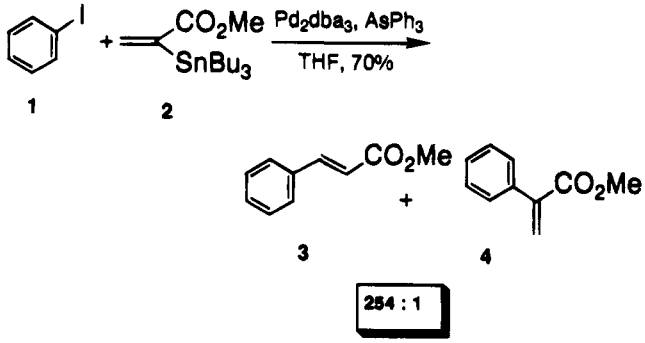
The Anomalous Stille Reactions of Methyl α-(Tributylstannyl)acrylate: Evidence for a Palladium Carbene Intermediate

Carl A. Busacca,* John Swestock, Robert E. Johnson, Thomas R. Bailey, Laszlo Musza, and Charles A. Rodger

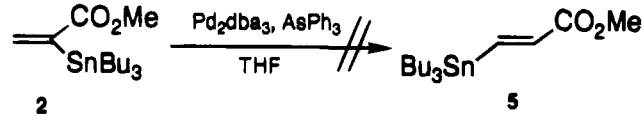
Departments of Medicinal and Analytical Chemistry, Sterling Winthrop, Inc., 1250 South Collegeville Road, Collegeville, Pennsylvania 19426-0900

Received July 19, 1994

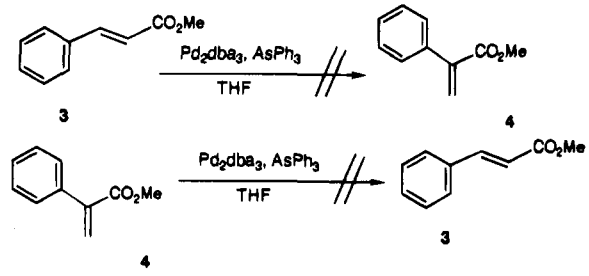
The construction of carbon–carbon bonds using palladium-catalyzed coupling of unsaturated tin species has emerged as a powerful synthetic tool with wide application.[1] The Stille reaction is also known to be tolerant of a wide array of functional groups,[1b] and a recent key report[2] has demonstrated techniques for performining these reactions under relatively mild reaction conditions. We sought to utilize the Stille reaction for rapid synthesis of substituted methyl atropates from various aryl iodides and the known[3] vinylstannane **2**. Contrary to expectations, the major product from this reaction was found to be methyl cinnamate **3**, while the Stille product **4** was only formed in trace amounts. An examination of the methyl atropate literature[4,5] revealed that cinnamates had previously been observed as side products in Stille type couplings of vinylstannane **2**. A proposal for this reaction mechanism is presented in this paper. A novel application of ^{119}Sn NMR is used to support the proposed mechanism.



On the basis of the accepted Stille mechanism, methyl cinnamate (**3**) would be the expected product from coupling of methyl β-(tributylstannyl)acrylate (**5**) and iodobenzene as shown above. To support this particular mechanism, a palladium-catalyzed rearrangement of the α-stannane **2** to the β-isomer **5** must take place. However, prolonged exposure of **2** under the reaction conditions described above does not lead to any rearranged product, **5**, the latter species having been prepared[6] as a standard.



Interconversions of the two products, **3** and **4**, was also considered. Treatment of each of the two pure materials under the reaction conditions, however, led to no isomerization.



Another explanation for methyl cinnamate formation might involve protodestannylation of either starting stannane **2** or a tin-containing intermediate along the reaction pathway. Protodestannylation would necessarily require release of HI. However, ^{119}Sn 2D NMR studies clearly show that n-Bu_3SnI is formed in stoichiometric quantities. Figure 1 is a composite diagram constructed from a series of 2D experiments showing consumption of starting material stannane **2** and formation of n-Bu_3SnI as a function of time. Further supporting evidence was obtained by substitution of methyl acrylate for α-stannane **2** in the reaction mixture. Aside from unreacted starting materials, only 2% of methyl cinnamate

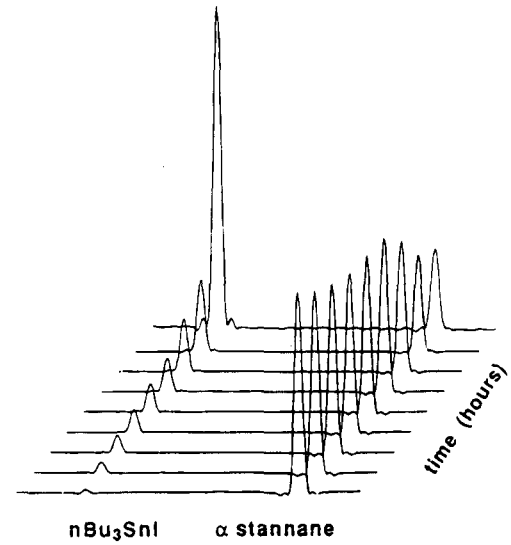


Figure 1. Slices taken from a series of 2D data sets to show consumption of **2** and formation of n-Bu_3SnI. The ^{119}Sn intensity is plotted as a function of time: 1–48 h.

(1) For reviews see: (a) Mitchell, T. N. *Synthesis* **1992**, 803. (b) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
(2) (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (b) See also: Farina, V.; Roth, G.; Krishnan, B.; Marshall, D. R. *J. Org. Chem.* **1993**, *58*, 5434.
(3) (a) Guibe, F.; Zhang, H. X.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. See also: (b) Leusink, A. J.; Budding, H. A.; Marsman, J. W. *J. Organomet. Chem.* **1967**, *9*, 285.
(4) Levin, J. I. *Tetrahedron Lett.* **1993**, *34*(39), 6211.
(5) Crisp, G. T.; Flynn, B. L.; Macolino, V. *Nucleosides Nucleotides* **1991**, *10*(4), 763. See also: Stork, G.; Isaacs, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7399.

(6) Reference 3a: in our experience, the use of $Pd(PPh_3)_2Cl_2$ invariably leads to ca. 5% of the β-stannyl product as an impurity, which has a slightly lower R_f than the desired α-stannyl material and may be separated chromatographically in this way. The use of $Pd(PPh_3)_4$ seems to alleviate this problem.

0022-3263/94/1959-7553$04.50/0

Table 1. Reaction of Iodobenzene with Stannane 2: Solvent Study[a]

PhI + **2** → **3** + **4**

entry	condns	temp, °C	solvent	3:4[b]
1	$Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl	25	DMF	1.8:1
2	Pd_2dba_3, $AsPh_3$	50	NMP	4.3:1
3	Pd_2dba_3, $AsPh_3$	50	5:1 THF:D_2O	48:1
4	Pd_2dba_3, $AsPh_3$, TEA	50	C_6H_6	55:1
5	Pd_2dba_3, $AsPh_3$	50	C_6H_6	213:1
6	Pd_2dba_3, $AsPh_3$	50	THF	254:1

[a] All reactions 0.4 M PhI, 0.45 M **2**, 0.024 M Pd, 0.048 M ligand. All reactions consumed **2** in 24 h. [b] GCMS upon completion.

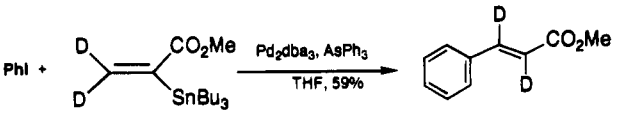
was obtained after 24 h. The relative rates of protodestannylation of numerous stannanes have been studied in detail;[7] carboalkoxy vinylstannanes were shown to be 1 order of magnitude *less* prone to protodestannylation than simple vinylstannanes. This finding is considered to be significant especially since Stille reactions are routinely and successfully performed in the absence of base. Similarly, we also evaluated the reaction with an excess of both triethylamine and $NaHCO_3$ (Table 1), and methyl cinnamate was still found to be the major product.

Scheme 1 illustrates the possible intermediates and pathways we have considered for the present work. Reversible oxidative addition of Pd(0) to iodobenzene and subsequent formation of a π-complex with stannane **2** would lead to species **6**. Transmetalation of **6** within the normal Stille reaction mechanism would lead to σ-vinyl species **7** which should rapidly eliminate methyl atropate (**4**) and regenerate Pd(0). However, the complex **6** may also be considered to be a precursor for the putative Heck adduct **8**. Since species **8** can in fact be considered as a tin enolate, it is shown in equilibrium with **9**. Metalloenolates such as tin enolate **9** and tin allenoate **10** have been proposed[7c,8a] in various reactions. In addition, α-(tributylstannyl)cyclopentenone[9] has been reported to undergo normal Stille coupling reactions. Cyclopentenones would be unable to form such an allenoate, and an explanation for the difference in reactivity between these two similar vinylstannanes seemed apparent. To this end, the reaction of iodobenzene with stannane **2** was performed in the presence of excess D_2O. Enolate **9** should lead to deuteriocinnamate **11** by a combination of β-hydride elimination and deuteration, yet when D_2O was present as a cosolvent (5:1 THF:D_2O) or added at the completion of the reaction as a "quench", no deuterium incorporation was detected by NMR or MS methods.

In order to address the issue of solvent mediation on this reaction, several conditions were examined as summarized in Table 1. A strong dependence of the product distribution on solvent polarity was observed. The greatest preponderance of anomalous product **3** was found in nonpolar solvents (entries 5 and 6), while polar solvents (entries 1 and 2) gave the largest amount of normal Stille product **4**. In our studies we have not been able to generate an excess of Stille product **4**. It should be noted in Table 1 (entries 1 and 4), that excess base has been used; once again, the results strongly argue against formation of **3** via protodestannylation of compound **12**.

Taking all the experimental evidence presented thus far, we propose that the formation of methyl cinnamate may involve a 4-center transmetalation of **8** to palladium(II) carbene intermediate **13**, in which the carbomethoxy group acts as a stabilizing moiety. In support of this, it should be noted that a number of palladium carbenes have been synthesized, characterized, and studied theoretically.[10] Trost[11] has similarly postulated a palladium carbene complex to explain unexpected products in a [2 + 2 + 2] 1,6-enyne cyclization which was performed once again in the presence of palladium, but in the absence of any tin species. In the present case, the proposed carbene **13** would be expected to undergo a β-hydride elimination to palladium hydride **15**, which could then reductively eliminate the observed product, **3**. No proposals have appeared in the literature to support an equilibrium between **7** and **13**. Moody[12] et al. have recently reported the unexpected formation of small amounts of ethyl cinnamate in the reaction of a *rhodium* carbenoid very similar in structure to our proposed palladium carbene **13** (Scheme 1).

The dideuterio version of the title stannane, **16**, was prepared in two steps from methyl propiolate[13] and subjected to the same reaction conditions as described previously. The product obtained, as expected from our proposed mechanism, was α,β-dideuteriomethyl cinnamate **17**, isolated in 59% yield. These results clearly support our proposal for a mechanism involving carbene **13**.



16 **17**

Transmetalation is considered to be the rate-determining step in Stille reactions,[1b,2a] and the product distribution in the present study might consequently depend upon the relative energies of the two transition states for formation of **7** and **13**, as shown in Scheme 2.

It has been suggested[1b] that in Stille reaction transmetalations (**6** to **7**) considerable charge is developed in the transition state and that tin acts as a nucleophile reacting with the Pd complex electrophile. The observed solvent effect in the present case, in which polar solvents lead to increased amounts of Stille product, then may simply represent stabilization of this polar transition state. By comparison, the apparent four-center transmetalation of **8** to carbene **13** could involve synchronous bond making and bond breaking and thus little or no charge development in the transition state. The hindered nature of species **8** might retard the normally facile palladium β-hydride elimination, allowing the four-center transmetalation to take precedence.

(7) (a) Cochran, J. C.; Phillips, H. K.; Samson, T.; Hurd, A.; Alexander, R.; Bronk, B. S. *Organometallics* **1994**, *13*, 947. (b) Cochran, J. C.; Terrence, K. M.; Phillips, H. K. *Organometallics* **1991**, *10*, 2411. (c) Cochran, J. C.; Williams, L. E.; Bronk, B. S.; Calhoun, J. A.; Fassberg, J.; Clark, K. G. *Organometallics* **1989**, *8*, 804.

(8) (a) Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron* **1992**, *48*(40), 8801. (b) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1983**, *48*, 4621.

(9) Negishi, E.; Owczarczyk, Z. R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*(35), 4453.

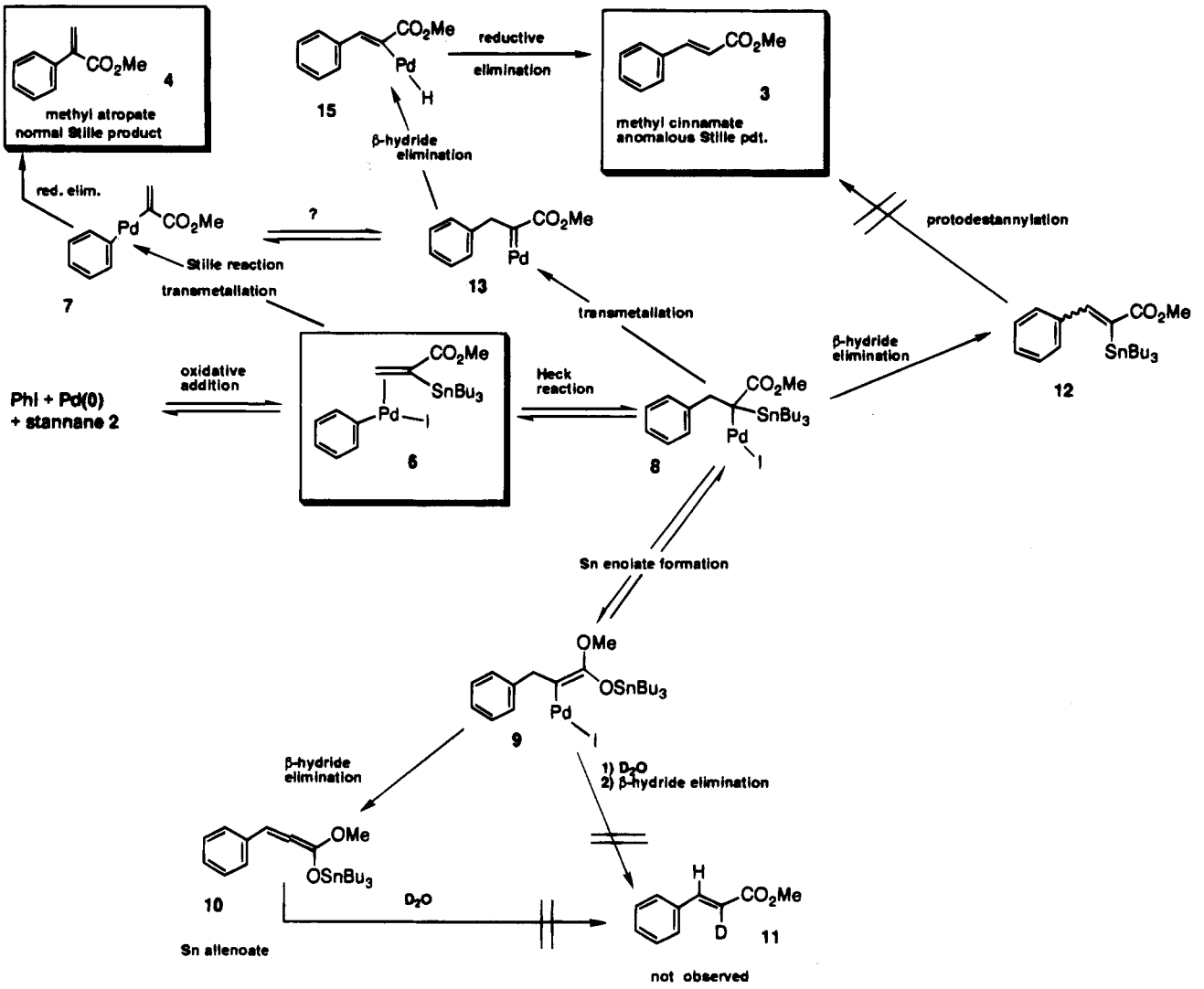
(10) (a) Belluco, U.; Crociani, B.; Michelin, R.; Uguagliani, P. *Pure Appl. Chem.* **1983**, *55*, 47. (b) Clark, H. C. *Pure Appl. Chem.* **1978**, *50*, 43. (c) Belluco, U.; Crociani, B.; Uguagliati, P.; *J. Organomet. Chem.* **1976**, *117*, 189. (d) Hall, M. B.; Taylor, T. E. *J. Am. Chem. Soc.* **1984**, *106*, 1576.

(11) (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. See also: (b) Trost, B. M.; Self, C. R.; *J. Am. Chem. Soc.* **1983**, *105*, 5942.

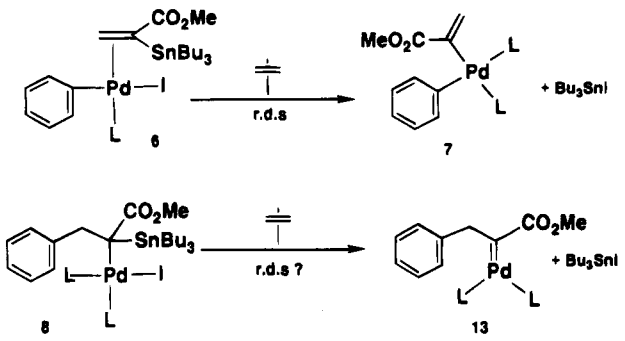
(12) Moody, C. J.; Cox, G. G.; Haigh, D.; Hindley, R. M.; Miller, D. J. *Tetrahedron Lett.* **1994**, *35*(19), 3139.

(13) See Experimental Section.

Scheme 1



Scheme 2



In order to increase our understanding of the transition state, the effect of ligands on the product distribution was examined, and the results are shown in Table 2. In general, very high ratios of **3**:**4** were observed in both benzene and THF. The greatest ratios in both solvents were seen with $(2\text{-Fur})_3P$,[14] in which the minor component could not be detected. The same trend was seen for each solvent, namely $(2\text{-Fur})_3P > PhP(C_6F_5)_2 > AsPH_3$ for production of **3**. These results suggest that π-acceptor ligands may work in concert with the electron-poor carbomethoxy group to stabilize the proposed carbene, although further studies will clearly be necessary to more ably interpret these findings.

(14) Allen, D. W.; Hutley, B. G.; Mellor, M. T. J. *J. Chem. Soc., Perkin Trans. 2* **1972**, 63.

Table 2. Reaction of Iodobenzene with Stannane 2: Ligand Study[a]

PhI + **2** → **3** + **4**

entry	catalyst	ligand	solvent	**3**:**4**[b]
1	Pd_2dba_3	none	THF	5.4:1[c]
2	Pd_2dba_3	$PhP(C_6F_5)_2$	THF	281:1
3	Pd_2dba_3	$Ph_2P(C_6F_5)$	THF	>300:1[c]
4	Pd_2dba_3	$AsPh_3$	THF	254:1
5	pd_2dba_3	$(2\text{-Fur})_3P$	THF	>300:1
6	Pd_2dba_3	PPh_3	THF	nr
7	Pd_2dba_3	$AsPh_3$	C_6H_6	213:1
8	Pd_2dba_3	$PhP(C_6F_5)_2$	C_6H_6	229:1
9	Pd_2dba_3	$(2\text{-Fur})_3P$	C_6H_6	>300:1

[a] All reactions 0.4 M PhI, 0.45 M, **2**, 0.024 M Pd, 0.048 M ligand, at 50 °C, complete within 24 h unless other noted. [b] GCMS. [c] Incomplete.

Conclusion

The Stille reaction of methyl α-(tributylstannyl)acrylate, **2**, with iodobenzene has been examined in detail. While the present reaction is closely related to both the Heck and Stille reactions, the mechanism appears to be

quite different. Palladium-catalyzed rearrangement of the starting stannane, rearrangement of either of the two products, protodestannylation, and tin enolate formation are probably not involved, and the results are consistent with the formation of a palladium carbene intermediate.

Experimental Section

^1H, ^{13}C, and ^{119}Sn NMR spectra were obtained at 500.13 MHz for H-1 observe, 125.77 MHz for C-13 observe, 186.5 MHz for Sn-119 observe, and utilizing inverse detection, or at 299.95 MHz for H-1 observe, and 75.4 MHz for C-13 observe. The column utilized for GCMS was a HPMS crosslinked 5% PhMe silicone 30 m × 0.25 mm × 0.25 mm film thickness column. Base line separation of every reaction component was achieved.

General Method for Couplings Using Pd_2dba_3. To 3.5 mL of dry THF stirring at 25 °C under Ar was added 42 mg of Pd_2dba_3 (0.045 mmol, 0.03 equiv), 59 mg of $AsPh_3$ (0.19 mmol, 0.12 equiv), 0.163 mL of PhI (1.45 mmol, 1 equiv), and 0.50 mL of stannane **2** (1.60 mmol, 1.1 equiv) in the order given and at 3 min intervals. The flask was placed in a pre-equilibrated 50 °C oil bath for 18 h, cooled, and the volatiles were removed in vacuo. The residue was dissolved in 15 mL of Et_2O, 15 mL of 10% aqueous KF was added, and the biphasic mixture was stirred vigorously for 2 h and then filtered through a Celite pad. The organic phase was dried (Na_2SO_4), the solvents were removed in vacuo, and the residue was chromatographed on silica (hexane, then 10:1 hexane:EtOAc) to give 166 mg of a colorless oil (70%), identical with authentic methyl cinnamate (**3**). GCMS analysis showed 254:1 **3**:**4**.

General Method for Couplings Using $Pd(OAc)_2$. A flask was charged with 9.17 g of $NaHCO_3$ (0.109 mol, 3.5 equiv), 0.43 g of $Pd(OAc)_2$ (1.9 mmol, 0.06 equiv), 8.85 g of n-$Bu_4NCl{\cdot}H_2O$ (31 mmol, 1 equiv), 50 mL of DMF, 3.56 mL of PhI (31 mmol, 1 equiv), and 14.0 g of stannane **2** (37 mmol, 1.2 equiv) in the order given. The contents were stirred 19 h at 25 °C under Ar. The mixture was diluted with 300 mL of half-saturated NaCl and extracted with Et_2O (4 × 100 mL). The Et_2O was passed through a pad of Celite and then successively washed with half-saturated NaCl (1 × 300 mL) and saturated NaCl (1 × 300 mL), dried (Na_2SO_4) and concentrated in vacuo. The resultant oil was dissolved in 20 mL of Et_2O, 15 mL of 10% aqueous KF was added, and the mixture was stirred vigorously for 17 h. The viscous mixture obtained was diluted with 50 mL of Et_2O and 50 mL of H_2O and filtered through Celite. Finally, 300 mL of Et_2O and 200 mL of H_2O were added and the phases separated. The organic phase was washed with saturated NaCl (2 × 200 mL), dried (Na_2SO_4), and concentrated in vacuo to a yellow oil. Careful chromatography on silica (hexane, then 1–3% EtOAc in hexane gradient elution) provided first 0.43 g of methyl atropate (**4**) contaminated by a small amount of starting stannane **2**, followed by 4.66 g of a mixture of **3** and **4**. Pure methyl atropate (0.34 g) was ultimately obtained by flash reversed phase chromatography of the 0.43 g sample using octadecyl functionalized silica with MeCN as eluent. This material was identical with literature[15] ^1H NMR data. ^{13}C and MS data reported here are also fully consistent with methyl atropate. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 167.0 (s), 141.2 (s), 136.6 (s), 128.1 (d), 128.0 (d), 127.9 (d), 126.5 (t); MS (EI) *m/z*: 162 (M^+), 131, 103, 77.

Methyl β,β-D_2-(α-Tributylstannyl)acrylate (16). To 65 mL of dry THF under Ar at 25 °C was added 1.58 mL of 3-D-methyl propiolate[12] (17.6 mmol, 1 equiv), followed by 0.41 g of $Pd(PPh_3)_4$ (0.35 mmol, 0.02 equiv). To this solution was slowly added 5.00 g of n-Bu_3SnD (17.1 mmol, 0.97 equiv) dropwise over 30 min. After 1 h the brown mixture was concentrated in vacuo and chromatographed on silica (hexane, then 20:1 hexane:EtOAc) to give 5.00 g of a colorless oil. Distillation (bp 120 °C/0.5 mm) provided 4.80 g of pure stannane **16** (74%) as a colorless oil. ^1H NMR (500.13 MHz, C_6D_6) δ: 3.38 (s, 3H), 1.58–1.47 (m, 6H, $^3Sn(H)$ = 52 Hz), 1.35–1.23 (m, 6H, $^4Sn(H)$ = 14 Hz), 1.02–0.96 (m, 6H, $^1Sn(H)$ = 54 Hz), 0.88–0.82 (m, 9H). ^{13}C NMR (125.77 MHz, C_6D_6) δ: 170.1 ($^2J_{Sn(C=O)}$ = 39 Hz), 146.4 ($^1J_{Sn(C\alpha)}$ = 338 Hz), 139.1 (m), 51.3 (q), 29.4 (t, $^3J_{Sn(C)}$ = 21 Hz), 27.6 (t, $^2J_{Sn(C)}$ = 58 Hz), 13.8 (q), 10.3 (t, $^1J_{Sn(C)}$ = 352, 336 Hz). Anal. Calcd for $C_{16}H_{30}D_2O_2Sn$: C, 50.96. Found: C, 50.90.

α,β-D_2-Methyl Cinnamate (17). To 4 mL of dry THF stirring under Ar at 25 °C was added 44 mg of Pd_2dba_3 (0.048 mmol, 0.03 equiv), 44 mg of $(2\text{-Fur})_3P$ (0.19 mmol, 0.12 equiv), 0.179 mL of PhI (1.60 mmol, 1 equiv), and 0.55 mL of D_2 stannane **16** (1.76 mmol, 1.1 equiv) in the order given and at 3 min intervals. The flask was placed in a pre-equilibrated 50 °C oil bath for 18 h and cooled, and the volatiles were removed in vacuo. The residue was dissolved in 15 mL of Et_2O, 15 mL of 10% aqueous KF was added, and the biphasic mixture was stirred vigorously for 2 h and filtered through a Celite pad. The organic layer was dried (Na_2SO_4), the solvents were removed in vacuo, and the residue was carefully chromatographed on silica (5:1 hexane:EtOAc) to give 140 mg (53%) of pure **17** as a colorless oil which crystallized on standing. Mp: 32–33 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.54–7.50 (m, 2H), 7.40–7.37 (m, 3H), 3.81 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 167.3 (s), 144.4 (m, $^1J_{C\beta(D)}$ = 24.2 Hz), 134.3 (s), 130.2 (d), 128.8 (d), 128.0 (d), 117.4 (m, $^1J_{C\alpha(D)}$ = 25.2 Hz), 51.6 (q). MS (DCI) *m/e*: 165 (MH^+), 164 (M^+), 133, 122, 105, 93, 77. Anal. Calcd for $C_{10}H_8D_2O_2$: C, 73.15; Found: C, 72.94.

(15) Watson, M. B.; Youngson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1597.