Allylic Sulfones in Solid-Phase Synthesis: Preparation of Cyclobutylidenes

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Polymer-bound allyl sulfones (cf. **9**) were utilized in geminal cycloalkylations with epichlorohydrin to generate a *cis*-phenylsulfonylcyclobutanol derivative (cf. **11**) in one step. In the final step of this solid-phase synthetic sequence, cuprate, organomolybdenum, and organopalladium reagents were screened to obtain an optimal protocol for "traceless" cleavage of cyclobutylidene products from the resin. Among these, palladium-catalyzed allylic alkylation was the most efficient. In addition, highly regioselective nucleophilic attack at the less hindered terminus of the allyl fragment (i.e., overall S_N2' sulfinate displacement) was observed. Cyclobutylidene diversification was demonstrated by incorporating different allylic substituents, *O*-functionalizations, and *C*-nucleophiles to prepare a demonstration library of eight cyclobutylidene derivatives (i.e., derivatives of **4**) in four steps and 30−38% overall yield from lithium polystyrene/divinylbenzene sulfinate.

Introduction

The construction of small organic molecules on polymer support,[1] which generally proceeds by chemical modification of insoluble resins[2,3] (solid-phase organic synthesis, SPOS),[4] has allowed organic chemists to generate a wide variety of compound classes with high efficiency. An important continuing objective in SPOS is the development of strategies and chemistries applicable to combinatorial techniques, but where reactions are not limited by the tether and where the target can be efficiently cleaved from the resin by a specialized reagent or transformation. In this regard, one of our goals has been to examine new tethering strategies for the attachment of small-molecule building blocks to insoluble resins and to explore new applications of these tethers in SPOS.[5] We recently reported the preparation of a sulfinate-functionalized resin[6] from styrene/2% divinylbenzene copolymer beads (PS/DVB = ●). Subsequent conversion of this resin to solid-phase allyl sulfone **1** followed by copper-mediated Grignard displacement of sulfinate[7] delivered trisubstituted olefin **2**.[6]

Herein, we report modification of this chemistry to accommodate cyclobutane formation by sulfone dianion alkylation[8] and subsequent "traceless" resin release[9] by a palladium-catalyzed S_N2' sulfinate displacement.[10] The resulting cyclobutanes may prove useful as a molecular scaffold for library production[11] as cyclobutane-containing compounds are both prevalant in nature and useful as building blocks for further transformations.[12] The conversion of sulfinate-functionalized resin **3** to cyclobutylidene **4** (Scheme 1) which is presented here proceeds by a four-step procedure consisting of (i) sulfinate *S*-allylation (see Scheme 3), (ii) *C*α-sulfone α,α-dialkylation with epichlorohydrin (see Scheme 4), (iii) *O*-alkylation (or *O*-acylation) (see Scheme 5), and (iv) S_N2' sulfinate displacement with carbon nucleophiles (see Scheme 5). Reagent variation in steps i, iii, and iv has been demonstrated, and the overall protocol appears suitable for library generation.

Results and Discussion

Solution-Phase Synthesis of Cyclobutylidenol 8. With the continuing evolution of SPOS[13] comes a growing appreciation for the importance of linker technology,[14] which ideally must accommodate a wide variety of

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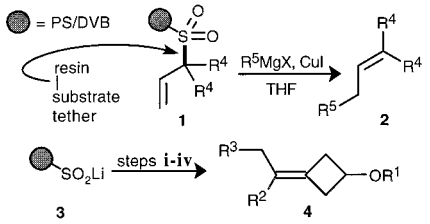
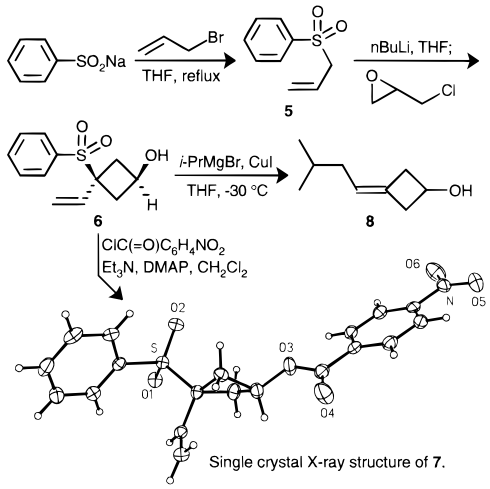
Scheme 1. Sulfone-Based SPOS Linker



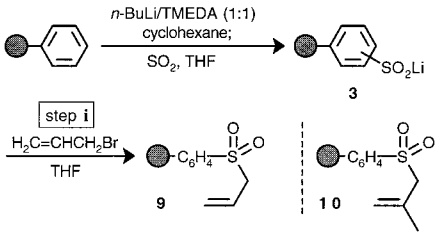
Scheme 2. Solution-Phase Sulfone α,α-Dialkylation and S_N2' Displacement



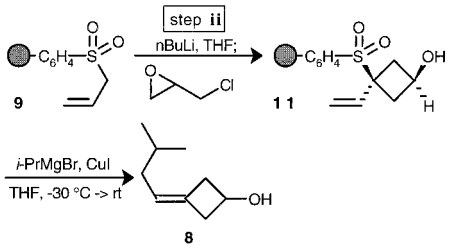
synthetic transformations and yet allow for ready product cleavage in the final solid-phase transformation. α,α-Dialkylated allyl sulfones of generalized structure **1** appear to be ideally suited for SPOS linker application where the allylic C−S bond serves as the substrate−resin tether.

Preliminary solution-phase experiments were conducted as outlined in Scheme 2. Allylation of benzenesulfinate with allyl bromide in THF furnished allyl phenyl sulfone in 85% yield. Higher yields were obtained using MeOH, but we chose to utilize solvents in these solution-phase studies that could be anticipated to swell PS/DVB so that the resulting protocol would be readily adaptable to SPOS. Lithiation[15] of allyl phenyl sulfone (**5**)[16] using *n*-BuLi and subsequent alkylation[17] with epichlorohydrin proceeded smoothly to give a single cyclobutanol product (75%) as evidenced by ^{1}H NMR. The *p*-nitrobenzoyl derivative **7** (55% yield) of this cyclobutanol was submitted for single-crystal X-ray analysis, establishing that the hydroxyl and phenylsulfonyl moieties are *cis*-arranged in **6**. Interestingly, the epoxy mesylate analogue of epichlorohydrin (i.e., −OMs replacing −Cl) gives a mixture of **6** and its hydroxyl epimer. Finally, treating allylic sulfone **6** with CuI and isopropylmagnesium chloride in THF delivered cyclobutylidenol **8** in 56% yield.

Scheme 3. Preparation of Solid-Phase Allyl Phenyl Sulfone



Scheme 4. Solid-Phase Cyclobutanol Formation (Step ii)



Preparation of Solid-Phase Allyl Phenyl Sulfone. With a solution-phase route to cyclobutylidene **8** from benzenesulfinate in hand, we turned to development of a solid-phase protocol which began with the preparation of polymer-bound benzenesulfinate. In parallel with Leznoff's strategy for PS/2% DVB functionalization,[18] commercially available PS/2% DVB copolymer (●C_6H_5) was metalated with *n*-BuLi/TMEDA (1:1 molar ratio) in cyclohexane (60 °C, 10 h) (Scheme 3). After the orange suspension of ●C_6H_4Li was washed at 0 °C with dry THF to remove excess *n*-BuLi, sulfur dioxide gas was bubbled through it, giving polymer **3** (pale yellow). The benzenesulfinate loading (1 mmol/g) of these beads was determined by titration of a THF suspension of the corresponding sulfinic acid with standardized aqueous NaOH.

S-Allylation of this benzenesulfinate was accomplished by treatment of a THF-swollen suspension of **3** with allyl bromide, giving resin-bound allyl phenyl sulfone **9**. This transformation could be monitored by FTIR [●Ar−SO_2Li (1600, 1497, 1458, 1200, 1028, 980 cm^{-1}) → ●Ar−SO_2CH_2CH=CH_2 (1600, 1492, 1452, 1320, 1139 cm^{-1})]. Other allylic alkylating agents can be used in the *S*-allylation step: for example, use of methallyl bromide in the reaction with **3** gives sulfone **10**.

Solid-Phase Synthesis of Cyclobutylidenol 8. Even though a hydroxyl moiety is introduced in **9** → **11** (Scheme 4), this α,α-dialkylation reaction proved impossible to monitor by FTIR since residual moisture after reaction workup and resin washing rendered the hydroxyl region of the IR spectrum unreliable. Therefore, the resin **11** obtained upon treatment of **9** with *n*-BuLi (8 equiv) and epichlorohydrin (10 equiv) in THF (0 °C → room temperature, 24 h) was employed without further purification in the next transformation.

In contrast to our experience with the straightforward solution-phase preparation of **8**, our efforts to effect the solid-phase variant of this reaction began with 13 unsuccessful attempted protocols for **11** → **8** consisting of various reaction temperatures and solvents as well as

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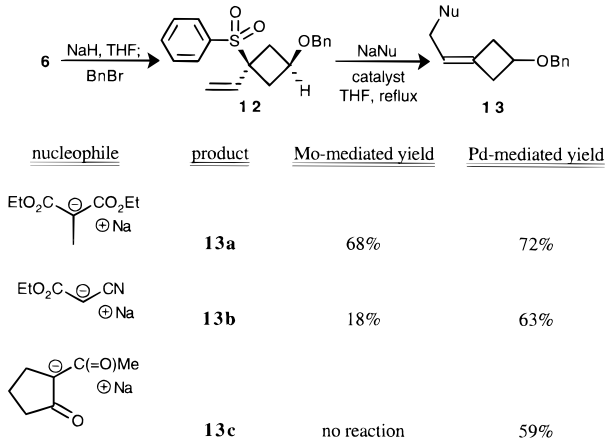
Scheme 5. Solution-Phase Mo- or Pd-Mediated S_N2' Displacement of Phenyl Sulfinate



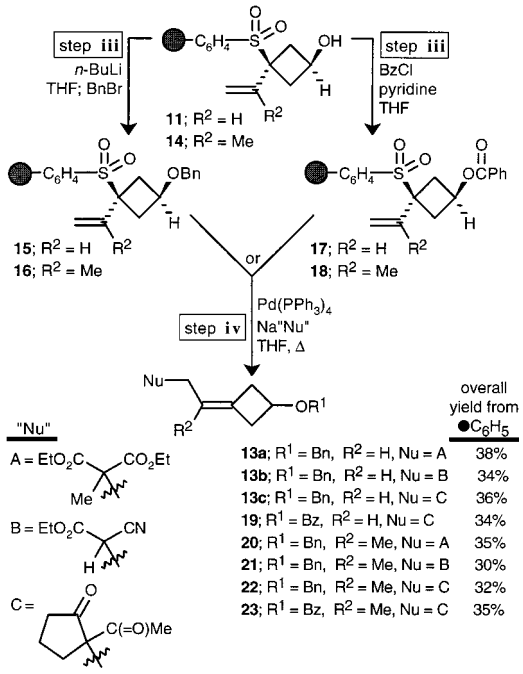
addition techniques. We were about to conclude that perhaps conversion of **9** to **11** had failed. Fortunately, in our 14th attempt, we were finally able to partially mimic solution results and isolate cyclobutylidenol **8**, albeit in low yield (~10%), by cannulating a premade cuprate solution (CuI, isopropylmagnesium chloride, THF) into THF-swollen polymer **11** at −30 °C → room temperature (stirring for 7 h).

Solution-Phase Mo- or Pd-Catalyzed S_N2' Displacement of Phenyl Sulfinate. In addition to being low yielding, we felt this release strategy (**11** → **8**) lacked generality and was also severely limited by the cleavage conditions (copper-assisted Grignard or cuprate conditions would preclude the incorporation of many electrophilic functional groups). We therefore reverted to the solution phase to investigate other metal-catalyzed allylic alkylations strategies for substrate release.

Drawing on the molybdenum $[Mo(CO)_6]$[19] and palladium $[Pd(PPh_3)_4]$[20] catalyzed allylic alkylation studies of Trost, we investigated the S_N2' sulfinate displacement reaction of cyclobutanol **6**. While the palladium-mediated transformation on this free hydroxyl-containing substrate was successful, the yield was low (30%). We found that *O*-blocked substrates not only improved the yield of this transformation, but also increased the diversity potential of the target cyclobutylidene. For example, *O*-alkylation of the hydroxyl functional group in cyclobutanol **6** (sodium hydride and benzyl bromide in THF) gave benzyl ether **12** in 95% yield, which then underwent metal-mediated conversion **12** → **13** (see Scheme 5). We found that palladium catalysis was uniformly more effective than molybdenum catalysis,[21] and in all cases, no competing S_N2 sulfinate displacement product was detected.[22]

Solid-Phase Pd-Catalyzed S_N2' Displacement of Phenyl Sulfinate. Returning to the solid phase, cyclobutanols **11** and **14** (obtained as in **9** → **11** but by

Scheme 6. Solid-Phase *O*-Functionalization (step iii) and Pd-Mediated S_N2' Displacement of Phenyl Sulfinate (Step iv)



treating resin **10** with *n*-BuLi in THF followed by addition of epichlorohydrin) were *O*-alkylated (→ **15** and **16**, respectively, *n*-BuLi in THF, BnBr) or *O*-acylated (→ **17** and **18**, respectively, BzCl/pyridine in THF). In the case of these *O*-acylations, we were pleased to obtained FTIR confirmation (an ester C═O signal was observed at 1718 cm^{-1}) that solid-phase α,α-dialkylative cyclobutanol formation (**9**/**10** → **11**/**14**) had been successful.

With these solid-phase substrates in hand, we were delighted to find that addition of the sodium salt of diethyl methylmalonate to a THF suspension of benzyl ether **15** containing 5−10 mol % $Pd(PPh_3)_4$ delivered cyclobutylidene **13a** (Scheme 6). Reaction workup consisted of addition of saturated aqueous NH_4Cl, removal of the polymer by filtration, extraction with ether, washing with brine, and drying ($MgSO_4$). This delivered the targeted cyclobutylidene contaminated primarily with excess nucleophile (neutral **A**−**C**) and triphenylphosphine. Purification by column chromatography gave **13a** in 38% overall isolated yield from $●C_6H_5$. This equates to an ~83% yield per step for sulfinate formation, *S*-allylation, α,α-dialkylation, *O*-alkylation, and S_N2' sulfinate displacement and was achieved on a scale which delivered 400 mg of **13a**.

Likewise, treatment of a THF suspension of benzoate **17** with the sodium salt of 2-acetylcyclopentanone and $Pd(PPh_3)_4$ delivered cyclobutylidene **19** in 34% overall yield, establishing that this solid-phase S_N2' sulfinate displacement transformation is mild enought to accommodate an ester moiety. In this way, reaction of **15**−**18** with the sodium salts of diethyl methylmalonate, ethyl cyanoacetate, and 2-acetylcyclopentanone and $Pd(PPh_3)_4$ in refluxing THF provided alkylation products **13a**−**c** and

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19−**23** in the yields listed in Scheme 5. In contrast to the limitation imposed when either cuprate- or copper-mediated Grignard reactions are employed in the S_N2' sulfinate displacement transformation, the mild conditions employed with catalytic $Pd(PPh_3)_4$[23] allow for diverse substrate functionality. The eight-compound demonstration library constructed in this study embraces two different *O*-functionalizations (R^1 in **4**), two different *S*-allylating reagents (R^2 in **4**), and three different nucleophiles (R^3 in **4**).

Summary

We have developed a route to cyclobutylidenes with three points of diversification (R^1, R^2, and R^3 in **4**) which incorporates two C,C bond-forming transformations (steps iii and iv). The key to successfully executing this solid-phase protocol was utilization of a palladium catalyst in the S_N2' sulfinate displacement step, which results in resin release and allows for functional diversity in the targeted cyclobutylidenes. Other experiments established complete diastereoselectivity in the cyclobutanol-forming sulfone α,α-dialkylation step. The solid-phase preparation of eight diverse cyclobutylidenes demonstrates the generality of this four-step protocol.

Experimental Section

General Procedures. All chemicals were obtained from commercial suppliers and used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light. Flash column chromatography was performed with silica (Merck, 70−230 mesh). NMR spectra (^1H at 300 MHz, ^{13}C at 75 MHz) were recorded in $CDCl_3$ solvent, and chemical shifts are expressed in parts per million relative to internal TMS. CC refers to column chromatography. Concentration refers to rotoevaporation.

Lithium PS/DVB Sulfinate (3). Cyclohexane (400 mL) was distilled directly into a flask containing PS/DVB (40 g). Under an argon atmosphere, TMEDA (60 mL, 0.4 mol) was introduced, the mixture was cooled to 0 °C with gentle stirring (overhead mechanical), and *n*-BuLi (1.6 M, 250 mL, 0.4 mol) was added. The resin changed from an off-white color to an orange color after being refluxed overnight, the resulting lithiated PS/DVB was washed with anhydrous THF (3 × 50 mL) and cooled to −78 °C, and SO_2(g) was bubbled through the THF-swollen polymer for 1 h using a fritted glass bubbler. The reaction was quenched by addition of H_2O (1 h), and the polymer was washed with THF, THF/H_2O (80:20), THF, and ether and collected by filtration. The polymer was dried in a vacuum oven overnight at 30 °C. This lithium sulfinate polymer proved to be stable and not air-sensitive: IR 1600, 1497, 1458, 1200(s), 1028(s), 980(s) cm^{-1}.

***cis*-3-Phenylsulfonyl-3-vinylcyclobutanol (6).** Allyl phenyl sulfone (**5**) (6.0 g, 30 mmol) was dissolved in THF and cooled to 0 °C, and *n*-BuLi (43 mL, 68 mmol, 1.6 M) was added dropwise with stirring for 1 h. Epichlorohydrin (3.6 g, 39 mmol) was added to the yellow solution, and the mixture was allowed to warm to room temperature for 12 h. Water was added, and the organic fraction was separated, washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil which was purified by CC (25% EtOAc in hexanes) to give **6** (5.35 g, 75%): IR ($CDCl_3$) 3469, 1446, 1284 (s), 1128(s), 1083 cm^{-1}; ^1H NMR δ 2.54−2.58 (m, 2H, J = 6.9 Hz), 2.78−2.82 (m, 2H, J = 6.9 Hz), 3.06 (s, 1H), 4.16 (t, 1H, J = 6.9 Hz), 5.03 (d, 1H, J = 17.1 Hz), 5.32 (d, 1H, J = 10.5 Hz), 5.93 (dd, 1H, J = 17.1, 10.5 Hz), 7.48−7.75 (m, 4H); ^{13}C NMR δ 135.3, 133.5, 133.7, 129.7, 128.6, 120.4, 61.2, 60.3, 38.3. Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92. Found: C, 60.41; H, 5.79.

3-(3-Methylbutylidenyl)cyclobutanol (8). Isopropylmagnesium chloride (10 mL, 20 mmol, 2.0 M in THF) was added dropwise to a suspension of CuI (0.2 g, 1.1 mmol) in THF (20 mL) at −30 °C. After 20 min, a solution of **6** (0.1 g, 0.42 mmol) in THF (10 mL) was added, and the mixture was stirred for an additional 6 h with warming to 0 °C. Saturated aqueous NH_4Cl was added, and following standard workup, cyclobutylidene **8** (30 mg, 51%) was isolated as a colorless oil after CC (17% EtOAc in hexanes): IR ($CDCl_3$) 3300, 1101 cm^{-1}; ^1H NMR δ 5.22 (m, 1H), 4.38 (m, 1H), 2.96 (m, 2H), 2.58 (m, 2H), 2.22 (s, 1H), 1.78 (m, 2H), 1.58 (m, 1H, J = 6 Hz), 0.85 (d, 6H, J = 6 Hz);^{13}C NMR δ 130.6, 121.4, 64.0, 42.2, 40.4, 37.9, 28.6, 22.3.

Allyl PS/DVB Sulfone (9). Polymer **3** (10 g) was swollen in THF (50 mL) and allyl bromide (12 mL) was added at reflux under nitrogen (24 h). The resin was collected by filtration using a medium sintered glass fritted Buchner funnel, washed with THF (2 × 15 mL), THF/H_2O (4:1, 2 × 20 mL), THF (2 × 20 mL), and ether (2 × 10 mL), and dried overnight in a vacuum oven (35 °C, 5 mmHg), affording polymer-bound allyl sulfone **9** as yellow beads: IR (single bead reflectance) 1600, 1492, 1452, 1320, 1139 cm^{-1}.

Methallyl PS/DVB Sulfone (10). Likewise, polymer **10** was prepared from lithium sulfinate polymer **3** except allylation was accomplished using 3-chloro-2-methylpropene in THF at reflux for 24 h: IR (single bead reflectance) 1600, 1497, 1450, 1317, 1150, 1129 cm^{-1}.

3-(PS/DVBsulfonyl)-3-vinylcyclobutanol (11). Polymer **9** (10 g, 10 mmol) was swollen in THF (200 mL) at 0 °C, and *n*-BuLi (50 mL, 80 mmol, 1.6 M) was added, turning the yellow suspension to dark orange. An excess of epichlorohydrin (9.44 g, 102 mmol) was added slowly over 30 min, and the reaction was stirred at room temperature for 24 h. The reaction was quenched with aqueous HCl (1 N, 20 mL), and polymer **11** was filtered out and washed with THF (2 × 20 mL), THF/H_2O (4:1, 2 × 25 mL), THF (2 × 20 mL), and ether (2 × 10 mL) and dried overnight in a vacuum oven (35 °C, 5 mmHg): IR (single bead reflectance) 1600, 1492, 1452, 1294, 1132 cm^{-1}.

Benzyl 3-(Phenylsulfonyl)-3-vinylcyclobutyl Ether (12). Benzyl bromide (0.6 g, 3.5 mmol) was added to a solution of NaH (1 g, 25 mmol, 60% in mineral oil) and **6** (0.83 g, 3.5 mmol) in THF at −20 °C, and the mixture was stirred for 3 h. When no starting material could be visualized by TLC, saturated aqueous NH_4Cl was added, and the organic layer was extracted with ether, dried over $MgSO_4$, and concentrated. The crude product was purified by CC (33% EtOAc in hexanes) to give **12** (1.09 g, 95%) as a yellow solid: IR ($CDCl_3$) 1446, 1303, 1139, 908 cm^{-1}; ^1H NMR δ 2.31−2.37 (m, 2H, J = 9.0, 6.0 Hz), 2.82−2.89 (m, 2H, J = 9.0, 6.0 Hz), 3.88 (t, 1H, J = 9 Hz), 4.38 (s, 2H), 5.00 (d, 1H, J = 18 Hz), 5.27 (d, 1H, J = 12 Hz), 5.88 (dd, 1H, J = 12, 18 Hz), 7.21−7.77 (m, 10H); ^{13}C NMR δ 137.5, 135.6, 133.4, 129.4, 128.2, 128.5, 127.5, 120.2, 70.1, 66.3, 59.6, 35.4. Anal. Calcd for $C_{19}H_{20}O_3S$: C, 69.48; H, 6.14. Found: C, 69.42; H, 6.17.

Diethyl (2-(3-Benzyloxycyclobutylidene)ethyl)methylmalonate (13a). A suspension of diethyl methylmalonate (290 mg, 1.7 mmol) and NaH (66 mg, 1.65 mmol, 60% in mineral oil) in toluene (8 mL) was stirred for 40 min at 0 °C. The resulting mixture was then added to a solution of **12** (180 mg, 0.55 mmol) and $Mo(CO)_6$ (21 mg, 0.08 mmol, 15 mol %) in toluene (8 mL). The reaction was refluxed for 22 h and monitored by TLC. After neutralization with saturated aqueous NH_4Cl, the reaction mixture was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by CC (25% EtOAc in hexanes) to give **13a** (130 mg, 68%) as a clear oil: IR (neat) 1727(s), 1240, 1197, 1103 cm^{-1}; ^1H NMR δ 1.21 (t, 6H, J = 9 Hz); 1.35 (s, 3H), 2.25 (d, 2H, J = 7.5 Hz), 2.59 (m, 2H), 2.81 (m, 2H), 4.04 (t, 1H, J = 6 Hz), 4.15 (q, 4H, J = 9 Hz), 4.43 (s, 2H), 5.12 (m, 1H), 7.32 (m, 5H); ^{13}C NMR δ 171.4, 137.7, 134.8, 127.9, 127.3, 127.2, 115.9, 69.9, 68.8, 60.6, 53.3, 39.0, 37.2, 34.5, 19.3, 13.6. Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 70.04; H, 7.86.

(23) (a) Schurer, S.; Blechert, S. *Synlett* **1998**, 166−8. (b) Flegelová, Z.; Pátek, M. *J. Org. Chem.* **1996**, *61*, 6735−8.

Under similar solution-phase conditions, but employing Pd(PPh$_3$)$_4$ (80 mg, 0.07 mmol, 5 mol %) as catalyst and THF as solvent, **12** (500 mg, 1.5 mmol) and diethyl methylmalonate (923 mg, 5.3 mmol) gave **13a** (380 mg, 72%). Solid-phase preparation from polymer **15** (3.0 g), diethyl methylmalonate (2.83 g, 16 mmol), and Pd(PPh$_3$)$_4$ (170 mg, 0.15 mmol, 5 mol %) in THF (reflux, 2 d) gave **13a** (400 mg, 38% overall yield from polymer **3**).

Ethyl (2-(3-benzyloxycyclobutylidene)ethyl)cyanoacetate (13b). The solution-phase, Mo(CO)$_6$-catalyzed preparation of **13a** was modified as follows: **12** (180 mg, 0.55 mmol), ethyl cyanoacetate (190 mg, 1.7 mmol), NaH (66 mg, 1.65 mmol, 60% in mineral oil), dry toluene (16 mL), Mo(CO)$_6$ (25 mg, 0.09 mmol, 17 mol %), and CC (17% EtOAc in hexanes) gave **13b** (30 mg, 18%) as a clear oil: IR (neat) 1750(s), 1202, 1103, 1026 cm^{-1}; ^{1}H NMR δ 1.20 (t, 3H, J = 9.4 Hz), 2.42 (t, 2H, J = 6 Hz), 2.59 (m, 2H), 2.83 (m, 2H), 3.39 (q, 1H, J = 6.3 Hz), 4.01 (t, 1H, J = 6.6 Hz), 4.14 (q, 2H, J = 9.4 Hz), 4.36 (s, 2H), 7.24 (m, 5H); ^{13}C NMR δ 165.5, 137.7, 137.3, 128.2, 127.6, 127.5, 116.2, 115.1, 70.3, 68.8, 62.8, 39.2, 37.5, 37.4, 29.1, 13.8. Anal. Calcd for C$_{18}$H$_{21}$O$_3$N: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.11; H, 7.08; N, 4.61.

Under similar solution-phase conditions, but employing Pd(PPh$_3$)$_4$ (120 mg, 0.11 mmol, 7 mol %) as catalyst and THF as solvent, **12** (500 mg, 1.5 mmol) and ethyl cyanoacetate (380 mg, 3.3 mmol) gave **13b** (280 mg, 63%). Solid-phase preparation from polymer **15** (3.0 g), ethyl cyanoacetate (1.73 g, 15 mmol), and Pd(PPh$_3$)$_4$ (170 mg, 0.15 mmol, 5 mol %) in THF (reflux, 3 d) gave **13b** (300 mg, 34% overall yield from polymer **3**).

2-Acetyl-2-(2-(3-benzyloxycyclobutylidene)ethyl)cyclopentanone (13c). The solution-phase, Pd(PPh$_3$)$_4$-catalyzed preparation of **13a** was modified as follows: **12** (500 mg, 1.5 mmol), 2-acetylcyclopentanone (630 mg, 5.0 mmol), NaH (200 mg, 5.0 mmol, 60% in mineral oil), dry THF (15 mL), Pd(PPh$_3$)$_4$ (100 mg, 0.08 mmol, 5.7 mol %), and CC (33% EtOAc in hexanes) gave **13c** (280 mg, 59%) as a clear oil: IR (neat) 1735(s), 1701, 1112 cm^{-1}; ^{1}H NMR δ 1.65 (m, 2H), 1.80 (m, 2H), 2.14 (s, 3H), 2.22 (m, 2H), 2.46−2.64 (m, 4H), 2.81 (m, 2H), 4.04 (t, 1H, J = 6 Hz), 4.39 (s, 2H), 4.97 (m, 1H), 7.28 (m, 5H); ^{13}C NMR δ 215.1, 203.6, 137.7, 135.2, 128.0, 127.4, 127.3, 115.9, 70.0, 68.7, 68.2, 34.0, 38.3, 37.3, 33.8, 29.9, 25.7, 19.0. Anal. Calcd for C$_{20}$H$_{24}$O$_3$: C, 76.89; H, 7.74. Found: C, 76.68; H, 7.72.

Solid-phase preparation from polymer **15** (3.0 g), 2-acetylcyclopentanone (1.89 g, 15 mmol), and Pd(PPh$_3$)$_4$ (170 mg, 0.15 mmol, 5 mol %) in THF (reflux, 3 d) gave **13c** (335 mg, 36% overall yield from polymer **3**).

3-(PS/DVBsulfonyl)-3-(1-methylvinyl)cyclobutanol (14). The preparation of polymer **11** from polymer **9** was modified as follows to give polymer **14**. Polymer **10** (10 g, 10 mmol), *n*-BuLi (50 mL, 80 mmol, 1.6 M), and epichlorohydrin (9.46 g, 102 mmol) gave polymer **14**: IR (single bead reflectance) 1450, 1403, 1295, 1132 cm^{-1}.

Benzyl 3-(PS/DVBsulfonyl)-3-vinylcyclobutyl Ether (15). *n*-BuLi (12.5 mL, 20 mmol, 1.6 M in hexanes) was added to polymer **11** (5 g) in THF (20 mL) at −20 °C. After 40 min, benzyl bromide (3.5 g, 21 mmol) was added at 0 °C, and the reaction was stirred for 10 h. Water was added, and polymer **15** was isolated by filtration and washed with THF (2 × 30 mL) and ether (2 × 20 mL): IR (KBr) 1492, 1460, 1295, 1128, 696 cm^{-1}.

Benzyl 3-(PS/DVBsulfonyl)-3-(1-methylvinyl)cyclobutyl Ether (16). The preparation of polymer **15** was modified as follows to give polymer **16**. *n*-BuLi (3.1 mL, 5 mmol, 1.6 M in hexanes), polymer **14** (1 g), THF (7 mL), and benzyl bromide (850 mg, 5 mmol) gave polymer **16** after the polymer was washed with THF (2 × 15 mL) and ether (2 × 10 mL): IR (single bead reflectance) 1452, 1295, 1128, 1085, 1047 cm^{-1}.

3-(PS/DVBsulfonyl)-3-vinylcyclobutyl Benzoate (17). Pyridine (5 mL) and benzoyl chloride (700 mg, 5.0 mmol) were added to polymer **11** (1 g) in THF (5 mL) at 0 °C. The reaction was warmed to room temperature with stirring over 24 h. Water was added, and polymer **17** was isolated by filtration and washed with THF (2 × 10 mL) and ether (2 × 10 mL): IR (single bead reflectance) 1718, 1450, 1299, 1270, 1114, 757, 696 cm^{-1}.

3-(PS/DVBsulfonyl)-3-(1-methylvinyl)cyclobutyl Benzoate (18). The preparation of polymer **17** was modified as follows to give polymer **18**. Pyridine (5 mL), benzoyl chloride (700 mg, 5 mmol), and THF (5 mL) gave **18**: IR (single bead reflectance) 1718, 1492, 1450, 1299, 1270, 1114 cm^{-1}.

2-Acteyl-(2-(3-benzoyloxycyclobutylidene)ethyl)cyclopentanone (19). 2-Acetylcyclopentanone (688 mg, 5.4 mmol) was added to a suspension of NaH (210 mg, 5.2 mmol, 60% in mineral oil) in THF (6 mL), and the mixture was stirred for 40 min at 0 °C. The resulting mixture was added to a THF (10 mL) suspension of polymer **17** (1.5 g) containing Pd(PPh$_3$)$_4$ (120 mg, 0.10 mmol, 7 mol %). The orange mixture was refluxed (60 h), neutralized with saturated aqueous NH$_4$Cl, and filtered to remove the polymer. This polymer was washed with ether (3 × 30 mL), and the resulting washings were combined with the collected filtrate, which was then dried (MgSO$_4$) and concentrated. The residue was purified by CC (20% EtOAc in hexanes) to give **19** (170 mg, 34% overall yield from polymer **3**) as a pale yellow oil: IR (neat) 1716(s), 1270, 1110, 1069, 711 cm^{-1}; ^{1}H NMR δ 1.70−1.90 (m, 4H), 2.19 (s, 3H), 2.28 (m, 2H), 2.48−2.60 (m, 2H), 2.84 (m, 2H), 3.15 (m, 2H), 5.07 (s, 1H), 5.22 (t, 1H, J = 6 Hz), 7.40−8.01 (m, 5H); ^{13}C NMR δ 215.3, 203.8, 165.9, 135.0, 132.9, 129.7, 128.2, 116.9, 68.4, 65.8, 39.4, 38.5, 37.8, 33.9, 30.3, 25.9, 19.2. Anal. Calcd for C$_{20}$H$_{22}$O$_4$: C, 73.59; H, 6.79. Found: C, 73.33; H, 6.78.

Diethyl (2-(3-Benzyloxycyclobutylidene)-2-methylethyl)methylmalonate (20). Diethyl methylmalonate (1.80 g, 10.4 mmol) was added to a suspension of NaH (0.40 g, 10.0 mmol, 60% in mineral oil) in THF (8 mL) and stirred for 40 min at 0 °C. This mixture was added to a suspension of polymer **16** (2.0 g) and Pd(PPh$_3$)$_4$ (120 mg, 0.10 mmol, 5 mol %) in dry THF (10 mL), which was refluxed for 48 h. The reaction was cooled to room temperature, and a solution of saturated aqueous NH$_4$Cl was added. The polymer was removed by filtration and washed with ether (3 × 30 mL). The combined filtrate and washings were dried (MgSO$_4$) and concentrated. The residue was purified by CC (20% EtOAc in hexanes) to give 270 mg of **20** (270 mg, 35% overall yield from polymer **3**) as a pale yellow oil: IR (neat) 1741, 1265, 1084, 732 cm^{-1}; ^{1}H NMR δ 1.30 (t, 6H, J = 9 Hz), 1.40 (s, 3H), 1.49 (s, 3H), 2.60−2.67 (m, 4H), 2.91 (m, 1H), 4.11 (t, 1H, J = 6.5 Hz), 4.22 (q, 4H, J = 9 Hz), 4.50 (s, 2H), 7.40 (m, 5H); ^{13}C NMR δ 172.5, 138.1, 129.6, 128.4, 127.6, 127.8, 123.4, 70.4, 68.5, 61.2, 53.4, 38.6, 37.9, 37.6, 19.7, 17.3, 14.0. Anal. Calcd for C$_{22}$H$_{30}$O$_5$: C, 70.56; H, 8.07. Found: C, 70.62; H, 8.08.

Ethyl (2-(3-Benzyloxycyclobutylidene)-2-methylethyl)-cyanoacetate (21). The preparation of **20** was modified as follows to give **21**. Polymer **16** (2.0 g), ethyl cyanoacetate (1.15 g, 10.2 mmol), NaH (0.40 g, 10.0 mmol, 60% in mineral oil), Pd(PPh$_3$)$_4$ (150 mg, 0.13 mmol, 7 mol %), 60 h of reflux, and CC (20% EtOAc in hexanes) gave **21** (180 mg, 30%): IR (neat) 1741, 1244, 1203, 1083, 1026 cm^{-1}; ^{1}H NMR δ 1.31 (t, 3H, J = 7.2 Hz), 1.58 (s, 3H), 2.54−2.64 (m, 4H), 2.89 (m, 2H), 3.56 (t, 1H, J = 8.1 Hz), 4.08 (m, 1H, J = 6.9 Hz), 4.24 (q, 2H, J = 7.2 Hz), 4.43 (s, 2H), 7.33 (m, 5H); ^{13}C NMR δ 166.0, 137.9, 130.7, 128.3, 127.8, 127.6, 121.6, 116.4, 70.4, 68.4, 62.7, 37.6, 37.4, 36.2, 33.8, 16.1, 13.9. Anal. Calcd for C$_{19}$H$_{23}$O$_3$N: C, 72.82; H, 7.39; N, 4.47. Found: C, 72.79; H, 7.44; N, 4.53.

2-Acetyl-(2-(3-benzyloxycyclobutylidene)-2-methylethyl)cyclopentanone (22). The preparation of **20** was modified as follows to give **22**. Polymer **16** (3.0 g), 2-acetylcyclopentanone (1.89 g, 15.0 mmol), NaH (0.60 g, 15.0 mmol, 60% in mineral oil), Pd(PPh$_3$)$_4$ (150 mg, 0.13 mmol, 5 mol %), 65 h of reflux, and CC (20% EtOAc in hexanes) gave **22** (340 mg, 32%): IR (neat) 1735(s), 1698, 1453, 1100 cm^{-1}; ^{1}H NMR δ 1.37 (s, 3H), 2.52−2.61 (m, 4H), 2.83 (m, 2H), 4.04 (t, 1H, J = 6 Hz), 1.66−1.84 (m, 4 H), 2.28−2.42 (m, 2H), 2.21 (s, 3H), 4.43 (s, 2H), 7.33 (m, 5H); ^{13}C NMR δ 220.0, 204.1, 138.0, 129.6, 128.5, 127.8, 127.6, 123.9, 70.4, 68.4, 68.4, 38.2, 37.6, 37.8, 30.1,

29.9, 25.9, 19.3, 17.4. Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.02. Found: C, 77.18; H, 8.09.

2-Acetyl-(2-(3-benzoyloxycyclobutylidene)-2-methylethyl)cyclopentanone (23). The preparation of **19** was modified as follows to give **23**. Polymer **18** (1.5 g), 2-acetylcyclopentanone (0.94 g, 7.5 mmol), NaH (0.30 g, 7.5 mmol, 60% in mineral oil), $Pd(PPh_3)_4$ (100 mg, 0.08 mmol, 6 mol %), 60 h of reflux, and CC (20% EtOAc in hexanes) gave **23** (175 mg, 35%): IR(neat) 1701(s), 1451, 1356, 1273, 1110 cm^{-1}; ^1H NMR δ 1.37 (s, 3H), 2.75 (m, 2H), 3.07 (m, 2H), 5.16 (t, 1H, $J = 6$ Hz), 2.19 (s, 3H), 1.62−1.86 (m, 4H), 2.22−2.64 (m, 4H), 7.37−7.98 (m, 5H); ^{13}C NMR δ 215.3, 203.5, 165.8, 132.7, 129.7, 129.2, 128.6, 128.1, 124.5, 68.6, 65.0, 37.9, 37.7, 37.5, 29.9, 29.7, 25.7, 19.1, 17.2. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.10. Found: C, 74.00; H, 7.20.

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Supporting Information Available: X-ray crystallographic data for **7** and ^1H NMR and ^{13}C NMR spectra for compound **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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