Copper(I) chloride-mediated oxidative coupling of alkenyltrialkylstannyl functions: efficient stereocontrolled syntheses of uniquely functionalized conjugated diene systems

Edward Piers, Ernest J. McEachern, Miguel A. Romero, and Patricia L. Gladstone

Abstract: Treatment of the β-trialkylstannyl α,β-unsaturated esters **1–9** with 2.5 equivalents of copper(I) chloride in *N,N*-dimethylformamide at room temperature results in the efficient, stereocontrolled production of the highly functionalized conjugated dienes **10–18**, respectively. In each of these oxidative couplings, production of 1 equivalent of product is accompanied by the formation of 2 equivalents of both the trialkylstannyl chloride and copper metal.

Key words: alkenyltrialkylstannanes, copper(I) chloride, transmetalation, conjugated dienes, oxidative coupling, β-trialkylstannyl α,β-unsaturated esters, substituted dialkyl muconates, organostannane, organocopper.

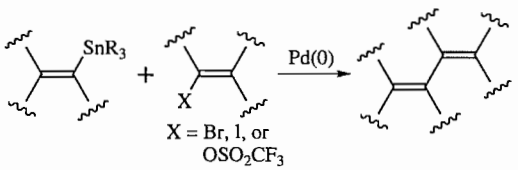
Résumé : La réaction des esters β-trialkylstannyl-α,β-insaturés **1–9** avec 2,5 équivalents de chlorure cuivreux, dans le *N,N*-diméthylformamide, à la température ambiante, conduit à la formation efficace et stéréocontrôlée des diènes conjugués hautement fonctionnalisés **10–18** respectivement. Dans chacun de ces couplages oxydants, la production d'un équivalent de produit s'accompagne de la formation de deux équivalents respectivement de chlorure de trialkylstannyle et de cuivre métallique.

Mots clés : alcénytrialkylstannanes, chlorure cuivreux, transmétalation, diènes conjugués, couplage oxydant, esters β-trialkylstannyl-α,β-insaturés, muconates de dialkyle substitués, organostannane, organocuivre.

[Traduit par la rédaction]

Introduction

The palladium(0)-catalyzed intermolecular cross-couplings represented in general terms by eq. [1], collectively known as the Stille coupling, are now well known protocols for the stereospecific syntheses of conjugated diene systems (1–5). Indeed, both the inter- and intramolecular versions of this process have been employed effectively in the synthesis of a wide variety of structurally complex organic compounds (1–5). In 1990, an important paper by Liebeskind and Fengl (6) disclosed that Pd(0)-catalyzed cross-couplings of alkenyltrialkylstannanes with alkenyl bromides and iodides are cocatalyzed by Cu(I) salts. This modified protocol, which generally leads to increased reaction rates and higher product yields, has been employed to advantage in a number of different contexts (see references 7–10 and citations therein) and has proven to be particularly good for successfully carrying out Stille-type couplings that are sluggish or inefficient under the "conventional" experimental conditions. A recent detailed study of this process led to very reasonable proposals regarding the cocatalytic role of Cu(I) in the overall coupling reaction (11).

[1] 

In 1993, a report (12) from this laboratory disclosed that *intra*molecular couplings of alkenyltrimethylstannane and alkenyl halide (I, Br) functions can be accomplished smoothly and efficiently by treatment of the requisite substrates with copper(I) chloride (~2–3 equivalents) in *N,N*-dimethylformamide (DMF). Examples are shown in eqs. [2] and [3]. The presence of a palladium(0) catalyst is not required and, in fact, we have subsequently found[2] that the CuCl-mediated processes are, in some instances, cleaner and more efficient than the corresponding Pd(0)-catalyzed transformations.

Very recently, a synthetically valuable extension to this

Received November 12, 1996.

This paper is dedicated to Professor William A. Ayer on the occasion of his 65th birthday.

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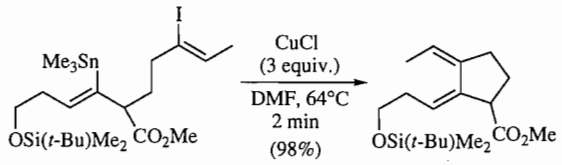
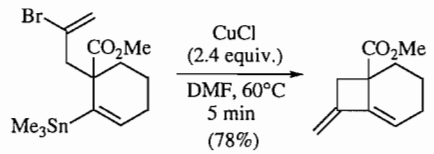
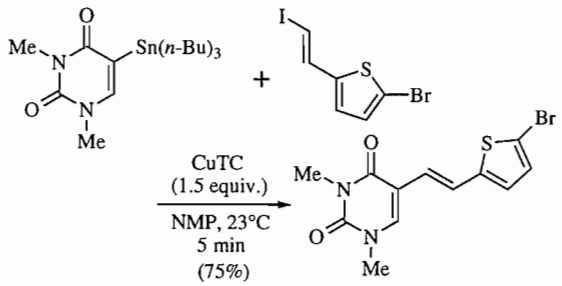
[2] E. Piers, T. Wong, and K.E. Ellis. Unpublished results.

[2] 

[3] 

methodology was described by Allred and Liebeskind (13), who found that *inter*molecular cross-couplings of alkenyl- and aryltributylstannanes with alkenyl and aryl iodides can be successfully mediated by copper(I) thiophene-2-carboxylate (CuTC) in *N*-methylpyrrolidone (NMP). An example is provided in eq. [4].

[4] 

Further research in our laboratory related to the use of Cu(I)-mediated processes in organic synthesis has led to the discovery that CuCl also effects the inter- (14) and intramolecular (15) coupling of two alkenyltrimethylstannane functions. We report herein the details of a study (14) that revealed that treatment of alkyl 3-trialkylstannyl-2-alkenoates and alkyl 2-trimethylstannyl-1-cycloalkenecarboxylates with 2.5 equivalents of CuCl in DMF at room temperature results in the assembly of structurally novel, highly functionalized conjugated diene systems via the stereospecific coupling of the vinylic carbons bearing the R_3Sn function.

In connection with the results described in this paper, recent reports (16–21) emanating from other laboratories should be mentioned. Four of these reports (16–19) describe the *copper(II) nitrate*-mediated intermolecular coupling of alkenyltributylstannane functions, although the papers by Kyler and co-workers (16), Zhang et al. (17), and Crisp and Glink (18) collectively give a total of only seven examples. On the other hand, in the work by Quayle and co-workers (19), the carbon atom bearing the Bu_3Sn group was, in each of the substrates, also attached to a heteroatom (oxygen or sulfur) and, therefore, all the products possess either vinyl ether or vinyl sulfide linkages. The recent publications by Falck et al. (20) and Takeda et al. (21) describe the copper(I) salt-mediated cross-coupling of α-heteroatom-substituted *alkyl*tributylstannane functions with a variety of organic halides and the CuI-promoted *allylation* of alkenyltributylstannanes, respectively.

Results and discussion

The coupling reactions

The structural formulas of the substrates (**1–9**) employed in this study are shown in Table 1. In connection with our continuing investigations into the preparation and synthetic uses of alkenyltrialkylstannanes, compounds **1** (22), **2** (23), **3** (23), **4** (24), **5** (25), **6** (23), and **7** (26) have been reported previously. The cyclic unsaturated esters **8** and **9** were prepared via a method modified from that described by Piers and Tse (26). Thus, sequential treatment of each of the keto esters **19** and **20** with potassium hydride and *N*-phenyltrifluoromethanesulfonimide in dry tetrahydrofuran (THF) provided excellent yields of the corresponding alkenyl trifluoromethanesulfonates **21** and **22** (eq. [5]). When the latter two compounds were allowed to react with lithium (phenylthio)(trimethylstannyl)cuprate (27) in THF containing hexamethylphosphoramide (HMPA), the substrates **8** and **9** were obtained in yields of 90 and 82%, respectively.

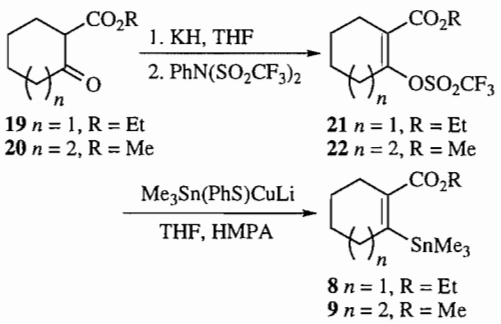
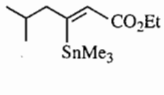
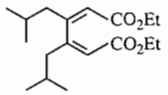
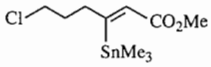
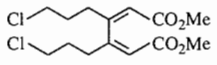
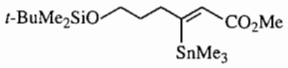
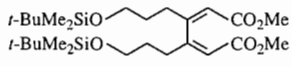
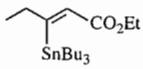
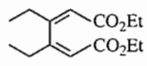
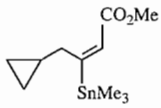
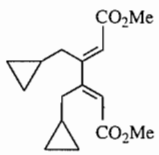
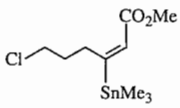
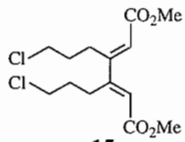
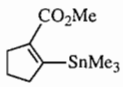
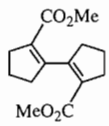
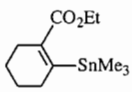
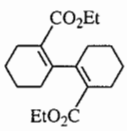
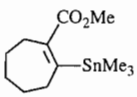
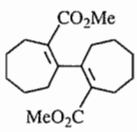
[5] 

Table 1 contains a summary of the coupling processes that were carried out during the course of this investigation. Addition of solid copper(I) chloride (2.5 equivalents) to a solution of ethyl (*Z*)-5-methyl-3-trimethylstannyl-2-hexenoate (**1**) in DMF, followed by stirring of the reaction mixture at room temperature for 1 h, provided diethyl (*Z*,*Z*)-3,4-bis(2-methylpropyl)muconate (**10**) in 96% yield (entry 1). In a very similar fashion, the β-trimethylstannyl α,β-unsaturated esters **2**, **3**, and **5–9** were transformed cleanly and efficiently into the corresponding functionalized dienes **11**, **12**, and **14–18** (entries 2, 3, and 5–9). Although we have not studied extensively the use of tributylstannanes in this research, the conversion of **4** into **13** (entry 4) indicates that this type of substrate can also be successfully employed in this coupling protocol.

The results summarized in Table 1 show that the new coupling method is efficient and tolerates a variety of functional groups. From the viewpoint of synthesis, it is particularly noteworthy that the process occurs without loss of configurational integrity. Indeed, the data given in Table 1 show that the coupling process is stereospecific and that each of the reactions proceeds with retention of configuration at the alkenyl centers that are being coupled.

Of the products listed in Table 1, ethyl 2-(2-ethoxycarbonyl-1-cyclohexen-1-yl)-1-cyclohexenecarboxylate (**17**) (28) has been reported previously. The geometric configurations of the products **10–15** were established by use of nuclear magnetic resonance (NMR) spectroscopy. An examination of the ^1H and ^{13}C NMR spectra of the substances **10–15** shows clearly that each of the products possesses an element of symmetry. For example, the ^1H NMR spectrum of the diester **11** displays a 6-proton singlet for the two methoxy groups, a 2-proton triplet (J = 1 Hz) for the two olefinic hydrogens, and three 4-proton multiplets derived from the three magnetically different methylene units of the two 3-chloropropyl groups. In a similar vein, the ^{13}C NMR spectrum of **11** contains reso-

Table 1. Intermolecular coupling of alkenyltrialkylstannane functions.[a]

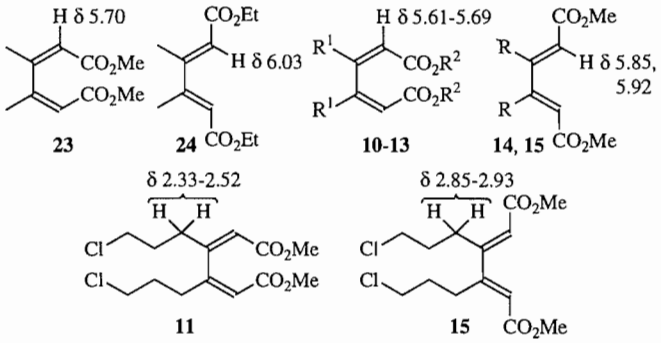
Entry	Starting material	Product (yield, %)
1	 **1**	 **10** (96)
2	 **2**	 **11** (90)
3	 **3**	 **12** (86)
4	 **4**	 **13** (97)
5	 **5**	 **14** (92)
6	 **6**	 **15** (82)
7	 **7**	 **16** (99)
8	 **8**	 **17** (80)
9	 **9**	 **18** (86)

[a]All the coupling reactions were carried out with 2.5 equivalents of CuCl in *N,N*-dimethylformamide at room temperature. The reaction time was 1 h in each case, except for the experiment summarized in entry 5; in this case, the reaction time was 2 h.

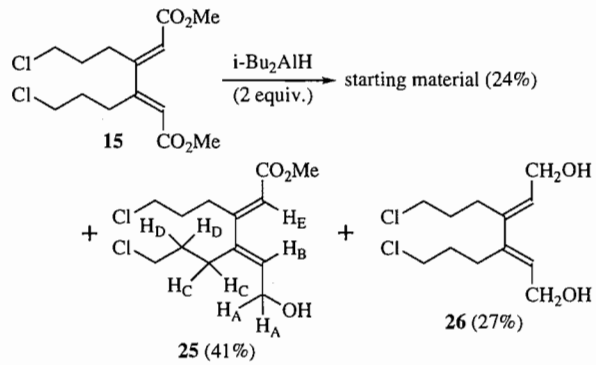
nances for only seven magnetically different carbon atoms. The ^{1}H and ^{13}C NMR spectra of the other acyclic products listed in Table 1 exhibit analogous characteristics.

In the ^{1}H NMR spectra ($CDCl_3$) of the known diesters **23** (29) and **24** (30), the olefinic protons resonate at δ 5.70 and 6.03, respectively. In the same solvent, the signals due to the olefinic hydrogens of compounds **10**–**13** appear at δ 5.63, 5.69, 5.68, and 5.61, respectively. On the other hand, the corresponding resonances in the spectra of **14** and **15** are found at δ 5.85 and 5.92, respectively. These data provide strong evi-

dence for the configurational assignments. It should also be noted that the protons of the allylic CH_2 groups in the (*Z,Z*)-diene **11** resonate at δ 2.33–2.52 (multiplet), while the corresponding protons of the (*E,E*)-diene **15** give rise to a multiplet at δ 2.85–2.93.[3] Since, in compounds **11** and **15**, the CH_2 groups in question are *trans* and *cis*, respectively, to the methoxycarbonyl group, the relative chemical shifts are as expected. Similar chemical shift patterns can be observed in the ^{1}H NMR spectra of substances **10** and **12–14**.



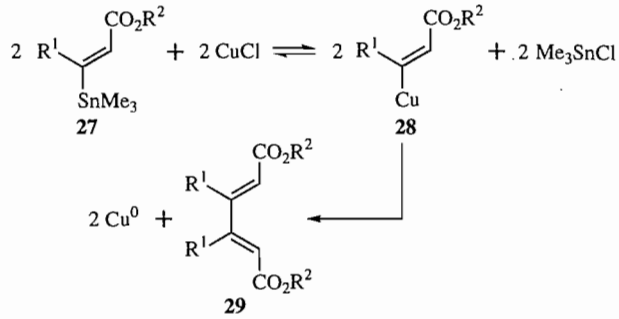
Further evidence for the structure of the diester **15** was obtained as follows. Treatment of this material with 2 equivalents of diisobutylaluminum hydride in diethyl ether at −78°C afforded a mixture consisting of the starting material **15**, the ester alcohol **25**, and the diol **26** (eq. [6]). Flash chromatography of this mixture on silica gel (31) provided, in addition to recovered **15** (24%), the two products **25** and **26** in yields of 41 and 27%, respectively. Key ^{1}H NMR nuclear Overhauser enhancement difference experiments were carried out on compound **25**. Thus, irradiation at δ 4.32 (doublet due to H_A protons)[3] caused enhancement of the signals derived from the olefinic proton H_B (triplet at δ 5.94) and the allylic protons H_C (triplet at δ 2.42). On the other hand, irradiation at δ 2.42 caused an increase in the intensity of each of the resonances at δ 1.74–1.83 (multiplet, H_D protons), 4.32, and 5.86 (singlet, H_E). These experiments clearly establish the configuration of **25** and confirm the earlier conclusions regarding the stereochemistry of the diester **15**.

[6]


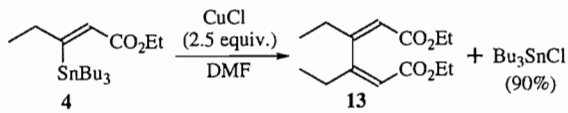
Mechanistic considerations

Detailed mechanistic studies related to the new coupling method have not been carried out. However, on the basis of observations derived from previous investigations (11, 13, 32), along with the results of experiments described below, it seems reasonable to propose, in a rather sketchy fashion, that the oxidative couplings take place via the pathway outlined in Scheme 1.

Scheme 1.



Liebeskind and co-workers (11) have shown that, in polar solvents, alkenyltrialkylstannanes undergo transmetalation with copper(I) halides to produce trialkylstannyl halides and, presumably, the corresponding alkenylcopper(I) derivatives. It has also been proposed that these reactions are reversible (13). The postulate that the overall coupling process is initiated by such a transmetalation process (initial equilibrium step shown in Scheme 1) was supported by an experiment involving the conversion of **4** into **13** (eq. [7]). Thus, flash chromatography (31) of the crude product derived from treatment of **4** with 2.5 equivalents of CuCl gave, in addition to the coupled product **13**, a 90% yield of tributylstannyl chloride.

[7]


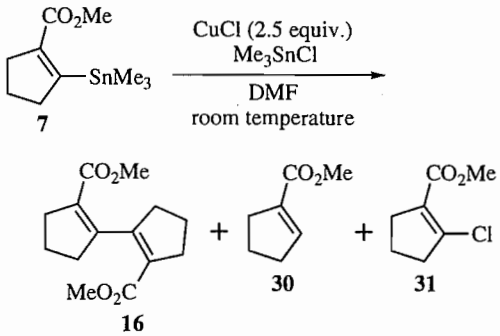
Support for the reversible nature of the transmetalation step was obtained from a number of experiments. Scheme 1 suggests that the conversion of starting material to product should proceed to completion by treatment of the former with 1 equivalent of CuCl. However, experiments show that when this quantity of the reagent is employed, the reaction is initially quite facile but becomes very sluggish with time. For example, a solution of **1** in DMF was treated with 1 equivalent of CuCl and the progress of the reaction was monitored by periodic removal of aliquots, which were subjected to an appropriate work-up procedure and analysis by gas–liquid chromatography (GLC). After a period of 30 min, approximately 50% of the starting material **1** had been converted to the product **10**. However, a reaction time of ~14 h was required for complete consumption of the starting material.[4] On the other hand, use of 2.5 equivalents of CuCl alleviates this problem and the reaction proceeds to completion within a relatively short reaction time (Table 1, entry 1). The same is true of the other coupling reactions summarized in Table 1. Presumably, the function of the excess reagent (CuCl) is to push the equilibrium between **27** and **28** (Scheme 1) to the right.

In connection with the conversion of substrate **7** into the diene diester **16**, it was demonstrated that addition of trimethylstannyl chloride to the reaction mixture prior to addi-

[3] The resonance assignments were readily confirmed by ^{1}H NMR COSY experiments.

[4] The isolated yield of the product **10** at this stage was ~90%.

tion of the CuCl reagent is also deleterious to the reaction efficiency (eq. [8]). In the absence of added Me_3SnCl, the reaction

[8] 

7 16 30 31

affords the product cleanly and efficiently (Table 1, entry 7). However, addition of the stannyl chloride decreased significantly the rate of consumption of the starting material **7**. Furthermore, under these conditions, the formation of the coupled product **16** was accompanied by the production of the protio- and chlorodestannylated products **30** and **31**, respectively.[5] For example, treatment of a solution of **7** in DMF with 1 equivalent of Me_3SnCl prior to the addition of 2.5 equivalents of CuCl increased the time necessary for consumption of the starting material from 1 h (Table 1, entry 7) to ~9 h. The product **16**, which was isolated in a yield of 75%, was accompanied by ~20% of a mixture of **30** and **31** in a ratio (GLC) of ~1:2, respectively. In a separate experiment, it was found that disappearance of the starting material **7** after addition of 2.5 equivalents of Me_3SnCl required ~20 h. In this case, the crude product consisted of **16** (isolated yield 57%) and a mixture (~35%) of **30** and **31** (ratio ~1:1.5). Although the overall role(s) that the added Me_3SnCl plays in these reactions is probably complex, it is reasonable to conclude that its function in decreasing the rate of starting material consumption is related primarily to shifting the equilibrium reaction shown in Scheme 1 to the left.

Observation of the reaction mixtures derived from the coupling processes summarized in Table 1 indicated that, in each case, copper metal was produced. The amount of Cu^0 formed per mmol of substrate employed was quantified by an experiment involving conversion of **1** into **10** (Table 1, entry 1). Suitable work-up of the reaction mixture derived from treatment of 1 equivalent of **1** with 2.5 equivalents of CuCl in DMF, followed by an appropriate analytical procedure (33), showed that 0.92 equivalents of Cu^0 had been produced. Thus, the coupling of two molecules of the alkenyltrimethylstannane **27** to produce one molecule of the diene **29** is accompanied by the production of two copper atoms (Scheme 1). Although, as discussed above, it seems likely that this process proceeds via the intermediacy of the alkenylcopper(I) species **28**, the mechanistic details of the transformation of **28** into **29** remain obscure.

[5] The presence of **30** and **31**, indicated by the ^1H NMR spectrum of the crude product, was confirmed by analysis of the mixture by GLC – high-resolution mass spectrometry, which showed the presence of three components with molecular masses 126.0684 (**30**, calcd. for $C_7H_{10}O_2$: 126.0681), 160.0291 (**31**, calcd. for $C_7H_9{}^{35}ClO_2$: 160.0291), and 250.1208 (**16**, calcd. for $C_{14}H_{18}O_4$: 250.1205).

Conclusion

The investigations described above show that copper(I) chloride effectively mediates the oxidative dimerization of β-trialkylstannyl α,β-unsaturated esters. This new coupling method should be of considerable value for the concise synthesis of usefully functionalized conjugated diene systems. Alkenyltrialkylstannanes possessing a wide variety of functionalized carbon skeletons are readily prepared (12, 22–27, 32, 34) and, therefore, several extensions to this work can be envisaged. A number of possibilities are currently being pursued.

Experimental

General information

Melting points and distillation temperatures (short-path Kugelrohr distillations) are uncorrected. Infrared (IR) spectra were recorded using potassium bromide pellets or liquid films on sodium chloride discs. Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded using $CDCl_3$ solutions. Signal positions in ^1H NMR spectra were measured relative to signals for Me_4Si (δ 0) (internal standard) or $CHCl_3$ (δ 7.24), while resonances in ^{13}C NMR spectra were recorded relative to the signal for $CDCl_3$ (δ 77.0). Tin–hydrogen coupling constants (J_{Sn-H}) are given as the average of the ^{117}Sn and ^{119}Sn values. Molecular mass determinations (high-resolution mass spectrometry) for substances containing Me_3Sn are based on ^{120}Sn. Flash chromatography (31) was carried out with 230–400 mesh silica gel (E. Merck). Thin-layer chromatography (TLC) was accomplished with commercial aluminum-backed plates (E. Merck, Type 5554). Gas–liquid chromatography (GLC) was performed on instruments equipped with flame ionization detectors and 25 m × 0.20 mm fused silica columns coated with HP-5 (cross-linked 5% phenyl methyl silicone).

Petroleum ether refers to a mixture of alkanes with bp 35–60°C. Commercial copper(I) chloride (99.995%) and *N*-phenyltrifluoromethanesulfonimide were used without further purification.

Aqueous NH_4Cl–NH_4OH (pH 8) was prepared by the addition of ~50 mL of aqueous ammonia (58%) to ~950 mL of saturated aqueous NH_4Cl.

Note: Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon in oven- (110°C) or flame-dried glassware.

General procedure 1. Preparation of the alkenyl trifluoromethanesulfonates 21 and 22

A suspension of KH (1.1 equiv.) in dry THF (~5 mL per mmol of substrate) was cooled to 0°C and the neat β-keto ester (**19** or **20**) (1 equiv.) was added dropwise. After the mixture had been stirred for 30 min, *N*-phenyltrifluoromethanesulfonimide (1.2 equiv.) was added as a solid in one portion and stirring was continued for 30 min at 0°C and for 1 h at room temperature. Petroleum ether (~1.5 mL per mmol of substrate) was added and the mixture was filtered through a plug of silica gel (~1.5 g per mmol substrate) presoaked with 1:1 petroleum ether – Et_2O. The silica gel was eluted with the same solvent mixture. The filtrate was concentrated and the crude oil was purified by flash chromatography on silica gel.

The following compounds were prepared via this general procedure.

*Ethyl 2-(trifluoromethanesulfonyloxy)-1-cyclohexene-carboxylate (**21**)*
Purification (flash chromatography, 230 g of silica gel, 95:5 to 3:1 petroleum ether – Et_2O) of the crude product obtained from 2-ethoxycarbonylcyclohexanone (5.32 g, 31.3 mmol) and *N*-phenyltrifluoromethanesulfonimide (12.8 g, 1.2 equiv.) gave 8.90 g (94%) of the alkenyl trifluoromethanesulfonate **21**, a colourless oil that displayed IR (neat): 1719, 1672, 1287, 1142, 1094, 1044, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, 3H, J = 7 Hz), 1.60–1.70 (m, 2H), 1.71–1.85 (m, 2H), 2.35–2.42 (m, 2H), 2.43–2.50 (m, 2H), 4.25 (q, 2H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0. 21.0, 22.2, 26.1, 28.5, 61.6, 120.4, 123.2, 151.3, 164.8. Exact Mass calcd. for $C_{10}H_{13}F_3O_5S$: 302.0436; found: 302.0435.

*Methyl 2-(trifluoromethanesulfonyloxy)-1-cycloheptene-carboxylate (**22**)*
This compound was prepared from 2-methoxycarbonylcycloheptanone (2.94 g, 17.3 mmol) and *N*-phenyltrifluoromethanesulfonimide (7.62 g, 1.2 equiv.). Flash chromatography of the crude product on silica gel (150 g, petroleum ether to 95:5 petroleum ether – Et_2O) gave 4.94 g (95%) of **22** as a colourless oil that exhibited IR (neat): 1728, 1659, 1423, 1249, 1212, 1141, 1003, 867 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.60–1.79 (m, 6H), 2.49–2.59 (m, 4H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.7, 25.2, 28.0, 30.7, 34.0, 52.3, 118.3, 127.8, 155.0, 166.1. Exact Mass calcd. for $C_{10}H_{13}F_3O_5S$: 302.0436; found: 302.0431. Anal. calcd. for $C_{10}H_{13}F_3O_5S$: C 39.74, H 4.33, S 10.61; found: C 39.97, H 4.41, S 10.57.

General procedure 2. Preparation of the alkenyltrimethylstannanes 8 and 9
To a cold (−20°C), stirred solution of lithium (phenylthio)(trimethylstannyl)cuprate (27) (1.5 equiv.) in dry THF (~15 mL per mmol of substrate) was added a solution of the alkenyl trifluoromethanesulfonate (**21** or **22**) (1 equiv.) in dry THF (~0.7 mL per mmol of substrate). After the mixture had been stirred at −20°C for 1 h, dry HMPA (2 equiv.) was added, the mixture was allowed to warm to 0°C, and was stirred for an additional 1 h. Saturated aqueous ammonium chloride (~14 mL per mmol of substrate) and 4:1 petroleum ether – Et_2O (~14 mL per mmol substrate) were added and the mixture was stirred until the organic layer was colourless. The mixture was filtered to remove the solid material. The filtrate was washed (saturated aqueous copper(II) sulfate, water, brine), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography on silica gel followed, for compound **8**, by distillation.

The following compounds were prepared via this general procedure.

*Ethyl 2-(trimethylstannyl)-1-cyclohexenecarboxylate (**8**)*
Flash chromatography (220 g of silica gel, 4:1 petroleum ether – benzene) of the crude product derived from the alkenyl trifluoromethanesulfonate **21** (8.90 g, 29.5 mmol), followed by distillation (85–95°C/0.1 Torr) of the derived oil, provided 8.41 g (90%) of **8** as a colourless oil that showed IR (neat): 1694, 1593, 1448, 1367, 1250, 1056, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.08 (s, 9H, $^2J_{Sn-H}$ = 54 Hz), 1.26 (t, 3H, J = 7 Hz), 1.50–1.69 (m, 4H), 2.26–2.43 (m, 4H), 4.16 (q, 2H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −7.4, 14.3, 22.2, 22.8, 26.4, 33.9, 60.6, 136.0, 163.1, 169.0. Exact Mass calcd. for $C_{11}H_{19}O_2Sn$ (M^+ − Me): 303.0407; found: 303.0401. Anal. calcd. for $C_{12}H_{22}O_2Sn$: C 45.27, H 7.00; found: C 45.39, H 7.16.

*Methyl 2-(trimethylstannyl)-1-cycloheptenecarboxylate (**9**)*
This substance was prepared from the alkenyl trifluoromethanesulfonate **22** (2.52 g, 8.34 mmol). Flash chromatography of the crude product on silica gel (53 g, petroleum ether to 30:1 petroleum ether – Et_2O) afforded 2.17 g (82%) of **9** as a colourless oil that exhibited IR (neat): 1694, 1583, 1435, 1281, 1259, 1205, 1156, 1071, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.09 (s, 9H, $^2J_{Sn-H}$ = 53 Hz), 1.38–1.45 (m, 4H), 1.75–1.81 (m, 2H), 2.53–2.63 (m, 4H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −6.8, 24.8, 26.0, 28.3, 32.6, 34.8, 51.9, 143.5, 169.7, 170.0. Exact Mass calcd. for $C_{11}H_{19}O_2Sn$ (M^+ − Me): 303.0407; found: 303.0407. Anal. calcd. for $C_{12}H_{22}O_2Sn$: C 45.27, H 7.00; found: C 45.35, H 6.97.

General procedure 3. Copper(I) chloride–mediated coupling reactions
To a stirred solution of the alkenyltrialkylstannane in DMF (~0.5 mL per mmol of substrate) at room temperature was added solid copper(I) chloride (2.5 equiv.) and the resulting brown solution was stirred for 1 h. Aqueous NH_4Cl–NH_4OH (pH 8, the same volume as DMF) was added and the mixture was stirred, open to the atmosphere, until the aqueous phase turned deep blue. The phases were separated and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed (water, brine), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography on silica gel.

The following compounds were prepared via this general procedure.

*Diethyl (Z,Z)-3,4-bis(2-methylpropyl)muconate (**10**)*
This material was synthesized from ethyl (*Z*)-5-methyl-3-trimethylstannyl-2-hexenoate (**1**) (250 mg, 0.78 mmol). Flash chromatography of the crude oil on silica gel (10 g, 4:1 pentane–Et_2O) afforded 117 mg (96%) of **10**, a colourless oil that displayed IR (neat): 1724, 1653, 1619, 1467, 1176, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.94 (br signal, 12H), 1.20 (t, 6H, J = 7 Hz), 1.87 (m, 2H, J = 7 Hz), 1.95–2.08 (br m, 2H), 2.22–2.35 (br m, 2H), 4.06 (q, 4H, J = 7 Hz), 5.63 (t, 2H, J = 1 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 14.2, 22.7, 25.5, 46.4, 59.7, 115.1, 159.9, 165.4. Exact Mass calcd. for $C_{18}H_{30}O_4$: 310.2144; found: 310.2148. Anal. calcd. for $C_{18}H_{30}O_4$: C 69.64, H 9.74; found: C 69.86, H 9.74.

*Dimethyl (Z,Z)-3,4-bis(3-chloropropyl)muconate (**11**)*
This compound was prepared from methyl (*Z*)-6-chloro-3-trimethylstannyl-2-hexenoate (**2**) (140 mg, 0.43 mmol). Flash chromatography of the crude product on silica gel (10 g, 4:1 pentane–Et_2O) afforded 63 mg (90%) of **11**, a colourless oil that showed IR (neat): 1724, 1621, 1435, 1176, 1040, 871, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.91–2.05 (br m, 4H), 2.33–2.52 (br m, 4H), 3.50–3.59 (br m, 4H), 3.60 (s, 6H), 5.69 (t, 2H, J = 1 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 29.7, 34.2,

44.2, 51.2, 114.9, 159.4, 165.6. Exact Mass calcd. for $C_{14}H_{20}{}^{35}Cl_2O_4$: 322.0739; found: 322.0731. Anal. calcd. for $C_{14}H_{20}Cl_2O_4$: C 52.03, H 6.24; found: C 52.20, H 6.24.

*Dimethyl (Z,Z)-3,4-bis(3-(*tert*-butyldimethylsiloxy)propyl)-muconate (**12**)*

Flash chromatography (2 g of silica gel, 9:1 to 3:2 pentane–Et_2O) of the crude oil obtained from methyl (*Z*)-6-(*tert*-butyldimethylsiloxy)-3-trimethylstannyl-2-hexenoate (**3**) (104 mg, 0.25 mmol) provided 55 mg (86%) of **12**, a colourless oil that exhibited IR (neat): 1732, 1655, 1621, 1473, 1436, 1256, 1105, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.01 (s, 12H), 0.85 (s, 18H), 1.65–1.80 (m, 4H), 2.21–2.46 (m, 4H), 3.51–3.70 (m, 4H), 3.60 (s, 6H), 5.68 (s, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: −5.3, 18.2, 25.9, 30.1, 33.8, 51.0, 62.3, 113.8, 161.9, 165.8. Exact Mass calcd. for $C_{26}H_{50}O_6Si_2$: 514.3146; found: 514.3146. Anal. calcd. for $C_{26}H_{50}O_6Si_2$: C 60.66, H 9.80; found: C 60.76, H 9.76.

*Diethyl (Z,Z)-3,4-diethylmuconate (**13**)*

Purification (flash chromatography, 10 g of silica gel, 4:1 pentane–Et_2O) of the crude product obtained from ethyl (*Z*)-3-tributylstannyl-2-pentenoate (**4**) (207 mg, 0.50 mmol) gave 74 mg (97%) of **13**, a colourless oil that displayed IR (neat): 1719, 1655, 1620, 1300, 1176, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.08 (t, 6H, *J* = 7 Hz), 1.18 (t, 6H, *J* = 7 Hz), 2.08–2.46 (br m, 4H), 4.04 (q, 4H, *J* = 7 Hz), 5.61 (t, 2H, *J* = 1 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 11.2, 14.1, 30.2, 59.7, 113.2, 163.5, 165.6. Exact Mass calcd. for $C_{14}H_{22}O_4$: 254.1518; found: 254.1512. Anal. calcd. for $C_{14}H_{22}O_4$: C 66.12, H 8.72; found: C 66.33, H 8.84.

*Dimethyl (E,E)-3,4-bis(cyclopropylmethyl)muconate (**14**)*

Note: The reaction time in this case was 2 h. Flash chromatography (10 g of silica gel, 4:1 pentane–Et_2O) of the crude product derived from methyl (*E*)-4-cyclopropyl-3-trimethylstannyl-2-butenoate (**5**) (250 mg, 0.83 mmol) afforded 106 mg (92%) of **14**, a colourless oil that showed IR (neat): 1719, 1629, 1340, 1173, 1020, 872 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.10–0.20 (m, 4H), 0.33–0.41 (m, 4H), 0.69–0.81 (m, 2H), 2.75 (d, 4H, *J* = 7 Hz), 3.66 (s, 6H), 5.85 (s, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 4.8, 10.0, 33.3, 51.2, 117.5, 161.2, 166.5. Exact Mass calcd. for $C_{16}H_{22}O_4$: 278.1518; found: 278.1519. Anal. calcd. for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 69.15, H 8.02.

*Dimethyl (E,E)-3,4-bis(3-chloropropyl)muconate (**15**)*

This compound was derived from methyl (*E*)-6-chloro-3-trimethylstannyl-2-hexenoate (**6**) (250 mg, 0.77 mmol). Flash chromatography (10 g of silica gel, 4:1 pentane–Et_2O) of the crude oil afforded 102 mg (82%) of **15**, a colourless, crystalline solid (mp 52–53° C) that exhibited IR (KBr): 1709, 1601, 1438, 1340, 1178, 869, 539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.79–1.89 (m, 4H), 2.85–2.93 (m, 4H), 3.52 (t, 4H, *J* = 6 Hz), 3.69 (s, 6H), 5.92 (s, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 26.5, 31.5, 44.5, 51.4, 119.3, 158.5, 166.1. Exact Mass calcd. for $C_{14}H_{20}{}^{35}Cl_2O_4$: 322.0739; found: 322.0739. Anal. calcd. for $C_{14}H_{20}Cl_2O_4$: C 52.03, H 6.24; found: C 52.02, H 6.40.

*Methyl 2-(2-methoxycarbonyl-1-cyclopenten-1-yl)-1-cyclopentenecarboxylate (**16**)*

This substance was prepared from methyl 2-(trimethylstannyl)-1-cyclopentenecarboxylate (**7**) (57 mg, 0.20 mmol). Flash chromatography of the crude product on silica gel (1 g, 9:1 to 3:2 pentane–Et_2O) afforded 25 mg (99%) of **16**, a colourless solid (mp 78–79°C) that displayed IR (KBr): 1718, 1667, 1604, 1439, 1257, 1050, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.94 (quintet, 4H, *J* = 8 Hz), 2.58–2.72 (m, 8H), 3.54 (s, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 22.5, 33.4, 38.1, 51.2, 128.4, 154.4, 165.4. Exact Mass calcd. for $C_{14}H_{18}O_4$: 250.1205; found: 250.1200. Anal. calcd. for $C_{14}H_{18}O_4$: C 67.17, H 7.25; found: C 67.46, H 7.45.

*Ethyl 2-(2-ethoxycarbonyl-1-cyclohexen-1-yl)-1-cyclohexenecarboxylate (**17**)*

Flash chromatography (2 g of silica gel, 9:1 to 3:2 pentane–Et_2O) of the crude product derived from ethyl 2-(trimethylstannyl)-1-cyclohexenecarboxylate (**8**) (100 mg, 0.315 mmol) gave 38 mg (80%) of **17**, a colourless oil that exhibited IR (neat): 1715, 1650, 1615, 1449, 1230, 1050, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.18 (t, 6H, *J* = 7 Hz), 1.64 (br signal, 8H), 2.16 (br signal, 4H), 2.29 (br signal, 4H), 4.05 (q, 4H, *J* = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 22.0, 22.2, 25.6, 31.0, 59.8, 122.0, 152.6, 167.7. Exact Mass calcd. for $C_{18}H_{26}O_4$: 306.1831; found: 306.1828. Anal. calcd. for $C_{18}H_{26}O_4$: C 70.55, H 8.56; found: C 70.32, H 8.47.

*Methyl 2-(2-methoxycarbonyl-1-cycloheptenyl-1-yl)-1-cycloheptenecarboxylate (**18**)*

This compound was derived from methyl 2-(trimethylstannyl)-1-cycloheptenecarboxylate (**9**) (68 mg, 0.21 mmol). Flash chromatography of the crude product on silica gel (5 g, 4:1 petroleum ether – Et_2O) provided 28 mg (86%) of **18** as a colourless oil that exhibited IR (neat): 1713, 1640, 1621, 1435, 1260, 1208, 1117, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.38–1.85 (m, 12H), 2.22–2.54 (m, 8H), 3.59 (s, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 25.7, 26.2, 29.8, 32.3, 35.2, 51.3, 128.4, 155.7, 169.8. Exact Mass calcd. for $C_{18}H_{26}O_4$: 306.1831; found: 306.1830. Anal. calcd. for $C_{18}H_{26}O_4$: C 70.55, H 8.56; found: C 70.62, H 8.67.

Methyl (*E,E*)-3,4-bis(3-chloropropyl)-6-hydroxy-2,4-hexadienoate (25) and (*E,E*)-3,4-bis(3-chloropropyl)-2,4-hexadiene-1,6-diol (26)

To a cold (−78°C), stirred solution of dimethyl (*E,E*)-3,4-bis(3-chloropropyl)muconate (**15**) (75 mg, 0.23 mmol) in dry Et_2O (2 mL) was added a 1.0 M solution of diisobutylaluminum hydride in hexanes (0.46 mL, 0.46 mmol). After 1 h, the solution was warmed to room temperature, saturated aqueous sodium potassium tartrate (2 mL) was added, and the resultant gelatinous emulsion was stirred for 2 h. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed (brine, 10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (5 g of silica gel, 1:1 pentane–Et_2O) of the crude oil afforded 18 mg (24%) of the starting material **15**, 17 mg (27%) of the diol **26**, and 28 mg (41%) of the partial reduction product **25**, a colourless crystalline solid (mp 87–88°C) that displayed IR (KBr): 3437, 1714, 1607, 1437, 1175, 1025, 875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.54 (br s, 1H), 1.74–1.83 (m, 2H), 1.83–1.92 (m, 2H), 2.42 (t, 2H, *J* = 8 Hz), 2.88–2.95 (m, 2H), 3.49 (t, 2H, *J* = 6 Hz), 3.56 (t, 2H, *J* = 7 Hz), 3.69 (s, 3H), 4.32 (d, 2H, *J* = 6 Hz), 5.86 (s, 1H), 5.94 (t, 1H, *J* = 6 Hz); ^{13}C NMR (50.3 MHz,

$CDCl_3$) δ: 25.1, 26.4, 31.1, 32.0, 44.3, 44.8, 51.2, 59.5, 116.9, 131.7, 140.7, 159.1, 166.8. Exact Mass calcd. for $C_{13}H_{20}{}^{35}Cl_2O_3$: 294.0790; found: 294.0781. Anal. calcd. for $C_{13}H_{20}Cl_2O_3$: C 52.89, H 6.83; found: C 53.14, H 7.00.

The diol **26**, a colourless crystalline solid (mp 92–93°C), showed IR (KBr): 3369, 1616, 1419, 1032, 844, 780, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.37 (br s, 2H), 1.75–1.84 (m, 4H), 2.39 (t, 4H, J = 8 Hz), 3.49 (t, 4H, J = 6 Hz), 4.28 (d, 4H, J = 7 Hz), 5.73 (t, 2H, J = 7 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 25.0, 31.3, 44.5, 59.4, 127.8, 141.2. Exact Mass calcd. for $C_{12}H_{20}{}^{35}Cl_2O_2$: 266.0841; found: 266.0839. Anal. calcd. for $C_{12}H_{20}Cl_2O_2$: C 53.94, H 7.54; found: C 53.63, H 7.43.

Oxidative coupling of 4: determination of the amount of Bu_3SnCl produced

Following general procedure 3, ethyl (*Z*)-3-tributylstannyl-2-pentenoate (**4**) (30 mg, 0.072 mmol) was treated with CuCl (18 mg, 2.5 equiv.) in DMF (0.5 mL). Flash chromatography (3 g of silica gel, Et_2O) of the resulting crude oil afforded 21 mg (0.90 equiv., 90%) of Bu_3SnCl. This material exhibited a ^1H NMR spectrum identical with that of an authentic sample and displayed in a low resolution mass spectrum a peak for the molecular ion at *m/e* = 326.

Oxidative coupling of 1: determination of the amount of copper metal produced

To a stirred solution of ethyl (*Z*)-5-methyl-3-trimethylstannyl-2-hexenoate (**1**) (244 mg, 0.76 mmol) in DMF (5 mL) at room temperature was added solid copper(I) chloride (189 mg, 2.5 equiv.) and the resulting brown solution was stirred for 1 h. Diethyl ether (3 mL) and saturated aqueous NH_4Cl (3 mL) were added and the resulting mixture was stirred, open to the atmosphere, for 10 min. The mixture was filtered through a medium-frit sintered glass funnel and the reaction flask and the collected material were washed successively with DMF (2 mL), hot distilled deionized water (20 mL), and diethyl ether (30 mL). The filtrate flask was replaced by a clean flask and the copper residue on the walls of the reaction flask was dissolved in 50% v/v aqueous HNO_3 (2 mL). This acidic solution was also used to dissolve the copper deposited on the funnel. The reaction flask and funnel were washed successively with 10% v/v aqueous HNO_3 (8 mL) and distilled, deionized water (15 mL). The collected acidic filtrate was neutralized with concentrated aqueous NH_4OH until a dark blue colour persisted, then the filtrate was reacidified to pH ~5 with a few drops of 50% v/v aqueous acetic acid. To the resulting solution was added solid urea (125 mg, 2.1 mmol), followed by a 50% w/w aqueous solution of KI (6 mL). The dark brown solution was immediately titrated with a 0.1073 M solution of $Na_2S_2O_3$ until the brown iodine colour had almost dissipated, then a freshly prepared 0.5% w/w aqueous solution of starch (1 mL) was added, and the titration was continued until the blue starch–iodine colour was discharged. The total volume of the $Na_2S_2O_3$ solution used in the titration was 6.52 mL. Thus, the amount of copper metal produced was determined to be 44.5 mg (0.92 equiv., 92% yield).

Acknowledgements

We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada and Merck Frosst Canada Inc. for financial support. An NSERC Postgraduate Scholarship (to E.J.M.) and an NSERC Postdoctoral Fellowship (to P.L.G.) are gratefully acknowledged.

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