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Vanadium-catalyzed oxidative bromination promoted by Brønsted acid or Lewis acid

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ABSTRACT

The oxidative bromination of arenes was induced by a vanadium catalyst in the presence of a bromide salt and a Brønsted acid or a Lewis acid under molecular oxygen, which provides an eco-friendly bromination method as compared with a conventional bromination one with bromine. This catalytic reaction could be applied to the bromination of alkenes and alkynes to give the corresponding *vic*-bromides. Use of aluminum halide as a Lewis acid in place of a Brønsted acid was demonstrated to provide a more practical protocol for the oxidative bromination. From ketones, α-bromination products were obtained. $AlBr_3$ was found to serve as both a bromide source and a Lewis acid to induce the bromination smoothly. ^{51}V NMR experiment showed that this catalytic bromination is likely to depend on the redox cycle of a vanadium catalyst under molecular oxygen.

1. Introduction

Organic bromides are regarded as important precursors for various transformations employed in organic and pharmaceutical syntheses. Conventional bromination reaction requires hazardous and toxic elemental bromine. Considerable efforts have been focused on developing an efficient bromination method by using a bromide ion as a bromide source instead of bromine.[1] In these methods, the bromination reaction proceeds by utilizing generation of a bromonium-like species through total two-electron oxidation of a bromide ion. As an oxidant, hydrogen peroxide,[2] oxone®,[3] cerium ammonium nitrate (CAN),[4] sodium periiodate,[5] lead tetraacetate,[6] and Selectfluor®[7] have been shown to induce oxidative bromination of alkenes and alkynes in the presence of bromide salts, such as alkali metal bromide or Bu_4NBr. Additionally, the bromination reaction mimicking a catalytic activity of vanadium bromoperoxidase[8] (VBrPO), a naturally occurring enzyme found in marine algae, has attracted much attention.[9] VBrPO catalyzes two-electron oxidation of the bromide ion in the presence of H_2O_2, forming to a bromonium-like species, which induces the bromination of organic compounds.[10,11] Other metals including tungsten[12] or molybdenum[13] complexes have been found to work as a bromination catalyst in the presence of stoichiometric hydrogen peroxide. These methodologies, however, require a stoichiometric amount of a strong oxidant to generate the bromonium-like species. On the other hand, oxidative bromination reactions under molecular oxygen as a terminal oxidant in place of a strong oxidant have been reported by few groups, developing the more advanced catalytic systems rather than the enzyme. The combination of cat. polyoxometalate/HBr gas/O_2 system[14] or cat. $NaNO_2$/HBr/air system[15] was demonstrated to induce the bromination reaction. Copper-catalyzed bromination through one-electron oxidation of substrates was also reported, although adaptable substrates are limited.[16] In our previous paper, ligand-free inexpensive NH_4VO_3 catalyst combined with Bu_4NBr and a Brønsted acid such as trifluoroacetic acid (TFA) or *p*-toluenesulfonic acid monohydrate (PTS·H_2O) under molecular oxygen has been performed to achieve the catalytic oxidative bromination.[17] These methodologies, however, require a stoichiometric amount of a strong protic acid. The findings prompted us to develop a more versatile bromination method. Recently, we have demonstrated the combination of a vanadium catalyst and $AlBr_3$ under molecular oxygen induces the oxidative bromination.[18] We herein summarized the catalytic oxidative bromination reaction by using a vanadium catalyst, a bromide salt, and a Brønsted acid or a Lewis acid under molecular oxygen (Fig. 1), including ^{51}V NMR study.

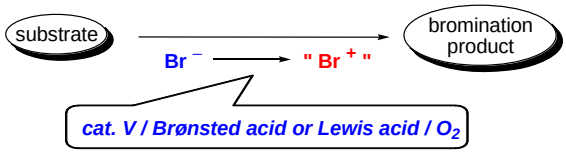

Figure 1. Bromination using cat. V/Brønsted acid or Lewis acid/O_2 system.

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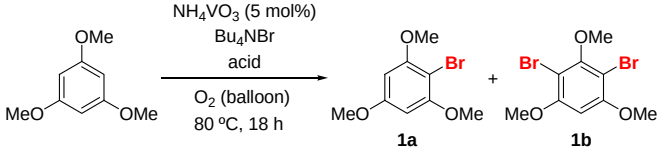
2. Results and discussion

2.1. Oxidative bromination reaction using cat. NH_4VO_3, Bu_4NBr, and Brønsted acid or Lewis acid under molecular oxygen

Initially, the oxidative bromination reaction of 1,3,5-trimethoxybenzene with 5 mol % of NH_4VO_3, 300 mol % of Bu_4NBr, and 300 mol % of trifluoroacetic acid (TFA) in 1,4-dioxane under atmospheric oxygen was investigated (Table 1). The bromination reaction proceeded to allow the formation of the monobromide **1a** in 80% isolated yield (entry 1). This bromination was not effectively performed under argon conditions (entry 2). The use of *p*-toluenesulfonic acid monohydrate (PTS·H_2O) instead of TFA under identical conditions showed a 20% drop in yield (entry 3). These results indicate that the presence of an acid and molecular oxygen is essential for the efficient catalytic bromination. The combination with a Lewis acid in place of a Brønsted acid is envisioned to provide the more practical bromination reaction. It should be noted that the dibromide **1b** was obtained in a quantitative yield by the bromination reaction of 1,3,5-trimethoxybenzene in the presence of 5 mol % of NH_4VO_3, 300 mol % of Bu_4NBr, and 300 mol % of $AlCl_3$ as a Lewis acid in 1,4-dioxane at 80 °C for 18 h under molecular oxygen (entry 4). $AlCl_3$ is found to be more effective than TFA as a Brønsted acid. The amounts of the bromide source and $AlCl_3$ were successfully reduced to 120 mol % at 80 °C, in which the monobromide **1a** was selectively produced in 92% isolated yield (entry 5). When $CuCl_2$ or $BF_3·OEt_2$ was used instead of $AlCl_3$, the bromination product **1a** was obtained in a lower yield (entries 6 and 10). $ZnCl_2$, $FeCl_3$, and $CoCl_2$ were less or not effective as a Lewis acid (entries 7–9).

Table 1
Bromination reaction of 1,3,5-trimethoxybenzene by using cat. NH_4VO_3/Brønsted acid or Lewis acid/Bu_4NBr/O_2 system[a]



Entry	Bu_4NBr (mol %)	Acid/(mol %)	NMR yield (%)	
			1a	**1b**
1[b]	300	CF_3COOH/300	80[c]	0
2[b,d]	300	CF_3COOH/300	6	0
3	300	PTS·H_2O[e]/300	62	0
4	300	$AlCl_3$/300	0	Quant[c]
5	120	$AlCl_3$/120	92[c]	0
6	120	$CuCl_2$/120	87	0
7	120	$ZnCl_2$/120	12	0
8	120	$FeCl_3$/120	0	0
9	120	$CoCl_2$/120	0	0
10	120	$BF_3·OEt_2$/120	48	0

[a] Conditions: 0.5 mmol of 1,3,5-trimethoxybenzene, 5 mol % NH_4VO_3, Bu_4NBr, and acid, 1.5 mL of 1,4-dioxane, under O_2.
[b] Conditions: 0.4 mmol of 1,3,5-trimethoxybenzene, 5 mol % NH_4VO_3, Bu_4NBr, and acid, 1.5 mL of 1,4-dioxane, under O_2.
[c] Isolated yield.
[d] Reaction under argon.
[e] *p*-Toluenesulfonic acid monohydrate.

The bromination in other solvents, such as acetonitrile, dimethoxyethane (DME), dichloroethane (DCE), and toluene resulted in a slightly decreased yield (Table 2, entries 1–6). The reactivity of the oxidative bromination reaction system with $AlCl_3$ is superior to the system with TFA. Using 1,4-dioxane or toluene as a solvent, the bromination reaction proceeded even at room temperature in a moderate yield (entries 7 and 8).

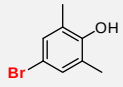
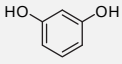
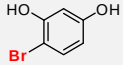
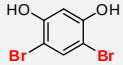
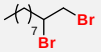
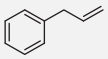
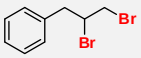
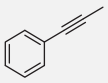
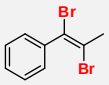
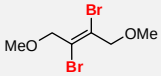
Table 2
Solvent effect in bromination reaction of 1,3,5-trimethoxy-benzene[a]

Entry	Bu_4NBr (mol %)	Acid/(mol %)	Solvent	NMR yield (%)	
				1a	**1b**
1[b]	300	CF_3COOH/300	MeCN	57	0
2[b]	300	CF_3COOH/300	DME[c]	25	0
3	120	$AlCl_3$/120	MeCN	75	0
4	120	$AlCl_3$/120	DME[c]	77	0
5	120	$AlCl_3$/120	DCE[d]	63	0
6	120	$AlCl_3$/120	Toluene	87	0
7[e]	120	$AlCl_3$/120	1,4-Dioxane	45	0
8[e]	120	$AlCl_3$/120	Toluene	54	0

[a] Conditions: 0.5 mmol of 1,3,5-trimethoxybenzene, 5 mol % NH_4VO_3, Bu_4NBr, and acid, 1.5 mL of solvent, under O_2, 80 °C, 18 h.
[b] Conditions: 0.4 mmol of 1,3,5-trimethoxybenzene, 5 mol % NH_4VO_3, Bu_4NBr, and acid, 1.5 mL of solvent, under O_2, 80 °C, 18 h.
[c] Dimethoxyethane.
[d] Dichloroethane.
[e] Reaction was conducted at 25 °C.

To investigate the scope of the cat. NH_4VO_3/Bu_4NBr/CF_3COOH or $AlCl_3$/O_2 system, the reaction of other substrates was surveyed in 1,4-dioxane at 80 °C for 18 h under molecular oxygen (method A or B) as shown in Table 3. The monobromination of 2,6-dimethylphenol proceeded without formation of the benzyl bromide (entry 2). The use of TFA instead of $AlCl_3$ exhibited a 20% drop in yield (entry 1).

Table 3
Bromination reaction by using cat. NH_4VO_3/CF_3COOH or $AlCl_3$/Bu_4NBr/O_2 system

Entry	Substrate	Conditions[a,b]	Product, isolated yield (%)
1		A, 300	 **2a**, 73
2		B, 120	**2a**, 95
3		A, 300	 **3a**, 72
4		B, 120	**3a**, 95
5		B, 400	 **3b**, 98
6			
7		A, 900	 **4c**, 97
8		C, 400	**4c**, 99
9		A, 900	 **5c**, 94
10		C, 400	**5c**, 95
11		A, 900	 **6d**, 94
12		B, 400	**6d**, Quant
13		A, 900	 **7d**, 77
14		B, 400	**7d**, 86

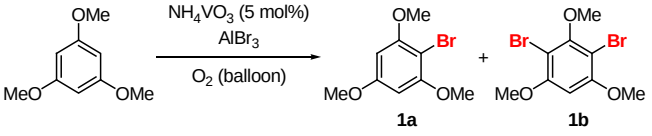
[a] Method, amount of Bu_4NBr and CF_3COOH or $AlCl_3$ (mol %).
[b] *Method A*: 0.4 mmol of substrate, 5 mol % NH_4VO_3, Bu_4NBr, and CF_3COOH, 1.5 mL of 1,4-dioxane, under O_2, 80 °C, 18 h. *Method B*: 0.5 mmol of substrate, 5 mol % NH_4VO_3, Bu_4NBr, and $AlCl_3$, 1.5 mL of 1,4-dioxane, under O_2, 80 °C, 18 h. *Method C*: 0.5 mmol of substrate, 5 mol % NH_4VO_3, Bu_4NBr, and $AlCl_3$, 1.5 mL of dimethoxyethane, under O_2, 50 °C, 18 h.

3-Hydroxyphenol underwent monobromination to give **3a** in a high yield in the presence of 120 mol % of $AlCl_3$ and Bu_4NBr (entry 4). Interestingly, the dibromide **3b** was produced in a high yield with 400 mol % of $AlCl_3$ and Bu_4NBr (entry 5) although monobromination product **3a** was obtained by using TFA. The efficiency of $AlCl_3$ than TFA was also observed in the oxidative bromination reaction. The bromination reaction of alkene by using 1,2-dimethoxyethane as a solvent at a lower temperature (method C) provided only the desired *vic*-dibromide in a high yield although the reaction in 1,4-dioxane at 80 °C resulted in a complex mixture. 1-Decene or allylbenzene was converted to the corresponding dibromide **4c** or **5c** in 99% or 95% yield, respectively (entries 8 and 10). Both aromatic and aliphatic alkynes underwent the selective *vic*-dibromination by using method A, as exemplified by the conversion of 1-phenyl-1-propyne or 1,4-dimethoxy-2-butyne to the *trans*-dibromide **6d** or **7d** in a quantitative or 86% yield, respectively (entries 12 and 14). This stereoselectivity suggests the involvement of a bromonium-like species as an intermediate for *anti*-bromination.

2.2. Oxidative bromination reaction using $AlBr_3$ as a Lewis acid and a bromide source

On the basis of the above-mentioned results, $AlBr_3$ is expected to serve as both a bromide source and a Lewis acid. Actually, the bromination reaction of 1,3,5-trimethoxybenzene with 5 mol % of NH_4VO_3 and 120 mol % of $AlBr_3$ under molecular oxygen led to the quantitative formation of the dibromide **1b** (Table 4, entry 1). This result indicates that two bromides of $AlBr_3$ are able to participate as a bromide source. When the amount of $AlBr_3$ was reduced to 50 mol %, the monobromide **1a** was selectively obtained in a high yield (entry 2). Next, the effects of solvent, reaction temperature, and time were screened (entries 3–9). Although 1,4-dioxane, dimethoxyethane, and MeCN were found to require heating for the bromination reaction, the high reactivity was observed in ether even at room temperature. Under these conditions, the use of 50 or 120 mol % of $AlBr_3$ gave the mono- or dibromide in almost quantitative yield, respectively (entries 9 and 10). The results obtained from the reaction in the absence of NH_4VO_3 or molecular oxygen indicate that the vanadium catalyst and molecular oxygen are essential for the transformation (entries 11 and 12).

Table 4
Bromination of 1,3,5-trimethoxybenzene by using cat. $NH_4VO_3/AlBr_3/O_2$ system[a]

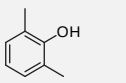
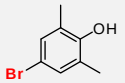
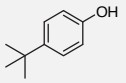
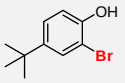
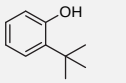
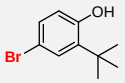
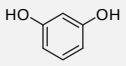
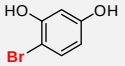
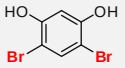
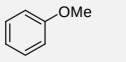
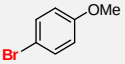
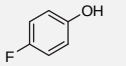
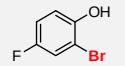
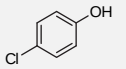
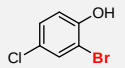
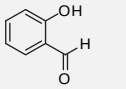
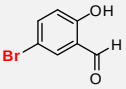
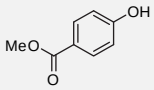
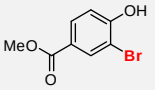
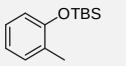
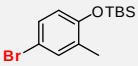
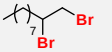
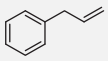
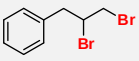
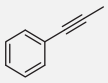
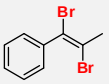
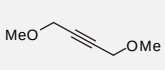
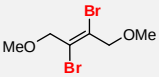


Entry	$AlBr_3$ (mol %)	Solvent	Temp (°C), time (h)	NMR yield (%)	
				1a	1b
1[b]	120	1,4-Dioxane	80, 4	0	Quant
2[b]	50	1,4-Dioxane	80, 4	92	0
3	50	DME [c]	80, 4	22	0
4	50	1,4-Dioxane	50, 12	93	0
5	50	MeCN	50, 12	93	0
6	50	1,4-Dioxane	25, 18	73	0
7	50	DME [c]	25, 18	9	0
8	50	MeCN	25, 18	28	0
9[b]	50	Ether	25, 18	99	0
10[b]	120	Ether	25, 18	0	98
11[d]	50	Ether	25, 18	0	0
12[e]	50	Ether	25, 18	3	0

[a] Conditions: 0.5 mmol of 1,3,5-trimethoxybenzene, 5 mol % NH_4VO_3, $AlBr_3$, 1.5 mL of solvent, under O_2.
[b] Isolated yield.
[c] Dimethoxyethane.
[d] Absence of NH_4VO_3.
[e] Reaction under argon.

The applicability for the bromination reaction was investigated by using NH_4VO_3 catalyst and $AlBr_3$ under molecular oxygen either in 1,4-dioxane at 80 °C (method D) or in ether at room temperature (method E), as shown in Table 5. In both conditions, the bromination

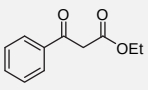
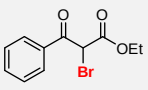
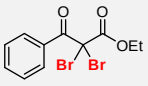
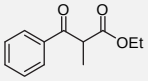
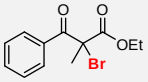
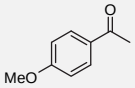
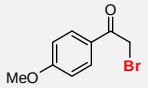
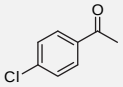
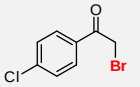
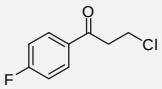
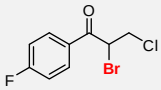
Table 5
Bromination of arenes, alkenes, and alkynes by using cat. $NH_4VO_3/AlBr_3/O_2$ system

substrate	Conditions[a,b]	Product, isolated yield (%)
	D, 60, 8 E, 60, 18	 **2a**, 94 95
	D, 60, 8	 **8a**, 98
	E, 110, 18	 **9a**, 99
	D, 40, 8	 **3a**, 80
	D, 80, 8	 **3b**, 66
	D, 120, 8	 **10a**, 96
	D, 120, 8	 **11a**, 95
	E, 110, 18	 **12a**, 97
	D, 60, 8	 **13a**, 86[c]
	D, 110, 18	 **14a**, Quant
	E, 120, 18	 **15a**, Quant
	F, 120, 18	 **4c**, 99[d,e] 76[e,f]
	F, 120, 18	 **5c**, 93[d,e]
	F, 120, 18	 **6d**, 98[d]
	F, 120, 18	 **7d**, 97[d]

[a] Method, amount of $AlBr_3$ (mol %), time (h).
[b] *Method D*: 0.5 mmol of substrate, 5 mol % NH_4VO_3, $AlBr_3$, 1.5 mL of 1,4-dioxane, under O_2, 80 °C. *Method E*: 0.5 mmol of substrate, 5 mol % NH_4VO_3, $AlBr_3$, 1.5 mL of ether, under O_2, rt. *Method F*: 0.5 mmol of substrate, 5 mol % NH_4VO_3, 120 mol % $AlBr_3$, 1.5 mL of MeCN, under O_2, 80 °C.
[c] Together with 3-bromosalicylaldehyde (11%).
[d] Bu_4NBr (120 mol %) was used as an additive.
[e] Reaction was conducted at 50 °C.
[f] KBr (1000 mol %) was used as an additive.

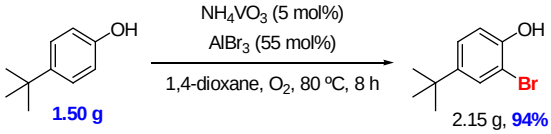
of phenol derivatives proceeded well to afford the mono- or dibromide in a high yield under the appropriate conditions. With the present bromination system, a simple aromatic compound like anisole was subjected to the monobromination to afford **10a**. Moreover, phenol derivatives bearing the electron-withdrawing group were brominated smoothly in high yields. Starting from 4-halophenols, dihalogenated products **11a** and **12a** were obtained. The bromination of phenol derivatives bearing formyl or methoxycarbonyl group resulted in the regioselective formation of the monobromides **13a** or **14a**, respectively. In these cases, the further oxidation of the aldehyde moiety or decomposition of the ester moiety was not observed. In the bromination of TBS-protected *o*-cresol, the TBS group was survived to give only the 4-brominated product **15a**. This oxidative bromination of alkenes and alkynes led to the corresponding dibromides by using 5 mol % of NH_4VO_3 together with $AlBr_3$ (method F), although the presence of the additional bromide salt was required. The bromination reaction of 1-decene proceeded well to afford the dibromide **4c** in 99% yield at 50 °C. The less expensive KBr could be effective as a bromide source. Allylbenzene underwent the selective *vic*-dibromination to give 1,2-dibromo-3-phenylpropane **5c** in 93% yield, without formation of the benzyl bromide. The selective *anti*-dibromination of aromatic and aliphatic alkynes, such as 1-phenylpropyne and 1,4-dimethoxy-2-butyne was observed by using method F at 80 °C to give the *trans*-dibromides **6d** and **7d** in high yields, respectively. Moreover, the oxidative bromination using cat. $NH_4VO_3/AlBr_3/O_2$ system could be applied to the α-bromination of ketones by method F (Table 6). β-Keto esters, such as ethyl benzoylacetate underwent the bromination to mono- or dibromination products **16e** and **16f** depending on the amount of $AlBr_3$. Substitution at α-position led to the monobromination product **17e**. The α-bromination of mono-ketones was also carried out. 4-Methoxyacetophenone was brominated to give the monobromide **18e** together with the dibromide. Bromination of 4-chloroacetophenone afforded the monobromide **19e** as a major product. Starting from 3-chloro-4′-fluoropropio-phenone, the trihalide **20e** was obtained.

Table 6
Bromination of ketones by using cat. $NH_4VO_3/AlBr_3/O_2$ system[a]

substrate	$AlBr_3$ (mol %)	Product, isolated yield (%)
	55	 **16e**, 95
	110	 **16f**, 98
	55	 **17e**, 96
	55	 **18e**, 52[b,c]
	55	 **19e**, 70[b,d]
	55	 **20e**, 72[b]

[a] Condition: 0.50 mmol of substrate, 5 mol % NH_4VO_3, $AlBr_3$, 1.5 mL of MeCN, under O_2, 80 °C, 18 h.
[b] NMR yield.
[c] Together with dibromide (45%).
[d] Together with dibromide (27%).

Notably, a gram-scale practical reaction was successfully carried out to give the bromination product in a high yield, as exemplified by the monobromination of 4-*tert*-butylphenol to the monobromide in 94% isolated yield (Scheme 1).



Scheme 1. Gram-scale reaction.

2.3. Mechanistic study

It has been known that the stoichiometric oxo-metal oxidizes the bromide ion.[19] Mn- and Ru-complexes have been reported to induce the formation of a hypobromite species through oxygen-atom transfer,[19a,b] whereas one-electron transfer was observed with the Cr ion.[19c] In the present bromination, benzyl bromide or dimerization products through a radical process were not obtained in the reaction of 2,6-dimethylphenol (Table 3, entry 1), indicating an ionic mechanism. Moreover, starting from alkyne, *trans*-dibromoalkene was selectively obtained as a sole isolable product. Thus, the key intermediate is proposed to be a bromonium-like species, which is considered to be generated by the oxidation of a bromide ion via oxygen-atom transfer of an oxovanadium species activated by a Lewis acid, although the mechanism via one-electron oxidation of the bromide or substrate could not be ruled out.

To verify the vanadium species in the reaction process, ^{51}V NMR experiment was investigated (Fig. 2). Since NH_4VO_3 is slightly soluble in 1,4-dioxane, the oxovanadium complex $N[DMBO]_3VO$ was prepared from $VO(Oi\text{-}Pr)_3$ and tris(2-hydroxy-3,5-dimethylbenzyl) amine ($N[DMBOH]_3$) (Scheme 2A).[20] $N[DMBO]_3VO$ was confirmed to serve as a bromination catalyst in the presence of $AlBr_3$ and molecular oxygen (Scheme 2B). The ^{51}V NMR spectrum of $N[DMBO]_3VO$, 1,3,5-trimethoxybenzene in dioxane/$CDCl_3$=2/1 under argon revealed one peak at −359 ppm (Fig. 2A, a). After the addition of $AlBr_3$, the solution color turned to blue and the peak disappeared (Fig. 2, b). These findings indicate that a V(V) species was reduced to a low-valent vanadium species, such as V(IV) or V(III). After O_2 bubbling of this blue solution at 80 °C for 4 h, the solution color was changed to red and a sharp strong peak at −358 ppm appeared again, suggesting that a pentavalent vanadium species is regenerated (Fig. 2, c). A redox cycle of a vanadium catalyst is considered to afford a bromonium-like species as depicted in Figure 2B.

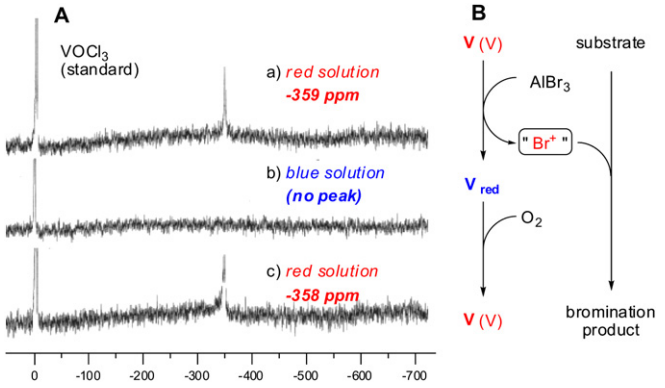
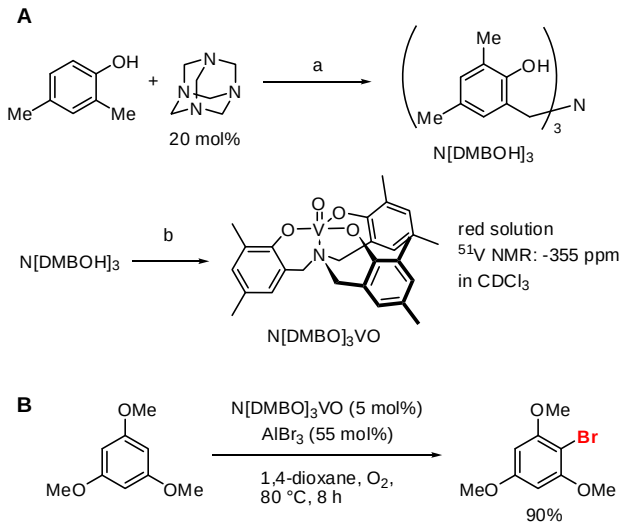


Figure 2. A: ^{51}V NMR spectra of $N[DMBO]_3VO$, 1,3,5-trimethoxybenzene and $AlBr_3$ dissolved in $CDCl_3$/1,4-dioxane=1/2 (0.75 mL). (a) $N[DMBO]_3VO$ (0.01 mmol) and 1,3,5-trimethoxybenzene (0.02 mmol) under argon. (b) $N[DMBO]_3VO$ (0.01 mmol), 1,3,5-trimethoxybenzene (0.02 mmol), and $AlBr_3$ (0.01 mmol) under argon. (c) $N[DMBO]_3VO$ (0.01 mmol), 1,3,5-trimethoxybenzene (0.02 mmol), and $AlBr_3$ (0.01 mmol), O_2 bubbling, 80 °C, 4 h. **B**: A proposed mechanism.



Scheme 2. A: Preparation of $N[DMBO]_3VO$. (a) 2,4-Dimethylphenol (100 mmol), hexamethylenetetramine (20 mmol), *p*-toluenesulfonic acid monohydrate (0.20 mmol), 120 °C, 3 days, then recrystallization from acetone. (b) $N[DMBOH]_3$ (1.0 mmol), $VO(Oi\text{-}Pr)_3$ (1.0 mmol), CH_2Cl_2, rt, 20 h. **B**: Bromination using $N[DMBO]_3VO$.

3. Conclusion

The bromination reaction of various arenes, alkenes, alkynes, and ketones without use of a strong oxidant was performed by a vanadium catalyst in the presence of a bromide salt and a Brønsted acid or a Lewis acid under molecular oxygen. Use of aluminum halide as a Lewis acid in place of a Brønsted acid was demonstrated to provide a more versatile and practical method for selective bromination of wide ranging substrates. $AlBr_3$ was found to serve as both a bromide source and a Lewis acid to induce the smooth bromination. The oxidation of a bromide anion is considered to proceed to generate a bromonium-like species by the combination of vanadium catalyst and a Lewis acid without using a stoichiometric strong oxidant or protic acid. ^{51}V NMR experiment indicates the reversible redox cycle of the vanadium species, wherein molecular oxygen served as a terminal oxidant. This methodology is more advantageous as a catalytic system than vanadium bromoperoxidase (VBrPO) requiring hydrogen peroxide as an oxidant. Further synthetic versatility and application of this practical method to other reactions are under investigation.

4. Experimental section

4.1. General information

All reagents and solvents were purchased from commercial sources and were further purified by the standard methods, if necessary. Infrared spectra were obtained with a JASCO FT/IR-480 Plus spectrometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian MERCURY 300 (300 MHz) spectrometer. $CDCl_3$ was used as a solvent and a residual solvent peak (^1H, δ=7.26; ^{13}C, 77.4 ppm) was used as an internal standard. ^{51}V NMR spectra were recorded on a JEOL JNM-ECP400 (105 MHz) spectrometer with $VOCl_3$ as an external standard (0 ppm). Mass spectra were measured on a SHIMADZU GC–MS-2010 spectrometer. Column chromatography was conducted on silica gel (Wakogel C-200).

4.2. A typical procedure for method A: 2-bromo-1,3,5-trimethoxybenzene (1a)

In a 10 mL two-necked flask equipped with a reflux condenser, NH_4VO_3 (0.020 mmol, 2.3 mg), 1,3,5-trimethoxybenzene (0.40 mmol, 67.3 mg), and Bu_4NBr (1.2 mmol, 387 mg) were placed. The flask was evacuated and backfilled with molecular oxygen. To the mixture, 1.5 mL of 1,4-dioxane and 90 μL of trifluoroacetic acid (1.2 mmol) were added. The mixture was stirred at 80 °C for 18 h, followed by treatment with satd $NaHCO_3$ aq and extraction with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The product was purified by preparative TLC (hexane/AcOEt=1/1) to give 2-bromo-1,3,5-trimethoxybenzene in 80% yield.

4.3. A typical procedure for method B: 2-bromo-1,3,5-trimethoxybenzene (1a)

In a 5 mL two-necked flask were placed NH_4VO_3 (2.9 mg, 0.025 mmol), $AlCl_3$ (80.0 mg, 0.60 mmol), and Bu_4NBr (193 mg, 0.60 mmol). The flask was evacuated and backfilled with molecular oxygen. 1,4-Dioxane (1.5 mL) and 84.1 mg (0.50 mmol) of 1,3,5-trimethoxybenzene were added. The mixture was stirred at 80 °C for 18 h, followed by treatment with 1 N HCl aq and extraction with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated. Column chromatography (SiO_2, AcOEt/hexane=1/4 v/v) gave 2-bromo-1,3,5-trimethoxybenzene in 92% yield.

4.4. A typical procedure for method C: 1,2-dibromodecane (4c)

In a 5 mL two-necked flask were placed NH_4VO_3 (2.9 mg, 0.025 mmol), $AlCl_3$ (267 mg, 2.0 mmol), and Bu_4NBr (645 mg, 2.0 mmol). The flask was evacuated and backfilled with molecular oxygen. Dimethoxyethane (1.5 mL) and 95 μL (0.50 mmol) of 1-decene were added. The mixture was stirred at 50 °C for 18 h, followed by treatment with 1 N HCl aq and extraction with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated. Column chromatography (SiO_2, AcOEt/hexane=1/9 v/v) gave 1,2-dibromodecane in 99% yield.

4.5. A typical procedure for method D: 4-bromo-2,6-dimethyl-phenol (2a)

In a 5 mL two-necked flask were placed NH_4VO_3 (2.9 mg, 0.025 mmol) and $AlBr_3$ (75.2 mg, 0.30 mmol). The flask was evacuated and backfilled with molecular oxygen. 1.5 mL of 1,4-dioxane and 61.1 mg (0.50 mmol) of 2,6-dimethylphenol were added. The mixture was stirred at 80 °C for 8 h, followed by treatment with 1 N HCl aq and extraction with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated. Column chromatography (SiO_2, AcOEt/hexane=1/4 v/v) gave 4-bromo-2,6-dimethylphenol in 94% yield.

4.6. A typical procedure for method E: 2-*tert*-butyl-4-bromophenol (9a)

In a 5 mL two-necked flask were placed NH_4VO_3 (2.9 mg, 0.025 mmol) and $AlBr_3$ (147 mg, 0.55 mmol). The flask was evacuated and backfilled with molecular oxygen. 1.5 mL of ether and 77 μL (0.50 mmol) of 2-*tert*-butylphenol were added. The mixture was stirred at room temperature for 18 h, followed by treatment with 1 N HCl aq and extraction with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated. Column chromatography (SiO_2, AcOEt/hexane=1/4 v/v) gave 2-*tert*-butyl-4-bromophenol in 99% yield.

4.7. A typical procedure for method F: 1,2-dibromo-3-phenylpropane (5c)

In a 5 mL two-necked flask were placed NH_4VO_3 (2.9 mg, 0.025 mmol), $AlBr_3$ (160 mg, 0.60 mmol), and Bu_4NBr (193 mg, 0.60 mmol). The flask was evacuated and backfilled with molecular oxygen. Acetonitrile (1.5 mL) and 66 μL (0.50 mmol) of allylbenzene were added. The mixture was stirred at 80 °C for 18 h, followed by treatment with 1 N HCl aq and extraction with ether. The organic

layer was dried over $MgSO_4$, filtered, and evaporated. Column chromatography (SiO_2, AcOEt/hexane=1/4 v/v) gave 1,2-dibromo-3-phenylpropane in 93% yield.

4.8. A typical procedure for bromination of ketone: ethyl 2-bromo-3-oxo-3-phenylpropanoate (16e)

In a 5 mL two-necked flask were placed NH_4VO_3 (2.9 mg, 0.025 mmol) and $AlBr_3$ (72.0 mg, 0.27 mmol). The flask was evacuated and backfilled with molecular oxygen. Acetonitrile (1.5 mL) and 87 μL (0.50 mmol) of ethyl benzoylacetate were added. The mixture was stirred at 80 °C for 18 h, followed by treatment with 1 N HCl aq and extraction with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated. Column chromatography (SiO_2, AcOEt/hexane=1/4 v/v) gave ethyl 2-bromo-3-oxo-3-phenylpropanoate in 95% yield.

4.9. Gram-scale reaction of 4-*tert*-butylphenol

In a 100 mL two-necked flask were placed, NH_4VO_3 (58.5 mg, 0.50 mmol), $AlBr_3$ (1.47 g, 5.5 mmol). The flask was evacuated and backfilled with molecular oxygen. 30 mL of 1,4-dioxane and 1.50 g of 4-*tert*-butylphenol (10 mmol) were added. The mixture was stirred at 80 °C for 8 h, followed by treatment with 1 N HCl aq and extraction with ether. The organic layer was dried over $MgSO_4$, filtered, and evaporated. Column chromatography (SiO_2, AcOEt/hexane=1/4 v/v) gave 2.15 g of 2-bromo-4-*tert*-butylphenol (94%).

4.10. Preparation of $N[DMBOH]_3$[20a,b]

A mixture of 2,6-dimethlphenol (5.0 mL, 41 mmol), hexamethylenetetramine (1.27 g, 9.0 mmol) and *p*-toluene/sulfonic acid monohydrate (30.0 mg, 0.16 mmol) was stirred at 120 °C for 48 h. Additionally, 2,6-dimethlphenol (16 mmol, 2.0 mL) was added and the mixture was stirred at 120 °C for 24 h. The mixture was diluted with acetone, and the desired compound was obtained by recrystallization as a yellow crystal.

4.11. Preparation of $N[DMBO]_3VO$[20c]

In a 50 mL flask, $N[DMBOH]_3$ (210 mg 0.50 mmol,) was dissolved in 25 mL of CH_2Cl_2 under argon. $VO(Oi\text{-}Pr)_3$ (0.12 mL, 0.50 mmol) was added slowly, and the mixture was stirred at room temperature for 4 h. Insoluble material was removed by filtration and the filtrate was concentrated. To the residue, toluene was added and the solution was filtered, followed by concentration to give $N[DMBO]_3VO$ as a red-black solid.

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Supplementary data

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