benzene was heated in a sealed tube at 178 °C for 19 h. Removal of the solvent under reduced pressure left a yellow oil which was chromatographed on a silica gel column with a 30% ethyl acetate–hexane mixture as the eluent to give 0.4 g (83%) of a clear oil whose structure was assigned as 2-nitro-3-(trimethylsilyl)bicyclo[2.2.2]oct-5-ene (**32**) on the basis of the following data: bp 80–81 °C (0.04 mm); IR (neat) 3100, 3020, 1620, 1550, 1460, 1310, 1255, 1160, 1035, 880, 840, 740, and 685 cm^{-1}; NMR (CCl_4, 90 MHz) δ 0.10 (s, 9 H), 1.0–1.7 (m, 5 H), 3.70 (m, 1 H), 3.35 (, 1 H), 4.45 (m, 1 H), 6.00 (t, 1 H, J = 6.0 Hz), and 6.52 (t, 1 H, J = 6.0 Hz); m/e 195, 179, 152, 135, 126, 106, and 78.

Anal. Calcd for $C_{11}H_{19}NO_2Si$: C, 58.63; H, 8.50; N, 6.21. Found: C, 58.74; H, 8.55; N, 6.15.

Reaction of (2-Nitrovinyl)trimethylsilane with 1-((Trimethylsilyl)oxy)butadiene (33). A solution containing 250 mg of **33** and 250 mg of (2-nitrovinyl)trimethylsilane in 2 mL of benzene was heated in a sealed tube at 100 °C for 37 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with a 30% ethyl acetate–hexane mixture. The major fraction contained 420 mg (83%) of a clear oil whose structure was assigned as 1-nitro-2-(trimethylsilyl)-6-((trimethylsilyl)oxy)cyclohex-4-ene (**34**) on the basis of its spectral data: IR (neat) 3000, 1640, 1550, 1420, 1370, 1300, 1250, 1160, 1100, 1070, 1035, 840, 740, and 680 cm^{-1}; NMR (CCl_4, 90 MHz) δ 0.15 (s, 9 H), 0.20 (s, 9 H), 1.9–2.3 (m, 3 H), 3.49 (s, 3 H), and 3.5–5.1 (m, 3 H); m/e 272, 241, 168, 151, 147, 142, and 103. This material was quite sensitive to moisture and consequently did not analyze properly.

Reaction of (2-Nitrovinyl)trimethylsilane with *trans*-1-Methoxy-3-((trimethylsilyl)oxy)-1,3-butadiene (35). A solution containing 200 mg of **35** and 200 mg of (2-nitrovinyl)trimethylsilane in 1 mL of benzene was heated in a sealed tube at 100 °C for 20 h. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography with a 30% ethyl acetate–hexane mixture as the eluent. The major fraction contained 300 mg (85%) of a colorless oil whose structure was assigned as 1-methoxy-2-nitro-3-(trimethylsilyl)-5-((trimethylsilyl)oxy)cyclohex-5-ene (**36**) on the basis of its spectral data: IR (neat) 3000, 2850, 1660, 1550, 1420, 1300, 1250, 1200, 1080, 1010, 835, and 740 cm^{-1}; NMR (CCl_4, 90 MHz) δ 0.17 (s, 9 H), 0.34 (s, 9 H), 1.6–2.3 (m, 2 H), 3.37 (s, 3 H), and 3.8–5.2 (m, 4 H); m/e 302, 271, 257, 244, 167, 151, 141, 125, 109, 97, and 73.

The structure of this material was further verified by an aqueous acid hydrolysis. To a solution containing 150 mg of **36** in 20 mL of tetrahydrofuran was added 4 mL of a 5% aqueous acetic acid solution. After stirring for 1 h the solution was poured into 60 mL of ice–water and extracted several times with ether. The combined ether extracts were washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The crude reaction mixture was subjected to silica gel chromatography with a 30% ethyl acetate–hexane mixture. The two major fractions isolated corresponded to *cis*- (67%) and *trans*-1-methoxy-2-nitro-3-(trimethylsilyl)cyclohexan-5-one (26%). The cis isomer (**37**) was a clear oil: bp 60–61 °C (0.04 mm); IR (neat) 3000, 1722, 1550, 1420, 1360, 1240, 1180, 1080, 1020, 980, 840, and 740 cm^{-1}; NMR (CCl_4, 90 MHz) δ 0.12 (s, 9 H), 1.8–2.9 (m, 5 H), 3.40 (s, 3 H), 4.10 (m, 1 H), and 4.86 (dd, 1 H, J = 8.0 and 3.0 Hz); m/e 230, 199, 185, 167, 151, 141, and 125.

Anal. Calcd for $C_{10}H_{19}NO_4Si$: C, 48.95; H, 7.81; N, 5.71. Found: C, 49.18; H, 7.86; N, 5.76.

The trans isomer (**38**) was a crystalline solid: mp 59–60 °C; IR (KBr) 2965, 1720, 1550, 1420, 1370, 1320, 1240, 1180, 990, 970, and 830 cm^{-1}; NMR (CCl_4, 90 MHz) δ 0.12 (s, 9 H), 1.0–2.9 (7, 5 H), 3.31 (s, 3 H), 3.90 (m, 1 H), and 4.60 (dd, 1 H, J = 12.0 and 9.0 Hz); m/e 230, 199, 185, 167, 151, 141, 125, 104, and 85.

Anal. Calcd for $C_{10}H_{19}NO_4Si$: C, 48.95; H, 7.81; N, 5.71. Found: C, 49.03; H, 7.89; N, 5.66.

Competitive Reactivity Studies. Relative reactivity studies were carried out on mixtures of two different dipolarophiles, an internal standard, and a solution containing 0.5 g of benzohydroximoyl chloride in 20 mL of carbon tetrachloride at 0 °C. To this mixture was slowly added 2.0 g of triethylamine; the resulting mixture was stirred at 0 °C for 2 h and was then filtered, and the solvent was removed under reduced pressure. The relative reactivities were determined by gas chromatography or quantitative NMR spectroscopy using the relation

$$k_{\text{rel}} = \log (A/A_0)/\log (B/B_0)$$

where A_0 and B_0 are the areas of the two dipolarophiles relative to the internal standard prior to the reaction and A and B are the same quantities after reaction. The final peak areas were determined by GLC after ca. 40% of the dipolarophiles had been consumed. The relative rate differences are good to ±10%.

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Boron Trifluoride Promoted Reaction of Alkyl Hypohalites with Alkenes. A New Synthesis of Fluoro Halides

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The reactions of the following alkenes with alkyl hypohalites and boron trifluoride (BF_3) were investigated: cyclohexene (**3**), 1-hexene (**8**), *trans*-1,2-dichloroethylene (**15**), methyl acrylate (**18**), methyl crotonate (**25**), methyl isocrotonate (**29**), butadiene (**33**), methyl vinyl ketone (**42**), and styrene (**45**). Reactions of these alkenes with methyl hypochlorite (**1**) and BF_3 in dichloromethane give fluoro chloride adducts as well as methoxy chlorides with the percentage of fluoro chlorides varying from 75% for **29** to 8% for **45**. Fluoro bromide adducts are obtained with methyl hypobromite (**2**). Reactions with the *tert*-butyl hypohalites and BF_3 also give fluoride incorporation. The percentage of fluoride incorporation with **1** or **2** is significantly greater in carbon tetrachloride than in dichloromethane.

Although alkyl hypohalites are well-known for radical reactions with alkenes,[1] their potential for ionic reactions has received less attention. Hypohalites react with alkenes by ionic mechanisms in polar and/or nucleophilic sol-

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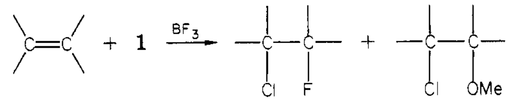
Table I. Products from the BF_3-Hypohalite Reaction of Various Alkenes

alkene	hypohalite, conditions	fluorohalides,[b] %		methoxy halides,[b] %		yield, %
cyclohexene (**3**)	MeOCl, *a*	**4** (66)		**5** (34)		92
3	MeOCl, CCl_4	**4** (77.5)		**5** (22.5)		68
3	*t*-BuOCl, *a*	**4** (55)[c]				55
3	MeOBr, *a*	**6** (35.5)		**7** (64.5)		71
3	MeOBr, CCl_4	**6** (63)		**7** (37)		93
3	MeOBr, −78 °C	**6** (19)		**7** (81)		81
1-hexene (**8**)	MeOCl, *a*	**9** (49.5)		**10** (34.5)	**11** (16)	99
8	*t*-BuOCl, *a*	**9** (56)[c]				56
8	MeOBr, *a*	**12** (23.5)		**13** (47.5)	**14** (29)	68
8	MeOBr, CCl_4	**12** (49.5)		**13** (31)	**14** (19.5)	56
8	MeOBr, −78 °C	**12** (11)		**13** (63)	**14** (26)	54
8	*t*-BuOBr, *a*	**12** (10)[c]				10
trans-1,2 dichloroethylene (**15**)	MeOCl, *a*	**16** (61)		**17** (39)		61
methyl acrylate (**18**)	MeOCl, *a*	**19** (43.5)		**20** (25.5)	**21** (31)	83
18	MeOBr, *a*	**22** (29)		**23** (24)	**24** (47)	48
methyl crotonate (**25**)	MeOCl, *a*	**26** (65.5)		**27** (10)	**28** (24.5)	90
methyl isocrotonate (**29**)	MeOCl, *a*	**30** (75.5)		**31** (4.5)	**32** (20)	70
butadiene (**33**)	MeOCl, *a*	**34** (31.5)	**35** (14)	**36** (37)	**37** (17.5)	63
33	MeOCl, CCl_4	**34** (53)	**35** (16.5)	**36** (25)	**37** (5.5)	53
33	*t*-BuOCl, *a*	**34** (14)[c]	**35** (12)[c]			26
33	MeOBr, *a*	**38** (25)	**39** (6)	**40** (51)	**41** (18)	79
methyl vinyl ketone (**42**)	MeOCl, *a*	**43** (45.5)		**44** (54.5)		71
styrene (**45**)	MeOCl, *a*	**46** (8)		**47** (68)		77[d]
45	MeOCl, CCl_4	**46** (37)		**47** (40)		76[d]
45	MeOBr, *a*	**49** (5)		**50** (95)		56

[a] Unless otherwise stated, reactions were run at 25 °C in CH_2Cl_2. [b] Products are identified as follows: **4**, *trans*-1-chloro-2-fluorocyclohexane; **5**, *trans*-1-chloro-2-methoxycyclohexane; **6**, *trans*-1-bromo-2-fluorocyclohexane; **7**, *trans*-1-bromo-2-methoxycyclohexane; **9**, 1-chloro-2-fluorohexane; **10**, 1-chloro-2-methoxyhexane; **11**, 2-chloro-1-methoxyhexane; **12**, 1-bromo-2-fluorohexane; **13**, 1-bromo-2-methoxyhexane; **14**, 2-bromo-1-methoxyhexane; **16**, 1,1,2-trichloro-2-fluoroethane; **17**, 1,1,2-trichloro-2-methoxyethane; **19**, methyl 3-chloro-2-fluoropropanoate; **20**, methyl 3-chloro-2-methoxypropanoate; **21**, methyl 2-chloro-3-methoxypropanoate; **22**, methyl 2-bromo-3-fluoropropanoate; **23**, methyl 3-bromo-2-methoxypropanoate; **24**, methyl 2-bromo-3-methoxypropanoate; methyl 2-chloro-3-fluorobutanoate (**26**, erythro, and **30** threo); methyl 3-chloro-2-methoxybutanoate (**27**, erythro, and **31**, threo); methyl 2-chloro-3-methoxybutanoate (**28**, erythro, and **32**, threo); **34**, 4-chloro-3-fluoro-butene; **35**, *trans*-1-chloro-4-fluoro-2-butene; **36**, 4-chloro-3-methoxy-butene; **37**, *trans*-1-chloro-4-methoxy-2-butene; **38**, 4-bromo-3-fluorobutene; **39**, *trans*-1-bromo-4-fluoro-2-butene; **40**, 4-bromo-3-methoxybutene; **41**, *trans*-1-bromo-4-methoxy-2-butene; **43**, 3-chloro-4-fluoro-2-butanone; **44**, 3-chloro-4-methoxy-2-butanone; **46**, 2-chloro-1-fluoro-1-phenylethane; **47**, 2-chloro-1-methoxy-1-phenylethane; **48**, β-chlorostyrene; **49**, 2-bromo-1-fluoro-1-phenylethane; **50**, 2-bromo-1-methoxy-1-phenylethane. [c] Yield of fluorohalide only. The amount of *tert*-butoxy halide was not determined. [d] The yield includes β-chlorostyrene (**48**), which is 24% of the total product in both CH_2Cl_2 and CCl_4.

vents[2a] but fail to react with most alkenes in aprotic, nonpolar solvents.[2b] Recently we successfully exploited the lack of reactivity of hypochlorites in nonpolar solvents by using Lewis acids such as boron trifluoride (BF_3)[3a] and trimethyl borate[3b] to promote ionic reactions with alkenes. In the first preliminary report,[3a] we showed that BF_3 catalyzes an ionic reaction of methyl hypochlorite (**1**) with α,β-unsaturated esters in methylene chloride. Large amounts of fluoro chloride incorporation occurred in competition with methoxide, as outlined in eq 1.



(1)

A more extensive investigation has shown that the BF_3–hypohalite reaction is a general reaction of alkenes with both alkyl hypochlorites and hypobromites. We are now prepared to describe the scope of the reaction.

Results

The data for reactions of nine different alkenes with BF_3 and hypohalites are shown in Table I. Some of the important findings are discussed below.

All of the alkenes shown in Table I give mixtures of fluoro halides and methoxy halides upon reaction with BF_3 and a hypohalite. The yield of fluoro halide is in many cases high enough to give the reaction definite synthetic utility. Boron trifluoride transforms the sluggish hypohalites into highly reactive electrophiles. Reactions with alkenes such as 1-hexene, cyclohexene, and styrene were completed upon mixing of reagents. Even deactivated alkenes such as methyl acrylate and *trans*-1,2-dichloroethylene gave complete reactions with methyl hypochlorite (**1**) in 5–30 min. We found that BF_3 (as anhydrous BF_3 or $BF_3 \cdot Et_2O$) and **1** could be mixed for long periods of time without a detectible effect on the hypochlorite. On the other hand, methyl hypobromite (**2**) and *tert*-butyl hypochlorite were not stable when mixed with BF_3. The BF_3-catalyzed reaction of the latter hypohalites with the alkene evidently takes place faster than their decomposition.

Factors Affecting Fluoride Incorporation. We examined several variables that may affect the ratio between fluoride and methoxide incorporation. All of the alkenes gave more fluoride incorporation with hypochlorite than

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(1) For example see: Pryor, W. A. "Free Radicals"; McGraw-Hill: New York, 1966; pp 120, 167.

(2) (a) See, for example: Hertel, L. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1979**, *101*, 7690. Heasley, G. E.; McCully, V. M.; Wiegman, R. T.; Heasley, V. L.; Skidgel, R. A. *J. Org. Chem.* **1976**, *41*, 644. (b) Methyl hypochlorite was found to react without catalyst with 2-cyclopropylpropene by an ionic mechanism in CH_2Cl_2 because a very stable cyclopropylcarbinyl cation intermediate was formed. See: Shellhamer, D. F.; McKee, D. B.; Leach, C. T. *Ibid.* **1976**, *41*, 1972. None of the alkenes reported in this study reacted at an appreciable rate with CH_3OCl or CH_3OBr in the absence of BF_3.

(3) (a) Heasley, V. L.; Shellhamer, D. F.; Gipe, R. K.; Wiese, H. C.; Oakes, M. L.; Heasley, G. E. *Tetrahedron Lett.* **1980**, *21*, 4133. (b) Heasley, G. E.; Duke, M.; Hoyer, D.; Hunnicutt, J.; Lawrence, M.; Smolik, M. J.; Heasley, V. L.; Shellhamer, D. F. *Ibid.* **1982**, *23*, 1459.

Table II. Effect of BF_3/CH_3OCl Mole Ratio in Reaction with 1-Hexene[a]

mol BF_3/ mol CH_3OCl	yield of 9, %	yield of 10 + 11, %
10:1	45	46
5:1	52	49
1:1	46	49
1:2	44	51
1:10[b]	47	62
1:20	*c*	*c*

[a] The calculated amount of boron trifluoride etherate was added to a solution of 3.2 mmol of 8 in 10 mL of dichloromethane followed by 1.6 mL (1.6 mmol) of a 1 M solution of 1. [b] Since 9 and 10 + 11 are formed in nearly equal amount, the quantity of BF_3 is nearly sufficient to form products in the same ratio as in the other runs. [c] Unreacted 1 remained after several hours.

with hypobromite. Examples are reactions of 1 with cyclohexene (**3**) and 1-hexene (**8**) in dichloromethane where the percentage of fluoride product was 66% and 49.5%, respectively; these alkenes gave about one-half as much fluoride incorporation—35.5% and 23.5%, respectively.

The results show that the amount of fluoride incorporation is significantly greater when CCl_4 is used as solvent instead of CH_2Cl_2. For example, in the reaction of cyclohexene and 1-hexene with **2** the percentage of fluoride incorporation is increased from 35.5% to 63% and from 23.5% to 49.5%, respectively, in changing from CH_2Cl_2 to CCl_4. This effect is especially pronounced with styrene (**45**), where 37% fluoride incorporation is obtained in CCl_4 but only 8% in CH_2Cl_2. Reactions of **45** with 1 in three other solvents of low polarity—benzene, 1,1,2-trichloro-1,2,2-trifluoroethane, and carbon disulfide—also gave larger amounts of fluoride (24%, 18%, and 17%, respectively) than were obtained in CH_2Cl_2.

A third factor that could affect the ratio of fluoride to alkoxide incorporation is the nature of the alkene. We were surprised to see little variation between the electron-rich alkenes (**3** and **8**) and the deactivated alkenes (**15**, **18**, **25**, and **29**). However, styrene gave a much smaller amount of fluoride incorporation (8%) in CH_2Cl_2. Butadiene gave an amount of fluoride product (1,2 and 1,4) comparable to the other alkenes, but piperylene, a more reactive alkene, did not give significant amounts of fluoro chloride upon reaction with 1 in CH_2Cl_2.

Temperature also affected the amount of fluoride incorporation with methyl hypobromite (**2**). Both cyclohexene and 1-hexene gave about twice as much fluoro bromide adduct at 25 °C as at −78 °C.

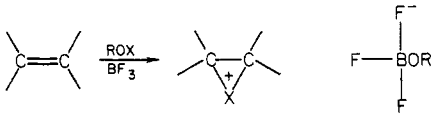
A final variable that we explored was the ratio of BF_3 to the hypohalite. A significant change in the fluoro halide to methoxy halide ratio did not occur with large changes in the BF_3 to hypohalite ratio. For example, experiments with 1-hexene and 1 (Table II) showed that variation of the BF_3:1 ratio from 10:1 to 1:10 did not produce large changes in the proportion of fluoride incorporation. These experiments also showed that BF_3 is consumed in stoichiometric amounts in the formation of fluoro halide from 1 and that all three of the fluorine atoms of BF_3 are about equally effective.

Discussion

First, we would like to direct some comments to the utility of the BF_3–hypohalite reaction as a practical synthesis of vicinyl fluoro halides. There are very few good methods for the direct addition of the elements Cl,F or Br,F to the carbon–carbon double bond. The most general procedures use anhydrous hydrogen fluoride along with a halogen electrophile such as *N*-bromo- or *N*-chlorosuccinimide.[4] Olah et al. recently achieved an important modification of this method by substituting 30% pyridine–70% hydrogen fluoride for anhydrous hydrogen fluoride.[5]

The BF_3–hypohalite reagent appears to have some advantages over the above procedures. The reaction is easily carried out and can be done with alkenes of widely varying reactivity. The reagents are readily available and, in the case of the hypochlorites, very inexpensive. The chief drawback to the procedure is that the fluoro halides must be separated from the halo ethers. We readily obtained separation on a small scale using either gas chromotography or liquid chromotography.

Finally, we comment briefly on the possible mechanism of the BF_3–hypohalite reaction. Our data suggest that the reaction proceeds via a halonium–tetraborate ion-pair intermediate as shown in eq 2. The cation could capture either fluoride or alkoxide from the tetraborate. This mechanism is capable of explaining the following facts about the reaction. (1) Fluoro chloride addition to the crotonates is 100% antistereospecific, suggesting a bridged chloronium intermediate. (2) The regioselectivity observed with alkenes **8**, **18**, **25**, **29**, and **42** is reasonable for this mechanism. The exclusive Markovnikov addition of fluoro halide to **8** is also observed with fluoro halide addition via NBS or NCS and hydrogen fluoride.[5]



(2)

We considered the possibility of a rapid pre-equilibrium to produce halogen monofluoride but believe this to be unlikely for the following reasons. If the fluoro halide was produced via this route (eq 3), styrene and the reactive dienes should yield fluoro halides (in CH_2Cl_2) in amounts comparable to the other reactive alkenes (e.g., **3**). Also, it would seem that unreactive alkenes such as dichloroethylene would give much more fluoro chloride adduct than reactive alkenes because the sluggish alkenes would have ample time for formation of highly reactive chlorine monofluoride.

$$ROX + BF_3 \rightleftharpoons ROBF_2 + XF \qquad (3)$$

Experimental Section

General Methods. NMR spectra were obtained with Varian T-60A or EM-360A instruments, and IR spectra were obtained with Beckman IR-10 and Perkin-Elmer 337 spectrophotometers. Hypochlorites were prepared as solutions in CH_2Cl_2 or CCl_4 from commercial bleach (e.g., Clorox) by the method of Jenner.[6] Methyl- (**2**)[7] and *tert*-butyl hypobromite were obtained as CCl_4 or CH_2Cl_2 solutions (0.4–1.0 M) from the following procedure, which was modified to use mercuric oxide in place of silver sulfate. Mercuric oxide (10 g, red or yellow) and 30 mL of water were shaken in an ice bath, 2 mL of bromine was added at once, and the mixture was shaken vigorously with cooling until the bromine had gone into solution. The mixture was filtered, and 20 mL of ice-cold 1 M H_2SO_4 was added to the filtrate. Free bromine was removed from the aqueous solution by several extractions with

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(4) Sheppard, W. A.; Sharts, C. M. "Organic Fluorine Chemistry"; W. A. Benjamin: New York, 1969.

(5) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872.

(6) Jenner, E. L. *J. Org. Chem.* **1962**, *27*, 1031.

(7) Heasley, V. L.; Frye, C. L.; Heasley, G. E.; Martin, K. A.; Redfield, D. A.; Wilday, P. S. *Tetrahedron Lett.* **1970**, 1573.

cold carbon tetrachloride. The aqueous hypobromous acid solution was placed in a stoppered flask (wrapped with aluminum foil), a cold solution of 10 mL of methanol in 40 mL of dichloromethane was added, and the mixture was shaken vigorously with cooling for 5–10 min. The dichloromethane solution of **2** was separated, dried with magnesium sulfate, and stored at freezer temperatures in a foil-wrapped container. The concentration of **2** was 0.5–0.7 M. Fresh preparations were essentially free from bromine (UV-410 μm) and were stable for several days.

VPC Separations. Analysis was done on F.I.D. instruments (Hewlett Packard 7620A or 5730) using the following packed columns (Chromosorb W-AW, 80/100 DMCS): column A, 1.5% dinonyl phthalate, 12 ft × 0.125 in. s.s; column B, 2.5% SE-30, 10 ft × 6 mm o.d. glass; column C, 2.5% FFAP, 10 ft × 0.125 in. s.s. Preparative VPC was generally done on an F&M 700 T.C. instrument equipped with a 5% DC-550, 8 ft × 9 mm o.d. glass column.

General Reaction Conditions. In runs for obtainment of analytical data (Table I), the hypohalite and boron trifluoride etherate were added to a 0.3 M solution of the alkene in dichloromethane at room temperature. The amount of hypohalite was sufficient to consume 20% of the alkene and was in a 1:1 molar ratio to the boron trifluoride. A typical reaction follows: To a stirred solution of methyl acrylate (0.67 mL, 7.5 mmol) in 24.5 mL of dichloromethane was added 2.0 mL (1.5 mmol) of a 0.75 M solution of methyl hypobromite in dichloromethane, followed immediately by 0.18 mL (1.5 mmol) of boron trifluoride etherate. After 5 min the reaction mixture was subjected to water workup and the dichloromethane solution was analyzed directly by VPC.[8]

Reactions on a preparatory scale were done at higher alkene concentrations with an amount of hypohalite sufficient to consume 50–80% of the alkene. Cooling was needed for large-scale reactions. In a typical large-scale reaction, 1.7 mL of cyclohexene (16 mmol) in 54 mL of CCl_4 was treated with 15 mL of a 0.55 M solution of CH_3OBr in CCl_4 (8.2 mmol) followed at once by 1 mL of boron trifluoride etherate. The reaction mixture was worked up with water (the yield of fluoro bromide (**6**) was 42% by VPC). The solvent was evaporated to a volume of 15 mL, distilled to a volume of 3 mL, and chromatographed on 10 g of thin-layer-grade silica gel contained in a small scintered funnel. Elution with pentane under suction yielded most of the fluorobromide (free from bromo ether) in the first two 25-mL fractions. Distillation of the pentane yielded 0.29 g of **6** (20% yield).

Products from Cyclohexene (3). Products from the reaction of **1** with **3** were separated on column A (73 °C) with retention times as follows (min): **4**, 8.4; **5**, 18.2. Product compositions and yields were found directly by NMR after solvent removal. Samples isolated by preparative VPC were identified as follows. **4**: bp 72 °C (42 mm) [lit.[9] bp 71–2 °C (42 mm)]; NMR (agreement with lit.).[10] **5**: bp 181–4 °C (760 mm) [lit.[11] bp 59–60 °C (10 mm)], calcd (760 mm) bp 180 °C; $n^{20}{}_D$ 1.4640 [lit.[11] $n^{20}{}_D$ 1.4680]; NMR (agreement with lit.).[11]

Analysis of products from the reaction of **2** with **3** was accomplished by VPC on column C (90 °C) with retention times (min) as follows: **6**, 9.3, and **7**, 15.5. Products were identified as follows. **6**: bp 67–70 °C (14 mm) [lit.[5] bp 76–8 °C (16 mm)]; $n^{20}{}_D$ 1.4813 [lit.[12] $n^{20}{}_D$ 1.4830]; NMR δ 1.0–2.6 (br m, 8, $(CH_2)_4$), 4.03 (m, 1, CHbr), 4.43 (m, 1, CHF, $J_{H\text{-}F}$ = 49.5). **7**:[13] IR, 2820 cm^{-1} (CH_3O); NMR δ 3.38 (s, 3, CH_3O), 3.78–4.20 (m, 1, CHBr).

Products from 1-Hexene (8). Products from the reaction of **1** with **8** were separated on column A (73 °C) with retention times as follows (min): **9**, 7.8; **11**, 15.8; and **10**, 15.8. Product compositions and yields were found directly by NMR after solvent removal. Samples isolated by preparative VPC were identified as follows. **9**: bp 148 °C (760 mm) [lit.[5] bp 58–60 °C (45 mm)], calcd (760 mm) bp 143–5 °C; NMR δ 0.93 (t, 3, CH_3) 1.1–2.3 (br m, 6, $(CH_2)_3$), 3.55 (dd, 2, CH_2Cl, $J_{H\text{-}F}$ = 17.3, J_{12} = 5.4 Hz); 4.53 (d of pentets, 1, CHF, $J_{H\text{-}F}$ = 52, J_{12} = 5.4 Hz); **10** and **11**, NMR agreed with that of the mixture of **10** and **11** obtained from chlorination of **8** in methanol.[14]

Products from the reaction of **2** with **8** were separated on column C (70 °C) with retention times (min) as follows: **12**, 9.5; **14**, 14.4; and **13**, 16.6. Product compositions and yields were determined by VPC. Compounds were isolated by preparative VPC and identified as follows. **12**: NMR (data agreed with lit.[15]). **13** and **14**: identified[16] by NMR and IR.

Products from *trans*-1,2-Dichloroethylene (15). Products from the reaction of **1** with **15** were separated on column A (73 °C) with retention times (min) as follows: **16**, 2.6; **17**, 9.8. Product compositions and yields were found directly by NMR after evaporation of solvent. Samples isolated by preparative VPC were identified as follows. **16**: bp 101–104 °C (760 mm) [lit.[17] bp 101–103 °C]; NMR δ 5.68 (m, 1, $CHCl_2$), 6.16 (dd, 1, CHF, $J_{H\text{-}F}$ = 45.2, J_{12} = 4.2 Hz). **17**: bp 170–5 °C (760 mm) [lit.[18] bp 50.5 °C (9 mm)], calcd bp 172 °C (760 mm); $n^{20}{}_D$ 1.4735 [lit.[18] $n^{20}{}_D$ 1.4722]; NMR δ 3.62 (s, 3, CH_3O), 5.50 (d, 1, $CHOCH_3$, J = 4.0 Hz), 5.73 (d, 1, $CHCl_2$, J = 4.0 Hz).

Products from Methyl Acrylate (18). Products from the reaction of **1** with **18** were separated on column A (60 °C) with retention times as follows (min): **19**, 5.0; **21**, 11.4; and **20**, 15.2. Product compositions and yields were determined directly by NMR after evaporation of solvent. Compounds were isolated by preparative VPC. The NMR identification of **19** has been described.[3a] Evidence for the structures of **20** and **21** will be described elsewhere.[19]

Products from the reaction of **2** with **18** were separated on column A (90 °C) with retention times as follows: **22**, 5.1; **24**, 13.2; and **23**, 18.2. Product composition and yields were determined by VPC. Compounds were isolated by preparative VPC and identified as follows. **22**: NMR spectrum was identical with the published spectrum.[20] **23** and **24**: NMR spectra agreed with reported values,[12] except that we observed the absorption of the methine proton for **23** at δ 3.86–4.05 instead of at δ 4.30 as reported.

Products from Methyl Crotonate (25) and Methyl Isocrotonate (29). Products from the reaction of **1** with **25** and **29** were separated on column A (75 °C) with retention times (min) as follows: **26**, 9.0; **30**, 12.6; **28**, 20.4; **27**, 21.8; **31** and **32**, 28.8. Product compositions and yields were obtained by VPC, except that the ratios between the regioisomers (**27**:**28** and **31**:**32**) were established by VPC collection of each as a mixture followed by NMR analysis. Compounds were isolated by preparative VPC. Structures of the fluoro chlorides (**26** and **30**) were established previously.[3a] Structural evidence for the methoxy chlorides will be given elsewhere.[19]

Products from Butadiene (33). Products from the reaction of **1** with **33** were separated on column C (40 °C) with retention times as follows (min): **34**, 4.2; **36**, 6.4; **35**, 10.7; and **37**, 22.4.

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(8) Our observations all indicate that the product mixtures obtained from these alkenes are kinetically controlled. For example, the erythro and threo fluorides (**26** and **30**) were obtained from methyl crotonate (**25**) and methyl isocrotonate (**29**) without a mixture of isomers. Other work that we have done with the 1-phenylpropenes (to be published at a later date) provides further evidence for product stability. *cis*- and *trans*-1-Phenylpropene reacted with CH_3OCl/BF_3 to give different mixtures of erythro and threo chlorofluorides; i.e., the reactions occured with considerable stereoselectivity. The composition of each reaction mixture did not change upon standing in contact with BF_3 over the period of more than an hour. Since the products are benzylic fluorides, they should be more sensitive to isomerization than would the products from other alkenes reported here.

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Product analysis and yields were obtained by VPC. Compounds were isolated by preparative VPC and identified as follows. **34**: NMR δ 3.53 (dd, 2, CH_2Cl, J_{H-F} = 16.2, J_{34} = 5.5 Hz), 4.98 (d of d of t, 1, CHF, J_{H-F} = 46, J_{34} = 5.5, J_{23} = 4.5 Hz), 5.13–6.07 (m, 3, $CH{=}CH_2$). Anal. Calcd for C_4H_6ClF: C, 44.26; H, 5.57; F, 17.50. Found: C, 44.27; H, 5.56; F, 18.62. **35**: NMR δ 3.90–4.20 (m, 2, CH_2Cl), 4.88 (dd, 2, CH_2F, J_{H-F} = 45, J_{34} = 4.0 Hz), 5.77–6.18 (m, 2, CH=CH); additional evidence for the structure of **35** was obtained by its independent synthesis from *trans*-1,4-dichloro-2-butene and potassium fluoride.[21] Anal. Calcd for C_4H_6ClF: C, 44.26; H, 5.57; F, 17.50. Found: C, 44.38; H, 5.40; F, 14.06. **36** and **37**: NMR (agreement with lit.—see Heasley et al.[2a]).

Products from the reaction of **2** and **33** were separated on column B (40 °C) with retention times as follows (min): **38**, 1.5; **39**, 3.0; **30**, 4.1; and **41**, 10.4. Analysis and yields were obtained by VPC. Compounds were isolated by preparative VPC and identified as follows. **38**: NMR δ 3.43 (dd, 2, CH_2Br, J_{H-F} = 16.2, J_{34} = 5.5 Hz), 4.98 (d of d of t, 1, CHF, J_{H-F} = 45, J_{34} = 5.5, J_{23} = 4.5 Hz), 5.20–6.23 (m, 3, $CH{=}CH_2$). Anal. Calcd for C_4H_6BrF: C, 31.40; H, 3.95; F, 12.42. Found: C, 31.52; H, 3.95; F, 11.79. **39** NMR δ 3.8–4.0 (m, 2, CH_2Br), 4.83 (dd, 2, CH_2F, J_{H-F} = 45.0, J_{34} = 4.0 Hz), 5.75–6.12 (m, 2, CH=CH). The structure of the compound was further confirmed by its independent synthesis from *trans*-1-4-dibromo-2-butene and potassium fluoride.[21] Anal. Calcd for C_4H_6BrF: C, 31.40; H, 3.95; F, 12.42. Found: C, 30.58; H, 3.96; F, 11.01. **40**: IR (agreement with lit.[22] for CH_3O and $CH{=}CH_2$); NMR δ 3.33 (s, 3, CH_3O), 3.18–4.02 (multiplets, 3, $CHOMeCH_2Br$), 5.08–6.08 (m, 3, $CH{=}CH_2$). **41**: IR (agreement with lit.[22] for CH_3O and CH=CH); NMR δ 3.25 (s, 3, CH_3O), 3.75–4.07 (m, 4, CH_2Br and CH_2OMe), 5.73–6.07 (m, 2, CH=CH).

Products from Methyl Vinyl Ketone (42). Products from the reaction of **1** with **42** were reported on column A (70 °C) with retention times as follows (min): **43**, 4.8; and **44**, 9.6. Product compositions and yields were found directly by NMR after solvent removal. Samples isolated by preparative VPC were identified as follows. **43**: NMR δ 2.36 (s, 3, CH_3) and 5.3–3.9 (complex multiplet, 3, CH_2FCHCl); IR, 1732 cm^{-1} (C=O); further proof of the structure was obtained by elimination with triethylamine, which formed only 3-chloro-3-butene-2-one; elemental analysis was not possible because the compound darkened quickly at room temperature. **44**: n^{20}_D 1.4368, lit.[23] n^{20}_D 1.4368; NMR δ 2.11 (s, 3, $CH_3C{=}O$), 3.20 (s, 3, CH_3O), 3.52 (d, 1, CH_2OCH_3, J_{34} = 5.6), 4.02 (t, 1, CHCl, J_{34} = 5.6 Hz); IR, 1721 (C=O); treatment with triethyl amine caused no elimination, showing that the chlorine was exclusively in the β position.

Products from Styrene (45). Products from the reaction of **1** with **45** were separated on column C (120 °C) with retention times as follows (min): **48**, 9.9; **46**, 15; and **47**, 17. Compounds were isolated by preparative VPC and identified by comparison of NMR spectra to those reported (**46**,[10] **47**,[24] and **48**[25]). Products from the reaction of **2** with **45** were separated on column B (100 °C) with retention times as follows (min): **49**, 4.2; and **50**, 7.2. Compounds were isolated by a combination of liquid chromotography on silica gel and preparative VPC. The structure of **49** was confirmed by preparation of an authentic sample and comparison of the NMR spectra. The NMR spectrum of **50** agreed with the reported spectrum.[26]

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Synthesis of Sugars by Aldolase-Catalyzed Condensation Reactions[1]

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Dihydroxyacetone phosphate was prepared in 200-mmol scale from dihydroxyacetone by two procedures: reaction with phosphorus oxytrichloride and glycerol kinase catalyzed phosphorylation using ATP with in situ regeneration of ATP by phosphoenolpyruvate or acetyl phosphate. Dihydroxyacetone phosphate was converted to fructose 6-phosphate in 80% yield by exposure to a mixture of co-immobilized triosephosphate isomerase and aldolase followed by acid hydrolysis of the condensation product fructose 1,6-bisphosphate. Fructose 6-phosphate was subsequently converted by chemical and enzymatic schemes into fructose, glucose 6-phosphate, and glucose. Practical procedures are described for the preparation of D- and L-glyceraldehyde 3-phosphate and for several hexoses labeled with ^{13}C in the C-2 and C-2,5 positions.

Introduction

The work reported in this manuscript is part of a program to evaluate the potential of aldolase-catalyzed aldol reactions as a route to isotopically labeled and uncommon sugars on scales from 0.01 to 1 mol. The aldolase used in this work (from rabbit muscle, E.C. 4.1.2.13) is commercially available. It is inexpensive, and it has high specific activity and good stability. It requires dihydroxyacetone phosphate (DHAP)[2] as one substrate, but will accept a

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