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The Syntheses of Functionalized 2-Alkenyl and Alkynyl-1-β-methyl-carbapenems via The Stille Cross-coupling Reaction

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Abstract: The Stille cross-coupling reaction is an extremely mild and versatile method for the coupling of organostannanes with vinyl triflates. This methodology has been extended to include functionalized 2-alkenyl and alkynyl-1-\beta-methylcarbapenems. © 1998 Elsevier Science Ltd. All rights reserved.

Carbapenem antibiotics have emerged as a burgeoning area of β -lactam research based on the their antimicrobial potency, broad spectrum activity and clinical success.¹ Since their discovery, an intensified synthetic effort has been directed toward the preparation of novel carbapenems, the majority of which, like the natural product thienamycin,² possess a sulfur atom at C-2.^{1,3} Recently, C-2 carbon based carbapenems have become increasingly prevalent, due primarily to facile carbon-carbon bond forming reactions⁴ that allow for the direct attachment of a variety of functionalized side chains to carbapenem-2-yl-triflates, and a continued search for novel antibiotics. Prompted by a recent report^{4a} from the Shionogi group describing the synthesis of the C-2 alkenylcarbapenems using the Heck reaction, we now report an extension of the palladium mediated Stille cross-coupling reaction to include functionalized C-2 alkenyl as well as, the heretofore unreported, functionalized C-2 alkynylcarbapenems (eq. 1 and 2).

The Stille cross-coupling reaction⁵ has been demonstrated as an extremely mild and versatile method for the coupling of vinyl triflates with organostannanes and has been widely employed in the syntheses of 2-aryl,^{4b,c} alkenyl and non-functionalized alkynylcarbapenems.^{4g} As an extension of our previous work on 1- β -methyl-2-arylcarbapenems^{4c} and as part of our medicinal chemistry effort, it was desirable to effect the production of the carbapenem carbinols 3 and 9, necessary for further derivatization.



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Although the Shionogi group has successfully utilized the Heck reaction for the introduction of functionalized (E)-olefinic groups at C-2 of the carbapenem nucleus, one deficiency of this approach was the generation of unfavorable mixtures of **4a** and **4b**, derived from the coupling of their PMB (*p*-methoxybenzyl)protected carbapenem-2-yl triflate and allyl alcohol. In contrast, a successful Stille coupling would preclude the formation of a product of type 4b and thus provide greater efficiency. To this end the olefinic (E) and (Z)stannanes, 2a and 2b, obtained in a 2:1 ratio as described by Jung⁶ from the reaction of propargyl alcohol with tri-n-butyltin hydride and catalytic AIBN, when coupled in a 50% stochiometric excess with triflate 1 using the protocol of Farina⁷ (5 mol % Pd2(dba)3 ·CHCl3 catalyst, 10 mol % tris-2-furylphosphine and 1.1 eq. of ZnCl2 in NMP), stereoselectively gave only the (E)-2-alkenylcarbapenem 3^8 after six hours at ambient temperature in 60% yield.⁹ Such specificity was also observed in the Heck process^{4a} and an analogous attempt to couple 1 with isomerically pure (Z)-stannane $2b^{10}$ resulted in the formation of cyclic lactone 5^{11} and p-nitrobenzyl alcohol, in low yield, as the only identifiable products. In contrast, the Stille cross-coupling of a nonfunctionalized (Z)-alkenyl stannane with an analogous cephalosporin-3-yl-triflate is readily accomplished in high yield as reported by Farina.⁷ The cross-coupling reaction to provide 3 could also be accomplished without the use of a phosphine source, as similarly reported by Baker,¹² however, a lower yield (43%) of the alkenylcarbapenem was obtained.



In an effort to avoid lactonization, and thereby access the desired (Z)-alkenylcarbapenem system, the reaction was repeated with a functionalized (Z)-stannyl derivative 6a,¹³ which was simply prepared via a Mitsunobu reaction¹⁴ of **2b** and *p*-phenyl benzoic acid in THF using DIAD and triphenylphosphine. An attempt to cross-couple 6a, using the aforementioned conditions, proved unsuccessful. More surprisingly, however, was the failure of the (E)-stannane 6b to couple under the identical parameters. This result suggested that inductive along with steric interactions ^{5b} and a judicious choice of functionality can play a significant role in the cross-coupling reaction.

In addition to 2-alkenylcarbapenems, the Stille methodology was further extended to include functionalized 2-alkynylcarbapenems. The alkynylstannane 7, required for the cross-coupling to produce 8, was readily obtained from propargyl alcohol.¹⁵



The initial coupling experiment with 7, using the conditions of Farina, gave a low yield of 8, while returning considerable amounts of 1. Difficulties in separating 1 from the coupled product necessitated that most of the vinyl triflate be consumed. In addition, palladium black was rapidly formed during the course of the reaction indicating catalyst decomposition. The rapid disappearance of stannane during the reaction, as indicated by ¹H NMR, suggested that alkynyl-alkynyl self-coupling was a competing process, while an attempt to cross-couple

1 and 7 without a phosphine source, gave mostly self- coupled product. This result confirmed that, in the case of the alkynyl system, phosphine ligation was necessary for cross-coupling to occur, and suggested that an alternative phosphine ligand may facilitate the rate of reaction by accelerating the transmetalation step, thought to be rate limiting in the Stille reaction.¹⁶

However, the use of similar phosphines like tris-2,4,6-trimethoxyphenylphosphine and triphenylphosphine were less effective in the coupling reaction than tris-2-furylphosphine. Higher yields of **8** could be obtained using 3 equivalents of stannane, with 15 mol% of phosphine, at 50°C. On the other hand, the use of 5 mol % bis-acetonitriledichloropalladium(II)¹⁷ as catalyst, as recently reported by Barrett¹⁵ in the preparation of 3-alkynylcephems, proved to be more fruitful. Thus, a DMF solution of **2**, alkynylstannane 7, LiBr, and Pd(CH₃CN)₂Cl₂ aged 1 hr., at 0°C, gave **8**¹⁸ in 64% yield.

The selective desilylation of 8 was accomplished with 1.1 equivalents of tetrabutylammonium fluoride and 1.5 equivalents of HOAc, in THF, at 0° C, for 1hr. to provide the desired carbinol 9. The derivatization of 9, the selective catalytic hydrogenation of the PNB group in the presence of the diene and ene-yne systems, and the anti-microbial activities of the resulting fully functionalized derivatives will be published elsewhere.

In summary, we have extended the palladium mediated Stille cross-coupling reaction to include functionalized C-2 alkenyl and alkynylcarbapenems and demonstrated its virtue as an efficient process for the introduction of carbon based side chains to the carbapenem nucleus.

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