Effect of Ligands and Additives on the Palladium-Promoted Carbonylative Coupling of Vinyl Stannanes and Electron-Poor Enol Triflates

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The presence of a substituted α-carboalkoxy-α,α′-dienone substructural element of type **2** can be recognized within the skeleton of important cytotoxic natural products of the eleutheside family, such as sarcodictyin A (**1**).[1] Our interest in the development of a practical synthetic route to **1**[2] led us to examine a possible approach to these extensively conjugated systems, which could be incorporated in the synthetic strategy at the crucial macrocyclization step. Although α-carboalkoxy-α,α′-dienones have been studied in the past as precursors of substituted cyclopentenones via the Nazarov cyclization reaction,[3] not many synthetic methods are known for their preparation. These generally involve titanium catalyzed Knoevenagel-type condensations[4] or reaction of organometallics with α,β-unsaturated acyl chlorides,[3,5] both unpractical methods for highly functionalized systems and suffering from limitations in scope.
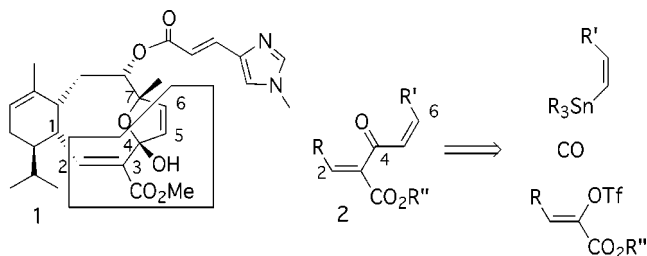
The presence of a doubly unsaturated ketone in compounds of type **2** suggests application of the Stille carbonylative coupling reaction,[6] which is a mild and efficient process generally requiring a moderate pressure of carbon monoxide (3–5 atm), tolerant of a wide range of functionalities, and well applicable to the synthesis of complex natural products.[7] The desired substructure **2**

might be synthesized with an unprecedented Stille carbonylative coupling reaction, i.e., by combining a vinyl stannane with an electron-poor (carboalkoxy-substituted) unsaturated halide or triflate in the presence of carbon monoxide.

The palladium-catalyzed cross coupling (non-carbonylative) reaction of electron-poor enol triflates or vinyl halides with vinyl stannanes has been recognized as a difficult case and shown to require special reaction conditions.[8] These generally include the use of soft ligands at palladium, such as triphenylarsine or trifurylphosphine (TFP), and the presence of cocatalytic copper-(I) iodide. Both these expedients, as well as the use of polar aprotic solvents [*N*-methylpyrrolidinone (NMP), dimethylformamide (DMF)], have been shown by Farina et al. to accelerate the rate-determining transmetalation step in the direct coupling,[9] but nothing is known on the effect of these modifications on the carbonylative version of the Stille reaction, where the species involved at the transmetalation level is an acyl– rather than an alkenyl–palladium complex.[10] Here we demonstrate that the use of a soft ligand ($AsPh_3$) and of CuI strongly affects the rate of the palladium-catalyzed carbonylative coupling reaction. In particular, acceleration of the carbon monoxide insertion over the transmetalation step is obtained, thus allowing to perform the carbonylative coupling at room temperature and atmospheric pressure of carbon monoxide even on electron-poor systems, without formation of the direct coupling products.

For this study, we selected enol triflate **6**, whose substitution pattern is similar to that of the desired substructure present in **1**. This can easily be accessed from cyclohexanecarboxyaldehyde **3** through Horner–Emmons reaction with a protected α-alkoxyphosphonate,[11] followed by desilylation and stereoselective triflation with 2-[(*N*,*N*-bistrifluoromethanesulfonyl)amino]pyridine under thermodynamic control (Scheme 1).[12] The resulting enol triflate **6** was coupled with both the commercially available tributyl vinyl stannane (**7a**) and the *cis*-substituted stannane **7b**, prepared in turn from (*R*)-cyclohexylidene glyceraldheyde **8** by applying Stork's methodology for the stereoselective synthesis of *Z* vinyl iodides[13] followed by tin–iodine exchange[14] (Scheme 1).

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Table 1. Palladium Catalyzed Coupling of Vinyl Triflate 6 and Tributylvinylstannane 7a in the Presence of Carbon Monoxide at Atmospheric Pressure

| entry	solvent, T, time	catalyst	additives	yield, % 10a	yield, % 11a + 12a
1	THF, 55 °C, 7 h	Pd(PPh₃)₄ (5%)	LiCl (3 equiv)	15	13[a] (73:27)[b]
2	NMP, RT, 5 h	Pd(PPh₃)₄ (5%)	LiCl (3 equiv)	39	60 (79:21)[b]
3	NMP, RT, 4 h	Pd(PPh₃)₄ (5%)	LiCl (3 equiv), CuI (10%)	17	79 (72:28)[b]
4	NMP, RT, 35 min	Pd₂dba₃ (5%); As(Ph)₃ (20%)	LiCl (3 equiv)	19	81 (82:17)[b]
5	NMP, RT, 6 min	Pd₂dba₃ (5%); As(Ph)₃ (20%)	LiCl (3 equiv), CuI (10%)	<1	74[c] (80:20)[b]
6	NMP, RT, 15 h	Pd(PPh₃)₄ (5%)	CuI (10%)	–	–[d]
7	NMP, RT, 17 h	Pd₂dba₃ (5%); As(Ph)₃ (20%)	CuI (10%)	–	–[d]

[a] Plus 71% recovered starting material. [b] Ratio determined by integration of the methyl signals in the ^{1}H NMR spectrum. [c] Plus 25% recovered starting material. [d] Pd black precipitates immediately after addition of substrates.

Scheme 1[a]
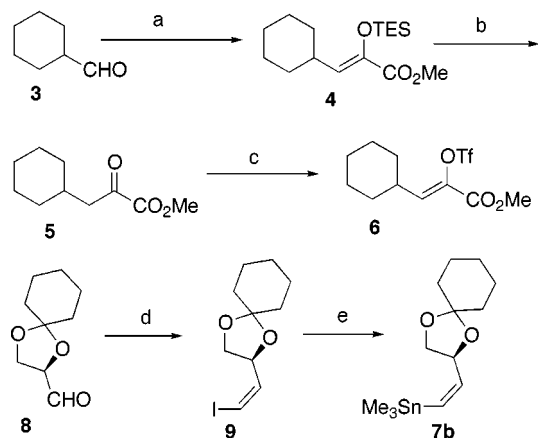
[a] Reagents and conditions: (a) (MeO)₂P(O)CH(OTES)CO₂Me, LiN(TMS)₂, then **3**, THF, 100%; (b) HF·Py, THF, 98%; (c) 2-[(*N,N*-bistrifluoromethanesulfonyl)amino]pyridine, NaN(TMS)₂, THF, 46% (+26% recovered starting material); (d) (Ph₃PCH₂)I, NaN-(TMS)₂, THF, 75%; (e) Me₆Sn₂, Pd₂dba₃, NMP, 78%.

While in THF the reaction between **6** and tributylvinylstannane **7a** suffers from a low conversion (Table 1, entry 1), reproducibly high yields are obtained using NMP (Table 1, entries 2−5). Using Pd(Ph₃)₄ as catalyst, coupling in the presence of carbon monoxide at room temperature and atmospheric pressure affords 39% of the direct coupling product **10a** together with the products resulting from carbonyl insertion **11a** and **12a** (Table 1, entry 2). A better outcome is obtained by adding 0.1 equiv of Cu(I) iodide to the reaction mixture, which brings the carbonylative coupling product to 79%, compared to 17% of direct coupling (Table 1, entry 3). The same result is obtained employing the soft ligand As(Ph)₃, and the rate of the reaction is notably increased (Table 1, entry 4). By performing the reaction in the presence of CuI with As(Ph)₃ as ligand and Pd₂dba₃ as a source of Pd(0) (Pd:L:CuI = 1:2:1), only the carbonylated products are obtained at atmospheric pressure and room temperature (Table 1, entry 5). Although the reaction is almost immediate, rapid precipitation of this unstable catalyst system prevents complete conversion. In all the cases examined, isomerization of the strongly electrophilic double bond (doubly conjugated) of **11a** is observed, and 17−28% of the isomeric product **12a** is obtained. The very similar ratio **11a/12a** (ca. 80:20) obtained under the various reaction conditions suggests that the mixture is thermodynamically controlled. In fact, in accord to what

reported by Brückner in ref 8a, the minor isomer **12a** is slowly converted to **11a** when exposed to a solution of LiCl in NMP. An attempt was made to limit the isomerization by eliminating LiCl, but in these cases the reaction is completely suppressed (Table 1, entries 6, 7).
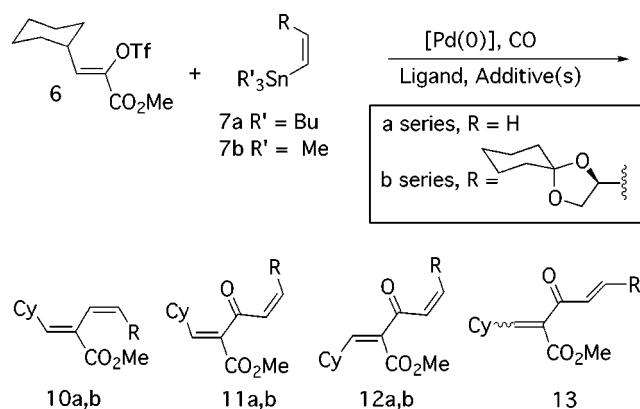
Since a reduced reactivity was to be expected for cis-substituted stannanes, the more stable catalytic system obtained combining Pd(PPh₃)₄ and CuI was first applied to the reaction of stannane **7b** with triflate **6**. In this case, heating is required for the reaction to occur, and only a modest yield of the carbonylated products **11b** and **12b** is obtained, accompanied by 18% of the direct coupling product **10b** and by a significant amount of products **13** where the Δ⁴,⁵ double bond has isomerized (Table 2, entry 1). Use of the softer ligand As(Ph)₃ in combination with CuI (Pd:L:CuI = 1:4:2) leads to a considerable improvement: the reaction can be conducted at room temperature, and only the desired carbonylated adducts are obtained in 80% yield (Table 2, entry 2), although with substantial isomerization (**11b:12b** = 50:50). Recourse to the less oxophilic ZnCl₂[8c] instead of LiCl failed to give any product (Table 2, entry 3), and the use of trifurylphosphine (reported to give more stereospecific reactions)[9a] instead of triphenylarsine (Table 2, entry 4) did not prevent the isomerization.

This drawback should not discourage application of this method to an intramolecular carbonylative coupling leading to the medium sized ring of **1**, where a marked control of the ring size over the position of the *E:Z* equilibrium is expected. In conclusion, the use of CuI and of the soft ligand AsPh₃ was demonstrated to promote the carbonylative coupling between substituted vinyl stannanes **7** and electron-poor enol triflates of type **6**. Acceleration of the carbon monoxide insertion over transmetalation is achieved, allowing only the carbonylated adducts to be obtained at room temperature and atmospheric pressure of carbon monoxide.

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Table 2. Palladium-Catalyzed Coupling of Vinyl Triflate 6 and Vinylstannane 7b in the Presence of Carbon Monoxide at Atmospheric Pressure

				yield, %		
entry	solvent, T, time	catalyst	additives	**10b**	**11b + 12b**	**13**
1	NMP, 60 °C, 3.5 h	Pd(PPh$_3$)$_4$ (7%)	LiCl (3 equiv), CuI (14%)	18	37 (35:65)^a	14
2	NMP, RT, 55 min	Pd$_2$dba$_3$ (5%); As(Ph)$_3$ (40%)	LiCl (3 equiv), CuI (20%)	−	80 (50:50)^a	−
3	NMP, RT	Pd$_2$dba$_3$ (5%); As(Ph)$_3$ (40%)	ZnCl$_2$ (3 equiv), CuI (20%)	−	−	−^{b}
4	NMP, RT, 5h	Pd$_2$dba$_3$ (5%); TFP (40%)	LiCl (3 equiv), CuI (20%)	−	(50:50)^c	

^{a} Ratio determined by integration of the methyl signals in the ^{1}H NMR spectrum. ^{b} Pd black precipitates immediately after addition of substrates. ^{c} Ratio based on crude ^{1}H NMR; yield not determined.

Experimental Section

General Procedure for the Palladium-Catalyzed Carbonylative Coupling of 6 and 7b. A flame-dried Schlenck tube is flushed with argon and charged with Pd$_2$dba$_3$ (0.05 equiv), AsPh$_3$ (0.40 equiv), and NMP. The mixture is stirred for 5 min, and then LiCl (3 equiv), CuI (0.20 equiv), and a solution of methyl (Z)-3-cyclohexyl-2-(trifluoromethanesulfonyloxy)propenoate (**6**) (1.0 equiv) and stannane (**7b**) (1.0 equiv) in NMP are added (final concentration: 0.05 M). The tube is sealed, purged, and filled with carbon monoxide. The mixture is stirred at room temperature until the reaction is judged complete by TLC analysis or the catalyst precipitates. The tube is then vented and the mixture diluted with Et$_2$O and washed with water, saturated NH$_4$Cl, and brine. The ethereal layer is dried (Na$_2$SO$_4$) and evaporated, and the residue is purified by flash chromatography, yielding the carbonylated products **11b** and **12b** (80%). The ratio **11b/12b** (50:50) was determined by integration of the methyl signals in the ^{1}H NMR spectrum. Analytically pure samples of **11b** and **12b** were obtained by chromatographic separation of the two isomers with DCM/Et$_2$O 99:1. **11b**: ^{1}H NMR (200 MHz, CDCl$_3$): δ 6.85 (1H, d, J = 10.59 Hz); 6.45−6.28 (2H, m); 5.42 (1H, m); 4.49 (1H, dd, J = 7.74 Hz); 3.77 (3H, s); 3.65 (1H, dd, J = 6.52 Hz, J = 7.74 Hz); 2.45−

2.30 (1H, m); 1.70−1.14 (20H,m). ^{13}C NMR (50 MHz, CDCl$_3$): δ 154.66; 148.94; 127.32; 73.95; 69.04; 52.07; 38.28; 36.10; 35.15; 31.76; 24.95; 24.94; 23.77; 23.72. IR (CDCl$_3$): ν(cm^{-1}) 2931; 2842; 1720; 1672; 1271; 1228. Anal. Calcd for C$_{21}$H$_{30}$O$_5$: C, 69.59; H, 8.34. Found: C, 69.71; H, 8.54. **12b**: ^{1}H NMR (200 MHz, CDCl$_3$): δ 6.68 (1H, d, J = 10.20 Hz); 6.50 (1H, d, J = 11.80 Hz); 6.39 (1H, dd, J = 6.00 Hz, 11.80 Hz); 5.32−5.23 (1H, m); 4.45 (1H, dd, J = 7.29 Hz, 8.24 Hz); 3.86 (3H, s); 3.63 (1H, dd, J = 6.71 Hz, 8.24 Hz); 2.45 (1H, m); 1.74−1.23 (20H, m). ^{13}C NMR (50 MHz, C$_6$D$_6$): δ 154.15; 150.34; 125.16; 75.30; 70.27; 52.25; 40.11; 37.54; 35.90; 32.53; 26.48; 26.25; 26.08; 25.04; 24.86. IR (CDCl$_3$): ν(cm^{-1}) 2930; 2852; 1724; 1667. Anal. Calcd for C$_{21}$H$_{30}$O$_5$: C, 69.59; H, 8.34. Found: C, 69.65; H, 8.58.

Supporting Information Available: Full characterization data for compounds **6**, **7b**, **10a,b**, **11a**, **12a**, and **13** and representative experimental procedures are available free of charge via the Internet at http://www.pubs.acs.org.