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On the bromination of aromatics, alkenes and alkynes using alkylammonium bromide: towards the mimic of bromoperoxidases reactivity

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Abstract

This article describes an efficient method of bromination of organic substrates including aromatics, alkenes and alkynes with NH_4VO_3 as a catalyst and H_2O_2 as an oxidant agent using a non-toxic and easy-to-handle source of bromine, tetrabutylammonium bromide. The process was developed under mild reaction conditions and is an innovation from reported methods in aspects such as: *i*) short reaction times, *ii*) the ability to work at room temperature, *iii*) regioselectivity and good yields.

Keywords: monoregioselective bromination, mild methods, ammonium metavanadate, tetrabutylammonium bromide, hydrogen peroxide.

1. Introduction

In recent years, considerable emphasis has been oriented to improve the environmental impact of industrial chemical processes.[1] The development of a mild and efficient method of bromination of organic substrates has received much attention due to the importance of these compounds as agrochemicals, flame retardants and specialty chemicals.[2] Organobromides are also intermediates for the synthesis of biologically active compounds such as antitumor, antibacterial, antifungal, antiviral and antioxidant agents.[3] Furthermore, organic bromides may result in the formation of macromolecules through the formation of C-C cross-coupling reactions for aromatic compounds, such as Heck,[4] Stille,[5] Suzuki,[6] Sonogashira,[7] Negishi[8] and Kharashch.[9]

To date, many catalysts have been developed for oxidative bromination with different oxidants.[10] The oxidants of choice to be considered within the green chemistry have been H_2O_2[11] and O_2,[12] but also, more sophisticated oxidants, always inspired by those transformations in nature which consists in generating the brominating reagent in situ from a bromine salt, such as oxone,[13] $NaIO_4$,[14] $PhI(OAc)_2$[15] and DMSO,[16] etc., have been developed for the oxidative bromination. Metal catalysts based on vanadium, molybdenum and tungsten have been developed for this purpose;[17] nevertheless, the vanadium has shown better performance in halogenation process. The two main catalysts are NH_4VO_3 and V_2O_5. Thus, there is still plenty of room for improvement, and much more efficient procedures could be developed.

Considering the interest on the vanadium reactivity in oxidative halogenation, we are investigating the experimental conditions which govern an efficient bromination reaction with considerable attention in the yields of reaction products and easy reaction conditions.

In nature, bromination of organic substrates occurs in the seabed. Vanadate-dependent haloperoxidases are enzymes that catalyse the two-electron oxidation of a halide to the corresponding hypohalous acids by hydrogen peroxide, as shown in Eq. 1:[18]

$$H_2O_2 + X^- + H^+ \rightarrow H_2O + HOX \qquad \text{Equation 1}$$

Haloperoxidases that are able to catalyse the oxidation of bromide in the presence of H_2O_2 are called bromoperoxidases (BPOs). Vanadium bromoperoxidases (VBPOs) are present in a great variety of brown and red seaweed. The active site in VBPOs contains a vanadate moiety in a trigonal bipyramidal or square pyramidal geometry.[19]

According to Equation 1, the HOBr that is formed will rapidly react with organic matter in seawater that consists mainly of fulvic and humic acids to create brominated compounds that, upon decay, lead to the formation of bromoform and dibromomethane. Traditional chemical halogenation usually requires harsh reaction conditions and forms by-products, in contrast with biocatalyzed processes.[20] According to this, it is possible to carry out the bromination of organic substrates using soft methods without toxic and corrosive Br_2 and HBr, which are commonly used in this type of synthesis.

In the present work, we show the advantages of developing a method of brominating of different types of substrates that is simple, safe, practical and efficient. We highlight the importance of pH in a reaction medium when using ammonium metavanadate/hydrogen peroxide (NH_4VO_3/H_2O_2) as a catalytic system. We show the results of bromination reactions of a series of aromatics, alkenes and alkynes using a non-toxic salt of tetrabutylammonium bromide (TBAB) as a source of bromine in mild conditions at room temperature. It is worth noting that the adopted process was the result of diverse catalysts systems (mainly NH_4VO_3) in function of bromide source evaluated with a model arene (see Table 1). Once established the experimental conditions, which may be useful with the best performance, we proceeded to evaluate some substrates with different functional groups. We discuss shortly the reactivity of vanadium complexes that are formed in function of pH and mechanistic details in the bromination of organic substrates.

2. Results and Discussions

Bromination of 2-tert-butylphenol with different methods

Initially, for the aromatics, due to the difficulty in obtaining a specific brominated compound in a certain position and a high yield of reaction, a series of soft reported methods were evaluated in terms of regioselectivity in the *para*-bromination of a model molecule. 2-*tert*-butylphenol (2-TBP) was chosen as a model to obtain as product 4-bromo-2-*tert*-butylphenol. Under the conditions described in Table 1, firstly the *para*-bromination of 2-TBP proceeded quickly using $AlBr_3$ as bromine source and (NH_4VO_3/H_2O_2) as catalytic system (Table 1, entry 1b). This value was much higher than those of previously reported[21] O_2-based system (Table 1, entry 1a). Nevertheless, the $AlBr_3$ is not a bromine source of easy handling due to its high volatility.

More stable bromine sources were also evaluated. A further method using *N*-Bromosuccinimide (NBS)[22] as bromine source (Table 1, entry 2) was also evaluated. The yield was rather low, came after 40 min (40%) and remained unchanged even after days of reaction. It has been shown that the reactivity of this brominating agent can be modulated with different catalysts,[23] because they have some drawbacks when using only NBS (long reaction times, low yields and low selectivity). A proposed mechanism for this bromination involves formation Br_2 and HBr, responsible for the final bromination of aromatic ring.[24]

When KBr was used as a bromine source with $NH_4VO_3/H_2O_2/HClO_4$ as catalytic system,[25] 40% yield was obtained, with the formation of *p*-monobrominated product in a short time (60 min) without by-products. Substrate conversion to brominated product remains unchanged after 60 min., even adding extra amount of H_2O_2. However, the yield of reaction is not the most desirable.

Tertiary butyl ammonium bromide was evaluated in entries 4a and 4b (Table 1). TBAB salt is crystalline, easy to handle and maintains the desired stoichiometry with the substrate. In the entry 4a the reaction was performed using the NH_4VO_3/H_2O_2 as catalytic system. Although reaction times longer than with other sources of bromine, this system is able to brominated the 2-TBP regioselectively with average of yield of 50% in 12 hours. If $HClO_4$ (1 ml of a 1N solution) is added to reaction in Et_2O/H_2O_2 medium, the reaction yield increases significantly up to 96% in just 5 minutes (entry 4b). As is summarized in the Table 1, the more efficient method is carried out in a biphasic system (entry 4b) in which the catalyst of V(V) and TBAB salt is present in the aqueous phase and the aromatic substrate is present in the organic phase (diethyl ether).

Table 1. Bromination of 2-*tert*-butylphenol with different Br^- sources.

Entry	Br^- source	Solvent	Conditions	Time	Yield (%)*	Ref.
1a	$AlBr_3$	Et_2O	$NH_4VO_3(5\ mol\%)/O_2$	48 h	<10	21
1b	$AlBr_3$	Et_2O	$NH_4VO_3(5\ mol\%)/H_2O_2(200\ mol\%)$	10 min	90	--
2	NBS	MeCN	NH_4OAc	40 min	40	22
3	KBr	Et_2O	$NH_4VO_3(5\ mol\%)/H_2O_2(200\ mol\%)/HClO_4$	60 min	40	25
4a	TBAB	Et_2O, or $CHCl_3$	$NH_4VO_3(5\ mol\%)/H_2O_2(200\ mol\%)$	12 h	50	--
4b	TBAB	Et_2O, or $CHCl_3$	$NH_4VO_3(5\ mol\%)/H_2O_2(200\ mol\%)/HClO_4$	5 min	96†	--

Conditions: (1a) NH_4VO_3 (5 mol%), $AlBr_3$ (0.55 mmol), O_2, Et_2O (1.5 ml) and 2-TBP (0.5 mmol) at room temperature; (1b) NH_4VO_3 (5 mol%), $AlBr_3$ (0.55 mmol), H_2O_2 (200 mol%), Et_2O (5 ml) and 2-TBP (0.5 mmol) at reflux; (2) 2-TBP (1 mmol), NH_4OAc (10 mol%), MeCN (5 ml) and NBS (1.05 mmol) at room temperature; (3) NH_4VO_3 (5 mol%), KBr (1.5 mmol), H_2O_2 (200 mol%), Et_2O (5 ml) and 2-TBP (0.5 mmol) at room temperature; (4a) NH_4VO_3 (5 mol%), TBAB (1.5 mmol), H_2O_2 (200 mol%), Et_2O (5 ml) and 2-TBP (0.5 mmol) at room temperature; (4b) NH_4VO_3 (5 mol%), TBAB (1.5 mmol), H_2O_2 (200 mol%), Et_2O or $CHCl_3$ (5 ml), $HClO_4$ (1 ml of a 1N solution) and 2-TBP (0.5 mmol) at room temperature.

†Lower yields are observed with other stoichiometric relations of 2-TBP/TBAB (1/1 and 1/2, with 30% and 40%, respectively).

*Yield was determined by GC.

Next, we examined the bromination of various aromatic compounds with NH_4VO_3 (5 mol%)/H_2O_2(200 mol%)/$HClO_4$ and the results are shown in the Table 2.

Reactivity of vanadium in bromide oxidation

It´s important to understand what is happening within the reaction media; to know the experimental factors that affect both *i*) the efficiency and *ii*) time of reaction; we find interesting that a small variation in the reaction conditions, *i.e*. pH, produces significant changes in the results. We observed the effect of strong acid: when the media was not sufficiently acid (1 ml $HClO_4$ of a0.1N solution), the bromination of arene are stopped; if an extra amount of $HClO_4$ is added, the reaction could be prolonged until total consumption of substrate. This effect suggests that there is a relation between the substrate and the catalytic specie present at that pH.

Coming up, we will discuss the role of the catalyst system in a synthetic bromination of organic compounds.

It is well known that the formation of a great variety of peroxometal complexes in solutions with high-valent transition metals is particularly promoted in the presence of hydrogen peroxide. These complex species can differ in function of the pH value in the reaction medium.[26] For the vanadium catalyst, the presence of hydrogen peroxide promotes the formation of peroxovanadates; in acid conditions, the addition of hydrogen peroxide to a catalyst of V(V) forms oxomonoperoxo $VO(O_2)^+$ (red) and oxodiperoxo $VO(O_2)_2^-$ (yellow), according to Equations 2 and 3:[27]

$$VO_2^+ + H_2O_2 \rightleftharpoons VO(O_2)^+ + H_2O \quad \text{Equation 2}$$

$$VO(O_2)^+ + H_2O_2 \rightleftharpoons VO(O_2)_2^- + 2H^+ \quad \text{Equation 3}$$

The formation of $VO(O_2)^+$ increases with increasing acidity and decreases with increasing oxidant agents. The presence of the species $VO(O_2)_2^-$ is favoured, increasing the concentration of hydrogen peroxide.

The vanadium specie that promotes the bromination of organic substrates is oxomonoperoxovanadium[27], which can be seen as the red-coloured complex $VO(O_2)^+$ in the reaction. On the other hand, when the reaction shifts to the formation of a $VO(O_2)_2^-$ complex, it is possible to see the yellow colour that is characteristic of that complex. This important signal tells us that the bromination reaction has stopped. However, it was observed that an excess of acidity in the medium contributes to poly-brominations on aromatic substrates. In this sense, the pH control is important for obtaining mono-brominated products regioselectively (pH 1–2). It is extremely important to have the active species $VO(O_2)^+$ in the reaction's bromination media as it is capable of oxidizing active "Br".

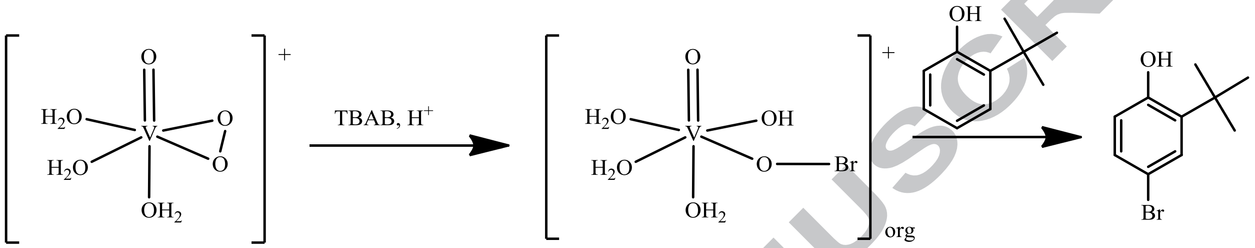
The mechanism of action for the brominating agent, "Br", remains controversial. Several contradictory opinions have been formulated based on the reactivity of the species. Various mechanisms have been proposed to justify the presence of species such as "HOBr", "Br_2^-" and "Br_3^-" that cannot be detected because the reaction of these species with H_2O_2 or organic substrates is too fast[28]. In addition, some authors have reported the presence of more complex species in the presence of vanadium peroxidases, such as vanadiumbromo peroxidases V-BrPO,[29] which is capable of producing brominated organic substrates. Others authors proposed that TBAB bromination is carried out after the formation of the species tri-brominated $TBABr_3$ (Equation 4),[30] species that has been successfully used in organic brominations (Eq. 5).[31] However, we could detect and isolate Br_3^- like $TBABr_3$ only in the absence of an organic substrate.

The reaction of TBAB without substrate was conducted with NH_4VO_3-H_2O_2-$HClO_4$ at room temperature leading to the isolation of orange–yellow quaternary ammonium tribromide ($TBABr_3$) in very high yields. The characterization of single-crystal was made by DRX and the details are included in the Supplementary Data file.

$$3TBABr \xrightarrow{V(V)H_2O_2} TBABr_3 + 2TBAOH \quad \text{Equation 4}$$

$$Ar\text{-}H + TBABr_3 \longrightarrow Ar\text{-}Br + HBr + TBABr \quad \text{Equation 5}$$

We think that bromination with TBAB in acid media and in presence of V(V) is carried out after the formation of vanadium bromoperoxide species. Some authors propose a mechanism where a hypobromite-like vanadium intermediate, generated by the reaction between monoperoxido vanadium and bromide ion is capable to react with organic substrates according to Scheme 1.[25]



Scheme 1. Mechanism for V-catalyzed oxybromination of aromatics in two-phase system

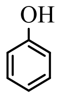
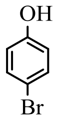
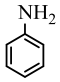
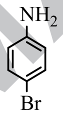
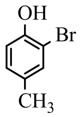
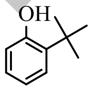
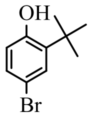
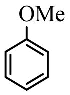
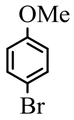
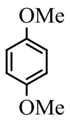
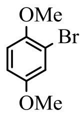
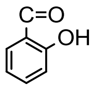
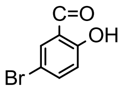
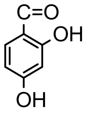
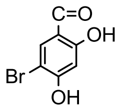
Bromination of aromatic compounds with TBAB and $NH_4VO_3/H_2O_2/HClO_4$

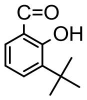
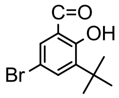
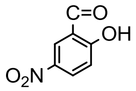
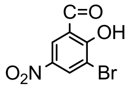
In the case of *p*-bromophenol (Table 2, entry 1) was obtained satisfactorily with an almost quantitative yield. Other methods under similar reaction conditions resulted in high conversions with the same product, but they are inconvenient for producing poly-brominated substrate.[30]

Aniline and anisole produce a *para*-monobrominated product with a very good yield. Substrates with two substituents on the aromatic ring (Table 2, entries 4, 5 and 7) showed a preference to yield monobrominated products. If the para position of the aromatic ring was already occupied, it is possible to obtain the *ortho*-brominated product.

When substituent deactivators are present in the aromatic ring (Table 2, entries 8-11) as aldehyde, nitro or a combination of the two (Table 2, entry 11), bromination was carried out with yields of 90% or less. However, the presence of one or more substituents activators increases the reaction yield (*i.e.*, selectivity and reactivity depend on the nature of the substituents on the aromatic ring). Aromatic compounds with electron-donating substituents were brominated readily with high conversion and invariably with high selectivity for the mono-brominated products. However, with electron-withdrawing substituents, bromination resulted in lower conversions. Based on our observations, we hypothesized that the presence of an electron-withdrawing group in combination with an OH group is required to facilitate the bromination of these substrates by this method.

Table 2. Bromination reaction of aromatic substrates using the catalytic system NH_4VO_3/H_2O_2 and TBAB

Entry	Substrate	Product	Yield (%)	Time
1			99	15 min
2		No reaction	-----	5 days
3			95	15 min
4			93	20 min
5			96	5 min
6			94	20 min
7			90	25 min
8			80	25 min
9			90	30 min

10			85	20 min
11			80	25 min

Conditions: 1 mmol of substrate, 3 mmol of TBAB, 10 ml of $CHCl_3$, 5 mol% catalyst, room temperature, 800 r.p.m. Conversion was followed by TLC and determined by GC.

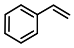
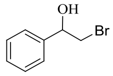
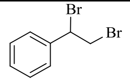
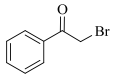
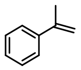
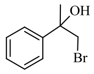
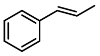
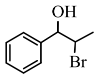
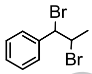
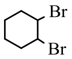
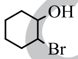
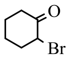
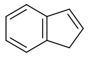
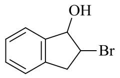
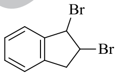
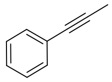
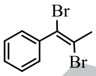
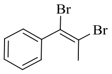
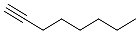
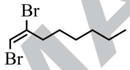
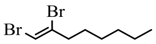
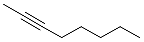
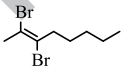
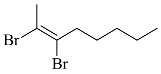
Bromination of alkenes and alkynes with TBAB and $NH_4VO_3/H_2O_2/HClO_4$

In order to know the scope of bromination method, we have extended the process to a variety of molecules. Various kinds of alkenes and alkynes structurally diverse were brominated with favourable results in the major of cases.

The bromination selectivity observed for the alkenes is low. In fact, the two-phase catalyst system resulted in the formation of the bromohydrins as a major product in almost all reactions. Nevertheless, it should be noted that the formation of the other products like dibrominated and bromoketones in some cases is present, such is the case of styrene and cyclohexene, entry 1 and 4, respectively (Table 3). Similar situations have been observed in other studies with similar catalytic methods[32].

Bromination of alkynes by this method leads to formation of dibrominated alkenes mainly (Table 3, entries 6, 7 and 8). As shown in Table 3, a terminal alkyne produces dibrominated *trans*-alkene in higher yield, compared with the evaluated secondary alkynes. In fact, together with the *trans*-alkene product, dibrominated *cis*-alkenes are also formed in moderated yields. This result is unusual, since normally the yield of *cis*-isomers is lower than *trans*-isomers[33]. Such situation led us to think that there is a superficial diffusion phenomena linked to reaction kinetics that may favor selectivity towards one of the products.

Table 3. Alkenes and alkynes evaluated in bromination reactions.

Entry	Substrate	Time	Products (Yield (%))			
1		0.5 h		75		10
				15		
2		40 min		100		
3		45 min		66		33
4		30 min		46		20
				24		
5		35 min		80		20
6		35 min		60		40
7		25 min		90		10
8		25 min		70		30

Conditions: 1 mmol of substrate, 3 mmol of TBAB, 10 ml of $CHCl_3$, 5 mol% catalyst, room temperature, 800 r.p.m.
Conversion was followed by TLC and determined by GC.

Conclusions

After optimizing the reaction conditions, we extended this innovative and more efficient method of aromatic bromination to alkenes and alkynes. In summary, the catalytic system could act as an efficient method with various substances, notability for bromination regioselective in aromatic compounds and dibromination of alkynes. We highlight the importance of pH in the medium reaction which controls the stability of the complex vanadium specie, able to realize the bromination, using NH_4VO_3 as a catalyst and H_2O_2 as an oxidant.

Acknowledgements

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Supplementary data

Supplementary data associated with this article (Experimental details, MS, ^{1}H and ^{13}C RMN spectra) can be found in the online version.

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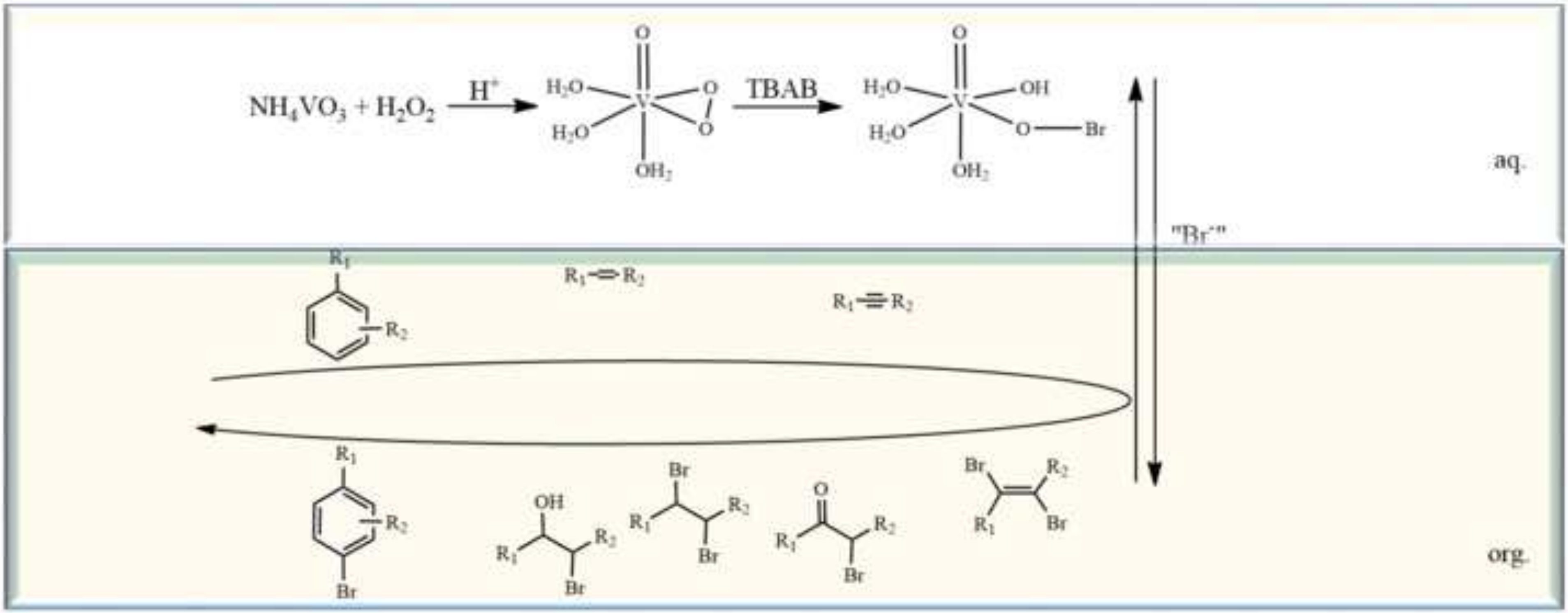
Graphical Abstract



Highlights

Efficient bromination method of aromatic substrates with NH_4VO_3/H_2O_2 in mild reaction conditions

Bromination of electron-rich aromatics with TBAB as bromine source.

$VO(O_2)^+$ is the vanadium specie that promotes the bromination of organic substrates.