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Catalyst Tailoring For Palladium-Mediated Cross Coupling Of Arylstannanes With Vinyl Triflates

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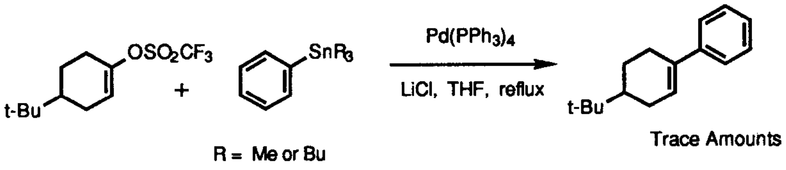
Summary: Vinyl triflates couple smoothly with a variety of arylstannanes provided a polar, aprotic solvent is used in conjunction with a "ligandless" palladium catalyst, or a catalytic system involving weak ligands such as triphenylarsine. Commonly employed ligands, for example, triphenylphosphine ,were found to strongly inhibit the coupling.

Carbon-carbon bond formation techniques based on the palladium catalysed cross coupling of vinyl triflates with organostannanes represent one of the most widely utilized and explored reactions since made popular by Stille and coworkers.[1] Although the structural diversity of the coupling partners can be varied greatly, one severe limitation is the apparent lack of reactivity of arylstannanes. It has been demonstrated that the reaction between 4-*tert*-butylcyclohexyl triflate and phenyltrialkyltin proceeds with low conversion if at all[2] (Eq. 1). Typical reaction conditions furnish trace amounts of 1-phenyl-4-*tert*-butylcyclohexene, as well as biphenyl, and 4-*tert*-butylcyclohexene. As a consequence of this shortcoming, procedures have been developed substituting arylzinc halides for arylstannanes.[3] To date, the scope of this methodology has been limited with respect to the coupling partners involved.

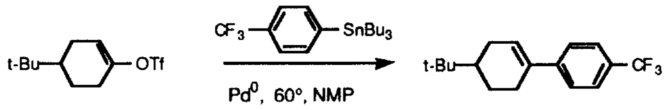


(Eq 1)

Recently, we have observed that arylstannanes can be effectively coupled with activated triflates derived from cephalosporins using alternative reaction conditions.[4] In conjunction with this, Rano and coworkers[5] have reported unusual ligand effects in the preparation of 2-aryl carbapenems.

We are pleased to report that the palladium catalysed coupling of arylstannanes and vinyl triflates is indeed a reaction of general synthetic utility. The key feature of this new protocol is the incorporation of "weak" palladium ligands. It is shown that the presence or absence of ligand and halide exerts a profound effect on the rate of reaction.

Table 1. Effect of Ligand and Halide on Relative Rate and Yield



Entry	Ligand	Halide	Rel. Rate	Yield (%)[a]
1	PPh_3	3 eq. LiCl	b	24
2	PPh_3	3 eq. LiCl	1.0	54
3	$Pfur_3$[c]	3 eq LiCl	3.5	75
4	$P((MeO)_3Ph)_3$[d]	3 eq LiCl	4.2	75
5	$P(o\text{-}MePh)_3$	3 eq LiCl	149	82
6	$AsPh_3$	3 eq LiCl	95	87
7	$AsPh_3$	2 eq $ZnCl_2$	151	89
8	$AsPh_3$	None	58	83
9	No Ligand	3 eq LiCl	1480	69
10	No Ligand	None	56	28

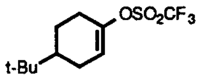
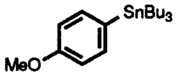
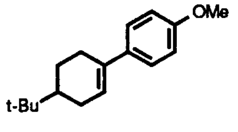
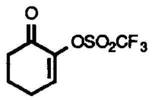
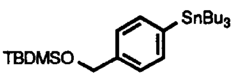
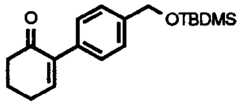
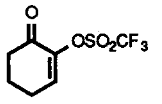
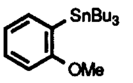
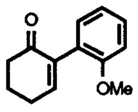
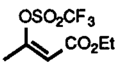
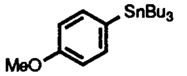
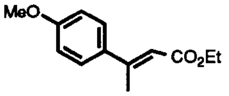
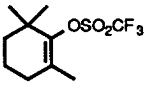
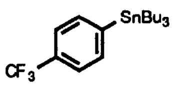
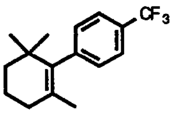
a. Yield was determined by ^1H NMR and quantitative HPLC analysis
b. Reaction conditions were that illustrated in Eq 1, refluxing for 48 hours
c. Tri(2-furyl)phosphine
d. Tri(2,4,6-trimethoxyphenyl)phosphine

Table 1 illustrates the subtle effects of catalyst tailoring on a model system that couples poorly using prescribed literature conditions (entry 1). Modification of the Stille procedure involving the use of NMP (N-methyl-2-pyrrolidinone) instead of THF allows coupling to proceed at an appreciable rate, hence defining the relative rate for the subsequent reactions in the table. In contrast to previous studies[4] with olefinic stannanes, the present coupling is not dramatically accelerated by tri-2-furylphosphine (entry 3). Interestingly, conducting this example in the absence of LiCl led to rapid consumption of starting material (rel. rate of 56) but furnished less than 10% of the desired product. Little change occurred when trimethoxyphenyl phosphine[5] was employed (entry 4). Improvement was observed when the ligand was switched to tri(o-tolyl)phosphine or triphenylarsine (entries 5-8). In the case of the arsine ligand added halide exerts only a minor effect on relative rate, as well as reaction yield. The reaction proceeds at such a rate that it can be run at ambient temperature.

Finally, ligandless conditions[6] (entry 9) led to the fastest coupling rate with only moderate drop in yield. The competing side reaction throughout this study was the formation of the corresponding biaryl. This oxidative process is especially prevalent *in the absence of halide* and seems to depend on the presence of oxygen in the reaction medium.[7]

Table 2 serves to illustrate the generality of this new protocol.[8] Both arylstannanes with electron withdrawing or donating substituents couple in high yield. Ortho substitution on the stannane is also well tolerated. It is worth noting that the hindered triflate shown in the last example only coupled efficiently in the absence of a ligand.

Table 2. Generalized Coupling Between Vinyl Triflates and Arylstannanes

Triflate	Stannane	Conditions	Product	Yield^a
		Pd_2dba_3 $AsPh_3$, RT		89
		Pd_2dba_3 LiCl, RT		83
		Pd_2dba_3, RT		77
		Pd_2dba_3 $AsPh_3$, RT		72^b
		Pd_2dba_3 LiCl, RT		60

a. Isolated yield of pure product, satisfactory analytical data obtained
b. Starting triflate was 100% Z-isomer, isolated product was 95% E-isomer

In summary, we have demonstrated that appropriate choice of a catalyst system makes the coupling of vinyl triflates and arylstannanes efficient enough to be of general synthetic utility. This study also raises some questions of mechanistic significance. Little is understood about the mechanistic details of the transmetalation step, especially with respect to the role of halide ion. This and other issues are currently being studied and will be addressed in a future publication.

Acknowledgements

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7. We believe that this competing homocoupling of the arylstannane has a radical component; preliminary studies show that this reaction is partially inhibited by BHT. A complete study of this reaction will be reported in due course.

8. Typical reaction procedure:
   To a degassed solution of triflate (1 mmol) in dry NMP was added $AsPh_3$ (0.08 mmol) or LiCl (3 mmol) followed by addition of Pd_2dba_3 (0.01 mmol). The resulting solution became pale yellow after 5 to 10 min. At this point, the appropriate stannane (1 mmol) was added. The reaction was typically allowed to stir overnight at ambient temperature. Workup consisted of partitioning the reaction between water and hexanes or ethyl acetate and the organic fraction was washed with additional water, then stirred over a saturated aqueous KF solution for 30 min. The organic fraction was dried ($MgSO_4$), and concentrated. Products were purified by flash chromatography, recrystallization, or distillation.

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