Oxidation of benzyl alcohols with difluoro(aryl)-λ^3-bromane: formation of benzyl fluoromethyl ethers via oxidative rearrangement

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ABSTRACT

Oxidative rearrangement of benzyl alcohols with difluoro(*p*-trifluoromethylphenyl)-λ^3-bromane (5×10^{-2} M) in chloroform at room temperature afforded aryl fluoromethyl ethers selectively in good yields, probably via 1,2-shift of aryl groups from benzylic carbon to oxygen atoms.

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Environmentally friendly hypervalent aryl-λ^3-iodanes (ArILL′: L, L′ = heteroatom ligands) with two heteroatom ligands are the reagents of choice for oxidative transformations of various kinds of functionalities in modern organic synthesis.[1] Both heteroatom ligands L and L′ on iodane(III) function as leaving groups in ligand exchange and reductive elimination steps during the oxidations.[2] Primary and secondary alcohols are oxidized to aldehydes, ketones, and/or carboxylic acids under mild conditions.[1] In marked contrast, oxidation of alcohols with hypervalent aryl-λ^3-bromanes remains virtually unexplored, although their oxidizing power seems to be greater than that of aryl-λ^3-iodanes.[3,4] In fact, ionization potential of bromobenzene (8.98 eV) is larger than that of iodobenzene (8.69 eV).[5] We report herein oxidation of benzyl alcohols with difluoro(*p*-trifluoromethylphenyl)-λ^3-bromane (**1**)[6] in chloroform at room temperature under argon. Instead of simple oxidation to benzaldehydes **3** and/or benzoic acids, the reaction afforded predominantly aryl fluoromethyl ethers **2** in good yields, probably via oxidative fluorination with 1,2-aryl rearrangement from benzylic carbon to oxygen atoms.

Aryl-λ^3-iodanes oxidize benzyl alcohols under mild conditions and afford the corresponding benzaldehydes or benzoic acids depending on the structures of λ^3-iodanes, additives such as RuCl$_3$, TEMPO, I$_2$, and KBr, and reaction conditions.[7,8] Exposure of benzyl alcohol to a dichloromethane solution of a stoichiometric amount of difluoro(aryl)-λ^3-bromane **1** (5×10^{-3} M) at room temperature

for 3 h under argon afforded the expected benzaldehyde (**3a**) (Ar = Ph) in only 2% yield (determined by ^{1}H NMR). In this reaction, a major product was found to be phenyl fluoromethyl ether (**2a**)[9] (Ar = Ph, 22%) and a large amount of benzyl alcohol (50%) was recovered unchanged, although almost all of the λ^3-bromane **1** was consumed and reduced predominantly to *p*-(trifluoromethyl)bromobenzene (91%). Very interestingly, the λ^3-bromane-induced oxidative rearrangement of benzyl alcohol to fluoromethyl ether **2a** is highly dependent on the concentration of the λ^3-bromane **1**, as shown in Figure 1. Thus, use of 5×10^{-2} M solution of **1** in dichloromethane dramatically increased the yield of fluoromethyl ether **2a** up to 69%. Further increases in the concentration of **1** decreased the yields of **2a** to around 50% (Scheme 1).

Solvents have a large effect on the oxidative rearrangement. Difluoro-λ^3-bromane **1** readily dissolves in dichloromethane, while it is sparingly soluble in hexane and carbon tetrachloride. The latter solvents gave decreased yields of fluoromethyl ether **2a** (22–48%, Table 1, entries 1 and 6). No reaction was observed in more polar MeCN, and both λ^3-bromane **1** and benzyl alcohol were recovered unchanged (entry 8). The nucleophilic solvent MeCN with a Gutmann donor number *DN* of 14.1[10] probably coordinates to the positively charged bromine(III) atom of λ^3-bromane **1** with formation of a square planar tetracoordinated species and stabilizes it, which, in turn, will decrease the reactivity of **1**.[11] Use of chloroform afforded a moderate yield of **2a** (52%); however, the competing simple oxidation to benzaldehyde (**3a**) was almost inhibited to less than 1%. Finally, we found that the use of 1.4 equiv of **1** (5×10^{-2} M) in chloroform afforded a high yield of **2a** (80%, entry 5).

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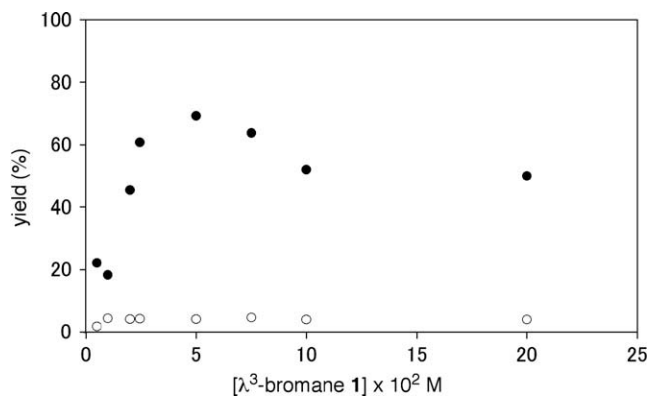
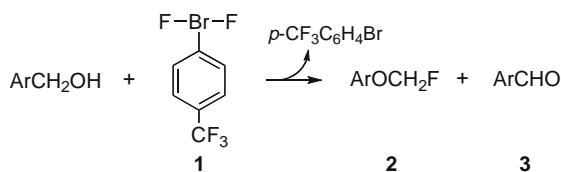**Figure 1.** Concentration dependence for oxidative rearrangement of benzyl alcohol with difluoro-λ^3-bromane **1** in dichloromethane at room temperature for 3 h under argon: (●) **2a** and (○) **3a**.

Table 1
Oxidation of benzyl alcohol with difluoro-λ^3-bromane **1**[a]

Entry	Bromane **1** (equiv)	Solvent	Yield[b] (%)	
			2a	**3a**
1	1	Hexane	22	5
2	1	ClCH$_2$CH$_2$Cl	44	6
3	1	CH$_2$Cl$_2$	69	4
4	1	CHCl$_3$	52	<1[c]
5	1.4	CHCl$_3$	80	<1
6	1	CCl$_4$	48	4
7	1	Et$_2$O	31	12
8	1	MeCN	—	—[c,d]
9	1.4[e]	CHCl$_3$	—	4[c]

[a] Conditions: bromane **1** (5×10^{-2} M)/room temperature/3 h/Ar.
[b] ^{1}H NMR yields.
[c] 44% (entry 4), 99% (entry 8), and 37% (entry 9) of PhCH$_2$OH were recovered unchanged.
[d] Difluoro-λ^3-bromane **1** (94%) was recovered unchanged.
[e] Difluoro-λ^3-iodane (p-CF$_3$C$_6$H$_4$IF$_2$), instead of **1**, was used.

Table 2
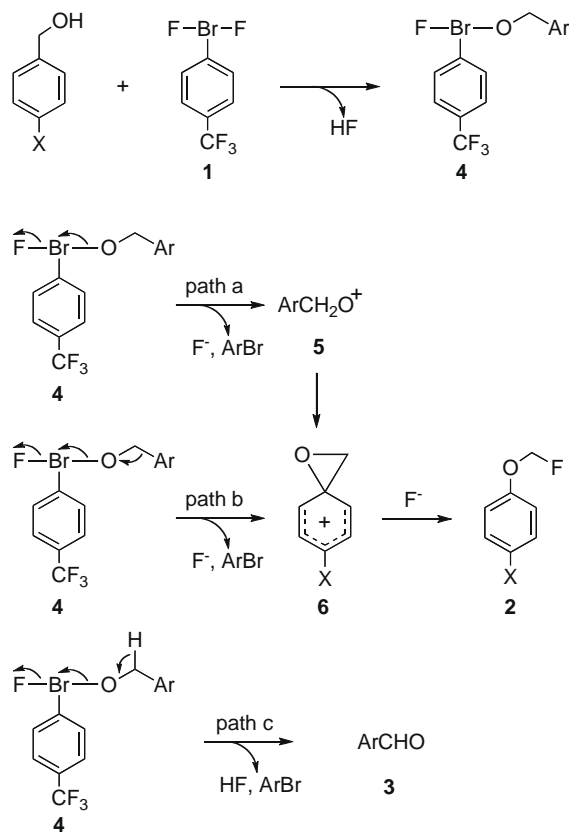Oxidation of substituted benzyl alcohols with difluoro-λ^3-bromane **1**[a]

Entry	Substrate	Yield[b] (%)			
		2		**3**	
1	p-MeOC$_6$H$_4$CH$_2$OH	**2b**	7	**3b**	—
2	p-MeC$_6$H$_4$CH$_2$OH	**2c**	17	**3c**	—
3	p-t-BuC$_6$H$_4$CH$_2$OH	**2d**	66	**3d**	<1
4	p-FC$_6$H$_4$CH$_2$OH	**2e**	68	**3e**	—
5	o-ClC$_6$H$_4$CH$_2$OH	**2f**	66	**3f**	—
6	p-ClC$_6$H$_4$CH$_2$OH	**2g**	90	**3g**	—
7	p-BrC$_6$H$_4$CH$_2$OH	**2h**	65	**3h**	<1
8	p-IC$_6$H$_4$CH$_2$OH	**2i**	67	**3i**	3
9	p-MeO$_2$CC$_6$H$_4$CH$_2$OH	**2j**	90	**3j**	—
10	p-CF$_3$C$_6$H$_4$CH$_2$OH	**2k**	63	**3k**	13
11	p-NCC$_6$H$_4$CH$_2$OH	**2l**	60	**3l**	8
12	p-NO$_2$C$_6$H$_4$CH$_2$OH	**2m**	44	**3m**	26
13	p-ClC$_6$H$_4$CH$_2$OTMS	**2g**	68	**3g**	2

[a] Conditions: bromane **1** (5×10^{-2} M, 1.4 equiv)/chloroform/room temperature/2 h/Ar.
[b] ^{1}H NMR yields.

Oxidation power of the λ^3-bromane **1** was compared with that of the λ^3-iodane. Thus, when benzyl alcohol was treated with difluoro(p-trifluoromethylphenyl)-λ^3-iodane[12] (1.4 equiv) in chloroform at room temperature for 3 h, formation of only a small amount of aldehyde **3a** (4%) was detected and large amounts of the alcohol (37%) and the λ^3-iodane (46%) were recovered. These results clearly reveal higher reactivity of the hypervalent difluoro-λ^3-bromane **1** in the oxidation of benzyl alcohol (compare entries 5 and 9).

Results for oxidation of substituted benzyl alcohols with the difluoro-λ^3-bromane **1** (1.4 equiv) in a chloroform solution are summarized in Table 2. Benzyl alcohols with electron-donating p-methoxy and p-methyl groups gave a complex mixture of products containing a small amount of aryl fluoromethyl ethers **2b** and **2c**. A rapid color change from colorless to brown and then to bright yellow on mixing these alcohols with the λ^3-bromane **1** in chloroform was observed, probably suggesting intervention of some electron transfer process. Interestingly, p-tert-butylbenzyl alcohol showed no such color change and afforded p-tert-butylphenyl fluoromethyl ether (**2d**) (66%) selectively (entry 3). Benzyl alcohols with moderately electron-withdrawing substituents such as p-fluoro, p-chloro, p-bromo, p-iodo, and p-methoxycarbonyl groups showed a high tendency toward the oxidative rearrangement rather than a simple oxidation to benzaldehydes **3**, yielding fluoromethyl ethers **2** in good to high yields (65–90%).[13] On the other hand, introduction of a highly electron-withdrawing p-trifluoromethyl group resulted in the formation of a considerable amount of byproduct and afforded a mixture of fluoromethyl ether **2k** (63%) and benzaldehyde **3k** (13%). The presence of a more powerful p-nitro group accelerated the simple oxidation at the expense of the desired oxidative rearrangement and produced **2m** and **3m** in 44 and 26% yields, respectively (entry 12). In addition to benzyl alcohols, benzyl trimethylsilyl ethers also undergo the oxidation to fluoromethyl ethers **2** (entry 13).

Scheme 2 depicts a reaction pathway for the formation of aryl fluoromethyl ethers **2** and benzaldehydes **3**, which involves initial generation of alkoxy(aryl)(fluoro)-λ^3-bromane intermediates **4** via

Scheme 1. Oxidation of benzyl alcohols with difluoro-λ^3-bromane **1**.

a facile ligand exchange of fluorine atom on hypervalent bromane(III) by a benzyl alcohol.[14] Leaving group ability of aryl-λ^3-bromanyl groups is greater than that of aryl-λ^3-iodanyl groups, so-called hyper-leaving groups.[15] Therefore, it is likely that the reductive elimination of alkoxy-λ^3-bromanes **4** produces benzyloxy cations **5**[16] with the concomitant liberation of p-(trifluoromethyl)bromobenzene (path a). Fluoromethyl ethers **2** will be produced from the cations **5** via intervention of spirobenzenium ions **6** and the subsequent nucleophilic ring-opening with fluoride anion.[17] Alternatively, the alkoxybromane **4** can generate benzenium ions **6** directly in a concerted manner (path b).[18] Both pathways a and b result in 1,2-shift of aryl groups of benzyl alcohols from the carbon to the oxygen atoms. On the other hand, competing β-elimination process of **4** involving a benzylic hydrogen abstraction will produce benzaldehydes **3** directly (path c).

As mentioned above, compared to the oxidation of benzyl alcohol in dichloromethane, 1,2-dichloroethane, and carbon tetrachloride, use of chloroform as a solvent diminished the relative ratios of simple oxidation to benzaldehyde (**3a**) versus 1,2-rearrangement yielding fluoromethyl ether **2a** to a negligible extent (Table 1, entries 2–6). Chloroform with a large solvent acceptor number (AN) of 23.1[19] will more efficiently solvate and stabilize an electron-rich species such as fluoride anion, which probably participates in benzylic hydrogen abstraction of alkoxy-λ^3-bromanes **4** during the β-elimination. In other words, solvent hydrogen bonding toward fluoride anion is more effective in chloroform solution than in

Scheme 2. Reaction pathway for oxidation of benzyl alcohols with **1**.

Figure 2. Concentration dependence for decomposition of difluoro-λ^3-bromane **1** in CD_2Cl_2 at 23 °C under argon (determined by ^1H NMR): (a) 5×10^{-3} M and (b) 5×10^{-2} M. The inset shows details of initial decomposition.

dichloromethane solution, because the former is more acidic with an estimated pK_a value of ca. 24.[20] Thus, the rate of β-elimination process (path c), compared to that of 1,2-rearrangement pathways (paths a and b), will be slowed down more remarkably in chloroform solution.

The difluoro-λ^3-bromane **1** is a colorless solid and can be kept for several months at −30 °C under argon without any decomposition.[6] In CD_2Cl_2 solution at 23 °C, however, the bromane **1** rapidly decomposes at a low concentration of 5×10^{-3} M and produces *p*-(trifluoromethyl)bromobenzene quantitatively with a half-life time ($t_{1/2}$) of approximately 3 min (Fig. 2a). This facile decomposition of the bromane **1** to bromobenzene will compete with the oxidative rearrangement of benzyl alcohol, which accounts nicely for a moderate yield formation of phenyl fluoromethyl ether (**2a**) at the low concentration of **1** (Fig. 1). Very interestingly, the rate of decomposition of the bromane **1** to bromobenzene seems to depend on the concentration in solution: thus, the increased concentration of **1** to 5×10^{-2} M in CD_2Cl_2 substantially decreased the rate of its decomposition and a half-life time of the bromane **1** was changed to more than one hour (Fig. 2b). This decreased decomposition rate of the bromane **1** will result in the increased yield of **2a** up to 69% (Fig. 1).

Solid state structure of difluoro(aryl)-λ^3-bromanes has never been reported; however, bromine trifluoride (BrF_3) was shown to be a pseudo trigonal bipyramidal molecule.[21] The single crystal X-ray diffraction revealed a polymeric chain structure through an intermolecular hypervalent Br(III)···F contact with a planar tetra-coordinated geometry around bromane(III).[22] Similar intermolecular contacts of I(III)···F bonding with formation of zigzag chain polymers were observed in the solid state structures of difluoro-λ^3-iodanes such as CF_3IF_2 and $C_6F_5IF_2$.[23] If these polymeric (or oligomeric) structures are adopted in the solid state structure of the

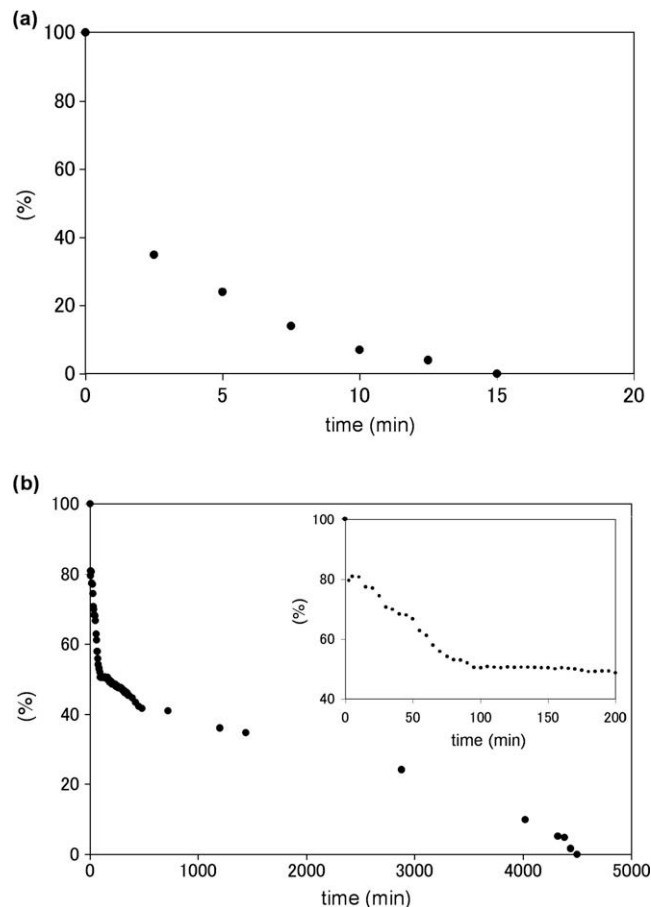difluoro-λ^3-bromane **1** and maintained even in solution to some extent, its stability in solution may depend on the concentrations.

We have uncovered the greater power of the difluoro-λ^3-bromane **1** in the oxidation of benzyl alcohols, compared with that of difluoro-λ^3-iodane analogue. The reaction affords aryl monofluoromethyl ethers **2** in good yields, probably via oxidative fluorination with 1,2-aryl migration from benzylic carbon to oxygen atoms.

Acknowledgment

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.042.

References and notes

1. (a) Zhdankin, V. V. *Sci. Synth.* **2007**, *31a*, 161. Chapter 31.4.1; (b) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656; (c) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111; (d)*Hypervalent Iodine Chemistry*; Wirth, T., Ed.Top. Curr. Chem.; Springer: Berlin, 2003; Vol. 224, (e) Zhdankin, V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299; (f) Quideau, S.; Pouysegu, L.; Deffieux, D. *Synlett* **2008**, 467; (g) Ochiai, M. In *Chemistry of Hypervalent Compounds*; Akiba, K., Ed.; VCH: New York, 1999; p 359; (h) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine;*; VCH: New York, 1992; (i) Ochiai, M.; Miyamoto, K. *Eur. J. Org. Chem.* **2008**, 4229.

2. Ochiai, M. *Chem. Record* **2007**, *7*, 12.

3. For oxidation of primary alcohols to acyl fluorides with bromine trifluoride, see: Rozen, S. *Acc. Chem. Res.* **2005**, *38*, 803.

4. For reviews of aryl-λ^3-bromanes, see: (a) Ochiai, M. *Synlett* **2009**, 159; (b) Farooq, U.; Shah, A. A.; Wirth, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 1018.

5. *CRC Handbook of Chemistry and Physics*; Lide, D. R., Ed.; CRC: Boca Raton, 1992.

6. (a) Frohn, H.-J.; Giesen, M. *J. Fluorine Chem.* **1998**, *89*, 59; (b) Frohn, H.-J.; Giesen, M. *J. Fluorine Chem.* **1984**, *24*, 9; (c) Ochiai, M.; Nishi, Y.; Goto, S.; Shiro, M.; Frohn, H.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15304; (d) Obaleye, J. A.; Sams, L. C. *J. Inorg. Nucl. Chem.* **1981**, *43*, 2259; (e) Frohn, H.-J.; Hirschberg, M. E.; Wenda, A.; Bardin, V. V. *J. Fluorine Chem.* **2008**, *129*, 459.

7. For oxidation of benzyl alcohols to benzaldehydes with aryl-λ^3-iodanes, see: (a) Geraskin, I. M.; Luedtke, M. W.; Neu, H. M.; Nemykin, V. N.; Zhdankin, V. V. *Tetrahedron Lett.* **2008**, *49*, 7410; (b) Koposov, A. Y.; Netzel, B. C.; Yusubov, M. S.; Nemykin, V. N.; Nazarenko, A. Y.; Zhdankin, V. V. *Eur. J. Org. Chem.* **2007**, 4475; (c) Yusubov, M. S.; Gilmkhanova, M. P.; Zhdankin, V. V.; Kirschning, A. *Synlett* **2007**, 563; (d) Yusubov, M. S.; Chi, K.-W.; Park, J. Y.; Karimov, R.; Zhdankin, V. V. *Tetrahedron Lett.* **2006**, *47*, 6305; (e) Herrerias, C. I.; Zhang, T. Y.; Li, C.-J. *Tetrahedron Lett.* **2006**, *47*, 13; (f) Qian, W.; Jin, E.; Bao, W.; Zhang, Y. *Tetrahedron* **2006**, *62*, 556; (g) Qian, W.; Jin, E.; Bao, W.; Zhang, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 952; (h) Kansara, A.; Sharma, P. K.; Banerji, K. K. *J. Chem. Res.* **2004**, 581; (i) Iwasa, S.; Morita, K.; Tajima, K.; Fakhruddin, A.; Nishiyama, H. *Chem. Lett.* **2002**, 284; (j) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974; (k) Varma, R. S.; Dahiya, R.; Saini, R. K. *Tetrahedron Lett.* **1997**, *38*, 7029; (l) Muller, P.; Godoy, J. *Helv. Chim. Acta* **1983**, *66*, 1790; (m) Takaya, T.; Enyo, H.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1032.

8. For oxidation of benzyl alcohols to benzoic acids or their derivatives with aryl-λ^3-iodanes, see: (a) Kunst, E.; Gallier, F.; Dujardin, G.; Yusubov, M. S.; Kirschning, A. *Org. Lett.* **2007**, *9*, 5199; (b) Karade, N. N.; Tiwari, G. B.; Huple, D. B. *Synlett* **2005**, 2039; (c) Tohma, H.; Takizawa, S.; Maegawa, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 1306; (d) Tohma, H.; Maegawa, T.; Takizawa, S.; Kita, Y. *Adv. Synth. Catal.* **2002**, *344*, 328; (e) Tohma, H.; Maegawa, T.; Kita, Y. *Synlett* **2003**, 723; (f) Wang, N.; Liu, R.; Xu, Q.; Liang, X. *Chem. Lett.* **2006**, *35*, 566.

9. For oxidation of benzyl alcohols to fluoromethyl aryl ethers with XeF_2, see: Stavber, S.; Zupan, M. *Tetrahedron Lett.* **1993**, *34*, 4355.

10. (a) Gutmann, V. *Chem. Tech.* **1977**, 255; (b) Reichardt, C. *Solvent Effects in Organic Chemistry*; Verlag Chemie: Weinheim, 1979.

11. (a) Ochiai, M.; Kaneaki, T.; Tada, N.; Miyamoto, K.; Chuman, H.; Shiro, M.; Hayashi, S.; Nakanishi, W. *J. Am. Chem. Soc.* **2007**, *129*, 12938; (b) Ochiai, M.; Kawano, Y.; Kaneaki, T.; Tada, N.; Miyamoto, K. *Org. Lett.* **2009**, *11*, 281.

12. Ochiai, M.; Yoshimura, A.; Mori, T.; Nishi, Y.; Hirobe, M. *J. Am. Chem. Soc.* **2008**, *130*, 3742.

13. Hammett substituents σ_p: p-F, 0.06; p-Cl, 0.23; p-Br, 0.23; p-I, 0.18; p-CO_2Me, 0.45; p-CF_3, 0.54; p-CN, 0.66; p-NO_2, 0.78. See: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

14. For a facile ligand exchange on hypervalent iodane(III), see: Ochiai, M. In *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Top. Curr. Chem.; Springer, 2003; Vol. 224, pp 5–68.

15. Ochiai, M.; Tada, N.; Okada, T.; Sota, A.; Miyamoto, K. *J. Am. Chem. Soc.* **2008**, *130*, 2118.

16. Katritzky, A. R.; Dega-Szafran, Z.; Watson, C. H.; Eyler, J. R. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1051.

17. AM1 calculations indicate that spirobenzenium ion **6** (X = H) is higher in energy than benzyloxy cation **5** (X = H). See Ref. 16.

18. Aryloxymethyl cations ($ArOCH_2^+$) are possible alternatives to spirobenzenium ions **6**.

19. Solvent acceptor numbers *AN*:CCl_4, 8.6; $ClCH_2CH_2Cl$, 16.7; CH_2Cl_2, 20.4. See: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; Wiley-VCH: Weinheim, 2003.

20. (a) Margolin, Z.; Long, F. A. *J. Am. Chem. Soc.* **1973**, *95*, 2757; (b) Bohme, D. K.; Lee-Ruff, E.; Young, L. B. *J. Am. Chem. Soc.* **1972**, *94*, 5153.

21. (a) Ellern, A. M.; Antipin, M. Y.; Struchkov, Y. T.; Sukhoverkhov, V. F. *Zh. Neorg. Khim.* **1991**, *36*, 1393; (b) Magnuson, D. W. *J. Chem. Phys.* **1957**, *27*, 223.

22. For a similar intermolecular hypervalent contact on iodane(III), see: (a) Ochiai, M. *Coord. Chem. Rev.* **2006**, *250*, 2771; (b) Alcock, N. W. *Adv. Inorg. Chem. Radiochem.* **1972**, *15*, 1; (c) Ochiai, M.; Suefuji, T.; Miyamoto, K.; Tada, N.; Goto, S.; Shiro, M.; Sakamoto, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **2003**, *125*, 769; (d) Ochiai, M.; Miyamoto, K.; Shiro, M.; Ozawa, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **2003**, *125*, 13006.

23. (a) Minkwitz, R.; Berkei, M. *Inorg. Chem.* **1998**, *37*, 5247; (b) Bailly, F.; Barthen, P.; Frohn, H.-J.; Giesen, M.; Helber, J.; Henkel, G.; Priwitzer, A. *Z. Anorg. Allg. Chem.* **2000**, *626*, 1406.