Stereospecific Cross-Coupling of Vinyl Halides with Vinyl Tin Reagents Catalyzed by Palladium

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Abstract: The palladium-catalyzed cross-coupling reaction of (*E*)- or (*Z*)-vinyl iodides with (*E*)- or (*Z*)-vinylstannanes gives good yields of stereoisomerically pure unsymmetrical dienes with the same double bond geometry as present in the coupling partners. The reaction takes place at ambient temperature in dimethylformamide in the presence of 1–2% bis(acetonitrile)dichloropalladium. Because this reaction is tolerant of a variety of functionality on either coupling partner, highly functionalized stereoisomerically pure *E,E*-, *E,Z*-, *Z,E*-, or *Z,Z*-1,3-dienes can be obtained under mild conditions by the coupling of the appropriate vinyl iodide with a suitable vinyl tin partner. The sex pheremone of the forest tent caterpillar, *Malacosoma disstria*, was synthesized by the coupling reaction of (*Z*)-1-iodo-1-hexen-6-ol with (*E*)-1-trimethylstannyl-1-hexene.

The stereospecific synthesis of conjugated dienes is of considerable importance, since a variety of aliphatic natural products contain the 1,3-diene unit or even multiple unsaturation with higher degrees of conjugation. The direct coupling reaction of two vinyl groups, particularly the transition-metal-catalyzed coupling of a stereodefined alkenyl-metallic compound with a stereodefined vinyl electrophile, such as a vinyl halide, represents one of the most straightforward routes to the construction of molecules containing *Z,Z*-, *Z,E*- and *E,E*-dienes. Until relatively recently, there were essentially no general coupling procedures for effecting such a reaction.

The best coupling methods that have become available include the cross-coupling reactions of vinyl halides with vinyl borates,[1] with vinyl zinc reagents prepared in situ from vinyl cuprates,[2] and with alkenylaluminum or zirconium reagents, particularly in the presence of zinc chloride.[3] For these organometallic reagents, there are some limitations on the functionality that can be tolerated on the vinyl partners. We have shown that organotin reagents are particularly valuable organometallic partners for cross-coupling reactions, since a wide variety of functionality can be tolerated on either partner, the yields of coupled products are high, and the organotin reagents can be readily synthesized, purified, and stored.[4] The coupling reaction of vinyl tin reagents with vinyl triflates has been reported[5] to give high yields of conjugated dienes, but stereopure vinyl triflates cannot be utilized in this reaction, since there are no good methods, at present, to obtain pure (*E*)- or (*Z*)-vinyl triflates.

The palladium-catalyzed cross-coupling reaction of vinyl iodides with acetylenic tin reagents proceeds stereospecifically to give excellent yields of enynes that can be converted to dienes by the selective reduction of the acetylenic unit.[6] Although reduction of the acetylenic group in the 1,3-enyne to a *Z* olefin can be accomplished quite easily, reduction to an *E* olefin is not readily achieved. Thus *E,E*-1,3-dienes cannot be made by this procedure, and the choice of the partner bearing the acetylenic group (the organotin reagent) is limiting.

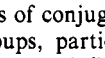
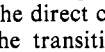
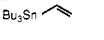
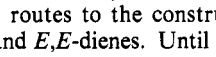
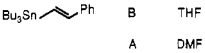
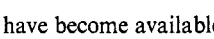
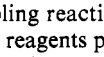
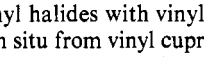
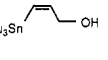
The palladium-catalyzed coupling reaction of vinyl halides with vinyl stannanes in the presence of carbon monoxide gives good yields of unsymmetrical divinyl ketones.[7] In this paper, we report the synthesis of stereodefined 1,3-dienes by the direct, stereospecific cross-coupling of vinyl halides with vinyl tin reagents catalyzed by palladium.

Results and Discussion

Reaction Conditions. In an effort to arrive at the optimum reaction conditions for the coupling, different reaction conditions (catalyst, solvent, and temperature) were varied for the coupling reactions of (*E*)-β-iodostyrene and cyclohexenyl iodide with vinyl tin reagents (Table I). The coupling of (*E*)-β-iodostyrene with tri-(*n*-butyl)vinylstannane takes place at ambient temperature in dimethylformamide (DMF) using the very active bis(acetonitrile)dichloropalladium(II) catalyst. The reaction is complete in 5 min; an 85% isolated yield of coupled product can be obtained (entry 1). The bis(triphenylphosphine)benzylchloropalladium(II) catalyst is less effective (entry 2), and the reaction in tetrahydrofuran required longer reaction times and a higher temperature to attain a comparable yield with this catalyst (entry 3). Attempting to carry out the reaction in coordinating solvents such as acetonitrile or acetone led to incomplete conversion of the starting materials.

Coupling of (*E*)-β-iodostyrene with a β-stannylstyrene gave lower yields of coupled product; a faster reaction occurred at ambient temperature in DMF (entries 4 and 5) while the trimethylvinyltin reagent gave higher yields of coupled product than

Table I. Reaction Conditions: Coupling of (*E*)-β-Iodostyrene and Cyclohexenyl Iodide[a]

Entry	Vinyl Iodide	Vinyl Tin	Catalyst[b]	Solvent	T°C	t(h)	Coupled Product	Yield %
1			A	DMF	25	0.1		85
2			B	DMF	25	12		53
3			B	THF	50	46		53
4			B	THF	50	34		52
5			A	DMF	25	0.1		53
6			A	DMF	25	0.1		71[c]
7			A	DMF	25	0.5		50
8			C	DMF	25	23		80
9			C	THF	50	23		75
10			D	THF	50	23		85
11			D	DMF	25	23		90

[a] Reactions were carried out with 1.5–2 mmol of each reagent in 5 mL of solvent and 2 mol% catalyst. [b] A = $(MeCN)_2PdCl_2$, B = $PhCH_2Pd(Cl)(PPh_3)_2$, C = $(Ph_3P)_4Pd$, D = $(Ph_3P)_2PdCl_2$. [c] *E,E*:*E,Z* = 6; 14% starting reagents remained.

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(5) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Scott, W. J.; Stille, J. K. *Ibid.* **1986**, *108*, 3033.
(6) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.*, in press.
(7) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417.

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Table II. Coupling Reactions of Vinyl Halides with Vinyl Tin Reagents[a]

$$RX + R'SnR_3'' \xrightarrow[DMF,\ 25\ °C]{(CH_3CN)_2PdCl_2} RR' + XSnR''_3$$

Entry	Vinyl Halide	Vinyl Tin	t (h)	Coupled Product	Yield%[b]
1	Ph, I[c]	n-Bu$_3$Sn	0.1	Ph	85
2		Me$_3$Sn, Ph[c]	0.1	Ph, Ph	71[d]
3	Ph, Br[c]	Me$_3$Sn, SiMe$_3$	23	Ph, SiMe$_3$	56[e]
4	n-Bu, I		6	n-Bu, SiMe$_3$	68[f]
5	n-Bu, I		6	n-Bu, SiMe$_3$	26[g]
6[h]	I	Me$_3$Sn	6.5		80
7	I	n-Bu$_3$Sn, CO$_2$Et	23.5	CO$_2$Et	69
8[h]		n-Bu$_3$Sn, CO$_2$Et	12	CO$_2$Et	59
9		n-Bu$_3$Sn, OH	8	OH	61
10	n-Bu, I	n-Bu$_3$Sn, CO$_2$Et	4	n-Bu, CO$_2$Et	83
11		n-Bu$_3$Sn, CO$_2$Et	4	n-Bu, CO$_2$Et	78
12		n-Bu$_3$Sn, OH	8.5	n-Bu, OH	74
13	n-Bu, I	n-Bu$_3$Sn, CO$_2$Et	4	n-Bu, CO$_2$Et	65
14		n-Bu$_3$Sn, CO$_2$Et	122	n-Bu, CO$_2$Et	62
15		n-Bu$_3$Sn	9	n-Bu, OH	78

[a] The reactions were carried out at ambient temperature in DMF with 1–2 mol% bis(acetonitrile)dichloropalladium (catalyst A). [b] Isolated yield. [c] *E*:*Z* = 93:7. [d] Product consisted of 60% (*E*,*E*)- and 10% (*E*,*Z*)-1,4-diphenyl-1,3-butadiene and 14% styrene. [e] 56% *E*,*E*: *E*,*Z* = 95:5, 34% 1,4-diphenylbutadiene based on (*E*)-β-bromostyrene, and 22% (*E*,*E*)-1,4-bis(trimethylsilyl)-1,3-butadiene (based on starting tin reagent). [f] A 57% yield of (*E*,*E*)-1,4-bis(trimethylsilyl)-1,3-butadiene also was obtained. [g] A 53% yield of (*E*,*Z*)-1,4-bis(trimethylsilyl)-1,3-octadiene also was obtained. [h] The catalyst in this reaction was tetrakis(triphenylphosphine)palladium (catalyst C). [i] *E*,*E*:*Z*,*E* = 94:6.

did the tributylvinyltin reagent (entry 5 vs. 6). While the trimethyltin reagents are somewhat more difficult to synthesize and purify, they are much more reactive than the tributyltin analogues, and the workup procedure is simpler since the trimethyltin halide can be removed with a water wash.

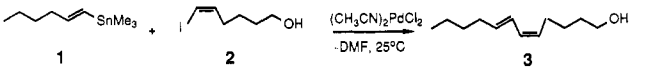
The highest yields of product from the coupling reactions of cyclohexenyl iodide with (*Z*)-3-(tri-*n*-butylstannyl)-2-propen-1-ol were obtained at ambient temperature in DMF with the bis(triphenylphosphine)dichloropalladium catalyst (entry 11), although (bis(acetonitrile)dichloropalladium appeared to be the most active (entry 7). Thus DMF is the solvent of choice, in most cases, and carrying out the reaction at low temperatures and short reaction times should minimize any olefin isomerization both in the reactants or the products. In order to run the reaction at ambient temperature a highly coordinatively unsaturated palladium catalyst appears to be necessary.

Reaction Scope. Coupling reactions of vinyl halides with vinyl stannanes were carried out at room temperature in DMF, usually with 1–2% of the bis(acetonitrile)dichloropalladium catalyst (Table II). With a few exceptions, good yields of geometrically pure 1,3-dienes could be obtained. *E*–*Z* isomerization of the vinyl iodide or the vinyl stannane did not take place. However, in one case, isomerization of the product was observed (entry 10, *E*,*E*: *Z*,*E* = 93:7). The 6:1 ratio of (*E*,*E*)-1,4-diphenylbutadiene to the *Z*,*E* isomer (entry 2) approximately reflects the ratio expected (6.6:1) from a random coupling of vinyl iodide and vinyl stannane, both of 93:7 *E*:*Z* purity. Since both the coupling partners (entry 10) and the product, ethyl (*E*,*E*)-2,4-nonadecadienoate, were not isomerized under the reaction conditions, isomerization may be taking place while the tin partner is bound to palladium, before reductive elimination. Carrying out this reaction in the dark did not suppress the small amount of isomerization.

One of the limitations of the coupling reaction shows up in coupling reactions involving 2-trimethylsilylethenyltrimethylstannane (entries 3–5). A substantial quantity of 1,4-bis(trimethylsilyl)-1,3-butadiene was formed as the result of apparent homocoupling of the vinyl tin partner. In addition, in the coupling of β-bromostyrene with this tin reagent (entry 3) some homocoupling occurred to yield 1,4-diphenylbutadiene.

In an earlier synthesis[6] of the sex pheremone of the forest tent caterpillar, *Malacosoma disstria*,[8] the coupling reaction of (*E*)-1-iodo-1-hexene and trimethyl[6-(tetrahydro-2*H*-pyran-2-yl)oxy-1-hexynyl]stannane was accomplished to give the alcohol-protected 1,3-enyne. This product was stereospecifically reduced with disiamylborane, followed by deprotection to yield pure (5*Z*,7*E*)-5,7-dodecadien-1-ol.[3]

A more direct route to this pheremone was achieved by the direct cross-coupling of the appropriate vinyl iodide with a vinyl stannane. (*Z*)-1-Iodo-1-hexen-6-ol (**2**), obtained from the reduction of 1-iodo-1-hexyl-6-ol with diimide, was coupled with (*E*)-1-trimethylstannyl-1-hexene (**1**) at ambient temperature with the bis(acetonitrile)dichloropalladium catalyst to give a 73% yield of pure **3**. This coupling was carried out without the protection–deprotection steps for the alcohol function.



1 2 3

Experimental Section

The NMR spectra were recorded on an IBM WP-270-SY (270 MHz, ^{1}H; 68 MHz, ^{13}C) in deuteriochloroform using tetramethylsilane (0.00 ppm, ^{1}H) or chloroform (7.25 ppm, ^{1}H; 77.06 ppm, ^{13}C) as an internal standard unless noted otherwise. Data are reported as follows: chemical shift, multiplicity, integration, and coupling constants. Infrared (IR) spectra were recorded neat on a Beckman Model 4240 grating spectrophotometer and are reported in cm^{-1}. Gas chromatograph/mass spectra (GC/MS) were obtained on a VG Micromass 16F spectrometer and are reported as *m*/*e* (relative intensity). Gas chromatographic analyses were performed on a Varian Model 3700 using a 30-m DB-1 capillary column. GC yields were determined using an internal standard after correction for the appropriate response factors unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone, and *N*,*N*-dimethylformamide (DMF) was distilled at reduced pressure from calcium hydride prior to use. High-resolution mass spectra (HRMS) were obtained from the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (Grant No. CHE 8211164), Lincoln, NE, and are reported as *m*/*e* (relative intensity). Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

Starting Materials. The following compounds were prepared according to literature procedures: (*E*)-β-iodostyrene,[9] tri-*n*-butylvinylstannane,[10] 4-*tert*-butyl-1-iodocyclohexene,[11] trimethylvinylstannane,[10] (*E*)-β-tri-*n*-butylstyrylstannane,[12] 1-iodocyclohexene,[11] (*E*)-1-(trimethylstannyl)-2-(trimethylsilyl)ethylene,[13] (*E*)-1-iodohexene,[14] (*Z*)-1-iodohexene,[15] bis(acetonitrile)palladium(II) dichloride[16] (catalyst A),

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benzylchlorobis(triphenylphosphine)palladium(II)[17] (catalyst B), tetrakis(triphenylphosphine)palladium(0)[18] (catalyst C), and bis(triphenylphosphine)palladium(II) dichloride[19] (catalyst D).

General Conditions for the Vinyl–Vinyl Coupling Reactions and Workup. To a flame-dried flask under a purge of argon were added the catalyst and solvent. The vinyl iodide was then added via syringe with the aid of additional solvent. Likewise, the organotin reagent was added. The reaction was then monitored by GC analysis until the starting materials were consumed. In the case of tri-*n*-butylstannane derivatives, a volume of 10% NH_4OH, equal to that of the solvent, was added and the mixture was stirred for several minutes. With trimethylstannane derivatives, 50% saturated aqueous $NaHCO_3$ was used in place of the NH_4OH. The product was then extracted into hexane or pentane or, in the case of dienes bearing polar substituents, ether. The organic layer was then washed with water, dried with anhydrous magnesium sulfate or sodium sulfate (with acid labile functional groups), filtered through Celite, and concentrated using a rotary evaporator. The product was then isolated by flash chromatography or medium-pressure liquid chromatography (MPLC) as described for individual examples. Final purification prior to elemental analysis was accomplished by Kugelrohr distillation, or in the case of solids, by recrystallization. Any modifications are noted separately for each example.

1-Phenyl-1,3-butadiene (Tables I and II, Entry 1). This diene was prepared from (*E*)-β-iodostyrene (317 mg, 1.38 mmol) and tri-*n*-butylvinylstannane (524 mg, 1.65 mmol) using catalyst A (6.3 mg, 1.8 mol %) in DMF (5 mL). The reaction was notably exothermic and was complete in 5 min. The product was obtained in 85% yield after flash chromatography (silica gel, hexanes). The ^1H NMR spectrum of the product was consistent with the reported spectrum.[20]

(*E*,*E*)-1,4-Diphenyl-1,3-butadiene (Table I, Entry 6; Table II, Entry 2). This diene was prepared by reaction of β-iodostyrene (303 mg, 1.66 mmol; *E*/*Z*, 93:7) with β-trimethylstannylstyrene (486 mg, 1.82 mmol; *E*/*Z*, 93:7) in the presence of catalyst A (6.0 mg, 1.4 mol %) in DMF (5 mL) at room temperature. The reaction was complete within 5 min. Flash chromatography (silica gel, pentane) after the usual workup afforded product (60%, after recrystallization), (*E*,*Z*)-1,4-diphenyl-1,3-butadiene (11%), and styrene (14%). The melting point of the *E*,*E* isomer matched the literature value[21] as did its ^1H NMR spectrum.[22] The *Z*,*E* isomer was identified on the basis of its ^1H NMR which was consistent with the reported spectrum.[23] Styrene was identified by comparison of its ^1H NMR spectrum with that of an authentic sample (Aldrich).

1-Trimethylsilyl-4-phenyl-1,3-butadiene (Table II, Entry 3). This diene was prepared from an *E*/*Z* mixture (93:7) of β-bromostyrene (628 mg, 3.73 mmol) and (*E*)-1-trimethylstannyl-2-(trimethylsilyl)ethylene (1071 mg, 4.07 mmol) using $(CH_3CN)_2PdCl_2$ (25 mg, 2.6 mol %) in DMF (10 mL) at room temperature. The reaction was complete in 23 h as determined by GC analysis. The reaction mixture was diluted with 50% saturated aqueous sodium bicarbonate and extracted with a 1:1 mixture of hexane and ether. A suspension was formed in the organic layer which was removed by filtration. The residual solid was insoluble in ether and was discarded. The organic layer was washed with water, dried with anhydrous magnesium sulfate, filtered, and concentrated using a rotary evaporator. The yellow solid obtained was subjected to flash chromatography (silica gel eluted with hexanes). Three products were obtained: the desired diene (*E*,*E*/*E*,*Z* 95:5; 56% yield or in 84% yield corrected for the formation of 1,4-diphenyl-1,3-butadiene), 1,4-diphenyl-1,3-butadiene (34% yield, based upon starting halide), and (*E*,*E*)-1,4-bis(trimethylsilyl)-1,3-butadiene (22% yield, based upon starting tin reagent). The product was characterized by ^1H NMR which matched the literature spectrum,[24] 1,4-diphenyl-1,3-butadiene which matched the ^1H NMR spectrum and melting point of an authentic sample prepared previously, and the bis(trimethylsilyl)butadiene which matched the ^1H NMR spectrum and GC retention time of an authentic sample prepared according to the literature procedure.[25]

(*E*,*E*)-1-Trimethylsilyl-1,3-octadiene (Table II, Entry 4). (*E*)-1-Iodohexene (60 mg, 0.29 mmol) and (*E*)-1-(trimethylstannyl)-2-(trimethylsilyl)ethylene (81 mg, 0.31 mmol) were coupled to yield a 68% yield (GC) of product in the presence of catalyst A (1.5 mg, 2 mol %), 6 h at room temperature in DMF. In addition, a 57% yield (GC) of (*E*,*E*)-1,4-bis(trimethylsilyl)-1,3-butadiene was also obtained, which was identified based upon its ^1H NMR, by spectral comparison with literature values,[26] and by comparison with an authentic sample prepared by a literature procedure.[25]

(*E*,*Z*)-1-Trimethylsilyl-1,3-octadiene (Table II, Entry 5). (*Z*)-1-Iodohexene (60 mg, 0.29 mmol) was coupled with (*E*)-1-(trimethylstannyl)-2-(trimethylsilyl)ethylene (83 mg, 0.31 mmol) using catalyst A (1.5 mg, 2 mol %) in DMF (1 mL) at ambient temperature. The reaction, complete in 6 h, afforded a 26% yield (GC) of the diene along with a 53% yield (GC) of (*E*,*Z*)-1,4-bis(trimethylsilyl)-1,3-octadiene.

Carrying out the reaction with (*E*)-1-(tri-*n*-butylstannyl)-2-(trimethylsilyl)ethylene gave nearly identical results.

4-*tert*-Butyl-1-vinylcyclohexene (Table II, Entry 6). This diene was prepared by reaction of 4-*tert*-butyl-1-iodocyclohexene (1410 mg, 5.34 mmol) with trimethylvinylstannane (1226 mg, 6.42 mmol) in the presence of catalyst C (140 mg, 2.27 mol %) in DMF (20 mL) at room temperature. The reaction was complete in 6.5 h. The product was obtained in 80% yield after flash chromatography (silica gel, pentane). The ^1H NMR spectrum of the product matched that taken of a sample prepared according to a literature procedure.[27]

Synthesis of Isomeric (*E*)- and (*Z*)-3-(Tri-*n*-butylstannyl)propenoic Acid Ethyl Esters. A mixture of ethyl propiolate (3.87 g, 39.5 mmol), tri-*n*-butylstannane (12.05 g, 41.4 mmol), and azobis(isobutyronitrile) (AIBN) was heated to 55 °C over a 2-h period. Within 13 h all of the ethyl propiolate (IR: C≡C, 2110 cm^{-1}) and nearly all of the tin hydride (IR: Sn–H, 1805 cm^{-1}) was consumed. The light yellow solution was then subjected to flash chromatography (silica gel eluted with hexanes to isolate the cis isomer, followed by 5% ethyl acetate in hexanes to elute the trans isomer). From this mixture a 28% yield of the cis isomer and a 54% yield of the trans isomer were obtained. Spectra matched those previously reported.[12]

(*E*)-3-(1-Cyclohexen-1-yl)-2-propenoic Acid Ethyl Ester (Table II, Entry 7). This diene was prepared, using the general procedure, from 1-iodocyclohexene (322 mg, 1.63 mmol) and (*E*)-2-(tri-*n*-butylstannyl)propenoic acid ethyl ester (602 mg, 1.55 mmol) using catalyst A (10.2 mg, 2.54 mol %) in DMF (10 mL) at room temperature. After 23.5 h the reaction was complete and was worked up as usual. The product was isolated in 69% yield after flash chromatography (silica gel, 2% ethyl acetate in hexanes). The ^1H NMR and IR spectra matched published values:[28] ^1H NMR δ 7.28 (d, 1 H, *J* = 15.8 Hz), 6.17 (br s, 1 H), 5.77 (d, 1 H, *J* = 15.8 Hz), 4.21 (q, 2 H, *J* = 7.3 Hz), 2.20 (m, 2 H), 2.14 (m, 2 H), 1.65 (m, 4 H), 1.30 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR δ 167.45, 147.79, 138.12, 135.05, 114.85, 59.34, 26.42, 24.20, 22.13 (two coincidental peaks), 14.27; IR 1720, 1620, 1610, 1450, 1435, 1170, 1025, 845 cm^{-1}.

(*Z*)-3-(1-Cyclohexen-1-yl)-2-propenoic Acid Ethyl Ester (Table II, Entry 8). This diene was prepared from 1-iodocyclohexene (349 mg, 1.71 mmol) and (*Z*)-3-(tri-*n*-butylstannyl)propenoic acid ethyl ester (633 mg, 1.63 mmol) using catalyst C (47 mg, 2.5 mol %) in DMF (10 mL) at room temperature. After 12 h the reaction was complete and was worked up as usual. The product was isolated in 59% yield after flash chromatography (silica gel, 5% ethyl acetate in hexanes): bulb-to-bulb distillation, 70 °C at 0.5 mmHg; ^1H NMR δ 6.31 (d, 1 H, *J* = 12.6 Hz), 6.00 (br s, 1 H), 5.58 (d, 1 H, *J* = 12.6 Hz), 4.17 (q, 2 H, *J* = 7.3 Hz), 2.26 (br s, 2 H), 2.17 (br s, 2 H), 1.61 (m, 4 H), 1.23 (t, 3 H, *J* = 7.30 Hz); ^{13}C NMR δ 166.83, 144.17, 135.40, 134.45, 116.35, 59.96, 27.09, 26.13, 22.63, 21.83, 14.16; IR 1720, 1630, 1160 cm^{-1}; HRMS 180 (54), 152 (29), 151 (58), 135 (38), 134 (23), 133 (22), 107 (36), 105 (58), 93 (13), 92 (27), 91 (79), 80 (24), 79 (100), 78 (41), 77 (58), 67 (37); calcd for $C_{11}H_{16}O_2$ *m*/*e* 180.1151, measured *m*/*e* 180.1160.

(*Z*)-3-(Tributylstannyl)-2-propenol. A solution of diisobutylaluminum hydride (32.0 mmol, 1.0 M in THF) was added dropwise to (*Z*)-ethyl-3-(tri-*n*-butylstannyl)propenoate (5.93 g, 15.2 mmol) in THF (70 mL) cooled to −78 °C. After the addition was complete the solution was warmed to 0 °C over a 1-h period. TLC of the mixture indicated that the reaction was complete and excess MeOH was added to the reaction to decompose the aluminum reagent. After addition of 10 mL of H_2O the suspension was filtered to remove aluminum salts, and the filtrate was extracted with hexane and water. The organic layer was dried with anhydrous magnesium sulfate and concentrated using a rotary evaporator. The residue was bulb-to-bulb distilled using a Kugelrohr apparatus

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(100 °C (0.1 mmHg)) to afford the product in 78% yield. The product was characterized by ^1H and ^{13}C NMR which matched the reported spectra.[29]

(*Z*)-3-(1-Cyclohexen-1-yl)-2-propen-1-ol (Table II, Entry 9). This diene was prepared from 1-iodocyclohexene (527 mg, 2.53 mmol) and (*Z*)-3-(tri-*n*-butylstannyl)propen-1-ol (800 mg, 2.30 mmol) using catalyst D (55 mg, 3.5 mol %) in DMF (5 mL) at room temperature. After 18 h the reaction mixture was treated with a volume of 10% aqueous NH_4OH equal to that of the solvent and then extracted with hexane. The organic layer was washed with water and dried with sodium sulfate. The hexane solution was extracted repeatedly with acetonitrile. The acetonitrile portion was then concentrated to give a yellow oil which was bulb-to-bulb distilled (50 °C (0.1 mmHg)) to afford product in 61% yield as a colorless liquid. Spectra of this product were consistent with the assigned structure: ^1H NMR δ 5.84 (d, 1 H, J = 11.8 Hz), 5.5 (m, 2 H), 4.34 (t, 2 H, J = 5.5 Hz), 2.08 (m, 4 H), 1.59 (m, 4 H), 1.46 (t, 1 H, J = 5.6 Hz); ^{13}C NMR (C_6D_6) δ 135.29, 133.17, 129.49, 128.36 (overlapped by solvent, but verified by an INEPT experiment), 59.98, 29.05, 25.83, 23.08, 22.34; IR 3320, 1670, 1640, 1620, 1450, 1435, 1035, 1015 cm^{-1}. Satisfactory elemental analysis could not be obtained on this compound which rapidly discolored upon standing. HRMS: calcd for $C_9H_{14}O$, 138.1045; found, 138.1045.

(*E*,*E*)-2,4-Nonadienoic Acid Ethyl Ester (Table II, Entry 10). This ester was prepared from (*E*)-1-iodohexene (400 mg, 1.90 mmol) and (*E*)-3-(tri-*n*-butylstannyl)propenoic acid ethyl ester (740 mg, 1.90 mmol) using catalyst A (12.3 mg, 2.50 mol %) in DMF (10 mL) at room temperature. The reaction was complete in 4 h and was worked up as usual. The desired product was isolated as a mixture with the *Z*,*E* isomer (*E*,*E*/*Z*,*E* ratio of 73:27) in 74% yield after flash chromatography (silica gel, 5% ethyl acetate in hexanes). Subsequently, it was determined that combining the reagents at −46 °C and allowing the mixture to warm to room temperature over a 2-h period, followed by stirring for 2 h, favored formation of the expected *E*,*E* isomer. The mixture of *E*,*E* and *Z*,*E* esters (94:6, respectively) was isolated in 83% yield after flash chromatography. The *E*,*E* isomer was identified based upon its ^1H NMR and IR.[30] The *Z*,*E* isomer was identified by spectral comparison with material previously prepared in this work. GC analysis indicated no observable isomerization of the stannane ester during the course of the reaction.

(*Z*,*E*)-2,4-Nonadienoic Acid Ethyl Ester (Table II, Entry 11). This *Z*,*E*-diene was prepared from (*E*)-1-iodohexene (310 mg, 1.48 mmol) and (*Z*)-3-(tri-*n*-butylstannyl)propenoic acid ethyl ester (547 mg, 1.41 mmol) using catalyst A (12.7 mg, 3.47 mol %) in DMF (10 mL) at room temperature. The reaction was complete in 4 h and was worked up as usual. The product was isolated in 78% yield after flash chromatography (silica gel, 5% ethyl acetate in hexanes) and was bulb-to-bulb distilled (70 °C (1.5 mmHg)) prior to elemental analysis. Spectra taken of the product were consistent with the assigned structure: ^1H NMR δ 7.36 (m, 1 H), 6.55 (d of d appears as a triplet, 1 H, J = 11.3 Hz), 6.07 (d of t, 1 H, J = 15.2 and 7.6 Hz), 5.56 (d, 1 H, J = 11.3 Hz), 4.19 (q, 2 H, J = 7.1 Hz), 2.21 (br q, 2 H, J = 6.8 Hz), 1.40 (m, 4 H), 1.30 (t, 3 H, J = 7.1 Hz), 0.91 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 166.44, 145.19, 145.10, 127.19, 115.76, 59.70, 32.58, 31.01, 22.25, 14.29, 13.74; IR 1720, 1640, 1605, 1420, 1175 cm^{-1}. Anal. Calcd for $C_{11}H_{18}$: C, 72.49; H, 9.95. Found: C, 72.39; H, 9.96.

(*Z*,*E*)-2,4-Nonadien-1-ol (Table II, Entry 12). This compound was prepared from (*E*)-1-iodohexene (390 mg, 1.86 mmol) and (*Z*)-3-(tri-*n*-butylstannyl)-2-propen-1-ol (600 mg, 1.73 mmol) using catalyst A (11.8 mg, 2.63 mol %) in DMF (4.5 mL) at room temperature. After 8.5 h the reaction mixture was treated with a volume of 10% aqueous NH_4OH equal to that of the solvent and then extracted with hexane, washed with water, and dried with sodium sulfate. The hexane was extracted repeatedly with acetonitrile. The acetonitrile portion was then concentrated to give a yellow oil which was bulb-to-bulb distilled (50 °C (0.1 mmHg)) to afford product in 74% yield as a colorless liquid. Spectra of the product were consistent with the assigned structure: ^1H NMR δ 6.29 (m, 1 H), 6.04 (d of d appears as a triplet, 1 H, J = 10.8 Hz), 5.63 (d of t, 1 H, J = 14.9 and 7.0 Hz), 5.74 (d of t, 1 H, J = 10.8 and 7.0 Hz), 4.28 (d of d, 2 H, J = 7.0 and 1.0 Hz), 2.10 (br q, 2 H, J = 7 Hz), 1.72 (s, 1 H), 1.36 (m, 4 H), 0.88 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 136.56, 130.59, 128.69, 125.84, 58.81, 32.76, 31.75, 22.52, 13.99; IR 3330, 1655, 1470, 1020, 980, 950, 830, 720 cm^{-1}. Satisfactory elemental analysis could not be obtained on this compound which rapidly discolored upon standing. HRMS: calcd for $C_9H_{16}O$, 140.1202; found, 140.1204.

Addition of this alcohol to $CDCl_3$ containing traces of HCl resulted in isomerization. Attempting to purify this alcohol by MPLC (silica gel) resulted in isomerization during chromatography.

(*E*,*Z*)-2,4-Nonadienoic Acid Ethyl Ester (Table II, Entry 13). The *E*,*Z* isomer was prepared from (*Z*)-1-iodohexene (393 mg, 1.87 mmol) and (*E*)-3-(tri-*n*-butylstannyl)propenoic acid ethyl ester (728 mg, 1.87 mmol) using catalyst A (12.8 mg, 3.60 mol %) in DMF (10 mL) at room temperature. The reaction was complete in 4 h and was worked up as usual. The product was isolated in 65% yield after flash chromatography (silica gel, 5% ethyl acetate in hexanes). Spectra taken of this product prepared previously[31] were consistent with the assigned structure: ^1H NMR δ 7.61 (d of d, 1 H, J = 14.9 and 11.5 Hz), 6.12 (d of d, 1 H, J = 10.9 and 11.5 Hz), 5.87 (d, 1 H, J = 14.9 Hz, determined by decoupling the overlapped multiplet at 5.84 ppm), 5.84 (m, 1 H), 4.22 (q, 2 H, J = 7.1 Hz), 2.21 (br d, 2 H, J = 7 Hz), 1.35 (m, 4 H), 1.28 (t, 3 H, J = 7.2 Hz), 0.91 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 162.32, 141.31, 139.42, 126.57, 121.57, 60.22, 31.68, 28.02, 22.31, 14.35, 14.00; IR 1715, 1635, 1605, 1460, 1440, 1410, 1365, 1300, 1265, 1130, 1090, 1030, 990, 960, 860 cm^{-1}.

(*Z*,*Z*)-2,4-Nonadienoic Acid Ethyl Ester (Table II, Entry 14). This *Z*,*Z*-diene was prepared from (*Z*)-1-iodohexene (402 mg, 1.91 mmol) and (*Z*)-3-(tri-*n*-butylstannyl)propenoic acid ethyl ester (745 mg, 1.91 mmol) using catalyst A (10.4 mg, 2.20 mol %) in DMF (10 mL) at room temperature. The reaction was complete in 122 h and was worked up as usual. The product was isolated in 62% yield after flash chromatography (silica gel, 5% ethyl acetate in hexanes) and was bulb-to-bulb distilled (70 °C (1.5 mmHg)) prior to elemental analysis. Spectra taken of the product were consistent with the assigned structure: ^1H NMR δ 7.28 (d of d, 1 H, J = 11.8 and 12.0 Hz), 6.93 (d of d, 1 H, J = 11.7 and 11.8 Hz), 5.90 (m, 1 H), 5.66 (d, 1 H, J = 12.0 Hz), 4.18 (q, 2 H, J = 7.1 Hz), 2.70 (br q, 2 H, J = 7.0 Hz), 1.38 (m, 4 H), 1.29 (t, 3 H, J = 7.1 Hz), 0.91 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 166.38, 141.02, 138.56, 124.74, 117.72, 59.77, 31.62, 27.22, 22.26, 14.29, 13.72; IR 1715, 1630, 1590, 1460, 1440, 1365, 1280, 1225, 1175, 1130, 1025, 815 cm^{-1}. Anal. Calcd for $C_{11}H_{18}$: C, 72.49; H, 9.95. Found: C, 72.43; H, 9.97.

(*Z*,*Z*)-2,4-Nonadien-1-ol (Table II, Entry 15). This dienol was prepared from (*Z*)-1-iodohexene (533 mg, 2.54 mmol) and (*Z*)-3-(tri-*n*-butylstannyl)propen-1-ol (800 mg, 2.30 mmol) using catalyst A (14.0 mg, 2.35 mol %) in DMF (5 mL) at room temperature. After 9 h the reaction mixture was treated with a volume of 10% aqueous NH_4OH equal to that of the solvent and then extracted with hexane. The organic layer was washed with water and dried with sodium sulfate. The hexane solution was extracted repeatedly with acetonitrile. The acetonitrile portion was then concentrated to give a yellow oil which was bulb-to-bulb distilled (50 °C (0.1 mmHg)) to afford product in 78% yield as a colorless liquid. Spectra taken of the product were consistent with the assigned structure: ^1H NMR δ 6.38 (d of d appears as an apparent t, 1 H, J = 11.0 Hz), 6.22 (d of d appears as a triplet, 1 H, J = 11.0 Hz), 5.58 (m, 2 H), 4.31 (m, 2 H), 2.17 (m, 2 H), 1.33 (m, 5 H), 0.89 (t, 3 H, J = 7.0 Hz); ^{13}C NMR (C_6D_6) δ 133.66, 130.76, 125.06, 123.77, 58.65, 32.02, 27.37, 22.51, 13.93; IR 3330, 1670, 1470, 1010 cm^{-1}. This compound rapidly discolored upon standing. HRMS: calcd for $C_9H_{16}O$, 140.1202; found, 140.1201.

1-Iodo-1-hexyn-6-ol. This compound was prepared from commercially available 5-hexyn-1-ol (Farchan) by reaction with KOH and I_2 in aqueous $MeOH/H_2O$ (5:1) according to the general procedure described.[32] The iodide was isolated in 92% yield after bulb-to-bulb distillation (90 °C (0.2 mmHg)): ^1H NMR δ 3.65 (t, 2 H, J = 6.2 Hz), 2.40 (t, 2 H, J = 6.6 Hz), 1.63 (m, 4 H), 1.45 (s, 1 H); ^{13}C NMR δ 94.29, 61.92, 31.50, 24.70, 20.51, −6.60; IR 3340, 2170, 1455, 1425, 1325, 1055, 1035 cm^{-1}. HRMS: calcd for C_6H_9IO, 223.9698; found, 223.9696.

(*Z*)-1-Iodo-1-hexen-6-ol. A mixture of iodoalkyne (4.000 g, 17.85 mmol) and dipotassium azodicarboxylate (prepared from 25.00 g (215.4 mmol) of azodicarbonamide and 33.3 g (594 mmol) of KOH[15]) in 112 mL of freshly distilled MeOH was treated with a solution of acetic acid (42 mL) in freshly distilled MeOH (112 mL) at a rate which maintained a gentle reflux. After complete addition of the acid, the opaque white mixture was stirred for 1 h at room temperature. The mixture was diluted with an equal volume of water and the product was repeatedly extracted with ether. The ether extract was washed with water and saturated $NaHCO_3$ until the acid was removed. The organic layer was then successively washed with water and saturated aqueous NaCl, dried over anhydrous magnesium sulfate, and concentrated using a rotary evaporator. The yellow oil obtained was a mixture of the *cis*-vinyl iodide, 1-iodohexen-6-ol, and starting alkyne (approximatately 4:1:1). Submission of this material to the reaction again afforded a mixture of only the *cis*-vinyl iodide and the saturated iodide. The latter was removed by treatment of the crude product mixture with *n*-butylamine (2.4 g) at

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room temperature for 2 h. Extraction of this mixture with ether and water, followed by 10% aqueous HCl (to remove excess amine), afforded the *cis*-vinyl iodide free of the saturated iodide. After drying the ether with magnesium sulfate, concentration afforded product. Bulb-to-bulb distillation (90 °C (0.1 mmHg)) gave the product as a light yellow oil in 62% yield (which darkened upon standing): ^{1}H NMR δ 6.17 (m, 2 H), 3.63 (t, 2 H, J = 6.3 Hz), 2.15 (q, 2 H, J = 6.5 Hz), 1.80 (s, 1 H), 1.62-1.40 (m, 4 H); ^{13}C NMR δ 141.02, 82.51, 62.63, 34.40, 32.14, 24.26; IR 3330, 1610, 1455, 1440, 1330, 1295, 1275, 1060, 985 cm^{-1}. HRMS: calcd for $C_6H_{11}IO$ (-I), 98.0810; found, 99.0809. This compound did not exhibit a parent peak.

(*E*)-1-Trimethylstannyl-1-hexene. The vinyl stannane was prepared from (*E*)-1-iodo-1-hexene according to the general procedure[33] in 63% yield. The ^{1}H NMR was consistent with that described.[12]

(*Z*)-5-(*E*)-7-Dodecadien-1-ol. This compound was prepared by coupling (*Z*)-1-iodo-1-hexen-6-ol (355 mg, 1.57 mmol) with (*E*)-1-trimethylstannyl-1-hexene (468 mg, 1.73 mmol) using catalyst A (10 mg, 2.5 mol %) in DMF (4 mL) at room temperature. The reaction was worked up after 36 h in the usual way. The crude mixture was then rapidly chromatographed by MPLC (silica gel, 30% ethyl acetate in hexanes) which produced an impure yellow oil. Careful MPLC of this oil (silica gel, 20% ethyl acetate in hexanes) gave the desired product in 73% yield: ^{1}H NMR δ 6.27 (m, 1 H), 5.93 (d of d appears as a triplet, 1 H, J = 10.9 Hz), 5.64 (d of t, 1 H, J = 15.0 and 7.0 Hz), 5.26 (d of t, 1 H, J = 10.8 and 7.6 Hz), 3.61 (t, 2 H, J = 6.5 Hz), 2.17 (m, 2 H), 2.07 (br q, 2 H, J = 6.7 Hz), 1.62-1.23 (m, 9 H), 0.87 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 134.94, 129.28, 129.18, 125.58, 62.79, 32.50, 32.40, 31.61, 27.38, 25.95, 22.25, 13.84; IR 3330, 1445, 1430, 1055, 980, 945 cm^{-1}. Spectra were consistent with literature values.[34] HRMS: calcd for $C_{12}H_{22}O$, 182.1671; found, 182.1670.

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Polymerization Reactions Involving the Side Chains of α-L-Amino Acids

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Abstract: The feasibility of polymerizing naturally occurring α-L-amino acids via their side chains by bonds other than the amide bond was investigated. Poly(Pal-Hpr-ester) [IUPAC name: poly[(1-palmitoyl-4,2-pyrrolidinediyl)carbonyloxy]] was obtained by melt transesterification of *N*-Pal-Hpr-Me [IUPAC name: *trans*-4-hydroxyl-1-palmitoyl-L-proline methyl ester] in the presence of aluminum isopropoxide as catalyst. M_n (8450) and M_w (15 500) were determined by gel permeation chromatography relative to polystyrene standards. The tyrosine dipeptide Z-Tyr-Tyr-Hex [IUPAC name: *N*-(*N*-benzyloxycarbonyl-L-tyrosyl)-L-tyrosine hexyl ester] was cyanylated at the tyrosine side chain hydroxyl groups to yield Z-Tyr-Tyr-Hex-dicyanate [IUPAC name: *N*-[*N*-benzyloxycarbonyl-3-(*p*-cyanatophenyl)-L-alanyl]-3-(*p*-cyanatophenyl)-L-alanine hexyl ester]. By solution polymerization of equimolar quantities of Z-Tyr-Tyr-Hex and Z-Tyr-Tyr-Hex-dicyanate in tetrahydrofuran, poly(Z-Tyr-Tyr-Hex-iminocarbonate) [IUPAC name: poly[oxyimidocarbonyloxy-*p*-phenylene[2-(hexyloxycarbonyl)ethylene]imino[2-[1-(benzyloxy)formamido]-1-oxotrimethylene]-*p*-phenylene]] was obtained with M_n = 11 500 and M_w = 19 500. The synthesis of such "pseudopoly(amino acids)", which may be regarded as structural analogues of conventional poly(amino acids), may be of interest in enzymology, immunology, pharmacology, and biotechnology (biomaterials for medical applications).

Here we report on the synthesis of structurally new poly(amino acids) in which α-L-amino acids or dipeptides are polymerized by non-amide bonds (e.g., ester, iminocarbonate) involving the functional groups located on the amino acid side chains, rather than the amino acid termini.[1] Previously, Greenstein[2] attempted to use the sulfhydryl group of cysteine for the synthesis of a polysulfide by synthesizing cyclo(L-cysteinyl-L-cysteine) as monomer but failed to obtain a linear polymer due to preferential formation of a cyclic dimer. Later, Fasman[3] attempted to convert poly(L-serine) to poly(L-serine-ester) by means of the N → O acyl shift of L-serine, but complete conversion of all amide bonds to ester bonds was not achieved. In contrast to the approach of Fasman, we attempted the direct polymerization of suitably protected amino acids or dipeptides by polymerization reactions involving the functional groups located on the amino acid side chains.

We considered this approach since it would permit the synthesis of biomaterials (for drug delivery systems, sutures, artificial organs, etc.) which are derived from nontoxic metabolites (amino acids and dipeptides) while also having other desirable properties; e.g., the incorporation of an anhydride linkage into the polymer backbone could result in rapid biodegradability,[4] an iminocarbonate bond may provide mechanical strength,[5] and an ester bond may result in better film and fiber formation.[6]

Furthermore, pseudopoly(amino acids) can be either analogues (compound **5**) or true structural isomers (compound **2**) of conventional poly(amino acids). Therefore these materials would make new substrates in enzymology as well as facilitate studies

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