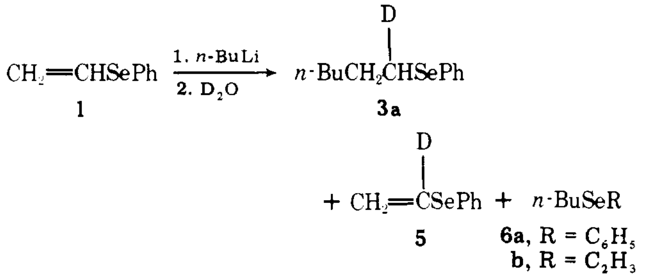
Table II. Solvent–Temperature Effects for the Reaction of *n*-BuLi with 1[a]

solvent	temp, °C	% products[b] 3a	5^c	6
$(CH_3O)_2CH_2$	0	97	3	0
Et_2O	0	90	10	0
Et_2O	−78	55	15^d	0
THF	0	70	20	10
THF	−78	5	15	80

[a] All reactions were 0.1 M in 1 and utilized 1.2 equiv of *n*-BuLi; after 1 h the reactions were quenched with excess D_2O. [b] Determined by VPC on 5 ft × ¼ in. 1.5% OV 101 on 100/120 Chromosorb G column. In all cases, mass balance was >80%. [c] Deuterium incorporation verified by NMR. [d] Amount of 5 estimated by NMR; unreacted 1 accounted for the remainder of the mass.

Scheme II



$$CH_2{=}CHSePh \xrightarrow[2.\ D_2O]{1.\ n\text{-BuLi}} n\text{-BuCH}_2\overset{D}{C}HSePh + CH_2{=}\overset{D}{C}SePh + n\text{-BuSeR}$$

1, 3a, 5, 6a, R = C_6H_5; b, R = C_2H_3

solvent and temperature effects are crucial, with dimethoxymethane or diethyl ether at 0 °C providing the best results in preliminary studies involving the addition of *n*-BuLi to 1 followed by quenching with D_2O (Table II). Related solvent effects have been previously observed for the reaction of alkyllithiums with alkenes, and, although complex, may be related to the state of aggregation of the alkyllithium reagent.[11]

We are currently investigating the use of vinyl phenyl selenides as synthons in a number of other reactions; these results will be reported in due course.

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(7) (a) Reaction of vinyl phenyl selenoxide with *n*-BuLi or *n*-Bu_2CuLi led to products resulting from carbon–selenium bond cleavage. (b) We have been unable to effect addition of methyllithium to **1**.

(8) (a) All new compounds were fully characterized by spectroscopic methods. Yields are given for chromatographically pure, isolated products. (b) A typical experimental procedure for the preparation of (*E*)-2-methyl-3-octen-2-ol (**4g**) follows. A solution of vinyl phenyl selenide (**1**) (305 mg, 1.67 mmol) in freshly dried (CaH_2) dimethoxymethane (1.5 mL) was added over 10 min to a solution of *n*-BuLi (2.4 M in hexane, 0.83 mL, 2.0 mmol) in dimethoxymethane (5.0 mL) at 0 °C under an atmosphere of argon. The clear solution was stirred at 0 °C for 1 h, cooled to −78 °C, and a solution of acetone (145 mg, 2.5 mmol) in THF (2.0 mL) was added over 10 s, and stirring was continued at −78 °C for 1 h. The reaction mixture was quenched with aqueous NH_4Cl, extracted with ether, and dried ($MgSO_4$), and the solvents were removed in vacuo to give crude 2-methyl-3-phenylseleno-2-octanol (**3g**), which was dissolved in CH_2Cl_2 (15 mL), cooled to −78 °C, and ozonized[5e] for 5 min. Diisopropylamine (1 mL)[4g] and CCl_4 (25 mL) were added, the mixture was refluxed for 30 min, the solvents were removed in vacuo, and the residue was purified on silica gel (20 g) with hexane–ether to give (*E*)-2-methyl-3-octen-2-ol as a clear liquid (117 mg, 50% overall from **1**): ^1H NMR (CCl_4) δ 0.70–2.20 (m) and 1.25 (s) [total 15 H], 2.75 (bs, 1 H, OH), 5.58 (m, 2 H). (c) Additional ^1H NMR data (CCl_4): **3a** δ 0.70–1.90 (m, 12 H), 2.85 (t, J = 6 Hz, 1 H), 7.10–7.60 (m, 5 H); **3b** δ 0.70–1.90 (m) and 1.34 (d, J = 7 Hz) [total 14 H], 3.20 (m, 1 H), 7.05–7.80 (m, 5 H); **3d** δ 0.70–2.10 (m, 11 H), 4.41 (t, J = 6 Hz, 1 H, $-CH(SePh)_2$), 7.10–7.70 (m, 10 H); **3e** δ 0.08 (s, 9 H), 0.67–1.75 (m, 11 H), 2.30 (t, J = 6 Hz, 1 H, $-CH(SePh)SiMe_3$), 7.00–7.60 (m, 5 H); **3f** δ 0.68–1.80 (m, 11 H), 3.30 (m) and 3.51 (bs) [total 2 H], 4.51 (d, J = 8 Hz, 1 H, PhC**H**(OH)CH<), 7.15–7.70 (m, 10 H); **3g** δ 0.70–2.00 (m), 1.28 (s) and 1.44 (s) [total 17 H], 2.80 (bs, 1 H), 3.18 (m, 1 H), 7.20–7.80 (m, 5 H); **3j** δ 0.92 (d, J = 7 Hz, 6 H), 1.12–1.98 (m, 4 H), 2.87 (t, J = 7 Hz, 1 H), 7.10–7.62 (m, 5 H); **3k** δ 0.75 (d, J = 7 Hz), 0.97 (d, J = 7 Hz), 1.21 (s), 1.33 (s), and 1.40–2.00 (m) [total 14 H], 2.72 (bs, 1 H), 3.15 (m, 1 H), 7.06–7.74 (m, 5 H); **3m** δ 0.88 (s, 9 H), 1.50 (m, 2 H), 2.83 (t, J = 9 Hz), 7.10–7.58 (m, 5 H); **4f** δ 0.70–1.65 (m, 7 H), 2.06 (m, 2 H), 2.88 (bs, 1 H), 5.04 (m, 1 H), 5.61 (m, 2 H), 7.20–7.42 (m, 5 H); **4h** δ 0.70–1.65 (m) and 1.57 (s) [total 9 H], 2.00 (m, 2 H), 5.47 (d of t, J = 14 and 5 Hz), 5.68 (d, J = 14 Hz) [total 2 H], 7.16–7.60 (m, 5 H); **4i** δ 0.70–1.80 (m, 7 H), 2.38 (m, 2 H), 6.95 (m, 2 H), 7.32–8.10 (m, 5 H); **4j** δ 0.98 (d, J = 7 Hz, 6 H), 1.26 (s, 6 H), 1.91 (m, 1 H), 2.42 (bs, 1 H), 5.53 (m, 2 H).

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Template Synthesis of Macromolecules. Selective Functionalization of an Organic Polymer

Summary: Hydrolysis of a copolymer of divinylbenzene and bis(vinylbenzyl) *trans*-1,2-cyclobutanedicarboxylate liberates polymer-bound benzyl alcohol groups; rebinding studies and chemical transformations of the benzyl alcohol groups suggest that the functional groups are capable of retaining some stereochemical information originally present in the cyclobutane diester.

Sir: The ability to selectively introduce organic functionality in fixed geometrical relationships has remained a longstanding challenge to chemists. A variety of ingenious approaches have been employed to accomplish this goal.[1] A technique recently developed by Wulff and co-workers[2] strikes us as having the

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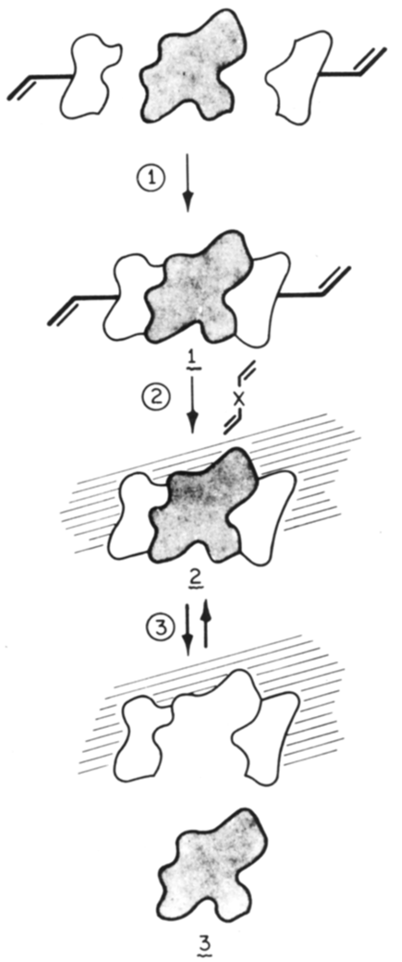
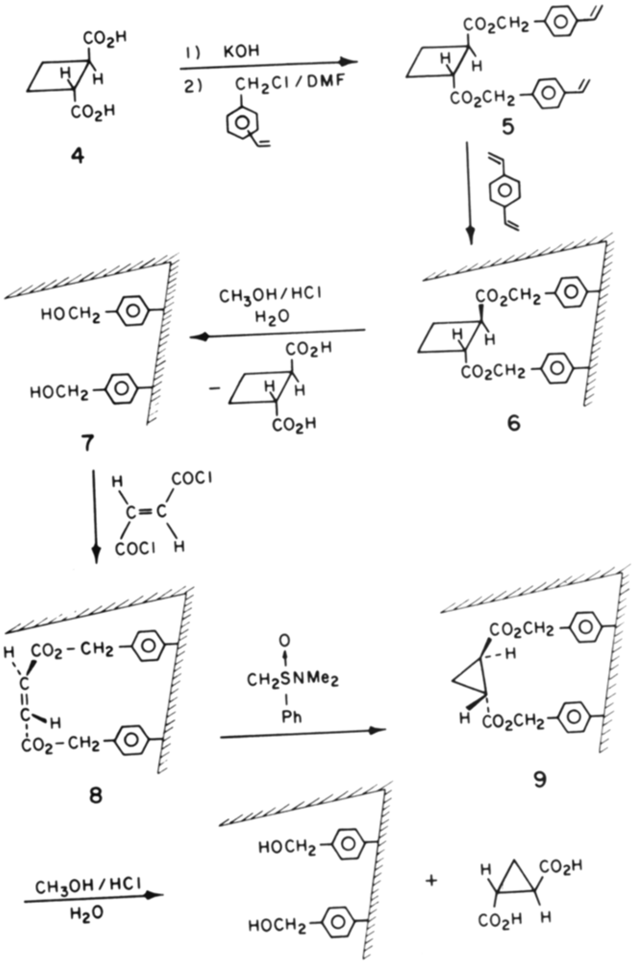
Scheme I



Scheme II



potential to be one of the more general methods for the controlled introduction of multiple organic functionality in organic polymers. The technique, which we term the template synthesis method, is illustrated in Scheme I. A template assembly (**1**), synthesized from three difunctional subunits (step 1), is copolymerized with a large excess of cross-linking monomer (step 2). Polymerization results in the formation of a three-dimensional polymeric matrix interspaced by an occasional template assembly (**2**). Hydrolysis of accessible template assemblies (step 3) liberates the incipient functionality to produce regions of multiple functionality on the macromolecule (**3**). Provided that the hydrolysis (step 3) does not introduce gross structural deformations in the macromolecule, the hydrolyzed polymer can exhibit a "memory" for the original template molecule (T).

We wish to describe a sequence of experiments that employs the template synthesis method to introduce masked organic functionality in a macromolecular solid. Conditions have been developed that permit the liberation of these functional groups and in subsequent reactions this functionality is utilized to covalently bind an organic substrate molecule to the macromolecular solid. Further chemical transformations on the covalently bound substrate molecule provide an opportunity to probe the local environment of the functionality. The overall series of reactions is illustrated in Scheme II.

Bis(vinylbenzyl) *trans*-1,2-cyclobutanedicarboxylate (**5**), prepared from the dipotassium salt of *trans*-1,2-cyclobutanedicarboxylic acid and vinylbenzyl chloride (mixture of meta and para isomers), is copolymerized under free-radical conditions with divinylbenzene (technical, 55% para, meta isomers) in acetonitrile (0.05:0.49:0.46, w/w/w)[3]. The resulting solid (**6**) is crushed and sized (75–250 μm), extracted with CH_3OH (to remove unreacted monomer), and dried in vacuo. The IR of this polymer exhibits the expected superimposition of the spectra of the diester $\bar{\nu}_{C=O}$ 1736 cm^{-1}) over that of poly(divinylbenzene). A variety of conditions were examined to effect the hydrolysis of dicarboxylic acid (**4**) from the polymer; optimum yields were obtained by refluxing in methanol–HCl (1:1) under a nitrogen atmosphere. After 8 h approximately 30% of the total template assemblies had undergone hydrolysis. Prolonged exposure to the reaction conditions did not appreciably increase this yield. The hydrolyzed polymer (**7**) contains 0.064 mequiv of sites/g; each site contains two polymer-bound benzyl alcohol groups. The presence of these functional groups is verified by treatment of **7** with trifluoroacetic anhydride; the resulting polymer exhibits a new IR absorption at 1788 cm^{-1} (trifluoromethylacetate group); control reactions with unhydrolyzed polymer did not produce this new absorption.[4]

Reaction of hydrolyzed polymer with difunctional reagents of similar geometry to the original template molecule can lead to two-point rebinding. Treatment of **7** with fumaryl chloride results in covalent attachment of the fumarate group to the polymer. The rebinding occurs by formation of new ester linkages between the polymer and the fumarate group. This rebinding can be monitored by examining the change in intensity in the carbonyl region of the polymer before and after exposure to fumaryl chloride. The individual carbonyl absorptions of polymer-bound fumaric and cyclobutanedicarboxylic acid esters are not resolved; nevertheless, upon treatment of **7** with fumaryl chloride the expected increase in carbonyl intensity is observed. That fumaric acid is *covalently bound* to the polymer is established by the finding that the acid can only be liberated by a second hydrolysis

(CH_3OH–HCl); the quantity of fumaric acid recovered indicates that 80% of the available sites in 7 have covalently bound the new template molecule.[5]

The sequence of transformations serves to illustrate several important points. The fractional recovery of template molecules (30%), even after prolonged hydrolysis, establishes that a significant number of template assemblies occupy inaccessible regions of the polymer. Unlike Merrifield polymers which, at least in their swollen state, undergo reaction throughout the polymer network,[6] hydrolysis occurs largely in the region that may be loosely defined as the surface of a solid polymer particle. This finding is undoubtedly a consequence of the higher degree of cross-linking in poly(divinylbenzene). Second, the uptake of fumaryl chloride is approximately equal to the theoretical number of *difunctional* sites and suggests that, at least in a significant number of cases, rebinding can occur in a manner similar to that which was found in the original polymer (two site).

The region in which the hydrolysis and rebinding occur is rather poorly defined. The area is at the interface between solvent phase and the highly cross-linked "nucleus" of the solid poly(divinylbenzene). Located in this region are pendant polymer and vinyl groups, template assemblies, rebinding sites, and more lightly cross-linked segments of the polymer.[7] If the hydrolyzed polymer is to exhibit a "memory" for the template molecule (T), the template assembly must "imprint" stereochemical information at the polymerization stage. Our first test for this "memory" is illustrated in Scheme II. The sequence involves at the penultimate step a methylene transfer to a prochiral alkene (fumaric acid) covalently bound to the macromolecule. When racemic template (**5**) is used for the polymer synthesis, racemic cyclopropanedicarboxylic acid would be the product from the methylenation step; however, when a chiral template is used for the polymer synthesis the "memory" can take the form of local asymmetry in the region of the functional groups; this asymmetry may induce formation of a chiral product in the methylenation step. The polymer-bound fumaric ester (**8**) was reacted with methylene transfer reagents to form 1,2-cyclopropanedicarboxylic acid ester (**9**). This transformation was successfully executed using (dimethylamino)phenyloxosulfonium methylide as the nucleophilic methylene transfer reagent.[8] Synthetic cyclopropanedicarboxylic acid is liberated by hydrolysis in 34% overall yield based upon available sites of the hydrolyzed polymer (**7**).

The preceding sequence was repeated using (−)-*trans*-1,2-cyclobutanedicarboxylic acid ($[\alpha]^{25}{}_D$ −158.7° (CH_3OH)) as the template.[9] After hydrolysis, rebinding of fumaryl chloride, cyclopropanation, and hydrolysis, *trans*-1,2-cyclopropanedicarboxylic acid was recovered as the dimethyl ester by preparative VPC. The diester exhibited a specific rotation, $[\alpha]^{21}{}_D$ 0.1°, which corresponds to a 0.05% enantiomeric excess.[10] The slight enantiomeric excess arises in the methylene transfer step and is the result of a chiral environment (of some unspecified nature) surrounding the reaction zone. Considering the severity of the hydrolysis conditions, the observed asymmetric induction is encouraging. Work is continuing in an effort to understand those factors which will influence the magnitude of asymmetric induction and to define the degree of stereochemical control available by the template synthesis approach.

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(3) The polymerization conditions result in the formation of an insoluble, highly porous (macroreticular) polymer with an average surface area of 200 m^2/g.

(4) Development of analytical procedures and detection of nonspecific reactions with the polymer was facilitated by a parallel series of reactions performed with a "blank" polymer; that is, one prepared in an identical manner only without template assemblies.

(5) In our idealized representation (Scheme II) we have assumed that two-point rebinding reconnects two functional groups that were previously connected by a template assembly (intersite) as opposed to two "unrelated" functional groups (intrasite). At present we have no evidence to confirm this assumption. Additional studies are underway to distinguish between these possibilities.

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Lithiation of Ethyl 2,4,6-Triisopropylbenzoate Adjacent to Oxygen: The α-Lithioalkyl Alcohol Synthon

Summary: Metalation of ethyl 2,4,6-triisopropylbenzoate (**1**) with *sec*-butyllithium/tetramethylethylenediamine in tetrahydrofuran provides α-lithioethyl 2,4,6-triisopropylbenzoate (**2**). Reaction of **2** with carbonyl and halide electrophiles provides the expected products **3a–g**. Reduction of typical products with lithium aluminum hydride gives the corresponding alcohols. Overall this sequence provides the α-lithioalkyl alcohol synthon from a primary alcohol.

Sir: The formation and use of α-heteroatom carbanions has been widely explored and exploited in recent years. In conjunction with our studies of prospectively dipole-stabilized carbanions, we have reported metalations adjacent to the heteroatom of methyl 2,4,6-triisopropylbenzoate, methyl and ethyl 2,4,6-trialkylthiobenzoates, and methyl- and ethyl-2,4,6-triisopropylbenzamides.[1,2] The metalations of the ester and thioesters have been shown to be key steps in providing the α-lithiomethyl alcohol and the α-lithiomethyl and α-lithioethyl thiol synthons, respectively. More recently Seebach et al. have observed similar metalations of 2,4,6-trialkylbenzoate derivatives and also have shown that dimethyltriphenylacetamide provides the (α-lithiomethyl)alkylamine synthon.[3] We now wish to report that ethyl 2,4,6-triisopropylbenzoate can be metalated adjacent to oxygen and to suggest that this approach will provide α-lithioalkyl alcohol synthons for the corresponding primary alcohols.

Reaction of ethyl 2,4,6-triisopropylbenzoate (**1**) with 2–4 equiv of *sec*-butyllithium/tetramethylethylenediamine (*s*-BuLi/TMEDA) in tetrahydrofuran (THF) at −78 °C for 3–6