vinyl ketone took place in this homogeneous system with no change in the optical yield. This modification, therefore, will allow the use of Michael acceptors that are not compatible with hydroxide bases.[9]

In summary, we have demonstrated a chiral catalytic process for the addition of MVK to indanone **1** which takes place in excellent chemical yield and up to 80% ee for the *S* enantiomer and 52% ee for the *R* enantiomer.

Experimental Section

Assays for Optical Purity. Assays for optical purity were obtained by chiral liquid chromatography. A poor separation of the enantiomers **2** was obtained on a Pirkle covalent *l*-leucine column (Regis Chemical) with 0.75% isopropyl alcohol in hexane. However, base line resolution of the diastereomeric ketals formed from **2** and (2*R*,3*R*)-(−)-2,3-butanediol[10] was obtained on a Pirkle ionic phenylglycine column with 88:12:0.5 hexane/chloroform/isopropyl alcohol, flow rate of 2 mL/min, UV detector at 254 nm. Retention times *S* enantiomer, 5.8 min; *R* enantiomer, 6.2 min.

Confirmation of the ee was obtained by NMR chiral shift studies on the enantiomeric mixture **2** with an equal weight (29 mol %) of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium (III) derivative. The shift was observed in the methyl group adjacent to the carbonyl with the *S* enantiomer shifting to lower field relative to the *R* enantiomer.

Catalysts. Catalysts **4** and **7** are commercially available from Chemical Dynamics Corporation, South Plainfield, NJ. Catalyst **5** was prepared from cinchonidine and 3,4-dichlorobenzyl chloride in refluxing THF. The reduced catalysts **6** and **8** were prepared by hydrogenation of **5** and **7**, respectively, at 40 psi with 10% Pt/C in methanol. Catalyst **9** was prepared from **7** on an ion-exchange resin.

Chiral Methyl Vinyl Ketone Additions. Preparation of 6,7-Dichloro-2,3-dihydro-5-methoxy-2-(3-oxobutyl)-2-propyl-1*H*-inden-1-one. Three sets of conditions were employed for the Michael additions: (1) liquid/liquid phase-transfer conditions using toluene/50% NaOH, (2) liquid/solid phase-transfer conditions using toluene/KOH pellets, and (3) homogeneous conditions using a solution of the preformed catalytic species. Liquid/solid conditions were equally effective as liquid/liquid in most cases and more convenient for large-scale work. Homogeneous conditions will allow the use of base-sensitive Michael acceptors and will facilitate the investigation of low-temperature reactions. All reactions were carried out under a nitrogen atmosphere.[11] The reaction was monitored by LC. Two systems have been developed for this purpose. Normal phase: μ-Porasil, 2:1 hexane/ethyl acetate, 2 mL/min, 300 nm, $t_r(1)$ = 2.7 min, $t_r(2)$ = 8.3 min. Reverse phase: Altex, Ultrasphere IP, 65:35 CH_3CN/H_2O with 0.1% H_3PO_4, 1.5 mL/min, 300 nm, $t_r(1)$ = 8.0 min, $t_r(2)$ = 6.5 min.

Liquid/Liquid Phase-Transfer System. The catalyst, dihydro-[*p*-(trifluoromethyl)benzyl]cinchonidinium bromide (**8**) (0.5 g, 0.9 mmol) followed by 25 mL of 50% aqueous NaOH, was added to a solution of 6,7-dichloro-2,3-dihydro-5-methoxy-2-propyl-1*H*-inden-1-one (**1**) (2.73 g, 10 mmol) in 70 mL of toluene. The mixture was stirred at 25 °C, and a solution of methyl vinyl ketone (0.72 g, 10 mmol)[12] in 30 mL of toluene was added dropwise over 0.5 h. The reaction was stirred for 5 min after the completion of the addition, and the reaction was shown to be complete by LC. The organic layer was separated and washed with 50 mL of 1 N HCl: LC assay, 93 wt % yield. An aliquot, removed and derivatized as the (2*R*,3*R*)-(−)-2,3-butanediol ketal,[10] assayed at 52% ee, the *R* enantiomer predominating. The toluene solution was dried over Na_2SO_4 and filtered and the solvent removed in vacuo to yield 3.3 g: ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (3 H, d, *J* = 7.3 Hz, $CH_2CH_2CH_3$), 1.00–1.30 (2 H, m, $CH_2CH_2CH_3$), 1.56 (2 H, m, CH_2CH_2CO), 1.89 (2 H, m, $CH_2CH_2CH_3$), 2.09 (3 H, s, $COCH_3$), 2.35 (2 H, m, CH_2CH_2CO), 2.90 (2 H, AB, indanone CH_2), 3.99 (3 H, s, OCH_3), 6.85 (1 H, s, Ar H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 17.6, 30.0, 30.8, 37.5, 38.4, 39.5, 52.7, 56.9, 106.6, 123.0, 126.5, 131.7, 154.6, 160.9, 205.4, 208.1. Anal. Calcd for $C_{17}H_{20}Cl_2O_3$: C, 59.49; H, 5.87; Cl, 20.66. Found: C, 59.36; H, 5.92; Cl, 20.60

Liquid/Solid Phase-Transfer System. The catalyst, dihydro(3,4-dichlorobenzyl)cinchonidinium chloride (**6**) (10 g, 0.020 mol) and 40 g of KOH pellets were added to a solution of indanone **1** (100 g, 0.366 mol) in 2.5 L of toluene. A solution of methyl vinyl ketone (26.17 g, 0.366 mol) in 100 mL of toluene was added over 10 min. The reaction was stirred at 25 °C and monitored by LC to completion (1.5 h). The solid KOH was filtered and washed with 200 mL of toluene. The combined organics were washed with 1 L of 1 N HCl: assayed as above, 92 wt % yield, 40% ee.

Homogeneous System. The catalyst, dihydro(3,4-dichlorobenzyl)cinchonidinium chloride (**6**) (0.5 g) was partitioned between 60 mL of toluene and 25 mL of 50% aqueous NaOH with vigorous stirring, under N_2, for 30 min.[13] The layers were allowed to settle, and the toluene layer was removed by syringe to a clean, dry, N_2-flushed flask containing indanone **1** (2.73 g, 0.010 mol). Methyl vinyl ketone was added (0.72 g, 0.010 mol) and the reaction stirred for 30 min until complete as determined by LC. The reaction mixture was washed with 50 mL of 1 N HCl: assayed as above, 94 wt % yield, 40% ee.

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Registry No. (±)-**1**, 101375-36-4; (*S*)-**2**, 104833-01-4; (*R*)-**2**, 101165-85-9; **4**, 95088-20-3; **5**, 104778-30-5; **6**, 104761-86-6; **7**, 101311-12-0; **8**, 104761-87-7; **9**, 104761-88-8; MVK, 78-94-4; (2*R*,3*R*)-(−)-$H_3CCH(OH)CH(OH)CH_3$, 24347-58-8; cinchonidine, 485-71-2; 3,4-dichlorobenzyl chloride, 102-47-6.

(9) Work in our laboratories has been carried out with methyl and ethyl acrylate as Michael acceptors. Under phase-transfer conditions, saponification of the esters was competitive with Michael addition.

(10) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183. van Leusen, D.; Rouwetts, P. H. F. M.; van Leusen, A. M. *J. Org. Chem.* **1981**, *46*, 5159.

(11) Under phase-transfer conditions the indanone **1** can air oxidize to the 2-hydroxy compound.

(12) Use of excess MVK in the phase-transfer reactions led to over reaction products. In the homogeneous system, however, there is only a catalytic amount of base and excess MVK may be used.

(13) This reaction should not be prolonged since decomposition of the catalyst does take place under these conditions.

Cleavage of Methoxymethyl Ethers with BCl_3. A Convenient, Versatile Preparation of Chloromethyl Ether Derivatives

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In conjunction with our ongoing program directed toward the synthesis of potential reactivators of organophosphorous inhibited acetylcholinesterase,[1] we required a series of chloromethyl ethers **1** which were to be used to quaternize various oxime derivaties. Although the classical procedure for preparing type **1** compounds (eq 1)[2] generally

$$ROCH_2Cl$$
1, R = alkyl, aralkyl

(1) Bedford, C. D.; Harris, R. N., III; Howd, R. A.; Miller, A.; Nolen, H. W., III, *J. Med. Chem.* **1984**, *27*, 1431.

(2) (a) Henry, L. *Bull. Cl. Sci., Acad. R. Belg.* **1893**, *25*, 439. (b) Wedekind, E. German Patent 135 310, 1902. (c) Wedekind, E. *Ber.* **1903**, *36*, 1383. (d) Walker, J. F.; Chadwick, A. F. *Ind. Eng. Chem.* **1947**, *39*, 974. (e) Clark, F. E.; Cox, S. F.; Mack, E. *J. Am. Chem. Soc.* **1917**, *39*, 712. (f) Hill, A. J.; Keach, D. T. *J. Am. Chem. Soc.* **1926**, *48*, 257. (g) Kursanov, D. N.; Setkina, V. N. *J. Appl. Chem.* USSR (*Engl. Transl.*) **1943**, *16*, 36.

0022-3263/86/1951-4711$01.50/0

works well with most primary and secondary alcohols, we have encountered many cases in which the only isolable product from this procedure was the formal derivative of the starting alcohol (i.e., $ROCH_2OR$). In most of these

$$ROH + HCHO \xrightarrow[-H_2O]{\text{dry HCl}} [RO^+{=}CH_2] \xrightarrow{Cl^-} ROCH_2Cl \quad (1)$$

problem cases, attempts to suppress this undesirable side reaction by performing the reaction under higher solvent dilution were unsuccessful. A further deficiency of reaction 1 which we, as well as others,[2f,3] have noted is that the reaction works poorly with most benzylic alcohols and generally fails completely with tertiary alcohols. The main reaction products in these cases result from acid-catalyzed electrophilic substitution of Cl^- for OH^-. We therefore sought a new procedure for the preparation of compounds **1** which would avoid the use of protic acids and provide a general route to the above-mentioned, previously inaccessible chloromethyl ether derivatives.

The route initially examined was based on the recent report of the preparation of *tert*-butyl chloromethyl ether via the free radical chlorination of *tert*-butyl methyl ether with *N*-chlorosuccinimide.[3] Unfortunately, in our hands this procedure gave erratic results, and we were never able to obtain more than 70% conversion of *tert*-butyl methyl ether to *tert*-butyl chloromethyl ether as evidenced by NMR analysis of numerous attempts.[4] Since this procedure would also have been of limited utility for our needs, we considered alternate means.

The second possibility investigated, which proved to be more versatile, made use of known acetal chemistry. For almost a century it has been known that acetals undergo acid-catalyzed cleavage in the presence of acetic anhydride to yield hemiacetal esters.[5] Recently, the regioselectivity of this reaction in unsymmetrical cyclic acetals was reported.[6] Even more useful for our purposes was the previous report of the preparation of α-chloroalkyl ethers via the reaction of acetals with boron trichloride.[7] These previous examples of electrophilic cleavage of acetals suggested to us that a viable route to novel chloromethyl ethers might be realized starting from methoxymethylated alcohols (MOM ethers).

To investigate this possibility, we initially examined the regioselectivity of various electrophiles toward reaction with *tert*-butyl MOM ether. Upon treating an equimolar mixture of acetyl chloride and *tert*-butyl MOM ether (**2a**) in dichloromethane with catalytic zinc chloride[6] at room temperature, there resulted an exothermic reaction with total consumption of starting materials. Proton NMR analysis of the crude reaction mixture revealed an approximate 1:1 mixture of *tert*-butyl chloromethyl ether (**1a**) and chloromethyl methyl ether with signals also present corresponding to methyl acetate and *tert*-butyl acetate (eq 2). Although reaction had occurred smoothly, there was unfortunately no regioselectivity. Other electrophilic

$$\underset{\mathbf{2a}}{(CH_3)_3COCH_2OCH_3} + AcCl \xrightarrow{ZnCl_2} \underset{\mathbf{1a}}{(CH_3)_3COCH_2Cl} + CH_3OCH_2Cl + MeOAc + t\text{-}BuOAc \quad (2)$$

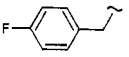
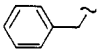
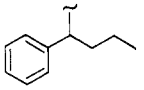
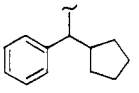
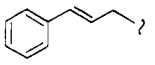
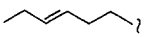
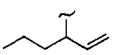
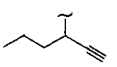
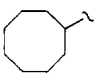
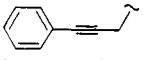
reagents such as oxalyl chloride, phosgene, and chlorotrimethylsilane were subsequently found to give little or no improvement in product distribution and to be much less reactive. In contrast to the above reagents, phosphorous pentachloride was found to react with **2a** to give exclusively **1a** with no detectable amount of chloromethyl methyl ether as evidenced by NMR. Even though we subsequently found PCl_5 to be a very efficient reagent for converting other MOM ethers to their corresponding chloromethyl ethers with good regioselectivity, the production of $POCl_3$ in the reactions often made purification of the desired product difficult and time-consuming. We therefore turned to a previous report by Black and Landor[7] in which they described the reaction of boron trichloride with symmetrical acetals to give α-chloroalkyl ethers. Although these workers reported good yields from this procedure, they made no mention of preparing simple chloromethyl ethers nor did they report the regioselectivity of BCl_3 toward reaction with unsymmetrical acetals. More recently, the use of various alkylboron halide derivatives as efficient reagents for the cleavage of MOM, MEM, and MTM ethers to their respective alcohols has been reported.[8] The intermediacy of halomethyl ethers in these cleavage reactions has been convincingly demonstrated by Guindon et al.[8a,b,9a] and exploited by him and others for the preparation of various α-substituted ethers.[9] We were therefore pleased to find, after treating benzyl MOM ether at 0 °C in pentane with 0.33 molar equiv of BCl_3, followed by warming to room temperature and stirring for 1 to 2 h, that benzyl chloromethyl ether and chloromethyl methyl ether were formed in the ratio of 3:1, respectively, as evidenced by NMR. Unlike the reaction with PCl_5, however, the major observable byproduct was trimethylborate which could be easily removed by concentration of the mixture under reduced pressure. Therefore, with BCl_3 as the reagent of choice to affect MOM ether cleavage, we extended the aforementioned conditions to the preparation of other chloromethyl ethers, many of which we were unable to prepare by way of reaction 1. The results of this effort are tabulated in Table I, which contains several examples worthy of further comment. It should be noted that most of the yields in Table I are distilled yields and that the yields of MOM ethers were not optimized.

The procedure appears to work exceptionally well for the preparation of both secondary and tertiary alkyl chloromethyl ethers and in this respect complements reaction 1. Indeed, we have found that cleavage of tertiary alkyl MOM ethers with BCl_3 normally gives a quantitative conversion to the corresponding *tert*-alkyl chloromethyl ether and even though these rather unstable derivatives are difficult to isolate pure without extensive decomposition, we have in certain cases obtained good distilled yields of product (entries n and o, Table I). Another notable example of the utility of this procedure is seen in entry h. The attempted preparation of acylic homoallylic chloromethyl ethers from homoallylic alcohols via reaction 1 has been reported[10] to give mostly the corresponding

(3) Pinnick, H. W.; Lajis, N. H. *J. Org. Chem.* **1978**, *43*, 3964.
(4) It has been brought to our attention by one of the reviewers that others have reported similar difficulties in obtaining useful yields of *tert*-butyl chloromethyl ether by the free radical chlorination of *tert*-butyl methyl ether with NCS. Colombo, R.; Colombo, F.; Jones, J. H. *J. Chem. Soc., Chem. Commun.* **1984**, 292.
(5) (a) Claisen, L. *Chem. Ber.* **1898**, *31*, 1010. (b) Hughes, W. B.; Kleene, R. D. *J. Am. Chem. Soc.* **1954**, *76*, 5161. (c) Akiyoshi, S.; Okuno, K. *J. Am. Chem. Soc.* **1954**, *76*, 693. (d) Keith, D. D.; Tortora, J. A.; Yang, R. *J. Org. Chem.* **1978**, *43*, 3711. (e) Nordlander, J. E.; Catalane, D. B.; Kotian, K. D.; Stevens, R. M.; Haky, J. E. *J. Org. Chem.* **1981**, *46*, 778. (f) Petrakis, K. S.; Fried, J. *Synthesis* **1983**, 891.
(6) Bailey, W. F.; Rivera, A. D. *J. Org. Chem.* **1984**, *49*, 4958.
(7) Black, D. K.; Landor, S. R. *J. Chem. Soc.* **1965**, 5225.
(8) (a) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912. (b) Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969. (c) Williams, D. R.; Sakdarat, S. *Tetrahedron Lett.* **1983**, *24*, 3965.
(9) (a) Morton, H. E.; Guindon, Y. *J. Org. Chem.* **1985**, *50*, 5379. (b) Corey, E. J.; Hua, D. H.; Seitz, S. P. *Tetrahedron Lett.* **1984**, *25*, 3.

Table I. Selected Data for MOM Ethers 2 and Chloromethyl Ethers 1

$$ROH \xrightarrow{NaH} RONa \xrightarrow{CH_3OCH_2Cl} \underset{\mathbf{2}}{ROCH_2OCH_3} \xrightarrow{BCl_3} \underset{\mathbf{1}}{ROCH_2Cl} + B(OCH_3)_3$$

		MOM ether 2			chloromethyl ether 1		
entry	R	% yield	bp °C (torr)	^{1}H NMR[a]	% yield[b]	bp, °C (torr)	^{1}H NMR[a]
a		21	101–105 (760)	4.78 (s, 2 H), 3.40 (s, 3 H), 1.27 (s, 9 H)	99[c] (0)		5.63 (s, 2 H), 1.33 (s, 9 H)
b		70	55 (0.4)	7.50–6.90 (m, 4 H), 4.73 (s, 2 H), 4.58 (s, 2 H), 3.42 (s, 3 H)	41 (0)	57–59 (0.1)	7.53–7.03 (m, 4 H), 5.55 (s, 2 H), 4.73 (s, 2 H)
c		77	80–84 (6)	7.40 (s, 5 H), 4.73 (s, 2 H), 4.63 (s, 2 H), 3.43 (s, 3 H)	75[c] (30)		7.43 (s, 5 H), 5.57 (s, 2 H), 4.80 (s, 2 H)
d		74	74–75 (0.2)	7.30 (s, 5 H), 4.53 (s, 2 H), 4.56 (t, J = 6.0 Hz, 1 H), 3.37 (s, 3 H), 2.00–1.00 (m, 4 H), 1.10–0.80 (m, 3 H)	81[d]	65–67 (0.15)	7.33 (s, 5 H), 5.50 and 5.13 (AB q, J = 5.0 Hz, 2 H), 4.77 (t, J = 5.5 Hz, 1 H), 2.15–1.10 (m, 4 H), 0.95 (m, 3 H)
e		65	107 (0.15)	7.38 (s, 5 H), 4.53 (s, 2 H), 4.34 (d, J = 8.0 Hz, 1 H), 3.40 (s, 3 H), 2.60–1.00 (m, 9 H)	60[d]	90–99 (0.1)	7.28 (s, 5 H), 5.53 and 5.12 (AB q, J = 5.5 Hz, 2 H), 3.85 (d, J = 8.0 Hz, 1 H), 2.73–0.85 (m, 9 H)
f		61	92–94 (0.25)	7.38 (br s, 5 H), 6.90–6.00 (m, 2 H), 4.70 (s, 2 H), 4.36–4.10 (m, 2 H), 3.40 (s, 3 H)	50[d] (0)	84–93 (0.1)	7.43 (s, 5 H), 7.06–5.93 (m, 2 H), 5.58 (s, 2 H), 4.35 (d, J = 6.0 Hz, 2 H)
g		36	108–110 (760)	5.03–4.87 (m, 2 H), 4.70 (s, 2 H), 4.01 (s, 2 H), 3.43 (s, 3 H), 1.80 (s, 3 H)	45 (0)	75–78 (120)	5.57 (s, 2 H), 5.10 (m, 2 H), 4.16 (s, 2 H), 1.77 (s, 3 H)
h		56	85 (50)	5.33–5.63 (m, 2 H), 4.67 (s, 2 H), 3.53 (t, J = 6.0 Hz, 2 H), 3.37 (s, 3 H), 1.73–2.50 (m, 4 H), 0.97 (t, J = 6.0 Hz, 3 H)	67[d]	84–85 (25)	5.56 (s, 2 H), 5.37–5.70 (m, 2 H), 3.77 (t, J = 7.0 Hz, 2 H), 1.77–2.57 (m, 4 H), 1.00 (t, J = 6.0 Hz, 3 H)
i		41	68–70 (50)	6.05–5.00 (m, 3 H), 4.72 and 4.52 (AB q, J = 6.5 Hz, 2 H), 4.00 (m, 1 H), 3.40 (s, 3 H), 1.73–1.16 (m, 4 H), 0.94 (br t, 3 H)	74[d]	74–75 (35)	6.00–5.10 (m, 3 H), 5.46 (m, 2 H), 4.18 (m, 1 H), 2.00–1.00 (m, 4 H), 1.15–0.54 (br t, 3 H)
j		57	70–75 (45)	5.00 and 4.65 (AB q, J = 6.5 Hz, 2 H), 4.75–4.16 (m, 1 H), 3.40 (s, 3 H), 2.45 (d, J = 2.5 Hz, 1 H), 2.00–1.25 (m, 4 H), 1.20–0.80 (t, 3 H)	31[d] (<31)	77–80 (45)	5.70 and 5.60 (AB q, J = 5.0 Hz, 2 H), 4.70–4.30 (m, 1 H), 2.52 (d, J = 2.5 Hz, 1 H), 2.00–1.20 (m, 4 H), 1.20–0.70 (t, 3 H)
k		31	67–70 (78)	4.67 (s, 2 H), 3.41 (d, J = 7.0 Hz, 2 H), 3.38 (s, 3 H), 1.43–0.77 (m, 1 H), 0.75–0.13 (m, 4 H)	66[d] (0)	53–55 (63)	5.60 (s, 2 H), 3.57 (d, J = 7.0 Hz, 2 H), 1.33–0.76 (m, 1 H), 0.75–0.06 (m, 4 H)
l		27	55–56 (60)	4.63 (s, 2 H), 4.40–3.90 (m, 1 H), 3.40 (s, 3 H), 2.57–1.07 (m, 6 H)	64[d] (0)	80–82 (105)	5.52 (s, 2 H), 4.32 (m, 1 H), 2.60–1.30 (m, 6 H)
m		55	53–55 (0.1)	4.65 (s, 2 H), 3.33 (s, 3 H), 3.93–3.50 (br m, 1 H), 2.00–1.30 (m, 14 H)	89 (16)	64 (0.2)	5.57 (s, 2 H), 3.90 (m, 1 H), 2.00–1.10 (m, 14 H)
n		52	41–47 (75)	4.93 (s, 2 H), 3.43 (s, 3 H), 2.47 (s, 1 H), 1.53 (s, 6 H)	51 (0)	59–64 (70)	5.83 (s, 2 H), 2.82 (s, 1 H), 1.60 (s, 6 H)
o		51	48–58 (5)	4.73 (s, 2 H), 3.36 (s, 3 H), 1.20 (s, 6 H), 0.97 (s, 9 H)	60[d]	33–37 (0.25)	5.65 (s, 2 H), 1.27 (s, 6 H), 0.91 (s, 9 H)
p		47	58–62 (5.5)	4.73 (s, 2 H), 3.38 (s, 3 H), 2.00–1.30 (m, 8 H), 1.33 (s, 3 H)	15	36 (1)	5.61 (s, 2 H), 2.20–1.50 (m, 8 H), 1.41 (s, 3 H)
q		81	103–105 (45)	7.15 (m, 5 H), 5.22 (s, 2 H), 3.53 (s, 3 H)	0 (0)		
r		62	89–90 (0.15)	7.70–7.20 (m, 5 H), 4.85 (s, 2 H), 4.52 (s, 2 H), 3.47 (s, 3 H)	13[c]		7.70–7.20 (m, 5 H), 5.63 (s, 2 H), 4.85 (s, 2 H)
s	$CF_3(CF_2)_2CH_2$—	38	53–55 (105)	4.67 (s, 2 H), 4.00 (t, J = 12 Hz, 2 H), 3.36 (s, 3 H)	0 (0)		

[a] 60 MHz in $CDCl_3$ solvent. Shift values are reported in δ units relative to tetramethylsilane. [b] Refers to the distilled yield from the immediate precursor **2**. Numbers in parentheses refer to the yield obtained by the literature procedure.[2] [c] Yield is based on NMR analysis of the reaction mixture. [d] Previously unreported compound. Satisfactory analytical data (±0.4) was obtained for the salt resulting from quaternization of 2-[(hydroxyimino)methyl]-1-methylimidazole with the chloromethyl ether.

tetrahydropyran derivatives resulting from intramolecular electrophilic cyclization. The one example of this type which we report here presented no problem, and we were able to obtain a respectable yield of the homoallylic chloromethyl ether **1h**. These results, along with similar results from our laboratories with other homoallylic MOM ethers, are particularly interesting in view of the recent publication by Thompson et al.,[11] in which they report exclusive, highly stereoselective tetrahydropyran formation from the $TiCl_4$-mediated reaction of homoallylic MEM and ethyl vinyl ether acetals. Our procedure appears to be very useful for the preparation of chloromethyl ether derivatives of small, strained carbocyclic alcohols (entries k and l) which gave mostly formal products (i.e., $ROCH_2OR$) via reaction 1. Benzylic chloromethyl ethers are also conveniently prepared by this procedure and are generally obtained in better yield than by literature methods[2] (entries b–e). Finally, the last three entries in Table I list examples in which the procedure either failed or worked poorly. In these last examples, cleavage of the MOM ether occured with undesired regioselectivity and gave mostly or exclusively chloromethyl methyl ether.

In conclusion, the cleavage of MOM ethers with BCl_3 provides a convenient, versatile route to chloromethyl ether derivatives. The procedure complements existing methodology in that it avoids the use of protic acid and provides a route to chloromethyl ether derivatives previously unobtainable via the classical route 1.

Experimental Section

All proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM 360 spectrometer in either chloroform-*d* or carbon tetrachloride solvent with shift values reported in δ units relative to tetramethylsilane as internal reference. All starting alcohols for the preparation of the MOM ethers were commercially available materials and were used as purchased. Tetrahydrofuran was distilled from benzophenone ketyl before use. All other solvents were reagent grade. **Caution**: Chloromethyl ethers are powerful alkylating agents and potentially carcinogenic. Due care should be exercised when working with these materials.

General Procedure for the Preparation of MOM Ethers 2. The following general procedure was used to prepare all MOM ethers.

To a stirring suspension of NaH (0.11 mol, free from oil) in 100 mL of dry THF under N_2 was added the alcohol (0.10 mol) dropwise in 20 mL of THF. The mixture was then stirred until hydrogen evolution had subsided and then heated at reflux for 2 h. After the mixture was cooled in an ice bath, there was then added chloromethyl methyl ether (0.10 mol, Aldrich) dropwise, the ice bath removed, and stirring continued at room temperature for a minimum of 1 h. The mixture was then filtered through Celite and the solvent removed either by distillation through a Vigreux column at atmospheric pressure or by rotary evaporation depending on the volatility of the product. The MOM ethers were then purified by distillation (see Table I).

General Procedure for the Preparation of Chloromethyl Ethers 1. The following general procedure was used to prepare the chloromethyl ethers **1** from their corresponding MOM ethers **2**.

To an ice-cooled, stirring mixture of the MOM ether (0.06 mol) in pentane or dichloromethane (35 mL) was added a solution of 1 M BCl_3 in hexanes (20 mL, 0.02 mol, Aldrich). After being stirred in the cold for 15 min, the mixture was then warmed to room temperature and allowed to stir for 2 h. Proton NMR analysis after this time usually indicated complete reaction. The mixture was then concentrated under reduced pressure, and the chloromethyl ether derivatives were purified by distillation (see Table I).

(10) Colonge, J.; Boisde, P. *Bull. Soc. Chim. Fr.* **1956**, 824.
(11) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275.

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Registry No. **1a**, 40556-01-2; **1b**, 104620-66-8; **1c**, 3587-60-8; **1d**, 104620-67-9; **1e**, 104620-68-0; **1f**, 104620-69-1; **1g**, 58558-40-0; **1h**, 104620-70-4; **1i**, 104620-71-5; **1j**, 104620-72-6; **1k**, 104620-73-7; **1l**, 104620-74-8; **1m**, 58567-17-2; **1n**, 55812-22-1; **1o**, 104620-75-9; **1p**, 104620-76-0; **1r**, 90331-98-9; **2a**, 24209-75-4; **2b**, 104620-55-5; **2c**, 31600-55-2; **2d**, 91764-46-4; **2e**, 104620-56-6; **2f**, 91970-13-7; **2g**, 90344-72-2; **2h**, 104620-57-7; **2i**, 104620-58-8; **2j**, 104620-59-9; **2k**, 104620-60-2; **2l**, 104620-61-3; **2m**, 42604-11-5; **2n**, 17869-83-9; **2o**, 104620-62-4; **2p**, 104620-63-5; **2q**, 824-91-9; **2r**, 104620-64-6; **2s**, 104620-65-7; *p*-$FC_6H_4CH_2OH$, 459-56-3; $PhCH(OH)CH_2CH_2CH_3$, 614-14-2; $PhCH{=}CHCH_2OH$, 104-54-1; $CH_2{=}C(CH_3)CH_2OH$, 513-42-8; $CH_3CH_2CH{=}CHCH_2CH_2OH$, 544-12-7; $CH_3CH_2CH_2CH(OH)CH{=}CH_2$, 4798-44-1; $CH_3CH_2CH_2CH(OH)C{\equiv}CH$, 105-31-7; $CH{\equiv}CC(CH_3)_2OH$, 115-19-5; $(CH_3)_3CC(CH_3)_2OH$, 594-83-2; $PhC{\equiv}CCH_2OH$, 1504-58-1; $CF_3CF_2CF_2CH_2OH$, 375-01-9; $(CH_3)_3COH$, 75-65-0; $PhCH_2OH$, 100-51-6; C_6H_5OH, 108-95-2; CH_3OCH_2Cl, 107-30-2; BCl_3, 10294-34-5; cyclobutanol, 2919-23-5; cyclooctanol, 696-71-9; α-cyclohexybenzyl alcohol, 4397-01-7; (hydroxymethyl)cyclopropane, 2516-33-8; 1-methylcyclopentanol, 1462-03-9.

Palladium-Catalyzed Cyanation of Aryl Halides by Trimethylsilyl Cyanide[1]

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Among the various methods available for the synthesis of aryl cyanides, the most convenient one is that based on the displacement of aromatic bromides or iodides by cyanide anion. It is well-known that the stoichiometric reaction of aryl halides with Cu(I)CN gives corresponding cyanides.[2] The catalytic reaction of aryl halides with KCN (or NaCN) in the presence of a palladium complex at elevated temperatures affords aryl cyanides in good to excellent yields.[3] Nickel complexes have also been found effective for cyanation of aryl halides.[4] In recent years, trimethylsilyl cyanide, Me_3SiCN (1), has been widely used in organic synthesis as a useful reagent for cyanation.[5] In this paper, we describe a new synthetic method for aryl cyanides based on a palladium-catalyzed reaction of aryl halides with **1** (eq 1).[6]

$$\text{Ar-I} \xrightarrow[\text{Pd catalyst}]{\text{Me}_3\text{SiCN}} \text{Ar-CN} \qquad (1)$$

(1) Transition Metal Catalyzed Reaction of Me_3SiCN. 4. For the previous paper in this series, see: Chatani, N.; Hanafusa, T. *Tetrahedron Lett.*, **1986**, *27*, 4201.
(2) Newman, M. S.; Phillips, D. K. *J. Am. Chem. Soc.* **1959**, *81*, 3667. Friedman, L.; Shecter, H. *J. Org. Che.* **1961**, *26*, 2522. Bacon, R. G. R.; Hill, H. A. *J. Chem. Soc.* **1964**, 1097. House, H. O.; Fisher, W. F. *J. Org. Chem.* **1969**, *34*, 3626.
(3) (a) Sekiya, A.; Ishikawa, N. *Chem. Lett.* **1975**, 277. (b) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298. (c) Dalton, J. R.; Regen, S. L. *J. Org. Chem.* **1979**, *44*, 4443.
(4) Cassar, L. *J. Organomet. Chem.* **1973**, *54*, C57. Favero, G.; Gaddi, M.; Morvillo, A.; Turco, A. *Ibid.* **1978**, *149*, 395. Favero, G.; Morrillo, A.; Turo, A. *Ibid.* **1978**, *162*, 99. Cassar, L.; Foa, M.; Montanari, F.; Marinell, *Ibid.* **1979**, *173*, 335.
(5) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1981. Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. Magnus, P.; Sarkar, T.; Djuric, S. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: New York, 1982; Vol. 7.

0022-3263/86/1951-4714$01.50/0