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Articles

The Sulfone Linker in Solid-Phase Synthesis: Preparation of 3,5-Disubstituted Cyclopent-2-enones

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The preparation of functionalized 3,5-disubstituted cyclopent-2-enones via a solid-phase sulfone linker strategy is described. Polystyrene/divinylbenzene sulfinate **1** underwent S-alkylation followed by α,α-dialkylation with *cis*-1,4-dichloro-2-butene to form polymer-bound 3-phenylsulfonylcyclopentenes **8**. Subsequent epoxidation of the cyclopentene moiety in **8** was accomplished by treatment of *m*CPBA, and the resulting oxirane ring in resin **9** was opened with various nucleophiles, i.e., Grignard and cuprate reagents, azide ion, and amines. To complete the sulfone-based linker strategy, Swern or TPAP oxidation of **10** gave a transient γ-ketosulfone, which underwent sulfinate elimination, thus cleaving the sulfone linker. Eleven 3,5-disubstituted cyclopent-2-enones (**11**) were prepared with this five-step process in 18−40% overall yield from solid-phase benzene sulfinate **1**.

Sulfinate-functionalized resins[1] have been efficiently prepared and utilized in solid-phase organic synthesis (SPOS), and the resulting sulfone linker has been found to be both a robust and a versatile linker.[2] As an extension of our research involving sulfone linkers, we report here the preparation of functionalized 3,5-disubstituted cyclopent-2-enone via a sulfone-based solid-phase linker strategy. Our preparation of 3,5-disubstituted-2-cyclopentenones **11a**−**k** from sulfinate-functionalized resin **1** (Figure 1) proceeds via a five-step protocol consisting of (i) sulfinate S-alkylation, (ii) sulfone α,α-dialkylation,[2a,b,3] (iii) epoxidation[4] (see Scheme 2), (iv) epoxide-ring opening[5] (see Scheme 3), and modifying

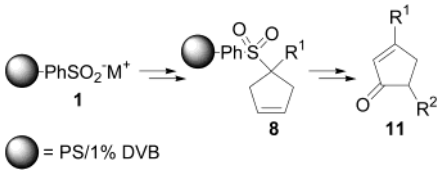

Figure 1. Five-step route for PS/1%DVB-$SO_2^-M^+$ → cyclpentenones.

Fuchs cyclopentenone-chemistry,[6] (v) oxidation with concomitant β-elimination of sulfinate[7] to release target molecules from the solid support (Scheme 4). The resulting cyclopentenones may prove useful as molecular

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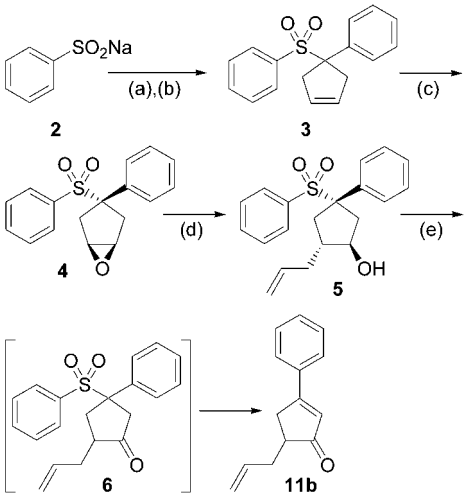
Scheme 1. Solution-Phase Synthesis of 3-Phenyl-5-allyl-2-cyclopentenone[a]



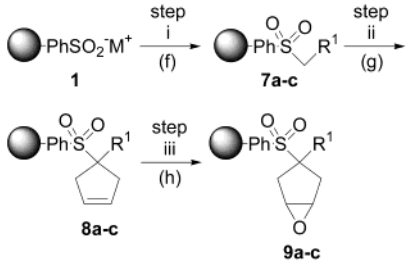
2 3 4 5 6 11b

[a] Reagents and conditions: (a) benzyl bromide, THF/DMF, 80 °C (90%). (b) ^{n}BuLi (2.2 equiv), *cis*-1,4-dichloro-2-butene (1.3 equiv), THF, 0 °C → rt (76%). (c) *m*CPBA, $CHCl_3$, 60 °C (75%). (d) allylmagnesium bromide, THF, 0 °C (69%). (e) Swern oxidation (88%).

scaffolds for library production, as cyclopentenone-containing compounds are both prevalent in nature and useful as building blocks for further transformations.[8]

Preliminary solution-phase experiments were undertaken to survey the requisite reaction conditions and establish modifications required for SPOS. To begin our investigation, cyclopentene **3** was prepared from sodium benzenesulfinate (**2**) in two steps, S-alkylation and sulfone α,α-dialkylation, in an overall yield of 68%. Treatment of **3** with *m*CPBA in $CHCl_3$ at 60 °C for 6 h delivered oxirane **4** as one diastereomer[9] in 75% yield. In contrast, epoxidation of **3** in CH_2Cl_2 at room temperature was sluggish. Subsequent nucleophilic ring opening[10] of the epoxide moiety in **4** was achieved by treatment with allylmagnesium bromide at 0 °C and afforded cyclopentanol **5**. Cleavage of the sulfone C,S-bond would, on solid-phase, constitute a release of substrate from the resin. Our plan was to take advantage of sulfinate elimination to effect this transformation, and to that end, the hydroxyl moiety of **5** was oxidized using the Swern procedure[11] to the corresponding ketone. To our delight, γ-ketosulfone **6** was not isolated upon reaction workup. Rather, the basic conditions of the Swern oxidation promoted the concomitant β-elimination of sulfinate leading directly to 5-allyl-3-phenyl-2-cyclopentenone (**11b**; Scheme 1). The success of these solution-phase transformations encouraged us to explore this protocol on solid phase.

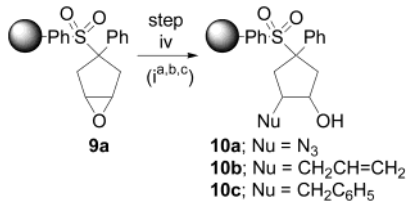
Scheme 2. Solid-Phase Synthesis of Oxirane 9[a]



1 7a-c 8a-c 9a-c

[a] Reagents and conditions: (f) R^1CH_2X, THF/DMF, 80 °C. (g) ^{n}BuLi (10 equiv), THF, rt; *cis*-1,4-dichloro-2-butene (10 equiv), THF. (h) *m*CPBA, $CHCl_3$, 60 °C.

Scheme 3. Solid-Phase Nucleophilic Epoxide Opening 9 → 10[a]



9a **10a**; Nu = N_3 **10b**; Nu = $CH_2CH{=}CH_2$ **10c**; Nu = $CH_2C_6H_5$

[a] Reagents and conditions: (i) (a) LiN_3 (14.7 equiv), DMF, 80 °C, 16 h; (b) allylmagnesium bromide (7.2 equiv), THF, −20 → 0 °C, 4 h; (c) benzylmagnesium chloride (7.2 equiv), THF, −20 → 0 °C, 4 h.

With a solution-phase route in hand, attention was next directed at development of a solid-phase protocol, and work began with step i, the S-alkylation of the sulfinate moiety of resin **1** (sulfinate loading = 0.5 mmol/g) with benzyl bromide, ethyl iodide, and ^{n}butyl iodide. While step i was amenable to FTIR monitoring (e.g., disappearance of sulfinate absorption at 1028 cm^{-1}; appearance of sulfone absorptions at ∼1320 and ∼1130 cm^{-1}), it was not possible to monitor step ii consisting of sulfone α,α-dialkylation with *cis*-1,4-dichloro-2-butene to construct the cyclopentene moiety (**7** → **8**)[6] or step iii consisting of epoxidation of the alkene with *m*CPBA in $CHCl_3$ at 60 °C for 12 h to deliver oxirane-functionalized resin **9** (Scheme 2).

Although a number of reagents could be employed to open the epoxide ring of **9** (step iv, Scheme 3), we chose lithium azide[12] as our first nucleophile, thinking that an azido absorption peak in the product FTIR would provide evidence that step ii and step iii had proceeded as anticipated. Indeed, treatment of oxirane resin **9a** with lithium azide in DMF at 80 °C for 10 h gave cyclopentanol resin **10a** as evidenced by the appearance of a new absorption peak at 2101 cm^{-1} in the IR spectrum of **10a**. Likewise, Grignard reagents allylmagnesium bromide and benzylmagnesium chloride reacted with oxirane **9a**, delivering cyclopentanols **10b** and **10c**, respectively.

The stage was now set for oxidation (CHOH → C═O) with concomitant sulfinate elimination to deliver the target cyclopentenone (**11**). As illustrated in Scheme 4, Swern oxidation of cyclopentanols **10a**−**c** indeed delivered the target 3,5-disubstituted cyclopent-2-enones **11a**−**c** in 35−38% overall isolated yield (including purification by column chromatography to remove trace impurities)

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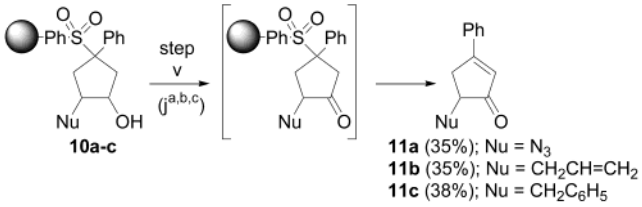
Scheme 4. Cyclopentenones by Solid-Phase Oxidation/Elimination[a]



[a] Reagents and conditions: (j) (a) Method A: Swern, CH_2Cl_2, −60 °C, 3 h; (b) Method B: SO_3/pyridine (6 equiv), Et_3N (10 equiv), DMSO, rt, 8 h; (c) Method C: TPAP (15 mol %), NMO (3 equiv), CH_2Cl_2, rt, 12 h.

Table 1. Comparative Methods for Solid-phase Oxidation/Sulfinate Elimination

cyclopentenone product	R^2	oxidation method[a]/yield[b] A	B	C
11a	N_3	35%	19%	36%
11b	allyl	35%	20%	38%
11c	benzyl	38%	25%	36%

[a] Oxidation method: A = Swern oxidation (−60 °C), B = DMSO·SO_3/pyridine (rt), C = TPAP/NMO (rt), Et_3N. [b] Overall yield from starting resin **1**; after column chromatography.

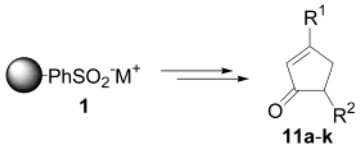
from starting resin **1**. That equates to an average yield per step of ca. 81−82% for the five solid-phase reactions.

Although cyclopentenones **11a**−**c** were successfully liberated from the solid support via this Swern oxidation, the inconvenience of low temperature for the oxidation[13] prompted us to consider other oxidation methods. Switching to the DMSO·SO_3/pyridine complex[14] allowed us to perform the oxidation at room temperature, but the cyclopentenone yields were lower than those achieved with Swern conditions (see Table 1). We next tried the TPAP/NMO[15] method in CH_2Cl_2 (rt, 8 h) followed by addition of Et_3N (rt, 3 h) and obtained cyclopentenones **11a**−**c** in yields similar to those obtained with the Swern oxidation, but with the distinct advantage that this oxidation/β-elimination sequence is run at room temperature.

With the results of Schemes 2−4 in hand, we set out to prepare a small library of cyclopentenones. As illustrated in Table 2, we employed three different 1°-alkyl halides in step i, allyl and benzyl Grignard, ^{n}Bu$_2$Cu(CN)Li$_2$,[16] azide, and piperidine[17] in step iv, and both Swern and TPAP/NMO conditions for step v. The five-step overall yields of cyclopentenones **11a**−**k** ranged from 18% to 40%, which translates to average per step yields of 71−83%. We believe some of the lower overall yields are a consequence of product volatility in the workup and isolation of step v.

In summary, this work further demonstrates the durability and chemical versatility of the sulfone moiety as a linker for SPOS. The mild cleavage conditions, base-mediated β-elimination during cyclopentanol to cyclopentenone oxidation, provide ready access to the resin-free target. Moreover, the solid-phase synthetic route presented here benefits from the fact that, aside from trace unidentified impurities, only molecules having successfully negotiated the entire reaction sequence (steps i−v) can be released from the solid support. The preparation of cyclopentenones with two functional groups has been developed and is suitable for library generation.

Table 2. PS/1%DVB-$SO_2^-M^+$ → Cyclopentenones Demonstration Library



11	step i	step iv	step v	overall yield
a	BnBr	LiN_3	see Table 1	see Table 1
b	BnBr	allyl-MgBr	see Table 1	see Table 1
c	BnBr	benzyl-MgCl	see Table 1	see Table 1
d	BnBr	^{n}Bu$_2$Cu(CN)Li$_2$	Swern	30%
e	BnBr	piperidine/LiOTf	Swern	20%
f	EtI	LiN_3	Swern	35%
g	EtI	benzyl-MgCl	Swern	40%
g	EtI	benzyl-MgCl	TPAP/NMO	38%
h	EtI	piperidine/LiOTf	Swern	18%
i	^{n}BuI	allyl-MgBr	Swern	33%
j	^{n}BuI	benzyl-MgCl	Swern	32%
j	^{n}BuI	benzyl-MgCl	TPAP/NMO	39%
k	^{n}BuI	^{n}Bu$_2$Cu(CN)Li$_2$	Swern	20%

Experimental Section

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

3-Phenylsulfonyl-3-phenylcyclopentene (3). To an ice-bath-cooled solution of benzyl phenyl sulfone (2.0 g, 8.6 mmol) in THF (50 mL) was added ^{n}BuLi (1.6 M, 2.2 equiv, 19.0 mmol, 12 mL). After 40 min, *cis*-1,4-dichloro-2-butene (1.2 equiv, 1.1 mL) was added slowly to the mixture under ice-bath cooling, and the reaction was allowed to stir for 30 min. The reaction was quenched with 10% HCl (30 mL) and extracted with ether (3×). The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated. The resulting compound was purified by CC (25% EtOAc in hexanes) to give **3** (1.8 g, 6.5 mmol) as a white solid in 76% yield: ^{1}H NMR δ 3.08 (d, 2H, J = 16.2 Hz), 3.65 (d, 2H, J = 16.2 Hz), 5.67 (s, 2H), 7.20−7.59 (m, 10H); ^{13}C NMR δ 137.5, 135.2, 133.2, 130.1, 130.0, 128.24, 128.22, 128.0, 127.7, 76.7, 41.1.

3-Benzenesulfonyl-3-phenyl-6-oxabicyclo[3,1,0]-hexane (4). A mixture of **3** (0.8 g, 2.8 mmol) and *m*CPBA (80%, 2 equiv, 1.2 g) in $CHCl_3$ (15 mL) was stirred at 60 °C for 6 h. The reaction was quenched with water (30 mL) and extracted with $CHCl_3$ (3×), and the combined organic solution was washed with saturated $NaHCO_3$ (5×), dried ($MgSO_4$), and concentrated. The resulting compound was purified by CC (50% EtOAc in hexanes) to give **4** (0.63 g, 2.1 mmol) as a white solid in 75% yield: ^{1}H NMR δ 2.75 (d, 2H, J = 15.0 Hz), 3.06 (d, 2H, J = 15.0 Hz), 3.65 (s, 2H), 7.04−7.51 (m, 10H); ^{13}C NMR δ 136.6, 134.7, 133.4, 129.7, 128.6, 128.0, 127.9, 127.6, 76.4, 57.3, 35.6.

2-Allyl-4-benzenesulfonyl-4-phenylcyclopentanol (5). Allylmagnesium bromide (1.0 M, 5.0 equiv, 3.35 mmol, 3.4 mL) was added to a THF (5 mL) solution of **4** (0.2 g, 0.67 mmol) at

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0 °C. After 1 h, the reaction mixture was allowed to warm to room temperature with stirring (3 h) and then cooled to 0 °C and quenched with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with ether (3×), and the combined organic solution was washed with brine, dried (Mg_2SO_4), and concentrated. The resulting residue was purified by CC (50% EtOAc in hexanes) to give **5** (0.16 g, 0.46 mmol) as a white solid in 69% yield: ^{1}H NMR δ 1.81−1.90 (m, 1H), 2.03 (s, 1H), 2.28 (dd, 1H, J = 14.1, 8.1 Hz), 2.40−2.49 (m, 1H), 2.57−2.61 (m, 2H), 3.06 (dd, 1H, J = 14.1, 7.2 Hz), 4.27−4.35 (m, 1H), 5.04 (d, 1H, J = 10.2 Hz), 5.14 (d, 1H, J = 17.1 Hz), 5.79−5.88 (m, 1H), 7.11−7.51 (m. 10 H); ^{13}C NMR δ 137.6, 136.5, 134.7, 133.3, 129.9, 129.1, 128.2, 128.0, 127.7, 116.4, 76.2, 73.9, 45.9, 42.5, 37.0, 36.6. Anal. Calcd for $C_{20}H_{22}O_3S$/0.3 H_2O: C, 69.05; H, 6.56. Found: C, 69.38; H, 6.84.

5-Allyl-3-phenylcyclopent-2-enone (11b). Compound **5** (0.20 g, 0.58 mmol) was oxidized via the normal Swern oxidation procedure[11] (oxalyl chloride, 1.3 equiv), DMSO (2.5 equiv), and Et_3N (5 equiv) in CH_2Cl_2 at −60 °C (4 h). The crude product was purified by CC (33% EtOAc in hexanes) to give **11b** (0.10 g, 88%) as a colorless oil: ^{1}H NMR δ 2.19−2.24 (m, 1H), 2.57−2.76 (m, 3H), 3.15 (dd, 1H, J = 18.0, 6.6 Hz), 5.02−5.13 (m, 2H), 5.72−5.85 (m, 1H), 6.53 (s, 1H), 7.40−7.45 (m, 3H), 7.62−7.65 (m, 2H); ^{13}C NMR δ 210.1, 172.3, 135.1, 133.6, 131.0, 128.6, 126.6, 126.3, 116.7, 45.2, 35.6, 34.4. Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.67; H, 7.18.

General Procedure for the Preparation of Polymer-Bound Alkyl Phenyl Sulfones (7). Specific for Polymer-Bound Phenyl Benzyl Sulfone (7a). Polymer-bound benzenesulfinate **1**[2] (10 g, 5 mmol; sulfinate loading = 0.5 mmol/g) was swollen in DMF/THF (1:1, 60 mL), benzyl bromide (20 mL) was added, and the mixture was gently stirred at 60 °C for 24 h. The resin was collected by filtration, washed with THF (2×), THF/H_2O (4:1, 2×), THF (2×), and ether, and dried to afford polymer-bound benzyl sulfone **7a** as yellow beads: IR (single bead reflectance) 1598, 1492, 1450, 1322(s), 1133-(s), 1029 cm^{-1}.

Polymer-Bound Phenyl Ethyl Sulfone (7b). As with **7a**, polymer **7b** was prepared from resin **1**, except S-alkylation was accomplished using ethyl iodide: IR (single bead reflectance) 1601, 1492, 1451, 1300(s), 1138(s) cm^{-1}.

Polymer-Bound Phenyl Butyl Sulfone (7c). As with **7a**, polymer **7c** was prepared from resin **1** except S-alkylation was accomplished using *n*-butyl iodide: IR (single bead reflectance) 1600, 1492, 1452, 1305(s), 1135(s) cm^{-1}.

General Procedure for the Preparation of Polymer-Bound Phenylsulfonyl Cyclopentene Derivatives 8. Specific for 3-(PS/DVB sulfonyl)-3-phenylcyclopentene (8a). *n*BuLi (16 mL, 24 mmol, 1.6 M) was added to a THF (40 mL) suspension of resin **7a** (5 g, 2.44 mmol) at 0 °C. The mixture was warmed to ambient temperature and stirred for 1 h. Excess ^{n}BuLi/THF was removed by anhydrous filtration, and dry THF (20 mL) was added under N_2. *cis*-1,4-Dichloro-2-butene (3 g, 24 mmol) was added dropwise to the reaction at 0 °C, and the mixture was allowed to stir for 40 min. The mixture was neutralized with 10% HCl, and the resin was collected by filtration and washed with THF (2×), THF/H_2O (4:1, 3×), THF (2×), and ether (2×) to give resin **8a**: IR (single bead reflectance) 1599, 1492, 1451, 1296(s), 1135(s) cm^{-1}. Resins **8b** and **8c** were prepared in similar fashion.

General Procedure for the Preparation of Polymer-Bound Phenyl Sulfonyl Oxiranes 9. Specific for 3-(PS/DVB sulfonyl)-3-phenyl-6-oxabicyclo[3,1,0]hexane (9a). Resin **8a** (3 g, 1.42 mmol) was swollen in $CHCl_3$ (30 mL), *m*CPBA (2.4 g, 14 mmol, 80%) was added at ambient temperature, and the mixture was then heated at 60 °C for 12 h. Filtration to collect the resin followed by washing with THF (2×), THF/H_2O (4:1, 2×), MeOH (2×), CH_2Cl_2 (2×), and ether gave **9a** (yellow beads), which was dried by storage in a desiccator overnight: IR (single bead reflectance) 1600, 1492, 1451, 1300(s), 1136(s) cm^{-1}. Resins **9b** and **9c** were prepared in similar fashion.

General Procedure for Epoxide Opening with Azide Anion. Polymer **9a** (1 g, 0.47 mmol) was swollen in DMF (15 mL), and lithium azide (0.34 g, 6.9 mmol) was added. The reaction was heated at 80 °C for 16 h and quenched with aqueous HCl (10%, 15 mL). Resin **10a** was collected by filtration, washed with THF/H_2O (4:1, 3×), THF, MeOH (2×), THF (2×), and dried: IR (single bead reflectance) ca. 2101 cm^{-1}. Resins **10a** and **10f** were prepared in similar fashion.

General Procedure for Epoxide Opening with Grignard Reagents. The resin **9a** (1 g, 0.47 mmol) was swollen in THF (10 mL) at −20 °C, and allylmagnesium bromide (3.4 mL, 3.4 mmol, 1 M) was added. The reaction was stirred at 0 °C for 4 h and quenched with 10% aqueous HCl (15 mL). Resin **10b** was collected by filtration, washed with THF/H_2O (4:1, 3×), THF (2×), MeOH, THF (2×), and dried. Resins **10b**, **10c** (benzylmagnesium chloride was used in place of allylmagnesium bromide), **10g** (benzylmagnesium chloride was used in place of allylmagnesium bromide), **10i**, and **10j** (benzylmagnesium chloride was used in place of allylmagnesium bromide) were prepared in similar fashion.

General Procedure for Epoxide Opening with Cuprate Reagents. A mixture of CuCN (0.22 g, 2.48 mmol) and ^{n}BuLi (3.12 mL, 5.0 mmol,1.6 M) in THF (10 mL) was stirred at −78 °C for 40 min, and the resulting solution was transferred to a THF (8 mL) suspension of polymer **9a** (1.2 g, 0.56 mmol). This reaction was stirred at −78 °C for 2 h and warmed to −20 °C. After an additional 2 h, the reaction was quenched with aqueous HCl (10%, 20 mL). Resin **10d** was collected by filtration and washed with THF/H_2O (4:1, 3×), THF, MeOH (2×), THF (2×), and dried. Resins **10d** and **10k** were prepared in similar fashion.

General Procedure for Epoxide Opening with Piperidine. Lithium triflate (0.25 g, 1.6 mmol) was added to a suspension of polymer **9a** (1.1.g, 0.52 mmol) in THF/CH_3CN (1:1, 10 mL), and the mixture was stirred for 30 min. Piperidine (0.27 g, 3.2 mmol) was then added, and the temperature was raised to 70 °C for 12 h. The reaction was neutralized with aqueous HCl (10%, 8 mL). Resin **10e** was collected by filtration, washed with THF/H2O (4:1, 2×), THF, MeOH, THF, MeOH, and dried. Resins **10e** and **10h** were prepared in similar fashion.

General Procedure for the Preparation of Cyclopentenones 11a−k. Specific for Azido-3-phenylcyclopent-2-enone (11a). Method A (Swern oxidation).[11] The solution-phase preparation of **11b** was modified as follows to give **11a**. Polymer **10a** (0.4 g, 0.18 mmol), DMSO (8 equiv), oxalyl chloride (4 equiv), Et_3N (10 equiv), and CC (20% EtOAc in hexanes) gave **11a** (13 mg, 35%). **Method B (DMSO−SO_3/pyridine).** To a DMSO (8 mL) suspension of polymer **10a** (0.55 g) was added SO_3/pyridine complex (6 equiv) and dry Et_3N (10 equiv). The mixture was stirred at ambient temperature for 8 h, and the resin was removed by filtration and washed with CH_2Cl_2 (2×), MeOH, CH_2Cl_2 (2×), and ether. The filtrate and washings were concentrated to remove organic solvent, and the residue was purified by CC (25% EtOAc in hexanes) to give **11a** (10 mg, 19%) as a pale yellow oil. **Method C (TPAP/NMO).** To a CH_2Cl_2 (6 mL) suspension of polymer **10a** (0.5 g) was added TPAP(15 mol %, 12 mg) and NMO (3 equiv, 80 mg). The reaction mixture was stirred at ambient temperature for 12 h, at which time the mixture was treated with Et_3N (5 equiv). After an additional 4 h, the polymer was removed by filtration and washed with CH_2Cl_2 (2×), ether, CH_2Cl_2 (2×), and ether. The filtrate and washings were concentrated to remove organic solvent, and the residue was passed through a short silica gel column, which was washed with CH_2Cl_2 to give **11a** as a pale yellow oil in 36% yield: IR ($CDCl_3$) 2103, 1701 cm^{-1}; ^{1}H NMR δ 2.82 (dd, 1H, J = 18, 3.3 Hz), 3.37(dd, 1H, J = 18, 7.2 Hz), 4.23(dd, 1H, J = 7.2, 3.3 Hz); ^{13}C NMR δ 203.5, 171.4, 132.8, 132.0, 128.9, 126.9, 124.4, 60.2, 35.1.

5-Allyl-3-phenylcyclopent-2-enone (11b). Methods A, B, and C were used to prepare **11b**: yields = 35% (A), 20% (B), and 38% (C).

5-Benzyl-3-phenylcyclopent-2-enone (11c). Methods A, B, and C were used to prepare **11c**: yields = 38% (A), 25% (B), and 36% (C); ^{1}H NMR δ 2.61 (dd, 1H, J = 13.8, 10.5 Hz), 2.67−2.75 (m, 1H, J = 18), 2.85−2.93 (m, 1H), 3.03 (dd, 1H, J = 18, 6.9 Hz), 3.32 (dd, 1H, J = 13.8, 4.2 Hz), 6.55 (s, 1H), 7.22−7.59 (m, 10 H); ^{13}C NMR δ 209.7, 172.3, 139.3, 133.5,

131.0, 128.6, 128.3, 126.6, 126.1, 126.1, 47.5, 37.1, 34.5. Anal. Calcd for $C_{18}H_{16}O/0.1\ H_2O$: C, 86.43; H, 6.54. Found: C, 86.59; H, 6.54.

5-Butyl-3-phenylcyclopent-2-enone (11d). Method C gave **11d** (30%): ^{1}H NMR δ 0.98 (t, 3H, J = 7.0 Hz), 1.33−1.36 (m, 5H), 1.84−1.87 (m, 1H), 2.50−2.54 (m, 1H), 2.88 (d, 1H, J = 18.3 Hz), 3.18 (dd, 1H, J = 18.3, 6.6 Hz), 6.50 (s, 1H), 7.40−7.44 (m, 3H), 7.60−7.65 (m, 2H); ^{13}C NMR δ 211.1, 172.0, 133.8, 130.9, 128.6, 126.6, 126.5, 46.1, 35.3, 31.3, 29.4, 22.7, 14.0. Anal. Calcd for $C_{15}H_{18}O/0.1H_2O$: C, 83.36; H, 8.50. Found: C, 83.09; H, 8.37.

3-Phenyl-5-(piperidin-1-yl)cyclopent-2-enone (11e). Method C gave **11e** (20%): IR ($CDCl_3$) 1695, 1598, 1571 cm^{-1}; ^{1}H NMR δ 1.44−1.46 (m, 2H), 1.60 (m, 4H), 2.52−2.76 (m, 4H), 3.00 (d, 1H, J = 17.7 Hz), 3.13 (dd, 1H, J = 17.7, 6.6 Hz), 3.59−3.62 (m, 1H), 6.54 (s, 1H), 7.47−7.67 (m, 5H); ^{13}C NMR δ 208.3, 171.0, 133.7, 131.3, 128.8, 126.8, 126.7, 68.3, 50.2, 30.4, 26.1, 24.3.

5-Azido-3-methyl-cyclopent-2-enone (11f). Method C gave **11f** (35%): IR ($CDCl_3$) 2103, 1710 cm^{-1}; ^{1}H NMR δ 2.11 (s, 3H), 2.34 (d, 1H, J = 17.7 Hz), 2.85 (dd, 1H, J = 17.7,6.9 Hz), 4.01 (dd, 1H, J = 6.9, 3.0 Hz), 5.92 (s, 1H); ^{13}C NMR δ 204.1, 176.8, 128.0, 60.4, 39.1, 19.6.

5-Benzyl-3-methyl-cyclopent-2-enone (11g). Methods A (40%) and C (38%) gave **11g**: IR ($CDCl_3$) 1705 cm^{-1}; ^{1}H NMR δ 2.06 (s, 3H), 2.29 (d, 1H, J = 18.6 Hz), 2.50−2.62 (m, 2H), 2.69−2.75 (m, 1H), 3.22 (dd, 1H, J = 13.8, 4.0 Hz), 5.92 (s, 1H), 7.17−7.30 (m, 5H); ^{13}C NMR δ 210.6, 177.4, 139.4, 129.6, 128.6, 128.2, 126.1, 48.0, 39.0, 36.9, 19.5.

3-Methyl-5-(piperidin-1-yl)cyclopent-2-enone (11h). Method C gave **11h** (18%): IR ($CDCl_3$) 1698, 1619 cm^{-1}; ^{1}H NMR δ 1.41 (m, 2H, J = 5.7 Hz), 1.57 (m, 4H, J = 5.7 Hz), 2.10 (s, 3H), 2.38−2.65 (m, 6H), 3.41 (m, 1H), 5.90 (s, 1H); ^{13}C NMR δ 208.7, 176.2, 130.3, 68.6, 50.1, 34.4, 25.9, 24.1, 19.8.

5-Allyl-3-propylcyclopent-2-enone (11i). Method C gave **11i** (33%): IR ($CDCl_3$) 2967, 1704(s), 1616 cm^{-1}; ^{1}H NMR δ 0.94 (t, 3H, J = 7.2 Hz), 1.59 (m, 2H, J = 7.2 Hz), 2.08−2.56 (m, 6H), 2.67 (dd, 1H, J = 18.3, 6.6 Hz), 4.98−5.08 (m, 2H), 5.65−5.78 (m, 1H), 5.89 (s, 1H); ^{13}C NMR δ 211.0, 181.6, 135.2, 128.5, 116.5, 45.2, 37.3, 35.5, 20.3, 13.8.

5-Benzyl-3-propylcyclopent-2-enone (11j). Methods A (32%) and C (39%) gave **11j**: IR ($CDCl_3$) 1701 cm^{-1}; ^{1}H NMR δ 0.88 (t, 3H, J = 7.2 Hz), 1.53 (2H, m, J = 7.2 Hz), 2.46−2.32 (m, 3H), 2.50−2.73 (m, 3H), 3.20 (dd, 1H, J = 13.8, 3.9 Hz), 5.91(s, 1H), 7.15−7.28(m, 5H); ^{13}C NMR δ 210.7, 181.6, 139.3, 128.6, 128.4, 128.2, 126.0, 47.4, 37.3, 36.9, 35.4, 20.3, 13.7; HRMS for $C_{15}H_{19}O$ (M + H) 215.1436, found 215.1498.

5-Butyl-3-propylcyclopent-2-enone (11k). Method C gave **11k** (20%): IR ($CDCl_3$) 1700(s), 1617 cm^{-1}; ^{1}H NMR δ 0.82 (s, br, 3H), 0.89 (t, 3H, J = 7.5 Hz), 1.24 (m, br, 6H), 1.54 (m, 2H, J = 7.5 Hz), 1.71 (s, br, 1H), 2.17 (d, 1H, J = 18.5 Hz), 2.28−2.32 (m, 2H), 2.66 (dd, 1H, J = 18.5 Hz), 5.82 (br s,1H); ^{13}C NMR δ 211.7, 181.0, 128.4, 46.0, 38.1, 35.3, 31.0, 29.3, 22.5, 20.2, 13.8, 13.7.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **3**, **4**, and **11a**,**e**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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