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UNSYMMETRICAL HETEROBIARYL SYNTHESIS. A HIGHLY EFFICIENT PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF HETEROARYL TRIALKYLSTANNANES WITH ARYL HALIDES

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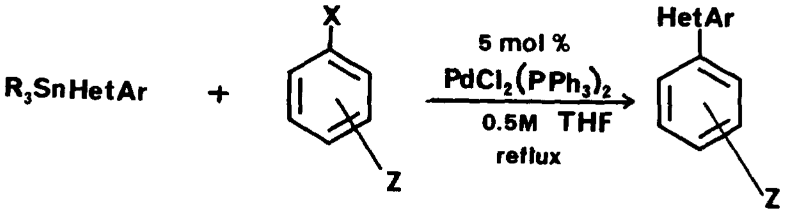
Summary: A general synthesis of heterobioaryls in good to excellent yields via Pd-catalyzed cross-coupling of trialkylheteroarylstannanes 1-5 with aryl halides is described.

The construction of biaryls persists as a synthetic challenge,[1] and in the past decade, a number of Pd-[2] and Ni-[3]catalyzed cross-coupling approaches have emerged. With the advantages of a catalytic process, it is surprising that for unsymmetrical heterobiaryls relatively few procedures have been developed using a Pd-catalyzed cross-coupling methodology. Methods presently available primarily involve the coupling of heteroaryl Grignards,[4,5] arylzinc chlorides,[5] or arylboronic acids[6] with aryl and heteroaryl halides. Of these three methods, only arylboronic acids are compatible with carbonyl moieties such as methyl esters.[6] We now present mild, general, highly efficient Pd-catalyzed cross-coupling between readily synthesized heteroaryl trialkylstannanes and aryl halides to yield unsymmetrical biaryls.

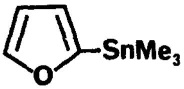


X-Br,I

R=-CH_3, -n-butyl

Z=-Cl, -OAc, -H, -CO_2R

Biaryl syntheses through Pd-catalyzed coupling of an arylstannane with aryl diazonium salts[7] and aryl halides[8,9] have been briefly described. However, only one example of this heterobiaryl cross-coupling between 2-iodothiophene with arylstannanes has been reported.[9,21] This procedure suffers the disadvantage of requiring HMPT and yielding up to 24% of the symmetrical aryl coupling byproduct of the trimethylarylstannane. In our work the known trialkyl heteroarylstannanes 1,[10] 2,[11] 3,[12] 4,[13] and the previously unknown N-methyl-pyrrole-2-trimethylstannane, 5[14] are used in the coupling. All stannanes are readily generated in excellent yield by quenching the α-lithio anion of the commercially available heteroaryl with trialkylstannyl



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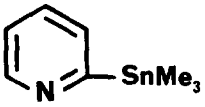

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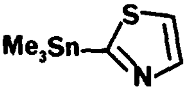

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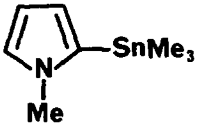

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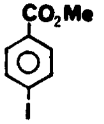
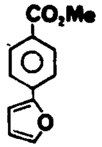
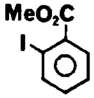
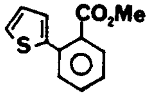
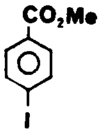
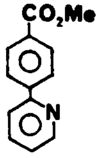
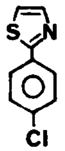
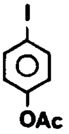
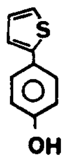
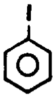
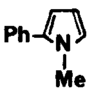
chloride. Unlike the aryl Grignard and aryl zinc reagents, heteroaryl stannanes are insensitive to moisture and are quite stable. These stannanes are then coupled with either aryl bromides or iodides in good to excellent yields using 5 mol % $PdCl_2(P\phi_3)_2$ under N_2 in refluxing THF over a period of 4-20 h (see Table). Symmetrical heteroaryl coupling of the stannanes is observed, but usually less than 5-12%. It should be noted that with the exception of entry F,[5] all previous methods for preparation of these heterobiaryls was accomplished by multi-step, or non-catalytic processes.

Table. Synthesis of Unsymmetrical Heterobiaryls from Heteroorganostannanes and Aryl Halides.

Entry	Organostannane	Aryl Halide	Product[a]	Yield[b]	mp (lit. mp) °C
A	1			73	119-120 (121-122)[15]
B	2			81	oil[c]
C	3			95	96-98[d]
D	4			80	37-38 (37-38)[16]
E	2			65	141 - 142[e] (143-146)[17]
F	5			54	49-50 (51)[5]

[a] Product assignment was consistent by ¹HNMR, ms, and comparison with mp of compounds reported in the literature.

[b] Yields reported are chromatographed (MPLC) materials.

[c] The ester was hydrolyzed to the known carboxylic acid mp 93-95°C (lit.[18] 93-94°C).

[d] The ester was converted to the known carboxylic acid mp 236-238°C (lit.[19] 235-237°C).

[e] Hydrolysis of the crude coupled acetate was accomplished with LiOH in 2:1 MeOH/H_2O.

In a typical experiment, a suspension of methyl 4-iodo-benzoate (2.0 g, 7.6 mmol) in 20 ml dry THF, 0.27 g (0.04 mmol) $PdCl_2(P\phi_3)_2$,[20] and 2.0 g (8.6 mmol) of 2-trimethylstannyl furan[10] was refluxed under N_2 for 20 hr. During the course of the reaction the color changed from yellow to black as Pd° was formed. The reaction mixture was cooled, diluted with diethyl ether and filtered through a pad of neutral alumina. The filtrate was washed several times with water, and the ether phase was dried over anhydrous K_2CO_3. Concentration and medium pressure liquid chromatography (9:1 hexane/EtOAc) afforded 1.1 g (73%) of methyl-4-(2-furanyl)-benzoate as a white solid mp 119-120°C (lit.[15] mp 121-122°C).

This general, catalytic procedure provides a gentle and efficient one-step construction of heterobiaryls from stable, readily available trialkyl heterostannanes and aryl bromides or iodides possessing varied and sensitive substituents. Practical applications of this methodology are currently being explored and the results will be reported in the near future.

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