Pure & Appl. Chem., Vol. 68, No. 1, pp. 73–78, 1996.
Printed in Great Britain.
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New perspectives in the cross-coupling reactions of organostannanes

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ABSTRACT

The palladium-catalyzed coupling of organostannanes (the Stille reaction) can be accelerated in a number of ways. Three approaches are described here. In the first one, it is shown that ligands of low donicity dramatically accelerate the Stille coupling, and a simple kinetic scheme is presented. In the second approach, intramolecular nucleophilic assistance at tin is provided. The mechanistic implications of our data are briefly discussed. Finally, bimetallic catalysis (in this case with Cu(I) salts) is shown to lead to faster coupling rates and better selectivities.

INTRODUCTION

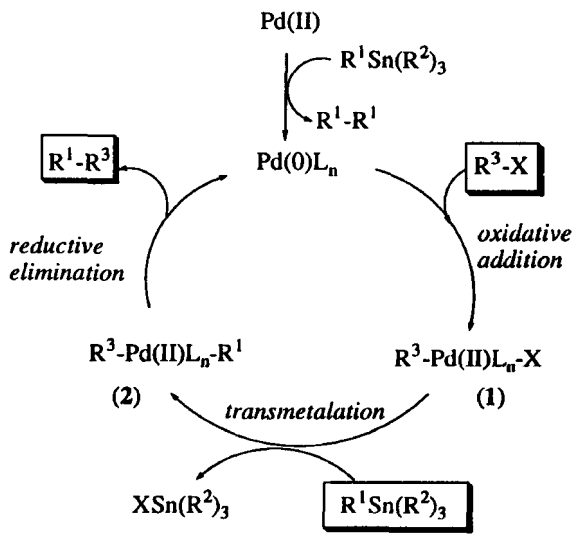
The palladium-catalyzed coupling of organostannanes with organic electrophiles, developed in recent years by Stille (Eq. 1), is rapidly becoming a very popular synthetic tool.[1,2] Although it is only one within the large family of cross-coupling reactions which includes, among others, the coupling of organomagnesium,[3] -zinc,[4] -boron,[5] and -silicon reagents,[6] the Stille reaction enjoys perhaps a wider scope than any other cross-coupling reaction, due to the stability and low cross-reactivity of organotin compounds.

$$R^1Sn(R^2)_3 + R^3X \xrightarrow{Pd(0)L_n} R^1\text{-}R^3 + (R^2)_3SnX \qquad \text{(Eq.1)}$$

Unfortunately, the low reactivity of organostannanes can also be a drawback in their coupling. Many of the original conditions described by Stille[7] require rather harsh temperatures (up to 100°C), to which some substrates simply do not stand up. In addition, side reactions can ensue under these drastic conditions. We recognized as early as in 1988 that, in order to augment the utility of this reaction, tools that would accelerate the transmetalation, *i.e.*, the rate-determining step in all Stille coupling that employ reactive electrophiles (unsaturated iodides and triflates, *etc.*), would be very important.[8]

The generally accepted catalytic cycle for the Stille reaction is shown in Scheme 1, which also shows that the palladium catalyst can be introduced either as Pd(II), in which case a pre-reduction reaction takes place, or directly as the "active" Pd(0) species.

Scheme 1: *Catalytic Cycle for the Stille Reaction*



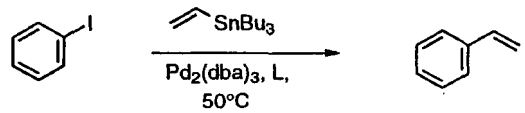
In this account I would like to present three approaches that we have investigated with an aim at increasing the rate of the transmetalation: the first employs the use of new ligands of low donicity to enhance the electrophilicity and hence the reactivity of the Pd(II) intermediate (**1**) toward the stannane; the second attempts to provide intramolecular nucleophilic assistance at departing tin in the transition state, or to increase the nucleophilicity of the stannane by enforcing pentacoordination at tin; the third introduces a further transmetalation step to yield a more reactive organometallic species (in this particular case an organocopper compound), thus leading to increased reactivity and, in the few cases examined, better selectivity. I will discuss how these three approaches have led to synthetic advances in this field, and I will also show that they have enhanced our mechanistic understanding of this important reaction.

LIGAND EFFECTS IN THE STILLE REACTION

Prior to our study on the effect of ligands on the rate of the Stille reaction, ligand effects had apparently never been systematically investigated in the field of cross-coupling chemistry. We discovered a very substantial ligand effect in a model coupling, the one between iodobenzene and vinyltributyltin (Scheme 2), and showed that this kind of effect is quite general for a variety of Stille couplings.[9]

In general, ligands of low donicity are associated with the fastest rates, whereas strong donors like the traditional PPh_3 are inhibitors of the reaction. Rate enhancements of 10^2-10^3 can be effected with tri(2-furyl)phosphine and $AsPh_3$. In addition, free ligand inhibits the reaction: the degree of inhibition is considerable for ligands of high donicity, but is small for the poorer donors. A minimal kinetic scheme that is consistent with all experimental data is shown in Scheme 3.[2] It proposes a pre-equilibrium between fully coordinated species **3** and a coordinatively unsaturated intermediate, **4**.

Scheme 2:
Summary of Ligand Effects in the Stille Reaction

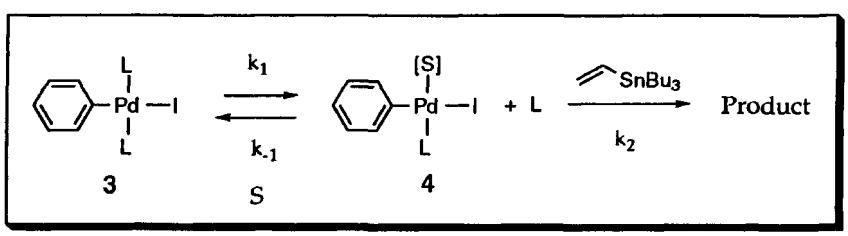


Ligand=L	Rel k_{obs}	Inhib. Factor
(*p*-MeO-C_6H_5)$_3$P	<0.07	>100
PPh_3	1.0	19
(tri-2-furyl)$_3$P	105	3.7
$AsPh_3$	1100	1.3

Reactions at 50°C in THF (0.16M Reagents, 3.2 mM Pd, 12.8 mM Ligand)

From this scheme, one can derive an expression for the observed kinetic constant k_{obs} (Eq. 2, 3). As predicted from a knowledge of the rate-determining step, the kinetics are first order in stannane and zero order in iodobenzene. From measuring the coupling rate at different ligand concentration, and plotting 1/k *vs.* [L] (Eq. 4), the kinetic parameters can be extracted (Table 1).[2] As one can see, this model predicts wide variability in K (the pre-equilibrium constant), which therefore turns out to be the key parameter that governs the overall rate of the cross-coupling. Ligands of high donicity (PPh_3) inhibit the reaction because they allow only minute concentrations of the reactive species **4** at equilibrium.

Scheme 3:
Minimal Kinetic Scheme for the Transmetalation Reaction



$$[3] + [4] = [Pd] \qquad \frac{[4][L]}{[3]} = K = k_1/k_{-1} \qquad \text{(Eq. 2)}$$

$$\frac{d[P]}{dt} = K_{obs}[\text{stannane}] = \frac{k_2 K [Pd]}{[L] + K}[\text{stannane}] \qquad \text{(Eq. 3)}$$

$$\frac{1}{k_{obs}} = \frac{1}{Kk_2[Pd]}[L] + \frac{1}{k_2[Pd]} \qquad \text{(Eq. 4)}$$

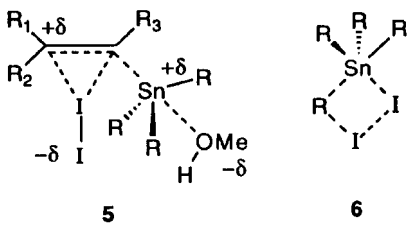
Table 1: *Kinetic Parameters from Eq. 4 for a Select Number of Ligands.*

Ligand	$K=k_1/k_{-1}$	$k_2(min^{-1})$
$AsPh_3$	0.86	0.29
Tri(2-furyl)phosphine	6×10^{-3}	1.68
PPh_3	$<5 \times 10^{-5}$	not det.

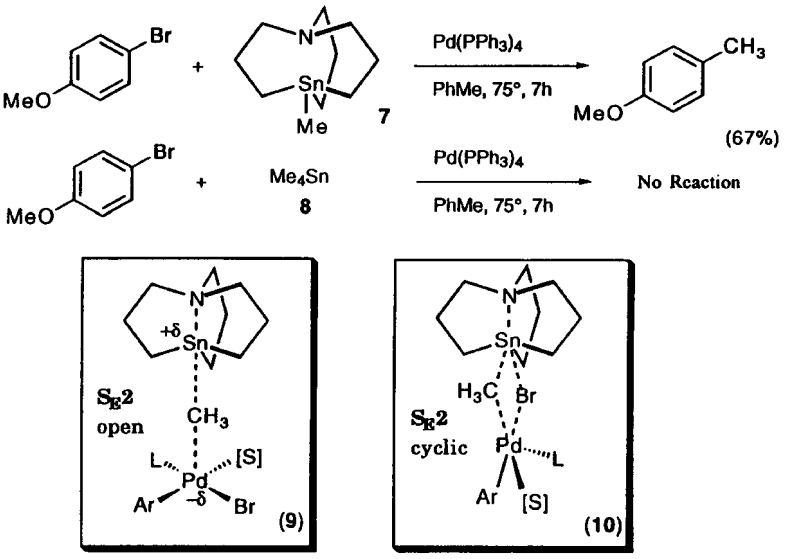
These studies have uncovered two new useful ligands for cross-coupling chemistry. Both tri(2-furyl)phosphine and $AsPh_3$ have been used widely by many workers in recent years. Their applicability to cross-coupling reactions other than the Stille protocol remains to be verified. Although substitution reactions at square planar Pd(II) complexes usually proceed associatively *via* pentacoordinated intermediates,[10] we have shown that in the case where the nucleophile is an organostannane, the Pd(II) electrophile must be coordinatively unsaturated to engage in transmetalation. Although this suggestion appeared at the time unprecedented, recent related observations show that these findings may be fairly general.[11]

INTRAMOLECULAR NUCLEOPHILIC ASSISTANCE AT TIN

In order to fully understand the mechanism of the transmetalation reaction, consideration of the coordination sphere of the Pd(II) intermediate is not sufficient. One must consider also the exact coordination sphere of tin in the transition state and its geometry. Electrophilic substitutions of organotin compounds have been studied by a variety of workers. Typically, at least two limiting mechanisms are considered: one, called S_E2(open) is exemplified by **5** (Scheme 4) for the iodinolysis of vinyltins.[12] In its transition state tin bears some positive charge. These transition states are common in highly polar and/or nucleophilic solvents, in which such positive charge can be somehow stabilized. Electrophilic reactions in non-polar solvents appear to proceed instead by S_E2(cyclic) mechanism, as exemplified by **6** (iodinolysis of tetraalkyltins in chlorobenzene).[13] The most common tool used in distinguishing between these mechanisms has been the effect of inert salts.[14]



Scheme 4: *Proposed Transition States for Electrophilic Substitutions at Tin*



Scheme 5: *Example of Nucleophilically-Accelerated Transmetalation and Possible Transition States.*

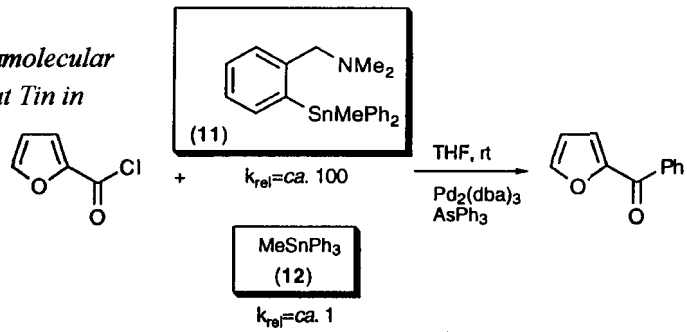
In addition, Stille has shown that when the electrophile is a Pd(II) intermediate, the transmetalation occurs with predominant *inversion of configuration* at carbon, which implies an S_E2(open) mechanism.[7] We have shown, in a Hammett study, that the transmetalation using organic triflates follows essentially different mechanisms depending on whether LiCl is added or not.[15]

It seems intuitive that, if nucleophilic assistance at tin is important in stabilizing the transition state of the transmetalation and related electrophilic cleavages, then a stannane that incorporated an intramolecular nucleophile may react at increased rates *vs.* its simple trialkyl counterpart. As we were exploring these ideas,[15] both Vedejs and Brown published two independent studies that seemed to confirm the validity of these concepts: Vedejs showed that stannane **7**, in which the Sn-Me bond is *anti* to the nucleophilic *N* atom, transfers a Me group much more rapidly than Me_4Sn (**8**) (Scheme 5).[16]

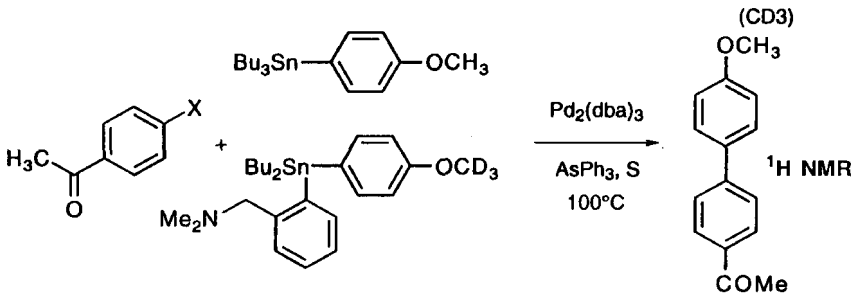
If the transition state is "open" (*e.g.* **9**), it is conceivable that the apical *N* in **7** may stabilize the partial positive charge at tin, much like the solvent does in **5**. But because the reaction was carried out in toluene, an open transition state appears unlikely. In the alternative "cyclic" model (**10**), the Sn-C bond may still be weakened by pentacoordination at tin, and methyl transfer facilitated as a result. Transition states **9** and **10** can be proposed based on Vedejs' results and the discussion in the previous section. In addition, Vedejs showed that a variety of alkyl groups may be transfered to palladium, whereas similar reactions failed with the corresponding tributyltin derivatives.

In the same vein, Brown showed that phenyl group transfer from tin to palladium is accelerated *ca.* 100-fold using stannane **11** *vs.* methyltriphenyltin (Scheme 6).[17] In all these experiments quantitative rate measurements were not given. In addition, since the solvent appears to control the mechanism of the transmetalation, we felt it would be important to obtain quantitative rate estimations in different solvents, in order to see whether the intramolecular nucleophilic assistance may be operative in the context of "open" or "cyclic" transition states, or both.

Scheme 6:
Another Example of Intramolecular Nucleophilic Assistance at Tin in the Transmetalation.



In order to extract preliminary quantitative data from our experiments, we decided to carry out the competition experiment shown in Scheme 7.[18] We studied the transfer of an aryl moiety from tin to palladium in three solvents of different polarity, labeling with deuterium the moiety originating from the nucleophilically "armed" stannane. Simple inspection of the ^{1}H NMR spectrum provided an estimation of the two transmetalation rates. As clear from Scheme 7, in none of the solvents does the nucleophilic "arm" exert a significant kinetic effect (negative or positive). We next investigated the use of a triflates as the electrophile. Triflates usually require the addition of LiCl to couple, but LiCl is not required in polar solvents such as NMP.[15] Since triflate is a weak Pd ligand, the occurrence of an S_E2(cyclic) transition state is virtually impossible here and the mechanism has to be of the "open" type. As clear from the data in Scheme 7, nucleophilic assistance is obviously unimportant in this case.



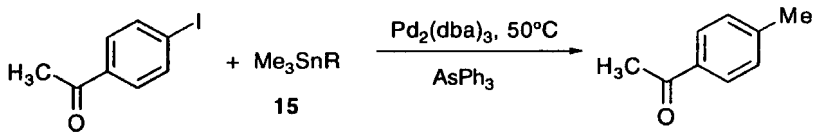
X	Solvent	ratio OCH_3/OCD_3
I	PhMe	1.2
I	dioxane	0.94
I	NMP	0.91
OTf	NMP	1.5

Scheme 7: *Quantitative Measurement of the Kinetic Effect in Intramolecularly-Assisted Transmetalations.*

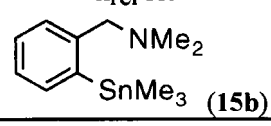
We have also shown that another coordinating ligand proposed by Brown, the 8-(dimethylamino)-1-naphthyl moiety, is completely ineffective at nucleophilically assisting tin during the transfer of aryl groups to Pd(II) under the above conditions.[18] These results are puzzling and clearly at odds with the literature. Importantly, these data pertain only to phenyl transfer. We elected to study the transfer of

an alkyl group (*i.e.* methyl), which may in principle proceed by a different mechanism. In this case no simple competition experiment could be devised, and we resorted to the absolute measurement of kinetic rate constants. Some results are shown in Scheme 8.

These preliminary data indeed show a modest but significant rate acceleration due to the chelating (dimethylamino)methyl substituent. The rates are corrected for the statistical factor. Whereas the effect is minor in NMP, the "promoting effect" of the arm reaches about one order of magnitude in toluene, the solvent with the lowest polarity. This points to a fundamental change in the the structure of the transition state on going from dipolar to non-polar solvents. In particular, it seems plausible that the transmetalation in toluene and dioxane may proceed through a "cyclic" S_E2 mechanism, and it seems therefore that the coordinating arm is uniquely capable of stabilizing these "closed" transition states as opposed to "open" ones. It appears possible that larger effects may be observable with better scaffolds.



a) R=Me
b) R= *o*-Me_2NCH_2-C_6H_4

Solvent	k_{rel} for Me_4Sn (**15a**)	k_{rel} for  (**15b**)	k(**15b**)/k(**15a**)
PhMe	1.0	9.2	9.2
dioxane	2.7	17.5	6.5
NMP	50	79.2	1.6

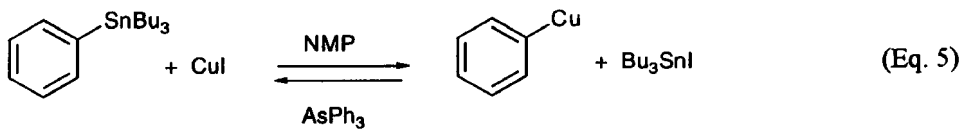
Scheme 8: *Quantitative Measurement of the Intramolecular Coordination at Tin in Methyl Group Transfer.*

Why such an effect is not seen in the aryl transfer reaction is very hard to say at this point. It is not clear how synthetically significant this intramolecularly assisted group transfer may turn out to be, but from a mechanistic viewpoint the dichotomy described here is certainly intriguing, and further kinetic work may enable us to propose a detailed model of the transition states.

EFFECT OF COPPER SALTS

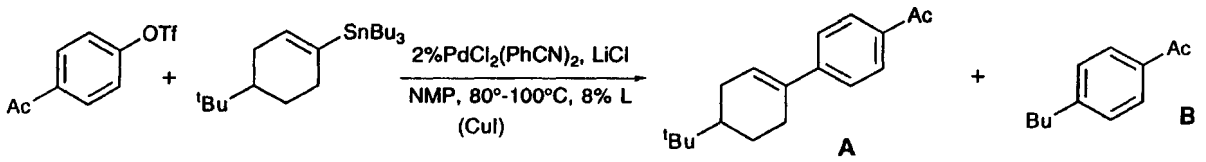
Application of a second metal salt in cross-coupling reaction has been a common approach to enhance reactivity and sometimes selectivity.[19] The use of co-catalytic copper(I) in the Stille coupling was introduced by Liebeskind.[20] In recent years, in collaboration with Prof. Liebeskind, we have begun to study the mechanistic basis of this effect.[21]

Our initial data in dioxane suggested that Cu(I) acted as a "phosphine scavenger" in these couplings. Since ligand dissociation from **3** (Scheme 3) is a key event in the transmetalation, any secondary metal ion with an affinity for phosphines may help shift this pre-equilibrium toward **4**. In this way, CuI provides up to 100-fold acceleration in conjunction with PPh_3 as a ligand, but is essentially ineffective with $AsPh_3$, a ligand endowed with low donicity. When working in NMP, however, a second effect becomes important. ^{119}Sn NMR data show that aryl and alkenyl stannanes react with CuI in NMP, in the presence of "soft" ligands like $AsPh_3$ (but not with strong donors like PPh_3), to afford an apparent equilibrium containing presumably an organo-copper species (Eq. 5). That this may be favored at equilibrium and be more effective in the transmetalation may seem a contradiction, but one must take into consideration both products formed in the reaction. The non-polar stannane is cleaved to a trialkyltin halide, which is strongly stabilized in NMP through pentacoordination, and this may constitute a substantial thermodynamic contribution to the reaction in Eq. 5.



(Eq. 5)

In addition to kinetic accelerations, this Sn/Cu transmetalation affects the selectivity of group transfer in the Stille reaction. Although methyl and butyl groups at tin are used as bystanders, in many cases they can compete with more reactive moieties in the transfer reaction onto Pd(II). One case is shown in Scheme 9.[15]



Ligand	Temp.(°C)/Time	A/B
tri(2-Furyl)phosphine	100°/5h	64:36
$AsPh_3$	80°/7h	90:10
$AsPh_3$ + 5% CuI	80°/6h	>98:2

Scheme 9: *Group Transfer Selectivity Enhancement in the Stille Reaction by Co-Catalytic Copper.*

In this case, although the appropriate choice of ligand ameliorates the selectivity, simple addition of 5% CuI renders alkenyl transfer virtually exclusive. This observation has obvious mechanistic and synthetic relevance. More dramatic examples of this selectivity effect have been reported by Levin.[22]

The formation of organocopper species directly from stannanes opens up new possibilities in tin chemistry, *e.g.* the cross-coupling of organostannanes promoted by copper salts only. Preliminary results have shown that this is indeed possible, and we are currently studying the generality of the process and its mechanistic aspects. Recent publications have also suggested that Cu-promoted coupling of organostannanes may become a synthetically important reaction.[23,24]

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