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Palladium-Catalyzed Cross-Coupling Reaction of Allyl Carbonates with Organostannanes

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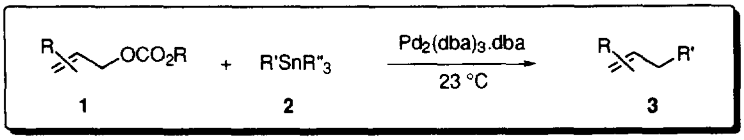
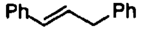
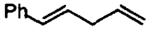
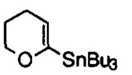
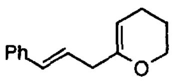
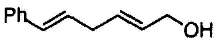
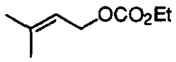
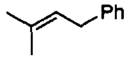
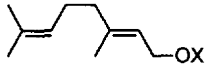
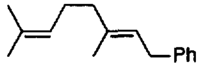
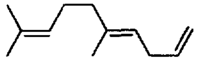
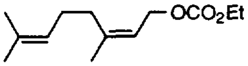
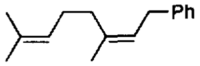
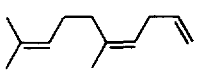
Abstract: Allyl carbonates are excellent substrates for the palladium(0)-catalyzed coupling reaction with stannanes under very mild conditions. The reaction proceeds via (η^3-allyl)palladium complexes which undergo syn-anti equilibration with a rate similar to that of the transmetallation step.

The palladium-catalyzed cross-coupling reaction of organic electrophiles with organometallic nucleophiles is one of the most versatile and efficient methods for the formation of carbon-carbon bonds.[1] A great variety of organic electrophiles have been shown to react with mild organometallic nucleophiles such as tetraorganostannanes (Stille reaction)[2] and organoboranes (Suzuki reaction).[3] The Stille coupling reaction has been widely applied in organic synthesis because of the availability and stability of organostannanes and their ample compatibility with most organic functional groups.[1,2] Allylic electrophiles readily react with palladium(0) to form (η^3-allyl)palladium(II) complexes which can transmetallate with stannanes.[4] The Pd(0)-catalyzed reaction of allylic halides with organostannanes was described in 1983,[5] while the use of the more readily available allylic acetates has been described more recently.[6,7] In this case, the coupling reaction was realized with $Pd_2(dba)_3$.dba[8] as the catalyst in DMF in the presence of excess LiCl.[9] As part of another project, we have experienced difficulties in performing an intramolecular coupling of an allyl acetate with a vinyl stannane.[10] Consequently, we decided to study the use of allylic carbonates as the starting electrophiles[11] in the cross-coupling process. Herein we report that allylic carbonates **1** are indeed excellent substrates for the palladium-catalyzed coupling reaction with organostannanes **2**, yielding coupled products **3** under mild conditions in shorter reaction times and, generally, with higher yields than the corresponding acetates. As expected, the reaction proceeds through (η^3-allyl)palladium intermediates which undergo syn-anti isomerization. Importantly, this palladium-catalyzed coupling reaction can also be carried out in water as the solvent at ambient temperature.



The reaction of allylic carbonates **1-4** with aryl and vinyl tributylstannanes **5-8** takes place smoothly using $Pd_2(dba)_3$.dba as the catalyst in DMF at room temperature. As has been observed before for this type of couplings,[6,9] no reaction was observed with phosphine-based catalysts. A selection of results is shown in Table 1. Both di- and trisubstitued ethyl carbonates undergo the cross coupling reaction. For most of the examples the addition of 2-3 equiv of water proved favorable in terms of reaction times and/or yields.[12]

Table 1. Pd(0)-Catalyzed Cross Coupling of Allyl Carbonates with Organotin Reagents.[a]

carbonate	*stannane*	*product*	*time (h)*	*yield (%)*[b]
 (1)	$PhSnBu_3$ (5)	 (9)	1	96
1	 (6)	 (10)	9.5	53[c]
1	 (7)	 (11)	3	92[d]
1	 (8)	 (12)	3	83
 (2)	5	 (13)	2	57
	5	 (14)		
3a : X = CO_2Et			24	57 (91% *E*)
3a			24	67 (93% *E*)[e]
3a			44	88 (93% *E*)[e]
3b : X = $CO_2CH_2CCl_3$			1.5	82 (74% *E*)
3c : X = $COCF_3$			1.5	93 (79% *E*)[f]
3d : X = $COCH_3$			42	65 (88% *E*)[e,f]
3a	6	 (15)	3	61 (91% *E*)[e]
 (4)	5	 (16)	24	85 (83% *Z*)
4	6	 (17)	3	88 (84% *Z*)[e,g]

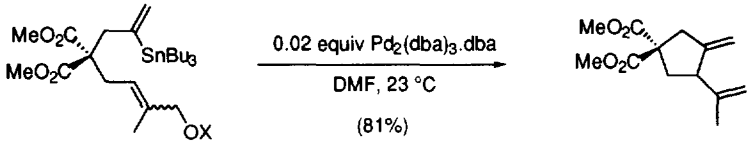
[a] Unless otherwise stated, the reactions were carried out as follows: $Pd_2(dba)_3$.dba (0.02 equiv) was added to a mixture of carbonate (0.5 mmol), stannane (1.1-1.3 equiv) and water (2-3 equiv) in DMF (1 mL) under Ar. The reaction mixture was stirred at 23 °C until TLC showed full conversion. [b] Isolated yields after flash chromatography. Figures in parenthesis show percentage of double bond stereochemistry, determined by GC-MS. [c] 4 mol% catalyst. [d] 5 mol% of catalyst and 1.4 equiv of 7 were used in anhydrous DMF. [e] LiCl (3 equiv) was added. [f] No water was added. [g] Reaction performed in DMF-THF (10:1).

However, the addition of water is not essential. Thus, hydrolytically labile dihydropyranyl stannane **7**[13] coupled with carbonate **1** efficiently in anhydrous DMF to furnish **11** in excellent yield. The reaction proceeds well with stannane **8** bearing an allylic alcohol, yielding a new allylic substrate **12** that could be further elongated by using this protocol. As expected, retention of the stereochemistry of the alkenyl stannane was observed in this reaction.

The reactivity of carbonates and carboxylates was compared with geranyl substrates **3**. Trichloroethyl carbonate (TROC) **3b** and trifluoroacetate **3c**[14] gave the fastest reactions, followed by ethyl carbonate **3a**. On the other hand, acetate **3d** gave the slowest coupling.[6] The initial reaction of **3a** in the presence of 4 equiv of LiCl[6] was considerably slower than that carried out in the absence of chloride (after 0.5 h at 23 °C: with LiCl, 10% conversion; without LiCl, 70% conversion), but the final conversion was slightly better (95% vs. 90%) due to some decomposition of the catalyst leading to palladium black in the absence of added chloride. This result suggests that LiCl leads to the formation of more stable palladium intermediates, which are less reactive. The decomposition of the palladium intermediates is augmented in wet DMF due to the inmiscibility of the tin by-products, which separate from the reaction solution favoring catalyst precipitation. This effect can be minimized by the addition of small amounts of THF.

It has been previously reported that allyl acetates couple with retention of the alkene stereochemistry in the allyl electrophile.[6] This result is somewhat surprising for a reaction that proceeds through (η^3-allyl)palladium complexes which are known to suffer facile syn-anti isomerization.[4] In fact, in all the experiments that we have carried out with geranyl or neryl substrates some loss of double bond stereochemistry was observed.[15] However, the equilibrium between the 3,3-disubstituted (η^3-allyl)palladium intermediates was not reached since predominant conservation of double bond stereochemistry was obtained in the coupling reactions of geranyl (**3**) and neryl derivatives (**4**).[16] This result indicates that the final transmetallation of the (η^3-allyl)palladium intermediates with the organostanne proceeds with a rate similar to that of the syn-anti isomerization.

This protocol proved very efficient in the cyclization of stannane **18**[10] to yield methylenecyclopentane derivative **20** in 81% yield after 5 h at 23 °C, whereas the reaction of acetate **19** in the presence of LiCl was very slow under otherwise identical conditions (<50% conversion after 15 h).[6]



18 : X = CO_2Et
19 : X = COMe

20

An interesting aspect of this palladium-catalyzed cross-coupling procedure is that it can be carried out in water, either in the presence or absence of added LiCl.[17] Thus, the reactions of carbonate **1** with stannanes **5** and **6** were performed in water at 23 °C with $Pd_2(dba)_3$.dba as the catalyst leading to **9** and **10** in 93% and 41% yields, respectively.

Although faster coupling reactions were obtained by using TROC or trifluoroacetyl derivatives, ethyl carbonates are more convenient substrates in terms of their stability towards hydrolysis. On the other hand, the enhanced reactivity of the substrates with better leaving groups demonstrates that the rate-determining step of this process is the oxidative addition of the allyl electrophile to palladium(0). Interestingly, preliminary mechanistic studies indicate that, contrary to what was expected,[11] no decarboxylation of the primary oxidative addition product takes place in these reactions.[18,19] Efforts aimed at determining the nature of the reactive palladium intermediate in this reaction are underway.

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