Synthesis of Substituted Cyclic Ethers from Halo Ketones and Halo Aldehydes by Palladium-Catalyzed Coupling with Organotin Reagents

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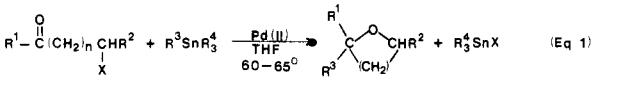
The palladium-catalyzed reaction of a variety of halo ketones or halo aldehydes with acetonyl- and allyltin reagents gives cyclic ethers in good yields. Oxiranes, oxetanes, and tetrahydrofurans can be obtained under mild reaction conditions. The use of palladium catalyst containing chiral monophosphine ligands gave a small enantiomeric excess (up to 19%) of a chiral oxirane from an α-halo ketone. The allyl- and acetonyloxirane products tend to undergo further transformations in prolonged reactions: allyloxiranes rearrange to α-allyl aldehydes and acetonyloxiranes dehydrate to give substituted furans. The mechanism of the reaction appears to involve addition of the organotin ligand to the carbonyl, followed by palladium(II)-catalyzed cyclization of the tin alkoxides.

Although the reaction of aldehydes and ketones with organometallic reagents to yield alcohols is relatively straight forward, the reaction of α-halo aldehydes with organometallics gives a variety of products. Grignard reagents react with α-chloro ketones,[2] α-halo aldehydes,[3] and α,α-dihalo ketones[4] to give carbonyl compounds by rearrangement of the intermediate magnesium alkoxide. The reaction of lithium cuprates with α-halo ketones yields products resulting from α-substitution or from copper enolate chemistry.[5]

The palladium-catalyzed reaction of α-halo ketones with allyltributylstannane to give mixtures of allyl-substituted oxiranes and their rearrangement products has been reported to take place under somewhat vigorous conditions (100 °C, 20 h).[6] Because this reaction with tin reagents appeared to be a promising method for the generation of a carbon–carbon bond and the simultaneous formation of an oxirane, a study of the scope and utility of this reaction was undertaken.

Results and Discussion

The palladium-catalyzed reaction can be carried out under relatively mild conditions and is quite general for halo ketones or halo aldehydes with reactive organotins. Only organostannanes containing the readily transferable allyl and acetonyl groups give good yields of ethers (eq 1).



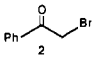
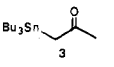
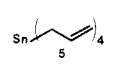
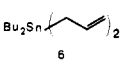
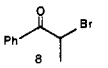
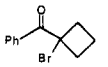
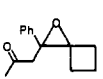
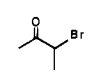
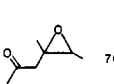
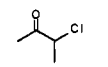
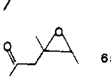
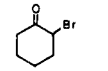
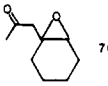
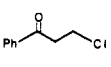
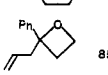
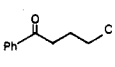
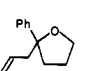
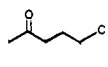
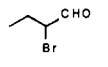
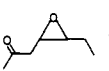
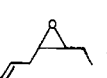
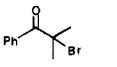
(Eq 1)

n = 0, 1, 2; X = Cl, Br

R^3 = $-CH_2-CH=CH_2$, $-CH_2-COCH_3$; R^4 = n-Bu

Carbonyl compounds containing α-, β-, or γ-halogens gave oxiranes, oxetanes, and tetrahydrofurans, respectively. When the reaction times with α-halo carbonyls were not excessive, no side products of oxirane rearrangement were observed. Purification of the product was simple: solvent was removed by evaporation and the tin halide byproduct could be precipitated from an ethereal solution by the addition of aqueous potassium fluoride.[7]

Table I. Reaction of Halo Carbonyls with Acetonyl- and Allyltin Reagents Catalyzed by Benzylchlorobis(triphenylphosphine)palladium(II) (1)[a]

	halo carbonyl	organotin	reaction time, h	product	yield,[b] %
1	 2	 3	5	 4	80
2	2	 5	3	 7	60
3	2	 6	5	7	75
4	 8		3	5	 55
5			3	48	 35
6			3	5	 70
7			3	5	 65
8			3	4	 70
9			6	48	 85
10			5	48	 90
11			5	48	 90
12			3	15	 80
13			5	48	 85
14			3 or 6	72	no reaction

[a] All reactions were carried out in THF at 63 °C in capped reaction vessels under an inert atmosphere. Benzylchlorobis(triphenylphosphine)palladium(II) (1) was used in 2.5% molar amounts based on the halocarbonyl. A slight excess (~10%) of the organotin reagent was used. [b] All compounds were isolated and identified. Yields (±5%) were determined by ^1H NMR using internal standards.

Reaction Scope. The reaction of acetonyltributyltin (3) with α-bromoacetophenone (2) to yield 2-acetonyl-2-

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(2) (a) Tiffeneau, M. *Bull. Soc. Chim. Fr.* **1945**, 621. (b) Kataoka, H. *Yuki Gosei Kagaku, Kyokaishi* **1959**, *17*, 777; *Chem. Abstr.* **1960**, *54*, 4492b. (c) Huang, R. L. *J. Chem. Soc.* **1957**, 4089.

(3) Kirrmann, A.; Chancel, P. *Bull. Soc. Chim. Fr.* **1951**, 227 and references cited therein.

(4) DeKimpe, N.; Verhe, R.; DeBuyck, L.; Schamp, N. *Tetrahedron Lett.* **1979**, 955.

(5) (a) Dubois, J.-E.; Lion, C. *Tetrahedron* **1975**, *31*, 1227. (b) Lion, C.; Dubois, J.-E. *Ibid.* **1975**, *31*, 1223. (c) Dubois, J.-E.; Lion, C.; Moulineau, C. *Tetrahedron Lett.* **1971**, 177. (d) Depres, J.-P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2036 and references cited therein.

(6) Kosugi, M.; Arai, H.; Yoshino, A.; Migita, T. *Chem. Lett.* **1978**, 795.

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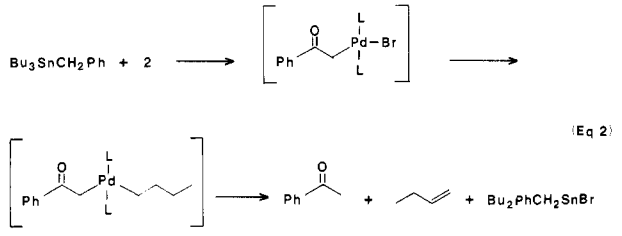
phenyloxirane (4) (Table I) is catalyzed by benzylchlorobis(triphenylphosphine)palladium(II) (1). Various other palladium catalysts either were as effective or gave lower yields (vide infra). The benzylpalladium catalyst (1) generally was used because it was easy to handle and afforded high yields. The reactions were run under an inert atmosphere; however, carrying out the reaction in air did not affect the yield.

The reaction of α-bromoacetophenone with allyltin reagents (5 and 6) gave 2-allyl-2-phenyloxirane (7). More than one allyl group on tin can participate in the reaction. Two allyl groups can transfer either from tetraallyltin (5) or diallyldibutyltin (6). In a reaction of α-bromoacetophenone with half the molar amount of 6, both allyl groups were transferred to give 7 and dibutyltin dibromide as the organotin product. With equimolar amounts of α-bromoacetophenone and 6, after complete conversion of the ketone, there was still 32% unreacted 6 and 35% of allyldibutyltin bromide present. Thus, allyldibutyltin bromide transfers an allyl group even in the presence of diallyldibutyltin (6). This is consistent with the high reactivity of trialkyltin halides toward additions to carbonyls.[8]

The palladium-catalyzed reactions of other tin reagents with α-bromoacetophenone did not yield oxiranes or products derived from oxiranes. Tetramethyltin and tetrabenzyltin failed to react with 2 and α-bromobutyraldehyde, respectively. Tributylbenzyltin, however, underwent a catalyzed reaction with α-bromoacetophenone (2) to yield acetophenone (87%), benzyldibutyltin bromide (99%), and 1-butene (80%) (eq 2). These products most

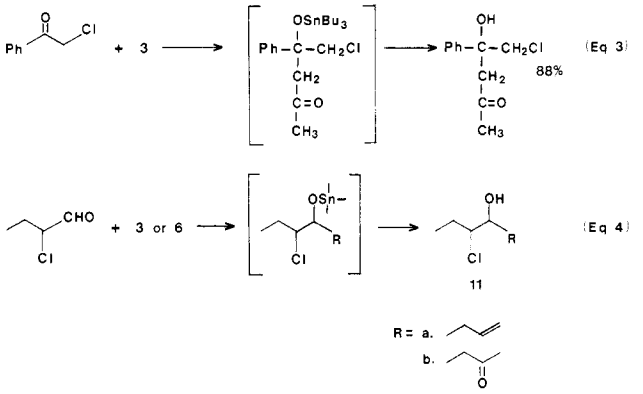


(Eq 2)

likely result from an oxidative addition at the carbon–bromine bond to a palladium(0) complex followed by a transmetalation reaction of a butyl group from tin with subsequent β-elimination and reductive elimination steps. The propensity of the butyl group to undergo transmetalation has been observed in other coupling reactions.[9]

A variety of other halocarbonyls undergo the reaction with acetonyl- and allyltin reagents. Generally longer reaction times were required with the less reactive α-halo carbonyls. Secondary α-halo carbonyls give good yields of oxirane (entries 4, 6–8, 12, and 13), but tertiary α-halo ketones either give lower yields (entry 5) or fail to react (entry 14). High yields of an oxetane and tetrahydrofurans (entries 9–11) were obtained from β- and γ-halo ketones. Longer reaction times were used with these ketones since no secondary reactions were observed under the reaction conditions. High yields of oxiranes also were obtained from 2-bromobutanal (entries 12 and 13).

Limitations. Although α-bromoacetophenone (2) and 2-bromobutanal react with both acetonyl- and allyltin reagents to give oxiranes, no cyclization occurred in reactions with α-chloroacetophenone or 2-chlorobutanal. Instead an addition reaction of the tin reagent to the carbonyl group took place. Hydrolysis of the addition product gave halohydrins (10 and 11) in good yields (eq 3 and 4). Somewhat surprisingly, 3-chloro-2-butanone

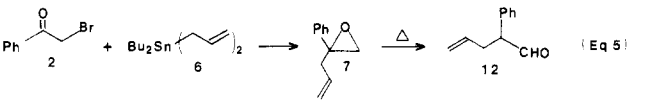


(Eq 3)

(Eq 4)

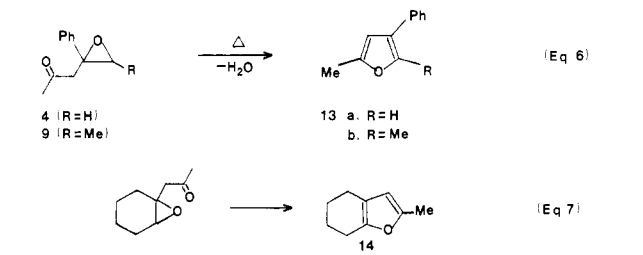
reacted with acetonyltributyltin to give 2-acetonyl-2,3-dimethyloxirane (entry 7) and in approximately the same yield as obtained from 3-bromo-2-butanone (entry 6).

The reactions of the tin reagents with the halocarbonyls usually were clean, with very few side reactions. However, the oxiranes tend to undergo rearrangement and dehydration reactions at prolonged reaction times at higher temperatures. When the reaction of α-bromoacetophenone (2) with dibutyldiallyltin (6) was allowed to proceed for 48 h at 90 °C, 38% of 2-phenyl-4-pentenal (12) was obtained as a product of rearrangement of 2-allyl-2-phenyloxirane (7, eq 5). Higher yields of 12 have been



(Eq 5)

reported from this reaction with α-chloroacetophenone carried out at 100 °C for 20 h.[6] Acetonyloxiranes undergo rearrangement with dehydration to yield 2-methylfurans either on prolonged heating or catalysis by acid (eq 6 and 7). Thus, 2-methyl-4-phenylfuran (13a) was isolated in



(Eq 6)

(Eq 7)

30% yield from reactions of α-bromoacetophenone (2) with acetonyltributyltin, but no attempt was made to optimize this yield. Similarly, 2,5-dimethyl-4-phenylfuran (13b) and 2-methyl-4,5,6,7-tetrahydrobenzo[*b*]furan (14) could be isolated from rearrangement reactions of the corresponding acetonyloxiranes.

Effect of Palladium Catalysts. In the absence of catalyst, neither diallyldibutyltin (5) nor tetraallyltin (6) reacts with α-bromoacetophenone (2). The reaction of acetonyltributyltin (3) with α-bromoacetophenone (2) in THF was catalyzed by benzylchlorobis(triphenylphosphine)palladium(II) (1) both at 60 °C and at ambient temperature (Table II). This reaction between 2 and 3 also took place without catalyst, but the reaction was slow, and a lower yield of oxirane was obtained. This is the only case in which an uncatalyzed reaction of acetonyltributyltin with a halocarbonyl took place. When this reaction of 2 and 3 was carried out in the absence of catalyst

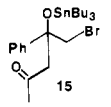
(7) Leibner, J. E. and Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.
(8) (a) Gambaro, A.; Peruzzo, V.; Plazzogna, G.; Tagliavini, G. *J. Organomet. Chem.* **1980**, *197*, 45. (b) Peruzzo, V.; Tagliavini, G. *Ibid.* **1978**, *162*, 37. (c) Gambaro, A.; Marton, D.; Peruzzo, V.; Tagliavini, G. *Ibid.* **1980**, *204*, 191 and references therein.
(9) (a) Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981.

Table II. Effect of Palladium Catalysts on the Reaction of α-Bromoacetophenone (2) with Acetonyltributyltin (3) To Give 2-Acetonyl-2-phenyloxirane (4)[a]

palladium complex	% yield 4[b] (ee)[c]
no catalyst	20
$PhCH_2Pd(PPh_3)_2Cl$ (1)	70[d,e]
(diphos)$PdCl_2$	55[f]
((+)-diop)$PdCl_2$[g]	40 (<5)
(R-camp)$_2PdCl_2$[h]	70 (9)
((+)-nmdpp)$_2PdCl_2$[i]	80 (19)

[a] Reactions were run in THF at 25 °C for 72 h unless otherwise noted. [b] Yields (±5%) were determined by ^1H NMR using dibromomethane as an internal standard. [c] Enantiomeric excess is based on the ^1H NMR integration of the methyl signals of the two enantiomers with tris[((3-heptafluoropropyl)hydroxymethylene)-α-camphorato]europium(III). [d] An 80% yield was obtained at 63 °C, 5 h. [e] Addition of an equimolar amount of triphenylphosphine to this reaction decreased the yield to 50%. [f] Unreacted starting material (~20%) and a 25% yield of 15 were observed. [g] (+)-diop = 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. [h] (R)-camp = (R)-cyclohexylanisylmethylphosphine. [i] (+)-nmdpp = (+)-neomenthyldiphenylphosphine.

at 60 °C for 5 h, 63% of the α-bromoacetophenone had disappeared, to give 33% of oxirane 4 and 30% of 5-bromo-4-(tributylstannyl)oxy-4-phenylpentan-2-one (15).



Although 15 could not be isolated, it was identified by comparison of its ^1H NMR spectrum in the crude reaction mixture with that of 5-chloro-4-hydroxy-4-phenylpentan-2-one (10), obtained from an analogous reaction of 3 with α-chloroacetophenone. When 2 and 3 were allowed to react for longer times (20 h, 63 °C) in the absence of catalyst, 15 was not observed and a 79% yield of acetonyloxirane 4 was obtained.

The effect of numerous other catalysts were examined for the reaction of 2 with 3. Generally, benzylchlorobis(triphenylphosphine)palladium(II) (1) was the most effective catalyst (Table II). Palladium catalysts such as dichlorobis(triphenylphosphine)palladium(II), dichlorobis(methyldiphenylphosphine)palladium(II), dichlorobis(benzonitrile)palladium(II), and dichlorobis(acetonitrile)palladium(II) gave lower yields (40–50%) of 4 under the same reaction conditions (25 °C, 72 h). The addition of phosphine to the reaction decreased the yield of oxirane 4.

The use of palladium catalysts containing optically active phosphines gave low asymmetric induction. The highest enantiomeric excess was achieved by using dichlorobis((+)-neomenthyldiphenylphosphine)palladium(II), but even in this case only a 19% enantiomeric excess was observed. The reaction of 2 with 3 in the presence of ((+) NMDPP)$_2PdCl_2$ at 0 °C for 7 days gave a much lower yield of oxirane (27%), and the enantiomeric excess was no higher. The low asymmetric induction is, in part, a result of a significant amount of noncatalyzed addition of the acetonyltin to the carbonyl function.

Mechanisms. The mechanism of this reaction was not investigated in detail; however, from these results, a number of features are evident. The first step of the reaction appears to be the addition of the organotin reagent across the carbonyl group. Acetonyltin reagents react more rapidly than the allyltin reagents, and in reactions of acetonyltributyltin (3) with α-bromoacetophenone, the reaction does proceed slowly without catalysis. Qualitatively, this reaction is 2 to 3 times as fast with the catalyst.

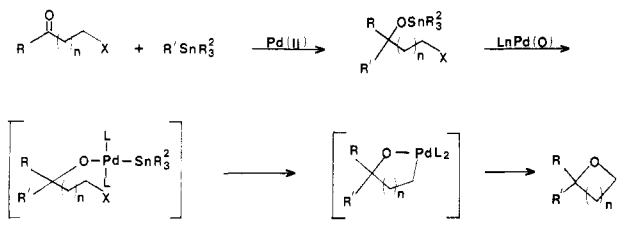
The uncatalyzed addition reactions of a variety of organotin reagents to carbonyl compounds are known to occur where allyl,[10] acetonyl,[11] acetonitrile,[11] ethyl acetate,[11] and diethylacetamide[11] groups are attached to tin. Acetonyltributyltin (3) reacts with aldehydes and cyclic ketones[11] in the absence of catalyst. The reaction of aldehydes with tin enolates related to 3 takes place without catalysts at −78 °C.[12] Acetonyltributyltin will not react with open-chain ketones such as acetophenone, however. Allyltrialkyltins will add to aldehydes and cyclic ketones in the presence of a Lewis acid,[10] but in the absence of a catalyst, the reaction takes place only with highly activated carbonyls such as in polyfluoro ketones.[13] By comparison, tetraallyltin[14] and allyltin halides[8] react with a variety of aldehydes and ketones in the absence of a catalyst.

Thus, with the exception of the reactions of 2 with 3 or α-halo aldehydes (Table I) the reactions of both allyl- and acetonyltin reagents with halocarbonyls require a catalyst, and the catalyst apparently is required for the addition to the carbonyl group. Indeed, in catalyzed reactions of α-chloroacetophenone with 3 and of 2-chlorobutanal with 3 or 6, alkoxytin intermediates are obtained that on hydrolysis, yield halohydrins. Also, in the reaction of α-bromoacetophenone (2) with 3, the intermediate alkoxytin compound could be observed. In addition, the asymmetric induction obtained in reactions of acetonyltributyltin (3) with α-bromoacetophenone (2) in the presence of palladium catalysts containing chiral phosphines requires involvement of the catalyst in the addition of the organotin across the carbonyl, since it is this step which generates the chiral center in the oxirane (4). Palladium possibly is acting as a Lewis acid for this addition; such addition reactions are known to be enhanced by Lewis acids.[14]

The second step in the reaction appears to be related to the thermal cyclization of haloalkoxytin compounds,[15,16] which have been reported to take place at temperatures ranging from 70 to 220 °C. In the absence of a palladium catalyst at 63 °C, the cyclization of the stannoxide was not observed, the reaction of 3 with α-bromoacetophenone being the exception. The intermediate stannoxy halohydrin derived from α-bromoacetophenone is the type (tertiary alcohol, primary bromide) of halohydrin derivative known[15] to undergo closure at the lowest temperature (~70 °C). Since other intermediate haloalkoxytin complexes require higher temperatures[15,16] to cyclize in the absence of palladium, the palladium catalysts must also be necessary for the cyclization step.

The possibility of an oxidative addition of palladium(0) to the carbon–halogen bond is unlikely since the rate of oxidative addition to a secondary or a tertiary halogenated carbon center is slow.[17] In addition, no β-elimination products were observed in the halo ketones containing β-hydrogens. Instead, the oxidative addition of the stan-

(10) Daude, G.; Pereyre, M. *J. Organometal. Chem.* **1980**, *190*, 43 and references cited therein.
(11) Noltes, J. G.; Verbeek, F.; Creemers, H. M. J. C. *Organomet. Chem. Synth.* **1970/71**, *1*, 57.
(12) Shenvi, S.; Stille, J. K. *Tetrahedron Lett.* **1982**, 627.
(13) Abel, E. W.; Rowley, R. J. *J. Organomet. Chem.* **1975**, *84*, 199.
(14) Hosomi, A.; Iguchi, H.; Endo, M.; Sakurai, H. *Chem. Lett.* **1979**, 977.
(15) Delmond, B.; Pommier, J.-C.; Valade, J. *J. Organomet. Chem.* **1973**, *50*, 121. Delmond, B.; Pommier, J.-C.; Valade, J. *Ibid.* **1973**, *47*, 337. Delmond, B.; Pommier, J.-C.; Valade, J. *Ibid.* 1972, *35*, 91.
(16) Biggs, J. *Tetrahedron Lett.* **1975**, 4285.
(17) (a) Collman, J. P.; MacLaury, M. R. *J. Am. Chem. Soc.* **1974**, *96*, 3019. (b) Pearson, R. G.; Figdore, P. E. *J. Am. Chem. Soc.* **1980**, *102*, 1541.



noxide to palladium(0) to give the alkoxypalladium(II) species is suggested. A similar palladium insertion into a silyl enolate silicon–oxygen bond has been shown[18] to give a palladium(II) enolate product. The elimination of triorganotin halide to give a cyclic palladium alkoxide followed by reductive elimination of palladium completes the sequence.

Experimental Section

Reactions were carried out with Schlenk tubes under an atmosphere of argon. ^{1}H NMR spectra were taken on a Varian EM360 or JEOL FX100 spectrometer, and ^{13}C NMR spectra were obtained on a JEOL FX100 (assignment of carbons were verified by off-resonance techniques). IR spectra were obtained on a Beckman IR4240 and routine mass spectra analysis was performed on a Micromass 16F spectrometer. GC separations and identifications were done on a Varian Aerograph 1520 equipped with a 20% SE30 on Chromosorb W column ($^1/_4$ in. × 10 ft). Preparative thin layer chromatography was carried out on precoated silica gel F-254 (2 mm) plates with hexane–ethyl acetate as eluants. Radial chromatography was carried out with a Chromatron (Harrison Research Co.). Commercial aldehydes and ketones were used after distillation at reduced pressure. Commercial halo ketones were used after recrystallization or distillation. Solvents were distilled and degassed prior to use.

Palladium Catalysts. Benzylchlorobis(triphenylphosphine)palladium(II),[19] dichlorobis(benzonitrile)palladium(II),[20] dichloro((+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane)palladium(II),[21] and dichloro(1,2-bis(diphenylphosphino)ethane)palladium(II)[22] were prepared by known methods. Other optically active palladium complexes were synthesized as follows: A solution of the chiral phosphine and bis(benzonitrile)dichloropalladium(II)[23] in a minimum volume of degassed acetone was stirred under argon at 25 °C overnight. The mixture was cooled to 0 °C and the precipitated complex was filtered and washed with degassed *n*-hexane. Dichlorobis((+)-neomethyldiphenylphosphine)palladium(II) was prepared in 72% yield. Anal. Calcd C, 63.97; H, 7.08; Cl, 8.58. Found: C, 63.28; H, 6.92; Cl, 8.60. Attempts to prepare pure dichlorobis((+)-anisylcyclohexylmethylphosphine)palladium(II)[24] by the same procedure gave a red oil, which was placed under reduced pressure at 40 °C (0.1 mm) to remove benzonitrile. The residual oil was used without further purification.

α-Halo Ketones and Aldehydes. α-Bromo ketones were prepared by bromination of the ketones with 1 equiv of bromine in chloroform or ether solutions. Thus, α-bromopropiophenone[25] was prepared in an 82% yield and distilled at 110–112 °C (0.5 mm) [lit.[25] 156–157.5 °C (42 mm)]. α-Bromocyclohexanone was prepared by the cupric bromide bromination of cyclohexanone[26] and was distilled at 70–72 °C (0.4 mm) [lit.[26] 66 °C (2.0 mm)]. α-Chloro aldehydes were obtained by treating the corresponding aldehydes with sulfonyl chloride.[27] α-Chlorobutyraldehyde distilled at 96–98 °C (700 mm) [lit.[27] 104–110 °C (760 mm)]; α-chloroisobutyraldehyde distilled 84–85 °C (20 mm) [lit.[28] 86–90 °C); α-bromobutyraldehyde was prepared by bromination with bromine in carbon disulfide solution containing 1 equiv of calcium carbonate[28] and was distilled at 33–35 °C (15 mm) [lit.[29] 47–50 °C (21 mm)].

Tin Reagents. Tetraallylstannane,[30] dibutyldiallylstannane,[31] acetonyltributylstannane,[32] benzyltributylstannane,[33] and allyltributylstannane[34] were prepared by known methods.

5-Chloro-4-hydroxy-4-phenylpentan-2-one (10). A solution of 310 mg (2.00 mmol) of α-chloroacetophenone in 8 mL of freshly distilled and degassed THF was introduced into the Schlenk tube which was first flushed with argon. To this solution was added 1.55 g (4.45 mmol) of acetonyltributylstannane (**3**), the tube was capped, and the mixture stirred at 25 °C for 72 h. The solvent was removed under reduced pressure, the residue was redissolved in 50 mL of ether, and the ether layer was extracted with water (2 × 50 mL) and aqueous ammonium chloride (1 × 4 mL). The organic layer was dried ($MgSO_4$) and the ether removed in vacuo. The residual tin compounds were removed by flash elution of the reaction mixture (dissolved in a minimum amount of ether) through a silica gel column (2 × 11 cm) with 1:4 ether–hexane. The crude product (**10**) was further purified by radial chromatography with *n*-hexane–ethyl acetate (10:1) at a flow rate of 5 mL of solvent a minute with a 2-mm silica gel plate: IR (neat) ν 3450 (O–H), 1700 (carbonyl), 1168 (C–O) cm^{-1}; ^{1}H NMR (CCl_4) δ 7.07 (m, 5, aromatic), 4.30 (s, 1, OH), 3.50 (s, 2, CH_2Cl), 2.99 (s, 2, CH_2CO), 1.99 (s, 2, CH_3CO); ^{13}C NMR ($CDCl_3$) δ 209.535 (carbonyl), 142.450, 128.145, 127.503, 124.817 (aromatic), 74.956 (PhCO), 48.974 (CH_2CO), 31.809 (CH_3CO), 52.886 (CH_2Cl). Anal. Calcd: C, 62.12; H, 6.16. Found: C, 61.79; H, 6.07.

Preparation of Substituted Cyclic Ethers. 2-Phenyl-2-acetonyloxirane (4). The preparation of **4** is a representative procedure. A solution of 400 mg (2.01 mmol) of α-bromoacetophenone in 4 mL of freshly distilled and degassed THF and 763 mg (2.20 mmol) of acetonyltributyltin (**3**) were introduced into the Schlenk tube which was first flushed with argon. To this solution was added 38 mg (0.050 mmol) of benzylchlorobis(triphenylphosphine)palladium(II), the tube was capped, and the mixture was heated for 5 h at 63 °C. After the mixture was cooled to 25 °C, the THF was removed under reduced pressure and the residue was redissolved in ether and treated with 10 mL of an aqueous potassium fluoride solution, followed by a saturated sodium bicarbonate solution. The aqueous layers were extracted with ether, the combined ether fractions were washed with water and dried ($MgSO_4$), and the ether was evaporated. Residual tin compounds and palladium complexes were removed by a flash elution of the reaction mixture (dissolved in a minimum volume of chloroform) through a silica gel column (2 × 20 cm) with *n*-hexane. The crude reaction product (**4**) 220 mg (63% yield) was further purified by TLC with *n*-hexane–ethyl acetate (10:3): R_f 0.3; IR (neat) ν 1715 (carbonyl), 1225, 925, 895 (oxirane) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 5, aromatic), 3.32–2.84 (m, 4, $COCH_2$ and oxirane CH_2O), 2.15 (s, 3, CH_3CO); ^{13}C NMR ($CDCl_3$) δ 204.748 (carbonyl), 138.772, 128.029, 127.386, 125.109 (aromatic), 56.273 (PhCO), 55.515 (CH_2O), 49.500 (CH_2); mass spectrum (relative intensity) 176 (parent, 0.9), 169 (100), 133 (48), 105 (92), 77 (45). Anal. Calcd: C, 74.98; H, 6.86. Found: C, 74.69; H, 6.71.

2-Phenyl-2-acetonyloxirane-*3,3-d*$_2$. This deuterated oxirane was made from α-bromoacetophenone-α-d_2 to make the assignments in the ^{1}H NMR spectrum of (**4**): ^{1}H NMR ($CDCl_3$) δ 7.39

(18) Ito, Y.; Nakatsuka, M.; Kise, N.; Saegusa, T. *Tetrahedron Lett.* **1980**, 2873.
(19) Fitton, P.; McKeon, J. E.; Ream, B. C. *J. Chem. Soc., Chem. Commun.* **1969**, 370.
(20) Kharasch, M. S.; Seyler, R. C.; Mayo, F. R. *J. Am. Chem. Soc.* **1938**, *60*, 882.
(21) Fiaud, J. C.; Gournay, A. H.; Larcheveque, M.; Kagan, H. B. *J. Organomet. Chem.* **1978**, *154*, 175.
(22) Calvin, G.; Coates, G. E. *J. Chem. Soc.* **1960**, 2008.
(23) Walton, R. A. *Spectrochim. Acta* **1965**, *21*, 1795.
(24) We wish to thank W. S. Knowles from Monsanto for the generous donation of this optically active phosphine.
(25) Borowitz, I. J.; Kirby, K. C.; Virkhaus, R. *J. Org. Chem.* **1966**, *31*, 4031.
(26) Brown, H. C.; Rogic, M. M.; Rathke, M. W. *J. Am. Chem. Soc.* **1968**, *90*, 6218.
(27) Stevens, C. L.; Farkas, E.; Gillis, B. *J. Am. Chem. Soc.* **1954**, *76*, 2695.
(28) Stevens, C. L.; Gillis, B. *J. Am. Chem. Soc.* **1957**, *79*, 3448.
(29) Takeda, A.; Tsuboi, S.; Wada, S.; Kato, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1217.
(30) Fishwick, M.; Smith, C. A.; Wallbridge, M. G. H. *J. Organomet. Chem.* **1970**, *21*(1), 9.
(31) Rosenberg, S. D.; Debreczeni, E.; Weinberg, E. L. *J. Am. Chem. Soc.* **1959**, *81*, 972.
(32) (a) Yasuhara, Y.; Nogi, T. *Chem. and Ind.* (London) **1967**, 229. b. Pereyre, M.; Bellegarde, B.; Mendelsohn, J.; Valade, J. *J. Organomet. Chem.* **1968**, *11*, 97.
(33) Davies, A. G.; Roberts, B. P.; Smith, J. M. *J. Chem. Soc., Perkins Trans. 2* **1972**, 2221.
(34) Seyferth, D.; Weiner, M. A. *J. Org. Chem.* **1961**, *26*, 4797.

(s, 5, aromatic), 3.07 (ABq, 2, J = 17 Hz, $COCH_2$), 2.15 (s, 3, CH_3CO).

2-Methyl-4-phenylfuran. By the use of $((R)\text{-CAMP})_2PdCl_2$ (7 mol %) as catalyst for the reaction of α-bromoacetophenone and tributylacetonyltin, 2-methyl-4-phenylfuran was formed in a 15% yield and was isolated by TLC, R_f 0.8. No dehydration occurred by using benzylchlorobis(triphenylphosphine)palladium as catalyst: mp 64–66 °C (lit.[35] 60–63 °C); ^1H NMR ($CDCl_3$) δ 7.7–7.25 (m, 6, aromatic and =CHO), 6.33 (s, 1, =CCPh), 2.34 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 153.018 (O(Me)C=), 136.436 (=CO), 132.758, 128.554, 126.564, 125.578 (aromatic), 127.095 (PhC=), 104.749 (=CH), 13.651 (CH_3); mass spectrum, m/e (relative intensity) 158 (parent, 100), 129 (49), 128 (24), 86 (24), 85 (40), 83 (62).

2-Phenyl-2-allyloxirane (7). From 400 mg (2.00 mmol) of α-bromoacetophenone (2) and 380 mg (1.20 mmol) of dibutyldiallyltin (6) in THF at 63 °C for 5 h was obtained 189 mg (59.0% yield) of 7, which was further purified by TLC (R_f 0.7); ^1H NMR ($CDCl_3$) δ 7.34 (s, 5, aromatic), 6.07–5.34 (m, 1, C=CH), 5.26–4.87 (m, 2, H_2C=C), 3.10–2.33 (m, 4, allylic and OCH_2). Anal. Calcd: C, 82.48; H, 7.55. Found: C, 82.53; H, 7.51.

2-Phenyl-2-acetonyl-3-methyloxirane (9). This compound was obtained by the reaction of tributylacetonylstannane (2) with α-bromopropiophenone (8) to give 252 mg (67.0% yield) of product that was purified by TLC (R_f 0.4); ^1H NMR ($CDCl_3$) δ 7.30 (s, 5, aromatic), 3.32–2.63 (m, 3, CH_2CO and OCH<), 2.10 (s, 3, $COCH_3$), 1.00 (d, 3, J = 4.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 204.806 (carbonyl), 187.020, 127.912, 127.678, 127.095 (aromatic), 61.586 (PhCO), 59.717 (MeCHO), 51.777 (CH_2CO), 30.524 (CH_3CO), 13.885 (CH_3). Anal. Calcd: C, 75.76; H, 7.41. Found: C, 75.19; H, 7.43.

2,5-Dimethyl-3-phenylfuran. When the reaction between 2 and α-bromopropiophenone (8) was allowed to continue for 48 h at 63 °C, 146 mg (42.0% yield) of furan product was isolated and purified by TLC (R_f 0.8): ^1H NMR ($CDCl_3$) δ 7.38 (s, 5, aromatic), 6.64 (s, 1, CH=C), 2.43 (s, 3, CH_3), 2.30 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 149.515 (=C(Me)O), 145.603 (=C(Me)O), 134.393, 128.379, 127.211, 125.927 (aromatic), 121.314 (PhC=), 106.893 (CH=), 13.476 (CH_3), 13.067 (CH_3). Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.64; H, 7.06.

1-Phenyl-1-acetonyl-5-oxaspiro[2.3]hexane. From 480 mg (2.00 mmol) of α-bromocyclobutyl phenyl ketone and 764 mg (2.20 mmol) of acetonyltributyltin (3) was obtained 132 mg (31.0%) of product, which was purified by TLC (R_f 0.3); ^1H NMR ($CDCl_3$) δ 7.26 (s, 5, aromatic), 2.93 (ABq, 2, J = 15 Hz, CH_2CO), 2.53–1.50 (m, 6, ring CH_2), 2.10 (s, 3, CH_3CO); ^{13}C NMR ($CDCl_3$) δ 205.507 (carbonyl), 137.546, 127.970, 127.270, 125.985 (aromatic), 69.877 (–CO–), 63.337 (CO), 48.741 (CH_2C=O), 30.233 (CH_3CO), 29.590, 29.006 (CH_2CO–), 12.367 (CH_2). Anal. Calcd: C, 77.75; H, 7.46. Found: C, 77.74; H, 7.34.

2,3-Dimethyl-2-acetonyloxirane. The reaction of 210 mg (2.0 mmol) of 3-chloro-2-butanone and 763 mg (2.2 mmol) of tributylacetonyltin (3) gave, after evaporation of the solvent and vacuum transfer of the reaction at 60 °C (0.1 mm), 166 mg (65.0% yield) of product which was then purified by TLC (R_f 0.3); ^1H NMR ($CDCl_3$) δ 2.80 (q, 1, J = 5.4 Hz, CHO–), 2.56 (ABq, 2, J = 16.1 Hz, CH_2CO), 2.10 (s, 3, CH_3CO), 1.27 (d, 3, J = 5.3 Hz, CH_3), 1.22 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 205.576 (carbonyl), 58.352 (–CHO–), 52.839 ($COCH_2$), 30.710 CH_3CO, 16.931 (MeCO), 13.895 (CH_3). Anal. Calcd: C, 65.60; H, 9.44. Found: C, 66.05; H, 9.42.

1-Acetonyl-7-oxabicyclo[4.1.0]heptane. This compound was obtained (170 mg, 55.0%) from 354 mg (2.00 mmol) of α-bromocyclohexanone and 760 mg (2.20 mmol) of tributylacetonyltin (3). Purification by TLC (R_f 0.4) gave pure product: ^1H NMR ($CDCl_3$) δ 4.32–4.22 (dd, 1, J = 9.9 Hz, –CHO–), 2.75 (ABq, 2, J = 16 Hz, CH_2CO), 2.20 (s, 3, CH_3CO), 2.50–1.10 (m, 8, ring methylenes); ^{13}C NMR ($CDCl_3$) δ 208.368 (carbonyl), 72.037 (–CO–), 63.221 (–CHO–), 53.178 (CH_2CO), 35.779 (CH_2), 33.210 (CH_2), 31.687 (CH_3CO), 26.671 (CH_2), 20.424 (CH_2); IR (neat) 1695 (carbonyl) cm^{-1}. A satisfactory analysis of 1-acetonyl-7-oxabicyclo[4.1.0]heptane could not be obtained due to the dehydration process which took place during purification to give the 2-methyl-4,5,6,7-tetrahydrobenzo[b]furan which was identified by comparison with an authentic sample prepared by the perbenzoic acid oxidation of 1-acetonylcyclohexene;[36] ^1H NMR ($CDCl_3$) δ 5.83 (s, 1, =CH), 3.22 (s, 3, CH_3), 2.30–1.13 (m, 8, ring CH_2).

2-Phenyl-2-allyloxetane. From the reaction of 337 mg (2.00 mmol) β-chloropropiophenone and 380 mg (1.10 mmol) of dibutyldiallyltin (6) was obtained 260 mg (75.0%) of product. Further purification was achieved by TLC (R_f 0.3): ^1H NMR ($CDCl_3$) δ 7.40 (s, 5, aromatic), 6.30–5.90 (m, 3, H_2C=CH), 3.85–2.93 (m, 2, $-CH_2O-$), 2.73–2.06 (m, 4, allylic and ring CH_2), ^{13}C NMR ($CDCl_3$) δ 132.998, 123.153, 119.644, 116.817 (aromatic), 118.426 (CH=C), 112.918 (CH_2=C), 75.391 (PhCO, 52.485 (–CH_2O–), 50.584 (allylic CH_2), 46.149 (ring CH_2); mass spectrum, m/e (relative intensity) 175 parent (2.3), 161 (72), 146 (14.1), 133 (7.6), 105 (23.4), 103 (37), 77 (15.2), 43 (100). Anal. Calcd: C, 82.72; H, 8.10. Found: C, 83.37; H, 7.66.

2-Phenyl-2-allyltetrahydrofuran. The reaction of 365 mg (2.00 mmol) of γ-chlorobutyrophenone and 315 mg (1.10 mmol) of tetraallyltin gave 295 mg (79.0%) of product which was purified by TLC (R_f 0.4): ^1H NMR ($CDCl_3$) δ 7.36 (s, 5, aromatic), 6.07–5.40 (m, 1, C=CH), 5.20–4.78 (m, 2, CH_2=C), 3.92 (t, 2, J = 5 Hz, $-CH_2O-$), 2.53 (d, 2, J = 7 Hz, allylic CH_2), 2.28–1.60 (m, 4, ring CH_2). Anal. Calcd: C, 82.96; H, 8.57. Found: C, 82.69; H, 8.51.

2-Methyl-2-allyltrahydrofuran. The reaction of 210 mg (2.00 mmol) of 5-chloro-2-pentanone and 315 mg (1.10 mmol) of tetraallyltin gave 230 mg (92.0%) of product which was vacuum transferred, at 70 °C (0.2 mm): ^1H NMR ($CDCl_3$) δ 6.24–5.57 (m, 1, CH=C), 5.28–4.84 (m, 2, CH_2=C), 3.57 (t, 2, J = 5 Hz, CH_2O–), 1.91 (d, 2, J = 6 Hz, allylic CH_2), 2.08–1.35 (m, 4, ring CH_2), 1.20 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 133.402 (CH=C), 118.046 (CH_2=C), 71.226 (–CO–), 46.290 (–CH_2O), 46.297 (ring CH_2), 38.582 (allylic CH_2), 26.962 (ring CH_2), 26.378 (CH_3). Anal. Calcd: C, 75.54; H, 11.98. Found: C, 75.30; H, 11.15.

2-Acetonyl-3-ethyloxirane. The reaction of 151 mg (2.00 mmol) α-bromobutyraldehyde and 760 mg (2.20 mmol) of tributylacetonyltin gave 205 mg (82.0% yield) of product. After the removal of the solvent by evaporation at 25 °C (20 mm) the product was vacuum transferred from the crude reaction mixture at reduced pressure at 60 °C (0.1 mm): IR (neat) ν 1715 (carbonyl) 1160, 908, 890 (oxirane CO); ^1H NMR ($CDCl_3$) δ 3.40–2.75 (m, 2, OCH–), 2.65 (d, 2, J = 4 Hz, CH_2CO), 2.20 (s, 3, CH_3CO), 1.53 (m, 2, J = 6 Hz, ethylene CH_2), 1.10 (t, 3, J = 7 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 209.982 (carbonyl), 58.783 (–OCH–), 52.828 (–OCH–), 45.763 (CH_2CO), 29.707 (CH_3CO), 24.336 (ethylene CH_2), 9.214 (CH_3). Anal. Calcd: C, 59.47; H, 17.89. Found: 59.08; H, 18.25.

2-Allyl-3-ethyloxirane. The reaction of 151 mg (2.00 mmol) of α-bromobutyraldehyde with 380 mg (1.10 mmol) of dibutyldiallyltin (3) gave 191 mg (86.0%) of product. After removal of the solvent at reduced pressure the product was isolated from the reaction mixture by vacuum transfer at reduced pressure at 60 °C (0.2 mm): ^1H NMR ($CDCl_3$) was identical with that reported,[37] δ 6.23–5.40 (m, 1, CH=C), 5.20–4.77 (m, 2, CH_2=C), 3.03–2.50 (m, 2, CHO–), 2.33 (dd, 2, J = 6 Hz, allylic CH_2), 1.75–1.30 (m, 2, ethylene CH_2), 0.97 (t, 3, J = 4 Hz, CH_3).

5-Chloro-4-hydroxy-1-heptene (11a). To 2 mL of a THF solution of 215 mg (2.00 mmol) of α-chlorobutyraldehyde was added 380 mg (1.20 mmol) of dibutyldiallytin. The mixture was stirred at 63 °C for 6 h; then the solvent was removed, and the residue was redissolved in ether. The ether solution of the addition product was then extracted with aqueous potassium fluoride and sodium bicarbonate saturated solutions. The ether solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residual 270 mg (92.0%) of product was purified by TLC (R_f 0.5). ^1H NMR was identical with the reported spectrum.[37] IR (neat) ν 3580–3260 (hydroxy) cm^{-1}.

5-Chloro-4-hydroxy-2-heptanone (11b). This compound was prepared by the reaction of 763 mg (2.20 mmol) of tributylacetonyltin with 215 mg (2.00 mmol) of α-chlorobutyraldehyde to give 280 mg (85.0%) of product. The product was purified by TLC (R_f 0.3) and then distilled at 95 °C (10 mm) to give a colorless liquid: ^1H NMR ($CDCl_3$) δ 4.35–3.65 (m, 2, CHOH, CHCl), 3.53–3.40 (br d, 1, OH), 3.03–2.85 (m, 2, CH_2CO), 2.30 (s, 3,

(35) Morel, T.; Verkade, P. E. *Recl. Trav. Chim. Pays-Bas* **1951**, *70*, 35–49.

(36) Fritel, H.; Baranger, P. B. *C.R. Hebd. Seances Acad. Sci., Ser. C* **1955**, *241*, 647.

(37) Miginiac, P.; Zamlouty, G. *Bull. Soc. Chim. Fr.* **1975**, *7–8*, 1740.

$OCCH_3$), 2.17–1.58 (m, 2, CH_2), 1.34 (t, J = 6 Hz, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 186.998 (carbonyl), 72.359 (CHCl), 69.056 (CH-OH), 51.169 (CH_2CO), 38.449 (CH_3CO), 35.232 (CH_2), 21.781 (CH_3); IR (neat) ν 3600–3200 (hydroxy) 1706 (carbonyl) cm^{-1}. Anal. Calcd: C, 51.07; H, 7.96. Found: C, 51.27; H, 7.63.

Reaction of Tributylbenzyltin with α-Bromoacetophenone. To a solution of 600 mg (3.00 mmol) of α-bromoacetophenone and 560 mg (3.00 mmol) of tributylbenzyltin in 2 mL of THF was added 150 mg (0.140 mmol) of benzylchlorobis(triphenylphosphine)palladium. The yellow solution was stirred at 63 °C in a capped Schlenk tube under argon for 20 h. The black reaction mixture was then allowed to cool to 25 °C and the solvent and the volatile products were distilled under reduced pressure into a cold (−50 °C) receiver containing 3.00 mmol bromine in 1 mL carbon tetrachloride solution. The bromination mixture was allowed to warm to 25 °C and was then stirred for an additional 2 h. After evaporation of the solvent, 515 mg (80.0%) of 1,2-dibromobutane was obtained as determined by the GC of this fraction (oven 100 °C, R_f 6.5 min). The nonvolatile residue of the reaction mixture contained acetophenone (313 mg, 87.0%) and dibutylbenzyltin bromide (1.2 g, 99.0%). Yields were determined by ^1H NMR integrations using dichloromethane as an internal standard. The nonvolatile residue was chromatographed (silica gel) with n-hexane. Dibutylbenzyltin bromide eluted with the first 5-mL fraction: bp 100–116 °C (0.08 mm) [lit.[38] 140–155 °C (1 mm)]; ^1H NMR ($CDCl_3$) δ 6.94 (s, 5, aromatic), 2.70 (s, 2, benzylic), 1.65–0.63 (m, 14, butylene); ^{13}C NMR ($CDCl_3$) δ 138.947, 128.379, 126.861, 123.942 (aromatic), 27.781, 26.321 (CH_2), 25.737 ($PhCH_2Sn$), 17.096 (CH_2Sn), 13.301 (CH_3).

Determination of Enantiomeric Excess of 4 Formed in a Reaction Catalyzed by Dichlorobis[(+)-neomenthyldiphenylphosphine)palladium(II). A reaction between tributylacetonylstannane (**3**) and α-bromoacetophenone (**2**) was carried out at 25 °C for 90 h. After workup and purification of the product as described for racemic **4**, a part of the product (36 mg, 0.19 mmol) was dissolved in chloroform-d in an NMR tube and 89.6 mg (0.075 mmol) of tris[((3-heptafluoropropyl)-hydroxymethylene)-α-camphorato]europium(III), $(hfdc)_3Eu(III)$, shift reagent was added (the molar ratio of 2.5:1 was found to give optimum separation between the methyl signals of the two enantiomers). The two methyl signals were separated by 6.6 Hz and were integrated to give a ratio of 109/75 equivalent to 19% ee.

(38) Bychkov, V. T.; Vyazankin, N. S. *Zh. Obshch. Khim.* **1965**, *35*, 687.

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Registry No. **1**, 22784-59-4; **2**, 70-11-1; **2**-α,α-d_2, 87372-49-4; **3**, 14583-98-3; (±)-**4**, 87372-50-7; (+)-**4**, 87411-83-4; (−)-**4**, 87372-51-8; **4**-3,3-d_2, 87372-52-9; **5**, 7393-43-3; **6**, 15336-98-8; **7**, 20924-82-7; **8**, 2114-00-3; **9**, 87372-53-0; **10**, 87372-54-1; **11a**, 58283-61-7; **11b**, 87372-55-2; **12**, 24401-36-3; **13a**, 21433-91-0; **13b**, 19842-57-0; **14**, 17392-08-4; **15**, 87372-56-3; (diphos)$PdCl_2$, 19978-61-1; ((+)-diop)$PdCl_2$, 59634-23-0; (R-camp)$_2PdCl_2$, 87372-48-3; ((+)-nmdpp)$_2PdCl_2$, 78251-24-8; α-bromocyclobutyl phenyl ketone, 51175-78-1; 3-bromo-2-butanone, 814-75-5; 3-chloro-2-butanone, 4091-39-8; α-bromocyclohexanone, 822-85-5; β-chloropropiophenone, 936-59-4; γ-chlorobutyrophenone, 939-52-6; 5-chloro-2-pentanone, 5891-21-4; α-bromobutyraldehyde, 24764-97-4; α-bromo-α-methylpropiophenone, 10409-54-8; 1-phenyl-1-acetonyl-5-oxaspiro[2.3]hexane, 87372-57-4; 2,3-dimethyl-2-acetonyloxirane, 87372-58-5; 1-acetonyl-7-oxabicyclo[4.1.0]heptane, 87372-59-6; 2-phenyl-2-allyloxetane, 87372-60-9; 2-phenyl-2-allyltetrahydrofuran, 87372-61-0; 2-methyl-2-allyltetrahydrofuran, 87372-62-1; 2-acetonyl-3-ethyloxirane, 87372-63-2; 2-allyl-3-ethyloxirane, 58325-53-4; α-chloroacetophenone, 532-27-4; α-chlorobutyraldehyde, 28832-55-5; dichlorobis(benzonitrile)palladium(II), 14220-64-5.

Synthetic Utility of the Palladium-Catalyzed Coupling Reaction of Acid Chlorides with Organotins

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The palladium coupling of acid chlorides with unsymmetrical organotin reagents R''_3SnR' can be carried out in chloroform under mild conditions in high yields to give the ketone RCOR′ in which only one of the four organic groups on tin appears in the ketone product. Alkyl partners (R″ = methyl or butyl) on tin serve as anchoring groups and do not transfer. When R′ is acetylenic, vinyl, aryl, methoxymethylene, allyl, or benzyl, transmetalation takes place preferentially, resulting in coupling with the acyl group from the acid chloride. The reaction is tolerant of functional groups both on the acid chloride and the tin reagent. A palladium-catalyzed coupling reaction of an organotin reagent bearing acrylate functionality with an acid chloride serves as a method to introduce both a ketone and an acrylate functionality into a carbon framework. The coupling reaction of 4-(*tert*-butyldiphenylsiloxy)pentanoyl chloride with benzyl 3-(tributylstannyl)acrylate gave a 71% yield of benzyl 7-(*tert*-butyldiphenylsiloxy)-4-oxo-2-octenoate, a precursor to the macrolide antibiotic pyrenophorin.

Introduction

The synthesis of ketones by the palladium-catalyzed coupling reaction of acid chlorides with organotin reagents[1,2] has been shown to be a mild, selective reaction that generally gives greater than 85% yields.[1] The reaction is especially useful in that other functionalies on the acid chloride such as ester, nitrile, nitro, halo, and aldehyde can survive the reaction unaltered. However, the solvent originally used in these reactions was hexamethylphosphoric triamide (HMPA), which not only makes workup difficult in certain reactions but also is a carcinogen.[3]

In the coupling reaction, the tetraorganotin reagent transfers the first organic group on tin rapidly, but the second leaves about 100 times slower from R''_3SnCl. Thus,

(1) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636; *J. Org. Chem.* **1979**, *44*, 1613.

(2) (a) Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423. (b) *J. Organomet. Chem.* **1977**, *129*, C36.

(3) Lee, K. P.; Trochimowicz, H. J. *Toxicol. Appl. Pharmacol.* **1982**, *62*, 90.

0022-3263/83/1948-4634$01.50/0