Pergamon

Tetrahedron 54 (1998) 9651–9666

TETRAHEDRON

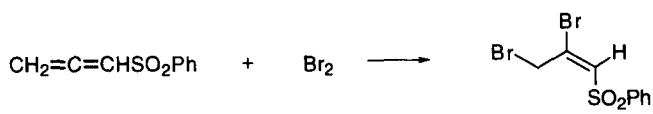
Alkylation Reactions of 3-(Phenylsulfonyl)methyl Substituted Cyclopentenones[¶]

Albert Padwa[‡]*, Cheryl L. Muller[‡], Augusto Rodriguez[¥], and Scott H. Watterson[‡]
[‡]Department of Chemistry, Emory University, Atlanta, GA 30322
[¥]Clark Atlanta University, Atlanta, GA 30314

Received 17 February 1998; accepted 29 May 1998

Abstract: The readily available 2,3-dibromo-1-(phenylsulfonyl)-1-propene (DBP) undergoes facile reaction with several 1,3-dicarbonyl compounds under basic conditions to give (phenylsulfonyl)methyl substituted cyclopentenones. The pendant sulfonyl group at the C_3 position of the cyclopentenone ring offers a versatile site for further elaboration *via* alkylation. These cyclic α-enone systems are easily metallated with sodium hydride, and the resultant carbanion undergoes both bimolecular and intramolecular alkylation reactions. The overall sequence provides a simple and efficient route to functionalized cyclopentenones. The alkylated sulfones were easily desulfonylated upon heating with tri *n*-butyltin hydride and AIBN in toluene at 110 °C. A novel base-induced transformation was observed using 3-(phenylsulfonyl)methyl-2-(4-iodobutyl)cyclopentenone. Treatment of this compound with one equivalent of NaH in the presence of HMPA afforded 4-methylene-spiro[4.4]non-2-en-1-one. This reaction proceeds by initial γ-alkylation followed by a 1,3-hydrogen shift and subsequent 1,4-elimination of sulfinate anion.

Functionalized allylic reagents which contain both a leaving group and a π-activating substituent have been extensively utilized in organic synthesis.[1-11] These substituted 1-propenes have been referred to as multicoupling reagents.[5,12] In this context we have recently demonstrated that 2,3-dibromo-1-(phenylsulfonyl)-1-propene (**1**) (DBP) is an extremely versatile synthetic reagent.[13] This compound was prepared by the addition of bromine to 1-phenylsulfonyl-1,2-propadiene.[13,14] The reaction proceeds smoothly at 25 °C and can be controlled so that the bromination may be terminated after 1 equiv of bromine is consumed. In previous work, DBP was shown to react with a variety of hetero- and carbon nucleophiles to give substituted vinyl sulfones



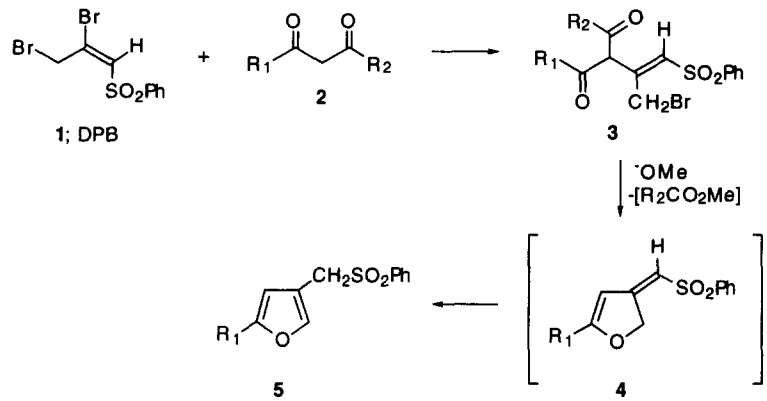
1; DPB

with predictable regiochemical control.[13] When carbonyl enolates were used, the reaction furnished [(phenylsulfonyl)methyl]-substituted furans.[15] This novel transformation was suggested to proceed by an initial addition-elimination of the carbanion onto the vinyl carbon of the unsaturated sulfone,[16] and was followed by

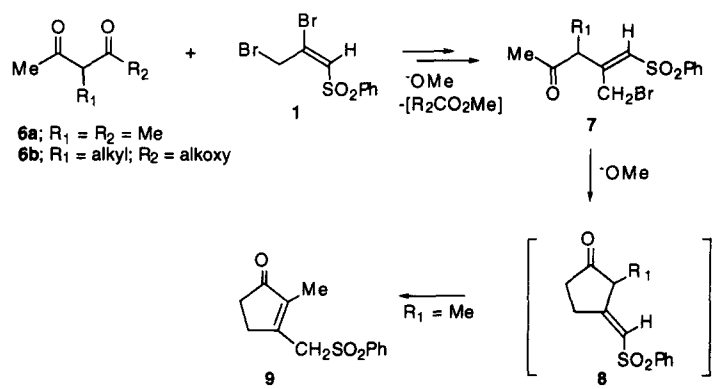
[¶] Dedicated with respect and admiration to Alan R. Katritzky on the occasion of his 70th birthday.

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00522-5

intramolecular ring closure on the enolate oxygen atom.[17] In practice, diactivated carbonyl compounds such as β-diketones, β-keto esters and malonates are preferable to simple ketones for use as nucleophiles, since simple enolate anions induce decomposition of the 2,3-dibromo sulfone.



Most interestingly, anions derived from 1,3-dicarbonyl compounds substituted in the C-2 position (*i.e.*, **6**) were found to induce a complete reversal in the mode of ring closure. The major products obtained are 3-[(phenylsulfonyl)methyl]-substituted cyclopentenones (**9**). The internal displacement reaction leading to the furan ring apparently encounters an unfavorable $A^{1,3}$-interaction in the transition state when a substituent group (*i.e.*, methyl) is present at the 2-position of the dicarbonyl compound. This steric interaction is not present in the transition state leading to the cyclopentenone ring.



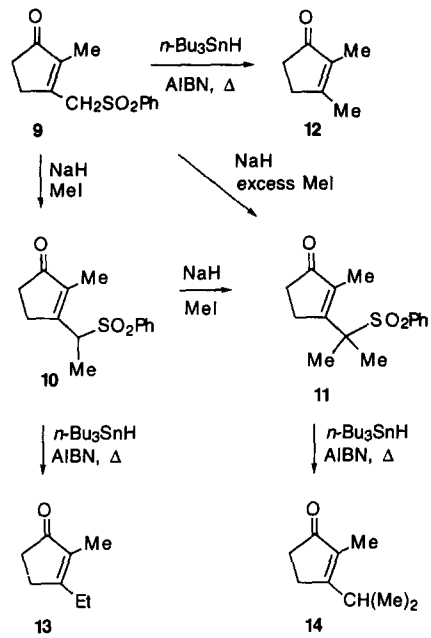
The synthetic application of sulfones to the preparation of natural products has increased enormously during the past decade.[18,19] This increased interest stems in part from the recognition that sulfones can stabilize

anions,[20] may be removed reductively,[21] and may be eliminated to form olefins.[22,23] The structure of carbanions stabilized by an α-sulfonyl group has received considerable scrutiny from both theoretical and experimental standpoints.[24] As part of our continuing interest in this area we have examined the base-induced behavior of 3-[(phenylsulfonyl)methyl]-substituted cyclopentenones as an approach toward the synthesis of complex carbocyclic ring systems. The present paper documents the results of these studies.

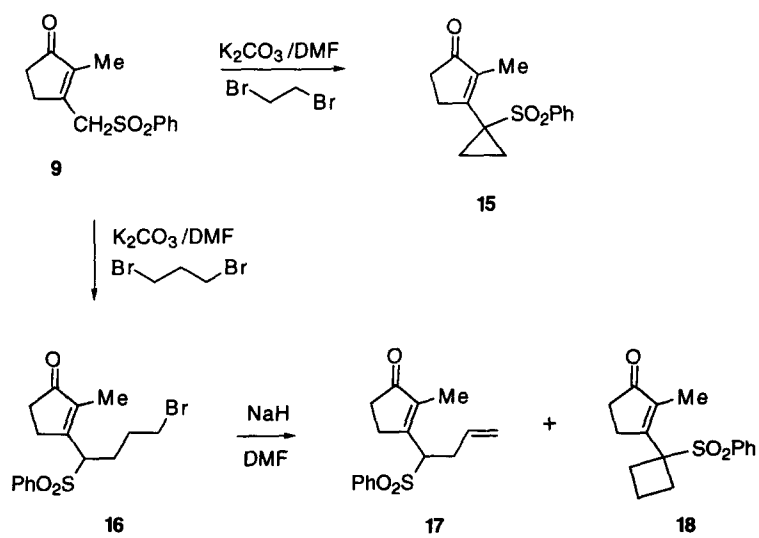
Results and Discussion

The anion stabilizing properties of sulfonyl groups has been extensively exploited for organic synthesis.[24] Considerable interest has been focused on the chemical transformations of allylic sulfones. The key step in these transformations involves the generation of an allyl sulfonyl carbanion and its reaction with electrophilic compounds leading to the formation of new C-C bonds.[24] Removal of the sulfonyl group is usually achieved by reduction with alkali metals[25] or with Raney nickel,[26] which simply replaces the sulfonyl group with a hydrogen atom, or by base-catalyzed[27] or reductive eliminations,[28] which leave behind a double bond. Previous studies with allylic sulfonyl carbanions illustrate their general tendency to undergo α- rather than γ-alkylation.[29] These alkylations can be carried out regioselectively on both acyclic and cyclic sulfones using either anhydrous conditions or phase-transfer conditions. Trost has represented allylic sulfones as triionic synthons because of the dual nucleophilic and electrophilic character of the carbon atom bearing the sulfonyl group.[30]

Monometallated allylic sulfones have played a particularly important role as reactive intermediates in total synthesis[24] and therefore, we decided to study the base induced behavior of the 3-[(phenylsulfonyl)methyl]-substituted cyclopentenone **9** in order to establish its synthetic versatility. The pendant sulfonyl group at the C_3 position of the cyclopentenone ring offers a versatile site for further elaboration *via* alkylation. Indeed, we have found that cyclopentenone **9** is easily metallated with sodium hydride. The resulting carbanion can be alkylated with 1 equivalent of methyl iodide to give sulfone **10** in 83% yield. The degree of alkylation is easily controlled by the methyl iodide/sulfone ratio. The reaction of **9** with a three-fold excess of methyl iodide resulted in the formation of the dialkylated cyclopentenone **11** in 73% yield. Treatment of the monomethylated sulfone **10** with 1 equivalent of methyl iodide also furnished **11** in 90% yield. The methylated cyclopentenone sulfones were readily desulfonylated by heating them with tri *n*-butyltin hydride and AIBN in toluene at 110 °C.[31] The product ketones were obtained in 85-95% yield and were efficiently separated from the tin by-products by simple gradient-elution flash chromatography.

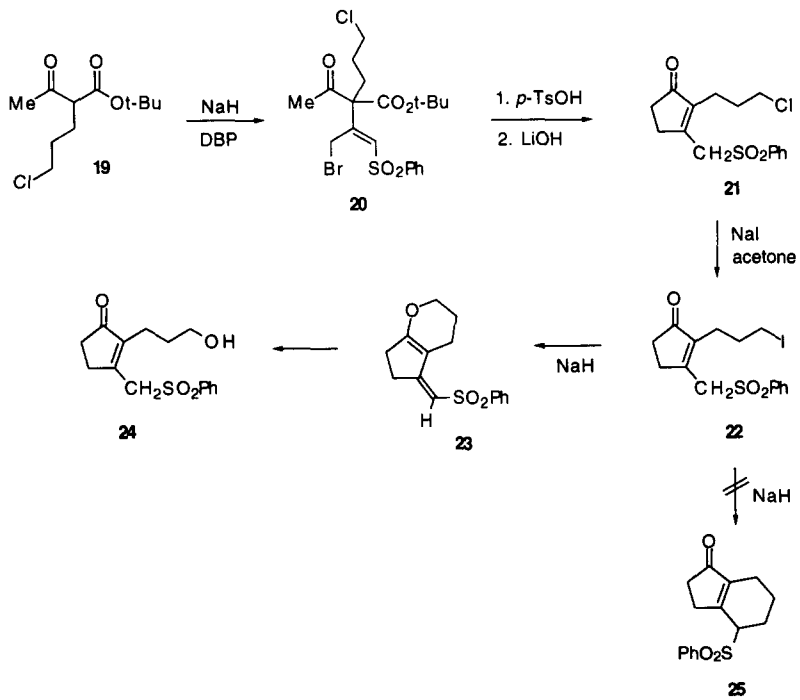


In an effort to extend the scope and generality of the alkylation reaction, cyclopentenone **9** was treated with K_2CO_3 in the presence of a dielectrophile such as 1,2-dibromoethene. The only product formed (75%) under these conditions was cyclopropyl sulfonyl **15**. In this case, the initial alkylation is followed by a subsequent deprotonation. The resulting sulfonyl-stabilized allylic carbanion reacts further at the α-position to give **15**. When 1,3-dibromopropane was used, it was possible to isolate the initially formed mono-alkylated



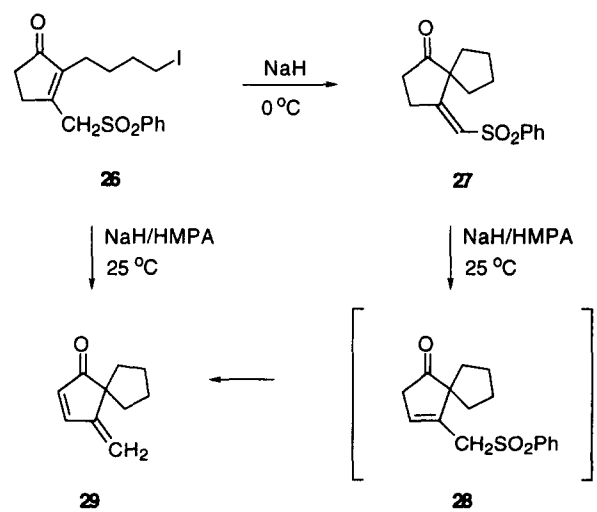
bromide **16** in 78% yield. Further reaction of **16** with NaH in DMF afforded a 1:1-mixture of **17** and the cyclobutyl substituted sulfone **18** in 96% yield. With this system, the dehydrobromination reaction leading to **17** becomes competitive with cyclobutane formation.

The biological importance and diversity of cyclopentanoid natural products have made these compounds important synthetic goals and have stimulated new methods and reagents for the preparation of cyclopentenyl ring systems.[32,33] Several successful approaches have been designed through free radical intermediates,[34] ring expansion of three-[35] or four-membered[36] carbocycles, [3+2]-cycloadditions,[37] [4+1]-annulations,[38] and cyclization methods forming more than one bond in a single step using transition metal complexes.[39] Our interest in the chemical behavior of carbanions generated from sulfonyl substituted cyclopentenones led us to investigate their intramolecular alkylation reactions, as this would provide an entry into the synthesis of various cyclopentyl ring systems. As a typical example, we envisaged that the initially formed sulfonyl stabilized carbanion derived from cyclopentenone **22** would result in the displacement of the proximal iodide to furnish the annulated cyclopentenone **25**. The desired cyclopentenone **22** was prepared by treating *t*-butyl acetoacetate with sodium hydride followed by reaction with 1-bromo-3-chloropropane to give ketoester **19** in 61% yield. A solution of 2,3-dibromo-1-(phenylsulfonyl)-1-propene (DBP) and **19** was allowed to react with one equivalent



of sodium hydride at 25 °C to give ketoester **20**. This compound was formed by attack of the carbanion on the vinyl carbon of DBP followed by elimination of bromide ion. Hydrolysis of the *t*-butyl ester and subsequent decarboxylation of the resulting acid in refluxing benzene using *p*-toluenesulfonic acid was followed by ring closure to afford the chloro-substituted cyclopentenone **21**. Treatment of **21** with sodium iodide in acetone furnished **22** in 85% overall yield for both steps. Subjection of **22** to sodium hydride did not produce the anticipated annulated cyclopentenone **25**. Rather, the reaction resulted in O-alkylation to form the hydrolytically sensitive enol ether **23**. On exposure to moisture, **23** was readily transformed into alcohol **24** in 83% yield.

In a similar vein, we studied the base-induced behavior of the closely related 3-(phenylsulfonyl)methyl-2-(4-iodobutyl)cyclopentenone **26**. This compound was prepared by a method similar to that used for **22**. We found that treatment of **26** with 1 equivalent of sodium hydride in ether containing 5 drops of HMPA at 25 °C resulted in the formation of the novel spiro substituted cyclopentenone **29** in 72% yield. The structure of **29** was assigned on the basis of its characteristic spectral data [^{1}H-NMR δ 1.6-2.1 (m, 8H), 5.19 (s, 1H), 5.22 (s, 1H), 6.17 (d, 1H, J = 5.0 Hz), and 7.65 (d, 1H, J = 5.0 Hz); ^{13}C-NMR δ 27.0, 37.3, 55.8, 110.4, 132.0, 155.6, 155.9, and 212.5]. When the reaction was carried out at 0 °C in the absence of HMPA, cyclopentenone **27** was the major product (83%). Further treatment of **27** under the more vigorous conditions furnished the desulfonylated cyclopentenone **29**. Formation of methylene cyclopentenone **29** is best rationalized by a process involving an initial 1,3-hydrogen shift to give the rearranged allylic sulfone **28** as a transient species which



undergoes a subsequent 1,4-elimination of sulfinate anion. It should be noted that in this case, five-membered ring cyclization at the γ-position of the allylic sulfonyl carbanion corresponds to the preferred path, presumably as a consequence of entropic factors.

In conclusion, we have demonstrated that the readily available 2,3-dibromo-1-(phenylsulfonyl)-1-propene (DBP) undergoes facile reaction with several 1,3-dicarbonyl compounds under basic conditions to give (phenylsulfonyl)methyl substituted cyclopentenones. Anions derived from these diactivated systems undergo both bimolecular and intramolecular alkylation reactions and provide a simple and efficient route to functionalized cyclopentenones. We are continuing to explore the scope, generality and synthetic application of these sulfonyl substituted cyclic enones and will report additional findings at a later date.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed under an atmosphere of dry argon in flame-dried glassware. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate-hexane mixture as the eluent unless specified otherwise.

3-(1-Phenylsulfonylethyl)-2-methylcyclopenten-2-one (10). To a stirred solution containing 125 mg (0.5 mmol) of cyclopentenone **9**[15] in 2 mL of dry DMF was added 3 mmol of K_2CO_3 followed by 282 mg (2 mmol) of methyl iodide. The resulting dark red suspension was stirred at rt for 12 h and then 20 mL of ether and 20 mL of an NH_4Cl solution was added. The organic layer was washed several times with water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 110 mg (83%) of **10** as a white crystalline solid; mp 100-101 °C; IR (KBr) 1692, 1632, 1445, and 1304 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 3H, J = 2.1 Hz), 1.62 (d, 3H, J = 6.9 Hz), 2.35 (t, 2H, J = 4.5 Hz), 2.50 (m, 1H), 2.80 (m, 1 H), 4.31 (q, 1H, J = 6.9 Hz), 7.51 (t, 2H, J = 7.5 Hz), 7.62 (t, 1H, J = 7.5 Hz), and 7.77 (d, 2H, J = 7.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 8.0, 11.5, 26.0, 33.9, 61.5, 128.7, 129.3, 134.2, 137.3, 142.4, 161.5, and 208.6; Anal. Calcd. for $C_{14}H_{16}O_3S$: C, 63.62; H, 6.11. Found: C, 63.61; H, 6.14.

A mixture containing 125 mg (0.5 mmol) of cyclopentenone **10**, 290 mg (1 mmol) of *n*-Bu_3SnH and 10 mg of AIBN in 3 mL of toluene under an argon atmosphere was heated at reflux for 5 h. The mixture was cooled, poured into an aqueous KF solution and the aqueous layer was extracted with ether. After drying over

$MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by flash silica gel chromatography to give 2-methyl-3-ethylcyclopenten-2-one (**13**) whose ^{1}H-NMR spectrum was consistent with literature values[40]: (300 MHz, $CDCl_3$) δ 1.11 (t, 3H, J = 7.5 Hz), 1.67 (s, 3H), and 2.30-2.53 (m, 6H).

3-(1-Phenylsulfonyl-1-methylethyl)-2-methylcyclopenten-2-one (11). To a stirred solution containing 250 mg (1 mmol) of cyclopentenone **9** in 2 mL of dry DMF was added 3 mmol of K_2CO_3 followed by 432 mg (3 mmol) of methyl iodide. The resulting dark red suspension was stirred at rt for 12 h, diluted with 20 mL of ether and the organic layer was washed several times with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to give 202 mg (73%) of cyclopentenone **11** as a crystalline solid; mp 171-172 °C; IR (KBr) 1693, 1616, 1439, and 1290 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.48 (brs, 3H), 1.66 (s, 6H), 2.25 (m, 2H), 2.44 (m, 2H), 7.48 (t, 2H, J = 7.5 Hz), 7.62 (t, 1H, J = 7.5 Hz), and 7.70 (d, 2H, J = 7.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 9.9, 22.3, 28.8, 33.4, 66.9, 128.9, 130.1, 134.1, 135.0, 142.6, 164.1, and 209.1; Anal. Calcd. for $C_{15}H_{18}O_3S$: C, 64.72; H, 6.52. Found: C: 64.44; H, 6.57.

A mixture containing 120 mg (0.5 mmol) of cyclopentenone **11**, 280 mg (1 mmol) of *n*-Bu_3SnH and 10 mg of AIBN in 3 mL of toluene under an argon atmosphere was heated at reflux for 5 h. The mixture was poured into a KF solution and the water layer was extracted with ether. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by flash silica gel chromatography to give 2-methyl-3-*iso*-propyl-cyclopenten-2-one (**14**) whose NMR spectrum was consistent with literature values[41] (300 MHz, $CDCl_3$) δ 1.15 (d, 6H, J = 7 Hz), 1.60 (s, 3H), 2.33 (m, 2H), 2.48 (m, 2H), and 3.03 (sept, 1H, J = 7 Hz).

3-(1-Phenylsulfonylcyclopropyl)-2-methylcyclopenten-2-one (15). To a stirred solution containing 250 mg (1 mmol) of cyclopentenone **9** in 2 mL of dry DMF was added 3 mmol of K_2CO_3 followed by 376 mg (2 mmol) of 1,2-dibromoethane. The resulting dark red suspension was stirred at rt for 12 h, diluted with 20 mL of ether and the organic layer was washed several times with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to give 209 mg (75%) of **15** as a white crystalline solid; mp 180-181 °C; IR (KBr) 2919, 1695, 1631, and 1133 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.04 (t, 3H, J = 1.8 Hz), 1.10 (m, 2H), 1.89 (m, 2H), 2.32 (m, 2H), 2.55 (m, 2H), 7.49 (t, 2H, J = 7.5 Hz), 7.62 (t, 1H, J = 7.5 Hz), and 7.71 (d, 2H, J = 7.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 8.2, 12.8, 29.4, 34.4, 43.2, 128.7, 129.3, 134.0, 138.1, 144.7, 161.3, and 209.6; Anal. Calcd. for

$C_{15}H_{16}O_3S$: C, 65.19; H, 5.84. Found: C, 65.09; H, 5.89.

3-(1-Phenylsulfonylcyclobutyl)-2-methylcyclopenten-2-one (18). To a stirred solution containing 250 mg (1 mmol) of cyclopentenone **9** in 2 mL of dry DMF was added 3 mmol of K_2CO_3 followed by 202 mg (1 mmol) of 1,3-dibromopropane. The resulting dark red suspension was stirred at rt for 12 h, diluted with 20 mL of ether and the organic layer was washed several times with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to give 280 mg (75%) of 3-(1-phenylsulfonyl-4-bromobutyl)-2-methylcyclopenten-2-one (**16**) as a crystalline solid; mp 102-103 °C; IR (neat) 1695, 1638, 1446, 1296, and 1140 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.17 (t, 3H, *J* = 2.1 Hz), 1.76 (m, 2H), 2.21-2.45 (m, 2H), 2.35 (t, 2H, *J* = 4.6 Hz), 2.50 (m, 1H), 2.85 (m, 1H), 3.25-3.45 (m, 2H), 4.18 (dd, 1H, *J* = 10.8 and 3.9 Hz), 7.50 (t, 2H, *J* = 7.5 Hz), 7.62 (t, 1H, *J* = 7.5 Hz), and 7.76 (d, 2H, *J* = 7.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$), d 8.0, 24.1, 25.9, 29.7, 32.1, 33.9, 65.9, 128.5, 129.4, 134.4, 137.4, 144.0, 160.0, and 208.2; Anal. Calcd. for $C_{16}H_{19}BrO_3S$: C, 51.89; H, 5.17. Found: C, 52.02; H, 5.26.

Treatment of a sample of **16** with 88 mg (2.2 mmol) of NaH afforded a 1:1-mixture of 3-(1-phenylsulfonyl-but-3-enyl)-2-methylcyclopenten-2-one (**17**) and 3-(1-phenylsulfonyl-cyclobutyl)-2-methyl-cyclopenten-2-one (**18**). These two products were separated by silica gel chromatography. Cyclopentenone **17** was a clear oil and exhibited the following spectral properties: IR (neat) 1703, 1642, 1447, 1308, 1148, and 1084 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 2.31 (t, 2H, *J* = 5 Hz), 2.50 (m, 1H), 2.85 (m, 2H), 3.05 (m, 1H), 4.2 (dd, 1H, *J* = 11 and 3 Hz), 5.05 (m, 2H), 5.50 (m, 1H), 7.50 (m, 2H), 7.65 (m, 1H), and 7.85 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 7.9, 26.0, 29.4, 33.9, 65.9, 118.7, 128.5, 129.4, 131.9, 134.3, 137.4, 143.7, 160.2, and 208.5; HRMS Calcd for $C_{16}H_{18}SO_3$: 290.0976. Found: 290.0975.

Cyclobutyl sulfone **18** was obtained as a white solid; mp 171-172 °C; IR (KBr) 1699, 1626, 1441, 1288, and 1142 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.10 (t, 3H, *J* = 1.8 Hz), 1.85-1.99 (m, 1H), 2.25-2.47 (m, 5H), 2.98-3.09 (m, 2H), 7.49 (t, 2H, *J* = 7.5 Hz), 7.63 (t, 1H, *J* = 7.5 Hz), and 7.73 (d, 2H, *J* = 7.5 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 8.7, 16.6, 27.2, 29.4, 34.0, 69.7, 129.1, 129.7, 134.2, 135.4, 141.9, 165.1, and 209.1; Anal. Calcd. for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25. Found: C, 66.03; H, 6.31.

Preparation and Base Induced Reaction of 3-Phenylsulfonylmethyl-2-(3-iodopropyl)-cyclopenten-2-one (22). A 1.6 g (10 mmol) sample of *tert*-butyl acetoacetate in 5 mL of THF was slowly added to a suspension of 440 mg (11 mmol) of NaH (60% dispersion in mineral oil) in 20 mL of THF at 0 °C. The mixture was stirred for an additional 30 min and 240 mg (1.5 mmol) of 1-bromo-3-chloropropane in 2 mL

of THF was added. The mixture was heated at reflux for 24 h, poured into a saturated NH_4Cl solution and the aqueous layer was extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by molecular distillation to give 1.41 g (61%) of 2-acetyl-5-chloro-pentanoic acid *tert*-butyl ester (**19**) as a clear oil; IR (neat) 1731, 1712, 1362, 1250, and 1137 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.73 (m, 2H), 1.90 (m, 2H), 2.22 (s, 3H), 3.33 (t, 1H, J = 7.2 Hz), and 3.50 (t, 2H, J = 6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.3, 27.9, 28.7, 30.1, 44.3, 60.0, 82.1, 168.6, and 202.8.

2-Acetyl-4-phenylsulfonyl-3-bromomethyl-2-(3-chloropropyl)butenoic acid *tert*-butyl ester (**20**) was prepared from 1.37 g (5.85 mmole) of *tert*-butyl ester **19**, 240 mg (5.7 mmol) of NaH (60% dispersion in mineral oil) and 1.0 g (3 mmol) of 2,3-dibromo-1-(phenylsulfonyl)-1-propene (DBP) in 25 mL of THF. The reaction was subjected to an aqueous workup and the residue was chromatographed on silica gel to provide 873 mg (60%) of **20** as a clear oil; IR (neat) 1726, 1708, 1305, 1251, and 1150 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.70 (m, 1H), 1.85 (m, 1H), 2.15 (m, 2H), 2.37 (s, 3H), 3.53 (t, 2H, J = 7 Hz), 4.34 (d, 1H, J = 14 Hz), 4.71 (d, 1H, J = 14 Hz), 6.58 (s, 1H), 7.55 (m, 2H), 7.65 (m, 1H), and 7.92 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 27.8, 27.9, 28.0, 34.9, 44.8, 56.8, 68.1, 84.2, 118.5, 128.2, 129.3, 130.8, 133.9, 140.2, 168.3, and 202.1; Anal. Calcd. for $C_{20}H_{26}BrClO_5S$: C, 48.64; H, 5.30. Found: C, 48.77; H, 5.32.

A mixture containing 273 mg (0.6 mmol) of the above compound and 100 mg of *p*-toluenesulfonic acid in benzene was heated at reflux under nitrogen for 3 h. The solution was filtered through a short column of silica gel and concentrated under reduced pressure. The residue was dissolved in 5 mL of methanol and 77 mg (1.8 mmol) of lithium hydroxide monohydrate was added. The solution was stirred for 30 min at rt and a pH 7 buffer was added after 30 min. The solvent was removed under reduced pressure and the mixture was extracted with several portions of $CHCl_3$. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 122 mg (74%) of 3-phenylsulfonylmethyl-2-(3-chloropropyl)cyclopenten-2-one (**21**) as a colorless oil; IR (neat) 2927, 1702, 1641, 1449, 1325, and 1151 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.71 (m, 2H), 2.05 (t, 2H, J = 7 Hz), 2.42 (m, 2H), 2.83 (m, 2H), 3.40 (t, 2H, J = 7 Hz), 4.24 (s, 2H), 7.65 (m, 2H), 7.70 (m, 1H), and 7.95 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.3, 29.6, 30.0, 34.0, 44.5, 58.1, 128.0, 129.4, 138.5, 157.8, and 208.1; Anal. Calcd. for $C_{15}H_{17}ClSO_3$: C, 57.68; H, 5.49. Found: C, 57.53; H, 5.42.

A solution containing 275 mg (0.9 mmol) of the above compound and 200 mg (1.3 mmol) of sodium

iodide in 7 mL of acetone was heated at reflux under nitrogen for 14 h. The solution was cooled, diluted with CH_2Cl_2, passed through a short plug of neutral alumina and concentrated to give cyclopentenone **22**; IR (neat) 2925, 1701, 1645, 1447, 1319, and 1150 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.70 (m, 2H), 1.94 (m, 2H), 2.43 (m, 2H), 2.77 (m, 2H), 3.06 (t, 2H, *J* = 6 Hz), 4.26 (s, 2H), 7.59 (m, 2H), 7.63 (m, 1H), and 7.90 (m, 2H). This compound was used in the next step without further purification.

A suspension of 57 mg (1.4 mmol) of NaH in ether containing 6 drops of HMPA was cooled to 0 °C and stirred under an argon atmosphere. To this solution was added the above iodide in 2 mL of THF and the mixture was stirred at 0 °C for 3 h. The solution was quenched with a saturated NH_4Cl solution and extracted with several portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica to give 5-(phenylsulfonyl)methylene-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran (**23**); IR (neat) 1630, 1576, 1447, 1410, 1138, 1084, and 823 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.92 (m, 2H), 2.05 (m, 2H), 2.50 (m, 2H), 3.05 (m, 2H), 4.16 (t, 2H, *J* = 6 Hz), 5.71 (s, 1H), 7.50-7.65 (m, 3H), and 7.92 (m, 2H). On exposure to the atmosphere or upon standing in chloroform solution, pyran **23** was rapidly hydrolyzed to 3-phenylsulfonylmethyl-2-(3-hydroxypropyl)-cyclopenten-2-one (**24**) (83%) which was purified by silica gel chromatography; IR (neat) 1699, 1642, 1310, and 1150 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.48 (m, 2H), 1.98 (brs, 1H), 2.02 (t, 2H, *J* = 7 Hz), 2.44 (m, 2H), 2.76 (m, 2H), 3.42 (t, 2H, *J* = 6 Hz), 4.24 (s, 2H), 7.59 (m, 2H), 7.63 (m, 1H), and 7.90 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 18.7, 30.1, 30.2, 34.4, 58.3, 60.7, 128.0, 129.5, 134.3, 138.7, 146.3, 157.9, and 209.3; Anal. Calcd. for $C_{15}H_{18}O_4S$: C, 61.21; H, 6.17. Found: C, 61.09; H, 6.15.

4-Phenylsulfonylmethylene-spiro[4.4]nonan-1-one (27). To a suspension of 1.8 g NaH (44 mmol) (60% dispersion in mineral oil) in 50 mL of THF was added dropwise 6.3 g (40 mmol) of *tert*-butyl acetoacetate in 15 mL of THF at 0 °C. After the addition was complete, the mixture was stirred for 30 min and 10.6 g (44 mmol) of 4-iodobutyl acetate[42] was added slowly. The solution was allowed to warm to rt and was stirred overnight. The mixture was poured into a saturated NH_4Cl solution and the aqueous layer was extracted with ether. The organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure and the residue was purified by distillation to give 6.7 g (61%) of 6-acetoxy-2-acetylhexanoic acid *tert*-butyl ester as a clear oil; bp 120-130 °C (0.5 mm); IR (neat) 1740, 1714, 1370, 1244, and 1146 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.29 (m, 2H), 1.40 (s, 9H), 1.58 (m, 2H), 1.75 (m, 2H), 1.96 (s, 3H), 2.15 (s, 3H), 3.24 (t, 1H, *J* = 7.5 Hz), and 3.98 (t, 2H, *J* = 6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.8, 23.7, 27.5, 27.8, 28.3, 28.6,

60.6, 63.9, 81.8, 168.8, 170.9, and 203.1.

A sample of 2-(4-acetoxybutyl)-2-acetyl-4-phenylsulfonyl-3-bromomethyl-but-3-enoic acid *tert*-butyl ester was prepared from 660 mg (2.4 mmol) of the above ketoester, 100 mg (2.4 mmol) of NaH (60% dispersion in mineral oil) and 815 mg (2.4 mmol) of 2,3-dibromo-1-(phenylsulfonyl)-1-propene (DBP) in 25 mL of THF. The reaction was subjected to an aqueous workup and the residue was chromatographed on silica gel to provide 800 mg (92%) of the expected 2-(4-acetoxybutyl)-ketoester; IR (neat) 1736, 1710, 1248, 1155, and 1086 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.05-1.20 (m, 2H), 1.46 (s, 9H), 1.56 (m, 2H), 1.90 (m, 2H), 1.93 (s, 3H), 2.30 (s, 3H), 3.96 (d, 2H, J = 6.5 Hz), 4.24 (d, 1H, J = 14 Hz), 4.67 (d, 1H, J = 14 Hz), 6.47 (s, 1H), 7.55 (m, 2H), 7.60 (m, 1H), and 7.85 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.8, 21.2, 27.7, 28.0, 28.5, 37.1, 56.7, 63.7, 68.4, 83.7, 117.9, 128.0, 129.2, 130.9, 133.8, 140.1, 168.3, 170.8, and 202.0; HRMS Calcd. for $C_{23}H_{31}BrSO_7$: 530.0974. Found: 530.0968.

A stirred solution containing 385 mg (0.7 mmol) of the above compound and 135 mg (0.7 mmol) of *p*-toluenesulfonic acid in 10 mL of benzene was heated at reflux under argon for 45 min. The benzene was removed under reduced pressure and the residue was dissolved in 10 mL of methanol. A 125 mg (3 mmol) sample of lithium hydroxide monohydrate was added and the reaction mixture was stirred at 0 °C for 14 h. The methanol was removed under reduced pressure, and the residue was partitioned between chloroform and a pH 7 phosphate buffer. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel to provide 159 mg (73%) of 3-phenylsulfonyl-methyl-2-(4-hydroxybutyl)cyclopenten-2-one; IR (neat) 1692, 1637, 1442, 1312, and 1142 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 (m, 2H), 1.45 (m, 2H), 1.90 (t, 2H, J = 8 Hz), 2.42 (m, 2H), 2.73 (m, 2H), 3.60 (t, 2H, J = 6 Hz), 4.19 (s, 2H), 7.61 (m, 2H), 7.71 (m, 1H), and 7.89 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.7, 23.8, 29.9, 32.1, 34.4, 58.4, 62.0, 128.1, 129.5, 134.3, 138.6, 145.8, 156.6, and 208.6; Anal. Calcd. for $C_{16}H_{20}SO_4$: C, 62.32; H, 6.54. Found: C, 62.24; H, 6.45.

A mixture containing 134 mg (0.5 mmole) of triphenylphosphine, 50 mg (0.7 mmol) of imidazole and 77 mg (0.25 mmole) of the above cyclopentenone was dissolved in 8 mL of ether and 4 mL of acetonitrile. The mixture was cooled to 0 °C and 177 mg (0.7 mmol) of iodine was added. The solution was stirred at 0 °C for 1.5 h and was then diluted with ether and filtered. The ether solution was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 65 mg (60%) of 3-phenylsulfonyl-methyl-2-(4-iodobutyl)cyclopenten-2-one (**26**); IR (neat) 1699, 1643, 1321, 1150,

and 1084 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.26 (m, 2H), 1.66 (m, 2H), 1.81 (t, 2H, *J* = 8 Hz), 2.39 (m, 2H), 2.70 (m, 2H), 3.08 (t, 2H, *J* = 7 Hz), 4.18 (s, 2H), 7.50 (m, 2H), 7.65 (m, 1H), and 7.85 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 6.2, 21.8, 28.4, 29.9, 32.9, 34.3, 58.3, 128.0, 129.4, 134.3, 138.5, 146.1, 156.8, and 208.0; HRMS Calcd. for $C_{16}H_{19}SO_3$ (M-I): 291.1055. Found: 291.1048.

To a suspension containing 15 mg (0.35 mmol) of NaH (60% in mineral oil) in 5 mL of ether at 0 °C was added 120 mg (0.3 mmol) of cyclopentenone **26** in 1 mL of ether. The reaction mixture was stirred a 0 °C for 2 h and then quenched with a saturated NH_4Cl solution and extracted with several portions of ether. The combined organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel and the major product was crystallized from a 2:1-hexane/CH_2Cl_2 mixture to provide 65 mg (83%) of 4-phenyl-sulfonylmethylene-spiro[4.4]nonan-1-one (**27**): IR (neat) 1744, 1630, 1449, 1323, and 1150 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 2H), 1.70-1.95 (m, 4H), 2.00 (m, 2H), 2.52 (m, 2H), 3.25 (td, 2H, *J* = 8 and 2 Hz), 6.25 (t, 1H, *J* = 2 Hz), 7.5-7.65 (m, 3H), and 7.90 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 24.5, 26.5, 34.9, 38.2, 62.3, 122.6, 127.0, 129.2, 133.3, 141.6, 167.0, and 217.0; Anal. Calcd. for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25. Found: C, 66.08; H, 6.25.

4-Methylene-spiro[4.4]non-2-en-1-one (29). To a stirred suspension containing 88 mg (2.0 mmol) of NaH (60% dispersion in mineral oil) and 5 drops of HMPA in 5 mL of ether at 0 °C was added a solution of 240 mg (0.6 mmol) of ketosulfone **27** in 2 mL of THF. The solution was stirred at 25 °C for 2 h and the reaction mixture was quenched with a saturated NH_4Cl solution, followed by extraction with several portions of ether. The combined organic layer were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 76 mg (92%) of 4-methylene-spiro[4.4]non-2-en-1-one (**29**) as a pale yellow oil; IR (neat) 2867, 1709, 1636, and 1447 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.60-2.05 (m, 8H), 5.19 (s, 1H), 5.22 (s, 1H), 6.17 (d, 1H, *J* = 5 Hz), and 7.65 (d, 1H, *J* = 5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 27.0, 37.3, 55.8, 110.4, 132.0, 155.6, 155.9, and 212.5; Anal. Calcd. for $C_{10}H_{12}O$: C, 81.03; H, 8.17. Found: C, 80.96; H, 8.05.

Acknowledgement: We gratefully acknowledge the U.S. Army ERDEC (#DAAA15-94-K-0004) for generous support of this work. C. L. M. is pleased to acknowledge the NIH for a postdoctoral fellowship (CA-08845-01). We also wish to thank Dr. Helmut Lipke for some experimental assistance. Use of high-field ^{1}H-NMR spectrometer used in these studies was made possible through equipment grants from the NIH and NSF.

References and Notes

1. Nelson, R. P.; Lawton, R. G. *J. Am. Chem. Soc.* **1966**, *88*, 3884. Nelson, R. P.; McEuen, J. M.; Lawton, R. G. *J. Org. Chem.* **1969**, *34*, 1225. McEuen, J. M.; Nelson, R. P.; Lawton, R. G. *J. Org. Chem.* **1970**, *35*, 690.
2. Ferris, A. F. *J. Org. Chem.* **1955**, *20*, 780.
3. Villieras, J.; Rambourd, M. *Synthesis* **1982**, 924.
4. Klager, K. *Montasch Chem.* **1965**, *96*, 1.
5. Knochel, P.; Seebach, D. *Nouv. J. Chim.* **1981**, *5*, 75. Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1981**, *22*, 3223. Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 3897. Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261.
6. Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 1475; **1985**, *26*, 425; **1984**, *25*, 4383.
7. Collard, J. N.; Benezra, C. *Tetrahedron Lett.* **1982**, *23*, 3725.
8. Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075.
9. Donaldson, R. E.; Saddler, J. C.; Byrn, S.; McKenzie, A. T.; Fuchs, P. *J. Org. Chem.* **1983**, *48*, 2167.
10. Anzeveno, P. B.; Matthews, D. P.; Barney, C. L.; Barbuch, R. J. *J. Org. Chem.* **1984**, *49*, 3134.
11. Speckamp, W. N.; Dijkink, J.; Huisman, H. O. *J. Chem. Soc.* **1970**, 196. Speckamp, W. N.; Dijkink, J.; Dekkers, A. W.; Huisman, H. O. *Tetrahedron* **1971**, *27*, 3143.
12. A multicoupling reagent has been defined as a species whose reactivity allows the sequential formation of two or more new carbon-carbon bonds.[5]
13. Padwa, A.; Austin, D. J.; Ishida, M.; Muller, C. L.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1992**, *57*, 1161.
14. Stirling, C. J. M. *J. Chem. Soc.* **1964**, 5863. Clinquini, M.; Colonna, S.; Cozzi, F.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 2061.
15. Padwa, A.; Ishida, M.; Muller, C. L.; Murphree, S. S. *J. Org. Chem.* **1992**, *57*, 1170.
16. Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019.
17. For a related reaction using ethyl 3,4-dibromo-2-butenoate, see: Moubarak, I.; Vessiere, R. *Synthesis* **1980**, 52.

18. Conrad, P. C.; Kwiatkowski, P. L.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 586 and references cited therein.

19. Trost, B. M.; Schmuff, N. R.; Miller, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 5981. Trost, B. M.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 7260. Trost, B. M.; Schmuff, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 396. Moriyama, T.; Mandai, T.; Kawada, M.; Otera, J.; Trost, B. M. *J. Org. Chem.* **1986**, *51*, 3896.

20. Durst, T. *Compr. Org. Chem.* **1979**, *3*, 171.

21. Paquette, L. A.; Moerck, R. E.; Harirchian, B.; Magnus, P. D. *J. Am. Chem. Soc.* **1978**, *100*, 1597. Paquette, L. A.; Williams, R. V. *Tetrahedron Lett.* **1981**, *22*, 4643. DeLucchi, O.; Lucchini, V.; Pasquato, L.; Modena, G. *J. Org. Chem.* **1984**, *49*, 596.

22. Julia, M.; Stacino, J. *Tetrahedron* **1986**, *42*, 2469.

23. Tanaka, K.; Kaji, A. In *The Chemistry of Sulphones and Sulphoxides;* Patai, S., Ed.; Wiley and Sons: New York, 1988; p 774.

24. Simpkins, N. S. *Sulfones in Organic Synthesis;* Pergamon: Oxford, 1993.

25. Marshall, J. A.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 858. Paquette, L. A.; Fischer, J. W.; Browne, A. R.; Doecke, C. W. *J. Am. Chem. Soc.* **1985**, *107*, 686. Chou, T.; You, M. L. *Tetrahedron Lett.* **1985**, *26*, 4495. Chou, T.; Hung, S. H.; Peng, M. L.; Lee, S. J. *Tetrahedron Lett.* **1991**, *32*, 3551. Chou, T.; You, M. L. *J. Org. Chem.* **1987**, *52*, 2224.

26. Bonner, W. A.; Grimm, R. A. In *The Chemistry of Organic Sulphur Compounds;* Kharasch, N.; Meyers, C. Y., Eds.; Pergamon: Oxford, 1966; Vol. 2, p 35.

27. Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* **1973**, 746. Hervé du Penhoat, C.; Julia, M. *Tetrahedron* **1986**, *42*, 4807. Olson, G. L.; Cheung, H. C.; Morgan, K. D.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3287. Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 6969.

28. Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833. Kocienski, P. *Phosphorus Sulfur,* **1985**, *24*, 97. Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1990**, *31*, 7105.

29. Trost, B. M.; Schmuff, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 396. Hayakawa, K.; Nishiyama, H.; Kanematsu, K. *J. Org. Chem.* **1985**, *50*, 512.

30. Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107.

31. Smith, A. B., III; Hale, K. J.; McCauley, J. P., Jr. *Tetrahedron Lett.* **1989**, *30*, 5579.

32. Ellison, R. A. *Synthesis* **1973**, 397. Paquette, L. A. *Tetrahedron* **1981**, *37*, 452. Trost, B. M. *Chem. Soc. Rev.* **1982**, 141. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. Ramaiah, M. *Synthesis* **1984**, 529. Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284.

33. Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry;* Springer-Verlag: Berlin, 1987. Hudlicky, T.; Price, J. *Chem. Rev.* **1989**, *89*, 1467.

34. Giese, B. *Radicals in Organic Synthesis;* Pergamon Press: Oxford, England, 1986. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. Curran, D. P. *Synthesis* **1988**, 417. Jasperse, C. G.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

35. Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247. Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3. Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

36. Wong, H. N. C.; Lau, K.; Tam, K. *Top. Curr. Chem.* **1986**, *133*, 83. Greene, A. E.; Charbonnier, F.; Luche, M. J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752.

37. Mann, J. *Tetrahedron* **1986**, *42*, 4611. Trost, B. M.; Grese, T. A.; Chan, D. M. T. *J. Am. Chem. Soc.* **1989**, *54*, 1647. Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300.

38. Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691. Laabassi, M.; Gree, R. *Tetrahedron Lett.* **1988**, *29*, 611. Danheiser, R. L.; Bronson, J. J.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579. Barriere, F.; Barriere, J. C.; Barton, D. H. R.; Cleophax, J.; Gateaux-Olesker, A.; Gero, S. D.; Tadj, F. *Tetrahedron Lett.* **1985**, *26*, 3121.

39. Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394.

40. Berube, G.; Fallis, A. G. *Can. J. Chem.* **1991**, *69*, 77.

41. Autczak, K.; Kingston, J. F.; Alward, S. J.; Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 829.

42. Oku, A.; Harada, T.; Kita, K. *Tetrahedron Lett.* **1982**, *23*, 681.