VOLUME 116, NUMBER 1
JANUARY 12, 1994

JOURNAL
OF THE
AMERICAN
CHEMICAL
SOCIETY

Stereospecific Palladium/Copper Cocatalyzed Cross-Coupling of α-Alkoxy- and α-Aminostannanes with Acyl Chlorides[1]

Jianhua Ye,[2] Rama K. Bhatt, and J. R. Falck*

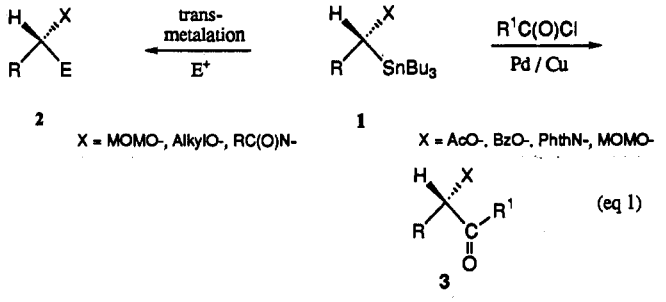
Contribution from the Departments of Molecular Genetics and Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas 75235

Received September 13, 1993®

Abstract: Stille-type cross-coupling between α-alkoxy(amino)stannanes and acyl chlorides affords α-hetero-substituted ketones in moderate to good yields when cocatalyzed by Pd and Cu(I) salts. The reaction is applicable to a wide range of tin compounds, especially those bearing α-electron-withdrawing groups such as benzoyloxy or acetyloxy, although some ethers (e.g., MOM) are also satisfactory. Aromatic acid chlorides give the best yields. Coupling of chiral α-alkoxystannanes, readily available by BINAL-H asymmetric reduction of acylstannanes, proceeds with retention of configuration.

Introduction

Transmetalation of organostannanes is a convenient and widely applicable route to reactive organometallics.[3] In the case of α-alkoxy- and α-aminostannanes **1**, the exchange proceeds with retention of configuration;[4] subsequent addition of the stereochemically stable anions to various electrophiles provides direct access to heteroatom-substituted chiral centers **2** (eq 1). Stille-type palladium-catalyzed[5] cross-coupling of organostannanes offers an attractive and complementary alternative to the aforementioned anionic processes for the creation of carbon–carbon bonds, but its preparative application to functionalized



(eq 1)

tins of type **1** has been elusive.[6] As part of our continuing investigations[7] into the preparation and synthetic utility of stereogenic Group IV derivatives, we report herein that cross-coupling[8] of **1** with acyl chlorides under mild, nearly neutral conditions affords α-heteroatom-substituted ketones **3** in moderate to good yields when cocatalyzed by palladium, especially $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$, *and* copper(I) salts[9] (eq 1). The beneficial effects of cocatalytic copper(I) in sluggish or otherwise unsuccessful Stille reactions, initially observed by Liebeskind,[10] have been limited heretofore to couplings involving tin-sp_2 bonds.[11]

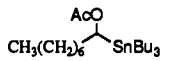
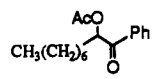
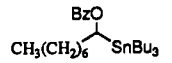
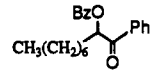
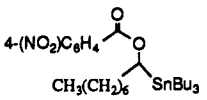
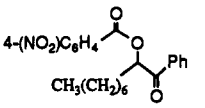
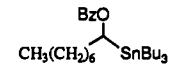
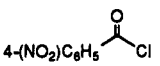
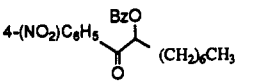
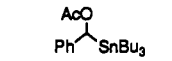
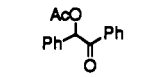
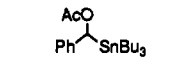
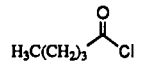
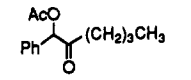
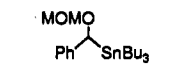
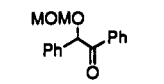
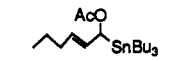
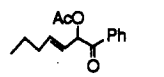
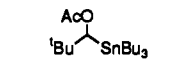
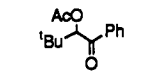
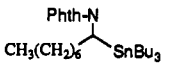
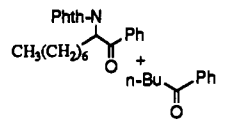
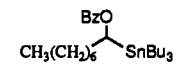
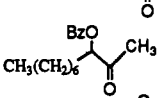
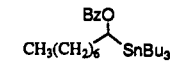
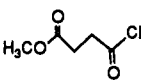
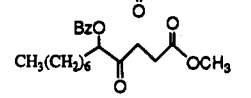
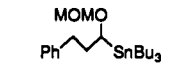
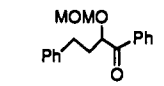
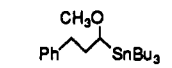
Results and Discussion

The scope of this transformation was defined using representative stannane and acyl chloride partners (Table 1). Coupling

• Abstract published in *Advance ACS Abstracts,* December 15, 1993.
(1) Presented in part at the 205th National Meeting of the American Chemical Society, Denver, CO, March 28–April 2, 1993; ORGN 63.
(2) Robert A. Welch Postdoctoral Fellow.
(3) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641–2643. Wardell, J. L. In *Chemistry of Tin*; Harrison, P. G., Ed.; Chapman and Hall: New York, 1989; p 169.
(4) (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202. (b) Sawyer, J. S.; Macdonald, T. L.; McGarvey, G. L. *Ibid.* **1984**, *106*, 3376–3377. (c) Lesimple, P.; Beau, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1985**, 894–895. (d) Linderman, R.-J.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491–5493. (e) McGarvey, G. L.; Kimura, M. *Ibid.* **1985**, *50*, 4657–4659. (f) Chong, J. M.; Park, S. B. *Ibid.* **1992**, *57*, 2220–2222. (g) Chong, J. M.; Mar, E. K. *Tetrahedron Lett.* **1990**, *31*, 1981–1984. (h) Chan, P. C.-M.; Chong, J. M. *Ibid.* **1990**, *31*, 1985–1988.
(5) Review: Mitchell, T. N. *Synthesis* **1992**, 803–815.

0002-7863/94/1516-0001$04.50/0

Table 1. Palladium/Copper Cocatalyzed Cross-Coupling of α-Alkoxy(amino)stannanes with Acyl Chlorides

entry	α-alkoxy(amino)stannane	acyl chloride	time (h)	adduct	isolated yield (%)
1			18		74[a]
2			18		70[a]
3			36		50[a]
4			24		40[a]
5			12		78[a]
6			32		68[a]
7			15		80[a]
8			60		57[b]
9			36		50[a]
10			36		45[b,c] 28[b]
11			16		<5[a]
12			64		40[a]
13			38		30[a]
14			38		0[a]

[a] Reaction conditions: $Pd(PPh_3)_2Cl_2$ (4 mol %)/CuCN (8 mol %), toluene, 75 °C, argon atm. [b] Reaction conditions: $Pd(PPh_3)_4$ (4 mol %)/CuCN (8 mol %), toluene, 75 °C, argon atm. [c] Phth = phthaloyl.

of benzoyl chloride with α-(acetyloxy)octyltributylstannane, mediated by $Pd(PPh_3)_2Cl_2$ and CuCN in toluene at 75 °C under an argon atmosphere,[12] gave rise to a good yield of α-(acetyloxy)-octyl phenyl ketone (entry 1). Other copper(I) salts could be used,[13] e.g., CuBr, but there is a strict requirement for both catalysts to obtain optimum results. The corresponding benzoate (entry 2) behaved analogously, while a 4-nitrobenzoate reacted more sluggishly and gave a lower yield (entry 3). Likewise, the presence of a nitro on the electrophile was also detrimental (entry 4). Coupling did not occur in HMPA or dichloroethane as solvent.

Generally, the best yields were observed with substituents

(6) A noteworthy, but singular, exception has been reported for an intramolecular coupling with unknown stereochemistry: Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438–7439. Also see, Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634–4642. Palladium-mediated hydroxymethylation in moderate yields of aryl bromides has been noted: Kosugi, M.; Sumiya, T.; Ohhashi, K.; Sano, H.; Migita, T. *Chem. Lett.* **1985**, 997–998.

(7) Reactivity of α-mesyloxystannanes with organocopper reagents: Ye, J.; Shin, D.-S.; Bhatt, R. K.; Swain, P. A.; Falck, J. R. *Synlett* **1993**, 205–206.

(8) The conceptually reverse situation, i.e., palladium-catalyzed coupling of unsymmetrical organostannanes with α-heteroatom-substituted electrophiles, provides unique access to chiral ethers and heterocycles: Bhatt, R. K.; Shin, D.-S.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **1992**, *33*, 4885–4888.

(9) The role of copper, however, is obscure, but may involve facilitation of the transmetalation step. Significantly, neither Cu(II), hydroquinone, nor Et_3N could be substituted for Cu(I).

(10) Liebeskind, L. S.; Foster, B. S. *J. Am. Chem. Soc.* **1990**, *112*, 8612–8613. Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359–5364.

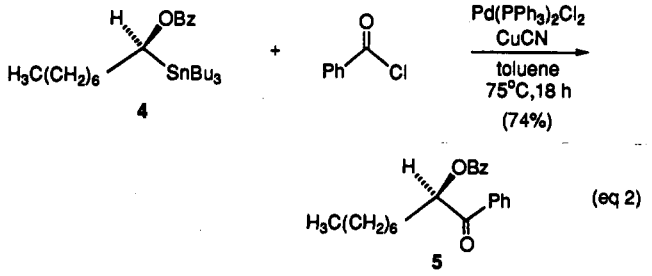
(11) Also see, Saa J. M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963–1966. Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993**, *58*, 408–413. Palmisano, G.; Santagostino, M. *Tetrahedron* **1993**, *49*, 2533–2542. Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 2127–2130. Ichikawa, J.; Minami, T.; Sonoda, T.; Kobayashi, H. *Ibid.* **1992**, *33*, 3779–3782. Labaudiniere, L.; Normant, J.-F. *Tetrahedron Lett.* **1992**, *33*, 6139–6142. Ichikawa, J.; Ikeura, C.; Minami, T. *Synlett* **1992**, 739–740. Gomez-Bengoa, E.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 3497–3501.

(12) Under a blanket of air, the yield of α-(acetyloxy)octyl phenyl ketone was severely reduced. Curiously, under 50 psi carbon monoxide the total yield of coupling product remained about the same at 78%, but the preference of ligand transfer changed dramatically, i.e., *ca.* 2:1 butyl vs α-(acetyloxy)octyl.

(13) Pd in the presence of $BF_3{\cdot}Et_2O$ or other metal salts, *inter alia*, $FeCl_2$, $FeCl_3$, $ZnCl_2$, and $CrCl_2$, yielded little, if any, coupled product. No acyl coupling was observed with Cu(I) salts in the absence of the Pd cocatalyst.

having the highest migratory aptitude. For instance, α-(acetyloxy)benzylstannane transferred smoothly to both aryl (entry 5) and aliphatic (entry 6) acid chlorides. Even an α-benzyl ether was well tolerated (entry 7) as was an allylic (acetyloxy)stannane (entry 8). The latter showed no proclivity toward allylic rearrangement as seen in Lewis acid-mediated additions.[14] Bulky substituents on the carbon center undergoing transfer seemed to diminish the yield only slightly (*cf.* entry 9 vs 8). In the case of an α-phthalimidoyl-bearing ligand (entry 10), migration of *n*-butyl from tin became somewhat competitive. Replacement of the imide with a primary or secondary amide abolished the reactivity altogether. Significantly, unions between α-oxygenated aliphatic stannanes and aliphatic acid chlorides (e.g., entry 11) were disappointing. While this will require further study, the successful addition of methyl succinyl chloride to an aliphatic stannane (entry 12) suggests stabilization of intermediates by intramolecular chelation may be beneficial. This is more evident in the comparison of a MOM ether (entry 13) with a simple methyl ether (entry 14).

To assess the stereochemical consequences of Pd/Cu-mediated carbon–carbon bond formation at stereogenic sites, (*S*)-[α-(benzoyloxy)octyl]tributylstannane (**4**) (94% ee) was prepared by sequential BINAL-H asymmetric reduction[15] of the related acylstannane and benzoylation. Coupling as above furnished α-(benzoyloxy)octyl phenyl ketone (**5**) (eq 2).[16] Chiral HPLC



(eq 2)

analysis using an independently synthesized standard[17] revealed the coupling proceeded with *ca. 98% retention of configuration.* This is in stark contrast with couplings between tetraalkylstannanes and benzoyl chloride where inversion of configuration has been demonstrated.[18] The origins of this phenomenon and the potential involvement of the α-heteroatom warrant further investigation.

As a consequence of the ready accessibility of chiral α-heterosubstituted stannanes,[15,19] mild coupling conditions, operational simplicity, and anticipated compatibility with common functionality, this method should find extensive use in asymmetric synthesis. Its application to natural products total synthesis as well as additions to other classes of electrophiles will be reported elsewhere.[20]

Experimental Section

Reagents and Methods. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-250 spectrometer using tetramethylsilane as internal reference. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter. Low-resolution mass spectra were obtained with a Finnigan SSQ 700 mass spectrometer. High-resolution mass spectra were provided by the Midwest Center for Mass Spectrometry with partial support from NSF (DIR9017262). Optical purities were measured either by analyzing the ^1H NMR spectrum of the corresponding Mosher's ester[21] or by chiral phase HPLC.

All reactions were maintained under an argon atmosphere. Anhydrous solvents were freshly distilled from sodium benzophenone ketyl, except for CH_2Cl_2 and HMPA which were distilled from CaH_2. Acid chlorides were freshly distilled. Tetrakis(triphenylphosphine)palladium(0)[22] and bis(triphenylphosphine)palladium(II) chloride[23] were prepared according to published procedures. Extracts were dried over anhydrous Na_2SO_4 and filtered prior to evaporation on a rotary evaporator under reduced pressure.

Racemic α-Alkoxy(amino)stannanes (General Procedure). Following the method of Still,[24] lithium diisopropylamide (3 mmol) in anhydrous THF (3 mL) was added dropwise to a stirring, 0 °C THF solution (5 mL) of tributyltin hydride (3 mmol). After 15 min, the resulting light yellow solution was cooled to −78 °C and a THF solution (1 mL) of aldehyde (2.9 mmol) was added. The reaction was quenched after 30 min with 5% NH_4Cl solution (5 mL) and extracted with Et_2O (2 × 15 mL). The combined ethereal extracts were washed with H_2O (2 × 10 mL), dried, and concentrated *in vacuo* at or below ambient temperature. Without delay, the crude α-(hydroxy)organostannane was dissolved in CH_2Cl_2 (5 mL) containing Et_3N (0.5 mL), DMAP (1.5 mmol), and acyl chloride/anhydride. When TLC analysis indicated the derivatization was complete (4–6 h), the reaction mixture was partitioned between H_2O (10 mL) and CH_2Cl_2 (5 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 × 3 mL), and the combined organic extracts were washed with brine (5 mL) and dried and volatiles removed *in vacuo*. Flash silica gel (230–400 mesh) chromatography initially using hexane to remove a nonpolar, tin-containing byproduct and then using the indicated solvent system afforded the protected α-alkoxystannane which can be stored indefinitely when maintained cold and under an inert atmosphere.

[α-(Acetyloxy)octyl]tributylstannane. Following the general procedure, *n*-octanal and Ac_2O gave the title compound (69%) as a colorless oil after chromatography using EtOAc/hexane (5:95): ^1H NMR δ 4.76 (dd, *J* = 5.3, 7.6 Hz, 1H), 2.00 (s, 3H), 1.25–1.55 (m, 24 H), 0.89–1.00 (m, 18 H); MS (CI, CH_4) *m/e* (rel inten) 462 (M^+, 1), 405 (M^+ − 57, 100), 291 (64), 233 (12); HRMS calcd for $C_{22}H_{46}O_2Sn$ *m/e* 462.2519, found 462.2524.

[α-(Benzoyloxy)octyl]tributylstannane. Following the general procedure, *n*-octanal and benzoyl chloride gave the title compound (70%) as a colorless oil after chromatography using EtOAc/hexane (5:95). ^1H NMR δ 7.92–8.05 (m, 2H), 7.35-7.55 (m, 3H), 5.05 (dd, *J* = 5.4, 9.0 Hz, 1H), 1.20–1.45 (m, 24H), 0.89–0.98 (m, 18H); MS (CI, CH_4) *m/e* (rel inten) 467 (M^+ − 57, 4), 405 (4), 343 (6), 281 (20), 223 (54), 207 (100); HRMS calcd for $C_{23}H_{39}O_2Sn$ (M^+ − Bu) *m/e* 467.1972, found 467.1962.

[α-[(4-Nitrobenzoyl)oxy]octyl]tributylstannane. Following the general procedure, *n*-octanal and 4-nitrobenzoyl chloride gave the title compound (55%) as a pale yellow oil after chromatography using EtOAc/hexane (5:95). ^1H NMR δ 8.25 (d, *J* = 9.0 Hz, 2H), 8.14 (d, *J* = 9.0 Hz, 2H), 5.10 (dd, *J* = 5.4, 9.0 Hz, 1H), 1.90-2.20 (m, 2H), 1.55–1.70 (m, 6H), 1.20–1.45 (m, 16H), 0.80–0.95 (m, 18 H); MS (Cl, CH_4) *m/e* (rel inten): 569 (M^+, 1), 512 (M^+ − 57, 100), 442 (17), 291 (22), 150 (32); HRMS calcd for $C_{23}H_{38}O_4NSn$ (M^+ − Bu) *m/e* 512.1823, found 512.1830.

[α-(Acetyloxy)benzyl]tributylstannane. Following the general procedure, benzaldehyde and Ac_2O gave the title compound (73%) as a colorless oil after chromatography using EtOAc/hexane (5:95): ^1H NMR δ 7.24–7.34 (m, 2H), 7.06–7.12 (m, 3H), 5.90 (s, 1H), 2.18 (s, 3H), 1.20–1.45 (m, 12H), 0.70–0.90 (m, 15H); MS (Cl, CH_4) *m/e* (rel inten): 383 (M^+ − 57, 68), 291 (90), 205 (100); HRMS calcd for $C_{17}H_{27}O_2Sn$ (M^+ − Bu) *m/e* 383.1033, found 383.1044.

[α-[(Methoxymethyl)oxy]benzyl]tributylstannane. Modification of the general procedure by substituting *N,N*-dimethylaniline in place of the DMAP and Et_3N gave the title compound (71%) as a colorless oil from benzaldehyde and chloromethyl methyl ether (MOM chloride) after chromatography using EtOAc/hexane (5:95). ^1H NMR δ 7.05–7.32 (m, 5H), 5.12 (s, 1H), 4.58 (dd, *J* = 6.6, 11.8 Hz, 2H), 3.38 (s, 3H), 1.37–1.48 (m, 6H), 1.20–1.35 (m, 6H), 0.80–0.95 (m, 15H); MS (CI,

(14) Marshall, J. A.; Gung, W.-Y. *Tetrahedron Lett.* **1989**, *30*, 2183–2186.
(15) Chan, P. C.-M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5586–5588.
(16) Coupling in the absence of copper catalyst furnishes **5** (~10% yield) with the same % ee and configuration as observed with the Pd/Cu cocatalyst system.
(17) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715–3717.
(18) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129–6137.
(19) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647–656.
(20) For the exploitation of Pd/Cu-mediated α-alkoxystannane coupling to the total synthesis of the anticancer *C*-glycoside (+)-goniofufurone see, Ye, J.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* in press.
(21) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.
(22) Greaves, E. O.; Lock, C. J. L.; Maitlis, P. M. *Can. J. Chem.* **1968**, *46*, 3879–3891.
(23) Itatani, H.; Bailar, J. C., Jr. *J. Am. Oil. Chem. Soc.* **1967**, *44*, 147–151.
(24) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487.

CH_4) *m/e* (rel inten): 397 ($M^+ - CH_2OCH_3$,38), 385 ($M^+ - 57$, 62), 291 (84), 207 (100); HRMS calcd for $C_{19}H_{33}OSn$ ($M^+ - CH_2OCH_3$) *m/e* 397.1553, found 397.1548.

[1-(Acetyloxy)hex-2-enyl]tributylstannane. Following the general procedure, *trans*-2-hexenal and Ac_2O gave the title compound (44%) as a colorless oil after chromatography using EtOAc/hexane (5:95): ^1H NMR δ 5.61–5.70 (m, 1H), 5.14–5.40 (m, 1H), 2.06 (s, 3H), 1.99–2.04 (m, 2H), 1.20–1.56 (m, 14H), 0.82-0.98 (m, 18H); MS (CI, CH_4) *m/e* (rel inten) 432 (M^+, 3) 375 (100), 291 (90), 235 (68), 179 (78); HRMS calcd for $C_{20}H_{40}O_2Sn$ *m/e* 432.2050, found 432.2059.

[1-(Acetyloxy)-2,2-dimethylpropyl]tributylstannane. Following the general procedure, pivalaldehyde and Ac_2O gave the title compound (65%) as a colorless oil after chromatography using EtOAc/hexane (5:95): ^1H NMR δ 4.85 (s, 1H), 2.03 (s, 3H), 1.24–1.46 (m, 12H), 0.91 (s, 9H), 0.80–0.90 (m, 15H); MS (CI, CH_4) *m/e* (rel inten): 363 ($M^+ - 57$, 100), 291 (86) 235 (17). HRMS calcd for $C_{15}H_{31}O_2Sn$ (M^+ - Bu) *m/e* 363.1346, found 363.1339.

[α-(Phthalimidoyl)octyl]tributylstannane. By the method of Chong and Park,[4f] the crude α-hydroxystannane, obtained from *n*-octanal (800 mg, 6.2 mmol) according to the general procedure above, was dissolved in anhydrous THF (15 mL) containing phthalimide (1.08 g, 7.4 mmol) and triphenylphosphine (1.94 g, 7.4 mmol) at 0 °C. A solution of diethyl azodicarboxylate (1.29 g, 7.4 mmol) in THF (3 mL) was added dropwise with stirring and then the reaction mixture was warmed to room temperature. After 30 min, the volatiles were removed under reduced pressure and the residue was purified by chromatography on silica gel using EtOAc/hexane (5:95) to give the title compound (1.51 g, 43%) as a colorless oil: HRMS calcd for $C_{24}H_{38}NO_2Sn$ ($M^+ - Bu$) *m/e* 492.1924, found 492.1918; ^1H NMR δ 7.85 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 3.95 (dd, J = 5.2, 7.8 Hz, 1H), 1.65–1.95 (m, 2H), 1.20–1.55 (m, 22H), 0.80–0.97 (m, 18H).

[1-[(Methoxymethyl)oxy]-3-phenylpropyl]tributylstannane. Modification of the general procedure by substituting diisopropylethylamine in place of the DMAP and Et_3N gave the title compound (73%) as a colorless oil from dihydrocinnamaldehyde and chloromethyl methyl ether following chromatography using EtOAc/hexane (5:95): ^1H NMR δ 7.15–7.30 (m, 5H), 4.58 (dd, J = 6.6, 11.9 Hz, 2H), 4.10 (dd, J = 5.4, 7.6 Hz, 1H), 3.38 (s, 3H), 2.60–2.80 (m, 2H), 2.06–2.15 (m, 2H), 1.42–1.55 (m, 6H), 1.23–1.40 (m, 6H), 0.90–1.00 (m, 15H); MS (Cl, CH_4) *m/e* (rel inten) 413 (M^+ - 57, 11), 343 (6), 331 (9), 268 (22), 223 (51), 207 (100); HRMS calcd for $C_{19}H_{33}O_2Sn$ ($M^+ - Bu$) *m/e* 413.1502, found 413.1511.

(1-Methoxy-3-phenylpropyl)tributylstannane. To a 0 °C solution of dihydrocinnamaldehyde dimethyl acetal (540 mg, 3 mmol) in CH_2Cl_2 (4 mL) was added acetyl chloride (4 mL) as described.[24] After stirring at room temperature overnight, the volatiles were removed *in vacuo* affording the somewhat labile 1-chloro-1-methoxy-3-phenylpropane (95%) as a pale yellow oil which was used directly in the next step. ^1H NMR δ 7.12–7.36 (m, 5H), 5.38 (t, J = 6.5 Hz, 1H), 3.50 (s, 3H), 2.81 (t, J = 7.8 Hz, 2H), 2.26–2.38 (m, 2H).

The above chloro ether in dry CH_2Cl_2 (2 mL) was added dropwise to a −78 °C THF (7 mL) solution of (tributylstannyl)lithium, generated according to the general procedure from tributyltin hydride and LDA (3.3 mmol each). After 30 min, the reaction mixture was quenched and the crude product purified chromatographically as described in the general procedure using EtOAc/hexane (5:95) to yield the title adduct (921 mg, 70%) as a colorless oil: ^1H NMR δ 7.15–7.30 (m, 5H), 4.18 (dd, J = 5.3, 7.6 Hz, 1H), 2.62–2.78 (m, 2H), 2.05–2.14 (m, 2H), 1.42–1.55 (m, 6H), 1.20-1.40 (m, 6H), 0.90–1.00 (m, 15H); MS (CI, CH_4) *m/e* (rel inten) 383 ($M^+ - 57$, 65), 291 (82), 207 (83), 117 (74), 91 (96), 57 (100); HRMS calcd for $C_{18}H_{31}OSn$ ($M^+ - Bu$) *m/e* 383.1397, found 383.1392.

Palladium/Copper Coupling (General Procedure). To a mixture of α-alkoxy(amino)stannane (1.8 mmol), bis(triphenylphosphine)palladium-(II) chloride or tetrakis(triphenylphosphine)palladium(0) (4 mol %), and copper cyanide (8 mol %) in anhydrous, degassed toluene (35 mL) was added benzoyl chloride (1.5 mmol). This resulting light yellow solution, with a small amount of undissolved CuCN, was heated in a sealed tube under an argon atmosphere at the temperatures and for the times indicated in Table 1. Completion of the reaction was generally indicated by a change in the reaction mixture color to brown or black and the deposition of a fine, black precipitant of Pd. Removal of the volatiles *in vacuo* and chromatography of the residue on silica gel afforded the keto-adducts listed in Table 1.

α-(Acetyloxy)octyl phenyl ketone: TLC (SiO_2) EtOAc/hexane (15:85), $R_f \sim 0.41$; ^1H NMR δ 7.91–7.95 (m, 2H), 7.42–7.62 (m, 3H), 5.86 (dd, J = 7.6, 4.9 Hz, 1H), 2.15 (s, 3H), 1.80–1.90 (m, 2H), 1.36–1.50 (m, 2H), 1.27 (br s, 8H), 0.86 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 196.72, 170.68, 134.83, 133.47, 128.75, 128.38, 75.35, 31.68, 31.38, 29.15, 28.98, 25.49, 22.57, 20.69, 14.03; MS (CI, CH_4) *m/e* (rel inten) 277 (M^+ + 1,64), 235 (32), 217 (43), 105 (100); HRMS calcd for $C_{17}H_{24}O_3$ *m/e* 276.1725, found 276.1715.

α-(Benzoyloxy)octyl phenyl ketone: TLC (SiO_2) EtOAc/hexane (1:4), $R_f \sim 0.55$; ^1H NMR δ 8.10–8.15 (m, 2H), 7.94–8.06 (m, 2H), 7.40–7.60 (m, 6H), 6.10 (t, J = 6.4 Hz, 1H), 1.98–2.03 (m, 2H), 1.48–1.60 (m, 2H), 1.20–1.40 (m, 8H), 0.82 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 196.51, 166.17, 134.81, 133.49, 133.22, 129.83, 129.79, 128.77, 128.42, 128.37, 75.74, 31.68, 29.17, 28.98, 25.88, 22.57, 14.03; MS (CI, CH_4) *m/e* (rel inten) 339 (M^+ + 1, 28), 240 (8), 217 (13), 210 (9), 105 (100); HRMS calcd for $C_{22}H_{26}O_3$ *m/e* 338.1882, found 338.1878.

α-[(4-Nitrobenzoyl)oxy]octyl phenyl ketone: TLC (SiO_2) EtOAc/hexane (15:85), $R_f \sim 0.37$; ^1H NMR δ 8.25–8.35 (m, 4H), 8.00 (d, J = 7.8 Hz, 2H), 7.48–7.65 (m, 4H), 6.15 (t, J = 6.3 Hz, 1H), 1.98–2.07 (m, 2H), 1.50–1.62 (m, 2H), 1.25–1.41 (m, 8H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 195.75, 164.36, 150.73, 135.04, 134.56, 133.80, 130.97, 128.92, 128.40, 123.59, 77.68, 31.76, 31.45, 29.15, 28.98, 25.58, 22.57, 14.04; MS (CI, CH_4) *m/e* (rel inten): 384 (M^+ + 1, 37), 285 (5), 255 (17), 217 (16), 150 (17), 105 (100); HRMS calcd for $C_{22}H_{25}NO_5$ *m/e* 383.1733, found 383.1737.

α-(Benzoyloxy)octyl 4-nitrophenyl ketone: TLC (SiO_2) EtOAc/hexane (1:4), $R_f \sim 0.21$; ^1H NMR δ 8.04–8.38 (m, 6H), 7.41–7.63 (m, 3H), 6.00 (dd, J = 7.7, 4.9 Hz, 1H), 1.96–2.03 (m, 2H), 1.40–1.62 (m, 2H), 1.10–1.40 (m, 8H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 195.80, 165.38, 150.18, 140.08, 133.60, 129.86, 129.48, 129.04, 128.54, 124.01, 75.98, 31.68, 31.16, 29.19, 28.98, 25.56, 22.58, 14.05. MS (CI, CH_4) *m/e* (rel inten) 384 (M^+ + 1, 3), 255 (5), 225 (2), 105 (100); HRMS calcd $C_{22}H_{25}NO_5$ *m/e* 383.1733, found 383.1741.

α-(Acetyloxy)benzyl phenyl ketone: TLC (SiO_2) EtOAc/hexane (15:85), $R_f \sim 0.33$; ^1H NMR δ 7.91–7.95 (m, 2H), 7.31–7.50 (m, 8H), 6.88 (s, 1H), 2.25 (s, 3H); ^{13}C NMR δ 193.69, 170.46, 134.57, 133.58, 133.46, 129.33, 129.13, 128.78, 128.69, 128.62, 77.19, 20.78; MS (CI, CH_4) *m/e* (rel inten) 255 (M^+ + 1, 4), 233 (4), 195 (100), 167 (16), 149 (14), 105 (54). A sample was solvolyzed using 5% NaOMe/MeOH (4 h) to give benzoin identical by TLC, mixture melting point (mmp) (134–136 °C), and ^1H NMR with an authentic sample.

α-(Acetyloxy)benzyl butyl ketone: TLC (SiO_2) EtOAc/hexane (15:85), $R_f \sim 0.22$; ^1H NMR δ 7.39 (br s, 5H), 5.96 (s, 1H), 2.19–2.50 (m, 2H), 2.18 (s, 3H), 1.45–1.56 (m, 2H), 1.14–1.23 (m, 2H), 0.80 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 204.08, 170.32, 133.30, 129.31, 129.02, 128.20, 80.70, 38.38, 25.32, 22.04, 20.72, 13.68; MS (CI, CH_4) *m/e* (rel inten) 235 (M^+ + 1, 63), 203 (14), 191 (2), 175 (100); HRMS calcd for $C_{14}H_{18}O_3$ *m/e* 234.1256, found 234.1259.

α-[(Methoxymethyl)oxy]benzyl phenyl ketone: TLC (SiO_2) EtOAc/hexane (1:4), $R_f \sim 0.37$; ^1H NMR δ 7.98 (d, J = 7.0 Hz, 2H), 7.20–7.48 (m, 8H), 6.00 (s, 1H), 4.75 (s, 2H), 3.35 (s, 3H); MS (CI, CH_4) *m/e* (rel inten) 257 (M^+ + 1, 0.5), 255 (26), 195 (100), 151 (77), 105 (47). A sample was solvolyzed using 5% methanolic HCl (6 h) to yield benzoin identical by TLC, mmp (134-136 °C), and ^1H NMR with an authentic sample.

1-(Acetyloxy)hex-2-enyl phenyl ketone: TLC (SiO_2) EtOAc/hexane (1:9), $R_f \sim 0.23$; ^1H NMR δ 7.91–7.95 (m, 2H), 7.42–7.62 (m, 3H), 6.28 (d, J = 7.0 Hz, 1H), 5.91–6.05 (m, 1H), 5.65–5.55 (m, 1H), 2.19 (s, 3H), 2.08–1.99 (m, 2H), 1.40–130 (m, 4H), 0.81 (t, J = 6.8 Hz, 3H); MS (CI, CH_4) *m/e* (rel inten): 247 (M^+ + 1, 1), 187 (56), 141 (9), 105 (100); HRMS calcd for $C_{15}H_{18}O_3$ *m/e* 246.1256, found 246.1263.

α-(Acetyloxy)-2,2-dimethylpropyl phenyl ketone: TLC (SiO_2) EtOAc/hexane (15:85), $R_f \sim 0.30$; ^1H NMR δ 7.95–7.99 (m, 2H), 7.42–7.59 (m, 3H), 5.65 (s, 1H), 2.15 (s, 3H), 0.97 (s, 9H); ^{13}C NMR δ 198.23, 170.99, 138.17, 133.08, 128.61, 128.38, 80.44, 34.17, 26.71, 20.56; MS (CI, CH_4) *m/e* (rel inten) 235 (M^+ + 1, 6), 207 (4), 193 (6), 105 (100); HRMS calcd for $C_{14}H_{18}O_3$ *m/e* 234.1256, found 234.1251.

α-(Phthalimidoyl)octyl phenyl ketone: TLC (SiO_2) EtOAc/hexane (15:85), $R_f \sim 0.37$; ^1H NMR δ 7.80–7.85 (m, 2H), 7.66–7.70 (m, 2H), 7.39–7.50 (m, 3H), 5.55 (dd, J = 7.7, 4.9 Hz, 1H), 2.15–2.35 (m, 2H), 1.20–1.70 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H); MS (CI, CH_4) *m/e* (rel inten) 364 (M^+ + 1, 83), 258 (100), 159 (62), 105 (36); HRMS calcd for $C_{23}H_{25}NO_3$ *m/e* 363.1834, found 363.1838.

α-(Benzoyloxy)octyl 2-carbomethoxyethyl ketone: TLC (SiO_2 EtOAc/hexane (1:4), $R_f \sim 0.50$; ^1H NMR δ 8.07–8.11 (m, 2H), 7.44–7.63 (m, 3H), 5.27 (t, J = 6.4 Hz, 1H), 3.67 (s, 3H), 2.81–2.97 (m, 2H), 2.63 (t, J = 6.3 Hz, 2H), 1.92–1.98 (m, 2H), 1.27–1.48 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 206.00, 172.92, 166.00, 133.40, 129.80, 129.37, 128.49, 78.93, 51.81, 33.44, 31.69, 30.69, 29.18, 29.00, 27.17, 25.23, 22.57, 14.03; MS (CI, CH_4) *m/e* (rel inten) 349 (M^+ + 1, 20), 317 (71),

250 (10), 227 (29), 115 (66), 105 (100); HRMS calcd for $C_{20}H_{28}O_5$ *m/e* 348.1937, found 348.1935.

α-[(Methoxymethyl)oxy]-3-phenylpropyl phenyl ketone: TLC (SiO_2) EtOAc/hexane (15:85), $R_f \sim 0.25$; ^1H NMR δ 7.85–8.00 (m, 2H), 7.05–7.50 (m, 8H), 4.95 (t, J = 6.3 Hz, 1H), 4.60 (dd, J = 6.6, 11.8 Hz, 2H), 3.39 (s, 3H), 2.72–2.90 (m, 2H), 1.95–2.08 (m, 2H); MS (CI, CH_4) *m/e* (rel inten) 285 (M^+ + 1, 12), 239 (28), 179 (100); HRMS calcd for $C_{18}H_{20}O_3$ *m/e* 284.1412, found 284.1409.

(*S*)-[α-(Benzoyloxy)octyl]tributylstannane (4): A THF solution (1 mL) of octanoyltributylstannane[15] (118 mg, 0.28 mmol) was added dropwise during 15 min to a cold THF solution (8 mL) of R-BINAL-H [prepared from $LiAlH_4$ (31.9 mg, 0.84 mmol), absolute EtOH (38.7 mg, 0.84 mmol), and *R*-(+)-1,1′-bi(2-napthol) (240.5 mg, 0.84 mmol)] at –78 °C. After 2 h, the reaction was quenched with 3 mL of saturated NH_4Cl and the mixture was diluted with ether (30 mL). The organic layer was washed with water (15 mL) and brine (10 mL), dried, and concentrated. The residue was suspended in hexane (8 mL) and undissolved binapthol was removed by filtration. Concentration of the filtrate afforded the crude α-hydroxystannane, which was immediately converted to the corresponding benzoyl ester using benzoyl chloride (1.5 equiv) and Et_3N (100 μL) in CH_2Cl_2 (1 mL). Standard aqueous workup and chromatographic purification (SiO_2) with 10% EtOAc/hexane yielded **4** (74 mg, 50%), spectrally identical with the racemic sample above. The enantioselectivity (94% ee) was determined by ^1H NMR analysis of the derived Mosher (*R*)-MTPA ester [R-(+)-MTPA, DCC/DMAP, CH_2Cl_2, 2 h].

(*R*)-α-(Benzoyloxy)octyl phenyl ketone [(–)-5]. The above (*S*)-[α-(benzoyloxy)octyl]tributylstannane (**4**) (35 mg, 0.067 mmol), bis-(triphenylphosphine) palladium(II) chloride (2 mg, 0.003 mmol), and CuCN (0.6 mg) were suspended in 4 mL of anhydrous toulene. To this was added benzoyl chloride (9 mg, 0.064 mmol). The reaction mixture was degassed and heated under an argon atmosphere in a sealed tube at 75 °C for 18 h. Concentration *invacuo* and chromatographic purification (SiO_2) using 10% EtOAc/hexane gave **5** as a colorless oil (16 mg, 74%), spectrally identical with the racemic sample above.

(*S*)-(+)-α-(Benzoyloxy)octyl phenyl ketone. A THF solution (2 mL) of octyl phenyl ketone (130 mg, 0.6 mmol) was cooled to –78 °C. To this was added dropwise a 1 M THF solution of sodium bis(trimethylsilyl)-amide (132 mg, 0.72 mmol), and the resulting yellow solution was stirred at this temperature for 1 h. To this was added via cannula a THF solution (1 mL) of (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine[17] (214 mg, 0.72 mmol), $[\alpha]^{20}_D$ +88.6° (*c* 0.98, $CHCl_3$). The reaction mixture was stirred at this temperature for 3 h, quenched with saturated NH_4Cl (3 mL), extracted with ether (25 mL), washed with water (25 mL) and brine (10 mL), dried, and concentrated *invacuo*. The residue was purified on a silica gel column with 15% EtOAc/hexane to yield α-hydroxyoctyl phenyl ketone, (89 mg, 63% yield), $[\alpha]^{20}_D$ –27.0° (*c* 1.51, $CHCl_3$). The enantioselectivity (91% ee) was determined by ^1H NMR analysis of the derived Mosher (*R*)-MTPA ester [*R*-(+)-MTPA, DCC/DMAP, CH_2Cl_2, 4 h] as well as by chiral HPLC analysis as described below: ^1H NMR δ 7.98–8.00 (m, 2H), 7.50–6.62 (m, 3H), 5.04 (br s, 2H), 3.70 (br s, 1H, D_2O exchangeable), 1.80–1.89 (m, 2H), 1.18–1.60 (m, 10H), 0.82 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 202.17, 133.86, 133.69, 128.83, 128.48, 73.10, 35.87, 31.68, 29.27, 29.05, 24.88, 22.57, 14.03

The above α-hydroxyoctyl phenyl ketone using benzoyl chloride (1.5 equiv) and Et_3N (0.2 mL) in CH_2Cl_2 (0.5 mL). Standard aqueous workup and column chromatography on SiO_2 with 10% EtOAc/hexane yielded (+)-**5** (96% yield), $[\alpha]^{20}_D$ +65.6° (*c* 1.62 $CHCl_3$), spectrally identical with the samples above.

Chiral HPLC Analysis. Isocratic, normal-phase HPLC analysis on a Chiralcel OD (Daicel Chem. Ind.) column (25 × 1 cm) using hexane/2-propanol (99.5/0.5) at a flow rate of 2 mL/min with uv monitoring at 254 nm showed authentic (+)-**5** produced by the method of Davis[17] had $t_R \sim 36$. Racemic-**5** showed two components of equal size with base-line resolution: $t_R \sim 36$ and 27 min. Analysis of (–)-**5** produced by Pd/Cu coupling revealed a major component (97%) with $t_R \sim 27$ min and a minor component (3%) with $t_R \sim 36$ min.

Acknowledgment. Gratitude is expressed to Dr. Rod Bates (Univ. North Texas) for helpful discussions. Supported financially by the Robert A. Welch Foundation (I-782) and the USPHS NIH (GM31278).