

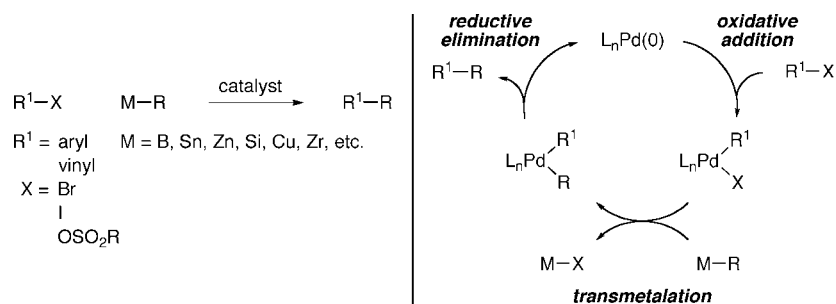
The Development of Versatile Methods for Palladium-Catalyzed Coupling Reactions of Aryl Electrophiles through the Use of $P(t\text{-Bu})_3$ and PCy_3 as Ligands

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RECEIVED ON JUNE 24, 2008

CON SPECTUS



Metal-catalyzed coupling reactions of aryl electrophiles with organometallics and with olefins serve as unusually effective tools for forming new carbon–carbon bonds. By 1998, researchers had developed catalysts that achieved reactions of aryl iodides, bromides, and triflates. Nevertheless, many noteworthy challenges remained; among them were couplings of aryl iodides, bromides, and triflates under *mild* conditions (at room temperature, for example), couplings of hindered reaction partners, and couplings of inexpensive aryl chlorides.

This Account highlights some of the progress that has been made in our laboratory over the past decade, largely through the appropriate choice of ligand, in achieving these synthetic objectives. In particular, we have established that palladium in combination with a bulky trialkylphosphine accomplishes a broad spectrum of coupling processes, including Suzuki, Stille, Negishi, and Heck reactions. These methods have been applied in a wide array of settings, such as natural-product synthesis, materials science, and bioorganic chemistry.

1. Introduction

By the late 1990s, palladium-catalyzed coupling reactions of aryl and vinyl halides and sulfonates had emerged as remarkably powerful tools for the construction of carbon–carbon bonds. Numerous reviews documented the increasing frequency with which cross-coupling processes (Figure 1) and Heck reactions (Figure 2) were applied to a broad spectrum of endeavors, ranging from synthetic organic chemistry to materials science.^{1,2}

Until 1998, nearly all reports of palladium-catalyzed coupling reactions described the use of aryl

and vinyl bromides, iodides, and sulfonates as substrates; chlorides were rarely employed, despite the fact that they are arguably the most useful single class of halides, due to their lower cost and the wider diversity of available compounds.^{3,4} However, aryl chlorides were unreactive under essentially all of the conditions that had been applied to bromides, iodides, and triflates.

The low reactivity of aryl chlorides was often attributed to the strength of the C–Cl bond (bond dissociation energies (kcal/mol) for Ph-X : Cl (95);

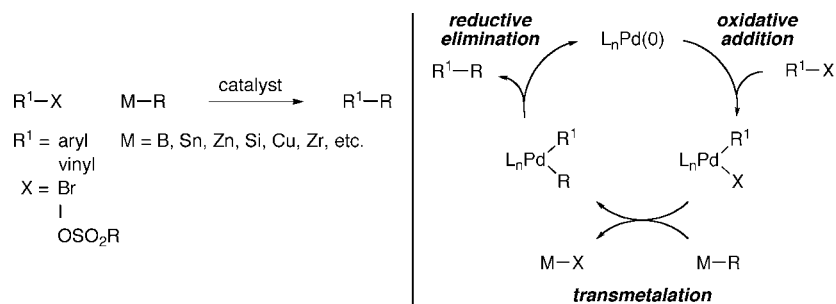


FIGURE 1. Metal-catalyzed cross-coupling reactions, including a generalized catalytic cycle for a palladium-catalyzed process.

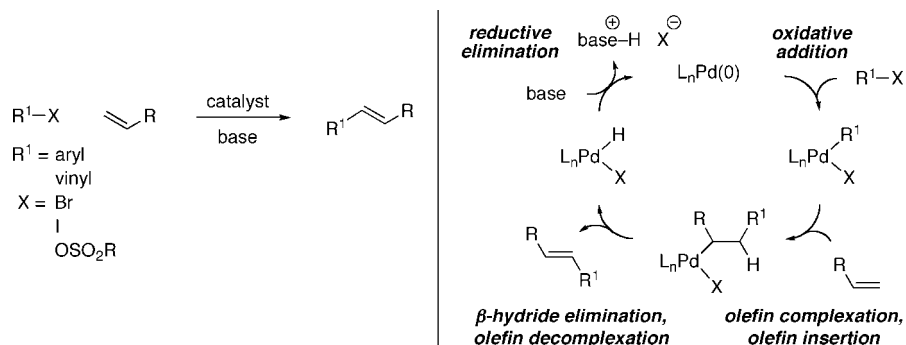
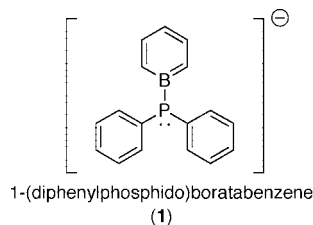
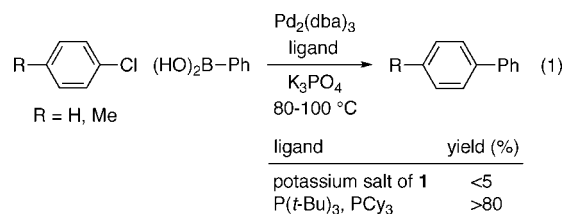


FIGURE 2. Metal-catalyzed Heck reactions, including a generalized catalytic cycle for a palladium-catalyzed process.

Br (80); I (65)),⁵ which could lead to reluctance to oxidatively add to Pd(0), a critical initial step in palladium-catalyzed coupling reactions (Figures 1 and 2). Of course, a more electron-rich metal complex would be expected to be more prone to oxidative addition. In 1996 we had reported a new phosphorus ligand, 1-(diphenylphosphido)boratabenzene (**1**),⁶ and we



had determined that it is virtually isosteric with and significantly more electron-donating than PPh₃, the most widely used ligand for palladium-catalyzed couplings. We therefore decided to examine the utility of 1-(diphenylphosphido)boratabenzene in coupling reactions of aryl chlorides.⁷

2. Suzuki Reactions

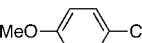
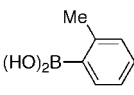
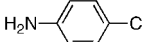
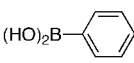

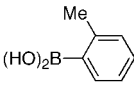

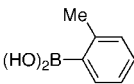
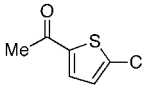
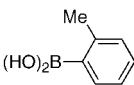

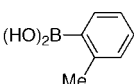
Due to the particular usefulness of Suzuki cross-couplings,⁸ we chose at the beginning of 1998 to focus our initial efforts on palladium-catalyzed reactions of arylboronic acids with unactivated (electron-poor \Rightarrow activated) aryl chlorides. Unfortunately, a preliminary study with Pd/**1** was disappointing: under the conditions illustrated in eq 1, almost none of the desired Suzuki coupling product was observed (<5%).

As part of this investigation, we benchmarked ligand **1** against a range of phosphines. We were interested to discover that commercially available P(*t*-Bu)₃ and PCy₃ furnish the target biaryl in over 80% yield (eq 1). To the best of our knowledge, this was one of the first examples of a palladium-catalyzed Suzuki coupling of an unactivated aryl chloride that proceeded in good yield.^{9–12}

Although we were initially surprised by the effectiveness of P(*t*-Bu)₃ and PCy₃, observations by others had in fact foreshadowed our discovery. Thus, Shen had reported that Pd(PCy₃)₂Cl₂ can achieve Suzuki couplings of highly activated aryl chlorides,¹³ and Koie had described the application of Pd/P(*t*-Bu)₃ in a C–N bond-forming reaction of an unactivated aryl chloride.^{14,15}

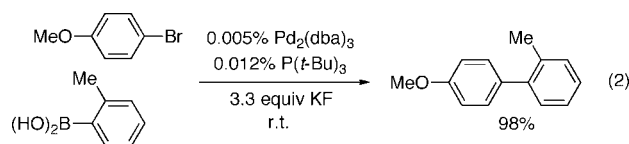
With the key results illustrated in eq 1 in hand, we turned our attention to developing a general method for Suzuki reactions of aryl chlorides. In our early work, we employed additives such as K₃PO₄ and Cs₂CO₃ to activate the boronic acid, but we later determined that KF is often more effective.¹⁶ Thus, through the use of Pd/P(*t*-Bu)₃/KF, we were able to achieve couplings of a wide array of aryl chlorides, including

TABLE 1. Suzuki Reactions of Aryl Chlorides Catalyzed by Pd/P(*t*-Bu)₃

entry	Ar-Cl	(HO) ₂ B-Ar ¹	yield (%)
1			88
2			82
3			97
4			77
5			99
6			93

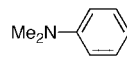
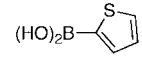
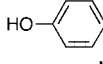
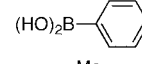

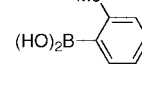

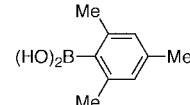
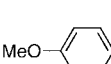
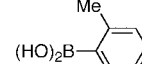

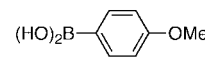
electronically deactivated (entries 1 and 2 of Table 1), heterocyclic (entries 3–5), and hindered (entry 6) compounds. Vinyl chlorides and alkylboronic acids also serve as suitable coupling partners.

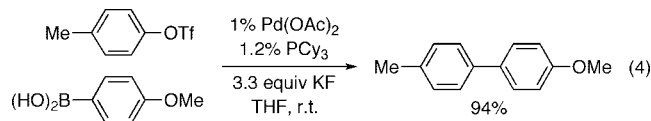
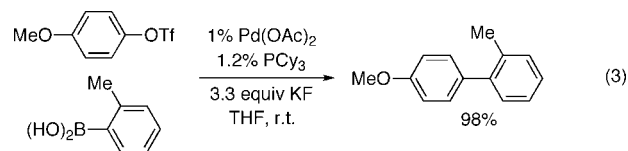
We further established that Pd/P(*t*-Bu)₃/KF is effective for Suzuki reactions of a broad spectrum of aryl bromides and iodides (Table 2). These cross-couplings occur under unusually mild conditions (i.e., at room temperature), even for deactivated (entries 1, 2, and 5) and hindered (entries 3, 4, and 6) substrates. A low catalyst loading can be employed (eq 2; turnover number ~10 000 for the cross-coupling of a deactivated aryl bromide with a hindered boronic acid). Suzuki couplings of vinyl bromides and iodides also proceed smoothly.



Interestingly, we observed relatively inefficient carbon–carbon bond formation when we attempted to employ Pd/P(*t*-Bu)₃ for Suzuki reactions of aryl triflates. However, by using a smaller trialkylphosphine, PCy₃, we were able to achieve cross-couplings in good yield at room temperature (eqs 3 and 4). PCy₃ has also proven to be useful for palladium-catalyzed Suzuki reactions of nitrogen heterocycles.¹⁷

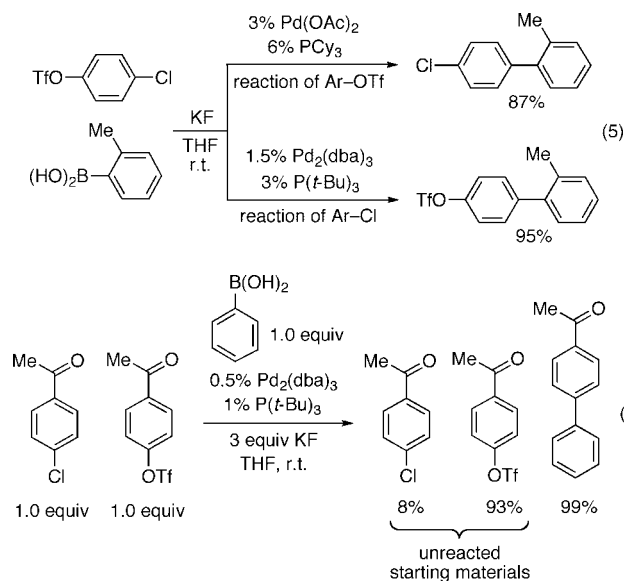
TABLE 2. Room-Temperature Suzuki Reactions of Aryl Bromides and Iodides Catalyzed by Pd/P(*t*-Bu)₃

entry	Ar-X	(HO) ₂ B-Ar ¹	yield (%)
1			99
2			97
3			98
4			97
5			97
6			94



The relative inertness of aryl triflates toward Pd/P(*t*-Bu)₃ can be exploited to accomplish unique site-selective functionalizations. Thus, the typical order of reactivity of aryl electrophiles in palladium-catalyzed cross-couplings is I > Br ≈ OTf ≫ Cl. For the process illustrated in eq 5, Pd/PCy₃ furnishes the expected product, which results from coupling of the aryl triflate (>20:1 selectivity). However, a change in the ligand from PCy₃ to P(*t*-Bu)₃ leads to a complete reversal of the usual preference: now, the aryl chloride reacts with excellent selectivity (>20:1). This strong propensity of Pd/P(*t*-Bu)₃ to couple an aryl chloride rather than a triflate, which was unprecedented for a palladium-catalyzed cross-coupling process, was confirmed through a competition experiment (eq 6).

On the basis of reactivity studies, we postulated that the unusually high activity of Pd/P(*t*-Bu)₃ in Suzuki reactions of aryl halides is a consequence of not only the electron-donating



ability of the ligand but also its steric demand, which leads to ready access to a key palladium–monophosphine complex.¹⁸ Numerous groups have applied Pd/P(*t*-Bu)₃ to Suzuki cross-couplings in a range of contexts.¹⁹

3. Stille Reactions

Having established that Pd/P(*t*-Bu)₃ is an unusually reactive catalyst for Suzuki couplings of aryl halides, we decided to examine its utility in other families of cross-coupling processes. The Stille reaction of organotin compounds is widely employed in organic chemistry, particularly in natural-product synthesis.²⁰ However, to the best of our knowledge, when we began to explore Stille cross-couplings in 1998, there were

TABLE 3. Stille Reactions of Aryl Chlorides Catalyzed by Pd/P(*t*-Bu)₃

entry	aryl chloride	Bu ₃ Sn-R	yield (%)
1			94
2			76
3			89
4			98
5			87
6			82

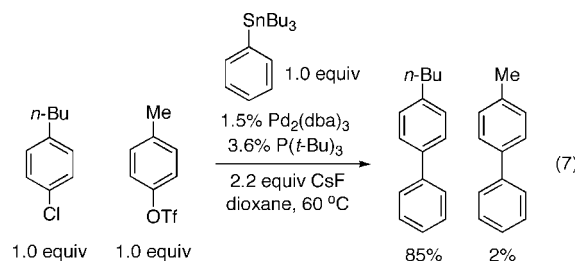
TABLE 4. Room-Temperature Stille Reactions of Aryl Bromides Catalyzed by Pd/P(*t*-Bu)₃

entry	aryl bromide	Bu ₃ Sn-R	yield (%)
1			85
2			95
3			94
4			95
5			97

no examples of palladium-catalyzed reactions of unactivated aryl chlorides.²¹

We were therefore pleased to determine that Pd/P(*t*-Bu)₃ is indeed a versatile catalyst for couplings of aryl chlorides with organotin reagents (Table 3).²² Deactivated (entries 1, 4, 5, and 6), heteroaryl (entry 2), and hindered (entry 3) chlorides are suitable substrates. As far as we are aware, the cross-coupling depicted in entry 3 is the first example of a Stille reaction that provides a tetra-ortho-substituted biaryl in good yield. In addition to aryltin compounds (entries 1–3), vinyl- (entry 4), allyl- (entry 5), and alkyltins (entry 6) can be employed. In the coupling illustrated in entry 6, a typically less reactive alkyl group is efficiently transferred from tin to a deactivated aryl chloride.

As for Suzuki reactions (eqs 5 and 6), Pd/P(*t*-Bu)₃ displays remarkable selectivity in Stille cross-couplings for an aryl chloride in preference to an aryl triflate (eq 7). Vinyl chlorides also serve as useful coupling partners.



Pd/P(*t*-Bu)₃ is an effective catalyst for Stille reactions not only of aryl chlorides but also of bromides (Table 4). Although

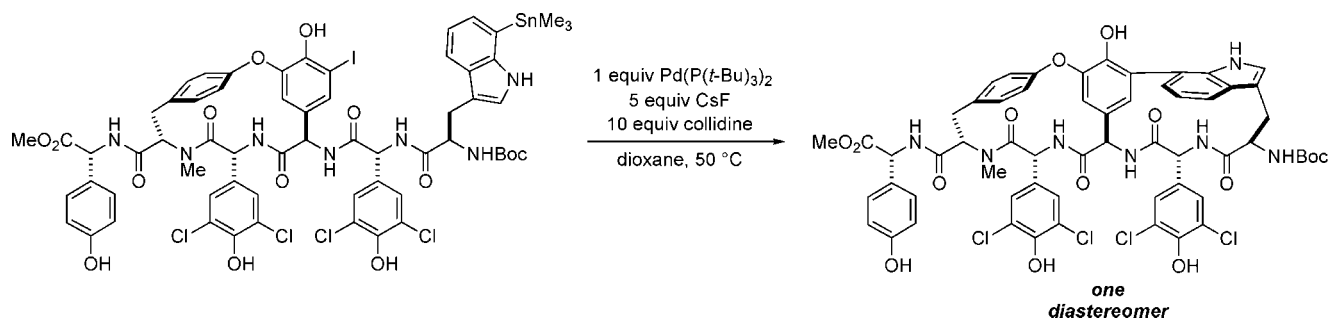


FIGURE 3. Application of Pd/P(*t*-Bu)₃ to a Stille cross-coupling: a diastereoselective macrocyclization en route to chloropeptin I (Snapper and Hoveyda).²³

TABLE 5. Negishi Reactions of Aryl Chlorides Catalyzed by Pd/P(*t*-Bu)₃

entry	aryl chloride	ClZn-R	yield (%)
1			94
2			87
3			92
4			89
5			91
6			76
7		ClZn- <i>n</i> -Bu	83

at the time of our study many methods had been described for Stille cross-couplings of aryl bromides, none of them operated at room temperature for unactivated substrates.

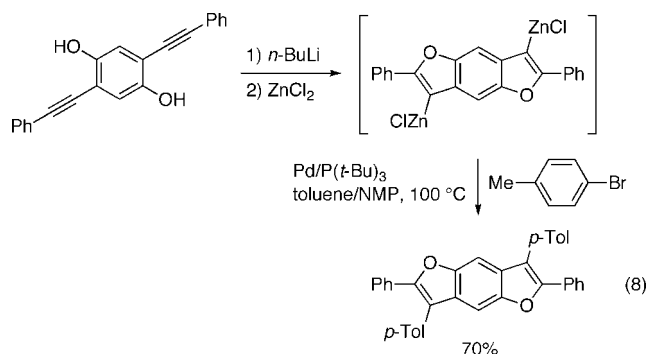
Snapper and Hoveyda applied Pd/P(*t*-Bu)₃ in a Stille reaction en route to an elegant total synthesis of chloropeptin I (Figure 3).²³ Specifically, they effected a late-stage construction of a macrocyclic biaryl bond, generating the desired atropisomer with excellent diastereoselectivity. Although it was necessary to employ a stoichiometric quantity of palladium, it is noteworthy that the cross-coupling proceeded in the presence of a wide array of functional groups (e.g., ester, phenol, secondary amide, aryl chloride, carbamate, and unprotected indole).²⁴

4. Negishi Reactions

A third powerful method for cross-coupling is the Negishi reaction of organozinc reagents.²⁵ At the time that we initiated our program, we were aware of one example of a palladium-catalyzed Negishi coupling of an unactivated aryl chloride (PhCl with PhZnBr).²⁶ Using a discrete, now commercially available Pd(P(*t*-Bu)₃)₂ complex,^{27,28} we were able to achieve Negishi reactions of a variety of aryl and heteroaryl chlorides in good yield (Table 5).²⁹

For example, Pd(P(*t*-Bu)₃)₂ efficiently catalyzes the coupling of a deactivated aryl chloride with a hindered arylzinc reagent (Table 5, entry 1). In the case of a chloride-substituted arylboronate ester, the carbon–boron bond is unreactive under these conditions, thereby permitting selective cross-coupling of the aryl chloride with the arylzinc (entry 2). Heteroaryl chlorides are suitable reaction partners (entries 3 and 4). Hindered chlorides can also be cross-coupled (entries 5 and 6); to the best of our knowledge, the coupling illustrated in entry 6 is the first example of the synthesis of a tetra-ortho-substituted biaryl via a Negishi reaction. Not only arylzinc but also *n*-alkylzinc compounds cross-couple cleanly in the presence of Pd(P(*t*-Bu)₃)₂ (entry 7).

Pd/P(*t*-Bu)₃-catalyzed Negishi reactions have found application in a variety of settings, including the synthesis of natural products³⁰ and of hole-transporting materials (eq 8; two Negishi reactions).^{31,32}



5. Heck Reactions

In addition to cross-couplings, we were interested in developing milder and more versatile palladium-based catalysts for other processes, including the Heck reaction.³³ By 1999, several groups had clearly established the viability of Heck couplings of aryl chlorides, although there were significant limitations with respect to scope (no reactions of highly hindered or electron-rich chlorides that proceeded in >50% yield or of olefins other than styrene and acrylic acid derivatives) and elevated temperatures were necessary (≥ 120 °C).³⁴

In an initial study, we determined that Pd/P(*t*-Bu)₃, with Cs₂CO₃ as the stoichiometric base, catalyzes Heck reactions of a range of aryl chlorides, including deactivated and ortho-substituted compounds.^{35,36} Stimulated by an investigation of my colleague, Steve Buchwald,³⁷ we subsequently discovered that the use of Cy₂NMe, rather than Cs₂CO₃, as the Brønsted base allows Pd/P(*t*-Bu)₃-catalyzed Heck reactions to proceed under even milder conditions.³⁸

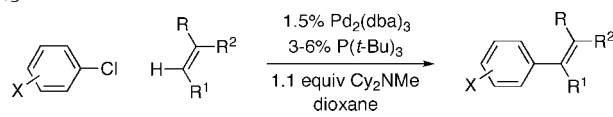
Thus, Pd/P(*t*-Bu)₃/Cy₂NMe achieves Heck couplings of an array of activated aryl chlorides with mono- and disubstituted olefins *at room temperature* with good *E/Z* selectivity (>20:1; Table 6, entries 1–4). Reactions of unactivated chlorides require heating (entries 6–8), but challenging substrates can be employed as coupling partners (e.g., highly electron-rich and di-ortho-substituted aryl chlorides; entries 6 and 7). The same catalyst system is effective for *room-temperature* Heck reactions of a variety of quite demanding aryl bromides (Table 7). Not only aryl but also vinyl halides can be coupled.

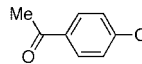

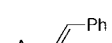
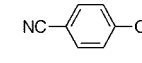

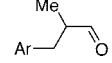
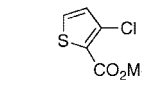

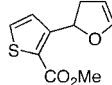
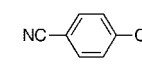

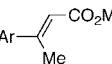
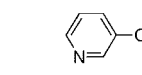

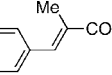
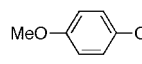

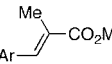
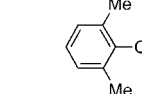

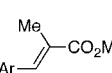
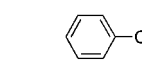

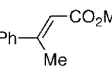
Pd/P(*t*-Bu)₃-catalyzed Heck reactions have been exploited in a range of contexts, including bioorganic chemistry³⁹ and materials science (e.g., organic light-emitting diode materials, eq 9).^{40,41}

6. Phosphonium Salts as Substitutes for Phosphines

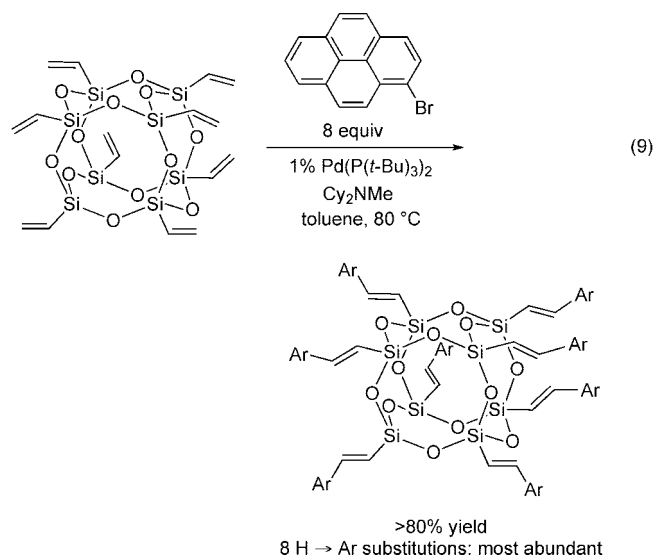
Trialkylphosphines can react with oxygen to produce the corresponding phosphine oxide. In our initial studies of Pd/P(*t*-Bu)₃-catalyzed coupling processes, we typically combined Pd₂(dba)₃ with P(*t*-Bu)₃ to generate our active catalyst. Handling P(*t*-Bu)₃ in the air could be avoided by using commercially available P(*t*-Bu)₃ in hexane or by employing a glovebox. In 2001, we demonstrated that Pd(P(*t*-Bu)₃)₂, which can be handled in air, provides another potential solution to this practical issue.²⁸

TABLE 6. Heck Reactions of Aryl Chlorides Catalyzed by Pd/P(*t*-Bu)₃^a



entry	aryl chloride	olefin	temperature	product	yield (%)
1			r.t.		78
2			r.t.		79
3			r.t.		87
4			r.t.		57
5			100 °C		76
6			120 °C		72
7			120 °C		80
8			120 °C		52

^a *E/Z* selectivity >20:1.



Not entirely satisfied with these approaches, we decided to pursue an alternative strategy, one that would be useful not only for Pd/P(*t*-Bu)₃-catalyzed coupling reactions but for trialkylphosphine chemistry in general. Specifically, we examined the simple idea of protecting the phosphine from

TABLE 7. Room-Temperature Heck Reactions of Aryl Bromides Catalyzed by Pd/P(*t*-Bu)₃^a

entry	aryl bromide	olefin	product	yield (%)
1				77
2				80
3				83

^a *E/Z* selectivity 10:1 for entry 1 and >20:1 for entries 2 and 3.

oxidation by protonating the phosphorus lone pair, thereby furnishing a storable, air-stable phosphonium salt (Figure 4).^{42,43}

PR ₃	HBF ₄	→	[HPR ₃]BF ₄
R	mp (°C) of [HPR ₃]BF ₄		
Me	212-213		
<i>n</i> -Bu	51-52		
<i>t</i> -Bu	261 (decomp)	(stable upon exposure to air at r.t. for three months)	

FIGURE 4. Synthesis and stability of phosphonium salts.

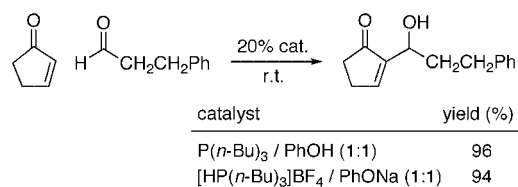
These salts do indeed serve as direct replacements, through in situ deprotonation by a Brønsted base, for the corresponding phosphines in a diverse set of catalytic processes,⁴⁴ including palladium-catalyzed coupling reactions (Figure 5).

A number of phosphonium tetrafluoroborate salts (e.g., [HP(*t*-Bu)₃]BF₄, [HP(*n*-Bu)₃]BF₄, [HPCy₃]BF₄, and [HPMe₃]BF₄) are now commercially available from an array of suppliers, and they have found application in a variety of contexts.⁴⁵

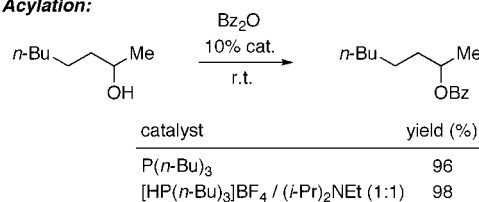
7. Mechanistic Observations

During the course of our methods development work on Pd/P(*t*-Bu)₃-catalyzed Suzuki, Stille, Negishi, and Heck reactions, we pursued mechanistic studies directed at a variety of issues, including the composition of the active palladium catalyst and the nature of the organometallic species that participates in the transmetalation step of the catalytic cycle for cross-coupling processes. Due to space limitations, those investigations will not be summarized in this Account. Instead, we will focus on a particular mechanistic study that was stimulated by intriguing observations made during our early work on the Suzuki and Heck reactions.⁴⁶

Baylis–Hillman reaction:



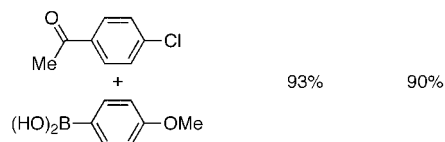
Acylation:



Palladium-catalyzed coupling reactions:

	P(<i>t</i> -Bu) ₃	[HP(<i>t</i> -Bu) ₃]BF ₄
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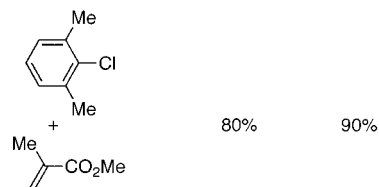
Suzuki (Pd₂(dba)₃, KF, r.t.):



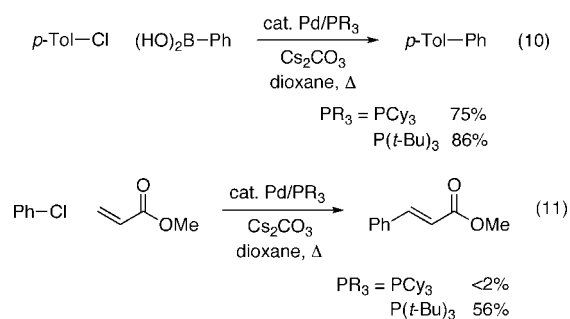
Stille (Pd₂(dba)₃, CsF, 100 °C):



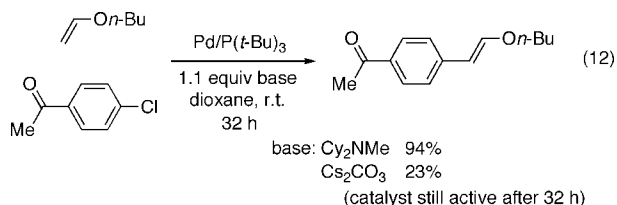
Heck (Pd₂(dba)₃, Cy₂NMe, 120 °C):

**FIGURE 5.** Phosphonium salts as substitutes for phosphines.

In our original report on palladium-catalyzed Suzuki cross-couplings, we noted that both P(*t*-Bu)₃ and PCy₃ are effective ligands for the reaction of an unactivated aryl chloride (eq 10).^{9a} In contrast, in our initial study of Heck couplings, we observed that, under very similar conditions, P(*t*-Bu)₃ provides an effective catalyst for the reaction of an unactivated aryl chloride, whereas Pd/PCy₃ does not (eq 11).³⁵

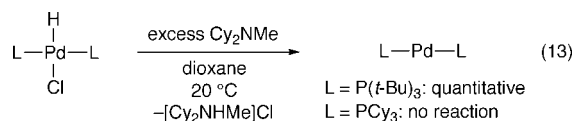


The data in eq 10 indicate that oxidative addition of an aryl chloride to palladium is viable in the presence of Pd/PCy₃/Cs₂CO₃. It therefore seemed likely that the failure of Pd/PCy₃ to catalyze a Heck reaction (eq 11) arises from a difficulty elsewhere in the catalytic cycle. A possible clue to this puzzle came from our earlier observation (section 5) that the choice of Brønsted base significantly impacts the efficiency of Pd/P(*t*-Bu)₃-catalyzed Heck reactions. An example of the effect of base on the rate of a Heck coupling is provided in eq 12.



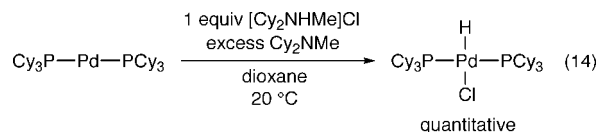
According to the commonly accepted mechanism for Heck reactions (Figure 2), the primary role of the Brønsted base is to regenerate a Pd(0) complex from a Pd(II) hydride in the final stage of the catalytic cycle. By ³¹P NMR spectroscopy, we have determined that, for the Heck coupling illustrated in eq 12, the resting state of the catalyst depends on the choice of base: for the more effective Brønsted base (Cy₂NMe), the resting state is a Pd(0) complex (PdL₂; L = P(*t*-Bu)₃), whereas for the less effective base (Cs₂CO₃), the resting state is a Pd(II) hydride (PdL₂HCl). As far as we are aware, this latter observation represents the first time that a palladium hydride has been identified during a catalyzed Heck reaction.

These data suggested that an improved understanding of the reductive-elimination step of the catalytic cycle might provide insight into the divergent behavior of Pd/P(*t*-Bu)₃ and Pd/PCy₃ in Heck reactions. We therefore synthesized and examined the reactivity of the two discrete PdL₂HCl complexes. Interestingly, upon treatment with Cy₂NMe, the P(*t*-Bu)₃ adduct reductively eliminates in quantitative yield, whereas under the same conditions the PCy₃ complex remains unchanged (eq 13).



To elucidate whether the failure to generate Pd(PCy₃)₂ is due to unfavorable kinetics or thermodynamics, we examined the reverse reaction (eq 14). Upon treatment of Pd(PCy₃)₂ with [Cy₂NHMe]Cl, Pd(PCy₃)₂HCl is rapidly formed, thereby establishing that reductive elimination is not observed in eq 13 (L = PCy₃) because it is endergonic. Thus, the relative reluctance of Pd(PCy₃)₂HCl to undergo reductive elimination

and regenerate Pd(0) may be responsible (in part) for the comparatively low reactivity of Pd/PCy₃ in Heck reactions of aryl chlorides.



8. Conclusions

Trialkylphosphines furnish unusually reactive and versatile catalysts for a variety of palladium-catalyzed coupling reactions. For example, in the presence of Pd/P(*t*-Bu)₃, a wide array of challenging substrates (e.g., aryl chlorides and hindered/electronically deactivated coupling partners) can be employed in powerful carbon–carbon bond-forming processes such as the Suzuki, Stille, Negishi, and Heck reactions under unusually mild conditions. These new methods have found application in a broad spectrum of settings, including natural-product synthesis, materials science, and bioorganic chemistry.

I am extremely grateful to the co-workers who contributed to this program, particularly Adam F. Littke, who initiated our studies. Primary support for this investigation has been provided by the National Institutes of Health (National Institute of General Medical Sciences, Grant R01-GM62871), with supplementary funding furnished by Merck Research Laboratories and by Novartis. I thank Prof. Amir Hoveyda (Boston College) and Prof. Alan Sellinger (Institute of Materials Research & Engineering) for assistance with two of the illustrations.

BIOGRAPHICAL INFORMATION

Gregory C. Fu received a B.S. degree in 1985 from MIT, where he worked in the laboratory of Prof. K. Barry Sharpless. After earning a Ph.D. from Harvard in 1991 under the guidance of Prof. David A. Evans, he spent two years as a postdoctoral fellow with Prof. Robert H. Grubbs at Caltech. In 1993, he returned to MIT, where he is currently the Firmenich Professor of Chemistry. Prof. Fu received the Springer Award in Organometallic Chemistry in 2001, the Corey Award of the American Chemical Society in 2004, and the Mukaiyama Award of the Society of Synthetic Organic Chemistry of Japan in 2006. He is a fellow of the Royal Society of Chemistry and of the American Academy of Arts and Sciences. Prof. Fu serves as an associate editor of the *Journal of the American Chemical Society*. His current research interests include metal-catalyzed coupling reactions, chiral-ligand design, and enantioselective nucleophilic catalysis.

FOOTNOTES

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