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Stille Coupling versus Cine Substitution. Electronic Effects also Influence Coupling Sterically Hindered Stannanes

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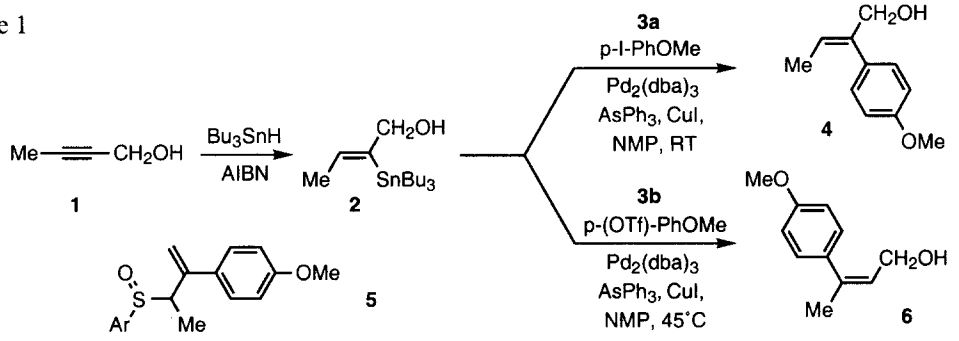
Abstract: Very low ligand to palladium ratios, especially weak ligands and iodides as electrophiles allow Stille couplings to very hindered stannanes, not possible under common conditions. In contrast, the usage of triflates and elevated temperatures yields exclusively the product of a Cine substitution. In this way, by the choice of the reaction conditions, two alternative stereoisomers can be obtained from the same stannane.

Keywords: Coupling reactions, Electronic effects, Catalysts, Palladium and compounds.

The palladium catalyzed coupling of stannanes with unsaturated carbon electrophiles, known as the Stille reaction, is one of the most powerful tools for the construction of substituted double bonds of defined stereochemistry.[1] Although sterically hindered halides or triflates typically couple well, hindered organotin reagents are often very problematic because of low reactivity. Also, the so called

Scheme 1



Cine substitution is frequently an undesired side reaction, directing the new substituent to the opposite side of the double bond. During investigations of antibody-catalyzed transformations of allylic sulfoxides of type **5**,[2] we attempted to synthesize the alcohol **4** via Stille coupling to the highly hindered stannane **2**. The latter is readily obtainable from 2-butyn-1-ol[3] **1** (scheme 1).

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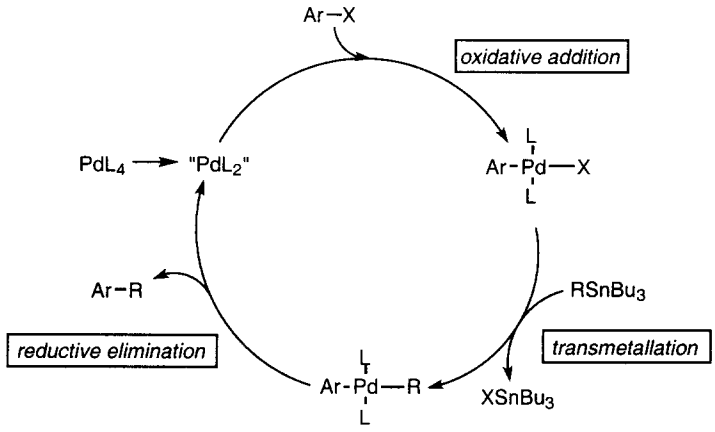
To the best of our knowledge, there is so far no coupling described to this stannane. Double bonds of the substitution pattern shown can be made by Wittig-type reactions,[4] but the E/Z-selectivity often is low and therefore the isomers have to be separated. Thus **4** was previously synthesized as 1:1 mixture with the (*Z*)-isomer starting from p-methoxyacetophenone in four steps with a total yield of 6%. The isomers then had to be derivatized and separated by HPLC, which dropped the yield to 1.8%, and the derivative was not converted back to the isomerically pure alcohol.[4] We have now found conditions for a Stille coupling to **2** that avoids the separation problem and produces pure **4** in 35% yield.[1] The results of our experiments also show for the first time that electronic effects in the electrophile influence the ratio of insertion (leading to Cine substitution) versus transmetallation (for Stille coupling) (scheme 1) and the choice of the catalyst.



Scheme 2

The Stille coupling is generally believed to proceed through the mechanism depicted in scheme 2.[1b] After freeing ligands from the palladium, the electrophile oxidatively adds to the palladium center and then the stannane (or in polar solvents probably a copper organyl intermediary formed with the copper iodide) undergoes a transmetallation, which is the rate limiting step. Finally, the product is released by rapid reductive elimination. It is easily seen from scheme 2 that the crucial transmetallation could be retarded by bulky substituents in the stannane and also by ligands on the

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[1] Preparation of (*E*)-2-(4-methoxyphenyl)-2-buten-1-ol (**4**): 500 mg (1.38mmol) (*E*)-2-(tributylstannyl)-but-2-en-1-ol (**2**), 63.5 mg (0.15eq) triphenylarsine and 217 mg (0.67eq) iodoanisole **3** are dissolved under nitrogen in 5 ml anhydrous NMP and the solution is carefully degassed. Then 63.5 mg (0.05eq) dipalladium tris(dibenzylideneacetone) are added and after 5 min 132 mg (0.5eq) with dichloromethane extracted and powdered copper iodide is added. The sealed reaction is stirred for 90 h at room temperature, then quenched by the addition of saturated NH_4Cl, and extracted twice with ether. The organic layers are extracted twice with 10% KF, dried with magnesium sulfate and evaporated in vacuo. Flash chromatography on silica with diethyl ether/hexanes 1:1 yields 50 mg **4** (35%) and 25 mg 3-(4-methoxyphenyl)-2-buten-1-ol **6** (18%), which is the *cis*-isomer as judged by the missing upfield shifts of the CH-Me signals in ^1H and ^{13}C NMR.[9] (*E*)-2-(4-methoxyphenyl)-2-buten-1-ol (**4**):^1H NMR (400 MHz, $CDCl_3$, TMS): δ= 1.64 (d, *J* = 6Hz, 3H, 4-H), 3.81 (s, 3H, OMe), 4.30 (d, *J* = 6Hz, 2H, 1-H), 5.78 (q, *J* = 6Hz, 1H, 3-H), 6.90 (dt, *J* = 9Hz, 3Hz, 2H, 2'-H), 7.16 (dt, *J* = 11.5Hz, 3Hz, 2H, 3'-H); ^{13}C NMR (125.7 MHz, $CDCl_3$, TMS): δ= 14.3 (s, C-4), 55.1 (s, OMe), 113.6 (s, C-2'), 123.0 (s, C-3), 129.7 (s, C-3'), 133.5 (s, C-4'), 140.2 (s, C-2), 158.5 (s, C-1'); HRMS (FAB, NBA/NaI): $C_{11}H_{14}O_2$ (M^+), calcd. 178.0990, found 178.0994. 3-(4-methoxyphenyl)-2-buten-1-ol (**6**):^1H NMR (400 MHz, $CDCl_3$, TMS): δ= 2.06 (d, *J* = 4Hz, 3H, 4-H), 3.80 (s, 3H, OMe), 4.09 (d, *J* =8Hz, 2H, 1-H), 5.67 (t, *J* = 7Hz, 1H, 2-H), 6.87 (d, *J* = 8Hz, 2H, 3'-H), 7.11 (d, *J* = 8Hz, 2H, 2'-H); ^{13}C NMR (125.7 MHz, $CDCl_3$, TMS): δ= 25.3 (s, C-4), 55.1 (s, OMe), 60.3 (s, C-1), 113.4 (s, C-2'), 125.4 (s, C-2), 128.8 (s, C-3'), 129.7 (s, C-4'), 139.7 (s, C-3), 158.6 (s, C-1').

palladium. Alternatively, with very hindered stannanes, then an insertion can take place (scheme 3) which is less obstructed by the steric constrains of the organotin reagent. Table 1 demonstrates that electronic effects also favor insertion over transmetallation (i.e. Cine over Stille reaction).

Table 1. Coupling stannane **2** with different electrophiles and $Pd_2(dba)_3$ as Pd^0-source.[a]

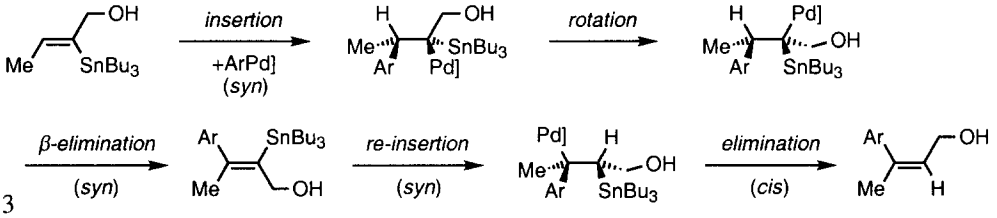
	Ar-X	ligand	(Pd/lig)	CuI	T [°C]	t [h]	Cine : Stille	conv. (%)
1	**3a** (X=I, Ar=PhOMe)	$AsPh_3$	(1:1,5)	cat.	rt	160h	1 : 2	>90
2	**3a** (X=I, Ar=PhOMe)	TFP	(1:4)	cat.	rt	90h	1 : 4	30
3	**3a** (X=I, Ar=PhOMe)	$AsPh_3$	(1:2)	cat.	45°C	44h	1 : 1.5	65
4	**3b** (X=OTf, Ar=PhOMe)	$AsPh_3$	(1:2)	cat.	45°C	40h	1 : –	30
5	**3b**,**3a** (X=OTf,I)	$AsPh_3$	(1:2)	cat.	45°C	80h	1 : –	50
6	**3c** (X=I, Ar=Ph)	$AsPh_3$	(1:1,4)	cat.	rt	90h	– : 1	50
7	**3a** (X=I, Ar=PhOMe)	TFP	(1:2)	cat.	65°C	90h	2 : 1	65
8	**3a** (X=I, Ar=PhOMe)	TFP	(1:2)	–	65°C	12h	– : 1	<10
9	**3b** (X=OTf, Ar=PhOMe)	TFP	(1:3.5)	LiCl	40°C	60h		–
10	**3b** (X=OTf, Ar=PhOMe)	–		–	50°C	20h		–

[a] All reactions with $Pd_2(dba)_3$ under nitrogen atmosphere in degassed NMP until precipitation of metallic palladium indicate breakdown of the palladium complex. Conversions determined by integration of the characteristic CH_2OH-signal in ^{1}H-NMR. Isolated yields typically are 10 to 15% lower. In entry 9 LiCl instead of CuI was used. Entry 10 is one example for "ligandless" conditions. TFP = tri(2-furyl)phosphine.

Entry 1 shows our optimized conditions, using Pd_2dba_3 as the Pd-source and $AsPh_3$[5] as coordinating ligand. The unusual low ratio of 1.5:1 (ligand:Pd) is less stable but much more reactive and required for successful coupling to **2**. "Ligandless" conditions[6] (with $Pd_2(dba)_3$ as Pd^0-source) and catalysts derived from $Bzl(Cl)Pd(PPh_3)_2$[7] failed to promote the reaction of **2** with certain electrophiles. For vinylstannanes, TFP typically is the ligand of choice.[1b] Compared with $AsPh_3$, TFP is a more selective but much less reactive ligand (entry 2). Enhancing its reactivity by raising the temperature (entry 7) favors the Cine-substitution. In contrast, with $AsPh_3$ at higher temperatures, the sensitive catalyst degrades more quickly, resulting in lower yields (entry 3). Entries 4 to 6 illustrate the influence of the electrophile on selectivity. Interestingly, with the less reactive aryltriflate, which is typically the preferred reagent for introducing p-methoxyphenyl groups,[8] no transmetallation takes place; instead the stannane only inserts in a Heck-type reaction to yield exclusively the above described Cine product (entry 4). Scheme 2 shows how the reaction pathway in this case is determined by the palladium complex formed by oxidative addition, and not by steric hindrance in the stannane. This explanation is supported by the fact that the more reactive iodobenzene exclusively yields the expected Stille product (entry 6). When iodoanisole is added subsequently to a reaction mixture with p-methoxyphenyl trifluoromethanesulfonate (entry 5), no further conversion to the Stille product is observed. This may indicate the presence of a different or degraded catalyst species that no longer can be attacked by oxidative addition. Finally, copper iodide is crucial for the reaction as indicated by much faster breakdown of the catalyst in its absence (entry 8). In the case of the triflate, the addition of lithium chloride seems to inhibit the reaction (entry 9).

These investigations provide conditions that enable Stille couplings to the highly hindered stannane **2**. The conditions differ in some important aspects from conventional procedures. Crucial is the use of the extremely reactive $AsPh_3$ as ligand in the very low ratio (ligand/Pd) of 1.5:1. The

addition of copper iodide is essential for successful coupling and aryl iodides must be used as electrophile. Further it is shown that steric clashes are not solely responsible for the competing Heck-type reactions leading to Cine substitution. The less reactive triflates probably add in a different way to the palladium and then insertion of palladium into the carbon tin bond becomes more favorable, leading to the "Cine isomer" of the desired product (scheme 3).



Scheme 3

In this way the Cine substitution may be used as a synthetically useful reaction even in cases where the Stille coupling is competing. The stereochemistry of the final elimination step in the Cine reaction (scheme 3) is not yet known, but the *cis*-geometry of **6** suggests a *cis*-elimination. More detailed investigations especially of the properties of the electrophile may yield even better conditions that will allow either the Cine or Stille product to be chosen in even more cases.

Acknowledgements

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