **127** directly into α-iodoketones **128**; in this case NaI/H_2O_2 is used together with a recoverable source of acidity, such as Amberlyst-wet-15 as a proton source (Scheme 43).[143]



Scheme 43. Tandem oxidation and oxidative iodination for the conversion of alcohols into α-iodoketones by using a recoverable polymer-bound acid.

3.5. Alternative Media, Activation Methods, and H_2O_2 Sources

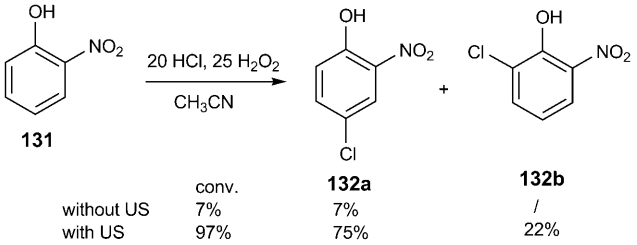
The oxidative chlorinating system HCl/H_2O_2 has the disadvantage that a large excess of HCl and a higher temperature are required, which creates problems concerning selectivity. An additional mode of activation would, therefore, be beneficial, and recently it was demonstrated that fluorinated alcohols are excellent activators of hydrogen peroxide.[144,145] Trifluoroethanol (TFE) was used as the solvent for the oxidative chlorination, and H_2O_2 was activated to an extent that only 1.5 equivalents of HCl was sufficient for the quantitative chlorination of non-activated aromatic compounds (Scheme 44).[146] The oxidative chlorination of anisole in TFE occurred twice as fast as in EtOH, while for toluene (**1f**) the reaction rate was accelerated by three orders of magnitude. The use of a fluorinated alcohol as solvent allows the oxidation of chloride at lower H^+ concentrations, and less-reactive arenes can be chlorinated effectively. DFT calculations shows how TFE stabilizes the polar transition state by acting as a charge template with complementary charges, thus lowering the energy barrier for the reaction relative to that in EtOH by about 6 kcal mol^{-1}.



	Yield		
108 R=H	73%	**1m** 100%	
1f R=CH_3	>99%	**129f** 64%	**130f** 36%
1g R=Et	>99%	**129g** 67%	**130g** 33%
1i R=*i*Pr	>99%	**129i** 79%	**130i** 21%
1m R=Cl	23%	**129m** 67%	**130m** 33%
1n R=NO_2	/	/	/

Scheme 44. Fluorinated alcohol activates the oxidative chlorination so that arenes can be transformed at lower temperatures and at a lower excess of reagents.

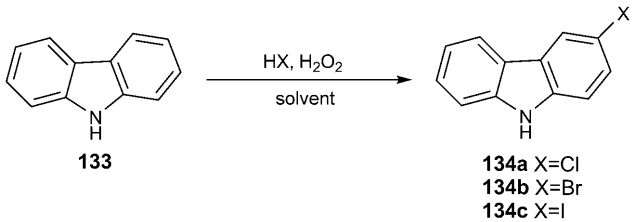
Ultrasound offers another interesting mode of activation. An example is the chlorination of phenol derivatives with HCl/H_2O_2: Phenol, 2-nitrophenol (**131**), and thymol were chlorinated in an ultrasound-promoted HCl/H_2O_2 reaction, while 1-naphthol and 1-hydroxy-2-naphthoic acid gave chlorinated quinones as the major products.[147] Scheme 45 clearly shows the effect of activation by ultrasound. However, 50% H_2O_2 still needs to be used in the reaction, but it would be interesting to know if a smaller amount of HCl would also be effective.



	conv.	**132a**	**132b**
without US	7%	7%	/
with US	97%	75%	22%

Scheme 45. Ultrasound activation in oxidative chlorination.

The activation of organic reactions by microwave (MW) irradiation is becoming ever more popular on account of it offering reduced reaction times, increased yields, and cleaner reactions.[148] Bogdal et al. used microwave irradiation for the oxyhalogenation of carbazole (**133**) and other arenes, and found that the chlorination was faster and yields higher than with conventional protocols. However, a threefold excess of HCl and H_2O_2 in the presence of 10 mol% catalyst (Na_2WO_4) were still required, together with heating the reaction mixture to 75 °C (Scheme 46). Bromination proceeded well at 50 °C, with 1.1 equivalents of HBr and 1.1 equivalents of H_2O_2 in a biphasic H_2O/DCE system, while for iodination a homoge-

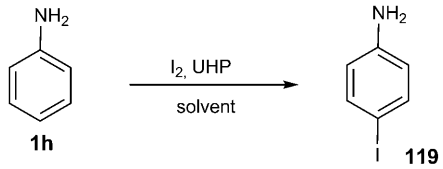


		134a
3.3 HCl, 3.3 H_2O_2, 10 mol% Na_2WO_4, DCE, 75 °C, 15 min	MW	73%
	no MW	56%
		134b
1.1 HBr, 1.1 H_2O_2, DCE, 50 °C, 10 min	MW	76%
	no MW	59%
		134c
1.1 HI, 1.1 H_2O_2, AcOH, 100 °C, 30 min	MW	80%
	no MW	59%

Scheme 46. An example of a microwave-assisted halogenation.

neous acetic acid system was used and the reaction had to be performed at 100 °C to achieve total conversion.[149]

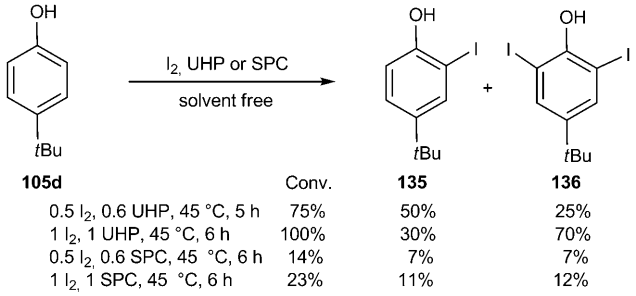
Microwave irradiation has also been used in the iodination of aromatic amines with molecular iodine and a solid urea–hydrogen peroxide adduct ($NH_2CONH_2{\cdot}H_2O_2$, UHP) as an oxidant. The iodination of aniline (**1h**) in boiling $CHCl_3$[150] occurred in lower yields than with conventional heating in EtOAc,[151] but the reaction times were much shorter (Scheme 47). Microwaves have also been used to activate the bromination of acetophenones in the solid phase by using UHP and NaBr in acetic acid impregnated on silica, with the brominated products being obtained in 40–120 s in a yield of 70–80 %.[152]



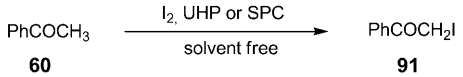
0. 5 I_2, 0.55 UHP, $CHCl_3$, MW, 10 min 58%
0.45 I_2, 0.57 UHP, EtOAc, RT→50 °C, 3 h 64%

Scheme 47. Application of solid H_2O_2 in the microwave-assisted iodination of anilines.

Similar to UHP, sodium percarbonate ($Na_2CO_3{\cdot}1.5\,H_2O_2$, SPC) and sodium perborate ($NaBO_3{\cdot}H_2O$ or $NaBO_3{\cdot}4H_2O$) are often used as "dry carriers" and safer alternatives to the hazardous and unstable concentrated liquid hydrogen peroxide. The best solvent in terms of "green" chemistry is "no solvent at all", and the use of solid forms of H_2O_2 allows such an approach. Thus, UHP and SPC (0.6 equiv) have been used for iodination with I_2 (0.5 equiv) under solvent-free conditions. Aniline (**1h**) was completely iodinated to 4-iodoaniline (**119**) at 45 °C with UHP, while the less-reactive SPC gave only 74 % conversion in 18 h.[153] A similar reactivity was observed for the iodination of 4-*tert*-butylphenol (**105d**), where both monoiodo **135** and diiodo **136** products were formed (Scheme 48). Acetophenone (**60**) was iodinated under identical reaction conditions at the α position to the carbonyl



105d	Conv.	**135**	**136**
0.5 I_2, 0.6 UHP, 45 °C, 5 h	75%	50%	25%
1 I_2, 1 UHP, 45 °C, 6 h	100%	30%	70%
0.5 I_2, 0.6 SPC, 45 °C, 6 h	14%	7%	7%
1 I_2, 1 SPC, 45 °C, 6 h	23%	11%	12%

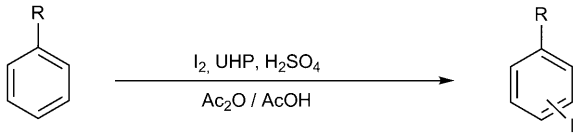


0.5 I_2, 0.6 UHP, 45 °C, 3 h 55%
0.5 I_2, 0.6 SPC, 45 °C, 7 h /

Scheme 48. Solvent-free oxidative iodination.

group. In all the solvent-free reactions described to date, UHP is superior to SPC.[153,154]

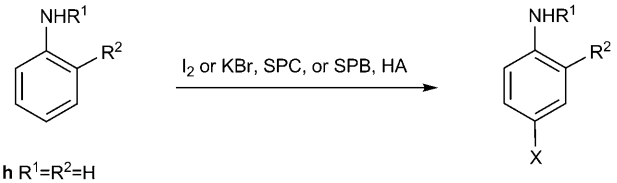
Harsh conditions need to be applied for the iodination of deactivated aromatic compounds. An example is the iodination with I_2/UHP in Ac_2O/AcOH. The reactivity of the system was regulated by controling the amount of sulfuric acid and by an excess of UHP (Scheme 49).[151]



	I_2 (equiv)	UHP (equiv)	H_2SO_4 (equiv)		
108 R=H	0.48	0.71	19	**137**	45%
109 R=Br	0.48	0.71	19	**138**	83% (4-iodo)
139 R=COOH	0.55	2.25	15	**140**	81% (3-iodo)
141 R=CF_3	0.55	2.25	30	**142**	18% (3-iodo)

Scheme 49. The iodination of deactivated arenes requires strong acidic conditions.

A similar procedure was applied to the oxidative iodination and bromination of various aromatic anilines and amides with either SPC or SPB as an oxidant. The iodination of anilines was performed with I_2/SPC in AcOH, while for acetanilide (**1j**) the reaction had to be performed in an anhydrous AcOH/Ac_2O mixture in the presence of H_2SO_4 (Scheme 50).[155] SPB was also used for the bromination of



1h R^1=R^2=H
0.48 I_2, 0.55 SPC, AcOH/EtOAc, 50 °C, 35 h **119** (X=I) 68%
143 R^1=H, R^2=Cl
0.48 I_2, 0.55 SPC, AcOH/EtOAc, 50 °C, 4 h **144** (X=I) 73%
1j R^1=Ac, R^2=H
0.48 I_2, 0.74 SPC, AcOH/Ac_2O, 19 H_2SO_4, 50 °C, 2 h **145** (X=I) 62%
1.1 KBr, 2.6 SPB, AcOH/Ac_2O, 5 H_2SO_4, RT **2j** (X=Br) 60%
2h R^1=H, R^2=Br
1.2 KBr, 1.2 SPB, AcOH, RT, 14.5 h **4h** (X=Br) 97%

Scheme 50. Oxidative halogenation of anilines with SPC or SPB.

acetanilide (**1j**) with KBr in AcOH/Ac_2O/H_2SO_4. The yield of **2j** was improved to 86 and 79 % by using either sodium tungstate or phosphomolybdic acid, respectively, as a catalyst.[156] Similarly, 2-bromoaniline (**2h**) was almost quantitatively brominated in AcOH without the need for a catalyst, although it was found that ammonium molybdate accelerates the reaction.[157] The same system was also applied to the dibromination of alkenes and alkynes.[9,158]

4. Aerobic Oxidative Halogenation

The most abundant and natural oxidant is oxygen or, in its diluted form, air, and the use of oxygen for organic reactions

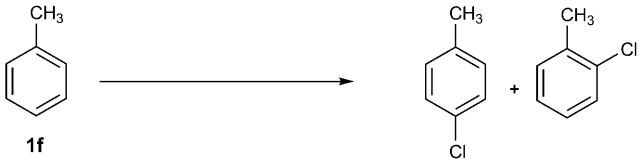
is both an attractive and challenging research field. In terms of oxidative halogenation, the topic of this Review, the use of oxygen is uncommon, but is beginning to receive more attention.

4.1. Nitrogen Compounds as Catalysts for Aerobic Oxidative Halogenation

Nitric acid is both a stoichiometric oxidant and a proton donor and has been used for the oxidative halogenation of various arenes with halide salts (KCl or KBr with 3% Bu_4NBr as phase-transfer catalyst).[159] The oxidative chlorination, bromination, and iodination of various aromatic compounds, including deactivated ones, was achieved by using halide salts in the presence of either nitrate or nitrite anions acting as stoichiometric oxidants (KNO_3, $NaNO_3$, NH_4NO_3, $NaNO_2$). Performing the experiments at 20°C in aqueous CF_3COOH gives the correct acidity of the system for the reaction to proceed.[160–162] An alternative is to use an organic nitrite (isoamyl nitrite), with HBr acting as the bromine source.[163]

In the above examples, the nitrogen compounds acting as stoichiometric oxidants generate a stoichiometric amount of nitrite salts or toxic nitrous oxides. To avoid this, ionic liquids with NO_3^- ions have been used as both an oxidant and a reaction medium for the chlorination and bromination of toluene, anisole, benzene, and naphthalene. The reaction of toluene (**1f**) in [bmim][NO_3] with hydrochloric acid gave 4-chlorotoluene (**129f**) and 2-chlorotoluene (**130f**) in yields of 38% and 60%, respectively. An almost identical result was obtained when the reaction was performed in the chloride-containing ionic liquid [C_{10}mim][Cl] together with nitric acid (Scheme 51).[164] Even benzene was chlorinated in 50 mol% [bmim][NO_3] and HCl in the presence of air. Another example is the use of [Hmim][NO_3] for chlorinating arenes and acetophenone and, again, [Hmim][NO_3]/37% HCl or [Hmim][Cl]/67% HNO_3 could be used.[165]

Dorfman and Aleshkova investigated the kinetics and mechanism of the oxidative bromination of aromatic compounds with HNO_3/HBr in sulfuric acid solutions.[166] In this case, HNO_3 is first reduced to HNO_2, which then decomposes under acidic conditions to give nitrous oxides. Besides HNO_3, various other nitrogen oxides are potential participants in this reaction, although only HNO_3 has the required redox potential to oxidize Br^- to Br^+.[166] The authors did not anticipate the involvement of nitrosyl halides in the reaction, despite the formation of NOBr when treating Br_2 with NO or Br^- with NO_2.[167] Furthermore, having the nitronium (NO_2^+) and nitrosonium (NO^+) ions present in the reaction mixture opens up the possibility for nitration and nitrosation reactions. The selectivity for bromination was explained by the formation of a more stable σ complex between the solvated Br^+ and arene. Nitrosation and nitration would proceed through the formation of a π complex, which is less possible because of the strong solvation of NO^+ and NO_2^+.[166]



1f

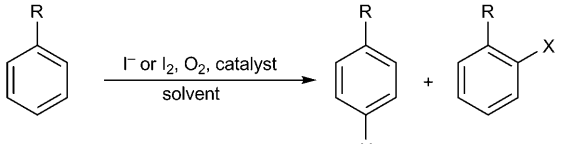
	Conv.	**129f**	**130f**
1.25 [bmim][NO_3] / 2 HCl, 100 °C, 96 h	98%	38%	60%
[C_{10}mim][Cl] / 3 HNO_3, 110 °C, 120 h	99%	36%	62%

Scheme 51. Nitrate ions in ionic liquids as oxidants for the synthesis of chlorinated products.

Since oxygen regenerates nitrogen compounds in low oxidation states back to HNO_3 or another active form of nitrogen, it is possible to use only catalytic amounts of HNO_3 or a similar compound. When nitrate was used as an oxidant for the iodination of aromatic molecules (with 0.57 equivalents of I_2 in acetic acid) at least 0.4 equivalents of $NaNO_3$ was required for the quantitative iodination of anisole in an oxygen-free atmosphere. However, if oxygen is bubbled through the reaction mixture, 0.2 equivalents of $NaNO_3$ is sufficient to produce the same effect (Table 3).[168] Catalytic amounts of sodium nitrite have been used as the catalyst in the presence of oxygen in aqueous TFA at room temperature to iodinate deactivated aromatic compounds in yields of 83–98% (Table 3).[161] Furthermore, the combination NH_4I/$NOBF_4$(cat.)/O_2 in TFA/TFAA/CH_2Cl_2 proved to be a potent system for the aerobic oxidative iodination of aromatic compounds; only strongly deactivated substrates, for example, benzonitrile and benzotrifluoride, failed to react (Table 3).[169]

In the above examples, the presence of an acid (AcOH or TFA) is obligatory since it converts $NaNO_2$ or $NOBF_4$ into

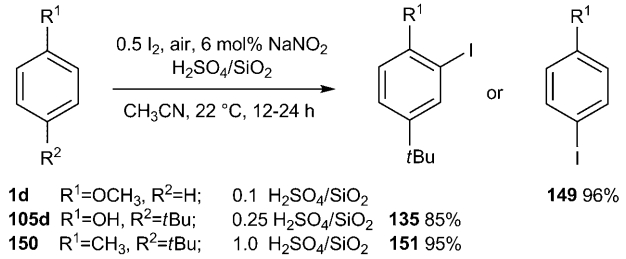
Table 3: Aerobic iodination of aromatic molecules with nitrogen species as catalysts.



146 **147** **148**

146	R		Cat. [mol%]	Conditions	Conv.	**147/148**
146a	OMe	0.57 I_2	0.4 $NaNO_3$	AcOH, 85°C	92%	100:0
146a	OMe	0.57 I_2	0.2 $NaNO_3$	O_2, AcOH, 85°C	92%	100:0
146b	F	1 KI	0.2 $NaNO_2$	O_2, TFA_{aq}, 20°C	98%	97:3
146c	Cl	1 KI	0.2 $NaNO_2$	O_2, TFA_{aq}, 20°C	90%	88:12
146d	Br	1 KI	0.2 $NaNO_2$	O_2, TFA_{aq}, 20°C	83%	88:12
146e	I	1 KI	0.2 $NaNO_2$	O_2, TFA_{aq}, 20°C	98%	83:17
146b	F	1.5 NH_4I	0.2 $NOBF_4$	O_2, TFA/TFAA/CH_2Cl_2, RT	86%	97:3
146c	Cl	1.5 NH_4I	0.2 $NOBF_4$	O_2, TFA/TFAA/CH_2Cl_2, RT	82%	91:9
146d	Br	1.5 NH_4I	0.2 $NOBF_4$	O_2, TFA/TFAA/CH_2Cl_2, RT	87%	90:10
146e	I	1.5 NH_4I	0.2 $NOBF_4$	O_2, TFA/TFAA/CH_2Cl_2, RT	92%	90:10

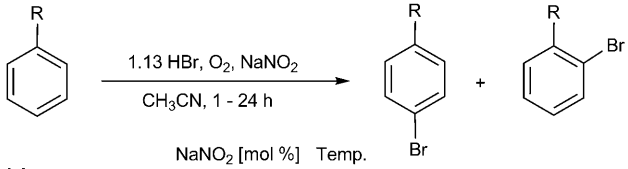
nitrogen oxides, which are the true catalysts in the reactions. The correct acidity for the reaction can be guaranteed by adding acid such as H_2SO_4 in a quantity that is dependent on the reactivity of the substrate. An example of this is the aerobic iodination of arenes and carbonyl compounds with I_2/air/$NaNO_2$ (Scheme 52).[170] The use of a solid-supported acid



Scheme 52. A solid-supported acid mediates the reactivity of sodium nitrite catalyzed iodination with air as the oxidant.

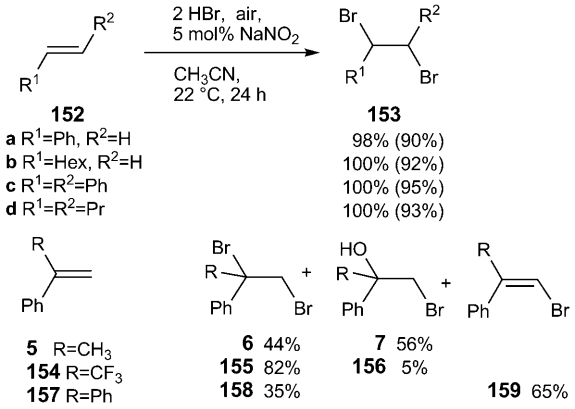
opens up the possibility of its reuse. KI/acid can also be used as an iodine source, and the best solvent is MeCN for arenes, EtOH for ketones, and TFA for deactivated substrates.[171] When molecular iodine (I_2/$NaNO_2$/air) is used, an additional amount of acid to generate HI from KI is no longer required and the reaction needs only a only catalytic amount of acid (Scheme 52). This iodinating system was efficient for the iodination of aromatic compounds, carbonyl compounds, and unsaturated C–C bonds.[170,171]

Hydrobromic acid can also be used for bromination, as it is both a source of bromine and an activator of $NaNO_2$. The reaction of anisole (**1d**) in CH_3CN at 25 °C with only 3% $NaNO_2$ was complete within one hour, and the product, **3d**, was obtained in quantitative yield. The bromination of less-reactive aromatic compounds such as toluene and benzene required the reaction temperature to be increased to 65 °C and 10 mol% of the catalyst used to give a relatively high yield (Scheme 53).[172]



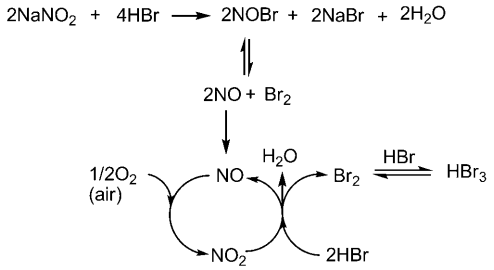
Scheme 53. HBr is a bromine source and activator of sodium nitrite in aerobic bromination.

Air has also been used as the oxidant for the bromination of various alkenes (internal and terminal with aryl and alkyl substituents). These were efficiently and selectively *trans*-dibrominated by using 2 equivalents of 48% aqueous HBr and 5 mol% $NaNO_2$ as the catalyst at room temperature (Scheme 54).[11] In the absence of the catalyst, the addition of HBr to the alkene is the sole reaction. The slow generation of



Scheme 54. Aerobic dibromination of alkenes with stoichiometric amounts of HBr.

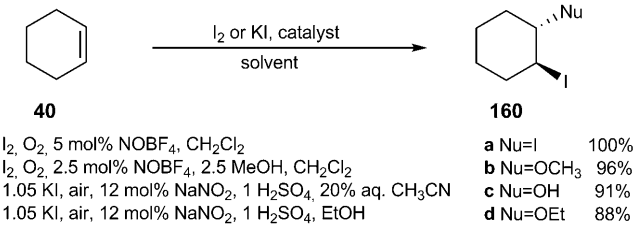
the brominating species is the key for the selective formation of vicinal dibromides and not bromohydrines, despite the presence of water. The possibilities of forming HBr_3 (because of the excess of HBr) at the early stages of the reaction and its responsibility for *anti*-bromination were not excluded. The authors established that NOBr is formed first from $NaNO_2$ and HBr and its decomposition leads to the generation of NO, which acts as the true catalyst (Scheme 55).[11] Thus, a small



Scheme 55. The course of the $NaNO_2$-catalyzed aerobic bromination.

amount of bromine is already formed in this precatalytic phase and is rapidly consumed by the alkene. This shifts the equilibrium towards complete decomposition of NOBr.

The iodination of cyclohexene (**40**) was demonstrated using molecular iodine together with a catalytic amount of $NOBF_4$ in CH_2Cl_2 in the presence of O_2 at ambient temperature. The product, 1,2-diiodocyclohexane (**160a**), was obtained in quantitative yield (Scheme 56). The addition of

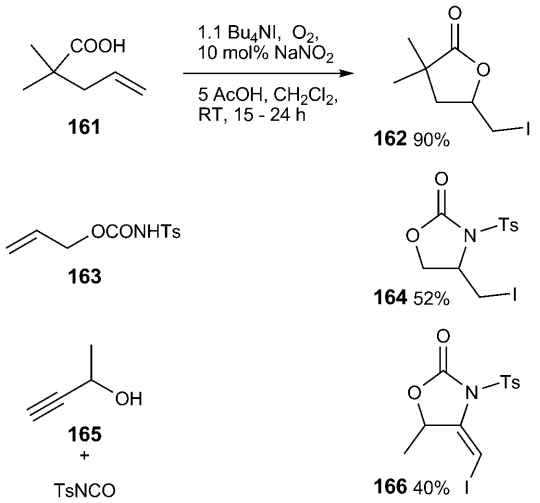


Scheme 56. Two possibilities in the aerobic iodination of alkenes.

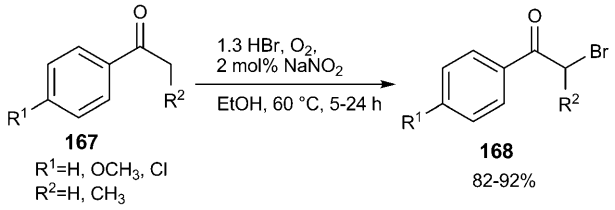
methanol resulted in the formation of 1-methoxy-2-iodocyclohexane (**160b**) in 96% yield.[173] The use of MeCN or ethanol as the solvent for the iodination with KI/H_2SO_4/air/$NaNO_2$(cat.) yields 1,2-iodocyclohexanol (**160c**) and the iodoethoxy product (**160d**), respectively (Scheme 56). Similarly, other alkenes can be transformed with Markovnikov regioselectivity and *anti* stereoselectivity into vicinal iodohydrins or vicinal iodohydroxy derivates.[171]

The use of Bu_4NI and $NaNO_2$ as a catalyst in the presence of O_2 and 5 equivalents of AcOH in CH_2Cl_2 led to the development of a convenient iodolactonization and iodoamination reaction as a starting point to various cyclic compounds (Scheme 57)[174]

Acetophenone derivatives were efficiently brominated by $NaNO_2$-catalyzed aerobic bromination; however, EtOH should be used as the solvent and HBr as the acid catalyst (Scheme 58).[172]

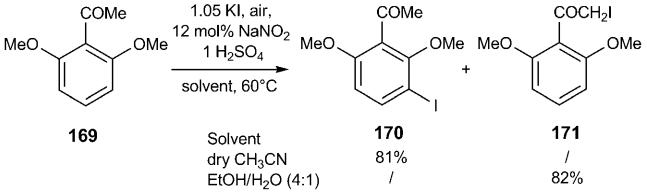


Scheme 57. Iodolactonization and iodoamination.



Scheme 58. Aerobic bromination of acetophenones in EtOH.

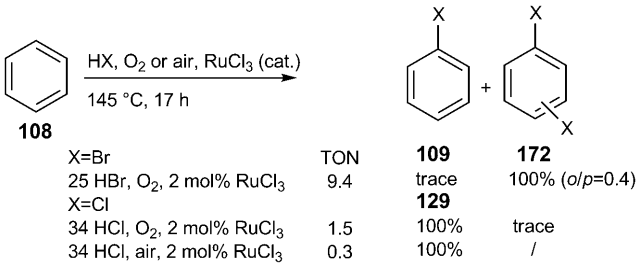
SiO_2-supported H_2SO_4 was used as a recyclable acid catalyst and air as the oxidant to efficiently iodinate various ketones (dialkyl, aryl alkyl, β-ketoesters, and cyclic ketones) and aldehydes.[170] The use of an analogous system with an iodide salt requires a higher amount of acid.[171] A study on an acetophenone derivative with an activated aromatic ring suitable for substitution (**169**) showed that iodination in CH_3CN gave the ring-iodinated product **170** in 81% yield, while in aqueous ethanol the α-iodo ketone **171** was formed (Scheme 59).[171]



Scheme 59. Effect of the solvent in aerobic iodination.

4.2. Metal-Catalyzed Aerobic Oxidative Halogenation

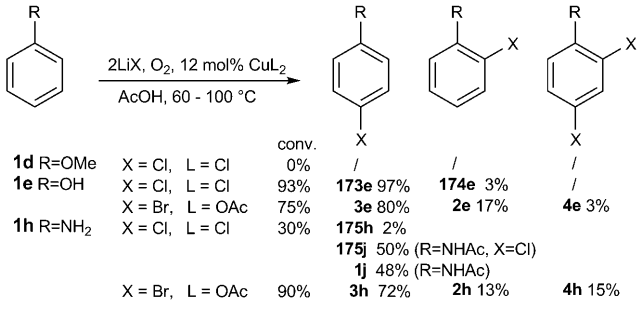
Several research groups have studied the use of metal salts (V, Cu, Ti, Fe, Mn) for the aerobic iodination of benzene (**108**), and found that an acidic solvent (CH_3SO_3H or CF_3COOH) is needed for the activation of iodination. Nevertheless, a metal catalyst and oxygen are still required to regenerate the I_2 from the residual HI to have a 100% iodine atom economy. The best yield of iodobenzene was obtained when using V_2O_5 in CF_3SO_3H, with a TON of 17.9 and a ratio between the mono- and diiodobenzene of 81.1:7.7.[175] A ruthenium catalyst ($RuCl_3$) was also found to be effective for aerobic bromination and chlorination with concentrated HBr or HCl, respectively, and O_2 in an aqueous/organic biphasic system in an atmosphere of pure oxygen at 1 bar (Scheme 60).[176] Alternatively, air can also be used



Scheme 60. Ruthenium(III) as a catalyst for oxidative halogenation.

when the pressure is increased to 4 bar. In the reaction with **108**, 9.4 mol bromine and 1.5 mol chlorine atoms were incorporated per mol of $RuCl_3$, with formation of the corresponding dibromobenzene **172** and chlorobenzene (**129**), respectively. Other unsaturated organic substrates were also halogenated.

Copper salts are the most studied metal catalysts for aerobic oxidative halogenation. It was demonstrated that $CuCl_2$ is able to catalyze the oxychlorination and oxybromination of various phenols and anilines. The reaction of phenol (**1e**) with 2 equivalents of LiCl in the presence of O_2 and 12 mol% $CuCl_2$ in acetic acid at 80°C resulted in 93% conversion and 90% selectivity towards 4-chlorophenol (**173e**; Scheme 61).[177] Analogously, the oxidative bromination of various phenols was performed with LiBr and a catalytic amount of $Cu(OAc)_2$; however, the *para* regioselectivity was generally lower for bromination than for chlorination.[178] The presence of a hydroxy group on the aromatic nucleus is essential for the reactivity of the aromatic substrate.



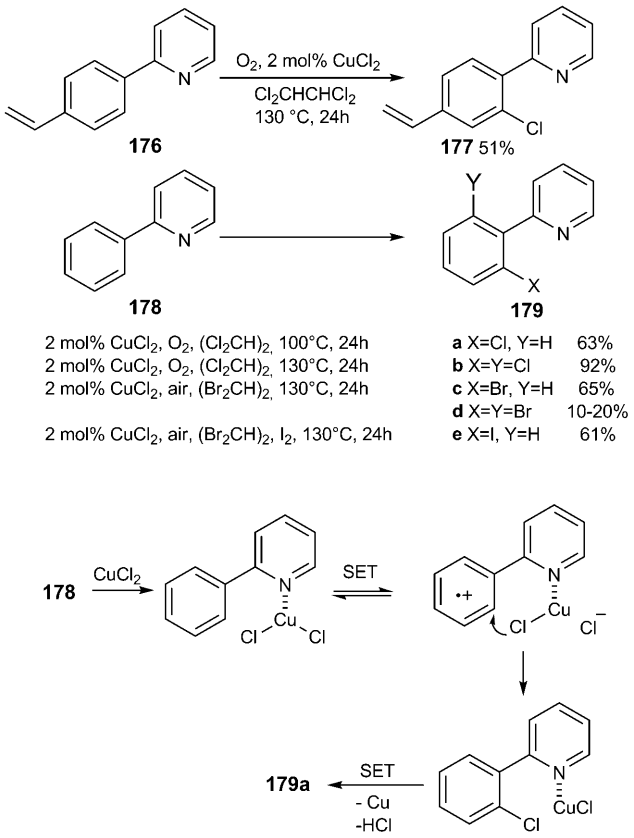
Scheme 61. Copper catalysts are potent catalysts for oxidative halogenation.

The reaction proceeds with the formation of a complex between phenolate and the copper catalyst as a key intermediate and follows a free-radical pathway.[179] Later it was determined that anilines undergo nuclear halogenation under similar conditions. The monobromination of aniline (**1h**) proceeded with a somewhat lower selectivity than the bromination of **1e**, while the chlorination of **1h** was less selective and the acetylation of the NH_2 group was the main reaction (Scheme 61).[180]

A $CuCl_2$-catalyzed aerobic halogenation under either oxygen or air has been used to convert heterocyclic 2-aryl pyridines. In this case, the source of the halogen atoms is the solvent, and the addition of I_2 results in iodination occurring (Scheme 62). Interestingly, the chlorination of **176** with 20 mol% $CuCl_2$ in $Cl_2CHCHCl_2$ at 130 °C is selective for the aromatic C–H bond, despite the presence of the double bond.[181] Again, coordination of the substrate through its nitrogen atom to Cu^{II} is necessary if the reaction is to proceed, since the biphenyl is unreactive. A radical-cation pathway was proposed in which a single-electron transfer (SET) from the aryl ring to the coordinated Cu^{II} center to give the cation-radical intermediate is the rate-limiting step. The observed *ortho* selectivity is explained by an intramolecular anion transfer from a nitrogen-bound Cu^{I} complex.[181] The same complexation of the copper to a nitrogen atom was observed in the 12β-chlorination of 17-(2-iminomethyl)pyridine steroids as a side reaction in the 12β-hydroxylation with molecular oxygen in the presence of benzoin/triethylamine when CH_2Cl_2 was employed as the solvent.[182] The copper–phthalocyanine catalyst was heterogenized by encapsulation in zeolites X, Y, and L for the aerobic oxyhalogenation and oxidation of the aromatic nucleus and the alkyl side chains under ambient conditions. Both H_2O_2 and O_2 have been used as oxidants, and HCl, alkali bromides, and chlorides as sources of halogens.[183]

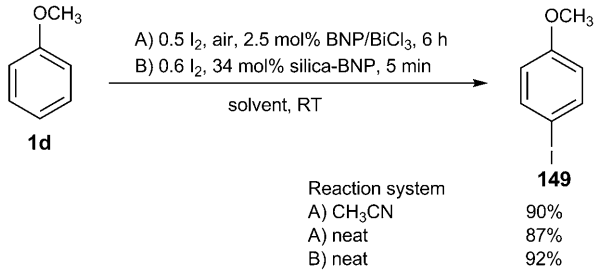
Cerium(IV) ammonium nitrate (CAN) has also been used as a catalyst for the iodination of aromatic compounds. However, only one equivalent of I_2 was used and thus it is difficult to elucidate whether or not CAN acts as either an oxidant or a Lewis acid.[184]

Lu and co-workers described an interesting transformation with the aerobic iodination of aromatic compounds and the subsequent palladium-catalyzed C–C coupling of iodoarenes and alkynes. The oxidative iodination was performed using I_2 and a (BNP)/$BiCl_3$ catalyst (BNP = Bi-



Scheme 62. Radical mechanism of the chlorination with $CuCl_2$, with coordination of the substrate to Cu^{II}.

$(NO_3)_3{\cdot}5H_2O$)in air at room temperature. Under these conditions, the reaction of anisole (**1d**) in CH_3CN gave **149** in 90% yield, while *m*-xylene was iodinated in 62% yield (Scheme 63).[185] The iodination of **1d** in the absence of solvent afforded **149** in 87% yield. Although various catalysts were investigated, only nitrate salts were active, while $BiCl_3$ or $CuCl_2$, for example, gave only a trace amount of the product. In contrast, only 6% of **149** was formed in the presence of $NaNO_3$. Silica-bound BNP was also used in combination with molecular iodine for the iodination of aromatic compounds (Scheme 63).[186] Activated aromatic compounds were iodinated in yields of 84–92% under solvent-free conditions with short reaction times, while less-activated substrates required longer reaction times and gave products in lower yields.

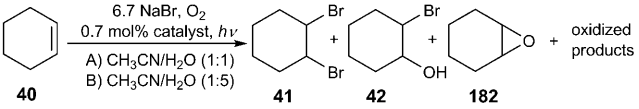


Scheme 63. Bismuth(III) catalysts for the aerobic iodination of arenes.

Heteropolyacids (HPAs) of the Keggin-type with the general formula $H_{3+n}PMo_{12-n}V_nO_{40}$ have often been used as oxidation catalysts. The complexation of the HPA $H_5PMo_{10}V_2O_{40}$ (PMoV-2) with dimethyl ethers of ethylene glycol oligomers enabled it to be dissolved in its acid form in nonpolar organic solvents such as DCE. PMoV-2 was then used as a catalyst for the bromination of organic compounds with gaseous hydrogen bromide (Scheme 64).[187] Upon completion, the reaction-reduced catalyst was reoxidized at room temperature using O_2 at 0.2 atm. Under these conditions the aromatic substrates afforded monobrominated products selectively. The monobromination was *para* regioselective for phenols, while ketones produced a mixture of α-mono, α,α-dibromo, and α,α′-dibromo products. The reaction of 1-octene proceeded by addition of Br_2 and HBr in a ratio of 73:23. Diethyl ether, THF, monoglyme, and diglyme can all solubilize the HPA compound, but the system remains catalytically inactive, while tetraglyme, [18]crown-6, or PEG-350 dissolved the PMoV-2 and promoted catalytic oxidation. Higher molecular weight polyethers (PEG-5000) do not complex the HPA compound.

PMoV-2 (1 mol%) was used as a heterogeneous catalyst for aerobic oxidative iodination with 0.5 equivalents of iodine in acetonitrile under oxygen (Scheme 65).[188] Even deactivated aromatic compounds are iodinated in high yields when nitrobenzene, which enables a higher reaction temperature, is used as the solvent. The catalytic activity of PMoV-2 is ascribed to its oxidizing and acidic properties.

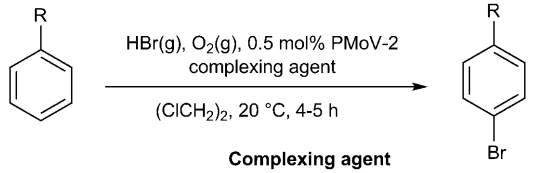
A different mechanism of oxidative bromination has been described when decatungstate $W_{10}O_{32}^{4-}$ immobilized on Amberlite IRA-900 was dispersed in a CH_3CN/H_2O mixture and photochemically exited. This led to the reductive activation of O_2 to form alkyl hydroperoxides. The active species Br^+ is formed as a consequence of the oxidation of Br^- by the photogenerated hydroperoxides. Alkenes, such as **40**, are converted at atmospheric pressure and room temperature into dibromide **41**, bromohydrin **42**, and epoxide **182** (Scheme 66). It was found that the anionic exchange resin plays a crucial role in enriching the bromide ions close to the surface and consequently in the reaction with the photogenerated hydroperoxdes.[189]



Catalyst	Solvent	Conv.				
$W_{10}O_{32}^{4-}$	A)	50%	7%	12%	12%	69%
$Amb/W_{10}O_{32}^{4-}$	A)	47%	42%	23%	13%	22%
$Amb/W_{10}O_{32}^{4-}$	B)	40%	27%	46%	27%	/

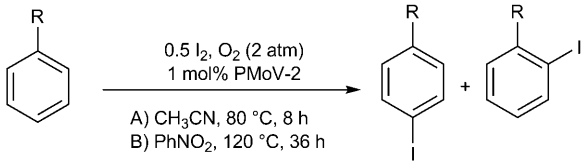
Scheme 66. Oxidative bromination with decatungstanate immobilized on Amberlite IRA-900.

2-Iodonaphthalene was predominantly formed from the reaction of naphthalene with iodine and oxygen over basic faujasite zeolites KX at 250 °C. The ratio of 2-iodonaphthalene to 1-iodonaphthalene can be reduced by substituting sodium for potassium in the zeolite, altering the faujasite zeolite Si/Al ratio, or increasing the amount of iodine.[190]



	Complexing agent	
1e R=OH	tetraglyme	**3e** 99%
1d R=OCH_3	tetraglyme	**3d** 98%
1f R=CH_3	tetraglyme	**3f** -
1e R=OH	Et_2O	**3e** -
1e R=OH	THF	**3e** -
1e R=OH	monoglyme	**3e** 4.2%
1e R=OH	diglyme	**3e** 3.8%
1e R=OH	PEGDME-350	**3e** 100%
1e R=OH	PEGDME-5000	**3e** -
1e R=OH	[18]Crown-6	**3e** 100%

Scheme 64. Aerobic oxidative bromination with heteropolyacid PMoV-2 in the presence of complex formation.



		Solvent	Conv.	**180**	**181**
1d	R=OCH_3	A)	98%	98.5%	/
1e	R=OH	A)	100%	98%	2%
1h	R=NH_2	A)	89%	83%	12%
1f	R=CH_3	B)	99%	85%	15%
180	R=Ph	B)	85%	80%	20%
109	R=Br	B)	91%	81%	19%

Scheme 65. Aerobic oxidative iodination with PMoV-2.

5. Summary and Outlook

Research into the properties and biochemical behavior of haloperoxidase has led to a revival in oxidative halogenation. This Review shows how this area has developed from the early work on metal-catalyzed H_2O_2-mediated halogenation. An abundance of methods for halogenation are available today, in which the highly reactive, toxic, corrosive, and hazardous molecular halogens are replaced.

Although iodination is an exception from this strategy, it does share important attributes of this more environmentally friendly halogenation reaction, for example, replacement of chlorinated solvents with alternative media, 100% halogen atom economy, and the used of recyclable catalysts. Oxidative fluorination is not possible because its oxidation potential is too high, even in the presence of catalysts, to react with either H_2O_2 or O_2. Of course, electrophilic fluorination with HF is high on the "wish list". Chloride has a lower oxidation potential, but it still needs a catalyst to be oxidized/activated. Chlorination is not very selective because of the high reactivity of the chlorinating reagent, and there is still a lot of room for creating more selective methods. This issue is less pronounced in bromination, and some oxidative bromination methods do need the use of a catalyst. Particularly attractive

is the use of "green" reaction media such as $scCO_2$, water, and ionic liquids. Iodination suffers from a different problem: the oxidation of iodide is facile, while iodination requires activation. There is still a need to create more efficient iodination protocols with recyclable activators.

Abbreviations

18-crown[6]	1,4,7,10,13,16-hexaoxacyclooctadecane, $[C_2H_4O]_6$
Ac	acetyl, CH_3COO
Ar	aryl
[bmim]	1-butyl-3-methylimidazolium
Bn	benzyl, $C_6H_5CH_2$
Bu	butyl, $CH_3(CH_2)_3$
[C_{10}mim]	1-decyl-3-methylimidizolium
CAN	cerium(VI) ammonium nitrate, $(NH_4)_2Ce(NO_3)_6$
DCE	1,2-dichloroethane
DFT	density functional theory
diglyme	diethylene glycol dimethyl ether
DMAP	4-(dimethylamino)pyridine
EATOS	environmental assessment tool for organic syntheses
Et	ethyl, CH_3CH_2
Hex	hexyl, $CH_3(CH_2)_5$
hida	2,2′-(hydroxyimino)diacetic acid (basic form)
hidpa	(*S*,*S*)-2,2′-(hydroxyimino)dipropionic acid (basic form)
[Hmim]	3-methylimidazolium
HPA	heteropolyacid
*i*Pr	isopropyl, $(CH_3)_2CH$
LDH	layered double hydroxide
Me	methyl, CH_3
monoglyme	ethylene glycol dimethyl ether
MTO	methyltrioxorhenium, CH_3ReO_3
MW	microwave
Oct	octyl, $CH_3(CH_2)_7$
PEG	polyethylene glycol
Pent	pentyl, $CH_3(CH_2)_4$
Ph	phenyl, C_6H_5
PMoV-2	$H_5PMo_{10}V_5O_{40}$
Pr	propyl, $CH_3(CH_2)_2$
PTC	phase-transfer catalyst
Py	pyridine
RTIL	room-temperature ionic liquid
$scCO_2$	supercritical carbon dioxide
SDS	sodium dodecylsulfate
*sec*Bu	*sec*-butyl, $CH_3CH_2CH(CH_3)$
SET	single-electron transfer
SPB	sodium perborate, $NaBO_3{\cdot}H_2O$
SPC	sodium percarbonate, $Na_2CO_3{\cdot}1.5\,H_2O$
TBAB	tetrabutylammonium bromide, Bu_4NBr
TBHP	*tert*-butylhydroperoxide, $(CH_3)_3COOH$
*t*Bu	*tert*-butyl, $(CH_3)_3C$
tetraglyme	tetraethylene glycol dimethyl ether
TFA	trifluoroacetic acid, CF_3COOH
TFAA	trifluoroacetic anhydride, $(CF_3CO)_2O$
TFE	1,1,1-trifluoroethanol, CF_3CH_2OH
THF	tetrahydrofuran
TiP	titanium phosphate
TOF	turnover frequency (molecules reacting per active site in unit time)
Tol	tolyl, p-$(CH_3)C_6H_4$
TON	turnover number (molecules reacting per active site)
TS	transition state
UHP	urea–hydrogen peroxide adduct
US	ultrasound
VOC	volatile organic solvent
X	halogen, Cl, Br, I
ZrP	zirconium phosphate

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