Cuprous Chloride Accelerated Stille Reactions. A General and Effective Coupling System for Sterically Congested Substrates and for Enantioselective Synthesis

Xiaojun Han, Brian M. Stoltz, and E. J. Corey*

Contribution from the Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, 02138

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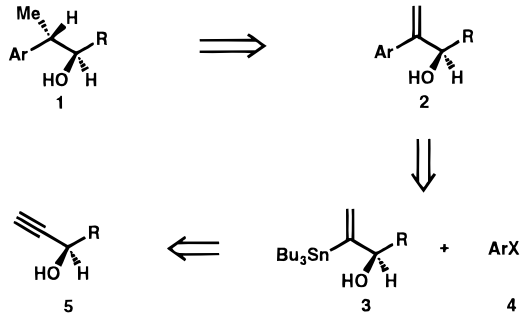
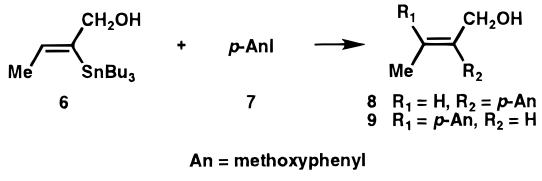
Abstract: A major limitation of Stille coupling reactions arises from steric screening, especially in the vinylstannane component. For example, with 1-substituted vinylstannanes and aryl perfluoroalkanesulfonates or halides negligible or low yields are generally observed, due to very slow reaction rates and competing *cine* substitution. This problem has been overcome in the present work through the discovery and application of cuprous chloride as an accelerant for coupling. Thus, using a protocol for coupling that involves the system $Pd(PPh_3)_4$/CuCl/LiCl under anaerobic conditions in dimethyl sulfoxide solution at 60 °C, a wide variety of Stille coupling reactions which otherwise fail can be effected in excellent yield (Table 1). The process has been applied to the enantioselective synthesis of the chiral 1-(arylethyl)alkylcarbinol **26**, a model for the natural product nicandrenone. The acceleration of Stille coupling by cuprous chloride can be explained by the intervention of a vinylstannane → vinylcopper(I) transmetalation step and a subsequent accelerated coupling of ArPdX with the vinylcopper(I) intermediate.

The (1-arylethyl)alkylcarbinol subunit **1**, which occurs in a number of novel natural product structures, can, in principle, be accessed from **5** via the intermediates **3**, **4**, and **2**. The conversion **2** → **1** finds precedence in J. M. Brown's hydroxyl-directed hydrogenation of allylic alcohols using homogeneous cationic Rh(I) catalysts.[1,2] However, although the Stille coupling **3** + **4** → **2** and the conversion of **5** to the vinylstannane **3** appear



to be straightforward, in reality there are no available procedures for effecting these transformations in good yield. With regard to the Stille coupling step, recent literature[3] confirms that the Stille coupling of **6** and **7**, for example, fails unless CuI is present, and even under optimal conditions (with CuI, Ph_3As, and $Pd_2(dba)_3$ in *N*-methylpyrrolidone) affords either a 2:1 mixture of isomeric coupling products **8** and **9** (<60 and <30%



yield, respectively) or **8** alone in 35% yield. Thus, despite extensive research in this area the goal of efficient Stille coupling with such sterically encumbered 1-substituted vinylstannanes has proved elusive and invariably either mixtures of direct Stille and *cine* type coupling products or only low yields of the former result.[4] Finally, the literature methods for synthesis of vinylstannanes **3** from acetylenes **5** either fail or afford mixtures of position-isomeric vinylstannanes which resist chromatographic separation.[5]

Development of a Generally Effective Procedure for Stille Coupling with 1-Substituted Vinylstannanes. The reaction of ArX (where X = Br, I, or OSO_2R_F) with $H_2C{=}C(R)SnBu_3$ (where R is a carbon group) under the originally described Stille conditions with Pd(0) catalysts generally affords low yields of mixtures of position-isomeric coupling products. In contrast,

(1) (a) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348. (b) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190. (c) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872.

(2) It should be noted that the stereochemistry of **1** corresponds to the anti-Felkin−Ahn product of addition of RMet to ArCH(Me)CHO. See: Reetz, M. T.; Stanchev, S.; Haning, H. *Tetrahedron* **1992**, *48*, 6813.

(3) Flohr, A. *Tetrahedron Lett.* **1998**, *39*, 5177.

(4) For background on Stille coupling, including Cu(I) mediated reactions, see: (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Org. React.* **1997**, *50*, 1. (b) Farina, V.; Roth, G. P. In *Advances in Metal-Organic Chemistry*; Liebskind, L. S., Ed.; JAI Press: Greenwich, CT, 1995; Vol. 5. (c) Mitchell, T. N. *Synthesis* **1992**, 803. (d) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905. (e) Liebeskind, L. S.; Fengl, R. *J. Org. Chem.* **1990**, *55*, 5359. (f) Marino, J. P.; Long, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 7916. (g) Levin, J. I. *Tetrahedron Lett.* **1993**, *34*, 6211.

(5) For example by hydrostannation using Rh-, Ni-, or Pd-catalyzed reactions or using Lipshutz's copper-mediated process. See: (a) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065. (b) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768. (c) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. (d) Kikukawa, K.; Umekawa, H.; Wada, F.; Matsuda, T. *Chem. Lett.* **1988**, 881. (e) Miyake, H.; Yamamura, K. *Chem. Lett.* **1989**, 981. (f) Zhang, H. X.; Guibé, F.; Balavoine, G. *Tetrahedron Lett.* **1988**, *29*, 619.

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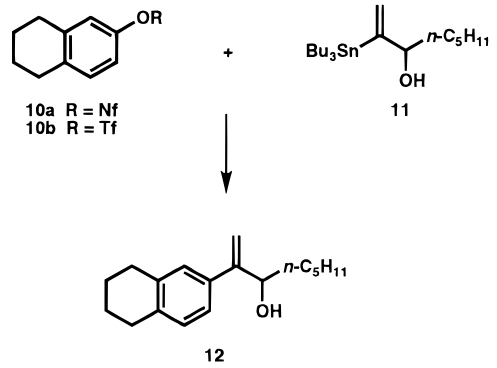
reactions of vinyltributylstannane itself with aryl substrates lead to good yields of Stille products.[6] Observations of this sort are common in the literature of Stille coupling and point to a major limitation on the scope of this process which is clearly associated with steric hindrance. As a result of such adverse steric effects, the rate of Stille coupling is decreased and an alternative reaction mode, *cine* substitution, sets in:

$$ArPdX + H_2C{=}C(R)SnBu_3 \rightarrow ArCH{=}CHR + Bu_3SnX$$

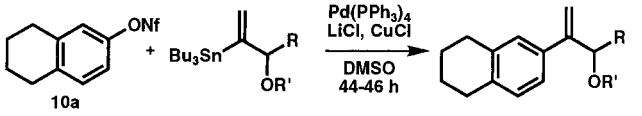
In the most recent literature the use of CuI or Cu(I) thiophene-2-carboxylate[7] has been recommended to alleviate these problems. We investigated extensively the reaction **10a** + **11** → **12** (Nf = *n*-$C_4F_9SO_2$) to explore the effect of reaction variables

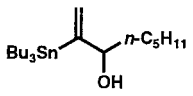
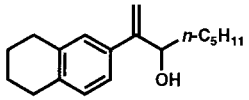
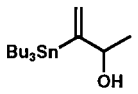
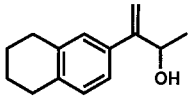
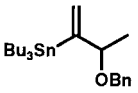
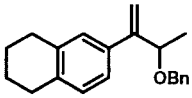
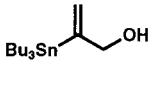
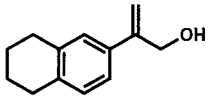
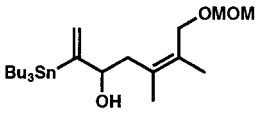
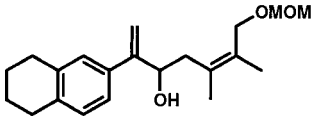


such as the use of Cu(I) promoters on the yield of Stille coupling product and the suppression of *cine* substitution. It was disappointing to observe that with CuI as promoter (even in large excess) the yield of Stille product **12** was very low, despite many variations in reaction conditions. The best yield of **12** (38%) from **10a** and **11** was obtained using 0.75 equiv of CuI, 10 mol % of $Pd(Ph_3P)_4$, and 6 equiv of LiCl in *N*,*N*-dimethylacetamide (DMA) at 60 °C for 40 h with rigorous exclusion of oxygen (*mandatory*, otherwise considerably lower yields of **12** are obtained). Under these optimum conditions, detectable but minor amounts of the *cine* substitution product are still formed. Use of Cu(I) thiophene-2-carboxylate[7] under the above conditions offered no advantage over CuI. At this point, we discovered that the inclusion of 0.3 equiv of *N*-methylmorpholine-*N*-oxide (NMO) in the CuI/Pd(0)-promoted Stille coupling in DMA at 60 °C resulted in a faster rate of reaction and a 58% yield of **12** after 22 h. Furthermore, none of the *cine* products could be detected in the crude product by ^{1}H NMR analysis.

We speculated that the effectiveness of NMO in promoting the CuI-mediated Stille coupling might be the result of coordination to give a more highly electrophilic cationic Cu(I) species, e.g. NMO → $Cu^+ X^-$. Such a cationic form of Cu(I) might effect a faster and more efficient transmetalation of the hindered vinylstannane **11** to the corresponding vinyl Cu(I) species. This surmise led us to study the use of CuCl as promoter of the Stille coupling of **10a** and **11** to form **12** and to the discovery that CuCl is indeed a superior cocatalyst for this reaction.[8] We were quickly able to optimize this reaction with respect to the amount of CuCl (5 equiv) and the solvent (dimethyl sulfoxide, DMSO). Thus, the reaction of **10a** and **11** under argon with 10 mol % of $Pd(Ph_3P)_4$, 5 equiv of CuCl, and 6 equiv of LiCl (relative to PhX) in DMSO at 60 °C for 47 h afforded **12** in 88% yield with no trace of *cine* isomer. Yields of **12** in the CuCl/Pd(0)/LiCl-promoted process were slightly lower using DMA, DMF, or *N*-methylpyrrolidone as solvent and the reaction rates were somewhat slower.

Table 1. Cu(I)/Pd(0)/LiCl-Promoted Coupling Reactions at 60 °C



vinyltin	product	% yield (isolated)
 **11**	 **12**	88
 **13**	 **14**	94
 **15**	 **16**	91
 **17**	 **18**	87
 **19**	 **20**	92

The outstanding effectiveness of the CuCl/Pd(0)/LiCl Stille coupling procedure described above is quite general as indicated by the results obtained for the coupling of nonaflate **10a** with a variety of vinylstannanes, as summarized in Table 1.[9a] Although most of our experiments were carried out using nonaflate **10a**,[9b] equally good yields of coupling products and similar reaction rates were observed with the corresponding triflate; for example, the coupling product **12** was obtained from the triflate analogue **10b** and stannane **11** in 95% yield after a reaction time of 46 h. In addition, the coupling of aryl bromides or iodides with stannane **11** also afforded high yields of Stille products, for instance 90% yield from iodobenzene and **11** after 14 h and 91% from bromobenzene and **11** after 40 h. As expected, the coupling reactions occurred more rapidly with aryl

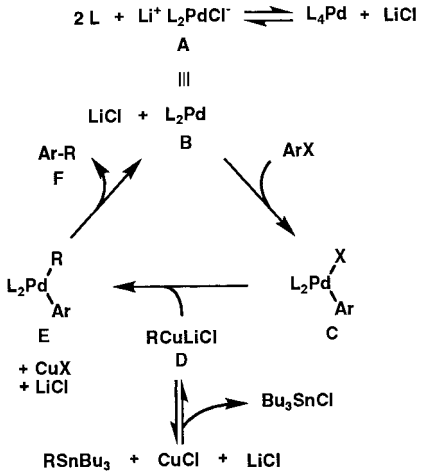
(6) (a) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771. (b) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc*. **1987**, *109*, 5478.

(7) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc*. **1996**, *118*, 2748.

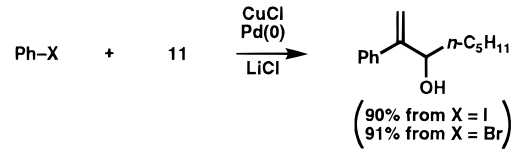
(8) Greater electrophilicity of CuCl relative to CuI was expected from the greater electronegativity of Cl relative to I and the greater covalency of CuI relative to CuCl.

(9) (a) It is clear that added lithium chloride plays a beneficial role in this CuCl/Pd(0)-promoted coupling reaction, since considerably lower yields are obtained in its absence. One reason for the positive effect of LiCl is suppression of homocoupling of the vinyl copper intermediate to form a substituted 1,3-butadiene in coupling reactions of aryl perfluoroalkanesulfonates, bromides, and iodides. (b) The nonaflate **10a**, which is easily prepared by reaction of commercially available perfluorobutanesulfonyl fluoride and triethylamine with the phenol in CH_2Cl_2 solution, is similar in reactivity to the triflate **10b**, but is less prone to O−SO_2 cleavage processes which form the corresponding phenol.

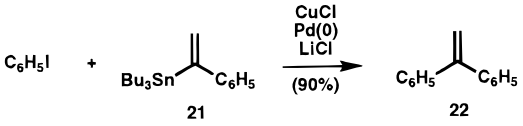
Scheme 1. Catalytic Cycle for CuCl/Pd(0)/LiCl-Promoted Stille Coupling



iodides than with bromides or perfluoroalkanesulfonates, and with comparable rates for ArBr and $ArOSO_2R_F$.



We also evaluated our coupling procedure for the case of iodobenzene and 1-phenylvinyltributylstannane (**21**) since these

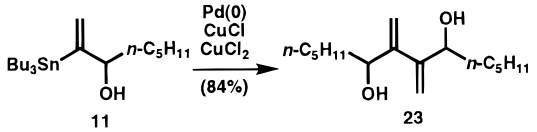


reactants have recently been reported[10] to afford none of the Stille product **22** and only a "low yield" of the *cine* product. It was found that the reaction proceeded smoothly (under the standard conditions) along the Stille pathway producing 1,1-diphenylethylene (90% isolated yield) after 16 h at 60 °C. None of the *cine* product was detected by ^{1}H NMR analysis.

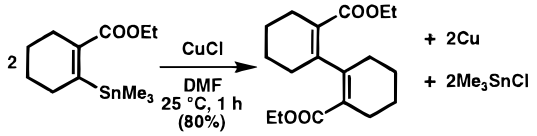
Another interesting test case was the reaction **6** + **7** → **8**, mentioned above as proceeding in unsatisfactory yield.[3] Under the standard CuCl/Pd(0)/LiCl conditions in DMSO, **8** was obtained either in 80% isolated yield in 24 h at 60 °C or in 79% yield in 112 h at 23 °C, free of any isomer from *cine* substitution. These conditions (60 °C) also cleanly converted *p*-methoxyphenyl triflate and nonaflate to **8** by coupling with the vinylstannane **6** (69% yield, 40 h for triflate; 65% yield, 48 h for nonaflate).

On the basis of all these results, including the data summarized in Table 1, it appears that the Stille coupling procedure outlined herein using the CuCl/Pd(0)/LiCl/DMSO system at 60 °C has broad applicability. The efficacy of this procedure can be rationalized in terms of current views on the mechanism of Stille coupling reactions,[11,12] and the catalytic cycle which is summarized in Scheme 1. The active Pd(0) species is a reactive Pd intermediate **A**[11] or its metenoid equivalent **B**,[12,13] which reacts with the aromatic substrate ArX to form intermediate **C** (where L represents Ph_3P and/or a nucleophilic solvent molecule). The function of CuCl is to convert the vinylstannane to a vinylcopper(I) species **D** (or a variant with respect to coordination/aggregation). Reaction of **D** with **C** forms the key Pd(II) species **E**, from which the coupling product **F** and active catalyst **A** and/or **B** are generated by reductive elimination. Scheme 1 thus depicts a variant on the original Stille coupling which is characterized by an additional transmetalation event that serves to generate a more reactive metalloid (RCu) than the initial organostannane ($RSnBu_3$). This greater reactivity accounts for the success of the CuCl/Pd(0)/LiCl-promoted Stille coupling with sterically hindered vinylstannanes. Our results clearly indicate the superiority of CuCl over previously utilized Cu(I) salts and the crucial role of Cu(I).[14]

The Bu_3Sn/CuCl transmetalation step was confirmed by the experiment in which the vinylstannane **11** was heated at 60 °C in DMSO with 10 mol % $Pd(Ph_3P)_4$, 5 equiv of CuCl, and 2 equiv of $CuCl_2$, which gave the homocoupling product **23** in



84% yield as a mixture of *meso* and *rac* diastereomers. These findings are also consistent with the observation of Piers and co-workers of CuCl-mediated homocoupling reactions such as **24** → **25** involving β-trimethylstannyl-α,β-unsaturated esters in DMF solution at room temperature.[15–17]



Synthesis of Vinylstannanes from Terminal Acetylenes. In principle, 1-trialkylstannylvinyl carbinols **3** can be formed by reaction of 1-substituted 2-propyn-1-ols **5** with tributylstannane under transition metal catalysis using, for example, Pd-, Ni-, or Rh-based reagents.[5b–f] In our experience, however, such processes invariably lead to formation of mixtures of **3**, the 2-trialkylstannyl position isomer, and simple vinyl carbinols (from reduction of HC≡CR to H_2C=CHR). In addition, the reaction of tri-*n*-butylstannylcuprate reagents with **5** was also

(10) Chen, S.-H. *Tetrahedron Lett*. **1997**, *38*, 4741.

(11) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc*. **1993**, *115*, 9531.

(12) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc*. **1995**, *117*, 11598.

(13) We use the term "metenoid" as a metal-centered reactive intermediate that is capable of the same types of reaction (σ bond insertion and π addition) as carbenoids.

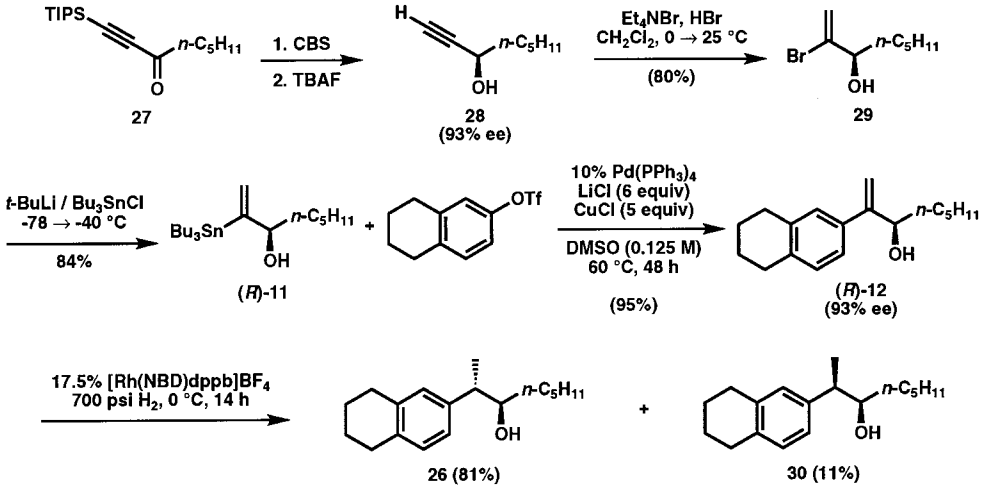
(14) The following evidence indicates that $CuCl_2$ is not the effective species: (1) the addition of a large excess of finely powdered copper metal (surface activated by washing with aqueous disodium EDTA and CH_3OH and drying in vacuo) to the CuCl/Pd(0)/LiCl-promoted reaction in DMSO has no adverse effect; (2) $CuCl_2$ is not an effective replacement for CuCl, and is actually detrimental.

(15) (a) Piers, E.; McEachern, E. J.; Romero, M. A. *Tetrahedron Lett.* **1996**, *37*, 1173. (b) Piers, E.; McEachern, E. J.; Romero, M. A.; Gladstone, P. L. *Can. J. Chem*. **1997**, *75*, 694. (c) Piers, E.; Gladstone, P. L.; Yee, J. G. K.; McEachern, E. J. *Tetrahedron* **1998**, *54*, 10609.

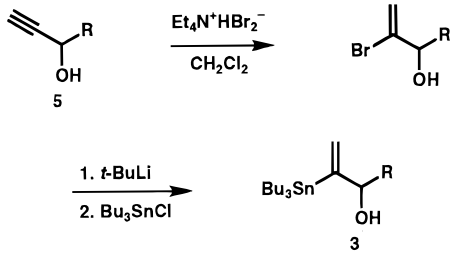
(16) Pd(II)-promoted homocoupling reactions of vinylstannanes have also been reported; see: (a) Alcaraz, L.; Taylor, R. J. K. *Synlett* **1997**, 791. (b) Kang, S.-K.; Namkoong, E.-Y.; Yamaguchi, T. *Synth. Commun.* **1997**, *27*, 641. (c) Borzelleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905.

(17) For Cu(II) transmetalation of alkenyl- and alkynylstannanes and coupling see: Ghosal, S.; Luke, G. P.; Kyler, K. S. *J. Org. Chem*. **1987**, *52*, 4296.

Scheme 2. Enantioselective Synthesis of **26**



unsuccessful.[5a] Consequently we have developed an alternative route for the conversion **5** → **3**, as follows. Treatment of



propargyl alcohols **5** with Et_4N^+ HBr_2^- in CH_2Cl_2 effects smooth Markovnikov addition of the elements of HBr to form the corresponding 1-substituted vinyl bromides,[18] which upon reaction with 3 equiv of *t*-BuLi followed by tri-*n*-butylstannyl chloride afforded the required vinylstannane **3** (R = *n*-C_5H_{11}, 67% or R = CH_3, 60% yield).

Synthesis of a Representative Chiral (1-Arylethyl)alkylcarbinol (26). The application of the methodology described herein to the enantioselective synthesis of **26** was achieved by the route that is outlined in Scheme 2. Oxazaborolidine-catalyzed enantioselective reduction (CBS) of the silylated octyn-3-one **27**[19,20] followed by desilylation produced (*R*)-1-octyn-3-ol (**28**) of 93% enantioexcess. The acetylenic alcohol **28** was converted via the vinyl bromide **29** to the vinylstannane (*R*)-**11**, as described above. Coupling of (*R*)-**11** with the triflate **10b** afforded (*R*)-**12** in excellent yield using our standard conditions for the CuCl/Pd(0)/LiCl-promoted Stille coupling. Finally, homogeneous catalytic hydrogenation of (*R*)-**12** in CH_2Cl_2 over Brown's Rh(I) catalyst,[1,21] bicyclo[2.2.1]hepta-2,5-diene 1,4-bis(diphenylphosphino)butane rhodium(I) tetrafluoroborate, gave chiral alcohol **26** in 81% yield and the diastereomer **30** (11%) after chromatography.[22]

Conclusion

A new procedure has been developed that utilizes CuCl/Pd(0)/LiCl for the coupling of aryl perfluoroalkanesulfonates, iodides, or bromides with 1-substituted vinylstannanes and provides excellent yields of Stille products, in contrast to previously described experimental methods. The use of dimethyl sulfoxide or *N*-methylpyrrolidone with rigorous exclusion of oxygen and moisture at 60 °C generally affords good results and, hence, is recommended for initial experiments. We believe that these conditions can be applied successfully to a wide range of Stille coupling reactions, and that it will be especially useful for those cases involving sterically hindered substrates. The enantioselective synthesis of **26** as outlined in Scheme 2 illustrates how important the new procedure can be in enantioselective synthesis. We are currently applying an approach similar to that summarized in Scheme 2 to a synthesis of the natural product nicandrenone (Nic-1),[23] a previously unsolved problem.

Experimental Section[24]

2-(Tri-*n*-butylstannyl)-1-octen-3-ol (11). To a cooled (−78 °C) solution of 2-bromo-1-octen-3-ol[18c] (1.24 g, 1.01 mL, 6.0 mmol) in Et_2O (20 mL) was added *t*-BuLi (1.7 M in pentane, 11.3 mL, 19.2 mmol) dropwise over 15 min. The reaction mixture was stirred at −78 °C for 30 min, then −40 °C for 1.5 h. Bu_3SnCl (2.93 mL, 10.8 mmol) was added over 6 min and the reaction mixture stirred for 1.5 h. The reaction mixture was quenched by the addition of a mixture of pH 7.0 buffer solution (10 mL) and water (10 mL) at −40 °C, and allowed to warm to room temperature. The mixture was extracted with Et_2O (3 ×

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(22) The relative stereochemistry of the major diastereomer **26** is assigned by analogy with the diastereoselective hydrogenations reported by Brown (refs 1a and 1b) and from ^{13}C NMR spectroscopic correlations. Specifically, in the case of **26** C(1) has a chemical shift of 18.2 ppm whereas the C(1) signal in **30** lies at 15.1 ppm (cf. refs 1c and 2).

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(24) Material and methods: Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen or an argon atmosphere, using freshly distilled solvents. LiCl was dried at 120 °C under high vacuum (0.4 mmHg) for 15 h and stored over $CaSO_4$. CuCl was recrystallized from concentrated HCl, and dried under high vacuum for 15 h. *N*,*N*-Dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), and *N*-methylpyrrolidone (NMP) were stirred over flame-dried $CaSO_4$ powder overnight and vacuum distilled with a bath temperature not higher than 80 °C. All other commercially obtained reagents were used as received. Reaction temperature was controlled by a Scientific Instruments temperature modulator model 2230. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25-mm). Silica gel (particle size 0.032−0.063 mm) was used for flash chromatography. ^1H and ^{13}C NMR chemical shifts are reported relative to Me_4Si (δ 0.0). High-resolution mass spectra were performed at The Harvard University Mass Spectrometry Center. Chiralcel HPLC columns were obtained from Daicel Chemical Industries, Ltd. Compounds **6**,[25] **10a**,[26a] **10b**,[26b] **17**,[5b,c] **21**,[5d] **28**,[19] and $Pd(PPh_3)_4$[27] were prepared as previously described (see also Supporting Information).

60 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to a residue that was chromatographed (1:30 EtOAc/hexanes containing 1% Et_3N as eluent) to give **11** (2.10 g, 84% yield) as a colorless liquid identical with that previously reported:[5c] (*R*)-**11** $[\alpha]^{23}_D$ −2.2 (*c* 1.0, $CHCl_3$).

2-(Tri-*n*-butylstannyl)-1-buten-3-ol (13). 1-Butyn-3-ol (0.16 mL, 2.0 mmol) was converted to 2-bromo-1-buten-3-ol (with complete position selectivity) by the method of Marshall[18c] and used as a crude oil in the following step. To a cooled (−78 °C) solution of crude 2-bromo-1-buten-3-ol in Et_2O (6 mL) was added *t*-BuLi (1.7 M in pentane, 4.0 mL, 6.8 mmol) dropwise over 15 min. The reaction mixture was stirred at −78 °C for 30 min, then −40 °C for 2.5 h. Bu_3SnCl (1.09 mL, 4.0 mmol) was added over 6 min and the reaction mixture stirred for 1.5 h. The reaction mixture was quenched by the addition of a mixture of pH 7.0 buffer solution (6 mL) and water (6 mL) at −40 °C, and allowed to warm to room temperature. The mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to a residue that was chromatographed (1:15 EtOAc/hexanes containing 1% Et_3N as eluent) to give **13** (0.43 g, 60% yield for two steps) as a colorless liquid identical with that previously reported.[5c]

2-(Tri-*n*-butylstannyl)-3-benzyloxyl-1-butene (15). A solution of alcohol **13** (1.05 g, 2.91 mmol) in DMF (25 mL) at 0 °C was treated portionwise with NaH (60% suspension, 0.58 g, 14.6 mmol). The resulting suspension was stirred at 0 °C for 2 min, the cooling bath was removed, and the reaction mixture was treated with BnBr (0.86 mL, 7.3 mmol) and Bu_4NI (1.18 g, 3.2 mmol). After the mixture was stirred at room temperature for 16 h, it was diluted with Et_2O (75 mL) and water (75 mL). The layers were separated and the aqueous layer further extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to a residue that was subjected to column chromatography (1:60 EtOAc/hexanes containing 1% Et_3N as eluent) to give **15** (1.15 g, 88% yield) as a colorless liquid: FTIR (film) 3042, 2928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.24 (m, 1H), 7.34−7.30 (m, 4H), 5.81 (dd, J = 2.4, 1.0 Hz, J_{SnH} = 64.8 Hz, 1H), 5.28 (dd, J = 2.4, 0.9 Hz, J_{SnH} = 30.8 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.34 (d, J = 12.1 Hz, 1H), 4.03 (q, J = 6.4 Hz, 1H), 1.56−1.43 (m, 6H), 1.35−1.24 (m 6H), 1.25 (d, J = 6.4 Hz, 3H), 0.97−0.86 (m, 6H), 0.88 (t, J = 7.3 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 139.0, 128.2, 127.5, 127.2, 125.1, 82.4, 69.9, 29.7, 27.4, 22.3, 13.7, 10.1; HRMS (EI) for $C_{19}H_{31}OSn$ [M − C_4H_9]$^+$, *m*/*z* calcd 395.1397, found 395.1396.

Stannane 19. 7-Methoxymethoxy-5,6-dimethylhept-5-en-1-yn-3-ol (410 mg, 2.07 mmol, see Supporting Information) was treated with $RhCl(PPh_3)_3$ (20 mg, 0.05 mmol) followed by Bu_3SnH (835 μL, 3.1 mmol) in a dropwise fashion over 10 min. The resulting dark solution was stirred for 20 h, diluted with Et_2O (10 mL), and filtered through SiO_2. The filtrate was evaporated and purified by flash chromatography (hexane → 10:1 hexane/EtOAc eluent) to provide stannane **19** (506 mg, 49% yield) as a slightly yellow oil: FTIR (film) 3478, 2928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (app t, J = 1.8 Hz, J_{SnH} = 66.4 Hz, 1H), 5.21 (app t, J = 1.6 Hz, J_{SnH} = 30.2 Hz, 1H), 4.63 (q, J = 6.6 Hz, 2H), 4.27 (dm, J = 10.4 Hz, 1H), 4.12 (d, J = 10.5 Hz, 1H), 3.97 (d, J = 10.5 Hz, 1H), 3.39 (s, 3H), 2.64 (d, J = 3.2 Hz, 1H), 2.49 (dd, J = 13.6, 10.4 Hz, 1H), 2.06 (d, J = 14.0 Hz, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.46−1.56 (m, 6H), 1.36−1.27 (m, 6H), 0.95−0.89 (m, 6H), 0.91 (t, J = 7.3 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 131.9, 128.4, 122.7, 95.5, 75.3, 67.9, 55.3, 43.4, 29.1, 27.4, 19.0, 18.0, 13.7, 10.2; HRMS (EI) for $C_{19}H_{37}O_3Sn$ [M − C_4H_9]$^+$, *m*/*z* calcd 433.1765, found 433.1766.

General Procedure for the Stille Coupling Reactions. A Schlenck tube (25 mL, ChemGlass-air free) was charged with LiCl (64 mg, 1.5 mmol) and flame dried under high vacuum. Upon cooling, $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and CuCl (124 mg, 1.25 mmol) were added, and the mixture was degassed (4×) under high vacuum with an Ar purge. DMSO (2.0 mL) was introduced with concomitant stirring, followed by the addition of an ArX (0.25 mmol) and a vinyltin compound (0.30 mmol). The resulting mixture was rigorously degassed (4 ×) by the freeze−thaw process (−78 → 25 °C, Ar). The reaction mixture was stirred at room temperature for 1 h, then heated to 60 °C for the necessary period of time (see Table 1 and text). Following completion of the coupling as monitored by TLC, the reaction mixture was cooled, diluted with Et_2O (30 mL), and washed with a mixture of brine (40 mL) and 5% aqueous NH_4OH (8 mL). The aqueous layer was further extracted with Et_2O (2 × 15 mL), and the combined organic layers were washed with water (2 × 40 mL) then brine (2 × 40 mL), dried over Na_2SO_4, and concentrated to a residue that was purified as stated below.

Alcohol (*R*)-12. Purification by flash chromatography (1:20 EtOAc/hexanes eluent) gave (*R*)-**12** (60 mg, 95% yield from **10b**) as a colorless oil of 93% ee (determined by HPLC): $[\alpha]^{23}_D$ −26.8 (*c* 1.2, $CHCl_3$); FTIR (film) 3390, 2930, 2858 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (dd, J = 7.9, 1.8 Hz, 1H), 7.09 (s, 1H), 7.03 (d, J = 7.9 Hz, 1H), 5.28 (s, 1H), 5.26 (s, 1H), 4.61−4.58 (m, 1H), 2.77 (br s, 4H), 1.82−1.78 (m, 4H), 1.68−1.57 (m, 2H), 1.53−1.42 (m, 2H), 1.39−1.20 (m, 4H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 137.2, 137.0, 136.7, 129.0, 127.5, 124.0, 111.5, 73.8, 36.1, 31.7, 29.5, 29.1, 25.4, 23.2 (2 C), 22.6, 14.0; HRMS (CI) for $[C_{18}H_{26}O + H]^+$, *m*/*z* calcd 259.2062, found 259.2056; HPLC (chiral) Chiralcel OD at 23 °C, λ = 254 nm (99:1 hexane/2-propanol eluent) retention times 12.24 (*S*) and 17.53 (*R*) min at 1 mL/min flow rate.

Alcohol 14. Purification by flash chromatography (1:15 EtOAc/hexanes eluent) gave **14** (47 mg, 94% yield from **10a**) as a colorless oil: FTIR (film) 3390, 2929, 2858, 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, J = 7.8, 1.8 Hz, 1H), 7.10 (s, 1H), 7.04 (d, J = 7.9 Hz, 1H), 5.30 (app t, J = 1.2 Hz, 1H), 5.25 (s, 1H), 4.81 (q, J = 6.4 Hz, 1H), 2.77 (br s, 4H), 1.83−1.78 (m, 4H), 1.69 (s, 1H), 1.34 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 137.0, 136.8, 129.1 (2 C), 127.4, 123.9, 110.6, 69.4, 29.5, 29.1, 23.2 (2 C), 22.6; HRMS (EI) for $[C_{14}H_{18}O]^+$, *m*/*z* calcd 202.1358, found 202.1353.

Ether 16. Purification by flash chromatography (1:60 EtOAc/hexanes eluent) gave **16** (66 mg, 91% yield from **10a**) as a colorless oil: FTIR (film) 3030, 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.34 (m, 4H), 7.31−7.29 (m, 1H), 7.19 (dd, J = 7.9, 1.9 Hz, 1H), 7.16 (s, 1H), 7.03 (d, J = 7.9 Hz, 1H), 5.39 (d, J = 1.6 Hz, 1H), 5.32 (dd, J = 1.4, 0.9 Hz, 1H), 4.70 (d, J = 11.9 Hz, 1H), 4.45 (d, J = 11.8 Hz, 1H), 4.39 (qd, J = 6.5, 0.6 Hz, 1H), 2.78 (app t, J = 6.4 Hz, 4H), 1.82−1.79 (m, 4H), 1.34 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 138.9, 137.0, 136.7, 129.1, 128.4 (2 C), 127.8, 127.5, 127.5, 124.1, 113.2, 77.6, 70.2, 29.5, 29.2, 23.2 (2 C), 21.7; HRMS (CI) for $[C_{21}H_{24}O + NH_4]^+$, *m*/*z* calcd 310.2171, found 310.2159.

Alcohol 18. Purification by flash chromatography (1:9 EtOAc/hexanes eluent) gave **18** (41 mg, 87% yield from **10a**) as a colorless oil: FTIR (film) 3346, 3017, 2928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, J = 7.9, 1.8 Hz, 1H), 7.15 (s, 1H), 7.06 (d, J = 7.9 Hz, 1H), 5.42 (s, 1H), 5.29 (app q, J = 1.3 Hz, 1H), 4.53 (s, 2H), 2.78 (app d, J = 5.5 Hz, 4H), 1.82−1.79 (m, 4H), 1.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 137.2, 137.1, 129.3, 126.7 (2 C), 123.3, 111.7, 65.1, 29.5, 29.1, 23.2 (2 C); HRMS (EI) for $[C_{13}H_{16}O]^+$, *m*/*z* calcd 188.1201, found 188.1203.

Alcohol 20. Purification by flash chromatography (1:5 EtOAc/hexanes eluent) gave **20** (76 mg, 92% yield from **10a**) as a colorless oil: FTIR (film) 3459, 2928, 2882 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, J = 7.8, 1.9 Hz, 1H), 7.10 (s, 1H), 7.03 (d, J = 7.8 Hz, 1H), 5.38 (app t, J = 1.5 Hz, 1H), 5.26 (app t, J = 0.7 Hz, 1H), 4.70−4.66 (m, 1H), 4.63 (q, J = 6.7 Hz, 2H), 4.16 (d, J = 10.5 Hz, 1H), 3.84 (d, J = 10.5 Hz, 1H), 3.39 (s, 3H), 3.17 (d, J = 4.2 Hz, 1H), 2.77 (br s, 4H), 2.44 (dd, J = 13.9, 10.1 Hz, 1H), 2.18 (d, J = 13.9 Hz, 1H), 1.81−1.78 (m, 4H), 1.78 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 137.4, 137.0, 136.5, 132.5, 129.1, 128.3, 127.4, 123.9, 111.1, 95.5, 70.7, 68.0, 55.4, 41.9, 29.5, 29.1, 23.2 (2 C), 18.7, 18.2; HRMS (CI) for $[C_{21}H_{30}O_3 + NH_4]^+$, *m*/*z* calcd 348.2539, found 348.2533.

2-Phenyloct-1-en-3-ol. Purification by flash chromatography (1:20 EtOAc/hexanes eluent) gave 2-phenyloct-1-en-3-ol (46 mg, 90% yield from PhI) as a colorless oil identical with that reported in the literature.[28]

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(*E*)-2-(4-Methoxyphenyl)but-2-en-1-ol (8). Purification by flash chromatography (1:4 EtOAc/hexanes eluent) gave (*E*)-2-(4-methoxyphenyl)but-2-en-1-ol (36 mg, 80% yield from **7**) as a colorless oil that was identical with that previously reported.[3]

1,1-Diphenylethylene (22). Purification by flash chromatography (hexanes containing 1% Et_3N as eluent) gave 1,1-diphenylethylene (41 mg, 90% yield) as a colorless liquid identical with that purchased from Aldrich.

Diene 23. A flame-dried Schlenk tube was charged with $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), CuCl (124 mg, 1.25 mmol), and $CuCl_2$ (67.2 mg, 0.50 mmol) and vacuum purged (4×) with Ar. DMSO (2 mL) was added to the mixture with concomitant stirring, followed by the addition of stannane **11** (104 μL, 0.25 mmol). The resulting mixture was vigorously degassed (4×) by the freeze−thaw process (−78 → 25 °C, Ar). The reaction mixture was stirred at room temperature for 10 min, then was heated at 60 °C for 2 h. The reaction mixture was cooled, diluted with Et_2O (30 mL), and washed with a mixture of brine (35 mL) and 5% aqueous NH_4OH (5 mL). The aqueous layers were back-extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with water (2 × 30 mL) and brine (2 × 30 mL), dried over Na_2SO_4, and concentrated to a residue that was chromatographed (1:5 EtOAc/hexanes eluent) to afford diene **23** (26.7 mg, 84% yield) as a 1:1 mixture of diastereomers: FTIR (film) 3319, 2932, 1027 $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$) δ 5.22 (t, J = 1.0 Hz, 1H), 5.18 (dd, J = 1.6, 1.0 Hz, 1H), 5.12 (d, J = 1.3 Hz, 1H), 5.05 (d, J = 1.7 Hz, 1H), 4.32 (dd, J = 7.7, 4.7 Hz, 1H), 4.25 (dd, J = 7.0, 6.0 Hz, 1H), 2.28 (br s, 2H), 1.66−1.24 (m, 16H), 0.94−0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 150.4, 114.5, 112.9, 74.2, 73.2, 36.0, 35.9, 31.72, 31.67, 25.6, 25.4, 22.6, 14.0; HRMS (CI) calcd for $[C_{16}H_{30}O_2 + NH_4]^+$, m/z 272.2590, found 272.2584.

Alcohols 26 and 30. A flame-dried 1 dram vial capped with a serum stopper was charged with $[Rh(NBD)dppb]BF_4$ (12.3 mg, 0.017 mmol) under an atmosphere of N_2 (glovebag). The catalyst was transferred as a solution in CH_2Cl_2 (0.75 mL) to a second vial containing azeotropically dried (PhH, 4 × 1 mL) alcohol **12** (25.6 mg, 0.099 mmol). The resulting reaction mixture was vigorously degassed (4×) by the freeze−thaw process (−196 → 25 °C, Ar) and transferred to a hydrogenation apparatus with the exclusion of air. After quick assembly of the bomb, the pressure was brought to 700 psi H_2, and the reaction mixture was stirred at 4 °C for 14 h. After the H_2 pressure was released, the solution was filtered through a pad of Celite. A small portion of this material (10%) was converted to the coresponding acetate (DMAP, Et_3N, Ac_2O, CH_2Cl_2) and the diastereoisomeric ratio was determined to be 88:12 (^1H NMR). The remainder of the material was concentrated to a residue that was purified by flash chromatography (1:15 EtOAc/hexanes eluent) to afford alcohols **26** (18.8 mg, 81% yield) with 93% ee (determined by HPLC analysis of the acetate) and **30** (2.4 mg, 11% yield) as colorless liquids: Alcohol **26**: $[\alpha]^{23}_D$ −10.0 (*c* 1.2, $CHCl_3$); FTIR (film) 3458, 3002, 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 7.8 Hz, 1H), 6.96 (dd, J = 7.8, 1.8 Hz, 1H), 6.93 (s, 1H), 3.61 (app td, J = 7.6, 2.8 Hz, 1H), 2.75 (d, J = 3.4 Hz, 4H), 2.66 (dq, J = 7.1, 7.0 Hz, 1H), 1.80−1.77 (m, 4H), 1.60−1.50 (m, 2H), 1.40−1.27 (m, 6H), 1.24 (d, J = 7.1 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 137.2, 135.4, 129.3, 128.8, 125.2, 76.0, 45.8, 34.5, 32.0, 29.5, 29.0, 25.4, 23.3, 23.2, 22.7, 18.2, 14.1; HRMS (EI) calcd for $[C_{18}H_{28}O]^+$ 260.2140, found 260.2127; HPLC (chiral) Chiralcel OJ at 23 °C, λ = 220 nm (99.75:0.25 hexane/2-propanol eluent) retention times 5.17 (2*S*, 3*R*) and 7.21 (2*R*, 3*S*) min at 1 mL/min flow rate. Alcohol **30**: $[\alpha]^{23}_D$ +12.4 (*c* 0.17, $CHCl_3$); FTIR (film) 3362, 3011, 2928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 7.8 Hz, 1H), 6.94 (dd, J = 7.8, 1.7 Hz, 1H), 6.91 (s, 1H), 3.66−3.63 (m, 1H), 2.76−2.69 (m, 5H), 1.82−1.78 (m, 4H), 1.46−1.24 (m, 11H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 137.1, 135.1, 129.2, 128.4, 124.9, 76.2, 45.0, 34.6, 31.8, 29.5, 29.0, 25.8, 23.3, 23.2, 22.7, 15.1, 14.0; HRMS (EI) calcd for $[C_{18}H_{28}O]^+$, m/z 260.2140, found 260.2130.

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Supporting Information Available: Experimental details for **6**, **10a**, **10b** and precursors to **19** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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