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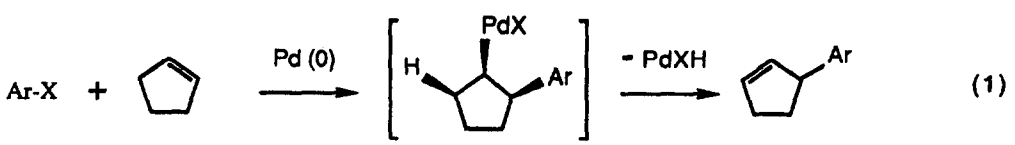
PALLADIUM-CATALYZED INTERMOLECULAR VINYLIC ARYLATION OF CYCLOALKENES. APPLICATIONS TO THE SYNTHESIS OF QUINOLONE ANTIBACTERIALS

Edgardo Laborde*, Lawrence E. Lesheski, and John S. Kiely
Chemistry Department
Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company
Ann Arbor, Michigan 48105, USA

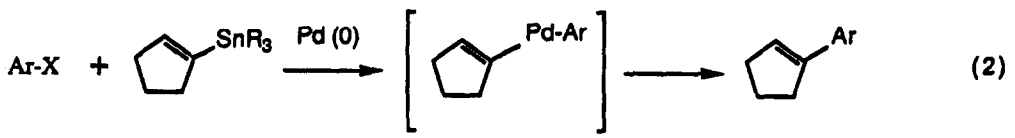
Summary: Cyclic β-tributylstannyl-α,β-unsaturated ketones, alcohols, and amines have been prepared by a highly efficient process. These reagents undergo palladium-catalyzed, intermolecular vinylic cross-coupling with 7-quinolyltriflates and 7-chloro-1,8-naphthyridines under very mild conditions.

Aryl and heteroaryl halides are known to undergo palladium-catalyzed inter- and intramolecular allylic cross-coupling with cyclic alkenes.[1-4] The reaction proceeds *via* oxidative addition of the aryl halide to the palladium catalyst, followed by *syn* addition of the arylpalladium complex to the carbon-carbon double bond and subsequent *syn* elimination of a palladium hydride species (eq. 1). Because of the nature of the last step, the reaction affords allylic cross-coupled products, since the formation of the corresponding vinylic counterparts would require an *anti* elimination of the palladium hydride.

The palladium-catalyzed cross coupling of aryl halides and triflates with vinylstannanes, on the other hand, has emerged as a versatile method for the synthesis of functionalized styrenes.[5-7] The reaction also involves an oxidative addition of the aryl halide to the palladium catalyst, followed by transmetallation with the vinylstannane to give an arylvinylpalladium complex, which rapidly undergoes reductive elimination to afford the coupled product (eq. 2).[8] Consequently, the reaction of aryl or heteroaryl halides with a 1-cycloalkenylstannane would be expected to provide the corresponding vinylic arylated cycloalkene. To our knowledge, however, the application of such a strategy in organic synthesis has not yet been reported.

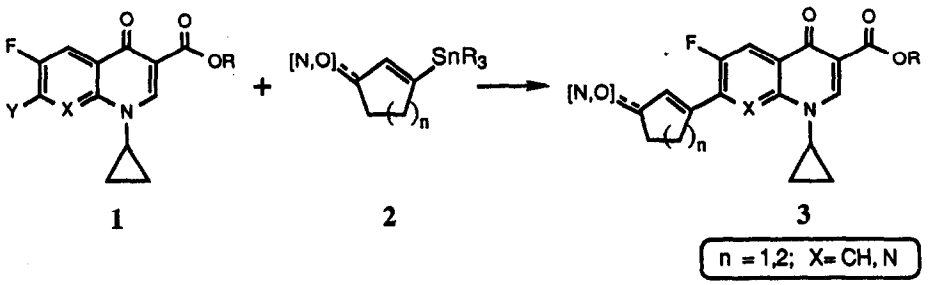


(1)



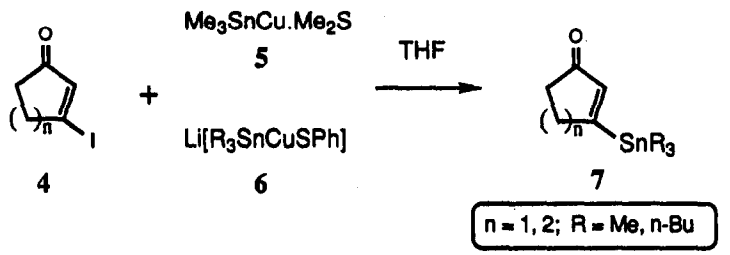
(2)

As part of our quinolone antibacterial program, we required an efficient and exceedingly mild procedure for the attachment of a highly functionalized quinolyl (X=CH) or 1,8-naphthyridyl (X=N) substrate 1 to the 1-position of a 3-substituted cycloalkene (eq. 3). It was envisioned that such an operation could be accomplished by a palladium-catalyzed cross-coupling of 1 (Y= Cl, OTf) with a 1-cycloalkenylstannane. We wish to report herein a practical preparation of several 3-substituted-1-cycloalkenylstannanes and their palladium-catalyzed coupling with 7-quinolyltriflates and 7-chloro-1,8-naphthyridines.



(3)

In contrast to acyclic vinylstannanes, few examples of functionalized 1-cycloalkenylstannanes are described in the literature. Piers and coworkers have reported the synthesis of 3-trialkylstannyl-2-cycloalkenones **7** by reaction of a β-iodo-α,β-unsaturated ketone **4** with a (trialkylstannyl)copper (I) reagent **5** or **6** (eq. 4).[9] Although these compounds appeared to be attractive intermediates for our synthetic purposes, their preparation in large scale according to eq. 4 was impractical. Indeed, the need to preform both the β-iodo enone and the tin-copper reagent, combined with the thermal instability and oxygen sensitivity of the latter, prompted us to examine more expeditious routes to enones **7**. We found that treatment of commercially available 3-ethoxy-2-cyclopentenone, **8a**, or its six-membered ring homolog **8b**, with one equivalent of lithium tributylstannate [10] in THF at -78°C affords the corresponding 3-tributylstannyl-2-cycloalkenones **7a,b** in 70-85% isolated yield for a 50 mmol-scale reaction (Scheme I).[11]



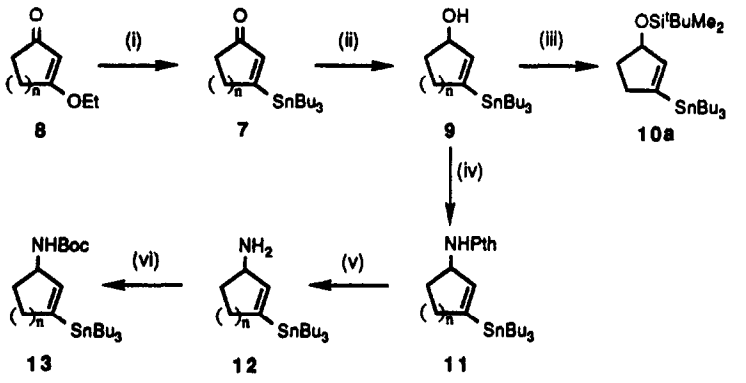
(4)

The elaboration of ketones **7a,b** into their hydroxy and amino derivatives was accomplished as illustrated in Scheme I. Selective reduction of the carbonyl group with lithium aluminum hydride in ether at -20°C afforded the 3-tributylstannyl-2-cycloalkenols **9a,b** in quantitative yield. The allylic alcohol **9a** was subsequently protected as a *tert*-butyldimethylsilyl ether to give **10a**. Treatment of **9a,b** with phthalimide under Mitsunobu's conditions,[12] on the other hand, provided the N-(3-tributylstannyl-2-cycloalken-1-yl)phthalimides **11a,b** in 65-80% yield. Removal of the phthaloyl group with hydrazine in ethanol furnished the free amines **12a,b**. For our synthetic objectives, however, we found it more convenient to isolate these amines as their N-BOC derivatives. Thus, the crude reaction mixture obtained from the treatment of **11a,b** with hydrazine was filtered to remove precipitated phthaloylhydrazide and concentrated *in vacuo*. The residue was dissolved in dichloromethane and treated successively with triethylamine and di-*tert*-butyl carbonate to afford the BOC-protected 3-amino-1-cycloalkenylstannanes **13a,b** in 70-80% overall yield from the corresponding phthaloyl derivative.

The palladium-catalyzed coupling of 7-quinolyltriflates and 7-chloro-1,8-naphthyridines with the above cycloalkenylstannanes proceeded with complete regio- and chemoselectivity to afford the corresponding (1-cycloalkenyl)-substituted derivatives.

Representative examples are given in eq. 5 and 6.[13] The reactions were carried out according to Stille's protocol for the coupling of organostannanes with aryl triflates,[6] except that in the case of 7-chloronaphthyridine **16** no lithium chloride was added to the reaction mixture. In addition, the standard work up with pyridine-pyridinium fluoride was substituted by a more expeditious and milder procedure involving stirring the residue obtained after evaporation of the reaction solvent with a large volume of cyclohexane for 15-30 minutes. This simple operation allowed the separation of the organotin by-products from the desired 7-substituted-quinolone or naphthyridine, which was collected by filtration and purified by column chromatography.

Scheme I[a]

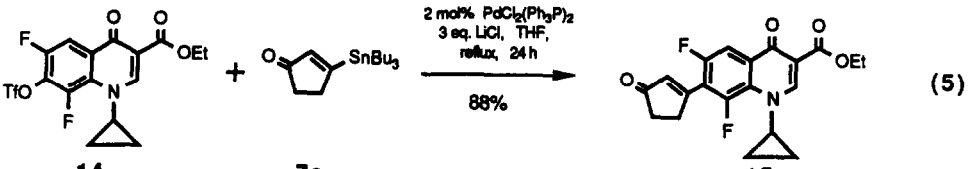


[a]Reagents: (i) Li(n-Bu_3Sn), THF, -78°C; then aq. NH_4Cl; (ii) $LiAlH_4$, Et_2O, -20°C; (iii) ^{t}$BuMe_2SiCl$, Imidazole, CH_2Cl_2; (iv) Phthalimide, DEAD, Ph_3P, THF; (v) NH_2NH_2, EtOH; (vi) $(BOC)_2O$, Et_3N, CH_2Cl_2.

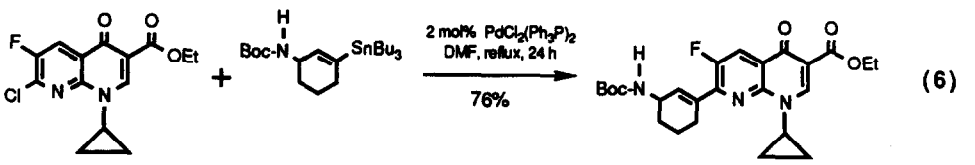
The following observations are noteworthy. First, the incorporation of the vinyl unit of a vinylstannane into a ring does not affect the cross-coupling process. Moderate to good yields of coupled product were obtained in all the cases examined, and no isomerization of the double bond of the cycloalkenylstannane was ever observed. Secondly, the reaction is extremely selective; the coupling takes place exclusively at the C-7 position of the quinolone or naphthyridine nucleus even in the presence of the C-6 fluorine and of the C-2 α,β-unsaturated ketoester moiety.[14] Thirdly, the coupling proceeds equally well with aryl triflates or heteroaryl halides.

Acid hydrolysis (5N HCl/THF-H_2O) of the protecting groups furnished the corresponding 7-(3-substituted-1-cycloalkenyl)quinolone or naphthyridine-3-carboxylic acids. Several of these novel compounds displayed a substantial antibacterial activity. A more detailed account of the chemistry, structure-activity-realtionships, and biological data of these compounds will be the object of a future publication.

In summary, 3-tributylstannyl-1-oxo, 1-hydroxy, or 1-amino-2-cyclopentenes and cyclohexenes have been prepared from commercially available materials *via* a sequence of reactions amenable to large scale preparation. These reagents are useful synthons for the vinylic cross-coupling of a functionalized cyclopentene or cyclohexene ring with aromatic electrophiles.



14 7a 15 (5)



16 13b 17 (6)

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10. Prepared from 1 eq. each of hexabutylditin and n-BuLi in THF at -78°C.
11. Small amounts of the β,β–bis(tributylstannyl)ketones were detected in some runs. These by-products could be easily removed by column chromatography on silica gel using 10% ethyl acetate in hexane.
12. (a) O. Mitsunobu, M. Wada, T. Sano, J. Am. Chem. Soc. 94, 679 (1972); (b) O. Mitsunobu, Synthesis, 1 (1981)
13. The 7-quinolyltriflate 14 was prepared from the corresponding 7-fluoroquinolone by successive treatment with 1N NaOH/EtOH-THF, triflic anhydride/pyridine, and EtOH.
14. All coupling products have been identified by high-resolution ^{1}H-NMR, IR, and MS, and their purities determined by combustion analysis and/or hplc. Representative physical data:
15: ^{1}H-NMR ($CDCl_3$): δ 1.15-1.18 (m, 2H), 1.21-1.33 (m, 2H), 1.42 (t, 3H, J=7.2 Hz), 2.59-2.63 (m, 2H), 3.90-4.02 (m, 2H), 4.40 (q, 2H, J=7.2 Hz), 6.60-6.63 (m, 1H), 8.06 (dd, 1H, J=10.4 Hz), 8.83 (s, 1H); MS (ei): m/z 374, 373 (M), 328, 301 (base), 300, 272. **17**: ^{1}H-NMR ($CDCl_3$): δ 1.01-1.08 (m, 2H), 1.24-1.32 (m, 2H), 1.41 (t, 3H, J=7.2 Hz), 1.48 (s, 9H), 1.78-1.92 (m, 2H), 2.59-2.67 (m, 2H), 3.60-3.68 (m, 1H), 4.40 (q, 2H, J=7.2 Hz), 4.40-4.50 (m, 1H), 6.76-6.80 (m, 1H), 8.33 (d, 1H, J=10.9 Hz), 8.67 (s, 1H); MS (ei): m/z 472 (M+1), 415 (base), 371, 343, 57.

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