Pergamon

Tetrahedron Vol. 51, No. 34, pp. 9301-9318, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00518-8

A Palladium-Mediated Tandem Carbon-Carbon Bond Forming Method Featuring Nucleophilic Substitution of Intermediate π-Allylpalladium Complexes Produced via the Heck Reaction

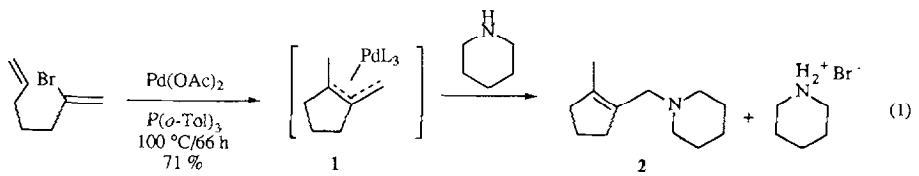
Christine S. Nylund, Daniel T. Smith, John M. Klopp, and Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, PA 16802

Abstract: Carbon nucleophiles are alkylated with π-allylpalladium complexes formed by the palladium-catalyzed Heck reaction of a vinyl bromide and an olefin. This methodology achieves the consecutive formation of two carbon-carbon bonds in one simple operation and can be applied both inter- and intramolecularly. The rapid construction of functionalized carbobicyclic compounds is effected by the intramolecular version of this condensation.

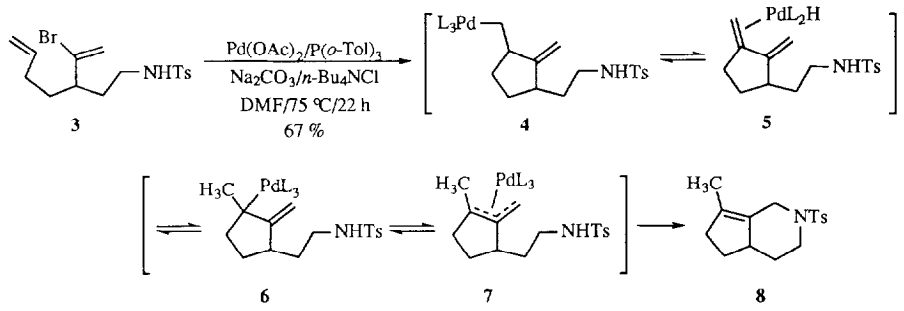
Introduction

The formation of a carbon-carbon bond by the palladium-catalyzed coupling of a vinyl or aryl halide with an olefin, known as the Heck reaction,[1] has become a powerful tool in organic chemistry. Both the inter[2]- and intramolecular[3] versions of this reaction have found widespread use in synthesis. One common problem with this methodology is that when a vinyl halide reacts with an unactivated olefin, a stable π-allylpalladium species may be formed which ends the catalytic cycle by sequestering the palladium. Heck found that the inclusion of a secondary amine in the reaction mixture resolved this problem by forming allylic amine products and freeing the palladium to continue the catalytic cycle.[4] For example, the Heck reaction of 2-bromo-1,6-heptadiene in the presence of piperidine under the conditions shown provides aminocyclopentene **2**, which results from the substitution of the π-allylpalladium intermediate **1** at the exocyclic terminus with piperidine (eq 1).[5]



Previous work in our laboratories has addressed the reactions of substrates which contain the vinyl halide, olefin, and a nitrogen nucleophile in one molecule.[6] It was found that π-allylpalladium intermediates are formed regiospecifically by an initial intramolecular Heck reaction and are substituted by internal sulfonamide nucleophiles under mild conditions to afford a variety of bicyclic heterocycles. For example, diene sulfonamide **3**, when subjected to the conditions shown, cyclized to the bicyclic sulfonamide **8** in 67 % yield (Scheme 1).

Scheme 1

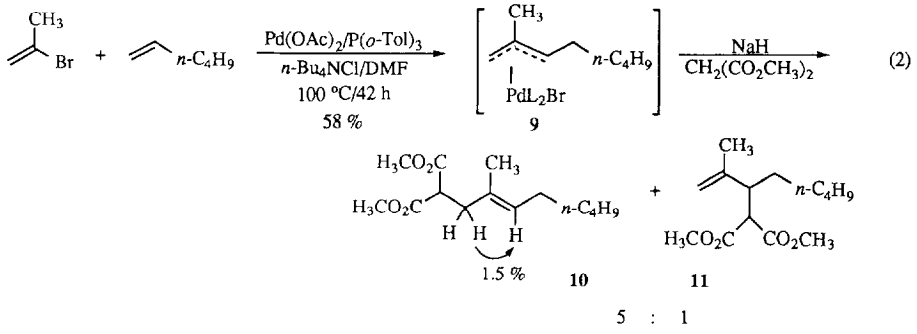


The transformation is thought to proceed by the ring closure of palladated **3** to form intermediate **4**, which β-hydrogen eliminates to form η^2-diene **5**. Palladium hydride then readds to the complexed olefin to produce σ-allylpalladium species **6** which rearranges to π-allylpalladium complex **7**. The internal sulfonamide nucleophile then attacks at the less substituted terminus of the π-allylpalladium species 7 to provide bicyclic sulfonamide **8**.

We have recently examined extending this three component cyclization to include carbon rather than nitrogen nucleophiles[7] since the alkylation of stabilized carbanions with π-allylpalladium species formed by other methods is well-documented.[8] In this paper we describe the details of these studies.

Results and Discussion

Feasibility studies first focused on the intermolecular condensation of a vinyl halide, olefin, and a malonate ester to address the possibility of forming two carbon-carbon bonds consecutively. Initial studies involved the reaction of 2-bromo-1-propene with 1-hexene and dimethyl malonate. To a mixture of 2 equiv of *n*-Bu_4NCl[9] and 2 equiv of NaH in DMF was added 2 equiv of dimethyl malonate. Once gas evolution ceased, 5 mole % of $Pd(OAc)_2$, 10 mole % of P(*o*-Tol)$_3$, 1 equiv of 1-hexene and 1 equiv of 2-bromo-1-propene were added, and the mixture was heated at 100 °C for 42 h in a sealed tube to produce an inseparable 5:1 mixture of olefinic diesters **10** and **11** in 58 % combined yield (eq 2). The product ratio was determined by ^{1}H NMR and the *E*

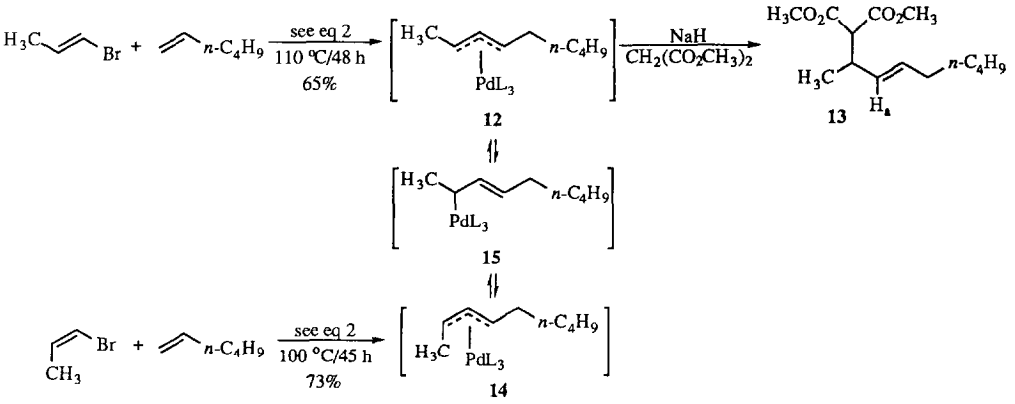


(2)

olefin geometry of compound **10** was determined by NOE experiments on the mixture. The reaction is proposed to occur through the π-allylpalladium species **9**, which as expected undergoes malonate attack preferentially at the less substituted or less sterically hindered site.[8b,10]

The effect of the stereochemistry of the vinyl bromide double bond in this condensation reaction was investigated by comparing the results from the reactions using *Z*- and *E*-1-bromo-1-propene as the vinyl halide component. *E*-1-Bromo-1-propene, 1-hexene, and dimethyl malonate (2:1:2 ratio) were heated in DMF at 110 °C for 48 h to provide *E*-alkenyl malonate **13** as the only detected product in 65 % yield (Scheme 2). The *E* configuration of the double bond was assigned from the couplings of proton H_a in the ^1H NMR, which appeared as a doublet of doublets with coupling constants of 15.7 Hz (trans olefin) and 9.4 Hz. In this case, the malonate nucleophile attacks the π-allylpalladium intermediate **12** selectively at the methyl-substituted terminus.

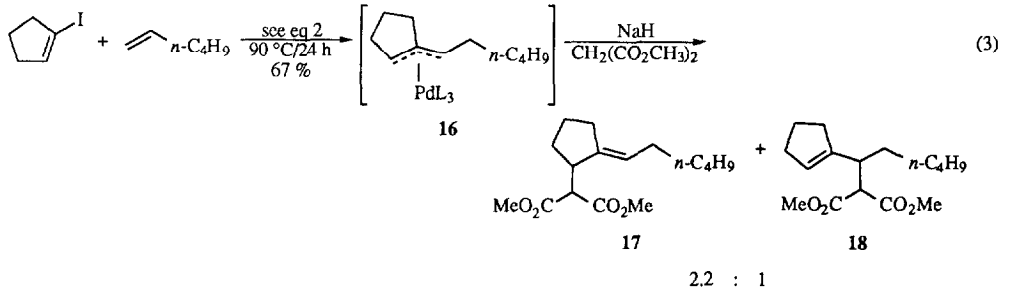
Scheme 2



12 **13** **14** **15**

Similarly, *Z*-1-bromo-1-propene, 1-hexene, and dimethyl malonate (2:1:2 ratio) were reacted (DMF, 100 °C, 45 h) to provide **13** in 73 % yield (Scheme 2). Since, in general, equilibration of π-allylpalladium stereoisomers to the sterically less congested *syn,syn* form **12** is facile,[8c,11] it seems likely that an initially formed *anti,syn* π-allylpalladium complex **14** equilibrates via the σ-allylpalladium species **15** to **12**.

In another example of this condensation, the reaction of 1-iodo-1-cyclopentene,[12] 1-hexene, and dimethyl malonate (2:1:1 ratio) provided an inseparable 2.2:1 mixture of regioisomeric products **17** and **18** as determined by ^1H NMR (eq 3).[13] The stereochemistry of compound **17** is indeterminate, although the *E* olefin isomer is



(3)

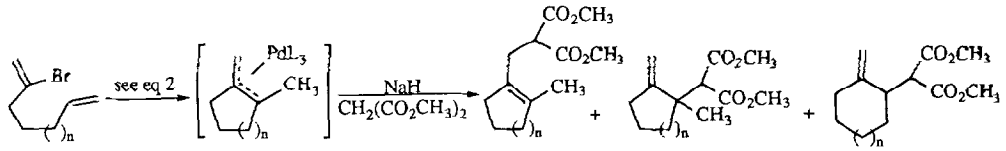
16 **17** **18**

2.2 : 1

the expected product.[8] The regioisomeric products arise from the nucleophilic attack of dimethyl malonate anion at the endocyclic and exocyclic termini of the intermediate π-allylpalladium species **16**.

Another variation of this chemistry involved the intramolecular Heck reaction of bifunctional substrates which contain both the olefin and vinyl halide. For instance, 2-bromo-1,7-octadiene (**19a**)[5] produced the

methylene cyclohexane derivative **22a** in 63 % yield (eq 4, n=2). This product arises from initial 6-exo cyclization of palladated **19a** to regiospecifically form the π-allylpalladium intermediate **20a**, which is substituted by dimethyl malonate anion at the endocyclic terminus. The endocyclic attack of the nucleophile



a) n=2	100 °C/43 h/63 %	0	:	100	:	0	(4)
b) n=1	90 °C/26 h/80 %	62	:	23	:	15	

upon the cyclohexenyl π-allylpalladium system **20a** has previously been rationalized by assuming that the rigid conformation of the cyclohexane ring promotes disfavorable steric interactions between the bulky *o*-tolylphosphine ligands on the palladium and the axial protons on the ring. As a result, the palladium is more closely complexed to the exo portion of the allyl group, liberating the endocyclic position for nucleophilic attack.[10,14]

When 2-bromo-1,6-heptadiene (**19b**)[5] and the malonate salt were heated at 90 °C for 26 h a mixture of condensation products was formed (eq 4, n=1). Nucleophilic attack of the malonate anion occurred predominantly at the exocyclic position of **20b** to give cyclopentene **21b** along with the minor regioisomeric methylene cyclopentane **22b**. Varying amounts of cyclohexane product **23b**, formed via initial 6-endo cyclization followed by malonate alkylation, were produced depending upon reaction conditions.[15] Thus when 5 mole % of $Pd(OAc)_2$, 10 mole % of P(*o*-Tol)3, and 2.0 equiv of *n*-Bu_4NCl were utilized, the ratio of products **21b**:**22b**:**23b** was 62:23:15 in 80 % combined yield. The effects of the phosphine ligand and *n*-Bu_4NCl were studied by experiments in which the reaction time, temperature, solvent, and molar ratio of $Pd(OAc)_2$, NaH, and dimethyl malonate were maintained. The results are shown in Table 1 with the product ratios determined by HPLC. It is clear that the inclusion of *n*-Bu_4NCl increases the yield of the reaction products, as well as affecting

Table 1. Effects of Ligand and *n*-Bu_4NCl in the Cyclization of Compound **19b**

Entry	Ligand	*n*-Bu_4NCl	% Yield	Product Ratio (21b : 22b : 23b)
1	10 % P(*o*-Tol)3	+	80	62 : 23 : 15
2	10 % P(*o*-Tol)3	-	60	56 : 13 : 31
3	5 % dppp	-	26	56 : 13 : 31
4	5 % dppp	+	41	27 : 24 : 49
5	10 % dppp	-	41	85 : 0 : 15

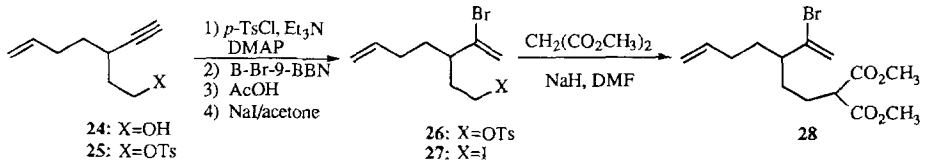
the product ratio (entry 1 vs. 2 and 4 vs. 3). The observation that *n*-Bu_4NCl significantly affects the product ratio suggests that its role is not merely one of phase transfer catalyst,[9] but that chloride may be also acting as a ligand on the palladium metal.[16]

The product ratio and yield of the reaction products are also altered by the phosphine ligand used. In this particular example, using P(*o*-Tol)3 as a ligand produces higher product yields than the less bulky bidentate

ligand 1,3-bis(diphenylphosphino)propane (dppp) (entry 1 vs. 4 and 2 vs. 3). Using 5 mole % of dppp in the presence of *n*-Bu_4NCl alters the product ratio so that the major product is now **23b**, arising from initial 6-endo cyclization (entry 4). Also, using 10 mole % of dppp without *n*-Bu_4NCl completely eliminates the minor 5-exo cyclization product, **22b** (entry 5). At this point the effects of the ligand are unpredictable, and the choice of the best ligand for a particular reaction remains an experimental parameter.

To achieve this tandem carbon-carbon bond-forming reaction completely intramolecularly, substrates were synthesized which contain all three components needed for the condensation. A dimethyl malonate-derived cyclization substrate was synthesized by the four-step route outlined in Scheme 3. Alcohol **24**[6a] was tosylated to afford compound **25** (86 % yield), which was treated with B-Br-9-BBN at 0 °C followed by glacial acetic

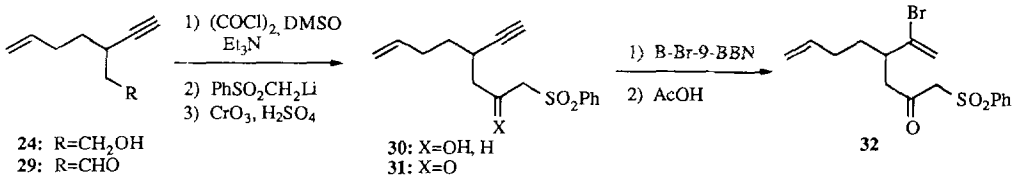
Scheme 3



acid to form vinyl bromide **26** (81 %).[17] The tosylate was then converted to iodide **27** with sodium iodide in acetone (82 %). Sodio dimethyl malonate was alkylated with iodide **27** to provide cyclization substrate **28** (84 %).

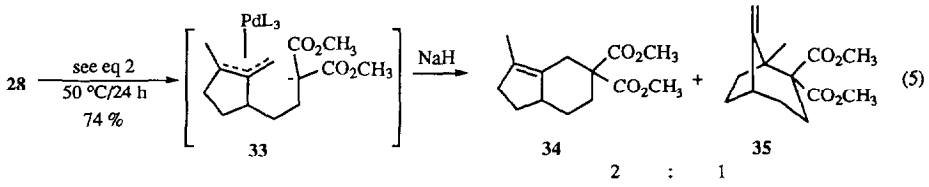
A structurally similar β-keto sulfone substrate was synthesized from the same starting alcohol in four steps as depicted in Scheme 4. Therefore, alcohol **24** was oxidized under Swern conditions[18] to the aldehyde **29** (100 % yield). The lithium anion of methyl phenyl sulfone was added to this aldehyde to provide the β-hydroxy

Scheme 4

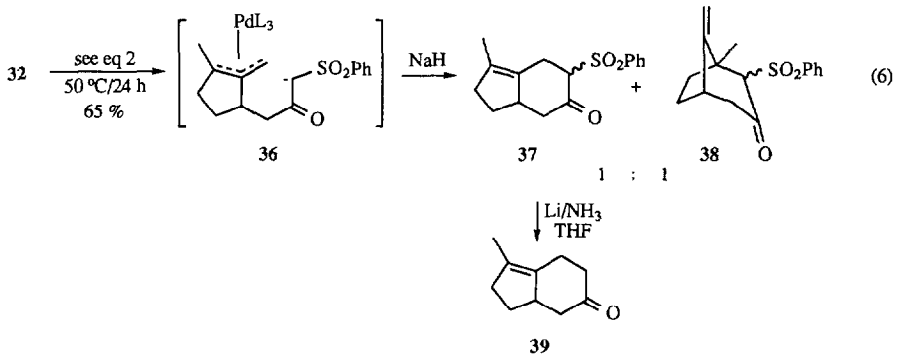


sulfone **30** (48 %). Jones oxidation[19] of **30** provided the β-keto sulfone **31** (79 %), which was treated with B-Br-9-BBN[17] to give the vinyl bromide cyclization substrate **32** in 64 % yield.

We were pleased to find that trifunctional malonate derivative **28** cyclized when treated with NaH, *n*-Bu_4NCl, $Pd(OAc)_2$, and P(*o*-Tol)$_3$, in DMF at 50 °C (eq 5). The product formed consisted of a 2:1 mixture of fused bicyclic diester **34** and bridged bicyclic compound **35** (74 % combined yield) as determined by ^1H NMR. The fused bicyclic compound **34** results from the internal nucleophilic attack at the exocyclic end of the π-allylpalladium complex **33**, whereas the bridged product **35** arises from substitution at the endocyclic position. This regioselectivity is in accord with our previous results, which indicated that attack at the less substituted terminus of the π-allylpalladium intermediate is usually favored. In an experiment using Et_3N as the base instead of NaH, only starting material was recovered, indicating that a base which can deprotonate the malonate is necessary for the cyclization to be successful.



β-Keto sulfone **32** was cyclized to provide a 1:1 mixture of bicyclic products **37** and **38** in 65 % yield (eq 6). The product ratio was determined by ^{1}H NMR. The bridged bicyclic β-keto sulfone **38,** which resulted from attack of the nucleophile at the endocyclic terminus of the π-allylpalladium intermediate **36**, was formed as one sulfone diastereomer of undetermined configuration. The fused bicyclic β-keto sulfone **37** was a mixture

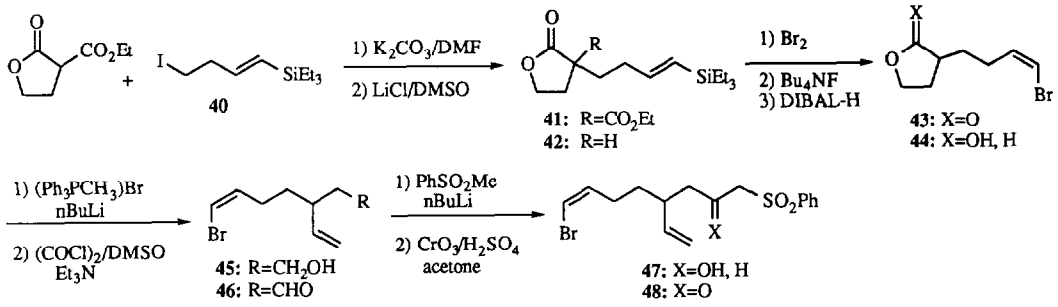


of diastereomers. To confirm the structure of cyclization product **37**, the sulfone was removed under dissolving metal conditions[20] to provide the bicyclic ketone **39** in 60 % yield.

The lack of regioselectivity in the nucleophilic substitution of π-allylpalladium complex **36** relative to complex **33** might be explained by the nature of the nucleophile. The malonate nucleophile is presumably bulkier than the β-keto sulfone and may experience greater steric interactions in its approach to the more crowded endocyclic terminus of **33**, thereby favoring attack at the exocyclic terminus to provide the fused bicyclic product **34** preferentially. The β-keto sulfone of **36** experiences less steric interaction and therefore attacks both ends of the π-allylpalladium intermediate equally well to afford a 1:1 ratio of regioisomeric products **37** and **38**.

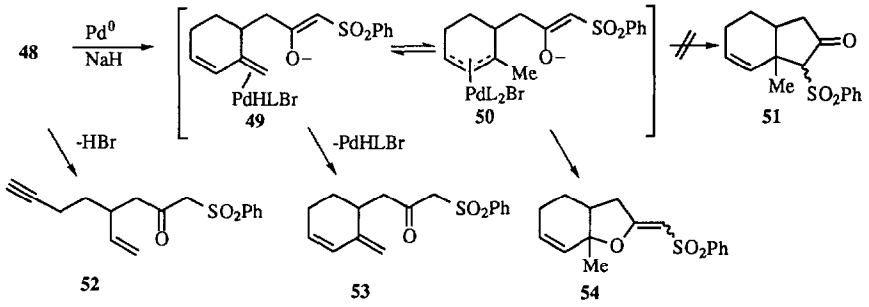
To test the applicability of this methodology to the synthesis of hydrindenones, compound **48** containing a terminal *Z*-vinyl bromide, olefin and β-keto sulfone was synthesized (Scheme 5). The synthesis of **48** began with 2-ethoxycarbonyl-γ-butyrolactone,[21] which was treated with potassium carbonate in DMF followed by 4-iodo-*E*-1-triethylsilyl-1-butene (**40**)[22] to give the alkylated ester lactone **41** (83 %). Decarboxylation was effected by LiCl in DMSO to provide the butenyl lactone **42** (77 %).[23] The olefin was brominated and then desilicobrominated[24] with tetrabutylammonium fluoride to afford the *Z*-vinyl bromide lactone **43** (80 %). Reduction of the lactone to the lactol **44** with DIBAL-H (83 %), followed by Wittig olefination gave the alcohol **45** (75 %). The alcohol was oxidized under Swern conditions[18] to provide the aldehyde **46** (99 %). Treatment of the aldehyde with the lithium anion of methyl phenyl sulfone, followed by oxidation of the resulting β-hydroxy sulfone **47** with Jones reagent[19] furnished the desired β-keto sulfone **48** (43 %).

Scheme 5



Unfortunately, when β-keto sulfone **48** was subjected to a variety of Heck reaction conditions the desired hydrindenone **51** was not formed (Scheme 6). The products that were in fact produced included alkyne **52**, which is formed by elimination of HBr from the vinyl bromide **48**, diene **53** from the dissociation of the palladium from the η^2-palladium complex **49**, and alkylidenetetrahydrofuran **54**, which results from O-alkylation of the β-keto sulfone enolate with the intermediate π-allylpalladium complex **50**.

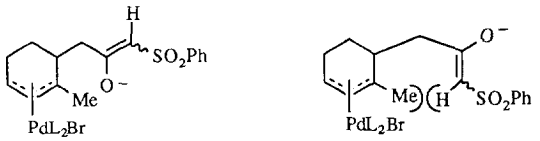
Scheme 6



In attempts to promote the formation of the desired adduct **51**, various phosphine ligands were tried including P(*o*-Tol)$_3$, 1,2-bis(diphenylphosphino)ethane (dppe or DIPHOS), and dppp, temperatures were varied from 80-130 °C, reaction times extended from 10-43.5 h, and solvents varied between DMF, CH_3CN, and DMSO. Since the addition of thallium salts is sometimes successful in promoting C-alkylation over O-alkylation,[25] TlOAc was added to the reaction mixture in some experiments, but the desired product **51** was not formed. In most cases, mixtures of **52**, **53**, and **54** were actually generated. However, when the reaction was conducted using 5 mol % of Pd(OAc)$_2$, 10 mole % of P(*o*-Tol)$_3$, and 2.0 equiv of *n*-Bu$_4$NCl in DMF at 90 °C for 24 h, alkylidenetetrahydrofuran **54** was the sole isolable product in 42 % yield.

In known examples where β-keto sulfones were reported to give O-alkylation products by the substitution of π-allylpalladium intermediates, the alkylidenetetrahydrofuran could be isomerized to the C-alkylation product via the π-allylpalladium intermediate or avoided altogether by using DIPHOS as the ligand in DMSO.[26] However, applying these conditions did not produce the C-alkylated product **51**. When the cyclization of **48** was tried using DIPHOS in DMF or CH_3CN only diene **53** and alkylidenetetrahydrofuran **54** were formed. Another bidentate ligand, dppp, was likewise unsuccessful in providing the desired product **51**.

A rationalization for the inability to form the desired hydrindenone **51** arises from an examination of the enolate rotamers of π-allylpalladium intermediate **50** (Figure 1). It appears that rotamer **B** suffers unfavorable



Rotamer **A** Rotamer **B**

Figure 1. Enolate Rotamers of **50**

steric interactions, whereas in rotamer **A** the steric interactions are minimized. Thus, since rotamer **A** leads to product **54** and rotamer **B** leads to the desired product **51**, the steric congestion that rotamer **B** experiences may explain why the bicyclic ketone **51** is not formed under any set of conditions.

In conclusion, we have demonstrated the usefulness of the palladium-mediated tandem carbon-carbon bond forming reaction in both inter- and intramolecular cases. Stabilized carbanions act as nucleophiles in the substitution of π-allylpalladium intermediates resulting from the Heck reaction of a vinyl halide and an olefin. In almost all of the examples, mixtures of regioisomers were formed with the major isomer resulting from nucleophilic attack at the less hindered terminus of the π-allylpalladium intermediate, as is the case when these species are formed by other methods. Simple acyclic compounds which contain the three requisite moieties of vinyl halide, olefin, and nucleophile are readily cyclized to afford functionalized carbobicyclic compounds. We are currently investigating applications of this methodology to the synthesis of some natural products.

Experimental Section

General Experimental. All non-aqueous reactions were run under a positive pressure of dry argon and organic solutions were dried over $MgSO_4$ unless otherwise noted. Preparative tlc was performed using VWR Scientific silica gel 60 PF-254. Flash chromatography was performed using VWR Scientific silica gel (230-400 mesh). HPLC was performed using a Beckman Ultrasphere Si 5 m, 10.0 mm x 25 cm column. THF and ether were dried over sodium/benzophenone ketyl. Methylene chloride, acetonitrile, and DMSO were distilled from calcium hydride. Methanol was distilled from magnesium turnings. DMF was dried over 4Å molecular sieves and distilled under reduced pressure.

General Procedure for the Condensation Reactions. To a rapidly stirred suspension of NaH (60 % in mineral oil, 2.0 equiv) and *n*-Bu_4NCl (2.0 equiv) in DMF under argon in a resealable tube was added dimethyl malonate (2.0 equiv). Once H_2 evolution had ceased $Pd(OAc)_2$ (5 mol %), P(*o*-Tol)$_3$ (10 mol %), and a solution of vinyl halide (1.0 equiv) and olefin (1.0 equiv) in DMF (final solution 0.1 M) were added. The reaction mixture was degassed by the freeze-thaw method, sealed under vacuum, and heated at the specified temperature for the specified time. The mixture was cooled to rt and filtered through a plug of flash silica gel eluting with 300 mL of 50 % ether/hexanes. The filtrate was washed with three 50 mL portions of water, once with brine, dried and concentrated.

Preparation of Malonate Derivatives 10 and 11. The general procedure was followed. 2-Bromo-1-propene (105 μL, 144 mg, 1.19 mmol) and 1-hexene (148 μL, 100 mg, 1.19 mmol) in 12 mL of DMF were

heated at 100 °C for 42 h. The residue was purified by flash chromatography (20 % ethyl acetate/hexanes) to give a 5:1 mixture of **10** and **11** (combined 177 mg, 58 %). The ratio of **10** to **11** was determined by integration of the vinylic protons in the ^{1}H NMR. These regioisomeric products were inseparable by HPLC. Mixture of **10** and **11**: IR (film) 2960, 2920, 2860, 1730, 1640, 1435 cm^{-1}; EI MS m/z (relative intensity) 256 (M^+, 32), 158 (64), 43 (100).

*Malonate derivative **10***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (1 H, t, J=7.2 Hz), 3.67 (6 H, s), 3.54 (1 H, t, J=7.9 Hz), 2.54 (2 H, d, J=7.9 Hz), 1.94-1.87 (2 H, m), 1.57 (3 H, s), 1.29-1.18 (6 H, m), 0.88-0.82 (3 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 130.3, 127.9, 52.2, 50.5, 38.6, 31.3, 29.1, 27.7, 22.4, 15.5, 13.9.

*Malonate derivative **11***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (2 H, d, J=13.8 Hz), 3.67 (6 H, s), 3.42 (1 H, d, J=11.2 Hz), 2.65-2.62 (1 H, m), 1.94-1.87 (2 H, m), 1.62 (3 H, s), 1.29-1.18 (6 H, m), 0.88-0.82 (3 H, m).

Preparation of Malonate Derivative 13 from E-1-Bromo-1-propene. The general procedure was followed. *E*-1-Bromo-1-propene (100 μL, 142 mg, 1.17 mmol) and 1-hexene (73 μL, 50 mg, 0.59 mmol) in 5 mL of DMF were heated at 110 °C for 48 h. The crude residue was purified by flash chromatography (10 % ethyl acetate/hexanes) to give malonate derivative **13** (97 mg, 65 %): IR (film) 2940, 2850, 1765, 1740, 1440 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51-5.40 (1 H, m), 5.27 (1 H, dd, J=15.7 Hz, 9.4 Hz), 3.72 (3 H, s), 3.64 (3 H, s), 3.23 (1 H, d, J=9.9 Hz), 2.86 (1 H, q, J=9.4 Hz), 1.97-1.86 (2 H, m), 1.64-1.58 (1 H, m), 1.29-1.14 (4 H, m), 1.02 (3 H, d, J=6.3 Hz), 0.88-0.79 (4 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 168.7, 131.9, 130.9, 57.9, 52.2, 52.0, 37.4, 32.3, 31.1, 28.9, 22.4, 18.5, 13.9; EI MS m/z (relative intensity) 256 (M^+, 5), 197 (14), 125 (75), 55 (100); exact mass calcd for $C_{14}H_{24}O_4$ 256.1674, found 256.1682.

Preparation of Malonate Derivative 13 from Z-1-Bromo-1-propene. The general procedure was followed. *Z*-1-Bromo-1-propene (99 μL, 140 mg, 1.16 mmol) and 1-hexene (73 μL, 50 mg, 0.582 mmol) in 5 mL of DMF were heated at 100 °C for 45 h. The crude product was purified by flash chromatography (5 % ethyl acetate/hexanes) to give malonate derivative **13** (110 mg, 73 %). The spectral data agreed with that listed above for **13**.

Preparation of Compounds 17 and 18. The general procedure was followed. 1-Iodo-1-cyclopentene (195 mg, 1.01 mmol) and 1-hexene (63 μL, 42 mg, 0.503 mmol) in 5 mL of DMF were heated at 90 °C for 24 h. The residue was purified by flash chromatography (10 % ethyl acetate/hexanes) to give an inseparable 2.2:1 mixture of malonate derivatives **17** and **18** (combined 96 mg, 67 %)whose ratio was determined by integration of the vinylic protons in the ^{1}H NMR. Mixture of **17** and **18**: IR ($CHCl_3$) 3024, 2958, 2929, 2856, 1729, 1602, 1458 cm^{-1}; EI MS m/z (relative intensity) 289 (M^+, 38), 223 (67), 150 (100).

*Cyclopentane **17***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17-5.11 (1 H, m), 3.72 (6 H, s), 3.48 (1 H, d, J=8.3 Hz), 3.13-3.07 (1 H, m), 2.30-2.15 (3 H, m), 1.95-1.89 (1 H, m), 1.85-1.71 (2 H, m), 1.68-1.57 (2 H, m), 1.39-1.16 (6 H, m), 0.92-0.86 (3 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 168.9, 142.9, 122.7, 55.3, 52.1, 43.9, 31.4, 30.2, 29.3, 29.1, 28.4, 23.5, 23.4, 22.5, 13.9.

*Cyclopentene **18***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48-5.46 (1 H, m), 3.76 (3 H, s), 3.55 (3 H, s), 3.44 (1 H, d, J=8.8 Hz), 3.09-2.99 (1 H, m), 2.30-2.15 (3 H, m), 1.95-1.89 (1 H, m), 1.85-1.71 (2 H, m), 1.68-1.57 (2 H, m), 1.39-1.16 (6 H, m), 0.92-0.86 (3 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.7, 142.3, 128.1, 56.5, 52.3, 41.5, 31.9, 31.5, 31.1, 31.0, 29.1, 26.6, 23.5, 22.4, 13.9.

Reaction of 2-Bromo-1,7-octadiene (19a) with Dimethyl Malonate. The general procedure was followed. 2-Bromo-1,7-octadiene (**19a**)[5] (100 mg, 0.53 mmol) was added to a solution of 5.3 mL of DMF and heated at 100 °C for 43 h. The crude residue was purified by flash chromatography (10 % ethyl acetate/hexanes) to give methylene cyclohexane **22a** (80 mg, 63 %): IR (film) 2920, 2850, 1730, 1630, 1430 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.75 (1 H, s), 4.68 (1 H, s), 4.01 (1 H, s), 3.68 (3 H, s), 3.58 (3 H, s), 2.30-2.15 (2 H, m), 1.60-1.40 (6 H, m), 1.30 (3 H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.4, 168.3, 152.1, 109.5, 54.4, 52.1, 51.9, 42.3, 38.3, 32.8, 28.0, 22.1, 21.8; EI MS m/z (relative intensity) 240 (M^+, 1), 133 (11), 109 (35), 108 (88); exact mass calcd for $C_{13}H_{20}O_4$ 240.1361, found 240.1362.

Reaction of 2-Bromo-1,6-heptadiene (19b) with Dimethyl Malonate. The general procedure was followed using 2.0 equiv of NaH, 2.0 equiv of dimethyl malonate, 1.0 equiv of **19b**,[5] 5 mol % of $Pd(OAc)_2$, and varying the reaction conditions as in Table 1 to give mixtures of compounds **21b**, **22b**, and **22c**. Product mixtures were purified by flash chromatography (10 % ethyl acetate/hexanes) and product ratios were determined by HPLC (5 % ethyl acetate/hexanes).

*Cyclopentene **21b**:* ^1H NMR (300 MHz, $CDCl_3$) δ 3.69 (6 H, s), 3.49 (1 H, t, J=7.8 Hz), 2.66 (2 H, d, J=7.8 Hz), 2.23 (4 H, t, J=7.3 Hz), 1.73 (2 H, m), 1.60 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 135.2, 130.1, 52.3, 50.3, 38.4, 35.1, 28.0, 21.6, 13.7; EI MS m/z 226 (M^+); exact mass calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1208.

*Cyclopentane **22b**:* ^1H NMR (300 MHz, $CDCl_3$) δ 4.92-4.91 (1 H, m), 4.73-4.72 (1 H, m), 3.72 (3 H, s), 3.67 (3 H, s), 3.62 (1 H, s), 2.49-2.32 (3 H, m), 1.81-1.69 (1 H, m), 1.64-1.53 (2 H, m), 1.20 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.5, 159.1, 104.9, 59.3, 52.1, 51.9, 46,4, 36.8, 33.9, 27.1, 22.7; CI MS m/z 277 (M^++1), 133, 95.

*Cyclohexane **23b**:* ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (1 H, s), 4.59 (1 H, s), 3.78 (3 H, s), 3.70 (3 H, s), 3.74 (1 H, d, J=10.5 Hz), 3.04-2.96 (1 H, m), 2.29-2.19 (2 H, m), 2.17-2.08 (1 H, m), 1.99-1.89 (1 H, m), 1.58-1.44 (4 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 168.9, 149.0, 108.1, 54.1, 52.5, 52.4, 43.3, 34.0, 30.9, 28.2, 23.3; CI MS m/z 227 (M^++1), 195, 167.

Tosylation of Alcohol 24. To a solution of alcohol **24**[6a] (502 mg, 3.63 mmol), triethylamine (1.01 mL, 7.26 mmol), and DMAP (catalytic amount) in 7 mL of CH_2Cl_2 cooled to 0 °C was added *p*-tosyl chloride (831 mg, 4.36 mmol) in one portion. The reaction mixture was slowly warmed to 25 °C and stirred overnight. A saturated aqueous solution of $NaHCO_3$ was added and the aqueous layer was extracted with three 20 mL portions of CH_2Cl_2. The combined organic extracts were washed with 5 % HCl, saturated $NaHCO_3$, brine, dried, and concentrated. The residue was purified by flash chromatography (6/1/0.7 hexanes/CH_2Cl_2/ethyl acetate) to afford the tosylate **25** (914 mg, 86 %): IR (film) 3280, 2910, 2100, 1630, 1590, 1360, 1190 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (2 H, d, J=8.3 Hz), 7.34 (2 H, d, J=8.1 Hz), 5.82-5.68 (1 H, m), 5.05-4.94 (2 H, m), 4.23-4.17 (2 H, m), 2.52-2.46 (1 H, m), 2.44 (3 H, s), 2.25-2.07 (2 H, m), 1.99 (1 H, d, J=2.4 Hz), 1.90-1.79 (1 H, m), 1.75-1.63 (1 H, m), 1.52-1.45 (2 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 137.5, 132.9, 129.8, 127.9, 115.2, 85.0, 70.7, 68.3, 33.9, 33.7, 31.0, 27.2, 21.5; exact mass calcd for $C_{16}H_{20}O_3S$ 292.1133, found 292.1161.

Conversion of Tosylate 25 to Vinyl Bromide 26. To a solution of B-Br-9-BBN (1 M in CH_2Cl_2, 1.79 mL, 1.79 mmol) in 3.1 mL of CH_2Cl_2 cooled to 0 °C was added dropwise a solution of alkyne **25** (238 mg, 0.815 mmol) in 1 mL of CH_2Cl_2. The solution was stirred at 0 °C for 3 h, and glacial acetic acid (0.821 mL, 14.35 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h, warmed to 25 °C, and water

was added. The aqueous layer was extracted with three 10 mL portions of CH_2Cl_2. The combined organic extracts were washed with water, brine, dried and concentrated. The crude residue was purified by flash chromatography (5 % ethyl acetate/hexanes) to give vinyl bromide **26** (245 mg, 81 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (2 H, d, J=8.3 Hz), 7.35 (2 H, d, J=8.3 Hz), 5.81-5.67 (1 H, m), 5.53 (1 H, d, J=1.5 Hz), 5.42 (1 H, d, J=1.5 Hz), 5.03-4.95 (2 H, m), 4.08-3.91 (2 H, m), 2.46 (3 H, s), 2.41-2.31 (1 H, m), 2.09-1.99 (1 H, m), 1.96-1.84 (1 H, m), 1.76-1.69 (2 H, m), 1.57-1.46 (1 H, m), 1.38-1.26 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 137.7, 136.9, 132.9, 129.8, 127.9, 119.5, 115.2, 67.9, 44.6, 32.4, 32.2, 30.8, 21.6.

Conversion of Tosylate 26 to Iodide 27. To a solution of tosylate **26** (705 mg, 1.89 mmol) in 13 mL of dry acetone was added NaI (1.42 g, 9.45 mmol) in one portion at rt. The solution was stirred overnight and water was added. The resulting solution was extracted with three 20 mL portions of ether. The combined extracts were washed with brine, dried and concentrated. The residue was purified by flash chromatography (hexanes) to afford the iodide **27** (508 mg, 82 %): IR (film) 3060, 2910, 1610, 1415, 1220 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86-5.72 (1 H, m), 5.77 (1 H, d, J=1.4 Hz), 5.56 (1 H, d, J=1.4 Hz), 5.07-4.97 (2 H, m), 3.30-3.23 (1 H, m), 3.04-2.95 (1 H, m), 2.47-2.36 (1 H, m), 2.14-2.03 (1 H, m), 2.01-1.86 (2 H, m), 1.84-1.74 (1 H, m), 1.68-1.55 (1 H, m), 1.46-1.35 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 136.9, 119.6, 115.2, 48.9, 36.3, 31.9, 30.9, 4.5.

Preparation of Dimethyl Malonate Derivative 28. Sodium hydride (60 % in mineral oil, 41 mg, 1.0 mmol) was rinsed once with distilled hexanes, then stirred rapidly in 8 mL of DMF. To the suspension was added dropwise a solution of dimethyl malonate (0.160 mL, 185 mg, 1.40 mmol) and iodide **27** (170 mg, 0.52 mmol) in 2 mL of DMF. The reaction mixture was stirred overnight at rt. Water was added and the solution was extracted with three 10 mL portions of ether. The combined extracts were washed with water, brine, dried and concentrated. The residue was purified by preparative tlc (20 % ethyl acetate/hexanes) to afford the dimethyl malonate derivative **28** (145 mg, 84 %): IR (film) 2920, 1725, 1615, 1430, 1230 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82-5.68 (1 H, m), 5.64 (1 H, d, J=1.4 Hz), 5.48 (1H, d, J=1.4 Hz), 5.02-4.93 (2 H, m), 3.73 (6 H, s), 3.33 (1 H, t, J=7.5 Hz), 2.21-2.10 (1 H, m), 2.09-1.98 (1 H, m), 1.96-1.71 (3 H, m), 1.57-1.26 (4 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 169.5, 138.4, 137.1, 118.4, 114.9, 52.4, 51.4, 48.5, 32.4, 30.9, 26.3; CI MS m/z 333 (M^++1), 253, 121; exact mass for $C_{13}H_{17}O_3Br$ (M^+-CH_3O) found 302.0331.

Preparation of Aldehyde 29. Alcohol **24**[6a] was oxidized under Swern conditions.[18] A solution of oxalyl chloride (0.161 mL, 1.85 mmol) in 4.1 mL of CH_2Cl_2 was cooled to -78 °C, and a solution of DMSO (0.288 mL, 4.06 mmol) in 0.8 mL of CH_2Cl_2 was added dropwise, maintaining the reaction temperature below -65 °C. After the mixture was stirred for 10 min, a solution of alcohol **24**[6a] (0.170 g, 1.23 mmol) in 1.2 mL of CH_2Cl_2 was added slowly, maintaining the temperature below -65 °C. After the mixture was stirred for 20 min, triethylamine (1.17 mL, 8.37 mmol) was added dropwise. The reaction mixture was warmed to 25 °C and water was added. The aqueous phase was extracted with three 10 mL portions of CH_2Cl_2. The combined organic extracts were washed with water, brine, dried and concentrated. The residue was dissolved in ether and filtered through a short plug of silica gel. The filtrate was concentrated to yield aldehyde **29** (167 mg, 100 %), which was not purified further: IR (film) 3280, 2910, 2830, 2710, 2100, 1710, 1630, 1400 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.82 (1 H, t, J=1.8 Hz), 5.89-5.69 (1 H, m), 5.17-4.96 (2 H, m), 2.97-2.82 (1 H, m), 2.64-2.54 (2 H, m), 2.34-2.14 (2 H, m), 2.12 (1 H, d, J=2.3 Hz), 1.63-1.52 (2 H, m).

Conversion of Aldehyde 29 to β-Hydroxy Sulfone 30. A solution of methyl phenyl sulfone (285 mg, 1.83 mmol) in 5 mL of THF was cooled to 0 °C and a solution of nBuLi (1.6 M in hexanes, 1.14 mL, 1.83 mmol) was added dropwise. The solution was stirred for 45 min at 0 °C, then cooled to -78 °C. A solution of aldehyde **29** (166 mg, 1.22 mmol) in 1 mL of THF was added dropwise. After 1 h at -78 °C, the solution was warmed to 0 °C and stirred for 4 h. Water was added to the solution and the aqueous layer was extracted with three 10 mL portions of ether. The combined organic extracts were washed with brine, dried and concentrated. The residue was purified by preparative tlc (40 % ethyl acetate/hexanes) to afford β-hydroxy sulfone **30** (171 mg, 48 %): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88-7.84 (2 H, m), 7.62-7.44 (3 H, m), 5.78-5.56 (1 H, m), 4.96-4.83 (2 H, m), 4.40-4.18 (1 H, m), 3.23-3.18 (2 H, m), 2.58-2.30 (1 H, m), 2.18-2.01 (2 H, m), 1.99 (1 H, d, J=2.5 Hz), 1.75-1.30 (4 H, m).

Preparation of β-Keto Sulfone 31. The above β-hydroxy sulfone **30** (416 mg, 1.42 mmol) in 10 mL of reagent grade acetone was stirred, open to the air, at rt. A solution of Jones reagent[19] was added dropwise until an orange color persisted and the mixture was stirred overnight. Water was added to dissolve the chromium salts and the solution was extracted with three 10 mL portions of ethyl acetate. The extracts were combined, washed with water, brine, dried and concentrated. Purification of the residue by flash chromatography (20 % ethyl acetate/hexanes) afforded β-keto sulfone **31** (328 mg, 79 %) as a colorless oil: IR (film) 3280, 3070, 2925, 2120, 1720, 1640, 1450, 1370, 1160 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88-7.84 (2 H, m), 7.66-7.50 (3 H, m), 5.84-5.64 (1 H, m), 5.05-4.92 (2 H, m), 4.18 (2 H, s), 2.95-2.72 (3 H, m), 2.27-2.11 (2 H, m), 2.04 (1 H, d, J=2.0 Hz), 1.52-1.42 (2 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 195.8, 138.4, 137.2, 134.2, 129.2, 128.1, 115.3, 85.2, 70.3, 66.9, 48.9, 33.1, 30.9, 25.8; CI MS m/z 291 (M^++1), 199, 149.

Preparation of Vinyl Bromide 32. The β-keto sulfone **31** (0.302 g, 1.04 mmol) in 1.2 mL of CH_2Cl_2 was added dropwise to a solution of B-Br-9-BBN (1 M in CH_2Cl_2, 3.12 mL, 3.12 mmol) in 4.0 mL of CH_2Cl_2 cooled to 0 °C. The solution was stirred at 0 °C for 3 h and glacial acetic acid (1.04 mL, 18.3 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h, warmed to 25 °C, and water was added. The aqueous layer was extracted with three 10 mL portions of CH_2Cl_2. The combined organic extracts were washed with water, brine, dried and concentrated. Purification of the residue by preparative tlc (30 % ethyl acetate/hexanes) yielded 0.246 g (64 %) of product (≥ 90 % pure by ^{1}H NMR). Further purification of the residue by HPLC (20 % ethyl acetate/hexanes) afforded pure vinyl bromide **32**: IR (film) 3060, 2920, 1710, 1620, 1445, 1320, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (2 H, d, J=8.1 Hz), 7.71-7.66 (1 H, m), 7.60-7.55 (2 H, m), 5.82-5.71 (1 H, m), 5.67 (1 H, s), 5.44 (1 H, s), 5.04-4.96 (2 H, m), 4.15 (2 H, dd, J=25.3 Hz, 13.4 Hz), 2.98 (1 H, dd, J=17.4 Hz, 7.1 Hz), 2.86-2.77 (1 H, m), 2.70 (1 H, dd, J=17.4 Hz, 5.3 Hz), 2.10-1.89 (2 H, m), 1.61-1.51 (1 H, m), 1.49-1.36 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 138.5, 137.4, 136.6, 134.3, 129.3, 128.2, 119.2, 115.3, 67.2, 48.4, 43.6, 31.8, 30.7; EI MS m/z (relative intensity) 370 (M^+, 0.08), 291 (15), 149 (80), 77 (100); exact mass calcd for $C_{16}H_{19}BrO_3S$ 370.0239, found 370.0225.

Cyclization of Malonate Substrate 28. The general procedure for the condensation reaction was followed. NaH (60 % in mineral oil, 26 mg, 0.65 mmol) and compound **28** (144 mg, 0.432 mmol) in 4.3 mL of DMF were heated at 50 °C for 24 h. The usual workup gave 125 mg of a 2:1 mixture of **34** and **35** as determined by ^{1}H NMR. The mixture was purified by preparative tlc (20 % ether/hexanes, 2 elutions) to give **34** (62 mg, 57 %) and **35** (18 mg, 17 %).

Fused bicyclic malonate 34: IR (film) 2920, 2840, 1720, 1430, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (3 H, s), 3.69 (3 H, s), 3.19 (1 H, dd, J=13.7 Hz, 2.3 Hz), 2.49-2.42 (1 H, m), 2.41-2.35 (1 H, m), 2.26-2.23 (2 H, m), 2.19-2.12 (1 H, m), 2.07-1.97 (1 H , m), 1.90-1.84 (1 H, m), 1.81-1.74 (1 H, dd, J=13.7 Hz, 3.7 Hz), 1.64 (3 H, s), 1.32-1.23 (1 H, m), 1.15-1.02 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 171.1, 131.8, 131.7, 55.9, 52.6, 52.2, 45.7, 37.3, 31.7, 31.6, 31.4, 28.5, 13.3; EI MS m/z (relative intensity) 252 (M^+, 16), 192 (100), 133 (54); exact mass calcd for $C_{14}H_{20}O_4$ 252.1361, found 252.1349.

Bridged bicyclic malonate 35: IR (film) 2920, 2850, 1715, 1425, 1250, 1220 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.82 (1 H, s), 4.61 (1 H, s), 3.69 (3 H, s), 3.66 (3 H, s), 2.63-2.61 (1 H, m), 2.56-2.48 (1 H, m), 2.24-2.18 (1 H, m), 2.09-1.99 (1 H, m), 1.97-1.87 (1 H, m), 1.79-1.69 (1 H, m), 1.62-1.55 (1 H, m), 1.49-1.40 (2 H, m), 1.39 (3 H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.4, 170.9, 158.5, 102.4, 64.3, 51.9, 51.7, 47.2, 43.4, 34.8, 32.6, 31.6, 27.7, 27.2, 22.6, 20.4, 14.1; CI MS m/z 253 (M^++1), 221, 192.

Cyclization of β-Keto Sulfone 32. The procedure for the cyclization of malonate derivative **28** was followed for β-keto sulfone **32** (71 mg, 0.19 mmol). ^1H NMR of the crude reaction mixture showed a 1:1 mixture of **37**:**38**. Purification of the residue by preparative tlc (20 % ethyl acetate/hexanes, 3 elutions) gave the yellow oil **37** (29 mg, 53 %) as an inseparable mixture of diastereomers and the white solid **38** (7 mg, 13 %).

Fused bicyclic β-keto sulfone 37: ^1H NMR (200 MHz, $CDCl_3$) δ 8.08-8.03 (1 H, m), 7.85-7.72 (1 H, m), 7.70-7.52 (3 H, m), 3.96-3.79 (1 H, m), 3.49-3.32 (1 H, m), 2.96-2.89 (1 H, m), 2.81-2.54 (2 H, m), 2.49-2.32 (3 H, m), 2.21-1.97 (2 H, m), 1.78 & 1.69 (3 H, s, diastereomers); EI MS m/z (relative intensity) 290 (M^+, 10), 149 (100); exact mass calcd for $C_{16}H_{18}O_3S$ 290.0977, found 290.0962.

Bridged bicyclic β-keto sulfone 38: ^1H NMR (200 MHz, $CDCl_3$) δ 7.78-7.73 (2 H, m), 7.65-7.49 (3 H, m), 5.27 (1 H, s), 5.22 (1 H, s), 3.75 (1 H, d, J=1.8 Hz), 3.24-3.14 (1 H, m), 2.97-2.94 (1 H, m), 2.49-2.40 (1 H, m), 1.87-1.71 (1 H, m), 1.66-1.58 (2 H, m), 1.62 (3 H, s), 1.48-1.41 (1 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.2, 152.2, 140.1, 133.8, 129.1, 128.3, 106.7, 85.6, 50.5, 46.2, 42.9, 38.7, 27.2, 21.4; EI MS m/z (relative intensity) 290 (M^+, 4), 149 (61), 107 (100); exact mass calcd for $C_{16}H_{18}O_3S$ 290.0977, found 290.0986.

Desulfonylation of 37.[20] Into a flask containing sulfone **37** (50 mg, 0.17 mmol) in 1 mL of THF cooled to -78 °C was condensed 10 mL of anhydrous NH_3. Lithium wire was added until a blue color persisted. The mixture was stirred at -78 °C for 3 min and quenched with saturated aqueous NH_4Cl. The mixture was warmed to rt, the NH_3 was evaporated, and the remaining solution was extracted with three 10 mL portions of ether. The extracts were washed with 10 mL of brine, dried and concentrated under aspirator pressure. The residue was purified by preparative tlc (20 % ether/hexanes) to give compound **39** (15 mg, 60 %). Further purification by HPLC (10 % ether/hexanes) gave 7 mg (28 %) of compound **39**: IR (CCl_4) 2928, 2854, 1716, 1446, 1261 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.94-2.83 (1 H, m), 2.80-2.73 (1 H, m), 2.62-2.55 (1 H, m), 2.45-2.31 (4 H, m), 2.29-2.05 (3 H, m), 1.69 (3 H, s), 1.49-1.40 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 132.5, 132.1, 49.8, 46.9, 40.7, 37.4, 29.7, 23.9, 13.7; CI MS m/z 151 (M^++1); exact mass calcd for $C_{10}H_{14}O$ 150.1045, found 150.1033.

Preparation of 4-Iodo-E-1-triethylsilyl-1-butene (40). 3-Butyn-1-ol (5.00 g, 71.3 mmol) was protected as its tetrahydropyranyl ether (19.5 mL, 214 mmol 3,4-dihydro-2H-pyran, catalytic PPTS, CH_2Cl_2, 0 °C to rt overnight).[27] The product was purified by flash chromatography (5 % ethyl acetate/hexanes) to afford pure 3-butynyl tetrahydropyranyl ether (10.2 g, 93 %): ^1H NMR (200 MHz, $CDCl_3$) δ 4.64 (1 H, t, J=3.2

Hz), 3.88-3.76 (2 H, m), 3.57-3.49 (2 H, m), 2.47 (2 H, td, J=7.0 Hz, 2.6 Hz), 1.95 (1 H, t, J=2.6 Hz), 1.79-1.48 (6 H, m).

The 3-butynyl tetrahydropyranyl ether (2.29 g, 14.8 mmol) was combined with triethylsilane (3.32 mL, 20.8 mmol) in 15 mL of ether cooled to 0 °C, and chloroplatinic acid (0.1 M in 2-propanol, 1.48 mL, 0.148 mmol) was added dropwise. The solution was stirred at 0 °C overnight. The solvent and excess triethylsilane were removed under reduced pressure. The product was purified by flash chromatography (5 % ethyl acetate/hexanes) to give an inseparable mixture of *E*-4-triethylsilyl-3-butenyl tetrahydropyranyl ether and its 3-triethylsilyl-3-butenyl tetrahydropyranyl ether in a 5:1 ratio (combined 2.91 g, 72 %). *E*-4-triethylsilyl-3-butenyl tetrahydropyranyl ether: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.07 (1 H, dt, J=18.0 Hz, 6.0 Hz), 5.65 (1 H, d, J=18.0 Hz), 4.64-4.60 (1 H, m), 3.94-3.72 (2 H, m), 3.57-3.41 (2 H, m), 2.45 (2 H, q, J=7.2 Hz), 1.65-1.47 (6 H, m), 0.93 (9 H, t, J=7.2 Hz), 0.56 (6 H, q, J=7.2 Hz).

The tetrahydropyranyl ether was removed from *E*-4-triethylsilyl-3-butenyl tetrahydropyranyl ether (186 mg, 0.688 mmol) by treating the compound in 8 mL of MeOH at rt with a catalytic amount of *p*-toluenesulfonic acid monohydrate for 2 h. Solid $NaHCO_3$ was then slowly added and the solvent was removed under reduced pressure. The residue was diluted with 30 mL of CH_2Cl_2, filtered, and concentrated to give *E*-1-triethylsilyl-1-buten-4-ol (114 mg, 89 %): ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.02 (1 H, dt, J=18.8 Hz, 5.6 Hz), 5.68 (1 H, d, J=18.8 Hz), 3.66 (2 H, t, J=5.6 Hz), 2.39 (2 H, q, J=5.6 Hz), 0.92 (9 H, t, J=7.9 Hz), 0.51 (6 H, t, J=7.9 Hz).

E-1-Triethylsilyl-1-buten-4-ol (1.77 g, 9.52 mmol) was converted to its tosylate (2.78 g, 84 %) following the procedure for the preparation of tosylate **25** from alcohol **24**. The crude product was purified by flash chromatography (5 % ethyl acetate/hexanes). *E*-1-Triethylsilyl-1-buten-4-ol tosylate: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (2 H, d, J=8.8 Hz), 7.36 (2 H, d, J=8.8 Hz), 5.87 (1 H, dt, J=18.8 Hz, 6.1 Hz), 5.61 (1 H, d, J=18.8 Hz), 4.06 (2 H, t, J=6.1 Hz), 2.48-2.36 (2 H, m), 2.41 (3 H, s), 0.85 (9 H, t, J=8.1 Hz), 0.47 (6 H, q, J=8.1 Hz).

The tosylate of *E*-1-triethylsilyl-1-buten-4-ol (1.25 g, 3.68 mmol) was added to a solution of NaI (1.37 g, 9.21 mmol) in 20 mL of dried acetone, stirred overnight at rt, and water was added. The mixture was extracted with three 30 mL portions of ether. The combined extracts were washed with brine, dried and concentrated. The residue was purified by flash chromatography (hexanes) to give 4-iodo-*E*-1-triethylsilyl-1-butene (**40**) (938 mg, 86 %): IR (film) 2960, 2900, 2870, 1610, 1460, 1410, 1230 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (1 H, dt, J=18.6 Hz, 6.1 Hz), 5.67 (1 H, dt, J=18.8 Hz, 1.4 Hz), 3.19 (2 H, t, J=7.3 Hz), 2.68 (2 H, q, J=7.3 Hz), 0.95 (9 H, t, J=7.9 Hz), 0.57 (6 H, q, J=7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 129.3, 40.5, 7.3, 4.5, 3.3; CI MS m/z 297 (M^++1), 267, 169.

Preparation of Ester Lactone 41. To a solution of 2-ethoxycarbonyl-γ-butyrolactone[21] (9.60 g, 60.8 mmol) in 200 mL of DMF at rt was added K_2CO_3 (16.79 g, 121.5 mmol). The mixture was stirred 2 h and a solution of **40** (17.98 g, 60.8 mmol) in 5 mL of DMF was added. After the mixture was stirred 2 d, water was added and the solution was extracted with three 50 mL portions of ether. The combined extracts were washed with water, brine, dried and concentrated. The residue was purified by flash chromatography (10 % ethyl acetate/hexanes) to give the ester lactone derivative **41** (15.88 g, 83 %): IR (film) 2990, 2910, 2880, 1775, 1725, 1610, 1450, 1380 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (1 H, dt, J=18.6 Hz, 5.8 Hz), 5.54 (1 H, d, J=18.6 Hz), 4.27-4.23 (2 H, m), 4.19-4.12 (2 H, m), 2.64 (1 H, dt, J=13.0 Hz, 4.8 Hz), 2.24-2.05 (4 H, m), 1.83-1.78 (1 H, m), 1.21 (3 H, t, J=7.1 Hz), 0.84 (9 H, t, J=7.8 Hz), 0.46 (6 H, q, J=7.8 Hz); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 174.5, 169.1, 145.8, 127.1, 65.9, 61.9, 53.6, 32.9, 31.8, 31.6, 13.7, 7.0, 3.1; CI MS m/z 327 (M^++1), 297.

Preparation of Butenyl Lactone 42. A solution of ester lactone **41** (5.86 g, 18.6 mmol) in 50 mL of wet DMSO was treated with LiCl (1.58 g, 37.3 mmol).[23] The mixture was heated at reflux for 3 h, cooled to rt, diluted with water the extracted with three 20 mL portions of ethyl acetate. The extracts were washed with three 20 mL portions of water, brine, dried, and concentrated to give butenyl lactone **42** (3.64 g, 77 %): IR (film) 2960, 2920, 2880, 1770, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (1 H, dt, J=18.6 Hz, 6.2 Hz), 5.58 (1 H, d, J=18.6 Hz), 4.30 (1 H, td, J=8.8 Hz, 2.7 Hz), 4.18-4.09 (1 H, m), 2.56-2.43 (1 H, m), 2.40-2.30 (1 H, m), 2.27-2.10 (2 H, m), 2.03-1.84 (2 H, m), 1.58-1.45 (1 H, m), 0.88 (9 H, t, J=7.8 Hz), 0.51 (6 H, q, J=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 146.3, 127.4, 66.3, 38.5, 34.3, 29.2, 28.5, 7.2, 3.3; CI MS m/z 255 (M^++1), 225.

Preparation of Z-Vinyl Bromide 43. To a solution of *E*-vinyl silane **42** (5.00 g, 19.7 mmol) in 75 mL of CH_2Cl_2 cooled to -78 °C was added a solution of Br_2 (1.52 mL, 29.5 mmol) in 30 mL of CH_2Cl_2 at a rate such that the color dissipated between drops. After 30 min, the mixture was gradually warmed to rt. A 10 % solution of Na_2SO_3 was added and the mixture was stirred until colorless. The mixture was extracted with three 30 mL portions of CH_2Cl_2. The combined extracts were washed with 10 % Na_2SO_3, brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in 100 mL of THF and cooled to 0 °C. A solution of tetrabutylammonium fluoride (1.0 M in THF, 23.6 mL, 23.6 mmol) was added dropwise and the solution was shielded from light as it was slowly warmed to rt and stirred overnight. A solution of saturated $NaHCO_3$ was added and the mixture was extracted with three 30 mL portions of ether. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash chromatography (10 % ethyl acetate/hexanes) to give *Z*-vinyl bromide **43** (3.44 g, 80 %): IR (film) 2920, 2860, 1770, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (1 H, d, J=6.9 Hz), 6.04 (1 H, q, J=6.9 Hz), 4.28 (1 H, td, J=8.9 Hz, 2.4 Hz), 4.16-4.08 (1 H, m), 2.51-2.34 (2 H, m), 2.28-2.12 (2 H, m), 1.98-1.83 (2 H, m), 1.54-1.42 (1 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 133.1, 108.8, 66.2, 38.3, 28.4, 28.1, 27.2; CI MS m/z 219 (M^++1), 139.

Preparation of Lactol 44. To a solution of lactone **43** (451 mg, 2.06 mmol) in 20 mL of ether cooled to -78 °C was added dropwise a solution of DIBAL-H (1.0 M in hexanes, 2.26 mL, 2.26 mmol). After 15 min, 1 mL of MeOH was added dropwise and the solution was warmed to rt. A saturated solution of potassium sodium tartrate was added and the mixture was stirred until two layers formed. The aqueous layer was extracted with three 20 mL portions of ether and the combined extracts were washed with brine, dried and concentrated. The residue was purified by flash chromatography (20 % ethyl acetate/hexanes) to afford the diastereomeric lactols **44** (377 mg, 83 %): IR (film) 3394, 2939, 1727, 1624, 1453 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.19 (1 H, d, J=6.9 Hz), 6.10 (1 H, q, J=6.9 Hz), 5.38-5.19 (1 H, m), 4.18-3.75 (2 H, m), 2.79-2.58 (1 H, m), 2.33-2.15 (2 H, m), 2.16-2.05 (1 H, m), 1.82-1.32 (4 H, m); CI MS m/z 221 (M^++1), 203.

Preparation of Alcohol 45. To a rapidly stirred suspension of methyltriphenylphosphonium bromide (5.88 g, 16.5 mmol) in 100 mL of THF at 0 °C was added dropwise a solution of nBuLi (2.5 M in hexanes, 6.59 mL, 16.5 mmol). After 2 h a solution of lactol **44** (1.82 g, 8.24 mmol) in 5 mL of THF was added dropwise. The mixture was slowly warmed to rt. After 5 h water was added and the solution was extracted with three 30 mL portions of ether. The extracts were washed with brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (20 % ethyl acetate/hexanes) to give alcohol **45** (1.36 g, 75 %):

IR (film) 3340, 3060, 2920, 1760, 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.18-6.02 (2 H, m), 5.68-5.38 (1 H, m), 5.10-5.02 (2 H, m), 3.69-3.60 (2 H, m), 2.24-2.06 (3 H, m), 1.77-1.59 (2 H, m), 1.57-1.30 (3 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 141.8, 134.5, 115.4, 107.7, 60.7, 40.5, 37.5, 33.3, 27.3; CI MS m/z 219 (M^++1), 201, 139.

Preparation of Aldehyde 46. Following the procedure for the Swern oxidation[18] of alcohol **24** to aldehyde **29**, alcohol **45** (1.36 g, 6.21 mmol) was converted to aldehyde **46** (1.33 g, 99 %): IR (film) 3300, 2930, 2860, 1720, 1615 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.74 (1 H, t, J=2.3 Hz), 6.19 (1 H, d, J=6.1 Hz), 6.09 (1 H, q, J=6.1 Hz), 5.78-5.58 (1 H, m), 5.16-5.05 (2 H, m), 2.70-2.51 (1 H, m), 2.48-2.41 (2 H, m), 2.29-2.13 (2 H, m), 1.60-1.41 (2 H, m); CI MS m/z 217 (M^++1), 199, 137.

Preparation of β-Keto Sulfone 48. To a solution of methyl phenyl sulfone (195 mg, 1.25 mmol) and distilled DMPU (0.151 mL, 1.25 mmol) in 8.3 mL of THF at -78 °C was added dropwise a solution of nBuLi (2.5 M in hexanes, 0.500 mL, 1.25 mmol). After 2 h a solution of aldehyde **46** (181 mg, 0.835 mmol) in 0.5 mL of THF was added dropwise. The solution was stirred overnight at -78 °C, water was added and the mixture was extracted with three 15 mL portions of ethyl acetate. The extracts were washed with 5 % HCl, brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (20 % ethyl acetate/hexanes) to give an inseparable mixture of β-hydroxy sulfone **47** and methyl phenyl sulfone.

The above mixture of β-hydroxy sulfone **47** and methyl phenyl sulfone was dissolved in 10 mL of dried acetone, combined with a solution of Jones reagent[19] (0.7 M in water, 1.1 mL, 0.77 mmol), and stirred at rt overnight. Water was added and the solution was extracted with three 10 mL portions of ethyl acetate. The combined extracts were washed twice with water, once with brine, dried and concentrated *in vacuo*. The residue was purified by preparative tlc (30 % ethyl acetate/hexanes) to afford β-keto sulfone **48** (134 mg, 43 % from **46**): ^1H NMR (200 MHz, $CDCl_3$) δ 7.87 (2 H, d, J=7.5 Hz), 7.67-7.52 (3 H, m), 6.14-5.93 (2 H, m), 5.65-5.42 (1 H, m), 5.03-4.92 (2 H, m), 4.11 (2 H, s), 2.71-2.67 (2 H, m), 2.60-2.42 (1 H, m), 2.15-1.88 (2 H, m), 1.43-1.24 (2 H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 196.6, 139.7, 134.2, 134.1, 133.9, 129.2, 128.1, 116.0, 108.1, 66.9, 49.2, 38.2, 32.4, 27.1; CI MS m/z 371 (M^++1).

Cyclization of β-Keto Sulfone 48. Many attempts to cyclize β-keto sulfone **48** to hydrindenone **51** were made using NaH as the base, DMF, DMSO, or CH_3CN as the solvent, $Pd(OAc)_2$ as the palladium source, P(*o*-Tol)$_3$, 1,3-bis(diphenylphosphino)propane (dppp), or 1,2-bis(diphenylphosphino)ethane (dppe or DIPHOS) as the ligand, and tetrabutylammonium chloride and TlOAc as additives. *Typical procedure*: NaH (1.5 equiv) was combined with a solution of β-keto sulfone **48** (1.0 equiv) in solvent (to 0.2 M in sulfone) and stirred until H_2 evolution ceased. $Pd(OAc)_2$ (0.05 equiv), ligand (0.05-0.10 equiv), and other additives (1.0-2.0 equiv of *n*-Bu_4NCl and 0-1.0 equiv of TlOAc) were added followed by another aliquot of solvent (total volume to make the mixture 0.10 M in sulfone). The mixture was degassed by the freeze-thaw method, sealed under vacuum and heated at 80 °C-130 °C for 19-44 h. After cooling to rt, the mixture was filtered through a short plug of flash silica gel with ether as the eluent and concentrated. The crude residue was purified by preparative tlc (20-30 % ethyl acetate/hexanes) to give products. Various mixtures of alkyne **52**, diene **53**, and alkylidenetetrahydrofuran **54** were formed (see text).

Alkyne 52: ^1H NMR (200 MHz, $CDCl_3$) δ 7.91-7.86 (2 H, m), 7.74-7.53 (3 H, m), 5.70-5.46 (1 H, m), 5.13-5.01 (2 H, m), 4.14 (2 H, s), 2.79-2.61 (3 H, m), 2.21-2.00 (2 H, m), 1.93 (1 H, t, J=3.0 Hz), 1.69-1.44 (2 H, m); EI MS m/z (relative intensity) 149 (M^+-$C_6H_5SO_2$, 20), 141 (20), 107 (10), 91 (37), 77 (100).

Diene ***53***: IR (film) 2930, 1710, 1610, 1560, 1310, 1150 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.94-7.87 (2 H, m), 7.70-7.53 (3 H, m), 6.09 (1 H, d, J=10.0 Hz), 5.82 (1 H, dt, J=10.0 Hz, 4.0 Hz), 4.75 (2 H, d, J=15.2 Hz), 4.18 (1 H, d, J=13.2 Hz), 4.08 (1 H, d, J=13.2 Hz), 2.94-2.66 (3 H, m), 2.17-2.06 (2 H, m), 1.81-1.62 (2 H, m); EI MS m/z (relative intensity) 149 (M^+-$C_6H_5SO_2$, 6), 141 (4), 91 (52), 77 (100).

Z-Alkylidenetetrahydrofuran ***54***: IR (film) 2927, 1718, 1140 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.91-7.82 (2 H, m), 7.62-7.45 (3 H, m), 5.84 (1 H, dt, J=10.2 Hz, 3.7 Hz), 5.65 (1 H, s), 5.57 (1 H, d, J=10.2 Hz), 3.37 (1 H, dd, J=18.0 Hz, 8.0 Hz), 3.03 (1 H, dd, J=18.1 Hz, 7.7 Hz), 2.29-2.21 (1 H, m), 2.18-1.95 (1 H, m), 1.80-1.17 (1 H, m), 1.68-1.57 (1 H, m), 1.56 (3 H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 132.1, 130.2, 129.5, 129.1, 128.7, 126.1, 99.5, 86.6, 40.0, 34.0, 25.4, 22.1, 21.8; EI MS m/z (relative intensity) 290 (M^+, 17), 149 (100), 91 (38), 77 (78).

E-Alkylidenetetrahydrofuran ***54a***: ^1H NMR (200 MHz, $CDCl_3$) δ 8.02-7.98 (2 H, m), 7.63-7.39 (3 H, m), 5.76 (1 H, dt, J=10.0 Hz, 4.0 Hz), 5.49 (1 H, d, J=10.0 Hz), 5.40 (1 H, s), 2.74 (1 H, dd, J=16.8 Hz, 8.0 Hz), 2.62-2.51 (1 H, m), 2.21-2.05 (2 H, m), 1.98-1.89 (2 H, m), 1.72-1.61 (1 H, m), 1.34 (3 H, s); EI MS m/z (relative intensity) 290 (M^+, 5), 149 (31), 91 (44), 77 (100).

Acknowledgement. We are grateful to the National Science Foundation for financial support on grants CHE-92-02848 and CHE-94-23670.

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(*Received in USA* 18 *May* 1995; *accepted* 27 *June* 1995)