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Palladium(II)-Catalyzed Coupling of 2-Carboxyethyl Enol Triflates with Organostannanes.

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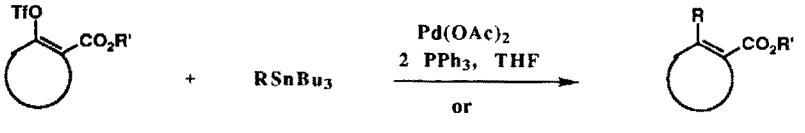
Summary : Enol triflates **1-5**, derived from the corresponding dicarbonyl compound, were coupled with tin reagents **6-8** using $Pd(OAc)_2$ and PPh_3 as the catalyst, at 7 mole %, in 56-91% yield.

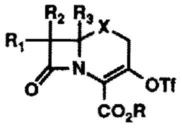
Substituted α,β unsaturated esters, such as **B**, are functional moieties common to several natural products[1] as well as useful precursors to sp^3 quaternary centers and, when R= vinyl, Diels-Alder dienes. The most common strategy for formation of the C_β -C_γ bond is the displacement of β-leaving groups, (eg. RPO_3-, RSO_2- and CH_3CO_2-)[2,3,4] derived from β-ketoesters, with alkyl cuprates. This method suffers from the limitations typically associated with cuprate chemistry: (a) allylic cuprates react sluggishly, (b) alkynyl groups are not transfered at all, and (c) the reaction requires rigorous exclusion of oxygen and water.

Stille-type[5] palladium (0) catalyzed coupling of β-trifluoromethanesulfonate α,β unsaturated esters with stannanes presents an attractive alternative (eq 1).



A **B** eq 1

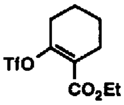
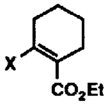
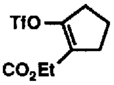
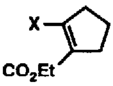
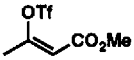
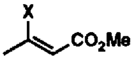
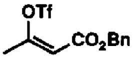
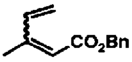
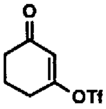
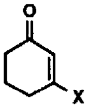
Tf= $-SO_2CF_3$



C

Indeed, the chemistry of such triflates has been examined in the synthesis of cephalosporin derivatives of the general structure **C**.[6,7] These investigations revealed that the usual Stille conditions [stannane, $Pd(PPh_3)_4$, LiCl, THF reflux] fail to produce coupling products with compounds **C**. Use of $Pd_2(dba)_3$ and tri(2-furyl)phosphine in the presence of $ZnCl_2$ in N-methylpyrrolidinone was necessary to achieve useful yields of coupling product.[7]

TABLE 1: Results of the Coupling of Enol Triflates 1-5 with Organotins 6-8

Enol Triflate	Organotin	Product	Reaction time[a]	Isolated yield %
 1				
	 6	X= CH_2=CH- 10	4 h	81
	 7	X= CH_2=CH-CH_2- 11	6 h	66
	Ph—≡—$SnBu_3$ 8	X= Ph—≡— 12	1 h	78
	Ph–$SnBu_3$ 9	X= Ph	–	N. R.
 2				
	6	X= CH_2=CH- 13	6 h	61[b]
	7	X= CH_2=CH-CH_2- 14	12 h	56[c]
	8	X= Ph—≡— 15	20 min	83
	9	X= Ph	–	N. R.
 3	8	 X= Ph—≡— 16[e]	30 min	56
 4	6	 17a / 17b = 1 : 1.5[d]	4.5 h	78
 5				
	6	X= CH_2=CH-	1 h	60
	8	X= Ph—≡—	40 min	91

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a All reactions were run using $Pd(OAc)_2$ (7 mole %), PPh_3 (14 mole %), in THF at 55 °C using 20 mole % excess of the organotin.
b Yield is low due to volatility of the product.
c 25% Of starting material was recovered.
d Determined by NMR analysis of the crude reaction mixture.
e Only one isomer detected by NMR.

In this letter we would like to report results that indicate that in the case of simple hydrocarbon derivatives such specialized reaction conditions are not required. The coupling can be accomplished efficiently with commercial $Pd(OAc)_2$ and triphenylphosphine in tetrahydrofuran under mild and neutral conditions. Recently we also discovered that commercial $Pd(PPh_3)_4$ in the absence of LiCl gave results comparable to the Pd(II) process.[8]

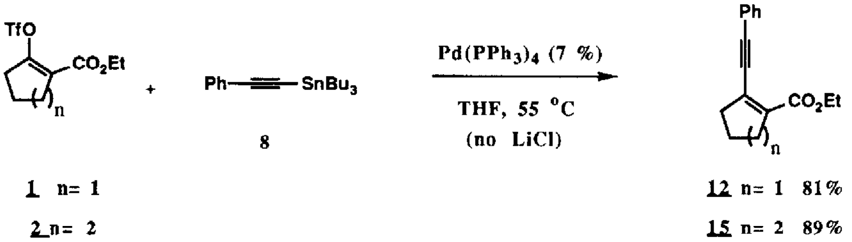
The enol triflates can be prepared in good yield from the corresponding ketoesters by treatment with NaH followed by N, N-bis-(trifluoromethanesulfonyl)-N-phenylimide and purification by flash chromatography. Commercial stannanes, $Pd(OAc)_2$, and triphenyl phosphine were used. No special purification or drying of the starting material or solvents was necessary (THF was simply dried over 4A molecular sieves and used without degassing or distilling from benzophenone ketyl).

A solution of enol triflate **1** (see Table 1 and eq 1) and vinyl tributyltin (**6**) in THF was treated with 14 mole % of PPh_3 and 7 mole % of $Pd(OAc)_2$[9] and heated at 55 °C for 4 hours under N_2. The resulting red homogeneous reaction mixture was concentrated in vacuo and the residue chromatographed (35:1 hexane-EtOAc) to furnish an 81% yield of the coupling product **10**[10]. Subsequently, esters **1-4** and ketone **5** were treated under these conditions with stannanes **6-8** with the results summarized in Table 1. Good yields of the products **10-19** were isolated in a convenient and robust process.

Inspection of Table 1 revealed some interesting trends. Alkynyltin **8** reacted ca. 10 times faster than vinyltin **6** while phenyltributyltin (**9**) failed to react with any of the enol triflates examined. Indeed **9** does not react even when $Pd(O_2CCF_3)_2$ was used in DMF at 110 °C for two days. The reaction of allyltin **7** with **1** and **2** was also interesting. The initial yellow solution turned black as Pd metal precipitated within a few minutes at 55 °C, and the progress of the reaction stopped. Only when additional **7** (0.5 equiv), $Pd(OAc)_2$ (0.07 equiv) and PPh_3 (0.14 equiv) were added did the reaction reach completion. This behavior was attributed to reduction of Pd(II) to Pd(0), which could be the result of a double transmetallation, to form the bis-allylpalladium species, followed by reductive elimination.

An intriguing result was obtained in the reaction of **4** with **6**. According to Stille's oxidative addition-reductive elimination mechanism, a single enol triflate isomer of **4** should give a single isomer of **17**[11]. However, when **4** (as a single C=C isomer by NMR) was treated with vinyltributyltin under the usual $Pd(OAc)_2$ conditions two double bond isomers, **17a** and **17b**, were formed in a ratio of 1:1.5. Surprised by this result we varied the reaction conditions in an attempt to better understand this reaction. Reaction of **4** with **6** in the presence of $Pd_2(dba)_3.CHCl_3$ (7 mole %) at 23 °C in THF for 48 hours gave **17b** exclusively although in only 30% conversion, while at 55 °C no coupling was observed presumably due to catalyst decomposition. In the presence of 4 equivalents of PPh_3 per equivalent of Pd(0), the coupling product was obtained within 2 hours, however the ratio of **17a** to **17b** was 2:1. The same result was observed when commercial $Pd(PPh_3)_4$ was used as the catalyst (87% yield). Control experiments showed no isomerization between **17a** and **17b** under either Pd(II) or Pd(0) catalysis. Although no firm mechanistic conclusions can be derived from these preliminary results, the mechanism is clearly more complicated than a simple oxidative addition of a Pd(0) species to the C-OTf bond followed by transmetallation and reductive elimination.

The $Pd(PPh_3)_4$ result prompted us to further investigate the Pd(0) catalyzed process (eq 2). Reaction of **1** or **2** with **8** using 7 mole % of commercial $Pd(PPh_3)_4$ in THF at 55 °C for 15 minutes, afforded **12** and **15** in 81 and 89% yield respectively. It is noteworthy that the Pd(0) catalyzed reactions proceeded at similar rates to the Pd(II) reaction even in the absence of LiCl. Similar results have been observed by Piers[12] in an intramolecular coupling.



eq 2

In conclusion, efficient and convenient coupling of allyl, alkynyl and vinyl stannanes with β-trifluoromethanesulfonate-α,β-unsaturated esters has been accomplished under $Pd(OAc)_2$ or $Pd(PPh_3)_4$ catalysis. No special reagents are required and scrupulous exclusion of oxygen and water are not necessary. The chemistry of other functionalized stannanes and vinyl triflates is currently under study.

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