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Copper(I) Chloride-Mediated Intramolecular Coupling of Vinyltrimethylstannane and Vinyl Halide Functions

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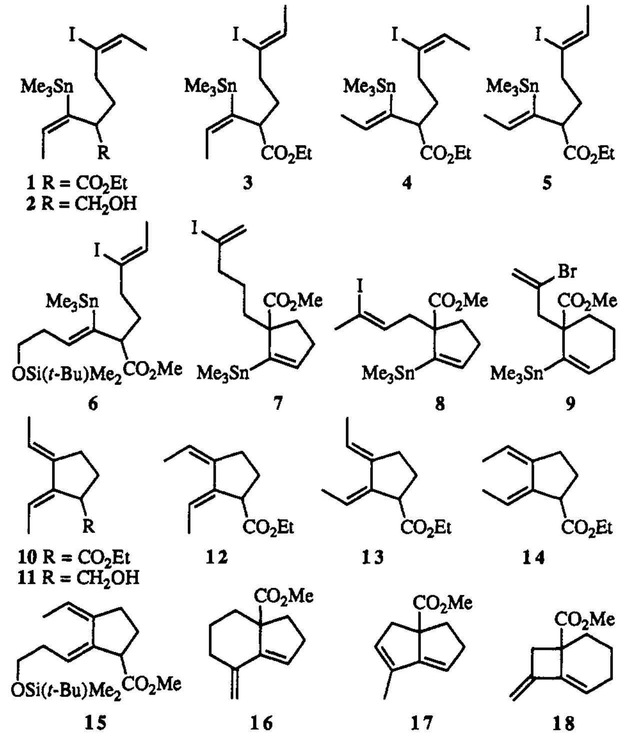
Summary: Treatment of substances possessing vinyltrimethylstannane and vinyl halide (I or Br) functions with copper(I) chloride in *N,N*-dimethylformamide (DMF) constitutes a new effective method for the stereospecific synthesis of cyclic conjugated dienes.

Due primarily to important studies by Stille and coworkers,[1] the *inter*molecular, palladium(0)-catalyzed coupling of vinyltrialkylstannanes with vinyl halides or triflates has become an excellent, well-known method for the synthesis of configurationally defined conjugated dienes. The *intra*molecular version of this coupling has also proven to be of notable use in organic synthesis.[2,3]

Recently, a number of publications[4] have reported that Pd(0)-catalyzed Stille-type couplings are facilitated by the use of copper(I) iodide as a cocatalyst. However, to our knowledge, the actual role that CuI plays in these processes has not been determined. We report herein the novel finding that intramolecular coupling of vinylstannane and vinyl halide (I, Br) functions can be achieved conveniently and efficiently by treatment of the requisite substrate with copper(I) chloride (~2–3 equiv) in DMF. No Pd(0) catalyst is necessary and, in fact, the CuCl-mediated reactions are generally faster and, in some instances, cleaner than the corresponding Pd(0)-catalyzed processes.

Alkylation (LDA, THF–HMPA, –78 to 0 °C; RI, –20 °C) of ethyl (*Z*)-3-(trimethylstannyl)-2-pentenoate[5] with each of the reagents (*E*)- and (*Z*)-3,5-diiodo-2-pentene[6,8] provided, stereoselectively,[2d] the functionalized esters **1** and **3** (86 and 89%, respectively) (see Chart I). Similarly, stereochemically defined[2d] alkylation of ethyl (*E*)-3-(trimethylstannyl)-2-pentenoate[5] with the same two diiodides and of methyl (*E*)-6-(*tert*-butyldimethylsiloxy)-3-(trimethylstannyl)-2-hexenoate[5] with the (*Z*)-diiodide afforded, in high yields (>85%), the substances **4**, **5**, and **6**. Reduction (*i*-Bu_2AlH, Et_2O) of **1** produced the alcohol **2** (74%).

Chart I



Representative monocyclic substrates employed in this study were also conveniently prepared via alkylation processes using conditions very similar to those outlined above. For example, treatment of the lithium enolate of methyl 2-(trimethylstannyl)-1-cyclopentenecarboxylate[9] with each of the alkylating agents 2,5-diiodo-1-pentene[10] and (*Z*)-1-bromo-3-iodo-2-butene[11] (THF–HMPA, –20 °C, 1 h, in each case) afforded the substituted cyclopentenecarboxylates **7** and **8**, respectively, in yields of 60–70%. Similarly, alkylation of methyl 2-(trimethylstannyl)-1-cyclohexenecarboxylate[9] with 2,3-dibromopropene (THF–HMPA, –78 °C, 5 min; –20 °C, 30 min) afforded the ester **9**, albeit in mediocre yield (43%).

Treatment of the iodo trimethylstannane **1** with 2.2 equiv of CuCl in warm DMF (62 °C) for 3 min provided, in 80% yield, the conjugated diene **10** (Chart I). The configuration of the diene system in the latter material was shown by nuclear Overhauser enhancement difference (NOED) experiments. Thus, in the ^1H NMR spectrum of **10**, irradiation at δ 3.60 (broad doublet, H_A) caused

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[1] Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986,** *108,* 3033. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986,** *25,* 508. Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987,** *109,* 813. Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990,** *55,* 3114. Stille, J. K.; Sweet, M. P. *Tetrahedron Lett.* **1989,** *30,* 3645. Stille, J. K.; Sweet, M. P. *Organometallics* **1990,** *9,* 3189. Scott, W. J.; Crisp, G. T.; Stille, J. K. *Org. Synth.* **1990,** *68,* 116.

[2] (a) Piers, E.; Friesen, R. W.; Keay, B. A. *Tetrahedron* **1991,** *47,* 4555. (b) Piers, E.; Friesen, R. W.; Rettig, S. J. *Can. J. Chem.* **1992,** *70,* 1385. (c) Piers, E.; Friesen, R. W. *Can. J. Chem.* **1992,** *70,* 1204. (d) Piers, E.; Lu, Y.-F. *J. Org. Chem.* **1988,** *53,* 926. (e) Piers, E.; Llinas-Brunet, M. *J. Org. Chem.* **1989,** *54,* 1483.

[3] Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987,** *109,* 3785.

[4] Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993,** *58,* 408. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992,** *33,* 919. Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990,** *55,* 5359. Marino, J. P.; Long, J. K. *J. Am. Chem. Soc.* **1988,** *110,* 7916.

[5] Piers, E.; Wong, T.; Ellis, K. A. *Can. J. Chem.* **1992,** *70,* 2058.

[6] These diiodides were readily prepared (>80% overall in each case) from the corresponding ethyl (*E*)- and (*Z*)-3-(trimethylstannyl)-3-pentenoates[7] via three-step reaction sequences involving reduction (*i*-Bu_2AlH, Et_2O), iododestannylation (I_2, CH_2Cl_2), and conversion (Ph_3PI_2, Et_3N, CH_2Cl_2) of the primary alcohol functions into iodides.

[7] Piers, E.; Gavai, A. V. *J. Org. Chem.* **1990,** *55,* 2374.

[8] All compounds reported herein exhibit spectra in full accord with assigned structures and gave satisfactory elemental (C, H) analyses and molecular mass determinations (high-resolution mass spectrometry).

[9] Piers, E.; Skerlj, R. T. *J. Chem. Soc., Chem. Commun.* **1986,** 626.

[10] This material was prepared by iododestannylation (I_2, CH_2Cl_2) of 5-iodo-2-(trimethylstannyl)-1-pentene.[2a]

[11] This material was prepared in two steps (*i*-Bu_2AlH, THF; Ph_3PBr_2, CH_2Cl_2) from ethyl (*Z*)-3-iodo-2-butenoate.[12]

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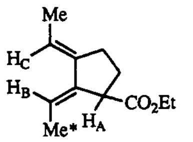
Table I. CuCl-Mediated Intramolecular Couplings[a]

entry	substrate	equiv CuCl	temp, °C	time, min	product	yield,[b] %
1	**1**	2.2	62	3	**10**	80
2	**2**	2.5	70	10	**11**	86
3	**3**	2.1	60	2	**12**	83
4	**4**	2.3	23	10	**13**[c]	94
5	**5**	3.0	60	2	**14**	89
6	**6**	3.0	64	2	**15**	98
7	**7**	2.5	90	5	**16**	75
8	**8**	2.1	60	5	**17**	93
9	**9**	2.4	60	5	**18**	78

[a] All reactions were performed employing dry, distilled *N,N*-dimethylformamide (DMF) as solvent. Structural formulas of the substrates **1–9** and the products **10–18** are shown in Chart I. [b] Yield of purified, distilled product. [c] This product contains ~3% of substance **10**.

enhancement of the doublet due to Me* (δ 1.73), while irradiation at δ 5.90 (broad quartet, H_B) increased the intensities of the resonances due to Me* and H_C (multiplet, δ 5.76).



10

The experiments involving CuCl-mediated ring closure of substrates **2–9** are summarized in Table I. The configuration of each of the dienes **11–15** (entries 2–6) was confirmed by NOED experiments similar to those outlined above for the diene **10**. Thus, it is evident that the cyclization reactions are highly stereospecific. In fact, of the cases that we have studied thus far the only deviation from complete stereospecificity was observed for substrate **4**. When **4** was treated with CuCl (3 equiv) in DMF at 60 °C for 2 min (conditions similar to those used for **1**, **3** and **5**), the dienes **13** and **10** were produced in a ratio of ~13:1. When the reaction was carried out at room temperature for 10 min, the ratio of **13**:**10** increased to ~30:1 (entry 4).[13]

As can be seen from the data summarized in Table I, most of the cyclizations were conveniently accomplished by use of 2–3 equiv of CuCl in DMF at 60–70 °C. In general, these reactions were fast (reaction times 2–10 min), clean, and efficient. In one case, a lower reaction temperature was found to be beneficial (entry 4, *vide supra*), while, in another, a superior result was obtained by use of a higher temperature. Ring closure of **7** at 60 °C (35 min) gave **16** (~74% of the product mixture, glc analysis; 65% isolated yield) accompanied by three side products, the major of which (~14% of the mixture) was an uncyclized material (**7**, Me_3Sn group replaced by H). However, at 90 °C the reaction was clean and produced **16** in 75% yield (entry 7).

The coupling process tolerates the presence of a number of functional groups, including alkoxycarbonyl, hydroxyl (entry 2), and Me_2(*t*-Bu)SiO (entry 6) functions. Furthermore, the utility of the method has been demonstrated by the efficient, stereocontrolled synthesis of novel, functionalized 1,2-bis(alkylidene)cyclopentane systems (compounds **10–15**) and by the preparation of bicyclic dienes via formation of 6-, 5-, and 4-membered rings (compounds **16–18**, respectively).

Although investigations into the synthetic and mechanistic aspects of the new coupling process are continuing, preliminary studies have disclosed the following insights into the process.

(1) Other sources of copper(I) (e.g., CuBr·Me_2S, CuI) are generally inferior (lower reaction rates and/or more side products) to CuCl.

(2) Use of at least 2 equiv of CuCl is ordinarily preferred. For example, treatment (DMF, 60 °C, 65 min) of **8** with 1 equiv of CuCl provided **17** (70%), the starting material **8** (15%), and an uncyclized material (**8**, Me_3Sn replaced by H, 8%). On the other hand, use of 1.5 equiv of CuCl (60 °C, 24 min) gave **17** in >90% yield, while employment of 2.1 equiv of the copper(I) salt (60°, 5 min) produced **17** in 93% yield (entry 8).

(3) Other solvents (e.g. DMSO, 10:1 DMF–H_2O) may be employed, but it appears that DMF is the preferred medium.

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Supplementary Material Available: Typical experimental procedures, involving the preparation of (*Z*)-3-(trimethylstannyl)-3-penten-1-ol, (*Z*)-3-iodo-3-penten-1-ol, (*Z*)-3,5-diiodo-2-pentene, and compounds **5**, **14**, **9**, and **18**; ^{1}H NMR spectral data for all new compounds reported (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[12] Marek, I.; Alexakis, A.; Normant, J.-F. *Tetrahedron Lett.* 1991, *32*, 5329.

[13] Interestingly, Pd(0)-catalyzed ring closures of **4** are not stereoselective either. These processes, under a variety of conditions (different Pd(0) catalysts, various solvents, additives, and reaction conditions) invariably produce mixtures of **13** and **10**. In fact, for the conversion of **4** into **13**, the CuCl-mediated method is notably superior to the Pd(0)-catalyzed protocols.