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A HIGHLY EFFICIENT METHOD FOR THE PREPARATION OF 2-ARYL SUBSTITUTED CARBAPENEMS EXPLOITING A Pd(0) MEDIATED CROSS-COUPLING REACTION

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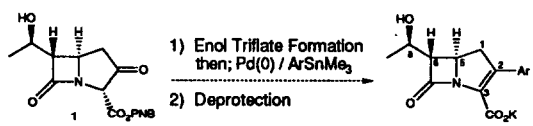
Summary: A remarkably mild procedure for the synthesis of 2-aryl substituted carbapenems *via* a palladium catalyzed coupling reaction of a vinyl triflate with aryl stannanes is described. Employing $Pd_2(DBA)_3$-$CHCl_3$ as the catalyst and tris(*2,4,6*-trimethoxyphenyl)phosphine as the ligand provides generous yields of the desired β-lactams. Reaction times are brief while reaction temperatures never exceed ambient.

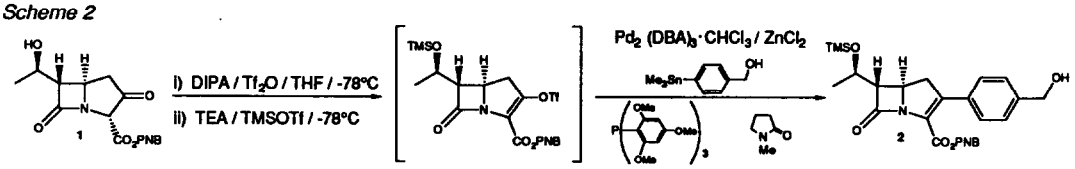
The discovery of thienamycin[1] in 1976 initiated a barrage of synthetic activity associated with this class of carbapenem antibiotic. Historically, research efforts directed toward the syntheses of carbapenem analogs have focused primarily on sulfur bearing substituents at C-2.[2] Less abundant are examples of carbon based substituents at C-2,[3] especially aryl,[4] partially due to the somewhat formidable routes to procure them.[5] In connection with the ongoing program directed toward the design and synthesis of potent β-lactam antibiotics in our laboratories, an efficient process for the preparation of carbapenem analogs bearing carbon substituents at C-2 became highly desirable. The readily available β-keto ester 1, an advanced intermediate in the total synthesis of thienamycin,[6] was an obvious candidate for further elaboration. Ultimately, formation of a carbon-carbon bond at C-2 would manifest itself in the form of a palladium(0) mediated cross-coupling reaction[7] between a requisite aryl stannane and the enol triflate derived from 1.

Scheme 1



The conditions of the palladium cross-coupling sequence are illustrated in Scheme 2. Treatment of the bicyclic β-keto ester 1 with Tf_2O and diisopropylamine in THF at -78 °C provided the enol triflate which was extremely labile.[8] The fact that this enol triflate decomposed when subjected to the Stille cross-coupling conditions [$Pd(PPh_3)_4$, $ZnCl_2$, an aryl stannane and heat][7] necessitated the development of an *in situ* protection of the C-8 hydroxyl. This could be easily accomplished by further treatment of the initially formed enol triflate with Et_3N and TMSOTf in THF at -78 °C. It was this metastable intermediate[9] which proved to be most practical for the cross-coupling reaction.

Scheme 2



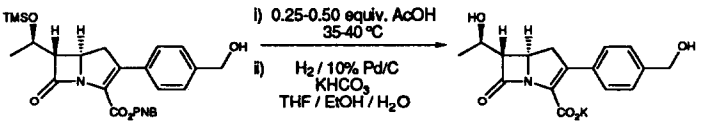
Although **1** had been successfully activated and protected, the subsequent cross-coupling reaction once again proved fruitless under the conventional Stille conditions. However, employing the conditions reported by Farina, *et al*[10a] did provide the desired carbapenem, albeit in modest yield. This report prompted us to examine a variety of phosphine ligands in conjunction with the catalyst tris-(dibenzylideneacetone)dipalladium-chloroform complex.[11] The ligands that we studied are presented in descending order of effectiveness: tris(*2,4,6*-trimethoxyphenyl)phosphine; tris(*2,6*-dimethoxyphenyl)phosphine; tris(*2*-furyl)phosphine ≅ tris(*4*-methoxyphenyl)phosphine; triphenylphosphine. The combination of 2 mol % $Pd_2(DBA)_3{\cdot}CHCl_3$ and 8 mol % tris(*2,4,6*-trimethoxyphenyl)phosphine permitted the coupling reaction to proceed smoothly and rapidly *at room temperature* (see Scheme 2). Thus a new phosphine ligand unprecedented in any Pd(0) catalyzed cross-coupling reaction of triflates and stannanes,[12] namely tris(*2,4,6*-trimethoxyphenyl)phosphine,[13] proved to be the most effective. These mild conditions preserved the integrity of the sensitive β-lactam moiety allowing ample yields of the desired products to be obtained.

Our results suggest that electron donating groups on the phosphine ligand enhance both the rate and the yield of the coupling to a great extent. It is hypothesized that these electron releasing groups facilitate the oxidative addition of the enol triflate to the palladium by rendering the palladium(0) intermediate more electron rich [therefore enabling an easier oxidation of palladium(0) to palladium(II)] while perhaps at the same time accelerating the reductive elimination step due to a steric compression effect.[14,15]

That this method would indeed be a viable route to *2*-arylcarbapenem antibiotics is illustrated in Schemes 2 & 3. *In one operation*, **1** could be converted to the phenyl derivative **2** in 67% yield.[16] A variety of functionalized aryl stannanes as well as heteroaryls were found to couple smoothly[17] (see Table). It is interesting to note that an earlier report by Stille[7b] suggests that aryl stannanes are poorly reactive when subjected to palladium catalyzed coupling reactions with enol triflates.

The preparation of the fully deprotected carbapenem is depicted in Scheme 3. Removal of the trimethylsilyl and the *p*-nitrobenzyl groups was achieved in a "one-pot" sequence by initial treatment of **2** with 0.25-0.50 equivalents of AcOH at 35-40°C followed by hydrogenolysis over Pd/C at ambient temperature. The known β-lactam carbapenem antibacterial **3**[4c] was obtained in 40% yield.[18]

Scheme 3

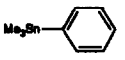
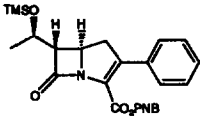
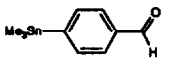
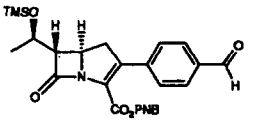
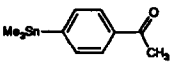
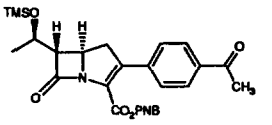
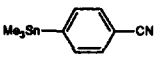
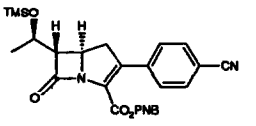
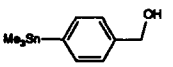
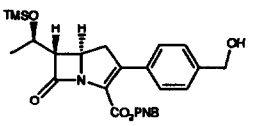
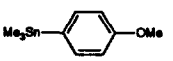
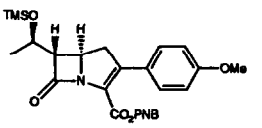
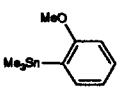
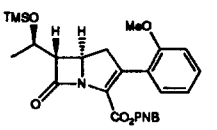
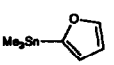
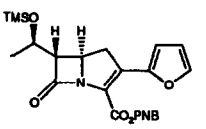
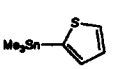
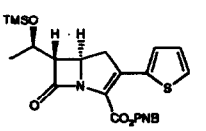


2 **3**

In summary, a new route to *2*-arylcarbapenems has been developed. The process is mild, efficient and will tolerate a wide variety of functional groups. Further investigation directed toward the extension of this method to the delivery of acetylenic, alkenyl, and alkyl tin reagents is currently underway.

Acknowledgements: The authors wish to thank Professor Barry M. Trost for several salutary and informative discussions, as well as Dr. Jim Heck for thought-provoking conversation.

Table

ENTRY	STANNANE	PRODUCT	YIELD
1			(73%)
2			(73%)
3			(77%)
4			(70%)
5			(67%)
6			(84%)
7			(82%)
8			(69%)
9			(41%)

Entry 9 required 4 mol % Pd(0) and 16 mol % phosphine

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3. See for example: (a)Schmitt, S.M.; Salzmann, T.N.; Shih, D.H.; Christensen, B.G. *J. Antibiot.*, **1988**, *41*, 780. (b)Ueda, Y.; Maynard, S.C. *Tetrahedron Lett.*, **1988**, *29*, 5197. (c)Ona, H.; Uyeo, S.; Fukao, T.; Doi, M., Yoshida, T. *Chem. Pharm. Bull.*, **1985**, *33*, 4382. (d)Shiozaki, M,; Ishida, N.; Maruyama, H.; Hiraoka, T.; Sugawara, S. *J. Antibiot.*, **1984**, *37*, 57.
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5. These derivatives are typically prepared *via* an intramolecular Wittig cyclization.
6. (a)Salzmann, T.N.; Ratcliffe, R.W.; Christensen, B.G.; Bouffard, F.A. *J. Am. Chem. Soc.*, **1980**, *102*, 6161. (b)Melillo, D.G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.*, **1980**, *21*, 2783.
7. (a)For an excellent review, see: Stille, J.K. *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 508. (b)Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.*, **1986**, *108*, 3033.
8. This is consistant with the findings of: Sletzinger, M.; Liu, T.; Reamer, R.A.; Shinkai, I. *Tetrahedron Lett.*, **1980**, *21*, 4221. A clean 300 MHz ^{1}H NMR of the enol triflate could be obtained, confirming its structure.
9. This triflate was also extremely labile upon isolation. The TBS protected alcohol, however, could be isolated by silica gel column chromatography as a white solid which was fully characterized.
10. (a)Two previous reports (Farina, V.; Baker, S.R.; Sapino, C. *Tetrahedron Lett.* **1988**, *29*, 6043; Farina, V.; Baker, S.R.; Benigni, D.A.; Sapino, C. *Tetrahedron Lett.* **1988**, *29*, 5739.) describe a similar type of coupling employing tris(*2*-furyl)phosphine as the ligand and bis(dibenzylideneacetonyl) palladium(0) as the catalyst. (b)For a similar cross-coupling reaction on a carbacephem nucleus employing the "ligandless" catalyst $\{(CH_3CN)_2PdCl_2\}$, see Cook, G.K.; Hornback, J.W.; Jordan, C.L.; McDonald III, J.H.; Munroe, J.E. *J. Org. Chem.*, **1989**, *54*, 5828.
11. Ukai, T.; Kawazura, H.; Ishii, Y. *J. Organometal. Chem.*, **1974**, *65*, 253.
12. During the preparation of this manuscript a communication by Trost, *et al*, disclosed the use of this phosphine (as well as the others involved in our study) in the cycloisomerization of α,ω-diynes to macrocycles. Trost, B.M.; Matsubara, S.; Caringi, J.J. *J. Am. Chem. Soc.*, **1989**, *111*, 8745.
13. Wada, M.; Higashizaki, S. *J. Chem. Soc. Chem. Commun.*, **1984**, 482.
14. For a similar result, see: (a)Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.*, **1989**, *111*, 8742. (b)Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc. Chem. Commun.*,**1989**, 1816.
15. A significantly different explanation for the rate acceleration afforded by tris(*2*-furyl)phosphine is offered by the Bristol workers [ref. 10(a)].
16. A representative procedure is as follows: To a stirred solution of β-keto ester **1**(143 mg; 0.41 mmol) in THF (2 mL) cooled to -78 °C under nitrogen was added diisopropylamine (1.1 equiv.; 63 μL). After 10 minutes Tf_2O (1.1 equiv.; 75 μL) was added to the resulting yellow solution. Fifteen minutes elapsed before triethylamine (1.1 equiv.; 62 μL) was added followed immediately by TMSOTf (1.1 equiv.; 87 μL). After 20 minutes, addition of *1*-methyl-*2*-pyrrolidinone (2 mL) was followed by tris(dibenzylideneacetone)dipalladium-chloroform (2 mol %; 8.5 mg), tris(*2,4,6*-trimethoxyphenyl)phosphine (8 mol %; 17.4 mg), and the aryl stannane (1.1 equiv.; 0.45 mmol). Zinc chloride in diethyl ether (1.1 equiv.; 300 μL) was added last. The -78 °C bath was removed and the reaction mixture quickly raised to ambient temperature using a lukewarm water bath during which time an intense wine red color developed. The reaction was then stirred for 5-20 minutes, depending on the stannane used. Upon completion (TLC; SiO_2), the reaction mixture was poured into Et_2O and washed with water and brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The products were purified using SiO_2 flash column chromatography.
17. The structure assigned to each new compound is in accord with its infrared, UV, and high field (300 MHz) ^{1}H NMR spectra.
18. Hydrogenolysis and isolation by reverse phase prep-plate chromatography provided >80% yield of the desired *2*-arylcarbapenem, accompanied by the corresponding *2,3*-dihydrocarbapenem (~10%). This undesired product could be removed by reverse phase HPLC with concomitant loss of yield.

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