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CuCl-Mediated Intramolecular Oxidative Coupling of Aryl- and Alkenyltrimethylstannane Functions

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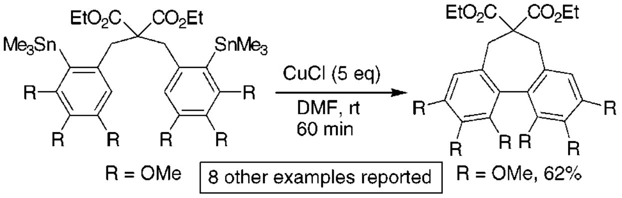
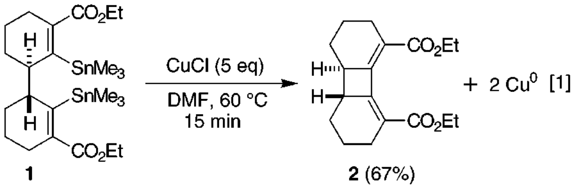
ABSTRACT



The syntheses of bis-trimethylstannanes 8, 10, 12–14, 16, 18, 21, and 22 are described. Treatment of these substances with ∼5 equiv of CuCl in DMF at rt for 30–60 min effects, in each case, oxidative coupling between the two sp^2 carbon centers bearing the Me_3Sn function to produce good-to-excellent yields of tricyclic products 23–31, respectively.

The *intramolecular* Stille coupling reaction, the first examples of which were reported in 1985,[1] has become a valuable method for the construction of functionalized carbocyclic diene systems.[2] A previous report[3a] from this laboratory disclosed that a substance containing two alkenyltrimethylstannane functions, when treated with copper(I) chloride in DMF, can be cyclized efficiently via an oxidative coupling process. This synthetic operation involves the connection of two alkenyl carbons via a single bond to form a diene and, thus, is a "relative" of the intramolecular Stille coupling. An example, involving the CuCl-mediated conversion of **1** into **2**, is shown in eq 1. In an intermolecular version of this coupling process, it has been determined[3b] that, for each carbon−carbon bond-forming event, 2 equiv of Cu(0) are produced. We report herein the intramolecular Cu(I)-mediated coupling of two aryltrimethylstannane functions and the "mixed" coupling of aryl- and alkenyltrimethylstannane moieties. This new methodology results in the concise syntheses of functionalized, structurally novel tricycles containing aromatic rings.



The starting materials utilized for these investigations were prepared via the protocols summarized in Scheme 1. Of the alkylating agents (Figure 1) employed in this work, bromide **6** has been reported[3] and bromides **3−5** were readily synthesized as follows. Treatment of benzyl alcohol with BuLi (2.4 equiv) in Et_2O containing 2.5 equiv of TMEDA,[4] followed by addition of Me_3SnCl (1.5 equiv), afforded (64%) 2-trimethylstannylbenzyl alcohol.[4] Reaction of the latter

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[1] (a) Piers, E.; Friesen, R. W.; Keay, B. A. *J. Chem. Soc., Chem. Commun.* **1985**, 809. (b) Piers, E.; Friesen, R. W.; Keay, B. A. *Tetrahedron* **1991**, 4555.

[2] (a) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235. (b) Farina, V.; Krishnamuthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

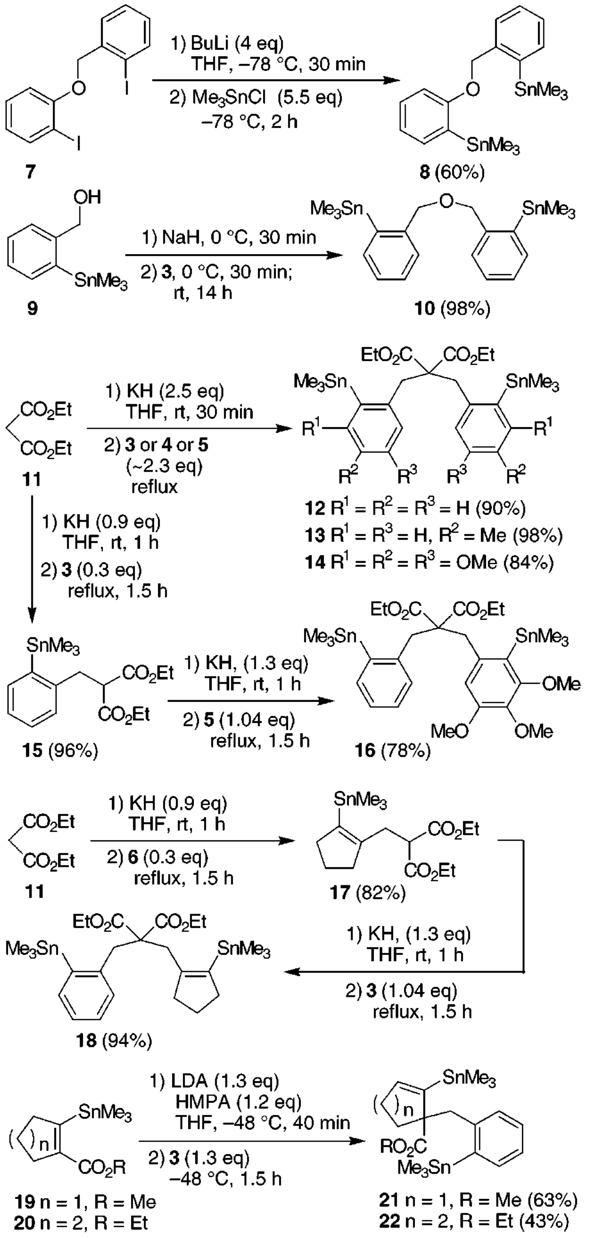
[3] (a) Piers, E.; Romero, M. A. *J. Am. Chem. Soc*. **1996**, *118*, 1215. (b) Piers, E.; McEachern, E. J.; Romero, M. A.; Gladstone, P. L. *Can. J. Chem.* **1997**, *75*, 694.

[4] Meyer, N.; Seebach, D. *Chem. Ber*. **1980**, *113*, 1304.

[5] (a) Wiley: G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964. (b) Schaefer, J. P.; Higgins, J. *J. Org. Chem.* **1967**, *32*, 1607.

10.1021/ol9903988 CCC: $19.00

Scheme 1



material with $Ph_3P{\cdot}Br_2$−imidazole[5] in CH_2Cl_2 provided bromide **3**[6] (88%). In a similar fashion, *p*-methylbenzyl alcohol and 3,4,5-trimethoxybenzyl alcohol were converted into the corresponding bromides **4** and **5** (overall yields 52% and 35%, respectively).

Diiodide **7** (Scheme 1) was prepared in 91% yield by sequential treatment of 2-iodophenol with NaH (0 °C, 30 min) and 2-iodobenzyl bromide[7] (0 °C, 2 h; rt, 13 h) in dry DMF. Reaction of **7** with BuLi as indicated in Scheme 1 (bis-lithium−iodine exchange), followed by addition of Me_3SnCl, furnished ether **8**. Symmetrical ether **10** was prepared via reaction of alkoxide of **9**[4] with bromide **3**. Alkylation of diethyl malonate (**11**) with 2 equiv of each of bromides **3**, **4**, and **5** provided distannanes **12**−**14**, respectively, in excellent yields. On the other hand, mono-alkylation of **11** with bromide **3** gave **15**, which, upon subjection to further alkylation with trimethoxybenzyl bromide **5**, was transformed into **16**. Similarly, sequential alkylation of **11** with **6** and **3** furnished **18** in 77% overall yield. Finally, alkylation of each of methyl 2-trimethylstannylcyclopent-1-enecarboxylate (**19**)[8] and ethyl 2-trimethylstannylcyclohex-1-enecarboxylate (**20**)[9] with bromide **3** produced the corresponding distannanes **21** and **22**.

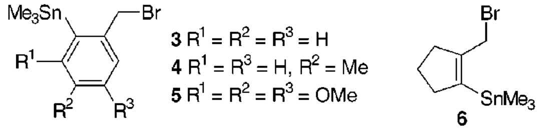


Figure 1.

The CuCl-mediated ring closures are summarized in Table 1. Treatment of a solution of distannane **8** in dry DMF with ~5 equiv of solid CuCl (99.995+%), followed by stirring of the resultant mixture for 30 min at room temperature (procedure A),[10] resulted in the clean formation of ether **23**[11] in excellent isolated yield (91%, Table 1, entry 1). Application of this procedure to the conversion of **10** into tricyclic ether **24**[12] (entry 2, closure of a seven-membered ring) was somewhat less efficient (75%). Analyses of the crude reaction mixtures by TLC suggested that, in addition to **24**, some

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

[7] This material was prepared by treatment of commercial 2-iodobenzyl alcohol with $Ph_3P{\cdot}Br_2$−imidazole[5] in CH_2Cl_2.

[8] Piers, E.; Lu, Y.-F. *J. Org. Chem.* **1988**, *53*, 926.

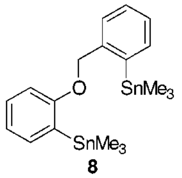
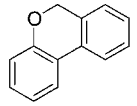
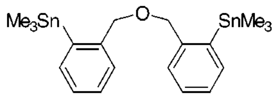
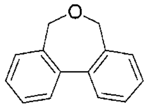
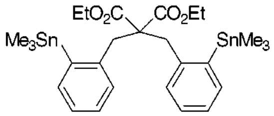
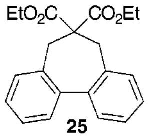
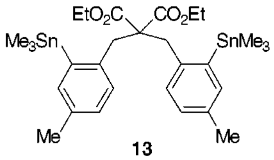
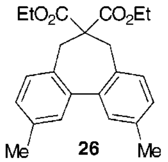
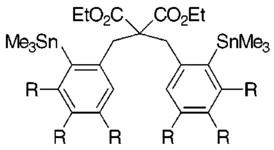
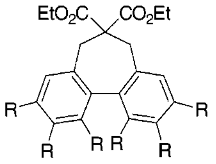
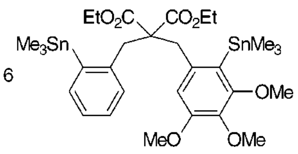
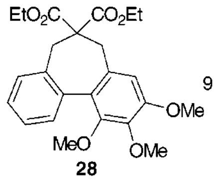
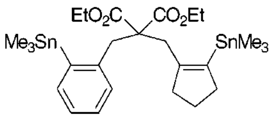
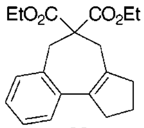
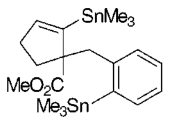
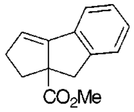
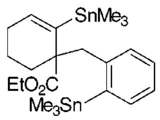
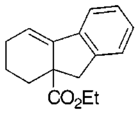
[9] Piers, E.; Tse, H. L. A. *Can J. Chem.* **1993**, *71*, 983.

[10] **Typical Procedure A** (conversion of **12** into **25**, Table 1, Entry 3): To a stirred solution of **12** (106 mg, 0.159 mmol) in dry DMF (6 mL, argon atmosphere) at room temperature was added CuCl (99.995+%, 80 mg, 0.81 mmol) in one portion. The mixture was stirred for 30 min. Saturated aqueous NH_4Cl-NH_3 (pH 8, 3 mL) was added, and the mixture was stirred, open to the atmosphere, until it became deep blue. The mixture was extracted three times with Et_2O, and the combined extracts were washed (brine), dried ($MgSO_4$), and concentrated. Flash chromatography (6 g of silica gel, 85:15 petroleum ether−Et_2O) of the crude material yielded 42 mg (78%) of **25**,[12] a colorless oil that displayed the following: IR (neat) 1729, 1446, 1256, 1207, 1107, 1056, 756 cm^{-1}; ^1H NMR (400 MHz) δ 1.28 (t, 6 H, $J = 7.0$ Hz), 2.91 (br s, 2 H), 3.19 (br s, 2 H), 4.22 (q, 4 H, $J = 7.0$ Hz), 7.25−7.40 (m, 8 H); ^{13}C NMR (50.3 MHz) δ 14.2, 36.9, 61.6, 64.9, 127.5, 127.6, 128.2, 130.1, 135.4, 140.6, 170.8. Exact mass calcd for $C_{21}H_{22}O_4$: 338.1518. Found: 338.1520. Anal. Calcd for $C_{21}H_{22}O_4$: C 74.54, H 6.55. Found: C 74.17, H 6.70. **Typical Procedure B** (conversion of **13** into **26**, Table 1, Entry 4): To a stirred mixture of CuCl (99.995+%, 62 mg, 0.63 mmol) in dry DMF (1.9 mL, argon atmosphere) at rt was added, via a syringe pump over a period of 30 min, a solution of **13** (86 mg, 0.12 mmol) in dry DMF (1.9 mL). The mixture was stirred for an additional 30 min. Saturated aqueous NH_4Cl-NH_3 (pH 8, 7 mL) was added, and the mixture was stirred, open to the atmosphere, until it became deep blue. The mixture was extracted three times with Et_2O, and the combined extracts were washed (brine), dried ($MgSO_4$), and concentrated. Flash chromatography (7 g of silica gel, 17:3 petroleum ether−Et_2O) of the crude material provided 43 mg (95%) of tricycle **26**, a colorless crystalline material that displayed the following: mp 88−89 °C; IR (KBr) 1729, 1266, 1197 cm^{-1}; ^1H NMR (400 MHz) δ 1.26 (t, 6 H, $J = 7.1$ Hz), 2.37 (s, 6 H), 2.82 (br s, 2 H), 3.14 (br s, 2 H), 4.20 (unresolved m, 4 H), 7.06 (m, 2 H), 7.16 (d, 2 H, $J = 7.6$ Hz), 7.19 (s, 2 H); ^{13}C NMR (50.3 MHz) δ 14.1, 21.2, 36.4, 61.4, 64.6, 128.0, 128.8, 129.9, 132.4, 137.0, 140.5, 170.9. Exact mass calcd for $C_{23}H_{26}O_4$: 366.1831. Found: 366.1831. Anal. Calcd for $C_{23}H_{26}O_4$: C 75.38, H 7.15. Found: C 75.41, H 7.24.

[11] Devlen, J. P. *Can J. Chem.* **1975**, *53*, 343.

[12] An alternative preparation of this material via an interesting new intramolecular coupling process was reported very recently: Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 1205.

Table 1. CuCl-Mediated Intramolecular Oxidative Coupling of Bis-trimethylstannanes

entry	starting material	product	yield (%)
1	 **8**	 **23**	91[a]
2	 **10**	 **24**	75[a] 91[b]
3	 **12**	 **25**	78[a]
4	 **13**	 **26**	95[b]
5	 **14** (R = OMe)	 **27** (R = OMe)	62[b]
6	 **16**	 **28**	92[b]
7	 **18**	 **29**	94[b]
8	 **21**	 **30**	97[a]
9	 **22**	 **31**	89[a]

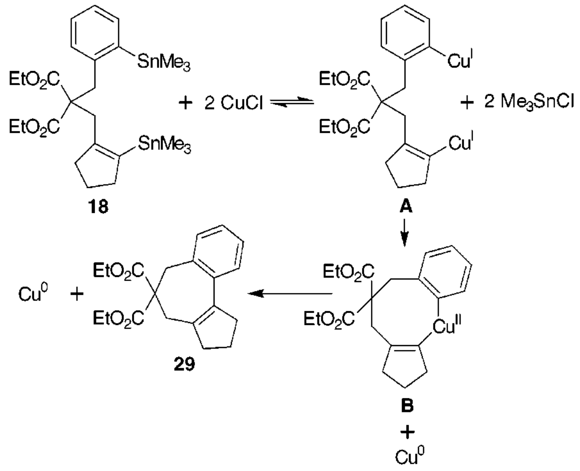
[a]Procedure A[10] was employed for this conversion.
[b]Procedure B[10] was employed for this conversion.

polymeric material was being produced. Fortunately, this situation could be ameliorated to a large degree by use of a modified protocol (procedure B)[10] in which a DMF solution of the substrate was added slowly to a stirred mixture of CuCl (∼5 equiv) in dry DMF. Under these conditions, the yield of the conversion **10** → **24** was 91% (entry 2).

The formations of seven-membered carbocycles via CuCl-mediated coupling of two aryltrimethylstannane functions are summarized in entries 3−6 of Table 1. Subjection of substrate **12** to procedure A[10] provided a satisfactory yield of **25**[12] (entry 3). Use of procedure B[10] for the conversion **13** → **26** (entry 4) proceeded in excellent yield. Although, not unexpectedly, ring closure of the highly substituted hexamethoxy compound **14** to provide the sterically congested substance **27** (entry 5) was less facile, the yield (62%) was still quite good. On the other hand, transformation of **16** into the unsymmetrical trimethoxy tricycle **28** (entry 6) was highly efficient.

The final three examples given in Table 1 involve "mixed" intramolecular coupling of aryl- and alkenyltrimethylstannane functions. Subjection of **18** to procedure B[10] (entry 7) afforded, again via closure of a seven-membered ring, the structurally novel tricycle **29** in high yield (94%). Finally, the formation of five-membered rings in the conversions **21** → **30** and **22** → **31**[13] (procedure A,[10] entries 8 and 9) are, not unexpectedly, very good reactions.

Scheme 2



Scheme 2, using the conversion **18** → **29** as an example, outlines a possible (undoubtedly simplistic) pathway via which the oxidative coupling processes could occur. It has been established[14] that, when treated with copper(I) salts (CuX) in polar solvents such as DMF, alkenyltrialkylstannanes undergo facile, reversible transmetalation to give R_3SnX and, presumably, an alkenylcopper(I) intermediate. In all probability, such a process would also be possible in the case of aryltrialkylstannanes. Consequently, it is reasonable to propose that the reaction of **18** with 2 equiv of CuCl would provide, reversibly,[14] 2 equiv of Me_3SnCl and a bis-copper(I) species (simplistically) represented by **A**. Disproportionation of **A** would produce Cu(0) and the copper(II) inter-

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(13) Mori, M.; Kaneta, N.; Shibaski, M. *J. Org. Chem.* **1991**, *56*, 3486.

(14) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

mediate **B**, which, upon reductive elimination, would afford a second equivalent of Cu(0) and the observed product **29**. The routine use of 5 equiv of CuCl would facilitate the overall process by "pushing" the initial equilibrium reaction toward **A**.

The examples presented in Table 1 demonstrate the efficacy and flexibility of the CuCl-induced intramolecular coupling of aryl- and alkenyltrimethylstannane functions to form five-, six-, and seven-membered rings. Especially impressive is the formation of the highly substituted, sterically congested hexamethoxy derivative **27**. The potential application of this methodology to natural and unnatural product synthesis is vast, and we are currently exploring a number of possibilities.

Acknowledgment. We thank NSERC of Canada and Merck Frosst Canada Inc. for financial support and NSERC of Canada for a Postgraduate Scholarship (to J.G.K.Y.) and for a Postdoctoral Fellowship (to P.L.G.).

Supporting Information Available: Spectroscopic and analytical data for compounds **27**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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