Tetrahedron Letters,Vol.29,No.45,pp 5739-5742,1988   0040-4039/88 \$3.00 + .00
Printed in Great Britain   Pergamon Press plc

PALLADIUM-CATALYZED COUPLING BETWEEN CEPHALOSPORIN DERIVATIVES AND UNSATURATED STANNANES:A NEW LIGAND FOR PALLADIUM CHEMISTRY

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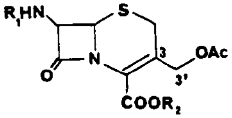
SUMMARY: We describe a general coupling procedure between 3-chloromethylcephems and unsaturated stannanes that employs a palladium catalyst featuring the new ligand tri(2-furyl)phosphine.

Chemical modifications of naturally occurring cephalosporins,(i.e. Cephalosporin C, **1a**) aimed at the discovery of novel antibiotics,have often entailed displacement of the acetoxy or synthetically equivalent group at C(3').



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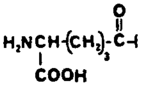
a: R_1 =  $H_2NCH(COOH)\text{-}(CH_2)_3\text{-}C(=O)\text{-}$ R_2 : H

b : R_1 = $PhCH_2CO$- R_2 = $CHPh_2$

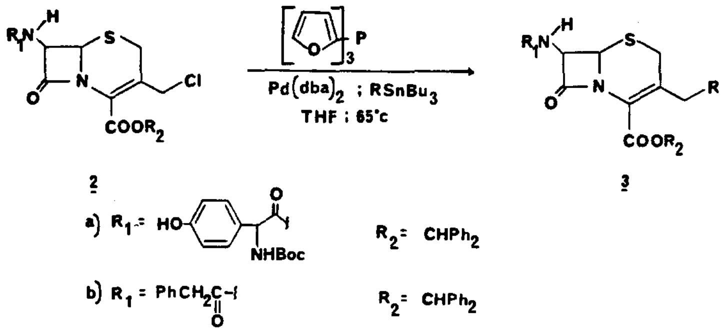
Thus,displacement by sulfur and nitrogen nucleophiles has led to the discovery of new classes of powerful broad-spectrum antibiotics[2]. Reports of carbon-carbon bond formation at C(3'),on the other hand,are few[3] ,and no methodology of general applicability has emerged. We now report that cephalosporin derivatives are amenable to palladium(0)-promoted allylic coupling with unsaturated stannanes[4] in what appears to be a general approach to a wide variety of novel semisynthetic cephalosporins bearing functionalized side chains at C(3).

Our initial attempts to couple **1b** with vinyltributylstannane in the presence of Pd(0) catalysts[5],in conjunction with different ligands and potential co-catalysts,were completely unsuccessful:we found **1b** to be inert under usual conditions.

Looking for a more reactive substrate,we reacted 3-chloromethylcephem[6] **2b** with organostannanes in the presence of $Pd(PPh_3)_4$ in THF and did observe some coupling,albeit at very slow rates,even at reflux.The use of more polar or higher-boiling solvents,as well as the use of additives[4] ,failed to improve the yield.

However,using a catalytic system prepared by adding tri(2-furyl)phosphine to a THF solution of bis(dibenzylideneacetonyl)palladium,the reaction proceeded at a much higher rate,and coupling with a variety of stannanes took place in good yield (Eq.1).

(1)



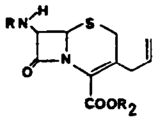
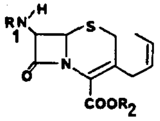
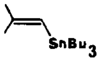
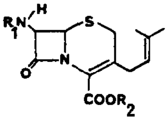
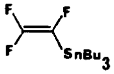
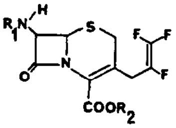
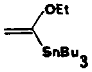
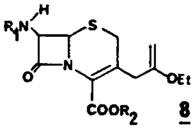
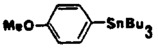
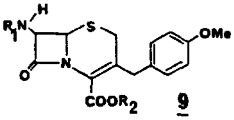
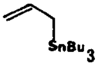
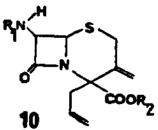
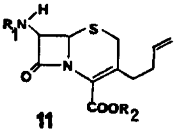
The coupling of olefinic stannanes appears to be general using the above conditions, although alkyl substitution at the unsaturated carbons caused a decrease in the reaction rate (Table I,Entries 1,2,3). Functionality on the olefinic stannanes is tolerated under our coupling conditions (Entries 4 and 5). Arylstannanes also couple efficiently to yield 3-benzylcephems[3a] (Entry 6). Allyltributyltin (Entry 7) gave a mixture of two products:the major one is the result of coupling at C(4),while "normal" coupling at C(3') seems to be a less favorable pathway in this case. Heating of **10** and **11** in toluene at reflux brought about a smooth Cope rearrangement to produce a good yield of **11** [7].

The formation of **10** suggests the involvement of a bis-η^3-allyl Pd species,although alternative explanations are possible. The use of tri(2-furyl)phosphine[8,9] as ligand was suggested by Allen's work[8] on the rate of alkaline hydrolysis of a series of phosphonium salts,which shows the substantial electron-withdrawing ability of the furan ring.

The observation that tri(2-furyl)phosphonium salts are hydrolyzed much more readily than the corresponding triphenylphosphonium salts (tri-thienyl ones show intermediate rates) is qualitatively mirrored by the behavior of the corresponding phosphines in our work. The rate of the Pd-promoted coupling as a function of the ligand used is shown in Table II[10]. We propose that tri(2-furyl)phosphine enhances the rate of the coupling by rendering the allyl-Pd(II) intermediate more electrophilic and therefore more reactive in the transmetalation step,which is thought to be the slow one in Pd-catalyzed couplings involving organostannanes[11,12].

We have observed this type of rate enhancement in another study[13],and we suggest that the use of tri(2-furyl)phosphine as a ligand in Pd-catalyzed couplings involving organostannanes may be of general value,especiallly when sensitive or unreactive substrates are involved,as in the present work[14]. Reaction of cephems **4-11** with trifluoroacetic acid gave the corresponding free acids. Their biological activity will be described elsewhere.

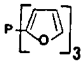
Table I: Coupling of Stannanes with 3-chloromethylcephem **2a**

Entry	Stannane	Product	Reaction Time	% Yield
1		 **4**	3 h	82
2		 **5**	16 h	78
3		 **6**	72 h	60
4		 **7**	72 h	65
5		 **8**	2 h	71
6		 **9**	24 h	81[a]
7		 **10**  **11**	16 h	57[b]

[a] Lactam **2b** was used instead of **2a** in this experiment.

[b] Ratio **10**/**11** was 5:1 (^{1}H-NMR). R_1, R_2: see Eq. 1

Table II: Relative rates in the coupling of **2a** with vinyltributylstannane.

Rate[a] (Sec^{-1})	Phosphine
1	P Ph_3
8.3	
45	

[a] Reactions in THF at reflux with 5% mole Pd(dba)$_2$ and 10% mole phosphine

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6. Readily available from natural cephalosporins (see ref.3d) or from penicillins: see Torii,S.;Tanaka,H.;Saitoh,N.;Siroi,T.;Sasaoka,M.;Nokami,J. Tetrahedron Lett.**1982**,2187.
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10. A quantitative reverse-phase HPLC method was used. All kinetics were first-order with respect to **2a**.Details will be reported in a full account of this work.
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12. Milstein,D.;Stille,J.K. J.Am.Chem.Soc. **1979**, 101,4992.
13. Farina,V.;Baker,S.R.;Sapino,C.,Jr. submitted for publication.
14. A typical procedure follows: **2b** (1 mmole), the stannane (1 mmole),Pd(dba)$_2$ (0.02 mmole) and tri(2-furyl)phosphine (0.04 mmole) in 5 mL dry THF were stirred at reflux under Argon for the indicated time,monitoring by TLC or reverse-phase HPLC. After evaporation of the solvent,acetonitrile was added and the tributyltin chloride was removed by washing several times with pentane.The product was purified by flash-chromatography.

(Received in USA 2 August 1988)