J|A|C|S COMMUNICATIONS

Published on Web 06/22/2010

Hypervalent λ^3-Bromane Strategy for Baeyer−Villiger Oxidation: Selective Transformation of Primary Aliphatic and Aromatic Aldehydes to Formates, Which is Missing in the Classical Baeyer−Villiger Oxidation

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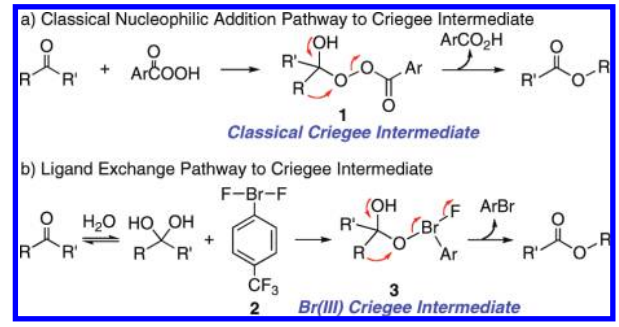
Abstract: A conceptually distinct, modern strategy for Baeyer−Villiger oxidation (BVO) was developed. Our novel method involves initial hydration of water to carbonyl compounds, followed by ligand exchange of hypervalent aryl-λ^3-bromane on bromane(III) with the resulting hydrate, yielding a new type of activated Criegee intermediate. The intermediate undergoes BV rearrangement and produces an ester via facile reductive elimination of an aryl-λ^3-bromanyl group, because of the hypernucleofugality. The novel strategy makes it possible to induce selectively the BV rearrangement of straight chain primary aliphatic as well as aromatic aldehydes, which is missing in the classical BVO: for instance, octanal and benzaldehyde afforded rearranged formate esters with high selectivity (>95%) under our conditions, while the attempted classical BVO produced only carboxylic acids. This firmly establishes the powerful nature of new methodology for BVO.

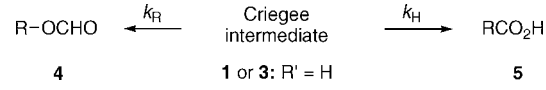
The Baeyer−Villiger oxidation (BVO) of carbonyl compounds with peracids, discovered as early as 1899,[1] directly affords valuable esters or lactones through a 1,2-shift of an alkyl group from a carbon to an oxygen atom in the initially formed Criegee intermediates **1**, with concomitant release of acid (Scheme 1a).[2] The migration step is concerted with retention of stereochemistry of the migrating group and rate-limiting in the vast majority of cases.[3] In contrast to this classical BVO, we envisioned a conceptually distinct, novel strategy for the BV reaction: our method involves initial hydration of water to carbonyl compounds, followed by a ligand exchange of hypervalent aryl-λ^3-bromane **2** with the resulting hydrate (*gem*-diol), producing a new kind of Criegee intermediate α-hydroxyalkoxy-λ^3-bromane **3** (Scheme 1b). An aryl-λ^3-bromanyl group exhibits vastly enhanced leaving group ability:[4] nucleofugality of $PhBr(BF_4)$ is greater than that of hyperleaving $PhI(BF_4)$, the latter being $\sim 10^6$ times greater than a superleaving group triflate.[5] Therefore, alkoxy-λ^3-bromane **3** would function as a highly activated Criegee intermediate, yielding a rearranged ester via facile reductive elimination of an aryl-λ^3-bromanyl group. Furthermore, the ligand exchange step of aryl-λ^3-bromane **2** with *gem*-diol, yielding Criegee adduct **3**, seems to be a low energy process, based on the chemistry of hypervalent organo-λ^3-iodanes.[6] The new methodology will be particularly suitable for the BVO of aldehydes, because the initial hydration equilibrium is shifted more efficiently toward *gem*-diols in aldehydes rather than in ketones.[7]

One of the well established events in the oxidation of aldehydes with peracids is the selective formation of carboxylic acids RCO_2H **5** instead of BVO products (formate esters **4**), owing to the facile β-elimination of acid $ArCO_2H$ (or preferential 1,2-shift of hydrogen over the carbon moiety) in Criegee intermediates **1** (Scheme 2):[2,8] thus, primary aliphatic aldehydes as well as aromatic aldehydes generally produce the corresponding carboxylic acids **5** upon peracid treatment. Oxidation of some α-branched and α-nitrogen-substituted aliphatic aldehydes[2,9] as well as electron-rich aromatic aldehydes (Dakin oxidation)[10] is an exception to the general rule and affords formates **4**. We report herein difluoro-λ^3-bromane-induced BVO of aliphatic and aromatic aldehydes in the presence of water, based on the unique ligand exchange strategy depicted in Scheme 1b. Most importantly, our method makes it possible to selectively induce the normal BV rearrangement of straight chain aliphatic and aromatic aldehydes, yielding formates **4**, which is missing in the classical BVO. This firmly establishes the powerful nature of the new methodology for BVO.

Scheme 1. Classical and Modern Strategies for BVO



Scheme 2



In the presence of 1 equiv of water, exposure of linear decanal to *p*-trifluoromethylphenyl(difluoro)-λ^3-bromane (**2**) (1.5 equiv) in dichloromethane at 0 °C for 3 h under argon resulted in the selective formation of nonyl formate (**4a**) in 70% yield (Table 1, entry 2).[11] A small amount (8%) of decanoic acid (**5a**) was produced in the reaction. This is the first example of highly selective BVO of unsubstituted linear primary aldehydes. Higher yields (76−88%) of BV product **4a** were obtained by the use of 2−10 equiv of water, while in the absence of water no formation of **4a** was detected. These results strongly suggest that the initial rapid hydration equilibrium of decanal plays a critical role in our BVO, which is in good agreement with our strategy, depicted in Scheme 1b. Use of acetonitrile as a solvent dramatically changed the reaction course

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10.1021/ja104330g

and afforded acid **5a** (69%) as a major product at the expense of the formate route (entry 8). Acetonitrile with a larger β value (0.40) of solvent hydrogen-bond acceptor basicities than that of dichloromethane (0.10) probably enhances the rate of β-elimination of Criegee adduct **3** (R′ = H) to yield acid **5a**.[12]

Table 1. BVO of Decanal with Difluorobromane **2**[a]

				yield (%)[b]	
entry	solvent	H_2O (equiv)	time (h)	**4a**	**5a**
1	CH_2Cl_2	0	3	0	0
2	CH_2Cl_2	1	3	70	8
3	CH_2Cl_2	2	1	88 (80)	6
4	CH_2Cl_2	3	1	82	5
5	CH_2Cl_2	10	1	76	5
6	$CHCl_3$	2	1	66	4
7	$Cl(CH_2)_2Cl$	2	1	80	5
8	MeCN	2	1	27	69
9[c]	CH_2Cl_2	2	1	0	0[d]

[a] Conditions: decanal (0.05 M)/bromane **2** (1.5 equiv)/0 °C/Ar. [b] GC yields. Parentheses are isolated yields. [c] Difluoroiodane *p*-$CF_3C_6H_4IF_2$ was used instead of **2**. [d] Decanal (80%) was recovered.

Frohn and Giesen reported that difluorobromane **2** is highly susceptible toward hydrolysis and undergoes a spontaneous redox reaction with generation of molecular dioxygen and *p*-$CF_3C_6H_4Br$ in aqueous acetonitrile solution at room temperature;[11a] however, the results of entry 5 indicate that ligand exchange of bromane **2** with *gem*-diol derived from decanal, yielding intermediate **3**, is faster than the redox reaction of **2** by a large excess (10 equiv) of water in dichloromethane at 0 °C. In contrast to bromane **2**, difluoro-λ^3-iodane *p*-$CF_3C_6H_4IF_2$ did not undergo BVO of decanal under our conditions (entry 9). Because the initial carbonyl hydration is a common step and because the subsequent ligand exchange of aryl-λ^3-iodane with *gem*-diol will be a rapid process with a low-energy barrier,[6] the differences in nucleofugality between fluoro(phenyl)-λ^3-iodanyl and -bromanyl groups during the 1,2-shift with reductive elimination of halobenzenes in the halogan(III) Criegee intermediate **3** probably reflect the observed differences in reactivity.[4]

To our delight, the new strategy has found general use in the BVO of aldehydes (Table 2): straight chain unsubstituted primary aldehydes with Et, Pr, Bu, *n*-C_5H_{11}, *n*-C_7H_{15}, and *n*-C_9H_{19} groups undergo λ^3-bromane-induced BVO in good to high yields in the presence of water (2 equiv) under mild conditions and afforded formates **4** with more than 80% selectivity. In marked contrast, the attempted classical BVO of pentanal and octanal with *m*-chloroperbenzoic acid (*m*-CPBA) exclusively afforded carboxylic acids **5** (entries 5, 8).[8b] The only exception is the reaction with acetaldehyde, which resulted in preferential formation of acetic acid with 95% selectivity over the formate route. This is probably due to the reported extremely low migratory aptitude of the methyl group compared to the other alkyl groups.[13]

α-Branching in the carbon chain of aldehydes enhanced a tendency for the 1,2-shift of alkyl moieties in Criegee intermediates **3**, which was reflected in the higher ratios (>98%) of formate production (Table 2, entries 14−17). On the other hand, introduction of electron-withdrawing chlorine and bromine atoms to the terminal methyl group of hexanal decreased the ratios of the formate route from 94% to approximately 80% (entries 6, 12, 13). The percent carbon chain migration seems to depend primarily upon the electron-donor ability of migrating alkyl groups: in fact, experimental relative rate factors k_R/k_H for formation of **4** relative to that of **5** (Scheme 2), calculated from the product ratios, correlate very well with Taft's polar substituent constants σ^* for alkyl groups (r = 0.97, Figure 1). Taft's σ^* is an electronic parameter and a measure of the inductively electron-donating power of an alkyl group.[14] The excellent linear σ^* plot clearly indicates that the rates of the 1,2-shift of an alkyl moiety to the electron-deficient oxygen atom attached to bromane(III) in Criegee intermediate **3** increase with an increase in the electron-donating power of an alkyl group. Similar electronic effects of alkyl substituents were reported in the classical BVO of methyl ketones by permaleic acid and trifluoroperacetic acid (see Figure S1).[13] The evaluated large negative ρ^* value of −15 strongly suggests a rate-determining migration of alkyl groups in the λ^3-bromane-induced BVO.[8a]

Table 2. λ^3-Bromane-Induced BVO of Aldehydes[a]

			yield (%)[b]		
entry	aldehyde	time (h)	**4**	**5**	ratio[c]
1	CH_3CHO	1	4	70	5:95
2	CH_3CH_2CHO	1	68	16	81:19
3	PrCHO	1	61	14	81:19
4	BuCHO	1	55	14	80:20
5[d]	BuCHO	2	0	100	0:100
6	*n*-$C_5H_{11}CHO$	1	85	5	94:6
7	*n*-$C_7H_{15}CHO$	1	91 (89)	5	95:5
8[d]	*n*-$C_7H_{15}CHO$	2	0	100	0:100
9	*n*-$C_9H_{19}CHO$	1	88 (80)	6	94:6
10	*i*-BuCHO	1	78	13	86:14
11	Me_3CCH_2CHO	1	63	7	90:10
12	$Cl(CH_2)_5CHO$	3	59 (58)	14	81:19
13	$Br(CH_2)_5CHO$	3	64 (55)	17	79:21
14	*i*-PrCHO	1	81	2	98:2
15	*c*-C_5H_9CHO	0.5	64	0	100:0
16	*c*-$C_6H_{11}CHO$	0.5	85	0	100:0
17	*c*-$C_7H_{13}CHO$	0.5	74 (63)	0	100:0
18	*p*-$MeOC_6H_4CHO$	1	45 (35)	0	100:0
19	*o*-MeC_6H_4CHO	1	69 (62)	0	100:0
20	*m*-MeC_6H_4CHO	1	71 (74)	0	100:0
21	*p*-MeC_6H_4CHO	1	72 (65)	0	100:0
22	*p*-*t*-BuC_6H_4CHO	1	67 (65)	0	100:0
23	PhCHO	1	98 (91)	0	100:0
24[d]	PhCHO		0	83	0:100
25	*p*-FC_6H_4CHO	1	64 (60)	0	100:0
26	*p*-ClC_6H_4CHO	1	68 (62)	0	100:0
27[d]	*p*-ClC_6H_4CHO		0	85	0:100
28	*p*-BrC_6H_4CHO	1	69 (65)	0	100:0
29	*p*-$CF_3C_6H_4CHO$	2	34 (33)	19	64:36

[a] Conditions: an aldehyde (0.05 M)/bromane **2** (1.5 equiv)/H_2O (2 equiv)/CH_2Cl_2/0 °C/Ar. [b] GC yields. Parentheses are isolated yields. [c] Ratios of **4**:**5**, determined by GC. [d] Classical BVO with *m*-CPBA or peroxomonophosphoric acid at room temperature. Data taken from refs 2a and 8b.

Aromatic aldehydes exclusively undergo the λ^3-bromane-induced BVO through a ligand exchange pathway (Table 2). The attempted classical BVO of benzaldehydes *p*-XC_6H_4CHO (X = H, Cl, Br, Me, etc.) with $PhCO_3H$, SeO_2/H_2O_2, or $[Me(n\text{-}C_8H_{17})_3N]HSO_4/H_2O_2$ produced only benzoic acids **5** (for instance, entries 24, 27),[2] while exclusive formation of aryl formate esters **4** was detected in our BVO. The only exception is *p*-$CF_3C_6H_4CHO$ with a powerful electron-withdrawing substituent (CF_3: σ_p = 0.54), which decelerates the 1,2-migration of the aryl group.[15]

Relative rates of BVO for a series of substituted benzaldehydes were measured by competitive reactions, in which a mixture of each 5-fold excess of two competing substrates was used. Electron-withdrawing *p*-Cl and *p*-Br groups decreased the relative rates k_{rel} of the reaction: 1.9 (*p*-MeC_6H_4CHO), 1.0 (PhCHO), 0.69 (*p*-FC_6H_4CHO), 0.57 (*p*-ClC_6H_4CHO), 0.60 (*p*-BrC_6H_4CHO). A Hammett plot showed a satisfactory correlation of the relative rate factors with σ_p constants and gave the reaction constant ρ = −1.2 (r = 0.96).[15] A similar moderately large and negative ρ value of −1.1

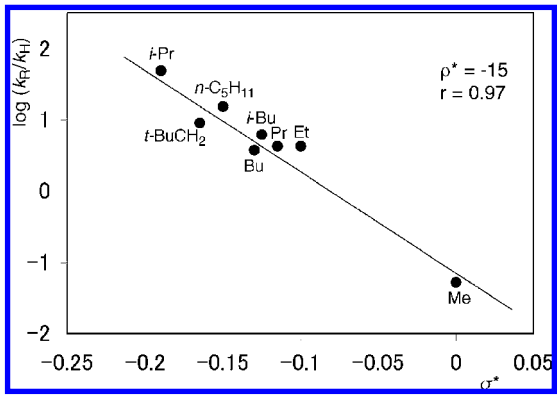
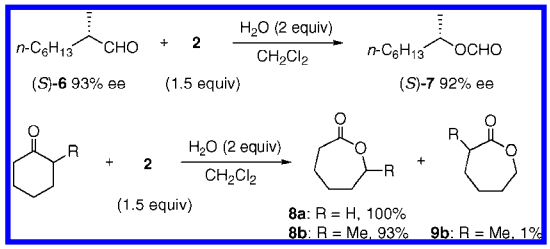


Figure 1. Plot of logarithm of **4**:**5** ratios log (k_R/k_H) vs Taft's polar substituent constants σ^* for aliphatic groups.

was reported for classical BVO of substituted acetophenones using trifluoroperacetic acid in dichloroethane, in which decomposition of the Criegee adduct constitutes the rate-limiting step.[16] Furthermore, these two relative rate factors for the λ^3-bromane-induced and the classical peracid-induced BV reactions correlate very well with each other (see Figure S2). These results indicate that our BVO of benzaldehydes probably involves a rate-limiting migration of aryl groups and that a similar kind of electronic effect of substituents operates in the transition states of both classical and modern BVO.

Scheme 3



Scheme 3 clearly demonstrates that the essential feature of the classical BVO holds for our unique BVO technology: oxidation of chiral (*S*)-aldehyde **6** with difluorobromane **2** takes place with extensive retention of stereochemistry at the migrating center. Scheme 3 also depicts BVO of cyclohexanones, producing seven-membered lactones in high yields. Preferential migration of the more substituted methine group of 2-methylcyclohexanone yielding lactone **8b** as a major product was observed, as in the case of the classical BVO.[2]

Calculated structures and the energy profile for the methyl and hydrogen migration of the activated (protonated) intermediate, α-hydroxyethoxy(phenyl)-λ^3-bromane **11**, in the bromane-induced BVO of acetaldehyde at the MP2/6-311G(d) method of the Gaussian 03 program are illustrated in Figure 2.[17] The leaving phenyl-λ^3-bromanyl and the migrating methyl groups in transition state **13** occupy an *anti* periplanar arrangement with a dihedral angle of −169.9° about the O−C bond, along which the migration takes place. A similar *anti* arrangement (−176.8°) in **10** was evaluated for the hydrogen migration (see also Figure S3). Transition state **10** for hydrogen shift is predicted to lie 25.3 kJ mol^{-1} higher in energy than **13** for the methyl shift, which is not compatible with the experimental observations of the preferred formation of acetic acid over methyl formate production (Table 2, entry 1). Therefore, it seems reasonable to assume that the acetic acid formation probably involves a β-elimination process, but not a 1,2-H shift of the hemiacetal group. A large activation barrier (91 kJ mol^{-1})

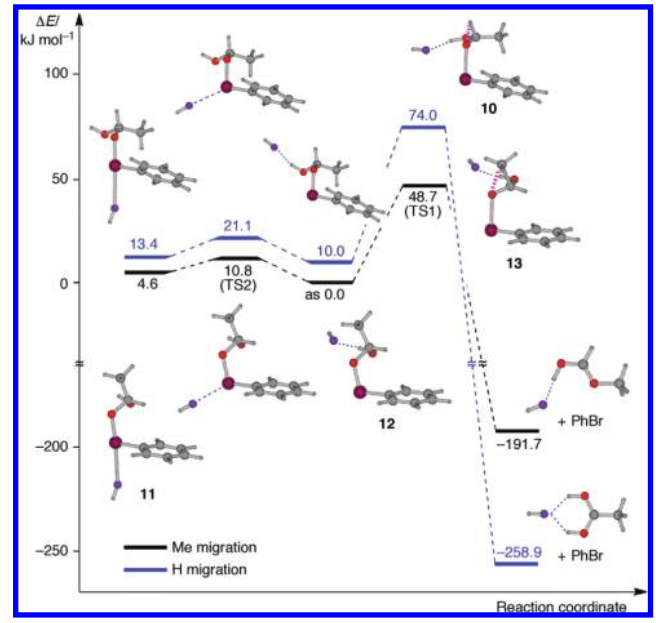


Figure 2. Energy profile for the Me and H migration in BVO of acetaldehyde based on ab initio calculations. Br (large dark purple), O (red), C (gray), and F (blue purple).

calculated for the 1,2-shift of the methyl group in λ^3-iodane-derived Criegee adducts (see Figure S4) agrees with our experimental findings (Table 1, entry 9). Thus, calculations strongly suggest that the reaction proceeds easily and reasonably to give the products via the protonated species such as **11** and **12**, although the solvent effect other than the protonation is not considered in the calculations.

Further calculations for BVO of aldehydes RCHO (R = Et, *i*-Pr, *t*-Bu) revealed that the activation energy for the concerted 1,2-shift of an alkyl group in λ^3-bromane-derived Criegee adducts decreases considerably with an increasing degree of alkyl substitution in the order (kJ mol^{-1}) Me (48.7), Et (24.5), *i*-Pr (16.2), and *t*-Bu migration (9.4). Differences in these estimated activation barriers are correlated well ($r = 0.95$) with Taft's σ^* values of alkyl groups (see Figure S5), again suggesting that the electronic nature of alkyl groups is of paramount importance in the BV rearrangement.[18]

Thus, we have developed a conceptually distinct, new strategy for the BVO. The method involves a hydration-ligand exchange sequence to Criegee intermediates using difluorobromane(III). Our method makes it possible to selectively induce the normal BVO of straight chain aliphatic as well as aromatic aldehydes, which is missing in the classical BVO.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (B) (JSPS). We thank Central Glass Co. Ltd., Japan for a generous gift of BrF_3.

Supporting Information Available: Experimental procedures, supplementary figures, and computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For transition state structures of bromane-induced BVO of aldehydes RCHO (R = Et, *i*-Pr, *t*-Bu), see Figure S6.

JA104330G