On the Nature of the "Copper Effect" in the Stille Cross-Coupling

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Received June 1, 1994®

The effect of added CuI on the kinetics of a typical Stille coupling was studied. With triphenylphosphine as Pd ligand, cocatalytic Cu(I) salts can yield a >100-fold rate increase over the traditional Stille conditions, but little effect was displayed when CuI was used in conjunction with a soft ligand, such as triphenylarsine. NMR studies suggest that CuI is an excellent scavenger for free ligand and, since strong ligands in solution are known to inhibit the rate-limiting transmetalation, one effect of copper salts is readily explained. In addition, however, when working in highly dipolar solvents like NMP and in the absence of strong ligands, unsaturated stannanes react with CuI to yield presumably an organocopper species, which then transmetalates to Pd(II). An example of altered group transfer selectivity due to cocatalytic copper is given, and it is suggested that this strategy may be of some general value.

Introduction

The Stille reaction,[1] defined as the cross-coupling between organic electrophiles (usually unsaturated halides or triflates) and organostannanes,[2] has recently become an extremely popular synthetic tool, and further developments in this arena are consequently quite desirable.

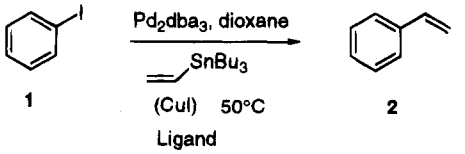
Among such developments, the discovery of a large ligand effect in this reaction has yielded rate enhancements of $>10^3$ over the original Stille conditions, in addition to furthering our mechanistic understanding of the rate-limiting transmetalation step.[3]

A second important development involves the use of cocatalytic Cu(I) and Pd(0) species in this coupling. This often results in largely improved rates and yields *vs* traditional catalysts like $Pd(PPh_3)_4$, although quantitative data in this area are lacking.[4] Among the many interesting subsequent applications of the "copper effect", Johnson has combined the use of soft palladium ligands like $AsPh_3$ with cocatalytic copper(I) in the particularly difficult Stille coupling of α-iodo enones,[5] and Falck has shown that the use of cocatalytic copper is the key for the successful Stille coupling of α-alkoxy- and α-(aminoalkyl)stannanes with acyl chlorides.[6]

In spite of the widespread use of cocatalytic Cu(I) in Stille cross-coupling chemistry, the exact role of copper in the reaction is not at all clear. Liebeskind[4] has suggested the possibility of a Sn/Cu transmetalation. The resulting organocopper species would then transmetalate onto Pd(II) at a higher rate than the stannane itself. Several features of the "copper effect" have not been discussed or examined. Specifically, a quantitative determination of the accelerating effect of Cu(I) over "Pd-only" couplings has not been reported. In addition, no attempts at demonstrating the Sn/Cu transmetalation have appeared. The relation between the well-characterized ligand effect and the "copper effect" is also of great interest. Will copper enhance the coupling rate in the presence of any palladium ligands or is the "copper effect" also ligand-sensitive? Finally, one of the problems in the Stille reaction is the lack of complete selectivity in the transfer of organic groups from the stannane. This is particularly acute with aryl trialkylstannanes[7] and even with some heavily substituted alkenyltrialkylstannanes,[8] where alkyl transfer can sometimes compete with the desired transfer of the unsaturated group. If copper(I) species are indeed involved in the transmetalation, one can envision the intriguing possibility that Cu(I) may alter the selectivity of such a step. The present paper deals with an examination of all the above issues and proposes *a dual mechanistic role for cocatalytic copper in the Stille reaction.*

Results

We first examined a simple, well-behaved Stille coupling, the reaction between iodobenzene and vinyltributyltin in dioxane at 50 °C,[2b,3] both in the presence and in the absence of copper(I) salts (eq 1).



(1)

We employed three ligands of different donicity, *i.e.*, the traditional PPh_3, then a ligand with moderate

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® Abstract published in *Advance ACS Abstracts,* September 1, 1994.

(1) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(2) Recent reviews: (a) Mitchell, T. N. *Synthesis* **1992**, 803. (b) Farina, V.; Roth, G. P. In *Advances in Metal–Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, Vol. 5, in press.
(3) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. Note that tri(2-furyl)phosphine is now commercially available (Aldrich).
(4) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.
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(6) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1. For other applications of the "copper effect", see references cited therein.
(7) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.
(8) Farina, V.; Baker, S. R.; Benigni, S. I.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833.

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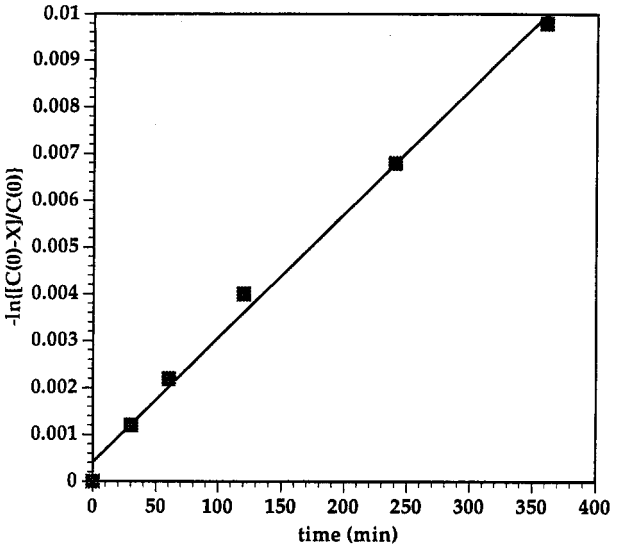
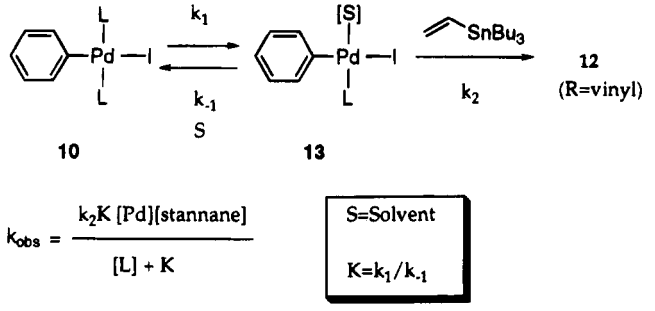


Figure 1. Kinetics of the coupling between iodobenzene (C_0 = 0.139 M) and vinyltributyltin (C_0 = 0.139 M), catalyzed by Pd_2dba_3 (5% mol Pd) and triphenylphosphine (20% ligand) in dioxane at 50 °C. k_{obs}: 2.66×10^{-5} min^{-1} (r^2 = 0.994).

Scheme 1



basicity, *i.e.*, (pentafluorophenyl)diphenylphosphine (comparable in donicity to the more popular trifurylphosphine, TFP),[3] and finally a "soft" highly dissociating ligand such as $AsPh_3$. Different ratios of Pd to ligand and Cu to Pd were explored. Concentrations of **1** and **2** were estimated at appropriate times during each run by quantitative HPLC analysis.[3]

In the absence of CuI, as already described previously,[2b,3] the kinetics were first order overall, and more specifically first order in stannane and zeroth order in iodobenzene, in agreement with a fast oxidative addition of Pd(0) to iodobenzene and a rate-determining transmetalation (see Scheme 1). Kinetics were well behaved only initially for L = PPh_3 (initial rates are therefore reported, see Figure 1) and throughout the coupling for the other two ligands. In the presence of CuI, a very good fit for all ligands (including PPh_3) was obtained by assuming overall first-order kinetics; a typical example is shown in Figure 2. The relative rate constants were then extracted from these plots and are shown in Table 1.

Entries 1–13 of Table 1 quantitatively document the "copper effect" in the presence of a typical ligand, PPh_3. While only a 5-fold increase was obtained when using a stoichiometry Pd:L:Cu of 1:4:1 (entries 1 and 2), better than 100-fold rate enhancements were obtained with a ratio of 1:4:2 (entry 3). Further increases in the proportion of CuI did not substantially increase the rates, but negatively affected the yield, due to reduced catalyst stability (entries 4 and 5). Use of CuBr instead of CuI also led to substantial rate enhancement (entry 6), while

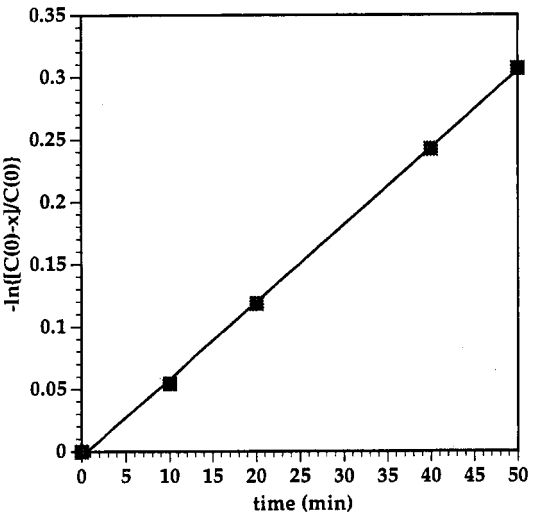


Figure 2. Kinetics of the coupling between iodobenzene (C_0 = 0.139 M) and vinyltributyltin (C_0 = 0.139 M), catalyzed by Pd_2dba_3 (5% mol Pd) and triphenylphosphine (20% ligand) *in the presence of 15% CuI* in dioxane at 50 °C. k_{obs}: 5.90×10^{-3} min^{-1} (r^2 = 1.00).

Table 1. Effect of Added CuI on the Rate of the Palladium-Catalyzed Coupling between Iodobenzene and Vinyltributyltin in Dioxane at 50 °C (Eq 1)[a]

entry	ligand	Pd:L:CuI molar ratio	10^5 k_{obs} (min^{-1}) [st dev][b]	HPLC yield[c] (%)
1	PPh_3	1:4:0	2.66 [0.35]	85
2	PPh_3	1:4:1	13.5 [1.1]	91
3	PPh_3	1:4:2	303 [31]	>95
4	PPh_3	1:4:3	590 [37]	78
5	PPh_3	1:4:4	523 [49]	45
6	PPh_3	1:4:2 (CuBr)[d]	260 [12]	90
7	PPh_3	1:2:0	170 [61]	91
8	PPh_3	1:2:2	547 [44]	56
9	PPh_3	1:4:2 + LiI (200%)	64.5 [9.8]	71
10	PPh_3	1:4:0 + LiI (200%)	1.70 [0.16]	nd
11	PPh_3	1:6:0	1.19 [0.08]	nd
12	PPh_3	1:6:2	5.82 [1.1]	nd
13	PPh_3	1:6:4	271 [77]	74
14	F_5C_6-PPh_2	1:4:0	185 [11]	>95
15	F_5C_6-PPh_2	1:4:1	367 [38]	>95
16	F_5C_6-PPh_2	1:4:2	401 [39]	>95
17	$AsPh_3$	1:4:0	7,210 [370]	>95
18	$AsPh_3$	1:4:1	9,200 [255]	>95
19	$AsPh_3$	1:4:2	9,640 [350]	>95
20	$AsPh_3$	1:4:4	9,350 [275]	>95

[a] PhI and vinyltin 0.14 M, 5% mol Pd (as Pd_2dba_3), plug ligand and additives as in the table. [b] Determined by HPLC. Kinetics were first order in stannane, zeroth order in iodobenzene. Each determination represents the average of two separate runs. [c] The yields (average of two runs) were determined by HPLC after the catalyst had decomposed, as shown by no further conversion (from 2 h for entries 17–20 to 175 h for entry 1). [d] CuBr was used instead of CuI, all other parameters being unchanged.

other salts, like CuCl, gave poor results (data not shown). Among other additives that were studied, halide salts are of special interest: even huge excesses of soluble iodide salts like LiI had minor effects on the rate increase caused by CuI (entries 9 and 10); on the other hand, excess PPh_3 had a major influence on the reaction. More specifically, 2 extra equiv of phosphine essentially eliminated the cocatalytic effect of copper (entry 12). This effect could be restored by doubling the amount of copper (entry 13). Noteworthy is the close match in reaction rates obtained with stoichiometries Pd:L:Cu of 1:4:1 and 1:6:2 (entries 2 and 12) on one hand and with ratios of 1:4:2 and 1:6:4 (entries 3 and 13). This suggests that it

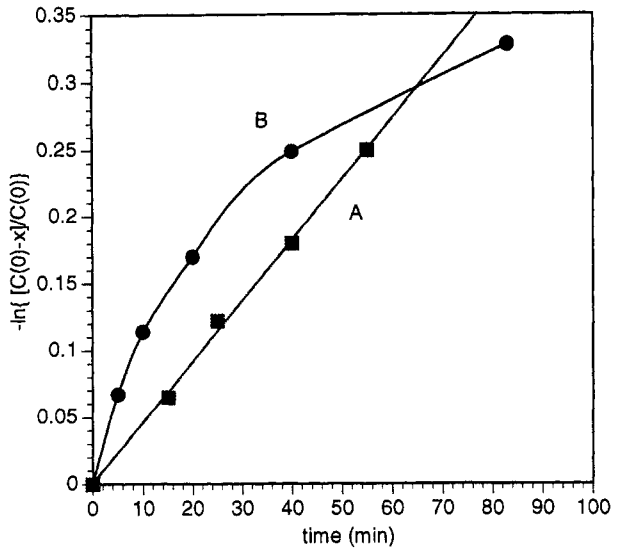
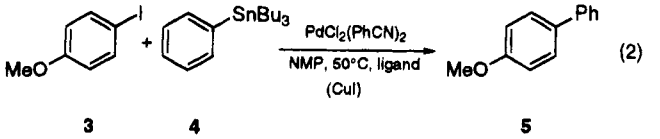


Figure 3. Kinetics of the couplings between *p*-iodoanisole and phenyltributyltin (1 equiv), catalyzed by Pd_2dba_3 (2% mol Pd) and triphenylarsine (8% ligand) in the absence (A) and presence (B) of CuI (8%) in NMP at 50 °C (k_{obs} shown in Table 2).

is the ratio between Cu and L that most affects the rates, not the ratio of Cu to Pd. Employing a Pd:L of 1:2 without copper yields rates that are very high and, at least in this particular case, not too far from the fastest rates obtained in the presence of CuI (entry 7). Addition of copper gave a 5-fold rate increase, but at the expense of catalyst stability (entry 8).

The picture was quite different with the "softer" ligands (Table 1, entries 14–20). Only a 2-fold rate increase was obtained when (pentafluorophenyl)diphenylphosphine was the Pd ligand (entries 14–16), and a modest 25% rate increase was seen with $AsPh_3$, regardless of the amount of copper used (entries 17–20). For the sake of a general comparison, the fastest rates were obtained with $AsPh_3$ in the presence of CuI (entry 19, a factor of *ca.* 3×10^3 over the PPh_3-containing catalyst of entry 1). $AsPh_3$ without copper yields, at least in this particular coupling, rates that are over 1 order of magnitude faster than PPh_3 in the presence of copper at optimum concentrations (entry 17 *vs* entries 3 and 4).

A second reaction that was examined is the coupling of *p*-iodoanisole (**3**) with phenyltributyltin (**4**) in NMP (eq 2). Here the yields are somewhat lower than in the above



reaction due to the competing oxidative dimerization of the stannane.[7] While a logarithmic plot of concentration *vs* time gave a linear relationship in the absence of CuI, such plots were severely curved in the presence of CuI. This is graphically shown in Figure 3.

In all cases, initial rate constants were derived within 10% conversion, *i.e.*, before appreciable deviation from linearity was detectable. Such rate constants are shown in Table 2 for two different ligands and different proportions of CuI. With PPh_3 as the ligand, a *ca.* 20-fold acceleration was realized by using the optimum amount of CuI (Table 2, entries 1–4). This enhancement is somewhat lower than the one realized for eq 1, but follows the same trend. When $AsPh_3$ was the ligand, roughly a 5-fold rate increase was seen with CuI present. This is different from the case of eq 1, where CuI showed essentially no effect. Also, the "copper effect" did not reach a plateau at a certain concentration of CuI as for the reaction in eq 1; instead, the initial rates increased proportionally with the concentration of CuI employed. Solubility problems limited the range of cocatalyst concentrations that could be explored. The final yield is also slightly better in the presence of CuI.

Table 2. Effect of Added CuI on the Rate of the Palladium-Catalyzed Coupling between *p*-Iodoanisole (3) and Phenyltributyltin (4) in NMP at 50 °C (Eq 2)[a]

entry	ligand	Pd:L:CuI molar ratio	$10^3 k_{obs}$ (min^{-1}) [st dev][b]	HPLC yield[c] (% recovered **3**)
1	PPh_3	1:4:0	0.27 [0.02]	28 (69)
2	PPh_3	1:4:2	5.6 [0.31]	44 (50)
3	PPh_3	1:4:4	7.5 [0.88]	35 (54)
4	PPh_3	1:4:8	7.3 [1.1]	28 (68)
5	$AsPh_3$	1:4:0	5.9 [0.95]	51 (41)
6	$AsPh_3$	1:4:2	14.7 [1.1]	65 (28)
7	$AsPh_3$	1:4:4	16.6 [1.0]	61 (27)
8	$AsPh_3$	1:4:8	21.0 [1.9]	52 (40)
9	$AsPh_3$	1:4:16	25.2 [1.7]	51 (44)

[a] ArI and phenyltin 0.165 M, 2% mol Pd, as $PdCl_2(PhCN)_2$, plus ligand and additives as in the table. [b] Initial rate determined by HPLC assuming overall first-order kinetics. Each value represents the average of two separate determinations. [c] Yields determined after 16 h by quantitative HPLC.

Table 3. Palladium-Catalyzed Coupling of Iodobenzene with 1 Molar Equiv of $RSnBu_3$ in DMF at 60 °C in the Presence of 4 Mol % Pd(0) (as Pd_2dba_3) and 16 Mol % $AsPh_3$

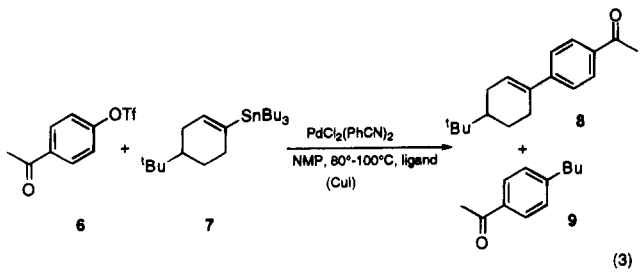
entry	R	CuI	% conversn after 5 min[a]	final % yield[b]
1	CH_2=CH–	none	35	56
		8%	47	76
2	CH_2=C(OEt)–	none	30	50
		8%	40	71
3	CH_2=$CHCH_2$–	none	28	49
		8%	39	61
4	Bu–	none	10	26
		8%	21	34
5	2-furyl–	none	22	45
		8%	31	58
6	2-pyridyl–	none		22
		8%	8.2	33
7	HC≡C–	none	28	40
		8%	40	58

[a] Determined by GLC vs an external standard. [b] Determined by GLC after 6 h.

Blank experiments demonstrated that no reaction occurred in the absence of Pd under the above conditions, although—interestingly—a 5% conversion to **5** could be observed at 100 °C, and a 27% yield at 140 °C, by using only 5% CuI as the catalyst.

In order to extend the above study to a broader range of stannanes, the couplings summarized in Table 3 were carried out. In these cases the initial rate was simply gauged by determining the product yield by quantitative GC analysis after 5 min. The final yield was also determined (after 6 h). The solvent employed was DMF. Experiments with NMP gave essentially identical rates. With $AsPh_3$ as ligand in each case, small—but consistent—rate enhancements were obtained in the presence of CuI *vs* the "Pd-only" catalyst. The yields were also typically 10–20% higher when CuI was present.

In order to determine the selectivity transfer of different organic groups, we selected a coupling (eq 3) that is



(3)

Ligand/Cu	Temp. (°C)	Time (h)	8:9
TFP	100	5	64:36
$AsPh_3$	80	7	90:10
$AsPh_3$+CuI	80	6	>98:<2

poorly selective under the "optimum" conditions for olefinic stannanes.[8] Cyclohexenylstannane **7** does not undergo appreciable coupling under traditional Stille conditions. Using TFP as ligand, clean reaction can be induced at *ca.* 100 °C, but substantial transfer of butyl group takes place. Switching ligand to $AsPh_3$ seems to facilitate the olefinic transfer appreciably. The reaction proceeded at 80 °C, and the selectivity was improved from *ca.* 2:1 to 9:1. Finally, in the presence of CuI, complete selectivity (>49:1) was observed and **8** was isolated in high yield (84%).

NMR Studies. Two main hypotheses could be put forward to explain the role of CuI in the Stille coupling. Since it is established that with activated electrophiles the transmetalation is the rate-determining step of the catalytic cycle,[3] and the two species interacting in this step are **10** and **11** (eq 4), CuI is expected to activate either one (or both) toward the metathesis reaction.

(4)

10 **11** **12**

We first probed the interaction of isolated **10** with CuI by ^{31}P-NMR. However, on mixing an equimolar proportion of **10** and CuI in NMP at room temperature, decomposition of the Pd complex was rapidly observed, without the formation of a discrete product. When **10** was prepared in situ from iodobenzene and a Pd_2dba_3/PPh_3 system, however, addition of CuI brought about well-characterizable line shape changes both in the resonance due to **10** (L = PPh_3) and the one due to free ligand in solution. A typical study is shown in Figure 4. More specifically, addition of CuI selectively broadens the line due to free ligand in a concentration-dependent fashion, and at high Cu(I) concentrations the peak doubles and then becomes unrecognizable (data not shown), while the peak due to **10** actually sharpens initially, and remains sharp upon further addition of CuI. Care was taken in these examples to use pure, recrystallized CuI,[9] as traces of paramagnetic Cu(II) cause nonspecific broadening of the whole spectrum.

Transmetalation reaction of olefinic stannanes with organocopper reagents to yield cuprates has been reported by Lipshutz,[10] but to the best of our knowledge there are no clear indications in the literature that simple

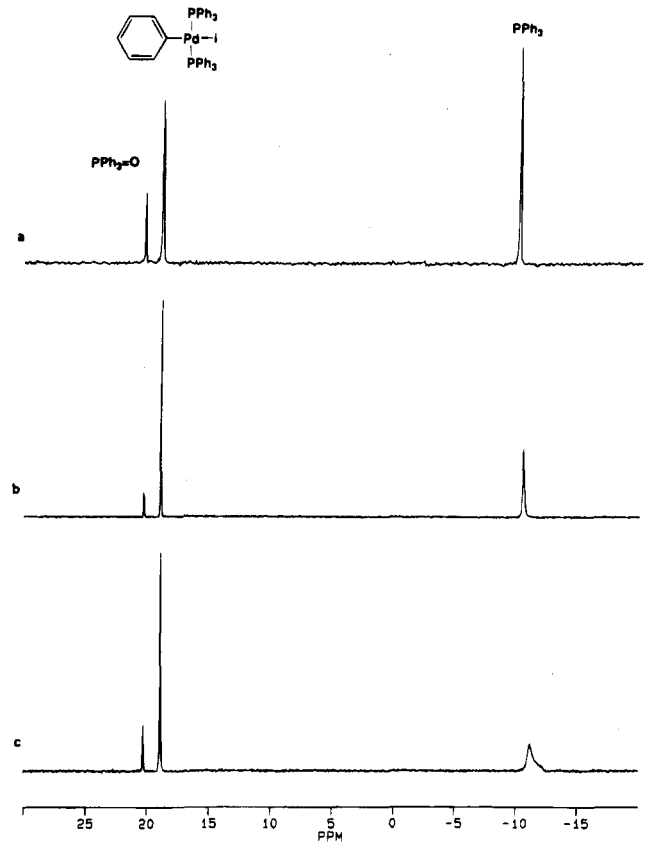


Figure 4. ^{31}P-NMR experiment: (a) 33 mM $PhPd(TPP)_2I$ (**A**, $\Delta\nu$ = 8.0 Hz) + 90 mM TPP (**B**, $\Delta\nu$ = 7.5 Hz). Also present: TPPO (**C**); (b) soln (a) + 16 mM in CuI; **A**, $\Delta\nu$ = 5 Hz, **B**, 20.0 Hz; (c) soln (a) + 32 mM CuI; **B**, $\Delta\nu$ = ca. 63 Hz.

inorganic Cu(I) salts may react with organostannanes.[11] In order to verify this possibility, we monitored the reaction of vinyltributyltin (**11**, R = CH_2=CH) and phenyltributyltin (**11**, R = Ph) with 1 molar equiv of CuI in a number of solvents, and in the presence or absence of ligands, by ^{119}Sn-NMR. A typical spectrum is shown in Figure 5. All reactions were done at a probe temperature of 30 °C.

In some cases the stannane was almost completely consumed, giving rise to a broad peak, identified as Bu_3SnI (δ 11.4) by comparison with an authentic sample. Traces of tributyltin hydroxide were also present in a few experiments. Although the peak for the tin iodide species was too broad to allow for quantitative measurements, the following qualitative observations were made: no reaction was observed in THF or dioxane. Only highly polar solvents like NMP and DMF supported the reaction, which usually took several hours or even overnight periods to go to completion. The reaction occurs with both vinyltributyltin and phenyltributyltin in NMP, yielding the same tin-containing product. The reaction is not affected by 1 molar equiv of $AsPh_3$, but is completely suppressed by 1 molar equiv of strong donors like PPh_3. The smooth reactivity of simple organostannane with CuI in polar aprotic solvents is quite unexpected and has important mechanistic implications, as discussed below.

(9) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9.
(10) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.
(11) A recently described conjugate addition of stannanes to certain allenyl esters promoted by CuCl may also involve organocopper species. See: Hanaka, H.; Kameyama, Y.; Sumida, S.; Torii, S. *Tetrahedron Lett.* **1992**, *33*, 7029. For a timely and thorough review on the transmetalation reaction between a veriety of organometallic species and Cu(I), see: Wipf, P. *Synthesis* **1993**, 537.

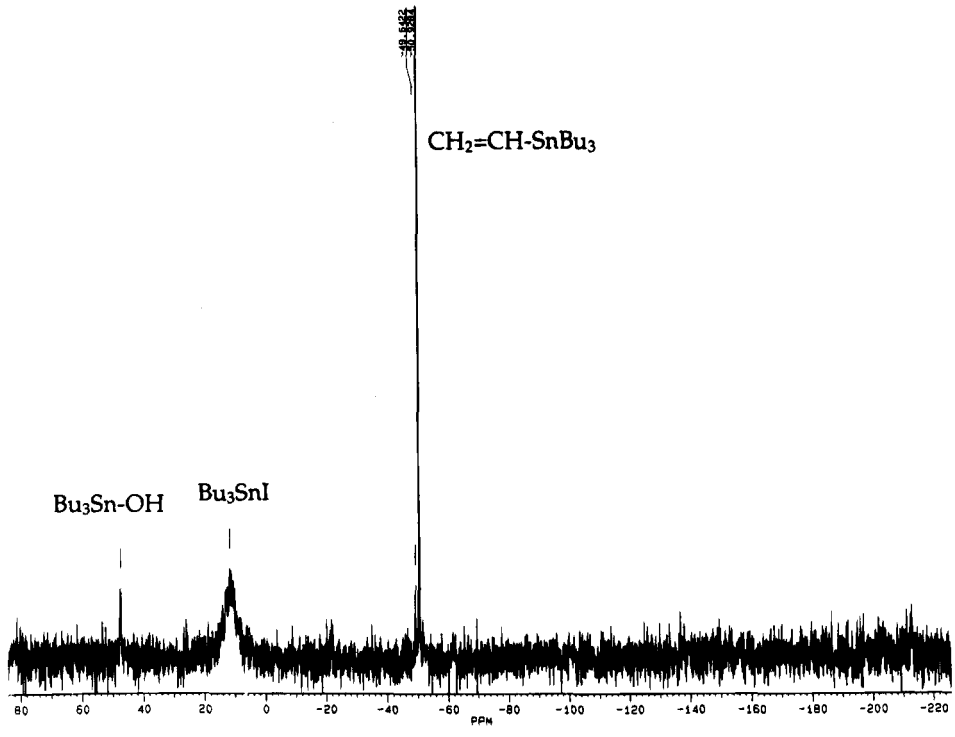


Figure 5. ^{119}Sn-NMR. Experiment 1: *0.18 M CuI in dry NMP + 1 equiv of vinyltributyltin, rt, 16 h.*

Discussion

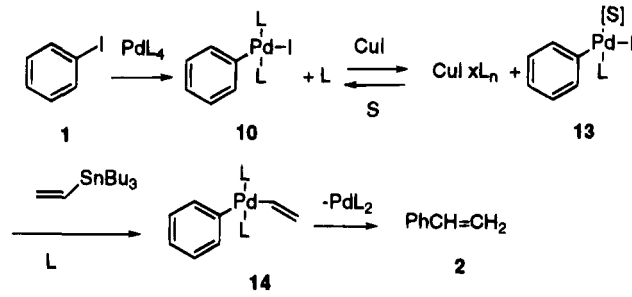
By inspection of the above results, it is clear that the "copper effect" is actually a complex phenomenon which is intimately dependent on the solvent and the palladium ligands used in a particular cross-coupling. The dependence of the copper effect on the ligand used is best explained by invoking the previously proposed "predissociation" mechanism for the transmetalation, as shown in Scheme 1.[2b,3] According to this proposal, a key event in the transmetalation is the dissociation of a ligand molecule from intermediate **10.** This predissociation event is thermodynamically unfavorable for "strong" ligands such as PPh_3, and in this case slow destruction of the ligand (by air oxidation) is necessary to induce coupling.[2b] Another strategy to diminish the concentration of PPh_3 in solution is apparently to allow its complexation with a second metal, in this case Cu(I).

This proposal is fully supported by the kinetic studies in Table 1. Indeed, it is the ratio L:Cu that affects the reaction rate: too little CuI will not effectively scavenge free ligand and therefore will yield less than optimum rates, while too much will extract ligand from **10** as well, causing it to decompose and leading to catalyst loss. The observation of first-order kinetics is also consistent with this proposal. As expressed above, k_{obs} and [L] are inversely related, and here the concentration of free ligand will be dictated by a series of equilibrium constants involving the various CuI/phosphine complexes formed.[12]

Thus, one effect of Cu(I) is simply to scavenge free ligand, which is inhibitory to the transmetalation, from the solution. As we have already discussed, in the presence of "soft" ligands such as $AsPh_3$, ligand dissociation from Pd(II) is not a problem, and indeed addition of CuI in this case produces minimal rate accelerations (Table 1, entries 17–20).

(12) Reichle, W. T. *Inorg. Chim. Acta* **1971**, *5*, 325.

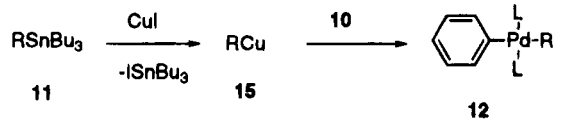
Scheme 2



The ^{31}P NMR experiments support this hypothesis, since selective broadening of the line due to free ligand is observed on complexation with CuI. Actual sharpening of the line for **10** suggests suppression (or reduction) by CuI of the background phosphine exchange involving **10** and PPh_3. Were CuI to interact directly with **10**, broadening of this signal would be expected. Also, were CuI to facilitate removal of the iodide leaving group from **10** by complexation with such ion, a dramatic kinetic effect would be expected when adding 20 mol equiv of LiI. Only a minor rate drop is observed instead (Table 1, entries 9 and 10), underlying the stronger affinity of CuI for phosphines instead of iodide ions under these particular conditions. *All our observations regarding the role of CuI in ethereal solvents are therefore readily explained by the modified mechanism shown in Scheme 2.*

On the other hand, as suggested by the ^{119}Sn-NMR experiments, CuI reacts with organostannanes *in highly polar solvents (e.g.,* NMP) to yield an iodostannane and, presumably, an organocopper derivative. This can then transmetalate onto **10** in a separate step. Kinetically, this would imply a succession of two transmetalations, leading presumably to non-first-order kinetic behavior. If two consecutive reactions are involved, indeed a plot of ln[*C*] vs time should be curved,[13] which is what we have observed (Figure 3). Nonlinear behavior could also be

Scheme 3



due to loss of catalyst, however. Our preliminary NMR data also suggest that the postulated Sn/Cu transmetalation is subject to the same kind of effects observed in the Sn/Pd counterpart, *i.e.*, the reaction is much faster in NMP than dioxane, and strong ligands such as PPh_3 strongly retard or block the reaction, while ligands such as $AsPh_3$ do not. We postulate therefore that, when the cross-coupling is carried out in NMP *in the absence of strong ligands like PPh_3, a second mechanism may intervene at least partially in the transmetalation*, as shown in Scheme 3.[14]

Species **11** and **15** may possibly be at equilibrium: if so, our preliminary NMR studies suggest that the equilibrium lies to the right in favor of **15**, although we do not know the stability of **15** in NMP in the absence of a coupling partner. The attack of **15** onto **10** may occur via ligand dissociation (*i.e., via* **13**) or by direct attack *via* a pentacoordinated intermediate. Kinetically, the largest rate enhancement seen in these experiments is a modest 5-fold rise.

Since the transmetalation step is responsible for the group transfer selectivity with nonsymmetrical stannanes, the Sn/Cu transmetalation, when operative, should affect such selectivity, hopefully in a synthetically useful way. Our Sn/Cu transmetalation theory was confirmed by the experiments in eq 3. Simply switching ligand from TFP to $AsPh_3$ boosts the selectivity in favor of the desired olefinic transfer to 9:1. Perhaps the lower selectivity with TFP is due to the higher temperature that had to be used in this experiment. A second possibility is that species **13** (Scheme 1) is more reactive, and therefore less discriminating, when L is the highly electron-deficient TFP instead of $AsPh_3$. Most interestingly, virtually complete selectivity is achieved by using cocatalytic copper, in support of the double transmetalation hypothesis.[15]

The suggestion that simply adding a catalytic amount of CuI may activate an organostannane and induce it to undergo chemistry that is typical of organocuprates[16] has, of course, interesting implications. An important one is the possibility of carrying out the Stille coupling with catalytic copper(I) instead of Pd(0).[17] Preliminary evidence suggests that, at least in some cases, this ought to be feasible. We are also trying to study the Sn/Cu transmetalation more thoroughly.[18]

(13) Connors, K. A. *Chemical Kinetics*; VCH: New York, 1990; p 66.

(14) Transmetalation from copper "ate" complexes to Pd(II) is implied in a number of synthetic papers. See: (a) Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1986**, *42*, 1369. (b) Corey, E. J.; Kigoshi, H. *Tetrahedron Lett.* **1991**, *32*, 5025.

(15) The generality of this observation remains to be verified. However, we have shown that the Stille coupling between *p*-(triflyloxy)-acetophenone and phenyltributyltin, which gives, under our optimized conditions, only a 15:1 selectivity in phenyl (*vs* butyl) transfer,[7] occurs with complete selectivity in the phenyl transfer (>99:1) simply by adding 5% CuI (Kapadia, S., unpublished results).

(16) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

(17) Piers has recently reported an isolated case of a Cu-only intramolecular Stille-type coupling, using an excess (>2 equiv) of CuCl as activating agent. See: Piers, E.; Wong, T. *J. Org. Chem.* **1993**, *58*, 3609.

(18) Liebeskind, L. S.; Allred, G.; Farina, V. Manuscript in preparation.

Experimental Section

All reactions were performed under an atmosphere of dry nitrogen or argon. Solvents were dried by distillation from CaH_2 or simply stored over molecular sieves (4 Å). Copper iodide was purified according to the literature.[9] The stannanes were purchased from Aldrich or, in the case of 2-(tributylstannyl)pyridine[19] and 2-(tributylstannyl)furan,[20] prepared according to the literature. (4-*tert*-Butylcyclohexen-1-yl)tributyltin was prepared according to the general procedure by Wulff.[21] Coupling products, unless otherwise stated, were compared spectroscopically (NMR) with commercially available samples. 2-Phenylfuran (Table 3, entry 5) was prepared independently according to the literature.[22] HPLC analyses were carried out on a Perkin-Elmer Series 410 instrument equipped with an LC-235 diode array detector operating at 250 nm. Phenomenex C-18 columns (30 × 3.9 cm) were used, eluting with mixtures of water and acetonitrile. GC analysis was performed on an HP 5890 instrument equipped with an FID detector using a J&W DB-5 phase capillary column (25 m long; film thickness 0.33 μm) at 80−250 °C (column temperature).

Nuclear magnetic resonance experiments were obtained on a Bruker WM-360 instrument. For ^{31}P NMR, positive shifts are downfield of 85% phosphoric acid. For ^{119}Sn NMR spectra, positive shifts are downfield of tetramethyltin.

Kinetic Experiments. The kinetics of Tables 1 and 2 were carried out as follows: an HPLC calibration curve was obtained by injecting standard solutions of reactant and product. The reactions were carried out in a thermostat at constant (within 0.5 °C) temperature under argon. At appropriate intervals, 50 μL aliquots were withdrawn by syringe through a septum, quenched in a volumetric flask by 100-fold dilution with acetonitrile, and sampled by HPLC. The concentration of starting material and product were then determined by comparison with the standard curves. First-order rate constants were obtained from the appropriate semilog plots by the least-squares methods. Final yields were determined by diluting the reaction mixture to a known volume, correcting for the aliquots withdrawn, and quantitating the product concentration by HPLC as above. The following procedure for the coupling is representative:

Iodobenzene (182.3 mg, 0.892 mmol) was dissolved in dry degassed dioxane or NMP (5 mL) in a two-necked round-bottomed flask equipped with condenser, magnetic stirring bar, and septum and treated with triphenylphosphine (18.7 mg, 0.08 equiv), Pd_2dba_3 (8.2 mg, 0.02 equiv of Pd), and the appropriate amount of CuI under a flow of argon. After a period of 10 min at rt, the flask was immersed in the thermostatic bath set at 50 °C and the internal temperature allowed to equilibrate. The stannane (1.0 equiv) was then added neat by syringe and the stopwatch started.

Runs in Table 3 were monitored by quantitative GC: reagent and product standard curves were obtained by making the appropriate stock solutions; octadecane was used as an internal standard. Calibration factors were used to obtain the desired concentrations. The following procedure is representative:

In a dry Schlenk flask under nitrogen, iodobenzene (18.2 mg, 0.0892 mmol) was placed, followed by CuI (8% mol, whenever appropriate) and the internal standard (10 mg), and dry degassed DMF (3 mL) was added. An appropriate amount of catalyst (2% mol Pd_2dba_3 and 16% $AsPh_3$) was added from a freshly made DMF stock solution, and then the flask was immersed in a 60 °C thermostatic bath and, after thermal equilibration, the stannane (1.15 equiv) was added by syringe and the stopwatch started. Aliquots were withdrawn at 5, 15, 120 min, and 6 h (for yield determination). Conversions at 5 min are representative, as shown in Table 3; they were determined by comparing the detector response with the previously obtained calibration curves.

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(20) Liebeskind, L. S.; Wang, J. *J. Org. Chem.* **1983**, *58*, 3550.

(21) Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett.* **1988**, *29*, 4795.

(22) Masamune, T.; Ono, M.; Matsue, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 491.

Coupling between 4-(Triflyloxy)acetophenone (6) and (4-*tert*-butylcyclohex-1-enyl)tributyltin (7). In a two-necked 25 mL round-bottomed flask were placed stannane **7** (167 mg, 0.380 mmol), triflate **6** (102 mg, 0.380 mmol), triphenylarsine (9.3 mg, 0.031 mmol), Pd_2dba_3 (4.5 mg, 0.0380 mmol), LiCl (48 mg, 1.150 mmol) and CuI (3.64 mg, 0.0191 mmol), dry degassed NMP (2 mL) was then added, and the solution was stirred at rt for 15 min. Then it was placed in an oil bath at the appropriate temperature (80 or 100 °C) for 5–7 h. After cooling, the mixture was treated with 1 M aqueous KF (5 mL) for 30 min and filtered with thorough rinsing with ethyl acetate, and the organics were further washed with water and brine and dried with sodium sulfate. Silica gel chromatography of the crude product (10% ethyl acetate/hexane) gave a mixture of **8** and **9**,[7] and their ratio was estimated by NMR integration. The experiments with different ligands or without CuI were run similarly. In this particular experiment, only **8** was obtained (82 mg, 84% yield). Data for **8** (mp 96–7 °C, from MeOH) are as follows: ^{1}H NMR ($CDCl_3$) δ 7.89 (dd, J = 6.6 Hz, J' = 1.8 Hz, 2H), 7.45 (d, J = 6.6 Hz, J' = 1.8 Hz, 2H), 6.28 (m, 1H), 2.59 (s, 3H), 2.49–0.99 (m, 7H), 0.91 (s, 9H); MS (DCI) 257 (MH). Anal. Calcd for $C_{18}H_{24}O{\cdot}0.5H_2O$: C, 81.46; H, 9.11. Found: C, 81.82; H, 9.16.

Acknowledgment. L.S.L. would like to acknowledge the use of a VG 70-S mass spectrometer purchased through funding from the National Institute of Health, S10-RR-02478, and 300 MHz and 360 MHz instruments purchased through funding by the National Science Foundation, NSF CHE-85-16614 and NSF CHE-8206103, respectively. L.S.L. would also like to thank Dr.R. Partyka and the Bristol-Myers Squibb Co. for support.