Palladium-Catalyzed Coupling of Allylic Acetates with Aryl- and Vinylstannanes

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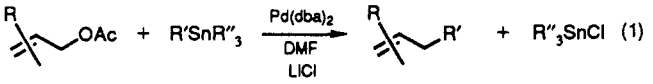
The palladium-catalyzed reaction of allyl acetates with aryl- and vinyltin reagents gave good yields of cross-coupled products. The reaction was mild and tolerant of functionality (CO_2R, OH, $OSiR_3$, OMe) in the tin reagent. Inversion of stereochemistry at the acetate center was observed, with retention of the geometry of the olefin of the allyl group and with exclusive coupling at the primary position. Retention of geometry of the olefin in the vinyltin reagents was also observed.

The palladium-catalyzed coupling of organotin reagents with aryl and vinyl halides and triflates, and with acid chlorides, is a versatile method for the formation of carbon–carbon bonds; it is being used extensively in the synthesis of functionalized organic compounds.[1] Although allylic halides undergo this coupling process efficiently,[2] the more readily available (from the allylic alcohol) allylic acetates are generally unreactive under the standard conditions used,[3] with the exception of allyl[4] and cinnamyl acetates.[5] The studies described below were carried out with the intent of increasing the scope and defining the limitations of the coupling of allylic acetates with aryl- and vinylstannanes.

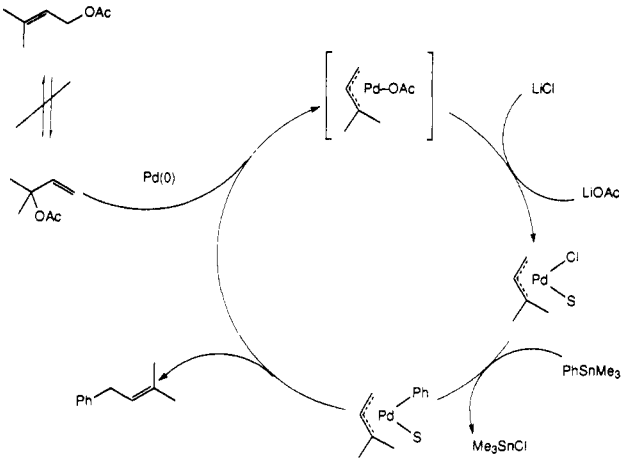
Results and Discussion

The standard reaction conditions for the palladium-catalyzed coupling of organotin reagents with allylic *halides* involves the heating of equimolar amounts of halides and tin reagent at 50 °C for 12–24 h in THF in the presence of 3 mol % bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$) and 6 mol % triphenylphosphine.[2a-d] Under these conditions, most allyl acetates failed to undergo reaction. A systematic study of the effects of reaction conditions on this process was carried out, and it revealed that, with the use of DMF as a solvent, adding 3 equiv LiCl/equiv of substrate to assist the transmetalation (see below) and using 3 mol % $Pd(dba)_2$ in the *absence* of added phosphine (which stops the reaction), simple allyl acetates were generally reactive toward a variety of aryl- and vinyltin reagents (eq 1, Table I).

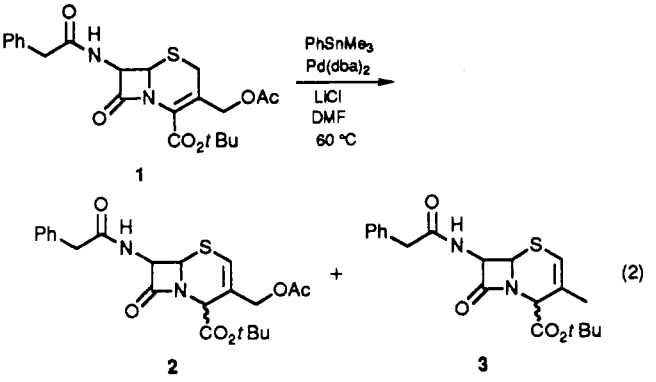


The results closely parallel those previously observed with allylic halides.[2d] Thus, secondary and tertiary allylic acetates underwent complete allylic transposition in the coupling reaction to result in exclusive coupling at the primary position (entries 1–4 and 8). The geometry of the olefin in the allylic substrate was cleanly retained in the products (entries 5, 6, and 9–14) as was the geometry of the olefin in the vinyltin reagents (entries 14–16). Clean inversion of stereochemistry at the acetate center was again observed (entry 7). A modest degree of functionality was tolerated (CO_2R, OH, $OSiR_3$, OMe) in the tin reagent, and on the basis of previous precedent,[1] a wide tolerance is anticipated. The potential for use in organic synthesis is illustrated by the clean coupling of (*E,E*)-farnesyl acetate to 3,5-dimethoxy-4-(trimethylstannyl)toluene (entry 10) to produce a precursor to the antibiotic grifolin,[6] in excellent yield in a single step.

Scheme I



A particularly useful substrate for direct alkylation would be cepham acetate (1) (eq 2), which was unreactive under conditions successful for halides.[3] Unfortunately, arylation also failed under the conditions developed here; instead, reduction and rearrangement without arylation occurred. The reasons for this are being examined.



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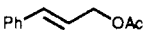
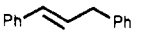
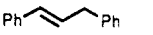
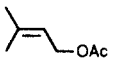
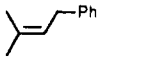
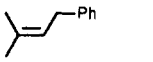
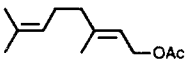
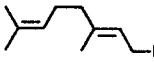
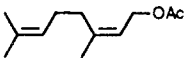
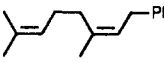
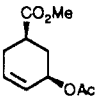
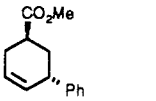
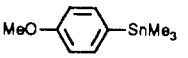
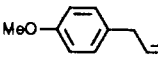
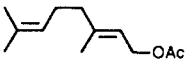
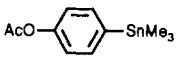
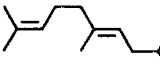
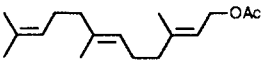
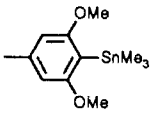
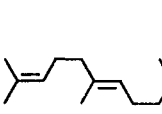
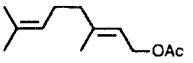
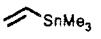
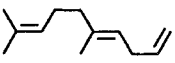
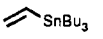
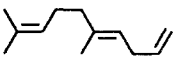
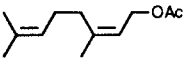
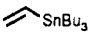
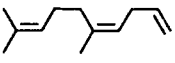
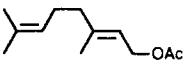
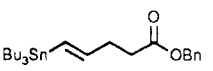
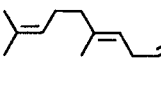
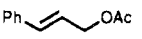
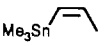
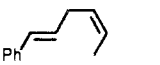
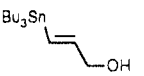
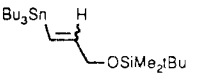
† Deceased.

(1) For a review see: Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(2) (a) Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599. (b) Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1983**, *24*, 1905. (c) Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7173. (d) Sheffy, F. K.; Godschalx, J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833. (e) Bumagin, N. A.; Bumagina, I. G.; Kashin, A. N.; Beletskaya, I. P. *Zh. Obschch. Khim.* **1982**, *52*, 714.
(3) For example: Farina, V.; Baker, S. R.; Benigni, D. A.; Sapino, C., Jr. Tetrahedron *Lett.* **1988**, *29*, 5739.
(4) (a) Beletskaya, I. P.; Kasatkin, A. N.; Lebedev, S. A.; Bumagin, N. A. *Izv. Akad. Nauk SSSR Ser. Khim.* **1981**, 2414. (b) Bumagin, N. A.; Kasatkin, A. N.; Beletskaya, I. P. *Dokl., Akad. Nauk SSSR* **1982**, *266*, 862.
(5) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595.
(6) (a) Besl, H.; Höfle, G.; Jendrny, B.; Jägers, E.; Steglich, W. *Chem. Ber.* **1977**, *110*, 3770. (b) Isobe, M.; Goto, T. *Tetrahedron* **1968**, *24*, 945.

0022-3263/90/1955-3019$02.50/0

Table I. Palladium-Catalyzed Coupling of Aryl- and Vinylstannanes with Allyl Acetates

no.	allyl acetate	stannane	T (°C)	t (h)	product	yield, (%)[a]
1		$PhSnMe_3$	23	69		57
2		$PhSnMe_3$	23	19		32
3		$PhSnMe_3$	23	27		65
4		$PhSnMe_3$	23	27		69
5		$PhSnMe_3$	23	47		81
6		$PhSnMe_3$	23	43		76
7		$PhSnMe_3$	55	19		47
8			56	47		50
9			23	22		80
10			100	31		71
11			10	38		68
12			23	20		68
13			23	44		40
14			60	48		81
15			23	22		80
16				44		69
17			23	62		60[b]
18			55	70		64[c]
19			23	20		88[d]
20			60	72		70

[a] Reported yields are for isolated, purified material. [b] Product: E/Z mixture 1/1. [c] DMF/THF 1/1. [d] After hydrolysis with 1 N HCl.

A mechanism for the palladium-catalyzed coupling reaction consistent with the experimental data is shown in Scheme I; it is typical of other reactions involving allylic substrates and transmetalation from tin. Thus, oxidative addition of the allyl acetate to palladium(0) produces an η^3-allylpalladium acetate. Exchange of acetate for chloride facilitates the transmetalation from tin to palladium, and reductive elimination produces the coupling product and regenerates the palladium(0) complex. The oxidative addition step goes with inversion, and the reductive elimination step goes with retention, accounting for the observed overall inversion. The intervention of an η^3-allyl species accounts for the observed allylic transposition since it was determined experimentally that the catalyst system does not promote allylic transposition in the allyl acetates under the reaction conditions (vide infra).

The role of η^3-allylpalladium intermediates in palladium(0)-catalyzed reactions of allylic substrates remains controversial.[7] While allylic transposition is expected for η^3-allyl intermediates, retention of geometry in systems involving neryl acetate is not always observed since η^3-allylpalladium complexes undergo facile syn–anti isomerization, leading to loss of stereochemistry of the allyl fragment. This, coupled with the fact that η^1-alkyl-η^3-allylpalladium complexes do not readily undergo reductive elimination in the absence of strong π-acceptor ligands,[8] prompted a closer examination of this system.

Treatment of separate samples of 1-acetoxy-3-methyl-2-butene and 2-acetoxy-2-methyl-3-butene with $^1/_2$ equiv of $Pd(dba)_2$ and 3 equiv of LiCl in dimethylformamide-d_7 produces samples whose ^1H NMR spectra were consistent with that of a 1:1 mixture of unreacted and unrearranged starting acetate and the η^3-allylpalladium complex. Except for minor differences in chemical shift, these spectra were also identical with that resulting from the treatment of η^3-(1,1-dimethylallyl)palladium chloride with 2 equiv of lithium acetate and 2 equiv of dibenzylideneacetone in DMF-d_7 (s, ~1.0 δ; s, ~1.3 δ; d, J = 13 Hz, ~3 δ; d, J = 8 Hz, ~3.5 δ; dd, J = 13, 8 Hz, ~4.8 δ). This same pattern of peaks is observed for the corresponding η^3-allylpalladium chloride in *non*coordinating solvents such as benzene or chloroform and different from that observed for the corresponding η^1-allyl species.[9] Thus, the η^3-allyl complex is the only *detectable* species in the reaction solution. These spectra remained unchanged for at least 72 h. Addition of phenyltrimethyltin to each of these solutions resulted in smooth production of the coupled product without detection of any other intermediate species. Thus, the mechanism shown in Scheme I is supported by these observations, although, as usual, the intervention of undetected amounts of other kinetically active species cannot be discounted.

Conclusion

Aryl- and vinylstannanes couple with a variety of allyl acetates in the presence of lithium chloride and a palladium(0) catalyst to form 1,4-dienes in good yields. The reaction is quite mild and is tolerant to functional groups, including CO_2R, OH and $OSiR_3$, OMe. The coupling proceeds with retention in the double-bond geometry in the vinyltin partner as well as of the Z and E configurations of neryl acetate and geranyl acetate. The allyl acetate undergoes regioselective coupling at the primary allylic carbon compared to secondary and tertiary. Thus, this reaction exhibits stereospecific and regioselective carbon–carbon bond formation.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on an IBM WO-270 (270-MHz) or a Bruker AC (300-MHz) spectrometer in $CDCl_3$ solvent with chemical shifts reported relative to tetramethylsilane. Infrared spectra were obtained on a Beckman 4250 spectrometer or Perkin-Elmer 1600 Series FTIR. Dimethylformamide and pyridine were distilled from calcium hydride and stored over 4-Å sieves. Acetic anhydride was used as received. Analytical thin-layer chromatography (TLC) were performed on glass-backed 0.25-mm-thick silica gel plates containing a 254-nm indicator (E. Merck, silica gel 60F-254). Column chromatography was performed with Woelm 32–63-mesh silica gel. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. Bis(dibenzylidene acetone)palladium(0) ($Pd(dba_2)$[10] was prepared according to published procedures.

Organostannanes. The following organostannanes were prepared according to literature methods: (*E,Z*)-1-(tributylstannyl)-3-[(*tert*-butyldimethylsilyl)oxy]-1-propene,[11] phenyltrimethylstannane,[12] tributylvinylstannane,[13] trimethylvinylstannane,[13] 4-(trimethylstannyl)phenyl acetate,[14] (*E*)-3-(tributylstannyl)-2-propen-1-ol,[15] (α-ethoxyvinyl)tributylstannane,[16] 4-(trimethylstannyl)anisole,[12] 1-[(*tert*-butylsilyl)oxy]-2-(tributylstannyl)-2-propene,[17] *cis*-1-(trimethylstannyl)-1-propene.[18]

Allyl Acetates. The following allyl acetates were prepared from the corresponding allyl alcohols and acetic anhydride in pyridine[21] and were identified by comparison with the reported data: 1-acetoxy-3-methyl-2-butene,[28] 2-acetoxy-2-methyl-3-butene,[21] *cis*-3-acetoxy-5-carbomethoxycyclohexene,[27] 1-acetoxy-1-phenyl-2-propene.[22] Cinnamyl acetate, geranyl acetate, neryl acetate, and (*E,E*)-farnesyl acetate were purchased from Aldrich Chemical Co.

General Procedure for Palladium-Catalyzed Cross-Coupling Reactions of Allyl Acetates with Organostannanes (Table I, Entries 1 and 2). To a mixture of cinnamyl acetate (0.88 g, 5.0 mmol), phenyltrimethylstannane (1.25 g, 5.2 mmol), and lithium chloride (0.631 g, 15.0 mmol) in DMF (8 mL) was added bis(dibenzylidene acetone)palladium(0) ($Pd(dba)_2$) (0.14 g, 0.25 mmol, 5 mol %). The mixture was stirred at 23 °C for 69 h and then partitioned between water (50 mL) and ether (50 mL). The ether layer was washed with water (3 × 25 mL) and brine, dried over $MgSO_4$, and concentrated. When tributyltin compounds were used, the ether layer was washed with a saturated potassium fluoride solution in 10% NH_4OH prior to being dried to remove tin-containing residuals. Flash chromatography (silica gel, hexanes) afforded 0.552 g (57%) of product. (This compound was identified by comparison with literature data.[24])

3,5-Dimethoxy-4-(trimethylstannyl)toluene (Entry 10). To a mixture of 3,5-dimethoxytoluene[19] (4.56 g, 30 mmol) in 20 mL of dry ether was added phenyllithium (16 mL, 30.5 mmol, 2 N cyclohexane/ether solution, 70/30). The mixture was stirred in the dark for 46 h. To this mixture was added trimethyltin chloride (6.0 g, 30 mmol) in 30 mL of ether. The solution was heated at reflux for 19 h. The reaction mixture was cooled to 0 °C and hydrolyzed with a saturated NH_4Cl solution. The aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with NaCl solution, dried over $MgSO_4$, and then concentrated. Fractional distillation afforded 6.7 g (71%)

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of product: bp 96 °C (0.42 mmHg); ^{1}H NMR (270 MHz) δ 6.37 (s, 2 H, Ar H), 3.76 (s, 6 H, OCH_3), 2.38 (s, 3 H, $ArCH_3$), 0.30 (s, 9 H, $Sn(CH_3)_3$); ^{13}C NMR (75 MHz) δ 165.10, 141.45, 112.71, 104.24 (Ar C), 55.23 (OCH_3), 22.02 ($ArCH_3$), −7.32 ($Sn(CH_3)_3$). Anal. Calcd for $C_{12}H_{20}O_2Sn$: C, 45.76; H, 6.35. Found: C, 45.86; H, 6.42.

(*E*)-Benzyl 5-(Tributylstannyl)pent-4-enoate (Entry 14). To a mixture of benzyl 4-pentynoate[20] (1.13 g, 6.0 mmol) and tributyltin hydride (1.88 mL, 7 mmol) was added AIBN (0.034 g, 0.20 mmol). The mixture was heated at 80 °C for 17 h. Purification by column chromatography (silica gel, 5% EtOAc/hexanes) afforded 2.0 g (70%) of product: R_f = 0.40; IR (neat) 3035, 2925, 1740, 1594, 1152 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.35 (s, 5 H, Ar H), 5.96 (m, 2 H, CH=CH), 5.12 (s, 2 H, CH_2Ph), 2.47 (m, 4 H, CH_2CH_2), 1.43 (m, 6 H, CH_2), 1.35 (m, 6 H, CH_2), 1.28 (m, 15 H, CH_3CH_2); ^{13}C NMR (75 MHz) δ 172.96 (C=O), 146.59, 136.04, 130.12, 128.81, 128.48, 128.10 (Ar C and C=C), 66.10 (OCH_2Ph), 33.57, 32.57 (CH_2CH_2), 29.04, 27.27, 13.66, 9.34 ($SnBu_3$). Anal. Calcd for $C_{24}H_{40}O_2Sn$: C, 60.16; H, 8.35. Found: C, 60.24; H, 8.41.

The following compounds were prepared according to the general procedure and identified by comparison with literature data: (2*E*)-1-phenyl-3,7-dimethyl-2,6-octadiene[23] (entry 5), (2*Z*)-1-phenyl-3,7-dimethyl-2,6-octadiene[23] (entry 6), *trans*-3-phenyl-5-carbomethoxycyclohexene[2d] (entry 7), 1-(4-methoxyphenyl)-3-methyl-2-butene[29] (entry 8), (6*E*)-2,6-dimethyl-2,6,9-decatriene[25] (entries 11 and 12), (6*Z*)-2,6-dimethyl-2,6,9-decatriene[25] (entry 13), (*E*)-5-phenyl-4-pentene-2-one[28] (entry 19).

1-Phenyl-3-methyl-2-butene (Entries 3 and 4). From 1-acetoxy-3-methyl-2-butene or 3-acetoxy-3-methyl-1-butene (0.64 g, 5 mmol), phenyltrimethylstannane (1.24 g, 5.2 mmol), lithium chloride (0.631 g, 15 mmol), and $Pd(dba)_2$ (0.144 g, 0.25 mmol, 5 mol %), flash chromatography (silica gel, hexanes) afforded 0.50 g (69%): R_f = 0.66, bp (bulb-to-bulb) 78 °C (18 mmHg); ^{1}H NMR (270 MHz) δ 7.36–7.15 (m, 5 H, ArH), 5.39 (t, 1 H, *J* = 7 Hz, =CH), 3.40 (d, 2 H, *J* = 7 Hz, CH_2Ph), 1.80 (s, 3 H, CH_3), 1.78 (s, 3 H, CH_3). Anal. Calcd for $C_{11}H_{14}$: C, 90.34; H, 9.65. Found: C, 90.14; H, 9.59.

(2*E*)-1-(4-Acetoxyphenyl)-3,7-dimethyl-2,6-octadiene (Entry 9). From 4-(trimethylstannyl)phenyl acetate (0.6 g, 2 mmol), geranyl acetate (0.21 mL, 0.196 g, 1 mmol), lithium chloride (0.126 g, 3 mmol), and $Pd(dba)_2$ (0.029 g, 0.05 mmol, 5 mol %), column chromatography (silica gel, 5% EtOAc/hexanes) afforded 0.217 g (80%): IR (neat) 3019, 2921, 1763 (C=O), 1501, 1202, 901; ^{1}H NMR (300 MHz) δ 7.15 (d, 1 H, *J* = 8 Hz, Ar H), 6.95 (d, 1 H, *J* = 8 Hz, Ar H), 5.28 (t, 1 H, *J* = 7 H, =CH), 5.08 (t, 1 H, *J* = 7 Hz, =CH), 3.32 (d, 2 H, *J* = 7 Hz, CH_2Ar), 2.27 (s, 3 H, CH_3C=O), 2.05 (m, 4 H, CH_2CH_2), 1.67 (s, 6 H, CH_3), 1.58 (s, 3 H, CH_3); ^{13}C NMR (75 MHz) δ 169.68 (C=O), 148.59, 139.27, 136.46, 131.46, 129.16, 124.17, 122.67, 121.33 (Ar C and C=C), 39.64, 33.47, 26.51, 25.68, 21.08, 17.66, 16.04 (CH_3 and CH_2). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.41; H, 8.42. Found: C, 79.48; H, 8.93.

(2*E*,6*E*)-1-(4-Methyl-2,6-dimethoxyphenyl)-3,7,11-trimethyl-2,6,10-dodecatriene (Entry 10). From 3,5-dimethoxy-4-(trimethylstannyl)toluene (1.57 g, 5 mmol), *trans*,*trans*-farnesyl acetate (1.32 g, 5 mmol), lithium chloride (0.632 g, 15 mmol), and $Pd(dba)_2$ (0.144 g, 0.25 mmol, 5 mol %), column chromatography (silica gel, 5% EtOAc/hexanes) afforded 1.26 g (71%): R_f = 0.53; IR (neat) 2900, 1605, 1583, 1117 cm^{-1}; ^{1}H NMR (270 MHz) δ 6.36 (s, 2 H, ArH), 5.25–5.06 (br m, 3 H, CH), 3.79 (s, 6 H, OCH_3), 3.33 (br d, 2 H, CH_2Ar), 2.32 (s, 3 H, $ArCH_3$), 2.0 (m, 8 H, CH_2C=), 1.6 (m, 12 H, CH_3); ^{13}C NMR (75 MHz) δ 157.82, 136.43, 134.44, 134.00, 131.00, 124.64, 123.75, 123.11, 115.34, 104.67 (Ar C and C=C), 55.52 (OCH_3), 39.76, 39.63, 31.85, 26.66, 25.58, 23.42, 21.85, 21.65, 17.56, 15.87 (CH_3 and CH_2); MS *m*/*e* 356 (2), 165 (90), 32 (100), 28 (100). Anal. Calcd for $C_{24}H_{36}O_2$: C, 80.89; H, 10.11. Found: C, 80.91; H, 10.20.

Benzyl (4*E*,7*E*)-8,12-Dimethyl-4,7,11-tridecatrienoate (Entry 14). From (*E*)-benzyl 5-(tributylstannyl)pent-4-enoate (0.196 g, 1 mmol), geranyl acetate (0.478 g, 1 mmol), lithium chloride (0.126 g, 3 mmol), and $Pd(dba)_2$ (0.029 g, 0.05 mmol, 5 mol %), column chromatography (silica gel, 5% EtOAc/hexanes) afforded 0.263 g (81%): R_f = 0.33; IR (neat) 3033, 2911, 1739 (C=O), 1666, 1605, 1150, 966 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.32 (s, 5 H, ArH), 5.39 (m, 2 H, =CH), 5.10 (br s, 4 H, CH_2 and CH_2O), 2.64 (m, 2 H, CH_2), 2.43–2.32 (m, 4 H, CH_2CH_2), 2.01 (m, 4 H, CH_2CH_2), 1.67 (s, 3 H, CH_3), 1.60 (s, 6 H, CH_3); ^{13}C NMR (75 MHz) δ 172.90 (C=O), 136.00, 135.87, 131.20, 130.08, 128.41, 128.06, 127.68, 127.04, 124.22, 121.87 (Ar C and C=C), 66.00 (OCH_2), 39.59, 34.21, 30.93, 27.78, 26.58, 25.59, 17.58, 15.85 (CH_3 and CH_2). Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.98; H, 9.20. Found: C, 81.08; H, 9.19.

(1*E*,4*Z*)-1-Phenyl-1,4-hexadiene (Entry 15). From *trans*-cinnamyl acetate (0.498 mL, 3 mmol), *cis*-1-(trimethylstannyl)-1-propene[18] (0.716 g, 3.5 mmol), lithium chloride (0.381 g, 9 mmol), and $Pd(dba)_2$ (0.086 g, 0.15 mmol, 5 mol %), column chromatography (silica gel, hexanes) afforded 0.38 g (80%): R_f = 0.66; IR (neat) 3035, 3015, 2915, 1649, 1594, 1493, 961 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.35–7.16 (m, 5 H, ArH), 6.39 (d, 1 H, *J* = 16 Hz, PhCH), 6.20 (dt, 1 H, *J* = 16 Hz, *J* = 6 Hz, =$CHCH_2$), 5.58 (dq, 1 H, *J* = 12 Hz, *J* = 7 Hz, =CH), 5.48 (dtd, 1 H, *J* = 12 Hz, *J* = 7 Hz, *J* = 1 Hz, =CH), 2.96 (t, 2 H, *J* = 6 Hz, CH_2), 1.66 (d, 3 H, *J* = 6 Hz, CH_3); ^{13}C NMR (75 MHz) δ 137.67, 129.91, 128.65, 128.35, 127.50, 126.78, 125.91, 125.09 (Ar C and C=C), 30.30, 12.68 (CH_2 and CH_3). Anal. Calcd for $C_{12}H_{14}$: C, 91.14; H, 8.86. Found: C, 90.91; H, 8.92.

(2*E*,5*E*)-6-Phenyl-2,5-hexadien-1-ol (Entry 16). From *trans*-cinnamyl acetate (0.33 mL, 2 mmol), (*E*)-3-(tributylstannyl)-2-propen-1-ol[15] (0.713 g, 2 mmol), lithium chloride (0.25 g, 6 mmol), and $Pd(dba)_2$ (0.057 g, 0.10 mmol, 5 mol %), column chromatography (silica gel, 20% EtOAc/hexanes) afforded 0.241 g (69%): R_f = 0.17; bp (bulb-to-bulb) 106 °C (0.25 mmHg); IR (neat) 3332 (OH), 3021, 2875, 1669, 1597, 1090, 970 cm^{-1}; ^{1}H NMR (270 MHz) δ 7.36–7.19 (m, 5 H, ArH), 6.40 (d, 1 H, *J* = 16 Hz, PhCH), 6.19 (dt, 1 H, *J* = 16 Hz, *J* = 7 Hz, C*H*CH_2), 5.83–5.65 (m, 2 H, CH=CH), 4.11 (d, 2 H, *J* = 4 Hz, CH_2O), 2.95 (t, 2 H, *J* = 6 Hz, CH_2); ^{13}C NMR (75 MHz) δ 137.32, 130.69, 130.12, 130.00, 128.37, 127.94, 126.90, 125.86 (Ar C and C=C), 63.10 (CH_2O), 35.32 (CH_2). Anal. Calcd for $C_{12}H_{14}O$: C, 82.76; H, 8.05. Found: C, 82.57; H, 8.11.

(1*E*,4*E*/*Z*)-1-Phenyl-6-[(*tert*-butyldimethylsilyl)oxy]-1,4-hexadiene (Entry 17). From *trans*-cinnamyl acetate (0.88 g, 5 mmol), (*E*,*Z*)-1-(tributylstannyl)-3-[(*tert*-butyldimethylsilyl)oxy]-1-propene (2.3 g, 5 mmol), lithium chloride (0.631 g, 15 mmol), and $Pd(dba)_2$ (0.144 g, 0.25 mmol, 5 mol %), flash chromatography (silica, EtOAc/hexanes, 1/10) afforded 0.864 g (60%): bp (bulb-to-bulb) 115 °C (0.37 mmHg); IR (neat) 3050, 3020, 2950, 1640, 1595, 1460, 1250, 1080, 950 cm^{-1}; ^{1}H NMR (270 MHz) (*E*/*Z* mixture 1:1) δ 7.38–7.21 (m, 5 H, ArH), 6.42 (d, 1 H, *J* = 15 Hz, PhCH), 6.24 (m, 1 H, =C*H*CH_2), 5.7 (m, 2 H, C*H*=C*H*CH_2O), 4.31 (d, 1 H, *J* = 6 Hz, CH_2O), 4.18 (dd, 1 H, *J* = 5 Hz, *J* = 1 Hz, CH_2O), 2.97 (m, 2 H, CH_2), 0.95 (s, 9 H, $SiC(CH_3)_3$), 0.11 (s, 6 H, $SiMe_2$). Anal. Calcd for $C_{18}H_{28}OSi$: C, 74.97; H, 9.71. Found: C, 74.84; H, 9.83.

(*E*)-1-Phenyl-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,4-pentadiene (Entry 18). From *trans*-cinnamyl acetate (0.83 mL, 5 mmol), 1-[(*tert*-butylsilyl)oxy]-2-(tributylstannyl)-2-propene[17] (2.29 g, 5 mmol), lithium chloride (0.631 g, 15 mmol), and $Pd(dba)_2$ (0.144 g, 0.25 mmol, 5 mol %), flash chromatography (silica gel, 5% EtOAc/hexanes) afforded 0.902 g (64%): IR (neat) 3050, 3000, 2920, 1640, 1590, 1450 1240, 1100, 820 cm^{-1}; ^{1}H NMR (270 MHz) δ 7.36–7.19 (m, 5 H, ArH), 6.39 (d, 1 H, *J* = 16 Hz, PhCH), 6.20 (dt, 1 H, *J* = 16 Hz, *J* = 7 Hz, =C*H*CH_2), 5.10 (br s, 1 H, C=CH), 4.90 (br s, 1 H, C=CH), 4.10 (s, 2 H, CH_2O), 2.91 (d, 2 H, *J* = 7 Hz, $CHCH_2$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz) δ 147.09, 137.48, 131.49, 128.44, 127.69, 126.98, 126.00, 109.94 (Ar C and C=C), 65.68 (CH_2O), 36.38 (CH_2), 25.89, 18.34 ($SiC(CH_3)_3$), −5.38 ($Si(CH_3)_2$). Anal. Calcd for $C_{18}H_{28}OSi$: C, 74.97; H, 9.72. Found: C, 74.98; H, 9.78.

Benzyl (4*E*,7*E*)-8-Phenyl-4,7-octadienoate (Entry 20). From *trans*-cinnamyl acetate (0.17 mL, 1 mmol), (*E*)-benzyl 5-(tributylstannyl)pent-4-enoate (0.48 g, 1 mmol), lithium chloride (0.126 g, 3 mmol), and $Pd(dba)_2$ (0.029 g, 0.05 mmol, 5 mol %), column chromatography (silica gel, 5% EtOAc/hexanes) afforded 0.215 g (70%): R_f = 0.28; IR (neat) 3055, 3022, 2944, 1733 (C=O), 1644, 1594, 1150, 967 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.34–7.15 (m, 10 H, ArH), 6.36 (d, 1 H, *J* = 15 Hz, PhCH), 6.16 (dt, 1 H, *J* = 9 Hz, *J* = 15 Hz, C*H*CH_2), 5.50 (m, 2 H, =CH), 5.10 (s, 2 H, CH_2O), 2.90 (m, 2 H, CH_2), 2.41 (m, 4 H, CH_2CH_2); ^{13}C NMR (75 MHz) δ 172.77 (C=O), 137.51, 135.94, 130.38, 130.07, 129.32, 129.09, 128.60, 128.41, 128.26, 128.08, 126.86, 125.90 (Ar C and C=C), 66.02 (OCH_2), 35.68, 34.04, 27.76 (CH_2). HRMS $C_{21}H_{22}O_2$,

calcd for 306.1611, found 306.1633.

Reaction of Cepham (1) with Phenyltrimethylstannane (Eq 2). To a mixture of 1 (0.221 g, 0.50 mmol), lithium chloride (0.063 g, 1.50 mmol), and phenyltrimethylstannane (0.144 g, 0.60 mmol) in DMF (1 mL) was added bis(dibenzylidene acetone)-palladium(0) ($Pd(dba)_2$) (0.014 g, 0.025 mmol, 5 mol %). The mixture was heated at 60 °C for 17 h, and then it was partitioned between ether (10 mL) and water (10 mL). The ether layer was washed with a NaCl solution (10 mL), dried over $MgSO_4$, and concentrated. Preparative thin-layer chromatography (silica gel, 20% EtOAc/hexanes) afforded **2** and **3** as mixtures of diastereomers. **2** (mixture of epimers): ^1H NMR (300 MHz) 7.50–7.20 (m, 5 H, Ar H), 6.32 (s, 1 H, C=CHS), 6.17–6.12 (d, 1 H, J = 9 Hz, NH), 5.80–5.67 (dd, 1 H, J = 12 Hz, J = 3 Hz, NCH), 5.23–4.84 (d, 1 H, J = 3 Hz, HCS), 5.00, 4.74, 4.70, 4.50 (d, 2 H, J = 12 Hz, CH_2OAc), 3.61 (s, 2 H, $PhCH_2$), 2.03 (s, 3 H, CH_3CO), 1.49, 1.44 (s, 9 H, $C(CH_3)_3$); mass spectrum (electron impact) m/e 446 (parent). **3** (mixture of epimers): ^1H NMR (300 MHz) δ 7.50–7.20 (m, 5 H, ArH), 6.12 (d, 1 H, J = 9 Hz, NH), 5.85 (s, 1 H, C=CHS), 5.74, 5.63 (dd, 1 H, J = 12 Hz, J = 3 Hz, NCH), 5.21–4.90 (d, 1 H, J = 3 Hz, HCS), 3.62 (d, 2 H, J = 3 Hz, $PhCH_2$), 2.03 (s, 3 H, CH_3), 1.48, 1.44 (s, 9 H, $C(CH_3)_3$); mass spectrum (electron impact) m/e 388 (parent). These compounds were not purified further.

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Competitive Base-Induced α-Elimination and Methanolysis of *N*-Aryl-*O*-pivaloylhydroxylamines

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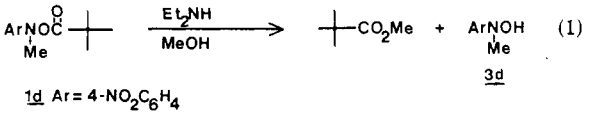
The *N*-aryl-*O*-pivaloylhydroxylamines **1a–c** are quite stable in MeOH under neutral conditions, but under mildly basic conditions (0.05 M Et_2NH or Et_3N) they undergo rapid decomposition ($t_{1/2} \approx$ 3–5 h at 25 °C) by two competitive processes: apparent α-elimination to generate the nitrenes **2a–c** and pivalic acid and basic ester methanolysis to generate the hydroxylamines **3a–c** and methyl pivalate. The nitrenes decompose into the corresponding anilines **5** and azobenzenes **7**, while the hydroxylamines undergo nitrene-mediated oxidation into the corresponding azoxybenzenes **6**. The mechanism of this latter process was probed by addition of excess hydroxylamine, and a mechanism for the oxidation consistent with available data (Scheme II) is proposed. It was also found that the nitrosobenzenes **8** undergo nucleophilic attack by the conjugate bases **4a–c** of the title compounds to produce one of the two possible isomeric nonsymmetrical azoxybenzenes.

In a recent investigation of the hydrolysis under mild conditions of ring-substituted *N*-aryl-*O*-pivaloylhydroxylamines **1**, we obtained products [4-nitroaniline (**5c**) and 4,4′-dinitroazoxybenzene (**6c**)] from the 4-nitro compound **1c**, which may have been formed by way of a nitrene intermediate.[1] Arylnitrenes have been generated via α-elimination of various aniline derivatives, but not under mild conditions in hydroxylic solvents.[2] The potential generation of nitrenes from **1** is also of interest since these species are model compounds for suspected carcinogenic metabolites of polycyclic aromatic amines.[3] The possibility that arylnitrenes may be generated from these species in vivo has not been considered.

Accordingly, we have investigated the decomposition of **1** under mildly basic conditions (0.01–0.10 M Et_2NH) in methanol in an effort to obtain evidence for arylnitrene generation. Methanol was chosen as the solvent for this initial study because the decomposition of **1a** and **1b** by simple pH-independent heterolysis of the N–O bond to generate a nitrenium ion, a facile process in H_2O,[1] will be suppressed in methanol.[4] In methanol it is also possible to easily distinguish α-elimination from base-induced methanolysis of the ester by determination of the yield of methyl pivalate (Scheme I).

Under our reaction conditions α-elimination to generate **2** and methanolysis to form **3** appear to be competitive processes, with the former path predominating for **1a** and **1b** and the latter for **1c**. The nitrenes **2a–c** decompose into the corresponding anilines **5a–c** in moderate to high yields and the azobenzenes **7a–c** in low yields. The hydroxylamines **3a–c** are oxidized under the reaction conditions to the corresponding azoxy compounds **6a–c** in a process that may be nitrene dependent. In contrast to **1a–c**, the ester **1d**, in which deprotonation is not possible, undergoes exclusive methanolysis to generate methyl pivalate and the corresponding hydroxylamine **3d** under our conditions (eq 1).



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