Stereoselective Cross-Coupling of Benzylic Bromides and Vinyl Stannanes

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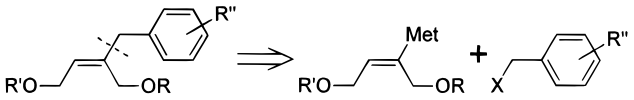
We found that benzyl-substituted butenediol derivatives (Scheme 1) bearing two differently protected hydroxy groups are useful intermediates in the synthesis of certain types of lignans. Stereoselective construction

Scheme 1

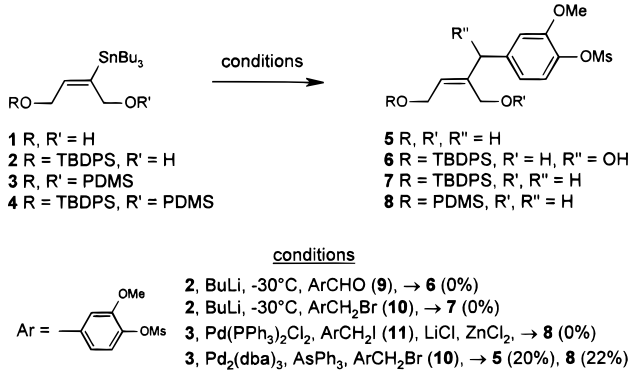


of the trisubstituted double bond can be achieved either in catalyzed or noncatalyzed reactions of suitable metal alkenyl derivatives. Highly active metals (e.g., Li,[1] Mg,[2] Al,[3] or Cu[4]) react with alkyl halides spontaneously, whereas other metals (e.g., Sn, B, Zr, and Zn) usually require Pd-complexes as catalysts to give the desired cross-coupling products, preferentially with vinyl or aryl halides as electrophiles.[5] Palladium-catalyzed reactions of metal alkenyls with alkyl or benzyl halides, however, are far less common, probably because good noncatalyzed reaction protocols exist. In a few cases, boron[6] or tin[7,8] alkenyls have been coupled employing an excess of the electrophile. In the case of tin alkenyls, only *unsubstituted* benzyl halides were employed.[7b] However, the use of various *aryl-substituted* benzyl halides as electrophile is of significant interest in organic synthesis.

Results and Discussion

2-(Tributylstannyl)but-2-en-1,4-diol (**1**) is readily available from the inexpensive butyne-1,4-diol by palladium-catalyzed *syn*-addition of tributyltin hydride.[9] Barrett et al.[10] reported the tin/lithium exchange of the mono TBDPS-protected derivative **2** with 2 equiv of BuLi and subsequent addition to an aliphatic aldehyde. Unfortunately, this reaction sequence failed to give any addition products either with 4-methanesulfonyl-3-methoxybenzaldehyde (**9**) or the corresponding benzyl bromide **10** (Scheme 2).[11]

Scheme 2



Stille coupling of vinyl stannanes and benzyl halides in the presence of palladium complexes and triphenylphosphine as ligand has been described.[8,12] However, using a protocol reported by Takle and Kocienski,[13] no cross-coupling product was observed either with isolated or with in situ formed 4-mesyl-3-methoxybenzyl iodide (**11**) (Scheme 2).

The reaction rate of the Stille coupling is often accelerated by using triphenylarsine instead of triphenylphosphine.[14] Recently, Crisp and Glink reported a procedure for the cross-coupling of vinyl stannanes and aryl triflates or halides in the presence of triphenylarsine.[7b] In addition, they have demonstrated high-yielding cross-couplings of vinyl stannanes with benzoyl chloride or benzyl bromide although an excess of the electrophile was employed.

In a first experiment, stoichiometric amounts of symmetrically protected stannane **3** and 4-mesyl-3-methoxybenzyl bromide (**10**), dissolved in THF, were added to a solution containing 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 40 mol % of triphenylarsine in THF. The reaction mixture was heated to reflux, and the solution soon turned black. After 6 h, the reaction mixture was poured into an aqueous KF solution and stirred for an additional 1 h. Standard workup and purification afforded the coupling products **5** and **8** in 20 and 22% yield.

When stannane **4**, bearing two different silyl protecting groups, was submitted to these reaction conditions, the C(1)−O desilylated coupling product **7** was obtained in

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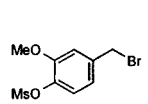
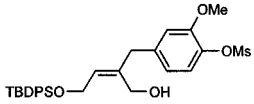
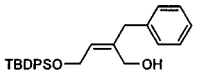
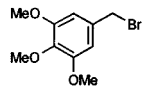
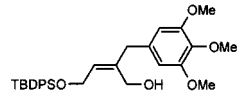
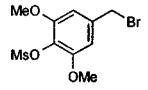
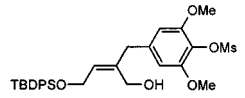
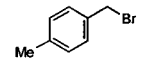
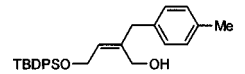
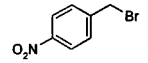
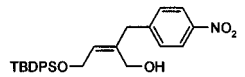
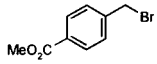
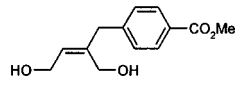
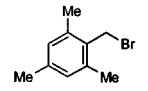
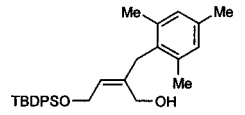
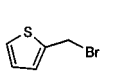
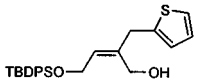
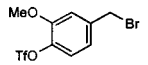
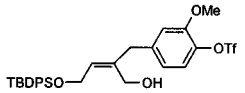
Table 1. Cross-Coupling of Stannane 1, 2 and 4 with Various Benzylic and Heteroaromatic Bromides

Entry	Bromide[a]	Stannane	Product	Yield[b,c,d]
1	 **10**	4	 **7**	44 (**A**)
2	**10**	2	**7**	68 (**A**) 76 (**B**)
3	**10**	1	**5**	72 (**A**)
4	 **12**	2	 **13**	66 (**A**)
5	 **14**	2	 **15**	57 (**A**)
6	 **16**	2	 **17**	55 (**A**)
7	 **18**	2	 **19**	53 (**A**)
8	 **20**	2	 **21**	59 (**A**)
9	 **22**	2	 **23**	84 (**A**)
10	 **24**	2	 **25**	70 (**B**)
11	 **26**	2	 **27**	53(**B**)
12	 **28**	2	 **29**	54(**B**)

[a] Bromides **12**, **18**, **20**, and **22** are commercially available; **14**, **24**, and **26** were prepared from commercially available alcohols using PBr_3 or CBr_4/PPh_3; **10**, **28**, and **16** were prepared in a three-step sequence from vanillin and syringaldehyde, respectively. [b] Yields of isolated product in %. [c] All reactions were carried out under nonoptimized conditions. [d] Workup method: (A) 10% aq KF solution; (B) brine.

44% yield (Table 1, entry 1). Unexpectedly, the mono TBDPS protected stannane **2** was an excellent substrate for the Stille coupling. Alkylation product **7** was prepared in 76% yield (entry 2). Even the dihydroxy butenyl stannane **1** was a suitable precursor for cross-coupling, giving product **5** in less than 5 h at reflux (72% isolated yield; entry 3). Furthermore, workup with brine instead of KF solution gave comparable results in some examples (see Table 1).

Scope and limitations of the cross-coupling reaction of butenyl stannane **2** were examined with a variety of benzylic bromides bearing sterically and electronically different substituents. Stille coupling of stannane **2** with benzyl bromide **12** provided the corresponding benzyl-butenol **13** in 66% yield (entry 4). Benzylic bromides **14**, **16**, and **18** reacted with stannane **2**, affording compounds **15**, **17**, and **19** in fair yields (entries 5−7). Deactivated (*p*-nitro and *p*-methoxycarbonyl) benzyl bromides **20** and **22** were also good substrates for the cross-coupling, producing compounds **21** and **23** in 59 and 84% yield (entries 8 and 9). In the latter case, alkene **23** was isolated as the diol. The sterically demanding benzyl bromide **24**, bearing two *ortho* methyl groups, and the sulfur-containing heterocycle **26**, reacted smoothly with stannane **2** affording the butene derivatives **25** and **27** in 70% and 53% yield, respectively (entries 10 and 11).

Finally, benzyl bromide **28** bearing a triflate group in *para* position was prepared in analogy to 4-mesyl-3-methoxybenzyl bromide (**10**) and reacted with vinyl stannane **2** using the standard conditions. Surprisingly, only benzylated butene derivative **29** was isolated. None of the aryl coupled regioisomer was detected even in traces (entry 12).

We have shown that palladium-catalyzed cross-coupling of stannanes can be carried out with a broad range of substituted benzylic bromides when triphenylarsine is used as the coligand. The reaction was even successful in the absence of hydroxy protecting groups. Under the conditions described, exclusively benzylation of a vinyl stannane was observed even if the electrophile has additionally a good leaving group at the aromatic nucleus, c.f. **28** (entry 12). Extension of the scope of this reaction to other classes of stannyl derivatives and electrophiles is currently under investigation.

Experimental Section

All reactions were performed in a vacuum-dried glassware under an inert (N_2) atmosphere. Solvents were distilled immediately before use. Unless otherwise stated, $CDCl_3$ was used as solvent for ^1H and ^{13}C NMR spectra. Infrared (IR) spectra were obtained from neat liquids, unless otherwise noted. The samples for ultraviolet (UV) spectra were dissolved in MeOH. Mass spectra were achieved by either electron impact (EI) or chemical ionization (CI) method. TLC was performed on silica gel plates.

General Procedure for the Cross-Coupling Reactions. $Pd_2(dba)_3{\cdot}CHCl_3$ (1 equiv) and $AsPh_3$ (8 equiv) were stirred in dry THF at room temp for 15 min by which time the solution turned yellow. The benzyl halide (25 equiv) and the vinyl stannane (25 equiv) were dissolved in THF and added to the solution of the catalyst. The reaction mixture was heated to reflux for 5 h and then cooled to room temperature. An aqueous 10% KF solution (25 mL/mmol substrate, workup method A) or brine (25 mL/mmol substrate, workup method B) was added and the aqueous phase extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$) and the solvents evaporated in vacuo. Silica gel chromatography of the residue with EtOAc/light petroleum mixtures gave the pure products.

Methanesulfonic Acid (*Z*)-4-(4-Hydroxy-2-(hydroxymethyl)but-2-enyl)-2-methoxyphenyl Ester (5). R_f value = 0.22 (EtOAc). Yield: 72%. ^1H NMR (CD_3OD): δ 3.17 (3 H, s), 3.27 (2 H, br s), 3.44 (2 H, s), 3.84 (3 H, s), 4.00 (2 H, s), 4.14 (2 H, d, J = 6.6 Hz), 5.47 (1 H, t, J = 6.6 Hz), 6.80 (1 H, d, J = 7.9 Hz), 6.97 (1 H, s), 7.13 (1 H, d, J = 7.9 Hz). ^{13}C NMR (CD_3OD): δ 38.35, 41.68, 56.40, 58.76, 59.41, 115.14, 122.53, 125.01, 138.27, 141.68, 141.80, 152.85. MS (EI): 302 (27), 187 (56). IR: 1600 cm^{-1}. UV_{max}: 276.5 nm.

Methanesulfonic Acid (*Z*)-4-[4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(hydroxymethyl)but-2-enyl]-2-methoxyphenyl Es-

ter (7). R_f value = 0.18 (light petroleum:EtOAc: 6:1). Yield: 76%. ^{1}H NMR: δ 1.05 (9 H, s), 1.73 (1 H, br s), 3.16 (3 H, s), 3.42 (2 H, s), 3.83 (3 H, s), 3.88 (2 H, s), 4.29 (2 H, d, J = 6.3 Hz), 5.57 (1 H, t, J = 6.3 Hz), 6.83−6.75 (3 H, m), 7.46−7.35 (6 H, m), 7.68−7.62 (4 H, m). ^{13}C NMR: δ 19.06, 26.71, 38.14, 41.25, 55.87, 59.88, 60.13, 113.49, 121.47, 124.25, 127.69, 128.73, 129.79, 133.31, 135.51, 136.69, 139.90, 140.26, 151.10. MS (CI): 541 (5), 267 (100), 187 (63).- IR: 1600 cm^{-1}. UV_{max}: 273.2 nm.

(*Z*)-2-Benzyl-4-[(*tert*-butyldiphenylsilyl)oxy]but-2-en-1-ol (13). R_f value = 0.25 (light petroleum:EtOAc = 4:1). Yield: 66%. ^{1}H NMR: δ 1.08 (9 H, s), 1.68 (1 H, br s), 3.45 (2 H, s), 3.89 (2 H, s), 4.32 (2 H, d, J = 6,4 Hz), 5.60 (1 H, t, J = 6.3 Hz), 7.46−7.10 (10 H, m), 7.72−7.70 (5 H, m). ^{13}C NMR: δ 19.06, 26.74, 41.57, 60.07, 60.26, 126.21, 127.66, 128.28, 128.36. 128.97, 129.71, 133.40, 135.57, 139.19, 140.87. MS (CI): 417 (2.4), 143 (100). IR: 1588 cm^{-1}. UV_{max}: 260.0 nm.

(*Z*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(3,4,5-trimethoxybenzyl)but-2-en-1-ol (15). R_f value = 0.18 (light petroleum: EtOAc = 3:1). Yield: 70%. ^{1}H NMR: δ 1.04 (9 H, s), 1.67 (1 H, br s), 3.38 (2 H, s), 3.81 (6 H, s), 3.83 (3 H, s), 3.92 (2 H, s), 4.29 (2 H, d, J = 6.4), 5.59 (1 H, t, J = 6.3 Hz), 6.41 (2 H, s), 7.35−7.45 (6 H, m), 7.66−7.69 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 19.06, 26.71, 41.92, 55.98, 60.19, 60.82, 105.79, 127.67, 128.29, 129.76, 133.36, 134.91, 135.53, 140.92, 153.10. MS (EI): 506 (1), 233 (100), 199 (82). IR: 1594 cm^{-1}. UV_{max}: 262.8 nm.

Methanesulfonic Acid (*Z*)-4-[4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(hydroxymethyl)but-2-enyl]-3,5-dimethoxyphenyl Ester (17). Yield: 55%. ^{1}H NMR: δ 1.05 (9 H, s), 1.85 (1 H, br s), 3.27 (3 H, s), 3.40 (2 H, s), 3.82 (6 H, s), 3.90 (2 H, s), 4.30 (2 H, d, J = 6.4 Hz), 5.60 (1 H, t, J = 6.4 Hz), 6.42 (2 H, s), 7.46−7.26 (6 H, m), 7.69−7.66 (4 H, m). ^{13}C NMR: δ 19.00, 26.64, 39.67, 41.76, 56.08, 59.68, 60.05, 105.57, 126.45, 127.62, 128.61, 129.72, 133.24, 135.43, 139.16, 140.18, 152.82. MS (CI): 571 (1.6), 315 (100). IR: 1604 cm^{-1}. UV_{max}: 244.5 nm.

***(Z)*-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(4-methylbenzyl)-but-2-en-1-ol (19).** Yield: 53%. ^{1}H NMR: δ 1.10 (9 H, s), 1.73 (1 H, br s), 2.37 (3 H, s), 3.42 (2 H, s), 3.91 (2 H, s), 4.33 (2 H, d, J = 6.3 Hz), 5.62 (1 H, t, J = 6.3 Hz), 7.09−7.15 (4 H, m), 7.39−7.50 (6 H, m), 7.73 (2 H, d, J = 6.3 Hz). ^{13}C NMR: δ 19.05, 20.99, 26.73, 41.19, 60.06, 60.28, 127.64, 128.08, 128.82, 129.05, 129.69, 133.41, 135.56, 136.06, 141.06. MS (CI): 431 (0.3), 157 (100). IR: 1588 cm^{-1}. UV_{max}: 266.4 nm.

4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(4-nitrobenzyl)but-2-en-1-ol (21). R_f value = 0.51 (light petroleum:EtOAc = 2:1). Yield: 59%. ^{1}H NMR: δ 1.04 (9 H, s), 1.66 (1 H, br s), 3.50 (2 H, s), 3.86 (2 H, s), 4.29 (2 H, d, J = 6.1 Hz), 5.53 (1 H, t, J = 6.0 Hz), 7.47−7.26 (8 H, m), 7.68−7.66 (4 H, m), 8.13 (2 H, d, J = 8.5 Hz). ^{13}C NMR: δ 19.04, 26.69, 40.96, 59.80, 60.09, 123.55, 127.68, 129.35, 129.79, 133.26, 135.53, 139.32, 146.52, 147.23. MS (CI): 462 (0.5), 257 (9). IR: 1604 cm^{-1}. UV_{max}: 272.5 nm.

Methyl (*Z*)-4-(4-Hydroxy-2-(hydroxymethyl)but-2-enyl)-benzoate (23). Yield: 84%. ^{1}H NMR: δ 3.46 (2 H, s), 3.55 (2 H, br s), 3.85 (3 H, s), 4.00 (2 H, s), 4.13 (2 H, d, J = 6.9 Hz), 5.54 (1 H, t, J = 6.9 Hz), 7.23 (2 H, d, J = 8.1 Hz), 7.90 (2 H, d, J = 8.1 Hz). ^{13}C NMR: δ 41.42, 52.02, 57.94, 59.27, 128.08, 128.48, 129.05, 129.64, 141.38, 144.62, 167,14. MS (CI): 219 (100), 149 (40). IR: 1712, 1610 cm^{-1}. UV_{max}: 246.8 nm.

(*Z*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(2,4,6-trimethylbenzyl)but-2-en-1-ol (25). R_f value = 0.3 (light petroleum: EtOAc = 6:1). Yield: 70%. ^{1}H NMR: δ 0.99 (9 H, s), 1.96 (1 H, br s), 2.18 (6 H, s), 2.28 (3 H, s), 3.40 (2 H, s), 4.04 (2 H, d, J = 3.3 Hz), 4.18 (2 H, d, J = 6.6 Hz), 5.01 (1 H, t, J = 6.6 Hz), 6.84 (2 H, s), 7.32−7.41 (6 H, m), 7.59−7.62 (4 H, m). ^{13}C NMR: δ 19.00, 19.69, 20.86, 26.66, 34.30, 60.11, 61.78, 125.12, 127.65, 127.68, 128.66, 128.76, 129.72, 133.34, 135.52, 137.00, 140.45. MS (CI): 459 (1.5), 203 (41), 133 (100). IR: 1614 cm^{-1}. UV_{max}: 327.0 nm.

(*Z*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(thiophen-2-ylmethyl)but-2-en-1-ol (27). Yield: 59%. ^{1}H NMR: δ 1.04 (9 H, s), 3.61 (2 H, s), 3.94 (2 H, s), 4.28 (2 H, d, J = 6.3 Hz), 5.64 (1 H, t, J = 6.3 Hz), 6.80 (1 H, d, J = 3.2), 6.90−6.93 (1 H, m), 7.14 (1 H, d, J = 5.1 Hz), 7.35−7.43 (6 H, m), 7.68 (4 H, d, J = 6.3 Hz). ^{13}C NMR: δ 19.10, 26.61, 26.96, 35.60, 59.99, 60.27, 123.99, 125.55, 126.89, 127.72, 128.50, 128.77, 133.45, 135.62, 140.24, 142.30. MS (CI): 423 (28), 167 (100). IR: 1588 cm^{-1}. UV_{max}: 271.6 nm.

Trifluoromethanesulfonic Acid (*Z*)-4-[4-(*tert*-Butyldiphenylsilyloxy)-2-(hydroxymethyl)but-2-enyl]-2-methoxyphenyl Ester (29). Yield: 54%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (9 H, s), 1.69 (1 H, br s), 3.38 (2 H, s), 3.81 (6 H, s), 3.83 (3 H, s), 3.93 (2 H, s), 4.30 (2 H, d, J = 6.4 Hz), 5.06 (1 H, t, J = 6.4 Hz), 6.42 (2 H, s), 7.43−7.35 m (6 H, arom), 7.69−7.66 (4 H, m). ^{13}C NMR: δ 19.05, 26.70, 41.16, 56.02, 60.11, 62.38, 113.72, 121.21, 122.07, 127.68, 127.72, 128.88, 129.79, 133.31, 135.53, 135.57, 140.01, 141.05, 151.10. MS (CI): 595 (5), 321 (100). IR: 1606 cm^{-1}. UV_{max}: 273.5 nm.

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Supporting Information Available: Copies of ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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