pulses on fully relaxed (>5 × T_1) samples. Resolution enhancements, where indicated, were performed by Lorentz–Gaussian multiplication of the FID prior to Fourier transformation. T_1 spin–lattice relaxation times were determined by exponential fits of data from inversion/recovery experiments. The hardware modifications necessary for single-frequency irradiations are described elsewhere.[22]

The following is a representative procedure for preparing samples for NMR spectroscopic analysis. Working in an inert atmosphere glovebox, [^{6}Li,^{15}N]-LiTMP (0.103 g, 0.70 mmol), [^{6}Ll]-LiBr (358 mg, 4.17 mmol), and diphenylacetic acid (200 mg, 0.942 mmol) were added to volumetric flasks containing stir fleas and capped with serum stoppers. An additional serum vial fitted with a stir flea and serum cap, the three samples prepared above, and four NMR tubes fitted with serum stoppers were removed from the glovebox and placed under positive nitrogen pressure with needle inlets. To the vial containing the [^{6}Li,^{15}N]-LiTMP cooled to −78 °C was added THF (1.40 mL) down the walls with constant agitation to minimize local heating. Solutions of [^{6}Li]-LiBr (0.417 M) and diphenylacetic acid (0.0942 M) were prepared by bringing the volumes to 10.0 mL with dry THF (accounting for the volume of the stir flea). The LiTMP titer was determined by adding 0.17 mL of the LiTMP stock solution to 0.5 mL of THF in the last serum vial and titrated to a yellow-to-colorless endpoint with diphenylacetic acid in THF at −20 °C. The NMR tubes were each charged with 190 μL of dry pentane, 100 μL of THF-d_8, 0.016 mmol of the [^{6}Li,^{15}N]-LiTMP stock solution, variable quantities of the LiBr stock solution, and enough THF to result in a final volume of 750 μL. Samples were flame sealed at −78 °C under reduced pressure and stored at −78 °C until the spectroscopic analyses were complete.

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Supplementary Material Available: Figures showing single-frequency ^{15}N decouplings of [^{6}Li,^{15}N]-LiTMP/lithium cyclohexenolate (**15**), [^{6}Li,^{15}N]-LiTMP/LiBr, and [^{6}Li,^{15}N]-LiTMP/LiCl (4 pages). Ordering information is given on any current masthead page.

Large Rate Accelerations in the Stille Reaction with Tri-2-furylphosphine and Triphenylarsine as Palladium Ligands: Mechanistic and Synthetic Implications

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Abstract: The effect of changing the palladium ligands on the rates of typical Stille cross-coupling reactions was studied. Large rate enhancements (typically 10^2–10^3 over triphenylphosphine-based catalysts) were observed with tri-2-furylphosphine (TFP) and triphenylarsine, which are recommended as the new ligands of choice in the palladium-catalyzed coupling between olefinic stannanes and electrophiles. On the basis of the evidence presented, the transmetalation, which is the rate-determining step in the catalytic cycle, is postulated to involve a π-complex between the metal and the stannane double bond. In general, ligands that readily dissociate from Pd(II) and allow ready formation of this π-complex are the ones that produce the fastest coupling rates. The utility of the new ligands is demonstrated with several synthetic examples.

Introduction

Transition-metal-catalyzed cross-coupling reactions are an extremely powerful tool in organic synthesis.[1] The choice of organometallic reagent and catalyst for a particular application is dictated by a variety of factors, including, for example, compatibility with other functional groups or protecting groups (chemoselectivity), the thermal stability of the substrate, the desire for regio- and stereospecificity, ease of operation, and economic factors. The palladium-catalyzed coupling of unsaturated halides or sulfonates with organostannanes,[2,3] now commonly referred to as the Stille reaction, is gaining the favor of the synthetic community at an impressive pace (eq 1). This is due to the growing

$$RX + R'SnR''_3 \xrightarrow{Pd(0)} RR' + XSnR''_3 \qquad (1)$$

R,R' = aryl,vinyl,allyl X = Br,I,OTf

availability of the organostannanes,[4] their stability to air and moisture, and the fact that the Stille chemistry is compatible with virtually any functional group, thereby eliminating the need for protection/deprotection strategies which are a necessity with most organometallic reactions. There is, however, a feature that may limit the usefulness of the Stille methodology: the relatively drastic conditions that must be sometimes used to induce coupling. Temperatures as high as 100 °C are not unusual, and this may reduce the yields due to thermal instability of substrates, products, or the catalyst itself.

This suggested to us that an improvement over the typical Stille conditions would be a useful development in organic synthesis, since it would help extend the range of applications of this already powerful methodology. Our interest in this chemistry was stimulated by the observation[5] that the classical Stille conditions failed when applied to a class of substrates, the 3-(triflyloxy)cephems, which are particularly sensitive to the rather harsh conditions described by Stille[6] for this type of coupling. Our observation

(1) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
(2) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–24.
(3) Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551–64.
(4) Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987.
(5) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833–47.
(6) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–40.

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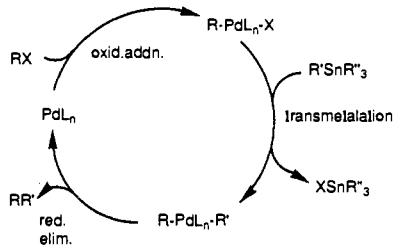
Scheme I



of a considerable ligand effect in the Stille reaction, and in particular of the remarkable catalytic activity displayed by a palladium catalyst employing tri-2-furylphosphine (TFP) as a ligand,[5] prompted us to undertake a more general study of the effect of ligands on the coupling rates between olefinic stannanes and various electrophiles.

The concept of "catalyst tailoring" in organometallic chemistry[7] has been often applied as a mechanistic tool or as a device to increase turnover rates. Surprisingly, however, little is known about the effect of the ligands on the rates of cross-coupling reactions. Stille assigns a key role to steric effects on the part of the ligand.[2] In studies where different catalysts have been compared,[6] the preferred one has usually been $Pd(PPh_3)_4$; the observation that excess phosphine slows down the coupling has prompted the use of the coordinatively unsaturated catalyst "$Pd(PPh_3)_2$", usually obtained in situ from a Pd(II) species. This catalyst yields faster turnover rates but is sometimes unsatisfactory because of thermal decomposition before the reaction is complete.[6,8] Chelating ligands have been found to be counterproductive in the coupling of vinyl triflates and organotins.[6] The so-called "ligandless catalysts", introduced by Beletskaya,[3] have been used less often; in these catalysts palladium is not coordinated by "strong" ligands (phosphines) and appears to have much higher turnover rates. These catalysts are therefore able to work under very mild conditions, usually room temperature or below. The lack of coordinating ligands negatively affects the stability of the catalyst, however, and in many applications "ligandless" catalysts are too unstable to be useful.

The currently accepted mechanism for the Stille coupling involves three basic steps, as shown in Scheme I.[2] While the mechanisms of the oxidative addition and the reductive elimination are reasonably well understood,[9] some evidence suggests that the transmetalation is the rate-determining step in most cross couplings of synthetic interest,[1,10] and yet little is known about the mechanism of this step. Much indirect information about this reaction comes from a series of studies on transmetalations at Pt(II).[11-16] While kinetic data are absent, one important observation is that strong σ-donors dramatically slow down the transmetalation of organotins at Pt(II).

It is very difficult to separate steric and electronic effects in phosphorus ligands: steric effects are conveniently gauged according to the "cone angle" concept, introduced by Tolman.[17] Unfortunately the cone angle of a ligand changes upon complexation, ligands with electron-withdrawing substituents usually becoming more pyramidalized.[18] The electronic effects of phosphorus ligands are not a constant but depend on the metal under consideration and its oxidation state. These effects are usually expressed by the parameter ν,[17,19] an infrared carbonyl stretching frequency measured in a system believed to be free of steric effects. Ligands are then classified as either σ-donors or σ-donors/π-acceptors, and recent quantitative treatments aimed at distinguishing these effects have been quite successful.[20-22]

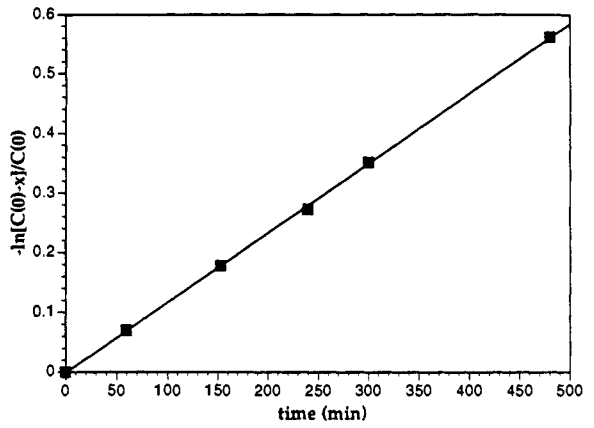
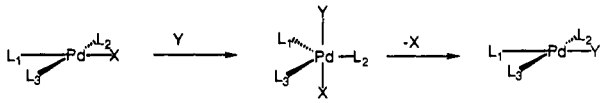


Figure 1. Kinetics of the coupling between iodobenzene and vinyltributyltin in the presence of Pd_2dba_3 and (pentafluorophenyl)diphenylphosphine in THF at 50 °C; 0.16 M each PhI and stannane, 3.2 mM Pd, and 12.8 mM phosphine. $C(0)$ = 0.16 M, x = extent of conversion to styrene. Observed first-order rate constant: 1.12×10^{-3} min^{-1}.

Scheme II



Since the transmetalation step consists of a substitution process at square-planar Pd(II), where the nucleophile is the organotin and the leaving group is the halide (or pseudohalide), one may expect the reaction to proceed via a classical associative[23,24] process in which the nucleophile approaches the plane of the complex from a perpendicular direction, leading to an unstable pentacoordinated intermediate, which then releases the leaving group with overall retention of configuration (Scheme II).

A major kinetic influence in these processes is exerted by the ligand trans to the leaving group,[25] while the cis ligands display minor electronic effects. Since we know from Stille's studies that the transmetalation substrate has two phosphine ligands (L_2 and L_3 in Scheme II) cis to the leaving group, one would conclude that, were the transmetalation a classical associative process, the effect of the ligands should be primarily steric and very little electronic influence should be observed.

Our observation[5] that tri-2-furylphosphine produces large kinetic effects in two types of Stille couplings suggested to us that the transmetalation of olefinic stannanes at Pd(II) may not follow a single-step associative mechanism. In the light of these considerations, a more systematic study of ligand effects in the Stille reaction may hold, in addition to the synthetic importance discussed above, also considerable promise as a tool in the mechanistic

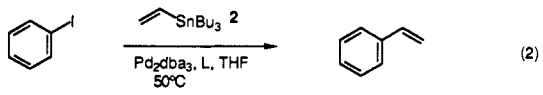
(7) Henrici-Olivé, G.; Olivé, S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 105-15.
(8) Crisp, G. T.; Papadopoulos, S. *Aust. J. Chem.* **1989**, *42*, 279-85.
(9) Stille, J. K. In *The Chemistry of the Metal-Carbon Bond*; Hartley, R. F., Patai, S., Eds.; John Wiley: New York, 1985; Vol. II, pp 625-787.
(10) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393-401.
(11) Celinkaya, B.; Lapperi, M. F.; McMeeking, J.; Palmer, D. E. *J. Chem. Soc., Dalton Trans.* **1973**, 1202-8.
(12) Eaborn, C.; Odell, K.; Pidcock, A. *J. Organomet. Chem.* **1975**, *96*, C38-40.
(13) Cardin, C. J.; Cardin, D. J.; Lappert, M. F. *J. Chem. Soc., Dalton Trans.* **1977**, 767-79.
(14) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Organomet. Chem.* **1978**, *146*, 17-21.
(15) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1978**, 357-68.
(16) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1979**, *758*-60.
(17) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313-48.
(18) Orpen, A. G.; Connelly, N. G. *Organometallics* **1990**, *9*, 1206-10.
(19) Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2953-6.
(20) Golovin, M. N.; Rahman, M. M.; Belmonte, J. E.; Giering, W. P. *Organometallics* **1985**, *4*, 1981-91.
(21) Rahman, M. M.; Liu, H. Y.; Prock, A.; Giering, W. P. *Organometallics* **1987**, *6*, 650-8.
(22) Rahman, M. M.; Liu, H. Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1-7.
(23) Alwood, J. D. *Inorganic and Organometallic Reaction Mechanisms*; Brooks-Cole: Monterey, CA, 1985.
(24) Langford, C. H.; Gray, H. *Ligand Substitution Processes*; W. A. Benjamin: New York, 1965.
(25) Appleton, T. G.; Clark, H. C.; Manzer, L. E. *Coord. Chem. Rev.* **1973**, *10*, 335-422.

understanding of the rate-determining step of this reaction.

In the present study we have examined in some detail the effect of ligands on the coupling reaction between iodobenzene and vinyltributyltin catalyzed by palladium(0). Other typical Stille couplings were also examined. A rather coherent picture has emerged from our study, and we describe herein large rate accelerations (up to 3 orders of magnitude over PPh_3) obtained with certain ligands, we recommend simple modifications in the Stille protocol that make this chemistry possible under much milder conditions than previously described, and we postulate a simple mechanistic rationale that accounts for the rate accelerations observed.

Results

Coupling of Iodobenzene with Vinyltributyltin. The palladium-catalyzed coupling of iodobenzene with vinyltributyltin (eq 2) was studied in the presence of several ligands. When the reaction was carried out with equal concentrations of the two reactants and 2% mol equiv of the catalyst, overall first-order kinetics were observed. Thus, a linear correlation between



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reactant concentration and reaction time was obtained by a semilogarithmic plot. A typical one (for $C_6F_5PPh_2$ as ligand) is shown in Figure 1 (k_{obsd} = 1.11 × 10^{-3} min^{-1}). Plots for hypothetical zeroth- or second-order kinetics gave instead severely curved plots (data not shown). This is typical of the Stille reaction.[6]

In order to establish the order with respect to the stannane, the reaction was carried out with a large molar excess of iodobenzene (L = $C_6F_5PPh_2$; [PhI] = 0.3 M; [stannane] = 17 mM; [Pd] = 3.2 mM). The kinetics were again first-order. The observed rate and rate constant k_{obsd} (1.15 × 10^{-3} min^{-1}) were unchanged with respect to the ones obtained when equimolar amounts of the reactants were used. When the concentration of PhI was doubled ([PhI] = 0.6 M) and the other concentrations were held equal, the observed rate constant (k = 1.10 × 10^{-3} min^{-1}) once again did not change, confirming that the kinetics are zeroth-order with respect to iodobenzene. Changing the initial concentration of stannane affected the rate but, as expected, k_{obsd} was unchanged. When the concentration of palladium in the above experiments was doubled to 6.4 mM (using 19.2 mM ligand to yield the same concentration of free ligand as above; for the effect of free ligand on the reaction rate, see the Discussion), the observed rate constant also doubled (k = 2.27 × 10^{-3} min^{-1}). All of this is consistent with the fact that the transmetalation is rate-determining (see the Discussion).

The relative rates for the ligands examined are collected in Table I. The table also shows the steric and electronic parameters (whenever known) for each ligand used. All reactions were carried out in anhydrous THF at 50 °C, and the progress of each reaction was monitored by quantitative HPLC. In all cases, no product other than styrene (in addition to Bu_3SnI, which is not detected) was observed, and quantitation showed that the sum of the concentrations of iodobenzene and styrene was essentially constant over the observation period. UV detection of the product, which has a high extinction coefficient at 250 nm, ensured that even very low (0.2%) conversion levels could be reproducibly and accurately determined.

The catalyst was formed in situ by introducing the weakly coordinated tris(dibenzylideneacetone)dipalladium (Pd_2dba_3)[26] and 4 equiv (for each Pd atom) of the ligand under study. The purple color of the dibenzylideneacetone (dba) catalyst was usually discharged to a pale yellow color within 5–10 min at room temperature to yield the formally PdL_4 catalyst. When the ligand was PPh_3, the rate obtained was within experimental error of the one obtained with preformed $Pd(PPh_3)_4$ or $Pd(OAc)_2$ + 4 equiv of PPh_3. In two cases, where bulky phosphines were employed (entries 5 and 8), a period of 30 min at 50 °C was necessary to discharge the purple color. In all cases, *initial* rates were measured using equal initial concentrations of the two reagents.

(26) Ishii, Y. *Ann. N. Y. Acad. Sci.* **1974**, *239*, 114–28.

Table I. Relative Initial Rates in the Coupling of Iodobenzene and Vinyltributyltin Catalyzed by Pd_2dba_3 in the Presence of Ligands (Pd:L ratio = 1:4)[a] at 50 °C in THF

entry	ligand	rel rate[b]	θ[c]	ν[d]	yield,[e] %
1	PPh_3	1.0 (0.38)	145	2068.9	15.2
2	$MePPh_2$	<0.07	136	2067.0	<2
3	$P(CH_2CH_2CN)_3$	<0.07	132	2078.0	<2
4	$(4\text{-}MeOC_6H_4)_3P$	<0.07	145	2066.1	<2
5	$[2,4,6\text{-}(MeO)_3C_6H_2]_3P$	<0.07	184		<2
6	$(4\text{-}FC_6H_4)_3P$	0.60 (0.08)	145	2071.3	10.7
7	$(4\text{-}ClC_6H_4)_3P$	0.71 (0.10)	145	2072.8	nd
8	$(2\text{-}MeC_6H_4)_3P$	35.2 (2.4)	194	2066.6	19
9	$(2\text{-furyl})_3P$	105 (2.4)			>95
10	$(2\text{-tienyl})_3P$	4.8 (0.5)			68.6
11	$Ph_2PC_6F_5$	24.3 (0.7)	158	2074.8	>95
12	$PhP(C_6H_5)_2$	950 (4.1)		2078.5	58.3[f]
13	$P(C_6F_5)_3$	[g]	184	2090.9	13.2
14	$P(OPh)_3$	95.2 (9.1)	130	2083.5	88[f]
15	$P(OiPr)_3$	42.8 (5.3)	131	2075.9	25[f]
16	$AsPh_3$	1100 (95)	142		>95
17	$SbPh_3$	13.2 (1.5)	142		56.4

[a] 0.16 M PhI and stannane, 3.2 mM Pd, 12.8 mM ligand. [b] For PPh_3 first-order rate constant was 4.6 × 10^{-5} min^{-1}; each rate is the average of two or three determinations. The figure in parentheses is the standard deviation. [c] Cone angle; see ref 17. [d] IR frequency of $Ni(CO)_3L$ complex; see ref 17. [e] HPLC yield after 72 h. [f] Catalyst decomposed. Catalyst apparently still active in all other cases. [g] Indicated conversion and catalyst decomposition were instantaneous (<2 min).

First-order kinetics were observed for up to 1 reaction half-life (25 turnovers) and often beyond, but in a few cases catalyst decomposition was responsible for deviations from linearity (notably entry 8, where the observed first-order rate slowed down much earlier than 1 half-life). Some catalysts visibly decomposed rather suddenly (entries 12, 14, and 15). Catalyst decomposition was confirmed by two quantitations 2 h apart, which gave identical conversion values.

The rather large standard deviations observed in a few cases are due without doubt to the large effect of excess ligand on the rate (vide infra), so that a small error in weighing the catalyst can lead to appreciable rate differences. The ranking of the ligands, whose rates span over 5 orders of magnitude, is not substantially affected by these variabilities.

The superiority of tri-2-furylphosphine over triphenylphosphine is evidenced by the data in Table I. The ligand affording the fastest rate is $AsPh_3$, which yields a quite remarkable rate acceleration over PPh_3 in this reaction (ca. 10^3).

The possibility of a dissociative mechanism, i.e., one involving prior dissociation of the leaving group followed by attack of the nucleophile,[24] was tested by studying the effect of added LiI on the rate. One equivalent of LiI *increased* the rate in entry 9 by a factor of 1.5, while the rate in entry 16 was increased by a factor of 2.5. Thus, added iodide has no inhibitory effect on the coupling rate.

The effect of bidentate ligands was explored next (Table II). Modest turnover rates were invariably observed. The best ligand in the table is dppp (entry 2), while a di-2-furylphosphino-containing ligand is quite inefficient. This is intriguing when compared with the excellent rates obtained with TFP.

Coordinatively unsaturated catalysts were tested by treating Pd_2dba_3 with enough ligand to produce a "formal" PdL_2 catalyst in situ (Table III). Rate and yield enhancements were obtained over the corresponding reactions with PdL_4 catalysts. From these rates we have estimated an "inhibition factor", i.e., the ratio of the rates obtained with a L:Pd ratio of 2 vs the ones with L:Pd = 4. This factor is a measure of the inhibitory effect of excess ligand on the coupling rate. This inhibition factor is by no means a constant for all ligands: tris(*p*-methoxyphenyl)phosphine has

Table II. Relative Initial Rates in the Coupling of Iodobenzene and Vinyltributyltin Catalyzed by Pd_2dba_3 in the Presence of Chelating Ligands (Pd:L ratio = 1:2) at 50 °C in THF[a]

entry	ligand	rel rate[b]	yield,[c] %
1	$Ph_2P(CH_2)_2PPh_2$	0.33 (0.09)	20
2	$Ph_2P(CH_2)_3PPh_2$	11.4 (2.9)	25
3	$Ph_2P(CH_2)_4PPh_2$	<0.2	<2
4	$(2\text{-furyl})_2P(CH_2)_2P(2\text{-furyl})_2$[d]	0.29 (0.07)	19
5	dppf[e]	<0.2	<2

[a] 0.16 M PhI and stannane, 3.2 mM Pd, 6.4 mM ligand. [b] Rates relative to PPh_3; see Table I. Determined by HPLC, average of two experiments. Figure in parentheses is the standard deviation. [c] HPLC yield after 48 h. [d] Ligand kindly supplied by Prof. L. S. Liebeskind (Emory University). [e] dppf = 1,1'-bis(diphenylphosphino)ferrocene.

Table III. Relative Initial Rates in the Coupling of Iodobenzene and Vinyltributyltin Catalyzed by Pd_2dba_3 in the Presence of Various Ligands Under Coordinatively Unsaturated Conditions (Pd:L ratio = 1:2) at 50 °C in THF[a]

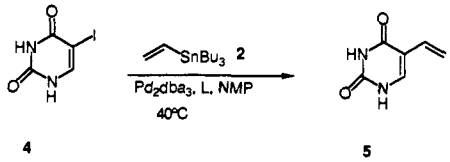
entry	ligand	rate[b]	inhibn factor[c]	yield,[d] %
1	PPh_3	19 (5.1)	19	>95
2	$(4\text{-}MeOC_6H_4)_3P$	7.2 (2.3)	>100	>95
3	$(4\text{-}FC_6H_4)_3P$	12.3 (3.1)	21.7	>95
4	$[2,4,6\text{-}(MeO)_3C_6H_2]_3P$	0.25	>3.5	3[e]
5	$(2\text{-}MeC_6H_4)_3P$	119 (22)	3.4	22
6	$(2\text{-furyl})_3P$	391 (5)	3.7	>95
7	$Ph_2P(C_6H_5)$	90 (2)	3.7	>95
8	$AsPh_3$	1480 (50)	1.3	94[f]
9	PPh_3 + $(2\text{-furyl})_3P$	3.4	5.6[g]	>95[e]

[a] 0.16 M PhI and stannane, 3.2 mM Pd, 6.4 mM ligand. [b] Rates relative to $Pd(PPh_3)_4$, from Table I, average of two determinations; figure in parentheses is the standard deviation. [c] Defined as the ratio of the rate for the coordinatively unsaturated catalyst (this table) with the rate using the saturated one, from Table I. [d] HPLC yield after 72 h. [e] One determination only. [f] Catalyst decomposed. [g] 3.2 mM Pd, 6.4 mM for each phosphine. The inhibition factor was calculated as the rate inhibition of excess TFP over the normal rate for "$Pd(PPh_3)_2$".

the largest one (>100), while $AsPh_3$ has the lowest (1.3). Indeed the reaction with $AsPh_3$ is inhibited very little by an excess of this ligand. In entry 9, a mixture of two ligands was employed. The rate obtained shows that PPh_3 essentially "controls" the coupling since the rate in this entry is very close to the one shown for "$Pd(PPh_3)_2$", corrected for the inhibitory effect of 2 equiv of TFP (from Table III, entry 6).

The kinetics with "PdL_2" catalysts were, however, less well-behaved than the ones measured in Table I, and in some cases (especially entry 2) the coupling rate apparently increased with time, while in other cases it decreased, most likely due to poorer catalyst stability. In these cases, initial rates refer to the first 2–10% of the reaction.

Coupling of 5-Iodouracil with Vinyltributyltin. As an example of a coupling between a vinylic iodide and a stannane,[27] we measured the rate of the coupling of 5-iodouracil with vinyltributyltin[28] (eq 3). The reaction was carried out in *N*-methyl-



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pyrrolidinone (NMP) at 40 °C and was monitored by HPLC. While TFP and $AsPh_3$ gave well-behaved kinetics during the first half-life, PPh_3 gave rise to an unstable catalyst, which led to incomplete conversion of **4** to **5** (Table IV). In contrast, TFP gave complete conversion to product with either "PdL_2" or "PdL_4" stoichiometry, while $AsPh_3$ gave the fastest initial rates (almost 4 orders of magnitude over PPh_3) and a catalyst that was more stable than the one with PPh_3 but less stable than the one with TFP.

Table IV. Relative Initial Rates in the Coupling of 5-Iodouracil and Vinyltributyltin Catalyzed by Pd_2dba_3 and Various Ligands Under Coordinatively Saturated vs Unsaturated Conditions at 40 °C in NMP[a]

entry	ligand	Pd:L	rel rate[b]	yield,[c] %
1	PPh_3	1:4	1.0 (0.06)	56[d]
2	PPh_3	1:2	34	50[d]
3	$(2\text{-furyl})_3P$	1:4	7.0×10^2 (12)	>95
4	$(2\text{-furyl})_3P$	1:2	3.0×10^3	>95
5	$AsPh_3$	1:4	5.7×10^3 (98)	95[d]
6	$AsPh_3$	1:2	7.3×10^3	91[d]

[a] 0.20 M iodouracil and stannane, 4 mM Pd. [b] Observed first-order rate constant for entry 1: 1.2×10^{-5} min^{-1}. Average of three determinations (HPLC). Figure in parentheses is standard deviation. [c] Determined by HPLC after 48 h. [d] Catalyst decomposed.

Table V. Relative Initial Rates in the Coupling of Cinnamyl Chloride and Vinyltributyltin Catalyzed by Pd_2dba_3 in the Presence of Ligands (Pd:L = 1:4) at 65 °C in THF[a]

entry	ligand	rel rate[b]	yield,[c] %
1	PPh_3	1.0	>95
2	$(2\text{-furyl})_3P$	12.1	>95
3	$AsPh_3$	361	>95

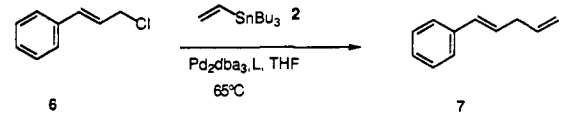
[a] 0.23 M cinnamyl chloride and stannane, 4.6 mM Pd, 18.4 mM ligand. [b] Observed first-order rate constant for entry 1: 8.3×10^{-5} min^{-1} by HPLC, one determination. [c] HPLC yield after 48 h.

Table VI. Approximate Relative Rates and Stereospecificity in the Coupling of Benzoyl Chloride and (*Z*)-1-Propenyltributyltin Catalyzed by Pd_2dba_3 in the Presence of Ligands (Pd:L = 1:4) at ca. 24 °C in THF[a]

entry	ligand	rel rate[b]	yield,[c] %	*Z*:*E* ratio[c]	stereospecificity, %
1	PPh_3	1.0	>90	70:30	71
2	$(2\text{-furyl})_3P$	95	97[d]	95.5:4.5	97
3	$AsPh_3$	727	>90	70:30	71

[a] 0.44 M benzoyl chloride and stannane, 4.4 mM Pd, 17.6 mM ligand. Stannane was 98.5% *Z*. [b] Determined by NMR at room temperature. [c] Estimated by NMR after 200 h for entry 1, after 16 h for entry 3. [d] Isolated yield.

Coupling of Cinnamyl Chloride with Vinyltributyltin. A synthetically very useful coupling is the one that takes place between allylic halides and stannanes.[29] As an example of this coupling, we have studied the coupling of cinnamyl chloride with vinyltributyltin to produce 1-phenyl-1,4-pentadiene (eq 4). The re-



6 7 (4)

action was conveniently carried out at 65 °C in dry THF with HPLC monitoring. The three ligands studied were PPh_3, $AsPh_3$, and TFP. Qualitatively these ligands behaved as in the previous two studies (Table V). $AsPh_3$ gave rates at least 2 orders of magnitude over PPh_3. Indeed, the reaction with this ligand could be easily carried out at room temperature. While yields were excellent with all ligands employed (an 84% yield of **7** was isolated in entry 2), we have described cases[5] where cephalosporin-derived allylic chlorides couple in poor yield with $Pd(PPh_3)_4$ but couple cleanly with a TFP-based catalyst.

Coupling of Benzoyl Chloride with (*Z*)-1-Propenyltributyltin. The palladium-catalyzed coupling between acyl chlorides and vinyltins is a very important general route to enones.[30] Unfortunately, the coupling is often not stereospecific, and even the relatively mild conditions used (refluxing chloroform) are sufficient to cause isomerization of the product.[30] We studied the coupling

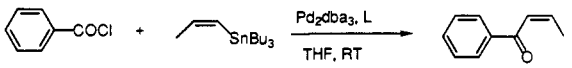
(27) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813–7.
(28) Farina, V.; Hauck, S. I. *Synlett* **1991**, 157–9.
(29) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833–40.
(30) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634–42.

Table VII. Relative Initial Rates in the Coupling of *p*-Acetylphenyl Triflate (**11**) and Vinyltributyltin Catalyzed by Pd_2dba_3 in the Presence of Ligands (Pd:L = 1:4) and LiCl at 40 °C in NMP[a]

entry	ligand	rel rate[b]	yield,[c] %
1	PPh_3	1.0	>95
2	$(2\text{-furyl})_3P$	10.1	>95
3	$AsPh_3$	73	>95
4	$[2,4,6\text{-}(MeO)_3C_6H_2]_3P$	0.07	*d*

[a] 0.16 M triflate and stannane, 3.2 mM Pd, 12.8 mM ligand, 0.48 M LiCl. [b] Rates by HPLC. Observed rate constant for entry 1: 4.1×10^{-3} min^{-1}, one determination. [c] HPLC yields after 48 h. [d] Yield not determined.

of benzoyl chloride with (*Z*)-1-propenyltributyltin (98.5% isomeric purity) (eq 5).

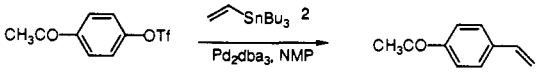


8 9 10 (5)

In order to verify the effect of the ligands on the rate and stereospecificity of the process, we screened PPh_3, $AsPh_3$, and TFP. The reactions were conveniently monitored by NMR. Aliquots were taken at suitable times, yielding conversion values and also a measure of the isomerization process.

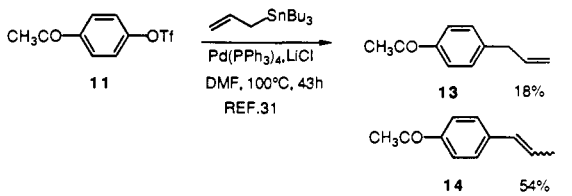
The coupling reactions were run under nonthermostated conditions and the rates reported are therefore approximate (Table VI). Large rate accelerations with TFP and $AsPh_3$ over PPh_3 were observed once again. Remarkable stereospecificity was obtained with TFP (97%), while with PPh_3 substantial isomerization took place. Stille reports[30] an *E*:*Z* ratio in the product of ca. 1:1. Even under our milder conditions, PPh_3 led to substantial loss of stereochemistry. Interestingly, $AsPh_3$ also led to isomerization.

Coupling of Aryl Triflates with Stannanes. Stille has recently described[31] an important extension of his chemistry to aryl triflates, which are easily obtained from phenols. His coupling conditions involve the use of PPh_3-based catalysts and temperatures around 100 °C. The use of LiCl was found to be necessary to induce coupling. We have measured the coupling rate of aryl triflate **11** with vinyltributyltin in the presence of palladium(0) in the presence of different ligands (eq 6). The initial relative rates



11 12 (6)

obtained are shown in Table VII. Use of tris(2,4,6-trimethoxyphenyl)phosphine (entry 4) was prompted by a recent report[32] in which this ligand was found to be the best in the coupling between carbapenem-derived vinyl triflates and arylstannanes. This ligand performs very poorly in our case, in complete analogy with the results in Table I, entry 5. The ligand ranking is the usual: $AsPh_3$ > TFP > PPh_3. While reactions are faster with the new ligands, the HPLC yields are excellent with PPh_3 as well. In order to illustrate the synthetic advantage of the milder conditions made possible by TFP, we have studied a coupling reaction that produces unsatisfactory results under classical Stille conditions (eq 7). Triflate **11** is known to couple with allyltributyltin to yield a mixture of isomers, **13** and **14**, the major product being the result of double bond migration into conjugation with the ring.[31]



11 13 18% 14 54% (7)

(31) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–86.

(32) Rano, T. A.; Greenlee, M. L.; DiNinno, F. P. *Tetrahedron Lett.* **1990**, *31*, 2853–56.

Table VIII. Relative Initial Rates in the Coupling of 4-Phenyl-1-trifloxycyclohexene (**15**) and Vinyltributyltin Catalyzed by Pd_2dba_3 in the Presence of Ligands at 35 °C in NMP[a]

entry	ligand	Pd:L	equiv of LiCl	rel rate[b]	yield,[c] %
1	PPh_3	1:4	3	1.0 (0.06)	>95
2	$(2\text{-furyl})_3P$	1:4	3	15 (0.6)	>95
3	$AsPh_3$	1:4	3	>350	>95
4	$Ph_2P(CH_2)_2PPh_2$	1:2[d]	3	<0.02	<2
5	$(2\text{-furyl})_3P$	1:4	0	36.7 (1.2)	>95
6	$(2\text{-furyl})_3P$	1:6	0	38.0 (1.0)	>95
7	$(2\text{-furyl})_3P$	1:6	3	11 (0.5)	

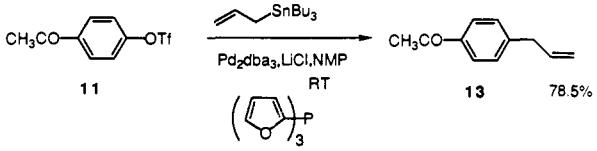
[a] 0.18 M triflate and stannane, 3.6 mM Pd. [b] Observed first-order rate constant for entry 1: 1.2×10^{-3} min^{-1} by HPLC, average of two experiments. Figure in parentheses is the standard deviation. [c] HPLC yield after 72 h. [d] This is equivalent to a Pd:P ratio of 1:4 as in entries 1–5.

Table IX. Relative Initial Rates in the Coupling of *p*-Acetylphenyl Triflate (**11**) and Tetramethyltin Catalyzed by Pd_2dba_3 in the Presence of Ligands (Pd:L = 1:4) at 60 °C in NMP with Added LiCl[a]

entry	ligand	rel rate[b]	yield,[c] %
1	PPh_3	1.0	78[d]
2	$(2\text{-furyl})_3P$	1.1	79[e]
3	$(4\text{-}MeOC_6H_4)_3P$	0.6	76
4	$P(OPh)_3$	3.5	>95
5	$AsPh_3$	7.4	>95

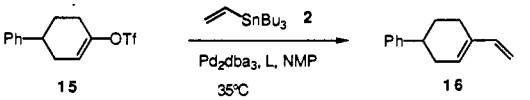
[a] 0.16 M **11**, 0.22 M Me_4Sn, 3.2 mM Pd, 0.48 M LiCl. [b] Observed first-order rate constant for entry 1: 1.9×10^{-4} min^{-1} (HPLC). [c] HPLC yield after 48 h. [d] Also obtained: 9% starting triflate, 13% 4-hydroxyacetophenone (NMR). [e] Also obtained: 21% 4-hydroxyacetophenone (NMR).

The use of TFP, on the other hand, allowed the reaction to proceed at room temperature, affording **13** in good yield as the only product with no traces of the conjugated isomer **14** (eq 8). It must be noted that aryl–allyl coupling without double bond migration has been observed in some cases[33] even at 100 °C.



11 13 78.5% (8)

Coupling of Vinyl Triflates with Vinyltributyltin. A synthetically very important reaction is the coupling between vinylstannanes and vinyl triflates.[6] We carried out a kinetic study of the prototype coupling shown in eq 9. The usual dependence of the rate upon



15 16 (9)

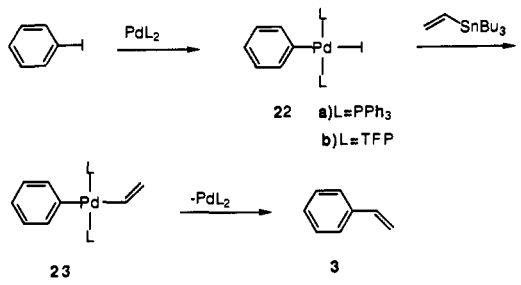
the ligand was found here as well (Table VIII). Some unusual features were discovered, however. Contrary to Stille's reports[6] and in agreement with Piers,[34] in our case use of LiCl was not necessary for the coupling to take place. The reaction rates were actually significantly *retarded by LiCl* (Table VIII, entry 2 vs 5). Once again, excess ligand slowed down the coupling to a small but significant extent (entry 2 vs 7) when LiCl was employed. When no LiCl was used, however, excess ligand did not significantly inhibit the reaction (entry 5 vs 6).

Coupling of Aryl Triflates with Tetramethyltin. The coupling of aryl triflates with tetramethyltin[31] (eq 10) should serve as a

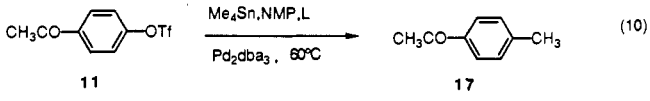
(33) (a) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931–3. (b) Tilley, J. W.; Sarabu, R.; Wagner, R.; Mulkerins, K. *J. Org. Chem.* **1990**, *55*, 906–10. (c) Martorell, G.; García-Raso, A.; Saá, J. M. *Tetrahedron Lett.* **1990**, *31*, 2357–60.

(34) (a) Piers, E.; Friesen, R. W. *J. Org. Chem.* **1986**, *51*, 3405–6. (b) Piers, E.; Friesen, R. W.; Keay, B. A. *J. Chem. Soc., Chem. Commun.* **1985**, 809–10.

Scheme III



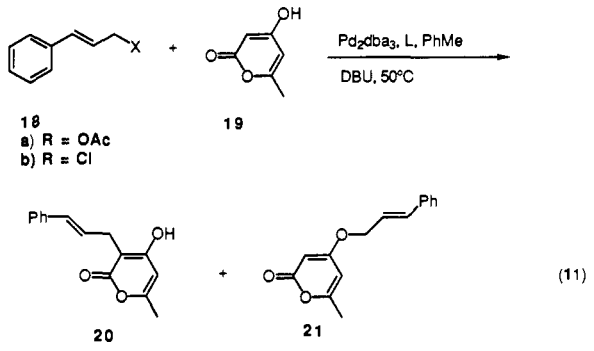
useful comparison with respect to the related coupling of vinyltins. Indeed the ligand effects in this reaction are quite different from all other cases so far examined (Table IX). Very little ligand



(10)

effect is seen in this reaction. In stark contrast with the analogous coupling of vinyltributyltin, PPh_3 and TFP induce coupling at essentially the same rate (entry 1 vs 2). The large inhibitory effect observed for tris(*p*-methoxyphenyl)phosphine in the coupling between iodobenzene and vinyltributyltin is not seen here (entry 3). Slight rate enhancements were obtained with triphenyl phosphite (entry 4) and especially with $AsPh_3$ (entry 5).

Allylic Alkylations with Soft Nucleophiles. In the light of the interesting ligand effect displayed by TFP in cross-coupling reactions, we briefly explored the possible utility of this ligand in π-allyl palladium chemistry, and we studied the allylation of pyrone **19** under the conditions described by Moreno–Manas[35] (eq 11). With allylic acetate **18a** as the substrate and the



(11)

PPh_3-based catalyst, allylation product **20** was obtained as described, while the TFP-based catalyst led to no reaction under the same conditions, presumably due to slower oxidative addition with the TFP-based catalyst (vide infra). Using a substrate capable of undergoing fast oxidative addition (**18b**), use of Pd–PPh_3 and Pd–TFP catalysts led to allylation at similar rates (half-lives of 40 and 41 min, respectively). In both cases, the same mixture of C- and O-allylated products (**20** and **21**) was obtained.

^{31}P NMR Studies. The palladium-catalyzed coupling of iodobenzene with vinyltributyltin was monitored by variable-temperature ^{31}P NMR spectroscopy (with proton decoupling) under stoichiometric conditions in THF (containing 10% THF-d_8 for lock). We began our studies with the species prepared in situ from $Pd(OAc)_2$, 4 equiv of PPh_3, and 2 equiv of *n*-BuLi.[36] The Pd–$(PPh_3)_4$ so obtained proved quite insoluble in THF at room temperature, but prolonged scanning produced a broad signal at δ 9 due to several equilibrating species, i.e., free phosphine (δ −6), PdL_4 (δ 18.4 in toluene[37-39]), PdL_3 (δ 22.6 in toluene[37]), and PdL_2

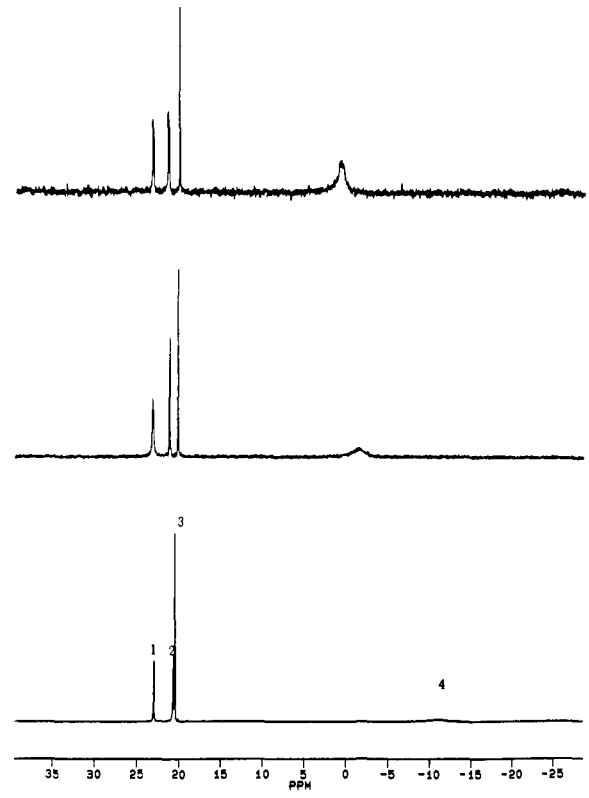


Figure 2. Low-temperature ^{31}P NMR study of Pd(0)–PPh_3 complexes: ca. 13 mM Pd_2dba_3 in THF with 4 equiv of PPh_3 per Pd. 1,2 = Mixed Pd/dba/PPh_3 complexes; 3 = PPh_3 oxide; 4 = average of $Pd(PPh_3)_2$, $Pd(PPh_3)_3$, $Pd(PPh_3)_4$, and PPh_3. Temperature: (a) 24 °C; (b) −23 °C; (c) −78 °C.

(δ 20.4 in THF–CD_2Cl_2[10]). Addition of free phosphine caused an upfield shift of the resonance without any new peaks appearing, supporting a fast equilibrium among all species on the NMR time scale.

Oxidative addition with iodobenzene proved difficult to monitor due to the heterogeneous nature of the palladium reagent, although we did observe fast reaction at room temperature with complete dissolution of the complex to yield a spectrum consisting of two sharp signals of roughly equal intensity: one, at δ 22.3, due to species **22a** (lit.[10] δ 23.6) (Scheme III), and the other, at δ −6, due to triphenylphosphine. An authentic sample of **22a**, prepared according to the literature,[40] gave a spectrum consisting of a sharp singlet of δ 22.3, in agreement with the above assignment.

In order to follow the oxidative addition, we resorted to the more soluble complex obtained by adding Pd_2dba_3 to PPh_3 (Pd:L = 1:4) in THF. This complex produced (Figure 2) a more complex NMR spectrum, consisting of a very broad singlet at δ 3.6, some phosphine oxide (δ 22.9), and two rather sharp signals at δ 24.3 and 26.1. These signals are most likely due to Pd species containing both dba and PPh_3 in the coordination sphere of the metal (stoichiometry unknown). Cooling caused further broadening and an upfield shift in the signal at δ 3.6, while the other signals changed little (Figure 2). Addition of PhI at −10 °C induced rapid oxidative addition, and after 1 h the only observable signals were sharp singlets at δ 22.3 (for **22a**) and −6 (for PPh_3) (Figure 4a).

The line width of the signal at δ 22.3 was identical to the line width observed for isolated **22a**, indicating no exchange with free PPh_3 on the NMR time scale, in sharp contrast with the measurable exchange observed even at lower temperatures for the Pd(0) complex.

The behavior of tri-2-furylphosphine was remarkably different (Figure 3). A solution consisting of Pd_2dba_3 and TFP in THF (Pd:L = 1:4) gave a broad spectrum at room temperature, with

(35) Moreno-Manas, M.; Ribas, J.; Virgil, A. *J. Org. Chem.* **1988**, *53*, 5328–35.
(36) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778–81.
(37) Mann, B. E.; Musco, A. *J. Chem. Soc., Dalton Trans.* **1975**, 1673–7.
(38) Tolman, C. A.; Seidel, W. C.; Gerlach, D. H. *J. Am. Chem. Soc.* **1972**, *94*, 2669–76.
(39) Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338–9.
(40) Fillon, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287–91.

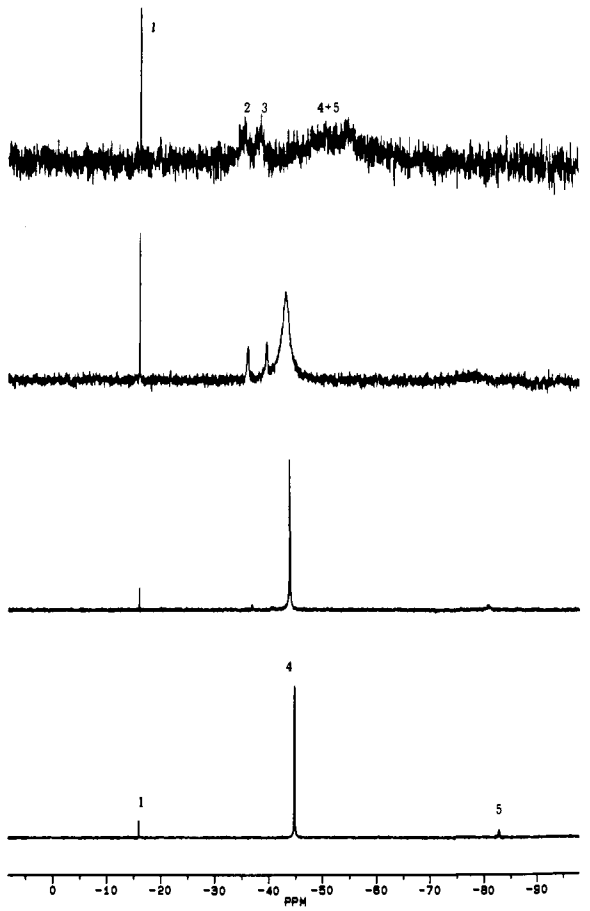


Figure 3. Low-temperature ^{31}P NMR study of Pd(0)–TFP complexes: ca. 13 mM Pd_2dba_3 in THF with 4 equiv of TFP per Pd. 1 = TFP oxide; 2,3 = mixed Pd/dba/TFP complexes; 4 = $Pd(TFP)_4$; 5 = TFP. Temperature: (a) 24 °C; (b) −23 °C; (c) −43 °C; (d) −60 °C.

a major broad peak at δ −54 and two sharper peaks at δ −38.1 and −35. Cooling produced sharpening of the major peak and a decrease in the relative intensity of the two minor peaks. At −60 °C essentially a single species is present at δ −42.4 (PdL_4), with only traces of free phosphine (δ −77.1, lit.[41] δ −76.4 in CH_2Cl_2) and phosphine oxide (δ −16.1). The other two peaks, presumably due to mixed dba/phosphine complexes as seen with PPh_3, essentially disappeared at low temperature.

Addition of PhI to this solution at −10 °C led, in analogy with PPh_3 but at reduced rate (completion time was ca. 4 h), to a spectrum consisting of only two sharp lines, one due to free phosphine (δ −77.1) and the other to **22b** (L = TFP) at δ −29.2 (Figure 4b).

Addition of 2 equiv of vinyltributyltin at room temperature followed by warming to 40 °C produced no shift or broadening of the line at δ −29.2 and only slow broadening and downfield shift for the line at δ −77.1, indicating the formation of the Pd(0) catalyst, with no signals due to intermediate **23b** being observed at any time, confirming that the transmetalation is the rate-determining step[10,42] in this coupling reaction.

An interesting phenomenon was observed when PPh_3 was added to the solution of **22b** and TFP (1:1) described above (Figure 4c). The resonance due to **22b** immediately disappeared, being replaced by the signal for **22a**. An increase in the intensity of the TFP signal was also noticed. This shows that the equilibrium in eq 12 is quickly established and lies very much in favor of **22a** and TFP. When a large excess of TFP was added to a solution of **22a** and PPh_3, no trace of **22b** was observed, the corresponding signal

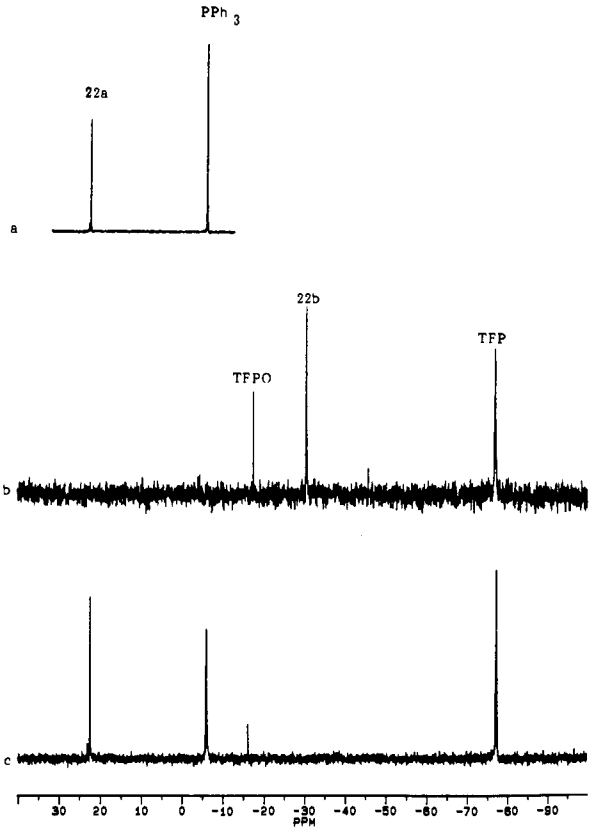
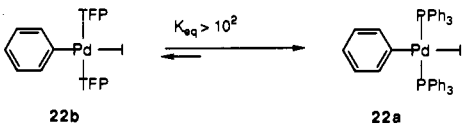


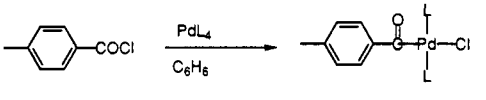
Figure 4. ^{31}P NMR study of oxidative addition; [Pd] = ca. 25 mM in THF. Solutions: (a) 1 equiv of PhI + 0.5 equiv of Pd_2dba_3 + 4 equiv of PPh_3; (b) 1 equiv of PhI + 0.5 equiv of Pd_2dba_3 + 4 equiv of TFP; (c) 4 equiv of PPh_3 added to solution b.

for TFP being the only new peak in the spectrum, in agreement with the above observation. We estimate the equilibrium constant for eq 12 to be at least 10^2 in THF at 24 °C.



22b **22a** (12)

Infrared Studies. In order to investigate the electronic properties of TFP as a ligand of Pd(II), the acyl complexes **24a,b** were prepared by a modification of the literature procedure.[43] In particular, for the preparation of **24b**, $Pd(OAc)_2$ was reduced in situ with vinyltributyltin in the presence of TFP and then treated with the acyl chloride at room temperature in benzene (eq 13).



(13)

24 a) L=PPh_3
b) L=TFP

The IR spectrum in $CHCl_3$ showed a major carbonyl band at 1640 cm^{-1} for the known **24a** (lit.[43] 1640 cm^{-1}) along with a second band at 1665 cm^{-1}. The novel TFP complex **24b** showed similar bands at 1644 and 1670 cm^{-1}. The relative intensity of the two carbonyl bands in each spectrum did not depend on the concentration, and the ^{31}P NMR spectrum of **24b** consisted of a single line at δ −36.

Carbonyl stretching frequencies for acyl–metal complexes have been correlated with the overall donicity of the ligand bound to the metal.[44,45]

(41) Allen, D. W.; Taylor, B. F. *J. Chem. Soc., Dalton Trans.* **1982**, 51–4.
(42) (a) Brown, J. M.; Cooley, N. A. *Organometallics* **1990**, *9*, 353–9. (b) Brown, J. M.; Cooley, N. A. *Philos. Trans. R. Soc. London, A* **1988**, *326*, 587–94.
(43) Suzuki, K.; Nishida, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2887–8.
(44) Bibler, J. P.; Wojcicki, A. *Inorg. Chem.* **1986**, *5*, 889–92.
(45) Otsuka, S.; Nakamura, S.; Yoshida, T.; Naruto, M.; Ataka, K. *J. Am. Chem. Soc.* **1973**, *95*, 3180–8.

Discussion

The catalytic scheme depicted in Scheme I makes considerable demands on the palladium catalyst. The oxidative addition requires an electron-rich metal so that oxidation will be favorable,[46,47] but the transmetalation presumably requires an electron-deficient palladium for the nucleophilic stannane to attack the metal center. Both oxidative addition and reductive elimination require ligand dissociation,[9] but ligands of good donicity, necessary to stabilize the Pd(0) species, are expected to dissociate less readily. Ligands of poor donicity may dissociate more easily but may also provide insufficient stabilization for the Pd(0) intermediate, leading to catalyst decomposition with precipitation of metallic Pd.[48]

It is therefore likely that the best ligands in a typical cross-coupling reaction will be of "intermediate" donicity, achieving a compromise among the diverse electronic requirements of each separate step of the coupling. The search for this "optimum" donicity was the goal of our study.

The rates in Table I are interpreted in this study as equivalent to the transmetalation rates in each case. The discussion that follows is based on our knowledge that the transmetalation is the rate-determining step of the coupling, as confirmed by the NMR study. This is also in agreement with the observed kinetics. Provided that oxidative addition and reductive elimination are both irreversible and much faster than the transmetalation, then the overall rate will be determined by the rate of the transmetalation (eq 14).

$$v = k_{trans}[PhPdL_2I][stannane] = k_{obsd}[stannane] \quad (14)$$

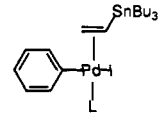
Since $[PhPdL_2I]$ is constant throughout the coupling (as all of the catalyst undergoes a rapid oxidative addition to iodobenzene), the kinetics are expected to be first-order with respect to stannane and zeroth-order vs iodobenzene, as observed.

The fact that doubling the concentration of catalyst also doubles k_{obsd} shows that, at least in the concentration range under study, the rate is indeed proportional to the concentration of $PhPdL_2I$, as in eq 14. In relation to this point, Stille has shown[6] that at high concentration of catalyst a nonlinear behavior can be observed.

While ligand effects in these reactions have previously been assumed to be of steric origin,[2] the results in Table I show that no correlation exists between the steric parameter θ and the observed rates. For example, tri-*o*-tolylphosphine, a ligand of bulk comparable to tris(2,4,6-trimethoxyphenyl)phosphine, yields coupling rates that are 500 times larger (entries 5 and 8). Similarly, triphenylarsine, which has essentially the same cone angle as triphenylphosphine, gives rates that are faster by 3 orders of magnitude (entries 1 and 16). Ligands with very small cone angles can lead to good rates (entries 14 and 15) or extremely sluggish ones (entries 2 and 3).

The correlation with the electronic parameter is much better but still not good. Thus, phosphines that are good σ-donors (entries 1, 2, 4, and 5) are generally poor at promoting coupling, while electron-deficient ligands (poor σ-donors or good π-acceptors) are much better (entries 11, 12, 14, and 15). Tri-*o*-tolylphosphine, however, is an exception, yielding much faster rates than the electronically similar PPh_3. Electronic parameters for TFP and $AsPh_3$ have not been reported in the literature. Very intriguing is the fact that chelating ligands bearing the diphenylphosphino or the difurylphosphino moiety both perform poorly in our coupling (Table II, entries 1 and 4). The better performance of dppp over dppe and dppb (entries 1, 2, and 3) is hard to interpret since it is not known whether chelation is actually involved in all cases. Table III provides a clue to the mechanism of the transmetalation: ligands that give slow rates also have large inhibition factors (entries 1, 2, and 3), while the best ligands have small ones. When TFP and PPh_3 were used in combination, PPh_3 apparently "controlled" the coupling, suggesting a tighter binding to palladium. This finds confirmation in the NMR study (Figure 4) and suggests that *ligand dissociation is a key step in the transmetalation.*

While several schemes explicitly involving ligand dissociation can be proposed that agree with the kinetic results, it seems reasonable to postulate, as a key intermediate, a π-complex between the Pd(II) intermediate and the olefinic stannane, i.e., **25**. Other intermediates may be involved in the transmetalation reaction, and our results do not allow us to propose a detailed mechanistic scheme.



25

Indirect evidence for a π-complex is provided in the recent work of Kikukawa[49a] and Stork.[49b] Further evidence is provided in this work by the lack of ligand effect in the coupling of aryl triflates with tetramethyltin (vide infra). The Heck reaction is also known to proceed via a π-complex between Pd(II) and the olefin,[50,51] and Norton[52] has elegantly shown that intramolecular insertion of an acylpalladium species across a triple bond proceeds by ligand predissociation and π-complex formation. An important role for the ligand may then be simply the dissociation from **22** to allow formation of **25**, a process that is presumably extremely unfavorable, especially with the strong σ-donors.

Two major opposing factors will influence the formation of **25** from **22**. Most importantly, the M–L bond enthalpy will play a key role: weaker donors will tend to dissociate more readily, while good donors will coordinate tightly. Good donors, on the other hand, will also strengthen the Pd–olefin bond by favoring back-donation of the metal into the olefin π^*-orbital.[38]

While representative bond enthalpies between Pd and our ligands are not available, Tolman[53] has shown that the bond between Pt(II) and $AsPh_3$ is weaker than the one between Pt(II) and PPh_3 by as much as 7 kcal/mol. Equilibrium measurements of affinity for Pt(II) also showed a ranking: $PPh_3 > C_6F_5PPh_2 > AsPh_3 > (C_6F_5)_2PPh_2$.[54] This correlates well with our rate data. Other data in the literature[55-57] support lower donicity of $AsPh_3$ for "soft"[58] metal centers. A series of elegant studies by Vrieze[59] has also clearly demonstrated that $AsPh_3$ is *kinetically* more labile than PPh_3 in π-allyl–palladium complexes.

The NMR study of the equilibrium in eq 12 supports a much stronger thermodynamic affinity of PPh_3 than TFP for Pd(II). Thus, both the kinetic and thermodynamic data available for our best ligands support a mechanism involving **25** as a key intermediate.

(46) (a) Fauvarque, J. F.; Pflüger, F.; Troupel, M. *J. Organomet. Chem.* **1981**, *208*, 419–27. (b) Fitton, P.; Johnson, M. P.; McKeon, J. E. *J. Chem. Soc., Chem. Commun.* **1968**, 6–7.

(47) Ugo, R.; Pasini, A.; Fusi, A.; Cenini, S. *J. Am. Chem. Soc.* **1972**, *94*, 7364–70.

(48) See, however: Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896–900.

(49) (a) Kikukawa, K.; Umekawa, H.; Matsuda, T. *J. Organomet. Chem.* **1986**, *311*, C44–6. (b) Stork, G.; Isaacs, R. C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7399–400.

(50) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941–6.

(51) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146–51.

(52) Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505–12.

(53) Manzer, L. E.; Tolman, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 1955–6.

(54) Kemmitt, R. D. W.; Nichols, D. I.; Peacock, R. D. *J. Chem. Soc. A* **1968**, 2149–52.

(55) Ahrland, S.; Chatt, J.; Davies, N. R. *Quart. Rev.* **1958**, 265–76.

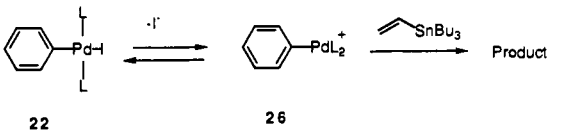
(56) Ahrland, S.; Berg, T.; Trinderup, P. *Acta Chem. Scand. Ser. A* **1977**, *31*, 775–82.

(57) Angelici, R. J.; Ingemanson, C. M. *Inorg. Chem.* **1969**, *8*, 83–6.

(58) Davies, J. A.; Hartley, F. R. *Chem. Rev.* **1981**, *81*, 79–90.

(59) (a) Vrieze, K.; Cossee, P.; Praat, A. P.; Hilbers, C. W. *J. Orgamomet. Chem.* **1968**, *11*, 353–75. (b) Vrieze, K.; Praat, A. P.; Cossee, P. *J. Organomet. Chem.* **1968**, *12*, 533–47. (c) Vrieze, K.; Volger, H. C. *J. Organomet. Chem.* **1967**, *9*, 537–48. (d) Vrieze, K.; Cossee, P.; MacLean, C.; Hilbers, C. W. *J. Organomet. Chem.* **1966**, *6*, 672–6. (e) Vrieze, K.; Cossee, P.; Hilbers, C. W.; Praat, A. P. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 769–94. (f) Vrieze, K.; MacLean, C.; Cossee, P.; Hilbers, C. W. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1077–98.

Scheme IV



22 26

In general, our data suggest that the single most important factor controlling the overall rate of the coupling is the *Pd–L bond enthalpy*. The large rate for tri-*o*-tolylphosphine is an example of *steric acceleration*, also described by Heck in the olefin insertion reaction.[60] Bulky ligands (of acceptable donicity) will accelerate the coupling by sterically promoting formation of **25**.

The higher IR carbonyl stretching frequencies for TFP vs PPh_3 in acylpalladium(II) complexes **24a,b** are in agreement with the reduced σ-donicity of TFP, which in turn decreases the degree of Pd back-bonding to the carbonyl group.[44,45] The presence of two carbonyl stretching frequencies in the IR spectra of acylpalladium complexes has been attributed to hindered rotation around the Pd–C bond.[60] The dilution studies rule out the presence of dimeric species, while the NMR results show the absence of cis/trans isomerism.

The behavior of bidentate ligands (Table II) is also readily understandable: TFP promotes the reaction by readily dissociating from Pd(II), and no rate enhancement in the difurylphosphino-containing ligand over the diphenylphosphino analogue is observed, since such dissociation is inhibited by chelation.

An alternative mechanism for the transmetalation is shown in Scheme IV. This mechanism, a dissociative one, is expected to be especially favored with bulky ligands (steric acceleration).[61] The fact that LiI does not inhibit the reaction suggests that this mechanism is not important here (vide infra, however). The small acceleration observed may be due to nucleophilic assistance on the part of the iodide ion at the departing tin, as already postulated by us in a previous paper.[5]

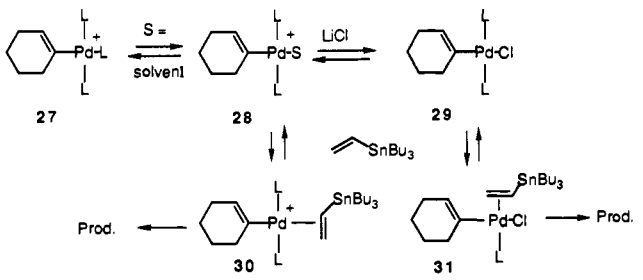
It must be noted that the rate for tris(2-cyanoethyl)phosphine (Table I, entry 3) does not seem to fit the trend of the other ligands. Triphenylstibine (entry 17) yielded a milky suspension when treated with Pd_2dba_3, and it is not known whether the rather sluggish rate is simply due to poor catalyst solubility. A milky suspension was obtained in NMP as well.

The NMR study on the composition of the Pd(0) catalysts was especially informative. Our data (Figures 2 and 3) show that the species resulting from the combination of Pd_2dba_3 and PPh_3 is quite different from $Pd(PPh_3)_4$, even though the two species have identical catalytic behavior. The Pd/dba/PPh_3 catalyst is much more soluble than $Pd(PPh_3)_4$, and dba appears to be still bound to Pd to some extent. Oxidative addition, on the other hand, yields species **22a** (Scheme III), where PPh_3 and not dba binds to Pd. Evidently palladium, in the higher oxidation state, is less electron-rich and strongly prefers to bind the better donor of the two ligands. All of our kinetic data suggest that dba has no effect on coupling rates, and its only role seems to be that of a solubilizing agent for the Pd(0) catalysts.

Even at −78 °C, $Pd(PPh_3)_4$ (whether preformed or formed in situ from Pd_2dba_3) is largely dissociated in THF solution and the equilibrium rate is of the order of the NMR time scale (broad lines). When TFP was added to Pd_2dba_3, however, a single species was present at −60 °C, consistent with the formulation $Pd(TFP)_4$. The lines are sharp at low temperatures, and the resonance for excess phosphine is sharp and separate from the one of the complex, indicating *slow exchange* on the NMR time scale.

These results point to the surprising conclusion that TFP binds Pd(0) more tightly than does PPh_3, while the reverse is true for Pd(II). This can be tentatively explained by assuming that PPh_3 behaves as a pure σ-donor toward Pd(0) or Pd(II), while TFP is a less effective σ-donor in general but behaves as a π-acceptor toward the electron-rich Pd(0) (not toward Pd(II), however), thus strengthening the Pd–P bond in these complexes. Alternatively,

Scheme V



27 28 29 30 31

the more extensive dissociation of PPh_3 from Pd(0) may be of steric origin.[17] Further studies on this very interesting ligand may shed light on this point.

The NMR studies then suggest that TFP should yield a catalyst *both more reactive and more stable*, a conclusion that, on the basis of the above discussion, is not self-contradictory. This is exactly what we have observed in a variety of cases. For example, in the coupling between 5-iodouracil and vinyltributyltin (Table IV), the PPh_3-derived catalyst only led to ca. 50% conversion, while the TFP-derived species led to complete conversion. We have found this to be a general phenomenon in the comparison between the two ligands. Triphenylarsine, though yielding in general the fastest rates, yields catalysts that are intermediate in stability between TFP- and PPh_3-based ones.

Phosphine decomposition during palladium-catalyzed reactions by Pd–C insertion is well-precedented,[62a,b] and oxidation to phosphine oxide is another possibility[62c] as is quarternization to phosphonium salts.[63] Other processes may be possible. Traces of phosphine oxides were usually detected in all of these couplings, but the relation to catalyst stability is not certain. Our proposed mechanism most likely applies to the coupling of vinylstannanes with other electrophiles. Observed kinetics were first-order in all cases.

For example, the behavior of allylic halides toward vinyltins (Table V) is fully consistent with our discussion, and we postulate that here also the origin of the ligand-promoted rate acceleration is traceable to effective ligand dissociation from Pd(II) at the transmetalation stage.

The coupling of acyl chlorides will organotins (Table VI) probably also requires ligand dissociation in the transmetalation, since the reactivity order is the usual $AsPh_3 > TFP > PPh_3$. Most interesting is the observation that TFP may offer a general solution to the stereospecificity problem encountered in this reaction.[30]

The coupling of aryl triflates with organotins (Table VII) shows the expected ligand effect, even though the rate differences here are less dramatic than in previous cases. The successful coupling with allyltributyltin (eq 8) without isomerization may provide a general solution to an important synthetic problem.

The data for the vinyl triflate–vinyltin coupling (Table VIII) confirm previous observations[5,34,64] that the requirement for chloride ion in this reaction[6] is not absolute. Lithium chloride appears to actually slow down the coupling. Most interesting is the fact that in the presence of LiCl excess ligand inhibits the coupling (Table VIII), while this is not the case in the absence of LiCl. These data, coupled with the inhibitory effect of LiCl, support the participation of a *dissociative* mechanism in our case. We postulate that upon oxidative addition the vinyl triflate forms **27**,[65] in which palladium is electron-rich and readily dissociates to **28**, where solvent and not triflate coordinates palladium.[66] When LiCl is present, **29** is produced[6] (Scheme V). Our data

(60) Brumbaugh, J. S.; Sen, A. *J. Am. Chem. Soc.* **1988**, *110*, 803–16.
(61) Romeo, R.; Minniti, D.; Trozzi, M. *Inorg. Chem.* **1976**, *15*, 1134–8.
(62) (a) Goel, A. B. *Inorg. Chim. Acta* **1984**, *86*, 177–8. (b) Yamana, T.; Kikukawa, K.; Takagi, M.; Matsuda, T. *Tetrahedron* **1973**, *29*, 955–62. (c) Halpern, J.; Pickard, A. L. *Inorg. Chem.* **1970**, *9*, 2798–800.
(63) Kowalski, M.; Hinkle, R. J.; Stang, P. J. *J. Org. Chem.* **1989**, *54*, 2783–4.
(64) Baker, S. R.; Roth, G. P.; Sapino, C. *Synth. Commun.* **1990**, *20*, 2185–89.
(65) Stang, P. J.; Kowalski, M. H.; Schiavelli, M. D.; Longford, D. *J. Am. Chem. Soc.* **1989**, *111*, 3347–56.
(66) Lawrance, G. A. *Chem. Rev.* **1986**, *86*, 17–33.

suggest that species **28** is more electrophilic than **29** and is on the preferred pathway to product (possibly through **30**, but a cis isomer of **30** is also possible), while in the presence of LiCl the reaction is forced to take, to some extent, the second pathway, which proceeds via *ligand* dissociation. The intervention of the cationic pathway is probably due to a change in solvent from THF to the much more polar NMP.

The above observations suggest that the requirement for halides in palladium-catalyzed couplings of vinyl triflates may be circumvented by the use of polar aprotic solvents and/or more active ligands. Chloride, however, appears to be necessary in the coupling of *aryl triflates*, even in NMP as a solvent.

Finally, a very different ligand effect is observed for the coupling of aryl triflates with tetramethyltin. This reaction cannot, of course, proceed via π-complex formation. Table IX shows that less than 1 order of magnitude is observed in the rate difference between the poorest and best ligand in this case. Interestingly, PPh_3 and TFP induce coupling at essentially the same rate. This reaction must then proceed through a different pathway. This is evidently a more difficult process than the one available to olefinic stannanes, as shown by the more drastic conditions necessary to induce reaction. We note that $AsPh_3$ is once again the ligand that yields the fastest rate. This is consistent with data demonstrating the larger cis influence of $AsPh_3$ (vs PPh_3) at Pt(II).[67,68] A more detailed investigation of this reaction is outside the scope of this study.

In unrelated experiments, which we include in this study for the purpose of more fully documenting the role of TFP in palladium catalysis, allylic alkylation with soft nucleophiles (eq 11) does not benefit from the use of TFP in lieu of PPh_3. Nucleophilic attack at the allylic carbon does not appear to be facilitated by TFP, since this reaction probably does not involve a ligand dissociation step. Any electronic effect of the ligand is "diluted" by the distance between phosphorus and the allylic carbon. In addition, oxidative addition with TFP-based catalysts may be more difficult than for $Pd(PPh_3)_4$, and this is likely to be very important when oxidative addition is the rate-determining step (i.e. allylic acetates).

Summary and Conclusion

The present study has more fully documented our previous observations of a substantial ligand effect in the Stille reaction. From a mechanistic viewpoint, our kinetic data provide evidence that the rate-determining transmetalation step proceeds via ligand dissociation and formation of a Pd–stannane π-complex. The key role of the ligand then becomes ready dissociation from the Pd(II) intermediate in order to facilitate formation of this intermediate, either in a kinetic or thermodynamic sense. Interestingly, of the many ligands examined, PPh_3, the classical ligand in many cross-coupling reactions including the Stille protocol, performs very poorly in terms of rates. This fact, coupled with the air-sensitivity of $Pd(PPh_3)_4$, makes the use of the air-stable Pd_2dba_3, in conjunction with TFP or $AsPh_3$, especially attractive. Experimental details of our modified protocol can be found in the Experimental Section for a variety of electrophiles. Typically, vinyl and aryl halides or triflates can be coupled in NMP at room temperature. Allylic halides react more cleanly in THF and react at room temperature when $AsPh_3$ is the ligand.

The TFP-derived catalyst is extremely stable, and when the catalyst stoichiometry is Pd:L = 1:2 somewhat faster rates are obtained, with no apparent loss in stability. Catalysts employing $AsPh_3$ usually yield the fastest rates but are also somewhat less stable than the ones employing TFP. In this case, a Pd:L catalyst stoichiometry of 1:4 is necessary for optimum yields.

Even though $Pd(AsPh_3)_4$ was described over 30 years ago,[69] its use in cross-coupling chemistry has not been described. Trost[70] has reported the use of $Pd(AsPh_3)_2(OAc)_2$ in his elegant cycloisomerization studies, while a similar catalyst was found to enhance certain carbonylation reactions.[71] Our findings that $AsPh_3$ is also the best ligand in couplings between aryl triflates and tetramethyltin (this study) and between arylstannanes and vinyl triflates[72] indicate that this ligand may find much further application in cross-coupling chemistry.

It is unknown whether other cross-coupling reactions are subject to this kind of ligand effect. In this connection the type of study described here may be used mechanistically to probe whether ligand dissociation is important in couplings utilizing other organometallic species. The role of the new ligands in carbonylative couplings is another area of possible exploration. We are currently trying to systematically correlate the ligand effects with structural parameters in the vinylstannane and in the electrophile; this should shed further light on the steric/electronic requirements of the transmetalation step of these couplings.

The comparison of the ligand effects in the coupling of vinylstannanes vs tetramethyltin points to the fact that the Stille coupling is actually a family of related reactions. In each one, the transmetalation proceeds in a fundamentally unique fashion and therefore is subject to unique effects by ligands and additives. Ligand effects in couplings involving alkynylstannanes, for example, are still unexplored, but we predict effects similar to the ones observed for vinylstannanes, since formation of π-complexes appears favorable here as well.

Experimental Section

Reactions were carried out under argon using oven-dried (130 °C, 24 h) glassware. Dry THF and benzene were obtained by distillation from Na/Benzophenone, and dry NMP was obtained by distillation from CaH_2 under reduced pressure. Nuclear magnetic resonance spectra were obtained on a Bruker WM-360 instrument. In the ^{31}P NMR spectra, positive shifts are downfield of 85% phosphoric acid. Mass spectra were obtained with a Kratos MS50RF mass spectrometer in the positive ion FAB mode, with *m*-nitrobenzyl alcohol as the matrix. HPLC monitoring was carried out on a Perkin-Elmer Series 410 instrument equipped with an LC-235 diode array detector set at 250 nm. A Phenomenex C-18 column (300 × 39 mm) was used; the elution system is specified below for each reaction. All reagents were commercially available except (*Z*)-propenyltributyltin, which was prepared as described.[5] Tri-2-furylphosphine was prepared according to ref 41.

Determination of Rate Constants. An HPLC calibration curve was obtained by injecting standard solutions of reactant (halide or triflate) and product. Each reaction was carried out in a thermostatic oil bath. Temperatures are estimated to be accurate within 0.5 °C. At appropriate intervals, small aliquots were withdrawn through a septum and immediately quenched by 100-fold dilution with acetonitrile (except for the reaction in eq 3, where adequate HPLC peak shape could only be obtained with methanol dilution). The resulting solutions were then injected into the HPLC, and the appropriate concentrations were calculated, each point being the average of two determinations. First-order rate constants were obtained from the appropriate logarithmic plots by the least-squares method. Initial rates refer to the initial 2–10% conversion, even though monitoring was continued for 48–72 h. HPLC yields were determined by diluting the reaction mixture to a known volume and injecting an aliquot into the HPLC. The concentration of product was calculated from the previously calculated response factor.

Coupling of Iodobenzene and Vinyltributyltin. Iodobenzene (182.3 mg, 0.892 mmol) was dissolved in THF (5 mL) and treated with tri-2-furylphosphine (8.3 mg, 0.04 equiv) and Pd_2dba_3 (8.2 mg, 0.02 equiv of Pd) under argon. After a period of 10 min at room temperature, the flask was immersed in a bath at 50 °C and vinyltributyltin (0.30 mL, 1.026 mmol) was added. The reaction was monitored by HPLC (C-18, 80% MeOH, 20% H_2O). After 5 h, the solution was concentrated in vacuo and styrene isolated by bulb-to-bulb distillation. Yield: 72.5 mg (78%). The proton NMR spectrum was identical to the one obtained with a commercial sample of styrene.

Coupling of 5-Iodouracil and Vinyltributyltin. 5-Iodouracil (Sigma, 927 mg, 3.895 mmol) was dissolved in NMP (6 mL) treated with TFP (36.1 mg, 0.04 equiv) and Pd_2dba_3 (35.6 mg, 0.02 equiv of Pd). After 10 min at room temperature, vinyltributyltin (1.250 mL, 4.277 mmol) was added and the solution was stirred at room temperature for 16 h. Monitoring was carried out by HPLC (C-18, 15% MeOH, 85% pH 6.5

(67) Fryer, C. W.; Smith, J. A. S. *J. Organomet. Chem.* **1969**, *18*, P35–8.
(68) Belluco, U.; Cattalini, L.; Basolo, F.; Pearson, R. G.; Turco, A. *J. Am. Chem. Soc.* **1965**, *87*, 241–7.
(69) Malatesta, L.; Angoletta, M. *J. Chem. Soc.* **1957**, 1186–8.
(70) Trosi, B. M.; Edstrom, E. D.; Carter-Petillo, M. B. *J. Org. Chem.* **1989**, *54*, 4489–90.
(71) Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1981**, *205*, C27–30.
(72) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243–6.

0.01 M ammonium phosphate buffer). The solvent was evaporated in vacuo (50 °C) and the residue absorbed onto silica with MeOH. Chromatography (1–10% MeOH in CH_2Cl_2) gave an off-white solid, which was further purified by trituration with MeOH. The yield was 447 mg (89%) of an amorphous powder which was better than 99% pure by HPLC. NMR and mp data were identical to those in the literature.[73]

Coupling of Cinnamyl Chloride and Vinyltributyltin. Cinnamyl chloride (265.8 mg, 1.741 mmol) was dissolved in THF (10 mL) treated with TFP (32.3 mg, 0.08 equiv) and Pd_2dba_3 (15.9 mg, 0.02 equiv of Pd). After 10 min at room temperature, vinyltributyltin (0.51 mL, 1.740 mmol) was added and the solution was stirred at 65 °C overnight. The reaction progress was monitored by HPLC (C-18, 80% MeOH, 20% H_2O). The solution was treated with saturated potassium fluoride and hexane for 30 min. Filtration, separation of the organic phase, drying, and evaporation gave the crude product. Filtration through silica (hexane) and bulb-to-bulb distillation (75–90 °C, 0.2 mmHg) gave 1-phenyl-1,4-pentadiene (**7**), 212 mg (84%): ^{1}H NMR ($CDCl_3$) δ 7.40–7.06 (m, 5 H), 6.56 (d, J = 16 Hz, 1 H), 6.26 (dt, J = 16 Hz, J' = 6.6 Hz, 1 H), 5.95 (m, 1 H), 5.18–5.08 (m, 2 H), 3.01 (m, 2 H); mass spectrum 144 (M^+). Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.38; H, 8.36.

Coupling of Benzoyl Chloride and (*Z*)-1-Propenyltributyltin. Freshly distilled benzoyl chloride (935 mg, 6.651 mmol) was dissolved in THF (15 mL) and treated with TFP (30.8 mg, 0.02 equiv) and Pd_2dba_3 (30.4 mg, 0.01 equiv of Pd). After 10 min at room temperature, the stannane was added (2.079 g, 6.279 mmol) with stirring at room temperature. Conversion to 1-phenyl-2-buten-1-one was monitored by NMR: an aliquot of the reaction mixture was withdrawn by syringe through a septum, the solvent was quickly evaporated and replaced with $CDCl_3$, and the ratio of starting material to product was determined by integration. After 40 h, the reaction was complete. Evaporation and silica gel glash chromatography (5% ethyl acetate–hexane) gave enone **10**. All fractions containing (*E*)- and (*Z*)-**10** were combined to yield 890 mg (97%) of **10** (*Z*:*E* = 95.4:4.5). The NMR spectrum was identical to the published one.[30]

Coupling of 4-(Triflyloxy)acetophenone and Vinyltributyltin. Triflate **11**[31] (204.8 mg, 0.763 mmol) was dissolved in NMP (3 mL) and treated with anhydrous lithium chloride (94 mg, 3 equiv), TFP (7.1 mg, 0.04 equiv), and Pd_2dba_3 (7.0 mg, 0.02 equiv of Pd). After 5 min at room temperature, vinyltributyltin (0.25 mL, 0.855 mmol) was added and the solution was stirred at room temperature for 2 h. Monitoring was carried out by HPLC (C-18, 75% MeOH, 25% H_2O). Dilution with saturated potassium fluoride solution and hexane, filtration, and separation of the organic phase was followed by drying and evaporation. Silica gel chromatography (5% ethyl acetate in hexane) gave **12** (106.6 mg, 95%) as a semisolid mass. The NMR spectrum was the same as the one in the literature.[31]

Coupling of 4-(Triflyloxy)acetophenone and Allyltributyltin. Triflate **11** (566.1 mg, 2.111 mmol) was dissolved in NMP (5 mL) and treated with anhydrous lithium chloride (268 mg, 3 equiv), TFP (39.2 mg, 0.08 equiv), and Pd_2dba_3 (19.3 mg, 0.02 equiv of Pd). After 10 min at room temperature, the solution was treated with vinyltributyltin (0.72 mL, 2.464 mmol) and the mixture was stirred at room temperature for 24 h. Dilution with a saturated potassium fluoride solution was followed by extraction with ethyl acetate, drying, and evaporation. Silica gel chromatography (5% ethyl acetate in hexane) gave **13** (with no traces of isomer **14**). 264 mg (78.5%): bp (Kugelrohr, oven temperature) 90–5 °C, 0.2 mmHg. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.11; H, 7.56. The NMR spectrum was identical to the one reported by Stille.[31]

Coupling of 4-Phenyl-1-(triflyloxy)-1-cyclohexene and Vinyltributyltin. Triflate **15**[74] (377 mg, 1.231 mmol) was dissolved in NMP (5 mL) and treated with anhydrous lithium chloride (156.5 mg, 3 equiv), TFP (11.4 mg, 0.04 equiv), and Pd_2dba_3 (11.3 mg, 0.02 equiv of Pd). After 10 min at room temperature, the yellow solution was treated with vinyltributyltin. The progress of the reaction was monitored by HPLC (C-18, 90% CH_3CN, 10% H_2O). After 18 h at room temperature, dilution with saturated potassium fluoride solution, hexane extraction, and drying gave the crude product. Silica gel filtration (hexane) gave pure **16**, 170.1 mg (75%), as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 7.30–7.18 (m, 5 H), 6.38 (dd, J = 17.4 Hz, J' = 10.5 Hz, 1 H), 5.82 (m, 1 H), 5.07 (d, J = 17.4 Hz, 1 H), 4.92 (d, J = 10.5 Hz, 1 H), 2.85–2.70 (m, 1 H), 2.46–0.60 (m, 6 H). Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.19; H, 8.69.

Coupling of 4-(Triflyloxy)acetophenone and Tetramethyltin. Triflate **11** (239.3 mg, 0.892 mmol) was dissolved in NMP (5 mL) and treated with anhydrous lithium chloride (113.5 mg, 3 equiv), triphenylarsine (21.8 mg, 0.08 equiv), and Pd_2dba_3 (8.2 mg, 0.02 equiv of Pd). After 10 min at room temperature, tetramethyltin (0.15 mL, 1.083 mmol) was added and the mixture heated at 60 °C overnight. Monitoring was carried out by HPLC (C-18, 70% MeOH, 30% H_2O). Dilution with a saturated potassium fluoride solution was followed by hexane extraction and evaporation. Chromatography over silica gel gave 96 mg (80%) of 4-methylacetophenone, identical (NMR, HPLC) to a commercially available sample.

Allylic Alkylation with 4-Hydroxy-6-methyl-2-pyrone. Allylic alkylation with cinnamyl acetate was carried out in toluene with DBU as the base according to the literature,[35] in order to obtain an authentic sample of **20**. Reaction with cinnamyl chloride was more conveniently carried out as follows. Cinnamyl chloride (152.6 mg, 1.000 mmol) in THF (6 mL) was treated with **19** (126.1 mg, 1.000 mmol), TFP (18.6 mg, 0.08 equiv), and Pd_2dba_3 (9.2 mg, 0.02 equiv of Pd). The mixture was immersed in a bath set at 50 °C, and triethylamine (0.14 mL, 1.000 mmol) was added. The half-life of the reaction (41 min) was estimated by monitoring the disappearance of cinnamyl chloride by HPLC (C-18, 80% MeOH, 20% H_2O). After 4 h, workup (water–ethyl acetate) gave a crude that was shown by NMR to consist of a 65:35 mixture of C-alkylated (**20**) and O-alkylated (**21**) materials. An authentic sample of **21** was obtained by silica gel chromatography (30% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 7.6–7.1 (m, 5 H), 6.68 (d, J = 16.2 Hz, 1 H), 6.28 (m, 1 H), 5.79 (d, J = ca. 1 Hz, 1 H), 5.43 (d, J = 2.1 Hz, 1 H), 4.61 (m, 2 H), 2.18 (s, 3 H); high-resolution mass spectrum calcd for $C_{15}H_{15}O_3$ 243.1021, found 243.1020. Repetition of the experiment by replacing TFP with an equimolar amount of PPh_3 produced essentially identical results (NMR integration). Reaction half-life: 40 min.

Chloro(4-methylbenzoyl)bis[tri-2-furylphosphine]palladium(II) (24b). TFP (212 mg, 0.914 mmol) was dissolved in dry benzene (15 mL), and palladium(II) acetate (51.3 mg, 0.228 mmol) was added followed by vinyltributyltin (0.133 mL, 0.456 mmol). After brief sonication to break up the chunks of palladium acetate, the mixture was stirred at room temperature for 4 h. Freshly distilled toluoyl chloride (0.166 mL, 1.256 mmol) was added and the yellow solution was kept for 48 h at room temperature. A fine yellow crystalline precipitate of **24b** formed and was filtered under argon, washing with several portions of cold benzene, and evaporated under vacuum. Yield, 83.8 mg (50%), mp 93–6 °C dec. A second crop (49 mg) could be obtained by diluting the filtrate with ether (20 mL): ^{1}H NMR ($CDCl_3$) δ 7.30 (br d, 2 H), 7.65 (br s, 6 H), 7.26 (br s, 6 H), 6.91 (br d, 2 H), 6.38 (br s, 6 H), 2.24 (s, 3 H); ^{31}P NMR (THF) δ −36; IR ($CHCl_3$) 1670, 1644, 1601 cm^{-1}. Anal. Calcd for $C_{32}H_{25}ClPdP_2O_7$: C, 53.0; H, 3.47. Found: C, 53.4; H, 3.65.

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Registry No. 2, 7486-35-3; **4**, 696-07-1; **5**, 37107-81-6; **6**, 2687-12-9; **7**, 55666-17-6; **8**, 98-88-4; **9**, 66680-84-0; (*Z*)-**10**, 35660-91-4; (*E*)-**10**, 35845-66-0; **11**, 109613-00-5; **12**, 10537-63-0; **13**, 62926-84-5; **14**, 17417-03-7; **15**, 122948-47-4; **16**, 131111-08-5; **17**, 122-00-9; **18**, 103-54-8; **19**, 675-10-5; **20**, 136667-00-0; **21**, 136667-01-1; **24b**, 136632-08-1; dppf, 12150-46-8; Pd_2dba_3, 51364-51-3; PPh_3, 603-35-0; $MePPh_2$, 1486-28-8; $P(CH_2CH_2CN)_3$, 4023-53-4; $(4\text{-}MeOC_6H_4)_3P$, 855-38-9; $[2,4,6\text{-}(MeO)_3C_6H_2]_3P$, 91608-15-0; $(4\text{-}FC_6H_4)_3P$, 18437-78-0; $(4\text{-}ClC_6H_4)_3P$, 1159-54-2; $(2\text{-}MeC_6H_4)_3P$, 6163-58-2; $(2\text{-furyl})_3P$, 5518-52-5; $(2\text{-thienyl})_3P$, 24171-89-9; $Ph_2PC_6F_5$, 5525-95-1; $PhP(C_6F_5)_2$, 5074-71-5; $P(C_6F_5)_3$, 1259-35-4; $P(OPh)_3$, 101-02-0; $P(OPr\text{-}i)_3$, 116-17-6; $AsPh_3$, 603-32-7; $SbPh_3$, 603-36-1; $Ph_2P(CH_2)_2PPh_2$, 1663-45-2; $Ph_2P(CH_2)_3PPh_2$, 6737-42-4; $Ph_2P(CH_2)_4PPh_2$, 7688-25-7; $(2\text{-furyl})_2P(CH_2)_2P(2\text{-furyl})_2$, 106308-28-5; $CH_2{=}CHCH_2SnBu_3$, 24850-33-7; $SnMe_4$, 594-27-4; $Pd(OAc)_2$, 3375-31-3; iodobenzene, 591-50-4; styrene, 100-42-5; *p*-toluoyl chloride, 106-43-4.

(73) Evans, C. H.; Jones, A. S.; Walker, R. T. *Tetrahedron* **1973**, *29*, 1611–4.

(74) Saulnier, M. G.; Kadow, J. F.; Tun, M. M.; Langley, D. R.; Vyas, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 8320–1.