Application of a Palladium/Tri-*tert*-butylphosphine Catalyst System Towards Mild and General Methods for Carbon-Carbon Bond Formation

by

Adam F. Littke

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Signature of Author: _____
Department of Chemistry
February 12, 2002

Certified by: _____
Gregory C. Fu
Thesis Supervisor

Accepted by: _____
Robert W. Field
Chairman, Departmental Committee on Graduate Students

This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Professor Timothy M. Swager_____
Chairman

Professor Gregory C. Fu_____
Thesis Supervisor

Professor Stephen L. Buchwald_____

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Abstract

Our research over the last four years has been focused on the development of mild and general methods for conducting palladium-catalyzed carbon-carbon bond forming reactions utilizing the bulky and electron-rich trialkylphosphine, tri-*tert*-butylphosphine ($P(t\text{-}Bu)_3$). We have concentrated on the utilization of aryl chlorides as substrates due to their lower cost and greater availability compared to traditionally employed aryl bromides, iodides, and triflates.

The Suzuki reaction was the first reaction that we investigated, and we were able to develop a first-generation protocol for coupling aryl chlorides with aryl-boronic acids utilizing $Pd_2(dba)_3/P(t\text{-}Bu)_3$ as catalyst and Cs_2CO_3 as base. A second-generation protocol utilizing KF as base offered significant improvements and provided an opportunity to expand the scope of the reaction. Electron-deficient aryl chlorides underwent Suzuki reaction at room temperature. Hindered substrates and unactivated vinyl chlorides could be coupled efficiently, and turnover numbers as high as 9,700 could be achieved. In addition, we discovered a highly unusual selective coupling of an aryl chloride in preference to an aryl triflate.

The next reaction that we examined was the Heck reaction, and we were able to develop a method for coupling aryl chlorides with olefins using $Pd/P(t\text{-}Bu)_3$ as catalyst and Cs_2CO_3 as base. A significant improvement in terms of scope and mildness of conditions was realized with the replacement of Cs_2CO_3 with Cy_2NMe, which allowed for the coupling of sterically and electronically diverse aryl bromides at room temperature, as well as the first room-temperature Heck couplings of aryl chlorides. A wide variety of olefins could be employed in these couplings, including disubstituted olefins. In addition, these Heck reactions could be performed on multigram scale with minimal purification of starting materials, emphasizing the practicality and robustness of this method.

Prior to 1999 there were no reports of palladium-catalyzed Stille couplings of unactivated aryl chlorides; utilizing $Pd/P(t\text{-}Bu)_3$ in tandem with a fluoride activation strategy, we were able to develop the first general method for Stille couplings of aryl chlorides. More recently, we have considerably increased the scope of this reaction, including the synthesis of tetra-ortho-substituted biaryls, selective couplings of chlorides over triflates, and couplings of some aryl chlorides at room temperature.

We have also undertaken mechanistic, kinetic, and reactivity studies using ^{1}H NMR, ^{31}P NMR, and GC. As a result of these studies, we believe that a monophosphine palladium species is the active catalyst in many of these couplings. The bisphosphine palladium complex $Pd(P(t\text{-}Bu)_3)_2$ is the resting state; yet by itself it is an ineffective catalyst for room-temperature couplings of aryl chlorides. The addition of phosphine-free $Pd_2(dba)_3$ to $Pd(P(t\text{-}Bu)_3)_2$ generates an efficient catalyst for room-temperature couplings and inspired us to try to utilize crystalline and now commercially available $Pd(P(t\text{-}Bu)_3)_2$ as a catalyst to eliminate the need to handle air-sensitive $P(t\text{-}Bu)_3$. For the most part we have been quite successful in this regard; mixtures of $Pd(P(t\text{-}Bu)_3)_2$ and $Pd_2(dba)_3$ are efficient catalysts for many room-temperature couplings of aryl chlorides. $Pd(P(t\text{-}Bu)_3)_2$ by itself is an excellent catalyst for both Heck and Stille couplings of aryl chlorides at elevated temperatures, and it can be used at low catalyst loadings.

Thesis Supervisor: Gregory C. Fu

Title: Professor of Chemistry

Preface

Portions of this work have been excerpted or adapted from the following articles that were co-written by the author:

Littke, A. F.; Fu, G. C. "A Convenient and General Method for Pd-Catalyzed Suzuki Cross-Couplings of Aryl Chlorides and Arylboronic Acids" *Angew. Chem. Int. Ed.* **1998**, *37*, 3387-3388.

Littke, A. F.; Fu, G. C. "Heck Reactions in the Presence of P(*t*-Bu)$_3$: Expanded Scope and Milder Reaction Conditions for the Coupling of Aryl Chorides" *J. Org. Chem.* **1999**, *64*, 10-11.

Littke, A. F.; Fu, G. C. "The First General Method for Stille Cross-Couplings of Aryl Chlorides" *Angew. Chem. Int. Ed.* **1999**, *38*, 2411-2413.

Littke, A. F.; Dai, C.; Fu, G. C. "Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions" *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.

Littke, A. F.; Fu, G. C. "A Versatile Catalyst for Heck Reactions of Aryl Chlorides and Aryl Bromides under Mild Conditions" *J. Am. Chem. Soc.* **2001**, *123*, 6989-7000.

Littke, A. F.; Schwarz, L.; Fu, G. C. "Pd/P(*t*-Bu)$_3$: A Mild and General Catalyst for Stille Reactions of Aryl Chlorides and Aryl Bromides" *submitted for publication.*

Acknowledgments

My interest in organic chemistry began when I took a first-year course in organic chemistry at the University of Ottawa taught by Professor Tony Durst. I remember fondly his enthusiasm for undergraduate teaching. My two summers and two semesters working in Professor Darrin Richeson's lab spawned my interest in academic research and ultimately lead to my decision to attend graduate school. Darrin's door was always open and witnessing his boundless energy and enthusiasm was an inspiration. I thank him for giving me the opportunity to work in his labs and for all his support both during my time at the University of Ottawa and after.

Dr. Erich Grimm gave me a great opportunity to work at Merck-Frosst in Montreal for one summer where I learned alot about organic chemistry and the pharmaceutical industry from Yves Leblanc and Claude Dufresne.

Of course, the one person who has had, by far, the most influence on my scientific career has been my advisor, Professor Greg Fu. I appreciate his confidence in me right from the beginning in allowing me to investigate and develop a very fruitful project that had no prior background in our group and arose somewhat serendipitously. I know that through all his guidance and (rare) criticism he has always tried to mold me into the best scientist that I could be and I think he has been successful in this regard.

Professor Steve Buchwald has always been very supportive and I learned an enormous amount about palladium chemistry from him and from attending joint group meetings with his group which has helped me a great deal.

Greg has always had a very talented group of undergraduates, graduate students, and postdocs that I have had the privilege of knowing and working with over the past four years. Their names are too numerous to mention but some do deserve to be highlighted. My first baymate, Dr. Jordi Tormo, and

Shuang Qiao were both very patient in helping me around the Fu lab during my first months and answering my many stupid questions. My subsequent baymates, Professor Mitchinori Suginome and Dr. Ken Tanaka are both blessed with an incredible knowledge of chemistry; I was very fortunate to have learned a little from both of them. My many conversations with David Hays and Jack Liang both during their time in the Fu lab and since they have left have always been enjoyable. Brian Hodous and Mike Smith are two great friends who I've shared many good times with over a beer or two (or three or four...). Brian, in particular, was always very helpful regarding my endless questions and concerns about the GC's. Beata Tao was somebody I could always talk to for some good advice. My conversations with Shih-Yuan Liu about chemistry and life in general have always been extremely entertaining; we certainly didn't agree about much but we still got along pretty well. Dr. Chaoyang Dai, Dr. Lothar Schwarz, Dr. Thomas Hundertmark and Dr. Matt Netherton were all members of the palladium team that I got a chance to work with closely. Special thanks to Dr. Jens Hildebrand, Dr. Matt Netherton, Ivory Hills and Shih-Yuan Liu for agreeing to proofread chapters of my thesis on such short notice.

Finally, thanks to my family, Mom, Dad, and Vincent for their continuous support and love, for always encouraging me to take time out of graduate school to enjoy life and for reminding me how fortunate I was.

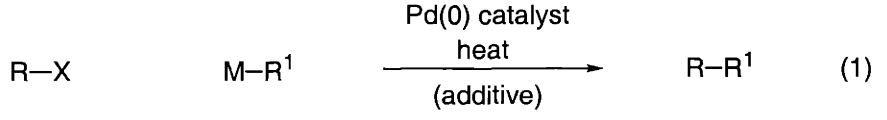
Table of Contents

Abbreviations

BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
eq	equation
equiv	equivalent(s)
EtOAc	ethyl acetate
Et_2O	diethyl ether
GC	gas chromatography
h	hours
HRMS	high resolution mass spectroscopy
IR	infrared
NMP	1-methyl-2-pyrrolidinone
p	page
r.t.	room temperature
THF	tetrahydrofuran
TLC	thin-layer chromatography
tol	tolyl

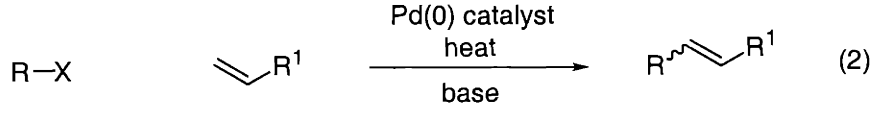
General Introduction

Palladium-catalyzed coupling reactions collectively represent some of the most powerful and versatile tools available to synthetic organic chemists.[1] These include cross-coupling reactions (eq 1) and the Heck reaction (eq 2).



R = aryl, vinyl
X = halide, OTf

R^1 = alkyl, alkynyl, aryl, vinyl, etc.



R = aryl, vinyl
X = halide, OTf

A very simplified mechanism for cross-coupling reactions is illustrated in Figure 1. The catalytic cycle begins with the oxidative addition of an aryl or vinyl halide/triflate to the Pd(0) catalyst. Pd(II) precatalysts such as $Pd(OAc)_2$ and $Pd(MeCN)_2Cl_2$ are commonly used, and these must be reduced to Pd(0) before entering the catalytic cycle. Oxidative addition is then followed by transmetalation by the organometallic reagent. Reductive elimination furnishes the desired cross-coupled product and regenerates the Pd(0) catalyst.

A variety of saturated or unsaturated groups (R^1) such as alkyl, alkynyl, aryl, vinyl, and allyl can be transferred. Most tin (Stille coupling), zinc (Negishi coupling), and magnesium (Kumada coupling) organometallic reagents are reactive enough to undergo transmetalation without the use of additives. Less reactive boron (Suzuki coupling) and silicon (Hiyama coupling) reagents require

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[1] *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J. Eds.; Wiley-VCH: New York, 1998.

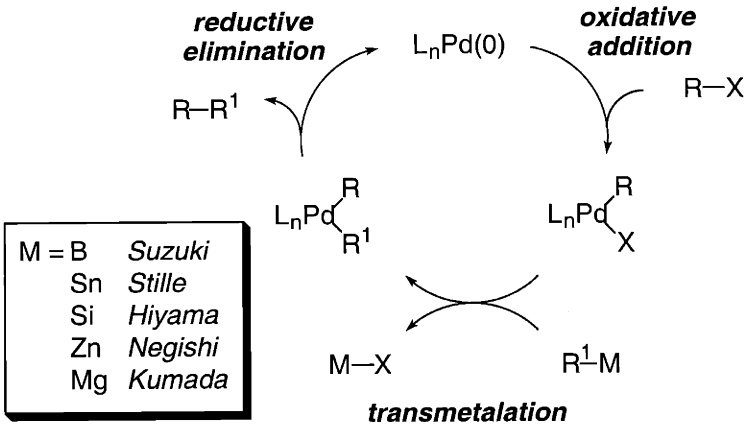

Figure 1. Outline of the catalytic cycle for cross-coupling reactions

the addition of a base whose role is to form an "ate" complex which is more reactive toward transmetalation.

The Heck reaction refers to the palladium-catalyzed coupling of aryl and vinyl halides and triflates with olefins (eq 2). As with cross-coupling reactions, the mechanism begins with the oxidative addition of an aryl or vinyl halide/triflate to Pd(0) (Figure 2). This is followed by olefin complexation, syn olefin insertion, syn β-hydride elimination, and finally reductive elimination of HX, which is neutralized by the stoichiometric base that is present.

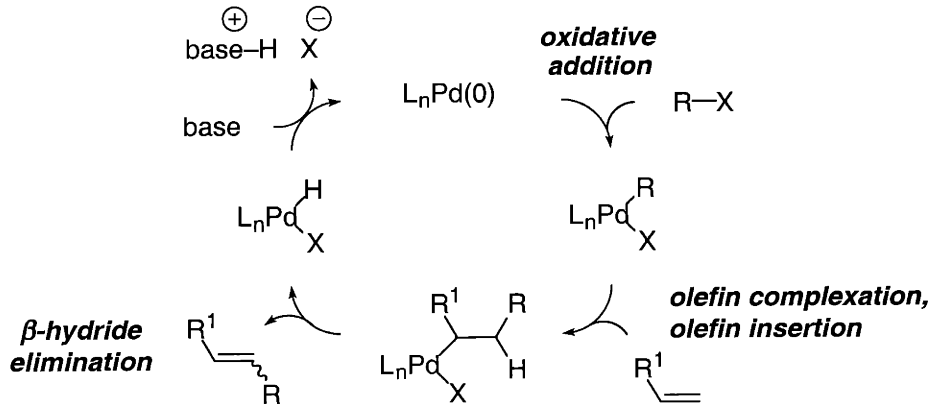

Figure 2. Outline of the catalytic cycle for the Heck reaction

Traditionally, palladium-catalyzed coupling reactions are performed in the presence of triarylphosphine ligands (L) such as PPh_3 or P(*o*-tol)$_3$. These ligands are either bound to the palladium (pre)catalyst from the beginning (e.g., $Pd(PPh_3)_4$) or are added to the reaction mixture along with an appropriate palladium source (e.g., $Pd(OAc)_2$ or $Pd_2(dba)_3$).

The wide-spread popularity of cross-coupling reactions and the Heck reaction stems from the fact that, in general, they are very tolerant of most functional groups, allowing them to be applied in the synthesis of fairly complex molecules (e.g., natural product synthesis). In addition, conditions can be quite mild depending on the substrates employed, and, in many cases, a high degree of regio- and stereoselectivity is observed.

However, for many years a major limitation of palladium-catalyzed coupling reactions has been the poor reactivity of aryl chlorides.[2] Aryl chlorides are arguably the most desirable class of substrates for coupling reactions as they are cheaper and more widely available than the traditionally employed aryl iodides, bromides, and triflates. This is particularly relevant for any industrial or pharmaceutical applications where cost and the ability to readily obtain bulk quantities of starting materials are major considerations. Examples of palladium-catalyzed coupling reactions that have been applied on an industrial scale toward the synthesis of fine chemicals, pharmaceuticals, and other important chemical intermediates are given in the following chapters of this thesis; however, these examples are not commonplace. The ability to effectively utilize aryl chlorides under fairly mild conditions would open up important possibilities for the pharmaceutical and chemical industries and greatly enhance the utility of palladium-catalyzed coupling reactions.

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[2] (a) Grushin, V. V.; Alper, H. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer-Verlag: Berlin, 1999; pp. 193-226. (b) Sturmer, R. *Angew. Chem. Int. Ed.* **1999**, *38*, 3307-3308. (c) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047-1062.

The poor reactivity of aryl chlorides has usually been ascribed to the difficult oxidative addition step. Oxidative addition of aryl iodides and bromides to Pd(0) is a considerably more facile process than for aryl chlorides,[3] and this observed reactivity parallels the Ar-X bond strengths (Ar-X bond strengths = 65, 81, 96 kcal/mol for Ar-I, Ar-Br, Ar-Cl, respectively). The reactivity of the Ar-Cl bond is enhanced by the presence of electron-withdrawing groups on the aromatic ring, and such aryl chlorides are referred to as "activated". In addition, certain nitrogen-containing heterocycles such as chloropyridines are also "activated" due to the inductive effect of nitrogen relative to carbon. For the above-mentioned substrates, traditional palladium-triarylphosphine complexes have often served as reasonably effective catalysts in a variety of reactions, although conditions are frequently quite harsh.

Until quite recently, the corresponding transformations of "unactivated" aryl chlorides, that is, electron-neutral and electron-rich aryl chlorides, have proven to be a considerably greater challenge with very little success. Usually, palladium/triarylphosphine-based catalysts are not effective for these types of substrates. While nickel-based catalysts can be effective for cross-coupling reactions of deactivated aryl chlorides,[4] the use of nickel over palladium catalysts has certain disadvantages, such as increased sensitivity to sterically hindered substrates, increased sensitivity to oxygen, and the higher toxicity of nickel compounds versus palladium.

Oxidative addition is favored by greater electron-density on the metal center.[5]

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3 Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287-291.

4 For some recent representative examples, see: (a) Lipshutz, B. H. *Adv. Synth. Catal.* **2001**, *343*, 313-326. (b) Bolm, V. P. W.; Weskamp, T.; Gstottmayr, C. W. K.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 1602-1604. (c) Shirakawa, E.; Yamasaki, K.; Hiyama, T. *Synthesis* **1998**, 1544-1549. (d) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024-8030. (e) Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513-3516. (f) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054-6058.

5 Spessard, G. O.; Meissler, G. L. *Organometallic Chemistry;* Prentice Hall: Upper Saddle River, New Jersey, 1996; pp 171-175.

Palladium complexes of simple triarylphosphine ligands are usually not electron-rich enough to undergo oxidative addition to unactivated aryl chlorides unless very high temperatures are employed. However, tri*alkyl*phosphines are considerably more electron-rich than their aryl counterparts, as an inspection of the pK_a's of their conjugate acids would suggest (Figure 3).[6] Thus, the reactivity of palladium-phosphine complexes toward oxidative addition of aryl chlorides can be enhanced by using these strongly donating trialkylphosphine ligands which render the Pd(0) metal center more electron-rich. This enhanced reactivity was observed as early as 1989 by Osborn and coworkers, who demonstrated that $Pd(PCy_3)_2(dba)$ undergoes oxidative addition with chlorobenzene at "only" 60 °C.[7] In contrast, the oxidative addition of chlorobenzene to $Pd(PPh_3)_2(dba)$ requires a temperature of 140 °C.[8] The trialkylphosphine that we have focused much of our own research on during the past four years is tri-*tert*-butylphosphine, P(*t*-Bu)$_3$, and we have found that Pd/P(*t*-Bu)$_3$-based catalysts are extremely effective for activating aryl chlorides for a variety of coupling processes.

	$P(OMe)_3$	PPh_3	$P(o\text{-tol})_3$	PCy_3	$P(t\text{-Bu})_3$
pK_a (conj. acid)	2.6	2.7	3.1	9.7	11.4
cone angle (degrees)	107	145	194	170	182

Figure 3. pK_a and cone angles for some phosphites and phosphines.

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6 For an extensive compilation of cone angles and pK_a data for phosphines, see: Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1-7.

7 Huser, M.; Youinou, M. -T.; Osborn, J. A. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1386-1388.

8 Herrmann, W. A.; Broßmer, C.; Priermeier, T.; Ofele, K. *J. Organomet. Chem.* **1994**, *481*, 97-108.

The steric bulk of P(*t*-Bu)$_3$ is also important, and a comparison of cone angles reveals that P(*t*-Bu)$_3$ is considerably more hindered than many other phosphines (Figure 3). Bulky ligands promote reductive elimination[9] and favor the generation of monophosphine palladium complexes, which we believe are the active catalysts in all of the couplings described in this thesis. Experimental evidence to support this hypothesis will be outlined in the following chapters.

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9 (a) Spessard, G. O.; Meissler, G. L. *Organometallic Chemistry;* Prentice Hall: Upper Saddle River, New Jersey, 1996; pp 178-184.

Part 1:

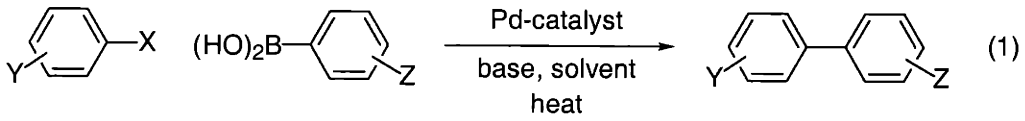
Suzuki Coupling using Pd/P(t-Bu)$_3$ Catalyst Systems

Chapter 1:

Suzuki Coupling of Aryl Chlorides using $Pd/P(t\text{-}Bu)_3/Cs_2CO_3$

Introduction

The Suzuki coupling is the cross-coupling of boronic acids, esters, or boranes with aryl or vinyl halides and triflates.[1] One of the more popular variants of this reaction is the coupling of arylboronic acids with aryl halides[2] and triflates[3] to synthesize biaryl compounds (eq 1). The reaction is typically catalyzed by palladium complexes, usually in the presence of triarylphosphine ligands, although nickel-based catalysts can also be effective for Suzuki couplings.[4] The mechanism of the Suzuki coupling follows the well-established catalytic cycle for all cross-coupling reactions outlined previously (Figure 1). One feature of the Suzuki coupling that distinguishes it from other cross-coupling reactions is that a base is usually required for the reaction to proceed. It is believed that the role of the base is to form a four-coordinate boron "ate" complex that then undergoes transmetalation with palladium (Figure 1).[1] Although aqueous sodium carbonate is the traditional base used in the Suzuki coupling, many others, mostly inorganic, have been employed.



X = halide, OTf

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[1] For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168. (c) Miyaura, N. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1998; Vol. 6, pp 187-243. (d) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J.; Eds.; Wiley-VCH: New York, 1998; Chapter 2. (e) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263-303.

[2] Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513-519.

[3] Fu, J. -m.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665-1668.

[4] For pioneering work on nickel-catalyzed Suzuki cross-couplings, see: (a) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024-8030. (b) Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513-3516.

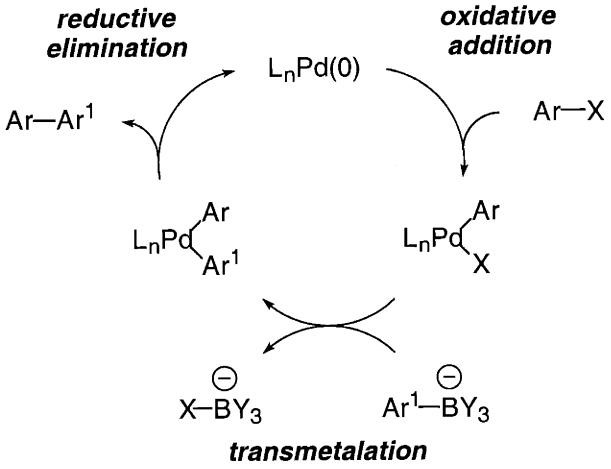

Figure 1. Outline of the catalytic cycle for the Suzuki cross-coupling reaction.

Of all the palladium-catalyzed coupling reactions, the Suzuki coupling has emerged as the most popular, especially from an industrial and pharmaceutical standpoint. This is in large part due to the innocuous nature of boronic acids, which are generally nontoxic, thermally, air-, and moisture-stable. Another attractive feature is that the boron-containing byproducts of the reaction are also nontoxic and can be readily separated from the desired product. In addition, a large variety of arylboronic acids can be purchased from commercial sources, due in large part to the development of new and improved catalyst systems for the Suzuki coupling that significantly expand the scope of the reaction.

The coupling of arylboronic acids with aryl halides and triflates is a powerful and convenient method to synthesize biaryl compounds, which have a diverse spectrum of applications, ranging from materials science[5] to pharmaceuticals.[6] For example, the biaryl linkage is found in important natural products such as the vancomycin antibiotics.[7] The biphenyl substructure is found in 4.3% of all

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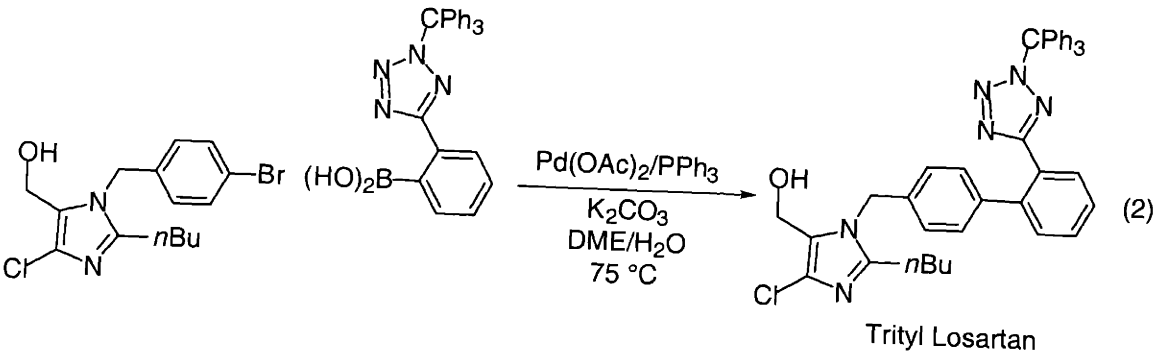
5 For example, see: (a) *Step-Growth Polymers for High-Performance Materials*; Hedrick, J. L., Labadie, J. W., Eds.; ACS Symp. Ser. 624; American Chemical Society: Washington, DC, 1996.

6 Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443-3447.

7 For a review, see: Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2096-2152.

known drugs,[6] such as the sartan family of drugs for high blood pressure.[8] The industrial synthesis of the first member of this family of drugs, Losartan, involves a late-stage Suzuki coupling (eq 2)[9] and is a powerful example of the importance and potential of the Suzuki coupling for the synthesis of pharmaceutically relevant compounds.



(2)

Traditionally, as with all palladium-catalyzed coupling reactions, the most commonly used substrates in the Suzuki coupling have been aryl iodides, bromides, and triflates. Readily available and inexpensive aryl chlorides have proven to be difficult substrates, as they usually exhibit poor reactivity when traditional palladium/triarylphosphine-based catalyst systems are employed. Prior to 1998, there were several accounts of palladium-catalyzed Suzuki reactions of heteroaryl chlorides[10] and a few examples of electron-deficient aryl chlorides participating in cross-couplings with arylboronic acids. Uemura had shown that tricarbonyl(η^6-arylchloride)chromium complexes undergo efficient Suzuki coupling using $Pd(PPh_3)_4$ as catalyst, even if the aryl group bears electron-donating functionality.[11] Suzuki couplings of electron-deficient aryl

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[8] For reviews on sartans and Losartan, see: (a) Birkenhager, W. H.; de Leeuw, P. W. *J. Hypertens.* **1999**, *17*, 873-881. (b) Goa, K. L.; Wagstaff, A. J. *Drugs* **1996**, *51*, 820-845.

[9] Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151-8156.

[10] Lie, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry;* Pergamon: Amsterdam, 2000 and references therein.

[11] Uemura, M.; Nishimura, H.; Kamikawa, K.; Nakayama, K.; Hayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 1909-1912.

chlorides can be accomplished with phosphorus-based palladacycles, introduced by Herrmann.[12] In 1996, Miyaura demonstrated that $Pd(PPh_3)_4$-catalyzed Suzuki couplings of 4-chlorobenzonitrile and 4'-chloroacetophenone with phenylboronic acid (Na_2CO_3, DME/H_2O, 80 °C) proceeded in good yields; however, when these conditions were applied to electron-neutral and electron-rich aryl chlorides, < 3% of the desired product(s) were obtained.[13] The water-soluble triply *meta*-sulfonated triphenylphosphine ligand, $P(m\text{-}C_6H_4SO_3Na)_3$ has been used by Hoechst for the commercial production (100 tons per year) of 2-cyano-4'-methylbiphenyl from the Suzuki coupling of 2-chlorobenzonitrile and *p*-tolylboronic acid.[14,15] Palladium catalysts containing *N*-heterocyclic carbenes as ligands have been shown by Herrmann to be moderately effective for the coupling of 4'-chloroacetophenone with phenylboronic acid.[16]

In 1997, Shen demonstrated that palladium complexes of the bulky, electron-rich trialkylphosphine PCy_3, were quite effective for couplings of electron-deficient aryl chlorides at 100 °C.[17] It was speculated that the more electron-donating nature of PCy_3 compared with PPh_3 might facilitate the oxidative addition of Pd(0) into the Ar-Cl bond, and that the increased steric bulk of PCy_3 might facilitate dissociation of the ligand. Subsequently, Firooznia and coworkers at Novartis reported a Pd/PCy_3-catalyzed Suzuki coupling of the only modestly activated 3-chloroanisole, albeit in 41% yield.[18]

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12 Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848-1849.

13 Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993-2996.

14 (a) Hoechst AG (S. Haber, H. J. Kleinert). DE-Appl. 195 27 118 and 195 35 528, 1997. (b) Cornils, B. *Orgn. Proc. Res. Dev.* **1998**, *2*, 121-127.

15 2-Cyano-4'-methylbiphenyl is a key intermediate in the synthesis of angiotension II receptor antagonists that are used for the treatment of hypertension; for leading references, see: Goubet, D.; Meric, P.; Dormoy, J. –R.; Moreau, P. *J. Org. Chem.* **1999**, *64*, 4516-4518.

16 Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93-96.

17 Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575-5578.

18 Firooznia, F.; Gude, C.; Chan, K.; Satoh, Y. *Tetrahedron Lett.* **1998**, *39*, 3985-3988.

The high activity of palladium catalysts ligated by bulky, electron-rich trialkylphosphines was also noted by chemists at Zeneca during the development of a viable manufacturing route to 2-cyano-4′-methylbiphenyl.[19] Ligand screening revealed PCy_3, $P(i\text{-}Pr)_3$, and $P(i\text{-}Bu)_3$ to be the most active ligands. Due to its low cost, $P(i\text{-}Bu)_3$ was eventually selected as the ligand for the coupling of 2-chlorobenzonitrile with *p*-tolylboronic acid.

Despite the important contributions mentioned above, in 1998 there were no examples of electron-neutral or electron-rich aryl chlorides participating in palladium-catalyzed Suzuki couplings.[20] Given the importance of the Suzuki coupling in organic synthesis and the increased availability and decreased expense of aryl chlorides relative to aryl iodides, bromides, and triflates, we felt that the development of conditions for palladium-catalyzed Suzuki couplings of arylboronic acids with a wide range of sterically and electronically diverse aryl chlorides would be a very worthwhile goal.

Results and Discussion

In our initial experiments, we established that 4-chlorotoluene and phenylboronic acid are efficiently cross-coupled in the presence of 1.5% $Pd_2(dba)_3$, 3.6% $P(t\text{-}Bu)_3$, and 2 equiv Cs_2CO_3 (dioxane, 80 °C; 86% yield by GC after 5.0 h) (Table 1, entry 9). The very bulky and electron-rich $P(t\text{-}Bu)_3$ had previously been demonstrated to be an extremely effective ligand for palladium-catalyzed aminations of aryl chlorides by Koie and coworkers at the Tosoh Corporation.[21] Little or no coupling was observed in the absence of phosphine

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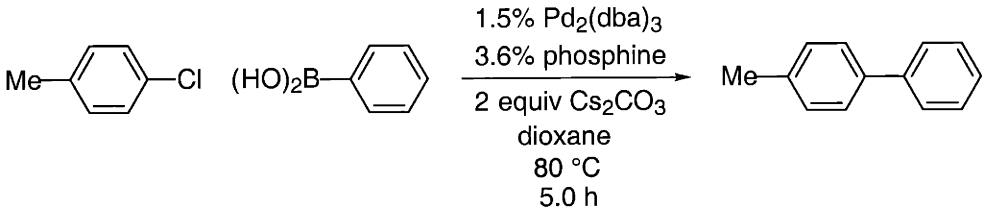
[19] (a) Zeneca Ltd. (Monteith, M. J.). WO-Appl. 9816486, 1998. (b) Monteith, M. J. *Spec. Chem.* **1998**, *18*, 436-438.

[20] For examples of nickel-catalyzed Suzuki couplings of electron-neutral and electron-rich aryl chlorides, see reference 4.

[21] (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617-620. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367-2370.

(Table 1, entry 1) or in the presence of commonly used triarylphosphines (Table 1, entries 2 and 5) and bidentate phosphines (Table 1, entries 3, 4, 6 and 7). Only another bulky, electron-rich trialkylphosphine, PCy_3, approached $P(t\text{-Bu})_3$ in terms of effectiveness (Table 1, entries 8 and 9). Interestingly, with $P(t\text{-Bu})_3$ as the ligand, use of a phosphine:Pd ratio between 1 and 1.5 appeared to be optimal, an observation that suggested that the active palladium catalyst was ligated with only one $P(t\text{-Bu})_3$.

Table 1. Effect of Phosphine on the Rate of Palladium-Catalyzed Suzuki Cross-Coupling of Aryl Chlorides



Entry	Phosphine	% Yield (GC)
1	none	0
2	PPh_3	0
3	BINAP	0
4	dppf	0
5	$P(o\text{-tol})_3$	10
6	$Ph_2P(CH_2)_3PPh_2$	0
7	$Cy_2P(CH_2)_2PCy_2$	0
8	PCy_3	75
9	$P(t\text{-Bu})_3$	86

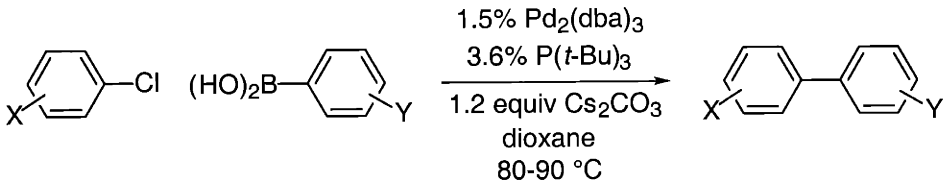
Cs_2CO_3 was initially selected as the base of choice among a number of bases screened, although both K_3PO_4 and CsF were also effective bases. Na_2CO_3, K_2CO_3, and NEt_3 all proved to be inferior choices. In contrast to most Suzuki couplings, two equivalents of base were *not* required (95% GC yield after 5 hours with 1.2 equiv Cs_2CO_3). With respect to palladium source, $Pd_2(dba)_3$ was

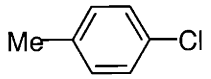
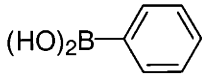
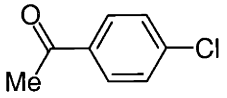
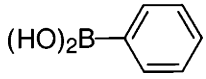
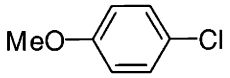
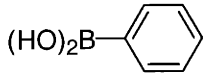
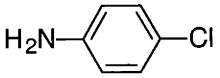
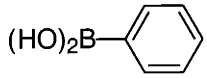
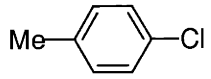
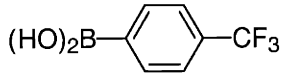
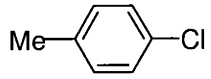
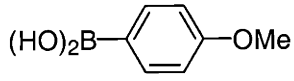
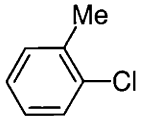
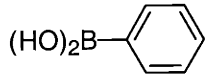
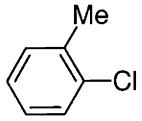
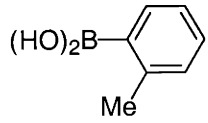
found to be superior to $Pd(OAc)_2$, and dioxane was found to be optimal as solvent.

In order to examine the scope of the reaction, a variety of sterically and electronically diverse aryl chlorides and arylboronic acids were subjected to Suzuki coupling under the optimized conditions (Table 2). Electron-neutral (Table 2, entry 1) and electron-deficient aryl chlorides (Table 2, entry 2) reacted in high yield with phenylboronic acid. Particularly satisfying was that aryl chlorides such as 4-chloroanisole (Table 2, entry 3) and the very electron-rich 4-chloroaniline (Table 2, entry 4) also underwent efficient coupling under these conditions. Electronic variation was also tolerated on the side of the boronic acid component as both electron-deficient (Table 2, entry 5) and electron-rich arylboronic acids (Table 2, entry 6) underwent smooth reaction with 4-chlorotoluene. Finally, ortho substitution on both the aryl chloride and arylboronic acid was not a problem, as a sterically hindered 2,2'-disubstituted biaryl could be synthesized in good yield (Table 2, entry 8).

In conclusion, a general method for Suzuki couplings of aryl chlorides with arylboronic acids was developed using commercially available components, namely, $Pd_2(dba)_3/P(t\text{-}Bu)_3$ as catalyst and Cs_2CO_3 as base. High yields of the desired biaryl products could be obtained with electronically diverse substrates, including challenging electron-rich aryl chlorides, and sterically hindered substrates could also be coupled in good yields.

Table 2. Scope of the Suzuki Cross-Coupling of Aryl Chlorides Catalyzed by $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cs_2CO_3$



Entry	Aryl Chloride	Arylboronic Acid	Isolated Yield[a]
1			87%
2			91%
3			89%
4			92%
5			86%
6			82%
7			90%
8			87%

[a]Isolated yield, average of two runs

Experimental Section

General Considerations. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian XL-300, Varian Unity 300, Varian Mercury 300 or a Varian VXR-500 spectrometer at ambient temperature. ^{1}H data are reported as follows: chemical shifts in parts per million downfield from tetramethylsilane (δ scale), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constant (Hz) and integration. ^{13}C chemical shifts are reported in parts per million relative to the chemical shift of $^{13}CDCl_3$ (δ = 77.23). All ^{13}C spectra were obtained with complete proton decoupling.

Analytical thin layer chromatography was performed using EM Reagents 0.25 mm silica gel 60 plates, and visualization was accomplished with ethanolic phosphomolybdic acid or aqueous potassium permanganate. Flash chromatography was performed on EM Reagents silica gel 60 (230-400 mesh).

All aryl chlorides (Aldrich) were purified by distillation, except for *p*-chloroaniline, which was purified by recrystallization (petroleum ether). Phenylboronic acid (Lancaster) was purified by recrystallization (water). 4-(Trifluoromethyl)phenylboronic acid (Lancaster), 4-methoxyphenylboronic acid (Aldrich), and *o*-tolylboronic acid (Lancaster) were used as received. Na_2CO_3 (Mallinckrodt), K_2CO_3 (Mallinckrodt), K_3PO_4 (Lancaster), and Cs_2CO_3 (Aldrich) were used as received. NEt_3 was distilled from CaH_2.

$Pd_2(dba)_3$ (Strem or Aldrich) and all phosphines (Strem) were used as received.

1,4-Dioxane was distilled from sodium/benzophenone.

All GC yields and conversions have been corrected with response factors.

All reactions were assembled under an inert atmosphere of nitrogen or argon either in a screw-cap vial or in a resealable Schlenk tube (oven-dried).

All yields that are reported in Table 2 are isolated yields and the average of two runs; the yields reported below for a specific experiment may differ from those values.

General Procedure for the $Pd_2(dba)_3$/P(*t*-Bu)$_3$-catalyzed Suzuki Coupling of Aryl Chlorides. In a Vacuum Atmospheres Glovebox, a dioxane solution of the aryl chloride and a dioxane solution of P(*t*-Bu)$_3$ are added in turn to a Schlenk tube charged with $Pd_2(dba)_3$, arylboronic acid, Cs_2CO_3, and a magnetic stir bar. The Schlenk tube is sealed with a teflon stopcock, removed from the glovebox and placed in a 80 or 90 °C oil bath and stirred for the indicated amount of time. At the conclusion of the reaction, the mixture was diluted with Et_2O or EtOAc, filtered through a pad of silica gel with copious washings, concentrated, and purified by column chromatography.

4-phenyltoluene (Table 2, entry 1). The general procedure was followed using 4-chlorotoluene (116 mg, 0.926 mmol), phenylboronic acid (125 mg, 1.02 mmol), Cs_2CO_3 (348 mg, 1.07 mmol), $Pd_2(dba)_3$ (12.8 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.10 M stock solution; 0.34 mL, 0.034 mmol) and dioxane (0.57 mL). After 5 hours at 80 °C, workup and column chromatography (hexane) yielded 138 mg (90%) of the title compound as a white solid which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

4-acetylbiphenyl (Table 2, entry 2). The general procedure was followed using 4-chloroacetophenone (167 mg, 1.08 mmol), phenylboronic acid (141 mg, 1.15 mmol), Cs_2CO_3 (420 mg, 1.29 mmol), $Pd_2(dba)_3$ (14.8 mg, 0.016 mmol), P(*t*-Bu)$_3$ (0.10 M stock solution; 0.39 mL, 0.039 mmol) and dioxane (0.69 mL). After 5 hours at 80 °C, workup and column chromatography (5% EtOAc/hexanes)

yielded 187 mg (88%) of the title compound as a white solid which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

4-methoxybiphenyl (Table 2, entry 3). The general procedure was followed using 4-chloroanisole (166 mg, 1.16 mmol), phenylboronic acid (149 mg, 1.22 mmol), Cs_2CO_3 (462 mg, 1.42 mmol), $Pd_2(dba)_3$ (15.8 mg, 0.017 mmol), P(*t*-Bu)$_3$ (0.10 M stock solution; 0.42 mL, 0.042 mmol) and dioxane (0.74 mL). After 6.5 hours at 90 °C, workup and column chromatography (3% EtOAc/hexanes) yielded 198 mg (93%) of the title compound as a white solid which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

4-aminobiphenyl (Table 2, entry 4). The general procedure was followed using 4-chloroaniline (110 mg, 0.864 mmol), phenylboronic acid (111 mg, 0.910 mmol), Cs_2CO_3 (332 mg, 1.02 mmol), $Pd_2(dba)_3$ (12.1 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.10 M stock solution; 0.31 mL, 0.031 mmol) and dioxane (0.55 mL). After 38 hours at 90 °C, workup and column chromatography (30% EtOAc/hexanes) yielded 134 mg (92%) of the title compound as a yellow-orange solid which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

4-methyl-4'-trifluoromethylbiphenyl (Table 2, entry 5) [97067-18-0].[22] The general procedure was followed using 4-chlorotoluene (111 mg, 0.874 mmol), 4-(Trifluoromethyl)phenylboronic acid (173 mg, 0.911 mmol), Cs_2CO_3 (339 mg, 1.04 mmol), $Pd_2(dba)_3$ (12.4 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.10 M stock solution; 0.32 mL, 0.032 mmol) and dioxane (0.55 mL). After 5 hours at 80 °C, workup and column chromatography (hexane) yielded 181 mg (88%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.66 (s, 4H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.8 (apparent d, *J* = 1.4 Hz), 138.4, 137.0, 129.9, 127.4, 127.3, 125.9 (q, *J* = 3.8 Hz), 21.4.

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[22] Gouda, K.-i.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232-7233.

4-methyl-4'-methoxybiphenyl (Table 2, entry 6) [53040-92-9].[23] The general procedure was followed using 4-chlorotoluene (114 mg, 0.898 mmol), 4-methoxyphenylboronic acid (147 mg, 0.965 mmol), Cs_2CO_3 (348 mg, 1.07 mmol), $Pd_2(dba)_3$ (12.7 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.10 M stock solution; 0.33 mL, 0.033 mmol) and dioxane (0.57 mL). After 9 hours at 80 °C, workup and column chromatography (3% EtOAc/hexane) yielded 150 mg (84%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 137.9, 136.3, 133.7, 129.4, 127.9, 126.6, 114.1, 55.3, 21.0.

2-phenyltoluene (Table 2, entry 7). The general procedure was followed using 2-chlorotoluene (115 mg, 0.912 mmol), phenylboronic acid (119 mg, 0.974 mmol), Cs_2CO_3 (357 mg, 1.10 mmol), $Pd_2(dba)_3$ (12.8 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.10 M stock solution; 0.34 mL, 0.034 mmol) and dioxane (0.57 mL). After 5 hours at 80 °C, workup and column chromatography (hexane) yielded 136 mg (89%) of the title compound as a colorless liquid which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

2, 2'-dimethylbiphenyl (Table 2, entry 8). The general procedure was followed using 2-chlorotoluene (121 mg, 0.957 mmol), *o*-tolylboronic acid (135 mg, 0.996 mmol), Cs_2CO_3 (380 mg, 1.17 mmol), $Pd_2(dba)_3$ (12.9 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.10 M stock solution; 0.33 mL, 0.033 mmol) and dioxane (0.63 mL). After 7 hours at 80 °C, workup and column chromatography (hexane) yielded 149 mg (86%) of the title compound as a colorless liquid which was identical to authentic material (TCI) by ^{1}H NMR, GC, and TLC.

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[23] Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434-5444.

Chapter 2:

Development of Milder and More General Reaction Conditions for the Suzuki Coupling of Aryl Chlorides using KF as Base

Introduction

Traditionally, Suzuki coupling reactions have required elevated temperatures to proceed efficiently.[1,2] Room-temperature processes are useful for substrates that are less stable than common model substrates, for example, in the context of natural products synthesis. From a practical perspective, room temperature is the most convenient temperature to perform a reaction, in particular for large-scale applications and parallel synthesis. While there were, prior to 1998, examples of Suzuki couplings that proceeded at room temperature,[3] none of these could be classified as a truly general method for effecting the room-temperature coupling of aryl halides with arylboronic acids. In addition, none of these examples included room-temperature Suzuki couplings of aryl chloride substrates. Thus, the development of room-temperature protocols for Suzuki coupling reactions that would encompass a wide variety of sterically and electronically diverse substrates would be beneficial from a number of standpoints.

The first general method for room-temperature Suzuki couplings of aryl bromides *and* aryl chlorides was developed by the Buchwald group concurrently with our own investigations on P(*t*-Bu)$_3$ and featured the use of biaryldialkyl phosphines as ligands for palladium and either CsF[4] or KF[5] as base.[6] Several

---

1 Chapter 1, reference 1.

2 "There are few examples of ambient temperature Suzuki-type biaryl couplings": Chapter 1, Reference 1b.

3 (a) Campi, E. M; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395. (b) Anderson, J. C.; Namli, H.; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123-15134. (c) Johnson, C. R.; Johns, B. A. *Synlett* **1997**, 1406-1408. (d) Bumagin, N. A.; Bykov, V. V. *Tetrahedron*, **1997**, *53*, 14437-14450. (e) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095-2096. (f) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384-3388. (g) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743-8744. (h) Bussolari, J. C.; Rehborn, D. C. *Org. Lett.* **1999**, *1*, 965-967.

4 Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722-9723.

5 (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413-2416. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561.

6 For early reports on the use of fluoride bases in Suzuki couplings, see: (a) Ichikawa, J.;

other research groups had developed ligands for palladium-catalyzed Suzuki couplings of aryl chlorides;[7,8] however, only one of these described a Suzuki coupling of an (activated) aryl chloride proceeding at room temperature.[9]

We already knew that CsF was an effective replacement for Cs_2CO_3 in our own $Pd_2(dba)_3$/P(*t*-Bu)$_3$-catalyzed Suzuki couplings. Given the success of the Buchwald group using cheaper KF, we decided to reinvestigate Suzuki couplings using KF as base.

Results and Discussion

We were very pleased to discover that by replacing Cs_2CO_3 with KF, we were able to couple electron-deficient aryl chlorides with hindered, electron-rich and electron-deficient arylboronic acids at room temperature using only 1% Pd/P(*t*-Bu)$_3$ (Table 1, entries 1-3). In addition, heteroaryl chlorides such as chloropyridines (Table 1, entries 4 and 5) and chlorothiophenes (Table 1, entry 6), which have the potential to bind to palladium through nitrogen or sulfur, also underwent clean reaction at room temperature. Dioxane and THF were both suitable solvents and, as with our first-generation system, $Pd_2(dba)_3$ was a superior palladium source to $Pd(OAc)_2$. A critical parameter was the P(*t*-Bu)$_3$:Pd ratio; while the use of a 1:1 ratio generated a very active catalyst, the use of a 2:1

Moriya, T.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1991**, 961-964. (b) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095-6097.

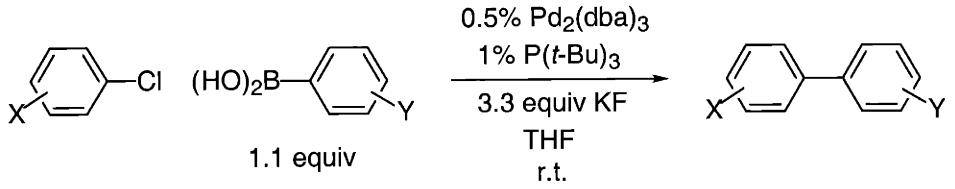
7 Aryldialkyl phosphine ligands: (a) Bei, X.; Crevier, T.; Guram, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855-3858. (b) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797-6803.

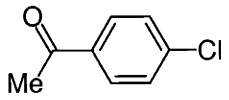
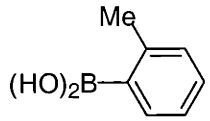
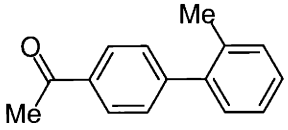
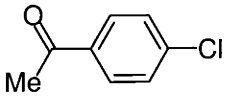
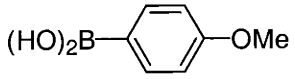
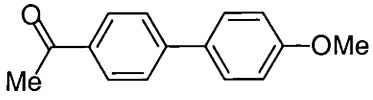
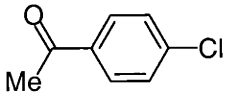
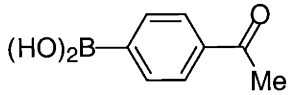
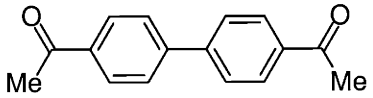
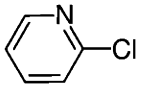
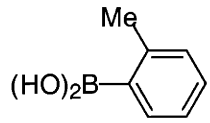
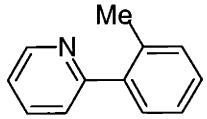
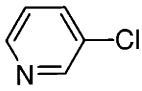
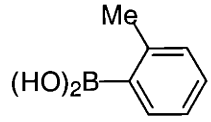
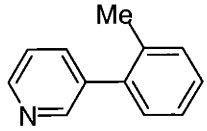
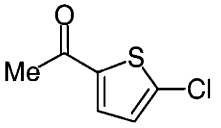
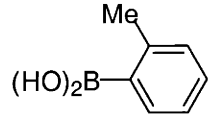
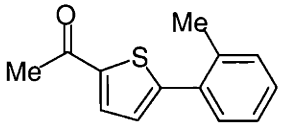
8 *N*-Heterocyclic carbene ligands: (a) Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348-352. (b) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804-3805. (c) Bohm, V. P. W.; Gstottmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186-190.

9 Kocovsky, P.; Vyskocil, S.; Cisarova, I.; Sejbal, J.; Tislerova, I.; Smrcina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714-7715.

ratio resulted in extremely sluggish reactions. This rather interesting observation will be discussed shortly.

Table 1. Suzuki Cross-Couplings of Activated Aryl Chlorides at Room Temperature



Entry	(Hetero)Aryl Chloride	Boronic Acid	Product	Yield[a]
1				99%
2				93%
3				84%
4				97%
5[b]				77%
6				99%

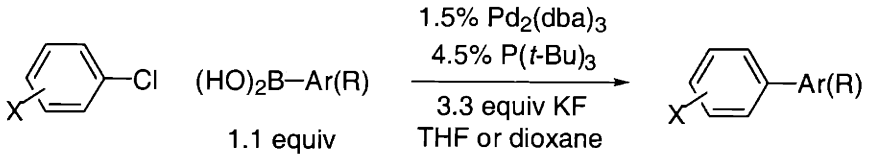
[a]Isolated yield, average of two runs. [b]1.5% $Pd_2(dba)_3$ and 3% P(*t*-Bu)$_3$ were used.

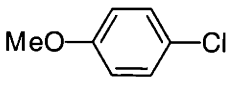
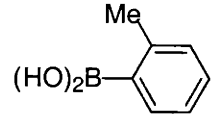
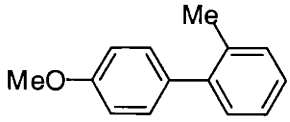
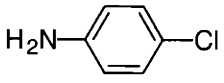
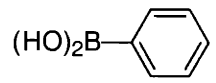
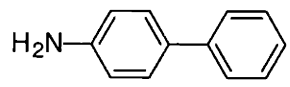
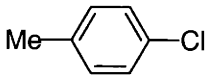
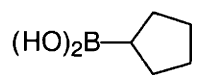
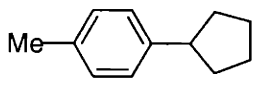
Electron-rich aryl chlorides still required elevated temperatures and slightly higher catalyst loadings to undergo Suzuki coupling with arylboronic acids (Table 2, entries 1 and 2), and in such cases it was found to be beneficial to use a

slightly higher P(*t*-Bu)$_3$:Pd ratio to help stabilize the catalyst at these higher temperatures. With a 1:1 P(*t*-Bu)$_3$:Pd ratio, the precipitation of catalytically inactive palladium metal was found to be a significant problem, while a 2:1 ratio resulted in slow conversions as was observed for room-temperature reactions. A 1.5:1 P(*t*-Bu)$_3$:Pd ratio was found to be the best compromise in terms of catalyst stability and activity.

Because alkylboronic acids have been reported to be less reactive coupling partners in other Suzuki couplings,[6b] it is noteworthy that cyclopentylboronic acid could be coupled with 4-chlorotoluene in good yield (Table 2, entry 3). Unfortunately, attempts to transfer alkyl groups to aryl chlorides via coupling with 9-alkyl-9-BBN derivatives or simple trialkylboranes such as Bu_3B resulted in low conversions (<40%) and/or complicated reaction mixtures.

Table 2. Suzuki Cross-Couplings of Unactivated Aryl Chlorides



Entry	Aryl Chloride	Boronic Acid	Product	Temp.	Yield[a]
1				70 °C	88%
2				90 °C	82%
3				100 °C	75%

[a]Isolated yield, average of two runs.

The synthesis of hindered biaryls (i.e., two or more ortho substituents) via Suzuki coupling can be a challenging task, as vigorous conditions are often

required and yields can be modest.[1] Certain bases, such as K_3PO_4,[10] $Ba(OH)_2$,[10] and TlOH,[11] have been reported to be particularly efficacious in Suzuki couplings of sterically demanding substrates; however, none of these protocols are effective for aryl chloride substrates. In fact, Suzuki couplings to form tri-ortho-substituted biaryls from aryl chloride precursors are quite rare.[5b,12,13]

As was the case in our initial protocol using Cs_2CO_3 as base, $Pd_2(dba)_3$/P(*t*-Bu)$_3$ can be used to synthesize a di-ortho-substituted biaryl in excellent yield (Table 3, entry 1). However, for more sterically demanding tri-ortho-substituted biaryls, the use of the slightly smaller PCy_3 was found to be somewhat more efficient than P(*t*-Bu)$_3$ (Table 3, entries 2 and 3).[14] Similar observations have been made by Buchwald with his biaryldialkyl phosphine ligands[5b] and may be attributed to a more facile transmetalation to the $L_nPd(Ar)X$ intermediate when sterically demanding aryl chlorides and/or boronic acids are employed.

The reaction appeared to be more sensitive to hindered boronic acids than to hindered aryl chlorides, as the coupling of mesitylboronic acid required a reaction temperature of 90 °C; in addition K_3PO_4 and toluene were found to be a better base/solvent combination than KF/dioxane. Attempts to synthesize tetra-ortho-substituted biaryls were unsuccessful, as low conversions and side reactions such as deboronation were observed.

The ability to selectively monofunctionalize substrates with more than one halide/triflate through Suzuki coupling can be a powerful tool to synthesize

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10 Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207-210.

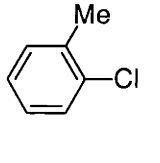
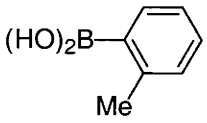
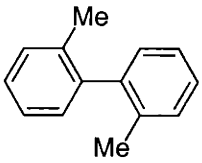
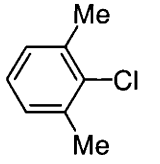
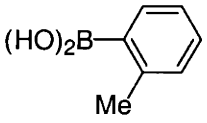
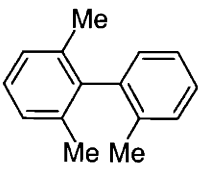
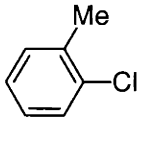
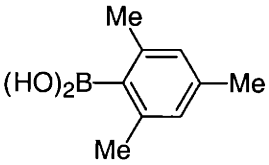
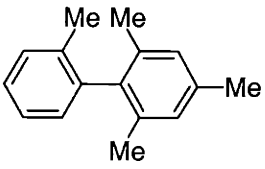
11 Anderson, J. C.; Namli, H.; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123-15134.

12 For examples utilizing *hetero*aryl chlorides as substrates, see: (a) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743-746. (b) Zhang, H.; Chan, K. S. *Tetrahedron Lett.* **1996**, *37*, 1043-1044.

13 For a nickel-catalyzed Suzuki coupling to form a tri-ortho-substituted biaryl, see: Galland, J.-C.; Savignac, M.; Genet, J.-P. *Tetrahedron Lett.* **1999**, *40*, 2323-2326.

14 For the reaction illustrated in entry 3 of Table 3, the use of PCy_3 lead to a 16:1 ratio (by GC) of product:starting material after 23 hours while the use of P(*t*-Bu)$_3$ lead to a 14:1 ratio after the same amount of time.

Table 3. Suzuki Cross-Couplings to Form Sterically Hindered Biaryls

Entry	Aryl Halide	Boronic Acid	Product	Conditions[a]	Yield[b]
1				1.5% $Pd_2(dba)_3$ 3.6% P(*t*-Bu)$_3$ 60 °C	93%
2				1.5% $Pd_2(dba)_3$ 4.2% PCy_3 60 °C	89%[c]
3				1.5% $Pd_2(dba)_3$ 4.5% PCy_3 90 °C	93%[d]

[a]Standard conditions: 1.0 equiv of aryl halide, 1.1 equiv of boronic acid, 3.3 equiv of KF, THF. [b]Isolated yield, average of two runs. [c]Product contained 4% 2,2'-dimethylbiphenyl. [d]1.5 equiv of boronic acid, 2.0 equiv of K_3PO_4, and toluene as solvent; the product from one run contained 5% mesitylene.

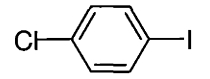
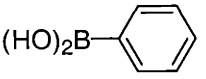
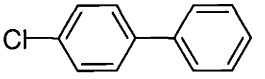
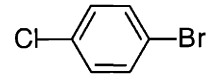
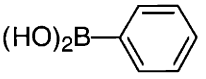
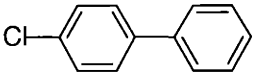
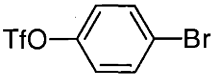
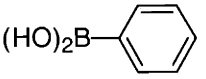
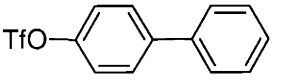
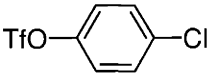
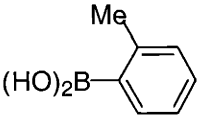
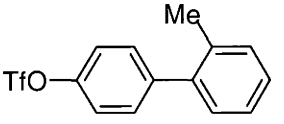
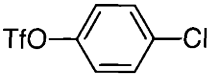
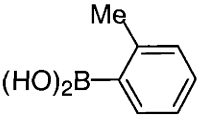
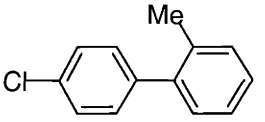
complex molecules.[15] As for most palladium-catalyzed coupling reactions, the general order of reactivity of aryl electrophiles in Suzuki couplings is I > Br >~ OTf >> Cl. Through the use of $Pd_2(dba)_3$/P(*t*-Bu)$_3$, highly selective monofunctionalizations of aryl electrophiles with two reactive sites can be accomplished in excellent yields (Table 4).

As one would anticipate, an iodide (Table 4, entry 1) or a bromide[16] (Table 4, entry 2) can be coupled at room temperature in the presence of a chloride, which is then ready for further functionalization. The selective coupling of a bromide in

[15] For example, see: (a) Kawada, K., Arimura, A.; Tsuri, T.; Fuji, M.; Komurasaki, T.; Yonezawa, S.; Kugimiya, A.; Haga, N.; Mitsumori, S.; Inagaki, M.; Nakatani, T.; Tamura, Y.; Takechi, S.; Taishi, T.; Kishino, J.; Ohtani, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 973-975. (b) Hird, M.; Gray, G. W.; Toyne, K. J. *Mol. Cryst. Liq. Cryst.* **1991**, *206*, 187-204.

[16] Dr. Chaoyang Dai, a postdoctoral associate in our group, demonstrated that $Pd_2(dba)_3$/P(*t*-Bu)$_3$/KF is a very effective system for room-temperature Suzuki couplings of a wide variety of aryl bromides and iodides with arylboronic acids.

Table 4. Chemoselective Suzuki Cross-Couplings

Entry	Aryl Halide	Boronic Acid	Product	Conditions[a]	Yield[b]
1				0.5% $Pd_2(dba)_3$ 1.2% P(*t*-Bu)$_3$	98%
2				0.5% $Pd_2(dba)_3$ 1.2% P(*t*-Bu)$_3$	97%
3				0.5% $Pd_2(dba)_3$ 1.2% P(*t*-Bu)$_3$	98%
4				1.5% $Pd_2(dba)_3$ 3.0% P(*t*-Bu)$_3$	95%
5				3.0% $Pd(OAc)_2$ 6.0% PCy_3	87%

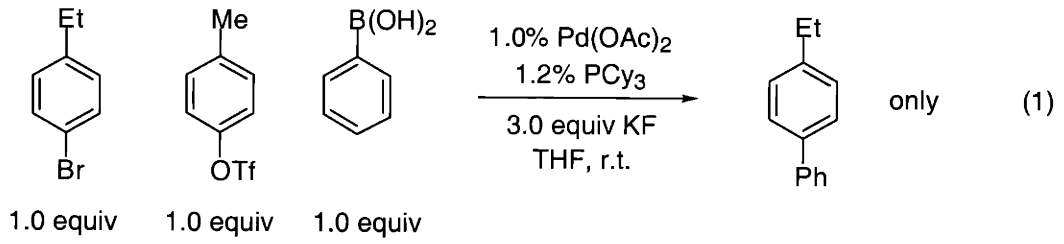
[a]Standard conditions: 1.0 equiv of aryl halide, 1.0 equiv of boronic acid, 3.0 equiv of KF, THF, r.t.
[b]Isolated yield.

the presence of a triflate (Table 4, entry 3) is a potentially useful result, as it can be quite difficult to control the relative reactivity of aryl bromides and triflates due to similar rates of oxidative addition to Pd(0).[17] The result in Table 4, entry 3 is not surprising since Dr. Chaoyang Dai demonstrated that $Pd_2(dba)_3$/P(*t*-Bu)$_3$ is a remarkably *ineffective* catalyst for couplings of aryl triflates with arylboronic acids at room temperature *or* elevated temperatures. Dr. Dai further demonstrated that Suzuki couplings of aryl triflates and arylboronic acids could in fact be carried out at room temperature if one used $Pd(OAc)_2/PCy_3$ as the catalyst. However, when this catalyst system is applied to the coupling of 4-bromophenyltriflate and phenylboronic acid, one still observes a highly selective

[17] It has been reported that aryl triflates are slightly more reactive than aryl bromides towards oxidative addition to $Pd(PPh_3)_4$ in DMF: Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810-1817.

coupling of the bromide over the triflate. Thus, using either $Pd/P(t\text{-}Bu)_3$ or Pd/PCy_3 we have been unable to selectively couple a triflate in the presence of a bromide.

Intermolecular competition experiments catalyzed by $Pd(OAc)_2/PCy_3$ also indicated that aryl bromides react exclusively in the presence of aryl triflates (eq 1); only the product arising from coupling with the aryl bromide was observed by GC. Although not a direct comparison, it is worth contrasting these results to those obtained by Suzuki and Miyaura in the $Pd(PPh_3)_4$-catalyzed Suzuki coupling of 9-alkyl-9-BBN derivatives.[18] While the bromide reacts in preference to the triflate in the coupling of 4-bromophenyltriflate with 9-alkyl-9-BBN compounds, in the intermolecular competition experiment of bromobenzene and phenyltriflate for 9-octyl-9-BBN, a relatively non-selective reaction results, as 24% of unreacted aryl bromide is obtained along with 66% of phenyltriflate.



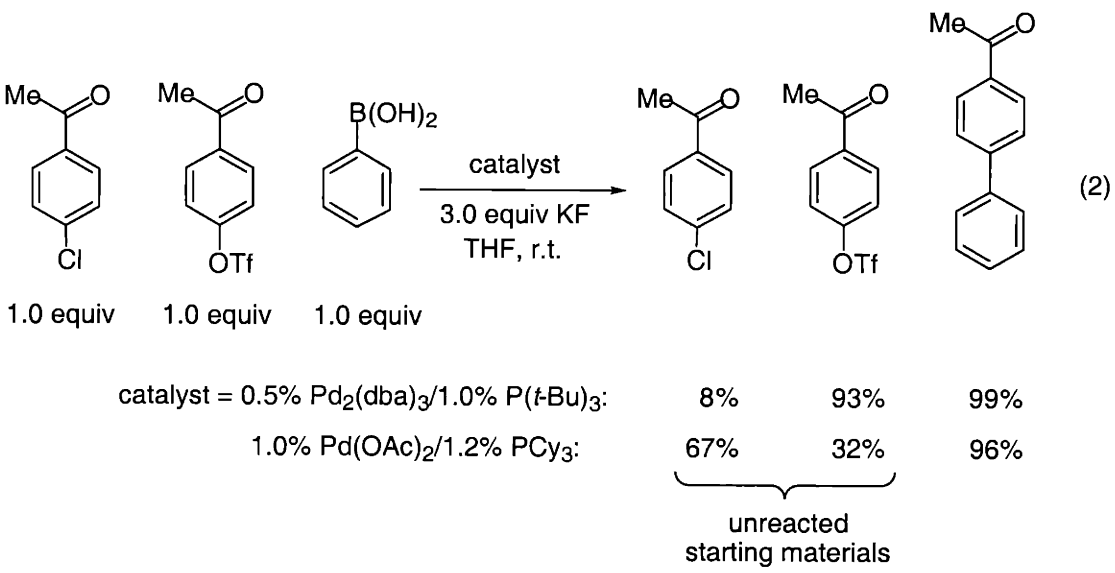
Given the low reactivity that the $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system exhibited towards aryl triflates, we speculated that it might even be possible to effect a selective Suzuki coupling of a chloride in the presence of a triflate. There is no precedent in *any* palladium-catalyzed coupling process for greater reactivity toward an aryl chloride than toward an aryl triflate. $Pd_2(dba)_3/P(t\text{-}Bu)_3$ does indeed react with the chloride of 4-chlorophenyltriflate in preference to the triflate, with excellent selectivity (Table 4, entry 4). This highly unusual selectivity

[18] Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201-2208.

can be reversed to the more conventional pattern of reactivity through the use of $Pd(OAc)_2/PCy_3$ (Table 4, entry 5). The use of a 2:1 ratio of PCy_3:Pd results in slower conversions than using a 1.2:1 ratio but is critical in order to obtain a highly selective reaction (*vide infra*).

The intramolecular competition experiment illustrated in entry 4 of Table 4 does not necessarily give a true measure of the degree of selectivity that $Pd_2(dba)_3/P(t\text{-}Bu)_3$ exhibits for reacting with chlorides in the presence of triflates, as the triflate activates the chloride and vice-versa but to different extents. In order to determine the true selectivity, an intermolecular competition experiment was performed (eq 2). The use of $Pd_2(dba)_3/P(t\text{-}Bu)_3$ results in only 8% recovery of unreacted aryl chloride and 93% recovery of unreacted aryl triflate. In contrast, $Pd(OAc)_2/PCy_3$ shows higher reactivity toward the aryl triflate than the aryl chloride; although the degree of selectivity is not nearly as high. Control experiments suggested that this reversal of selectivity when going from $P(t\text{-}Bu)_3$ to PCy_3 is due to the phosphine and not the palladium source; a competition experiment conducted with $Pd(OAc)_2/P(t\text{-}Bu)_3$ yielded results similar to the experiment conducted with $Pd_2(dba)_3/P(t\text{-}Bu)_3$; likewise, both $Pd_2(dba)_3/PCy_3$ and $Pd(OAc)_2/PCy_3$ exhibited higher reactivity for aryl triflates in the presence of aryl chlorides.

Although the catalyst system 1.0% $Pd(OAc)_2$/1.2% PCy_3 exhibits a preference for coupling an aryl triflate in the presence of an aryl chloride (eq 2), when this catalyst system is applied towards the coupling of phenylboronic acid with 4-chlorophenyltriflate, a mixture of starting material, 4-chlorobiphenyl, 4-biphenyltriflate and *p*-terphenyl is obtained, indicating a completely non-selective reaction. This result in most probably due to the activated nature of the carbon-chlorine bond in 4-chlorophenyltriflate towards oxidative addition by



virtue of the strong electron-withdrawing effect of the trifluoromethanesulfonyl group. The use of 2 equiv of PCy_3 per palladium seems to sufficiently suppress the reactivity of the catalyst towards the chloride site while only attenuating the reactivity at the triflate site (Table 4, entry 5).[19]

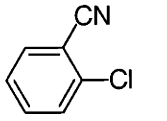
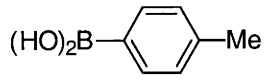
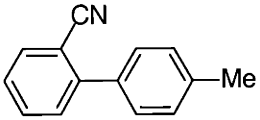
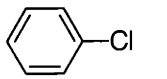
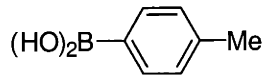
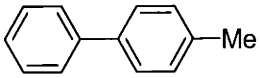
The surprising greater reactivity of aryl chlorides in the presence of aryl triflates observed with $Pd_2(dba)_3/P(t\text{-}Bu)_3$ may be steric in origin; a triflate is sterically larger than a chloride, and the palladium catalyst containing the very bulky $P(t\text{-}Bu)_3$ ligand may prefer to undergo oxidative addition at the less hindered site. The reversal of reactivity observed with Pd/PCy_3 is consistent with the above hypothesis, as PCy_3 is less bulky than $P(t\text{-}Bu)_3$.

All of the Suzuki coupling reactions discussed thus far have utilized 1-3% palladium as catalyst. Catalyst loadings were not optimized with respect to individual substrates in order to provide a general and reliable method that should work on the first try for a large majority of substrates that one may encounter. However, due to the high cost of palladium metal, these are

[19] Replacing *o*-tolylboronic acid with phenylboronic acid does not change the chemoselectivity of the reaction; one still observes coupling at the triflate site.

relatively high catalyst loadings for an industrial process. In particular, for the synthesis of pharmaceuticals and pharmaceutical intermediates, the complete and thorough separation of the palladium catalyst from the product is an essential process and can be an arduous and expensive undertaking if high catalyst loadings are required. Thus, in order to examine the turnover numbers that could be attained with $Pd_2(dba)_3/P(t\text{-}Bu)_3$, the Suzuki coupling of two sets of substrates were examined with low catalyst loadings (Table 5).

Table 5. Suzuki Cross-Couplings with Low Catalyst Loadings

Entry	Aryl Chloride	Boronic Acid	Product	Conditions[a]	Yield[b]
1				0.05% $Pd_2(dba)_3$ 0.1% $P(t\text{-}Bu)_3$ r.t., 24 h	99%
2				0.005% $Pd_2(dba)_3$ 0.01% $P(t\text{-}Bu)_3$ 90 °C, 25 h	97%
3				0.05% $Pd_2(dba)_3$ 0.12% $P(t\text{-}Bu)_3$ 100 °C, 43 h	92%

[a]Standard conditions: 1.0 equiv of aryl halide, 1.1 equiv of boronic acid, 3.3 equiv of KF, dioxane or THF. [b]Isolated yield, average of two runs.

As discussed in Chapter 1, 2-cyano-4'-methylbiphenyl is a key intermediate in the synthesis of angiotension II receptor antagonists that are used for the treatment of hypertension.[20] Thus, it seemed appropriate to explore the $Pd_2(dba)_3/P(t\text{-}Bu)_3$-catalyzed Suzuki coupling of 2-chlorobenzonitrile and *p*-tolylboronic with low catalyst loadings. At room temperature, this coupling proceeds in 99% yield with only 0.1% Pd, corresponding to a turnover number of nearly 1,000 (Table 5, entry 1). A turnover number of 9,700 can be achieved very simply by increasing the temperature to 90 °C (Table 5, entry 2; 0.01% Pd, 97%

[20] For leading references, see: Goubet, D.; Meric, P.; Dormoy, J.-R.; Moreau, P. *J. Org. Chem.* **1999**, *64*, 4516-4518.

yield). These results suggest that for many of the room-temperature Suzuki couplings illustrated previously, one should be able to use significantly lower catalyst loadings if one is simply willing to increase the temperature.

For the more challenging electron-neutral chlorobenzene, a turnover number of 920 could be obtained based on 92% yield with 0.1% Pd (Table 5, entry 3). Higher turnover numbers may be possible; very recently, Beller obtained a turnover number of 9,200 for the Suzuki coupling of 4-chlorotoluene and phenylboronic acid using $Pd(OAc)_2/P(t\text{-}Bu)_3$ as catalyst and K_3PO_4 /toluene as the base/solvent at 100 °C.[21]

Suzuki couplings of vinyl halides and triflates are particularly ubiquitous in natural product synthesis.[1] With regard to Suzuki couplings of vinyl chlorides, the only examples documented had been limited to cases where the vinyl chloride was conjugated to an electron-withdrawing group.[22] Thus, we were pleased to discover that unactivated vinyl chlorides could be coupled with arylboronic acids in good yields using $Pd_2(dba)_3/P(t\text{-}Bu)_3$ at 50-60 °C (Table 6); substituents that are geminal (Table 6, entries 1 and 2) or cis to the chloride (Table 6, entry 3) are tolerated.

In other palladium-catalyzed coupling processes, vinyl chlorides are more reactive than aryl chlorides.[23] Perhaps the best example of this is the Sonogashira coupling; the palladium-catalyzed coupling of unactivated aryl chlorides with terminal acetylenes is unknown at any temperature, yet the analogous coupling of unactivated vinyl chlorides has been demonstrated to

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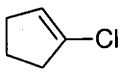
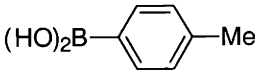
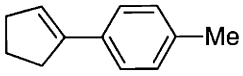
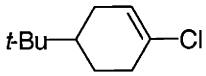
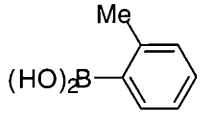
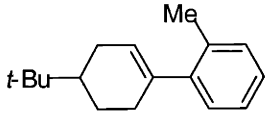
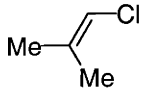
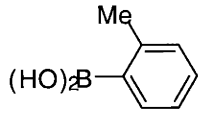
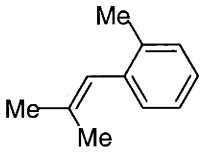
21 Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4153-4155.

22 (a) Satoh, N.; Ishiyama, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3471-3473. (b) Boland, G. M.; Donnelly, D. M. X.; Finet, J.-P.; Rea, M. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2591-2597.

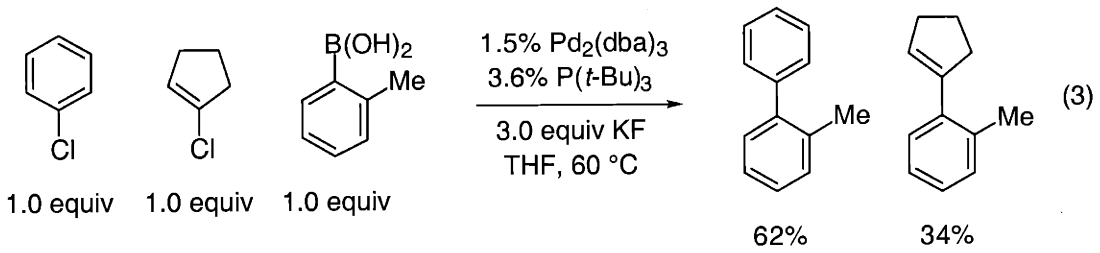
23 (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (b) Tsuji, J. *Palladium Reagents and Catalysis;* Wiley: New York, 1995. (c) Farina, V. In *Comprehensive Organometallic Chemistry 2*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 3.4.

Table 6. Suzuki Cross-Couplings of Vinyl Chlorides

Entry	Vinyl Chloride	Boronic Acid	Product	Conditions[a]	Yield[b]
1				1.5% $Pd_2(dba)_3$ 3.6% P(*t*-Bu)$_3$ 50 °C	87%
2				1.5% $Pd_2(dba)_3$ 3.6% P(*t*-Bu)$_3$ 60 °C	91%
3				1.5% $Pd_2(dba)_3$ 3.6% P(*t*-Bu)$_3$ 50 °C	76%

[a]Standard conditions: 1.0 equiv of vinyl chloride, 1.1 equiv of boronic acid, 3.3 equiv of KF, THF.
[b]Isolated yield, average of two runs.

proceed smoothly at room temperature.[24] We were curious about the relative reactivity of aryl and vinyl chlorides in Suzuki reactions catalyzed by $Pd_2(dba)_3$/P(*t*-Bu)$_3$, and to investigate this issue in more detail a competition experiment was performed (eq 3). Interestingly, Pd/P(*t*-Bu)$_3$ exhibits a rather novel higher reactivity for aryl chlorides in the presence of vinyl chlorides, as 62% of the product arising from coupling with chlorobenzene is isolated versus only 34% arising from coupling with 1-chlorocyclopentene.



(3)

Given the high activity of the $Pd_2(dba)_3$/P(*t*-Bu)$_3$ catalyst system towards typically unreactive aryl chlorides and the critical importance of the P(*t*-Bu)$_3$:Pd

24 Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1991**, *32*, 6109-6122.

ratio, a series of NMR and reactivity studies were pursued in order to try to gain some insight.

Initial studies focused on determining what species formed when $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ were mixed together. ^{31}P and ^{1}H NMR studies revealed that, for P(*t*-Bu)$_3$:Pd ratios between 0.5 and 1.5:1, Pd(P(*t*-Bu)$_3$)$_2$[25] is the only identifiable phosphine-containing species that is present (^{31}P: δ 85.6; THF-d_8).[26] As the P(*t*-Bu)$_3$:Pd ratio is increased to 2-4:1, the only *other* species that is observed is free P(*t*-Bu)$_3$. Thus, the bisphosphine adduct Pd(P(*t*-Bu)$_3$)$_2$ seems to be favored over the monophosphine and trisphosphine over a wide range of P(*t*-Bu)$_3$:Pd ratios.[27]

In order to help determine the resting state of the catalyst, the Suzuki coupling of 3-chloropyridine and *o*-tolylboronic acid was monitored by ^{31}P NMR (2.5% $Pd_2(dba)_3$/5% P(*t*-Bu)$_3$; THF-d_8). Essentially the only species that was observed during the course of the reaction was Pd(P(*t*-Bu)$_3$)$_2$.[28] Since the overall P(*t*-Bu)$_3$:Pd ratio is 1:1, this suggests that one-half of the palladium is in the form of Pd(P(*t*-Bu)$_3$)$_2$ and the other half of the palladium is in the form of a phosphine-free complex.

Despite the fact that Pd(P(*t*-Bu)$_3$)$_2$ appears to be the resting state, it does not seem to be the active catalyst. When Pd(P(*t*-Bu)$_3$)$_2$ is used as the catalyst for the coupling of 3-chloropyridine and *o*-tolylboronic acid, very little reaction is observed (eq 4). The addition of phosphine-free $Pd_2(dba)_3$ to the Pd(P(*t*-Bu)$_3$)$_2$ so as to adjust the P(*t*-Bu)$_3$:Pd ratio to the desired 1:1 ratio, produces a dramatic

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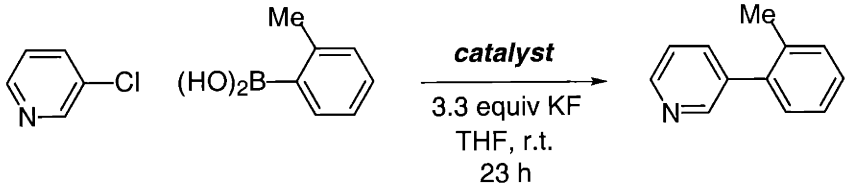
[25] (a) Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. *J. Am. Chem. Soc.* **1976**, *98*, 5850-5858. (b) Yoshida, T.; Otsuka, S. *J. Am. Chem. Soc.* **1977**, *99*, 2134-2140. (c) Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1990**, *28*, 113-119.

[26] (a) In the ^{1}H NMR spectrum, there is a small doublet at δ 1.27, which we have not yet been able to identify. (b) Through ^{31}P and ^{1}H NMR experiments, dba does not appear to be coordinated to Pd(P(*t*-Bu)$_3$)$_2$.

[27] (a) For a related study, see: Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030-3039. (b) The behavior of P(*t*-Bu)$_3$ stands in contrast to that of PPh$_3$: Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168-3178.

[28] A very small singlet at δ 90.7 is observed at the beginning of the reaction, but it disappears as the reaction progresses.

increase in the rate of coupling (eq 4). These results are consistent with the previously mentioned observation that room-temperature Suzuki couplings of aryl chlorides are very slow when using a 2:1 P(*t*-Bu)$_3$:Pd ratio.



(4)

3.0% $Pd(P(t\text{-}Bu)_3)_2$ *7% conversion*
1.5% $Pd(P(t\text{-}Bu)_3)_2$/0.75% $Pd_2(dba)_3$ *91% conversion*

These results suggest that a palladium monophosphine adduct may be the active catalyst in these Suzuki couplings[29,30] and that phosphine-free palladium complexes that are present in the reaction mixture may serve an important role by increasing the concentration of the active catalyst. In contrast, for most Pd/PPh_3-catalyzed Suzuki couplings, a palladium *bis*phosphine species is usually invoked as the active catalyst.[1] Thus, *both* the electron-richness and the steric bulk of P(*t*-Bu)$_3$ are critical to its unusual effectiveness; the steric demand of the ligand favors reductive elimination and dissociation (relative to less bulky phosphines) to a monophosphine complex that, due to the donating ability of P(*t*-Bu)$_3$, readily undergoes oxidative addition.

One way one could envision increasing the concentration of the active palladium monophosphine catalyst relative to $Pd(P(t\text{-}Bu)_3)_2$ is by using lower phosphine to palladium ratios. Indeed, the use of P(*t*-Bu)$_3$:Pd ratios < 1:1 does lead to an active catalyst, but no dramatic increase in reaction rates is observed (Table 7). Thus, for the Suzuki coupling of 4-chlorophenyltriflate with

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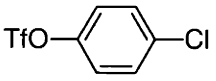
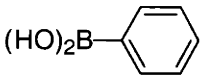
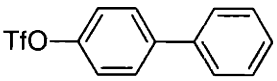
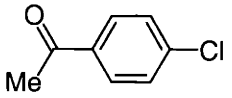
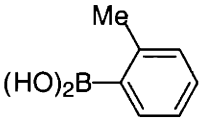
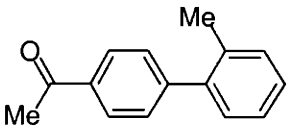
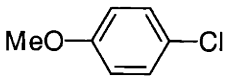
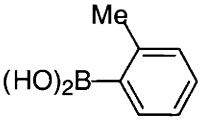
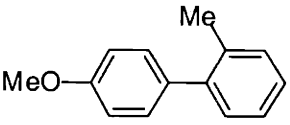
29 For a related conclusion regarding a different catalyst for the Suzuki coupling of aryl chlorides, see Reference 7b.

30 For a study of palladium complexes that contain one P(*t*-Bu)$_3$ ligand, see: Krause, J.; Cestaric, G; Haack, K.-J.; Seevogel, K.; Storm, W.; Pörschke, K.-R. *J. Am. Chem. Soc.* **1999**, *121*, 9807-9823.

phenylboronic acid catalyzed by 1.5% P(*t*-Bu)$_3$/1.5% $Pd_2(dba)_3$ (⇒ 1:2 P(*t*-Bu)$_3$:Pd), complete conversion is reached in 24 hours at room temperature (Table 7, entry 1; 97%). This reaction proceeds at a slightly elevated rate relative to that with twice the amount of P(*t*-Bu)$_3$. In fact, one can use P(*t*-Bu)$_3$:Pd ratios as low as 0.2:1 (Table 7, entries 2 and 3); these reactions proceed at approximately similar rates to those using a 1:1 ratio.[31]

Table 7. Suzuki Cross-Couplings Using a Low Loading of P(*t*-Bu)$_3$

Entry	Aryl Chloride	Boronic Acid	Product	Conditions[a]	Yield[b]
1				1.5% $Pd_2(dba)_3$ 1.5% P(*t*-Bu)$_3$ 24 h, r.t.	97%
2				1.5% $Pd_2(dba)_3$ 0.6% P(*t*-Bu)$_3$ 32 h, r.t.	93%
3				0.5% $Pd_2(dba)_3$ 0.2% P(*t*-Bu)$_3$ 8 h, r.t.	99%
4				1.5% $Pd_2(dba)_3$ 1.5% P(*t*-Bu)$_3$ 10 h, 70 °C	75%

[a]Standard conditions: 1.0 equiv of aryl chloride, 1.0-1.1 equiv of boronic acid, 3.0-3.3 equiv of KF, THF. [b]Isolated yield.

It is important to stress that these low-phosphine conditions are only applicable to room-temperature chemistry; although the coupling of 4-chloroanisole and *o*-tolylboronic acid at 70 °C proceeded in good (75%) yield (1:2 P(*t*-Bu)$_3$:Pd; Table 7, entry 4), the reaction did not reach 100% conversion with respect to the aryl chloride due to relatively rapid catalyst decomposition. Under

[31] Hartwig has noted parenthetically that an effective catalyst for palladium-catalyzed C-O bond formation can be formed from a 1:2 mixture of phosphine and palladium: Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224-3225.

these low-phosphine conditions above room temperature, there appears to be a greater tendency to form insoluble palladium(0).

In conclusion, a very versatile and general method for Suzuki couplings of aryl and vinyl chlorides under relatively mild conditions has been demonstrated using $Pd_2(dba)_3/P(t\text{-}Bu)_3$ as catalyst and KF as base. These conditions allow for room-temperature couplings of electron-deficient aryl chlorides and chloropyridines, coupling of very electron-rich aryl chlorides such as 4-chloroaniline, coupling of unactivated vinyl chlorides, and can be used at low catalyst loadings. Highly chemoselective couplings can be accomplished on substrates that bear more than one halide/triflate, including the coupling of a chloride in the presence of a triflate. For the synthesis of sterically demanding tri-ortho-substituted biaryls from aryl chloride substrates, $Pd_2(dba)_3/PCy_3$ has been shown to be particularly effective.

Preliminary mechanistic work suggests that a palladium monophosphine complex may be the active catalyst, and it is likely that the steric bulk and the electron-richness of the phosphine are the key to the activity of these systems.

The broad scope and mildness of conditions that $Pd/P(t\text{-}Bu)_3$-catalyzed Suzuki couplings allow for is perhaps best appreciated by the number of applications that have appeared in the last several years. Substrates have included aryl chlorides,[32] heteroaryl chlorides,[33] vinyl chlorides,[34] aryl bromides,[35] heteroaryl

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32 (a) Sutton, A. E.; Clardy, J. *Tetrahedron Lett.* **2001**, *42*, 547-551. (b) Sudo, A.; Uchino, S.; Endo, T. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 2093-2102. (c) Zou, G.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817-5819.

33 (a) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2501-2504. (b) Allegretti, M.; Arcadi, A.; Marinelli, F.; Nicolini, L. *Synlett* **2001**, 609-612. (c) Guery, S.; Parrot, I.; Rival, Y.; Wermuth, C. G. *Synthesis* **2001**, 699-701. (d) Brill, W. K.-D.; Riva-Toniola, C.; Muller, S. *Synlett* **2001**, 1097-1100. (e) Mello, J. V.; Finney, N. S. *Org. Lett.* **2001**, *3*, 4263-4265.

34 (a) Davies, I. W.; Wu, J.; Marcoux, J. -F.; Taylor, M.; Hughes, D.; Reider, P. J.; Deeth, R. J. *Tetrahedron* **2001**, *57*, 5061-5066. (b) Zou, G.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817-5819.

35 (a) Early, T. R.; Gordon, R. S.; Carroll, M. A.; Holmes, A. B.; Shute, R. E.; McConvey, I. F. *Chem. Commun.* **2001**, 1966-1967. (b) Xiong, Y.; Klopp, J.; Chapman, K. T. *Tetrahedron Lett.*

bromides,[36] and vinyl bromides.[37] Given the continuing heightened interest in the Suzuki coupling reaction as a versatile tool for carbon-carbon bond formation, the use of P(*t*-Bu)$_3$ should find even more applications.

Experimental Section

General Considerations. The general considerations are the same as the previous chapter with the following exceptions. $Pd_2(dba)_3$ (Aldrich), $Pd(OAc)_2$ (Aldrich), P(*t*-Bu)$_3$ (Strem), P(*t*-Bu)$_3$ (10 wt% solution in hexane; Strem), and PCy_3 (Strem) were used as received. $Pd(P(t\text{-}Bu)_3)_2$ was prepared according to literature procedures.[25]

o-Tolylboronic acid (Aldrich, Strem, or Frontier Scientific), 4-methoxyphenylboronic acid (Aldrich), 4-acetylphenylboronic acid (Aldrich) and phenylboronic acid (Lancaster) were recrystallized from water prior to use. Cyclopentylboronic acid (Frontier Scientific), 2,4,6-trimethylphenylboronic acid (Frontier Scientific), and *p*-tolylboronic acid (Alfa-Aesar or Frontier Scientific) were used as received. We have encountered one or two instances in which a Suzuki coupling did not work well when a boronic acid was used that had not been purified by recrystallization.

4-chlorophenyl trifluoromethanesulfonate[38] and 4-bromophenyl trifluoromethanesulfonate[39] were prepared by standard methods from the corresponding phenol. 1-Chloro-4-*t*-butylcyclohexene was prepared according

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2001, *42*, 8423-8427. (c) Cho, J. -Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E. Jr.; Smith, M. R. III. *Science* **2002**, *295*, 305-308.

36 (a) Mello, J. V.; Finney, N, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 1536-1538. (b) Collis, G. E.; Burrell, A. K.; Officer, D. L. *Tetrahedron Lett.* **2001**, *42*, 8733-8735. (c) Wong, K. -T.; Hung, T. S.; Lin, Y.; Wu, C. -C.; Lee, G. -H.; Peng, S. -M.; Chou, C. H.; Su, Y. O. *Org. Lett.* **2002**, *4*, 513-516.

37 (a) Weatherman, R. V.; Clegg, N. J.; Scanlan, T. S. *Chemistry and Biology* **2001**, *8*, 427-436. (b) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297-300.

38 Creary, X.; Benage, B.; Hilton, K. *J. Org. Chem.* **1983**, *48*, 2887-2891.

39 Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478-5486.

to a literature procedure.[40] All other (hetero)aryl and vinyl chlorides and bromides were purchased from commercial sources (Aldrich, Alfa-Aesar, and Lancaster) and distilled or recystallized prior to use with the exception of 2-chlorobenzonitrile, 4-bromochlorobenzene, 4-iodochlorobenzene, 2-acetyl-5-chlorothiophene and 4-chloroaniline, which were used as received, and 1-chlorocyclopentene and 1-chloro-2-methylpropene, which were degassed by three freeze-pump-thaw cycles prior to use. 4-acetylphenyltriflate and *p*-tolyltriflate (Aldrich) were used as received.

KF (Aldrich, spray-dried) was dried in an oven overnight prior to use. K_3PO_4 (Aldrich) was ground to a fine powder using a mortar and pestle prior to use. THF and dioxane were distilled under nitrogen from sodium/benzophenone. Toluene was distilled under nitrogen from molten sodium.

All yields that are reported in Tables 1-7 are isolated yields and the those in Tables 1-3 and 5, 6 are the average of two runs; the yields reported below for a specific experiment may differ from those values.

General Procedures for the Pd/P(*t*-Bu)$_3$ and Pd/PCy$_3$-catalyzed Suzuki Coupling.

Although most of these Suzuki coupling reactions are set up inside of a Vacuum Atmospheres Glovebox (Procedure A), due to convenience, every reaction that we have set up outside of a glove box (Procedures B) has also been successful.

Procedure A. In a glove box, the palladium source, the boronic acid, and KF are added to a reaction vessel that is equipped with a stir bar. The aryl/vinyl halide and THF are then added, followed by a solution of the phosphine in THF. The reaction mixture is then stirred at the indicated temperature for the indicated

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40 Lambert, J. B.; Wang, G.-t.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838-7845.

amount of time. At the conclusion of the reaction, the reaction mixture is diluted with Et_2O or EtOAc, filtered through a pad of silica gel with copious washings, concentrated, and purified by column chromatography on silica gel.

Procedure B (no glove box). The palladium source, the boronic acid, and KF are added to a Schlenk tube equipped with a stir bar and teflon stopcock under argon. The Schlenk tube is evacuated and then refilled with argon. Next, the aryl/vinyl halide (if a liquid; if a solid, then the aryl/vinyl halide is added prior to the evacuation-refill cycle) and THF are added, followed by a solution of the phosphine in THF. Three freeze-pump-thaw cycles are then performed (these do not appear to always be mandatory), and the reaction is stirred at the indicated temperature for the indicated amount of time. At the conclusion of the reaction, the reaction mixture is diluted with Et_2O or EtOAc, filtered through a pad of silica gel with copious washings, concentrated, and purified by column chromatography on silica gel.

4-Acetyl-2'-methylbiphenyl (Table 1, entry 1) [56917-39-6].[41] Procedure A was followed, using 4'-chloroacetophenone (187 mg, 1.21 mmol), *o*-tolylboronic acid (185 mg, 1.36 mmol), KF (250 mg, 4.30 mmol), $Pd_2(dba)_3$ (5.5 mg, 0.0060 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.060 mL, 0.012 mmol), and THF (2.4 mL). After 6 hours at room temperature, workup and column chromatography (10% Et_2O/hexane) yielded 256 mg (100%) of the title compound as a slightly pale-yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.01 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.30–7.20 (m, 4H), 2.65 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.0, 147.1, 140.8, 135.7, 135.3, 130.6, 129.6, 129.6, 128.4, 128.0, 126.1, 26.9, 20.7.

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[41] Wirth, H. O.; Kern, W.; Schmitz, E. *Makromol. Chem.* **1963**, *68*, 69-99.

4-Acetyl-4'-methoxybiphenyl (Table 1, entry 2) [13021-18-6].[42] Procedure A was followed, using 4'-chloroacetophenone (147 mg, 0.951 mmol), 4-methoxyphenylboronic acid (158 mg, 1.04 mmol), KF (184 mg, 3.16 mmol), $Pd_2(dba)_3$ (4.4 mg, 0.0048 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.050 mL, 0.010 mmol), and THF (1.8 mL). After 10 hours at room temperature, workup and column chromatography (60% CH_2Cl_2/hexane) yielded 209 mg (97%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H), 2.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.8, 160.0, 145.5, 135.4, 132.4, 129.1, 128.5, 126.7, 114.5, 55.6, 26.9.

4,4'-Diacetylbiphenyl (Table 1, entry 3). Procedure A was followed, using 4'-chloroacetophenone (123 mg, 0.797 mmol), 4-acetylphenylboronic acid (140 mg, 0.855 mmol), KF (155 mg, 2.67 mmol), $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.040 mL, 0.0080 mmol), and THF (2.4 mL). After 24 hours at room temperature, workup and column chromatography (1.5% EtOAc/ CH_2Cl_2) yielded 151 mg (80%) of the title compound as a white solid, which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

2-*o*-Tolylpyridine (Table 1, entry 4) [10273-89-9].[43] Procedure A was followed, using 2-chloropyridine (138 mg, 1.22 mmol), *o*-tolylboronic acid (184 mg, 1.35 mmol), KF (233 mg, 4.02 mmol), $Pd_2(dba)_3$ (5.6 mg, 0.0061 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.065 mL, 0.013 mmol), and THF (2.4 mL). After 24 hours at room temperature, workup and column chromatography (30% Et_2O/hexane) yielded 200 mg (97%) of the title compound as a pale-yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.70 (ddd, *J* = 4.8 Hz, 1.8 Hz, 0.9 Hz, 1H), 7.74 (apparent td, 1H), 7.42–7.38 (m, 2H), 7.31–7.22 (m, 4H), 2.36 (s, 3H). ^{13}C

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42 Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434-5444.

43 Terashima, M.; Seki, K.-I.; Yoshida, C.; Ohkura, K.; Kanaoka, Y. *Chem. Pharm. Bull.* **1985**, *33*, 1009-1015.

NMR ($CDCl_3$, 75 MHz): δ 160.1, 149.3, 140.5, 136.2, 135.9, 130.9, 129.7, 128.4, 126.0, 124.2, 121.8, 20.5.

3-*o*-Tolylpyridine (Table 1, entry 5) [90395-49-6].[44] Procedure A was followed, using 3-chloropyridine (97.3 mg, 0.857 mmol), *o*-tolylboronic acid (129 mg, 0.946 mmol), KF (174 mg, 2.99 mmol), $Pd_2(dba)_3$ (11.8 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.13 mL, 0.026 mmol), and THF (1.6 mL). After 72 hours at room temperature, workup and column chromatography (50% Et_2O/hexane) yielded 117 mg (80%) of the title compound as a clear, colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.61–8.58 (m, 2H), 7.66 (ddd, *J* = 7.8 Hz, 2.4 Hz, 1.8 Hz, 1H), 7.38–7.20 (m, 5H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.9, 148.1, 138.1, 137.5, 136.6, 135.7, 130.6, 130.0, 128.2, 126.2, 123.1, 20.7.

2-Acetyl-5-*o*-tolylthiophene (Table 1, entry 6). Procedure B was followed, using 2-acetyl-5-chlorothiophene (143 mg, 0.889 mmol), *o*-tolylboronic acid (140 mg, 1.03 mmol), KF (172 mg, 2.96 mmol), $Pd_2(dba)_3$ (4.1 mg, 0.0045 mmol), P(*t*-Bu)$_3$ (10 wt% solution in hexane; 0.025 mL, ~0.0090 mmol), and THF (1.8 mL). After 7 hours at room temperature, workup and column chromatography (15% Et_2O/hexanes) yielded 190 mg (99%) of the title compound as a pale-yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.67 (d, *J* = 3.9 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.30–7.21 (m, 3H), 7.08 (d, *J* = 3.9 Hz, 1H), 2.58 (s, 3H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.7, 152.1, 143.7, 136.1, 133.2, 132.7, 131.1, 130.3, 128.9, 127.6, 126.2, 26.9, 21.4. IR (neat, cm^{-1}): 3062, 3014, 2955, 2923, 2865, 1661, 1600, 1530, 1490, 1452, 1380, 1359, 1336, 1274, 1076, 1034, 925, 813, 762, 722. HRMS Calcd for $C_{13}H_{12}OS$: 216.0609. Found: 216.0605.

4-Methoxy-2'-methylbiphenyl (Table 2, entry 1) [92495-54-0].[42] Procedure A was followed, using 4-chloroanisole (130 mg, 0.910 mmol), *o*-tolylboronic acid

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[44] Ohkura, K.; Terashima, M.; Kanaoka, Y.; Seki, K.-I. *Chem. Pharm. Bull.* **1993**, *41*, 1920-1924.

(134 mg, 0.986 mmol), KF (176 mg, 3.03 mmol), $Pd_2(dba)_3$ (12.6 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.21 mL, 0.041 mmol), and THF (1.6 mL). After 40 hours at 70 °C, workup and column chromatography (1% Et_2O/hexane) yielded 156 mg (87%) of the title compound as a clear, colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.27–7.21 (m, 6H), 6.95 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.6, 141.6, 135.6, 134.5, 130.4, 130.4, 130.0, 127.1, 125.9, 113.6, 55.5, 20.8.

4-Aminobiphenyl (Table 2, entry 2). Procedure B was followed, using 4-chloroaniline (151 mg, 1.18 mmol), phenylboronic acid (156 mg, 1.28 mmol), KF (230 mg, 3.96 mmol), $Pd_2(dba)_3$ (16.3 mg, 0.018 mmol), P(*t*-Bu)$_3$ (0.19 M stock solution; 0.28 mL, 0.053 mmol), and dioxane (2.1 mL). After 29 hours at 90 °C, workup and column chromatography (40% Et_2O/hexane) yielded 164 mg (82%) of the title compound as a yellowish-orange solid, which was identical to authentic material (Aldrich) by ^1H NMR, GC, and TLC.

1-Cyclopentyl-4-methylbenzene (Table 2, entry 3) [827-55-4].[45] Procedure A was followed, using 4-chlorotoluene (127 mg, 1.00 mmol), cyclopentylboronic acid (130 mg, 1.14 mmol), KF (205 mg, 3.54 mmol), $Pd_2(dba)_3$ (13.6 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.22 mL, 0.044 mmol), and dioxane (1.8 mL). After 37 hours at 100 °C, workup and column chromatography (hexane) yielded 121 mg (75%) of the title compound as a clear, colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.14 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 2.95 (apparent quintet, 1H), 2.32 (s, 3H), 2.10–1.99 (m, 2H), 1.86–1.50 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.6, 135.3, 129.1, 127.2, 45.8, 34.9, 25.7, 21.2.

2,2'-Dimethylbiphenyl (Table 3, entry 1). Procedure B was followed, using 2-chlorotoluene (101 mg, 0.795 mmol), *o*-tolylboronic acid (124 mg, 0.91 mmol), KF

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45 Batke, B.; Lauterbach, G.; Pritzkow, W.; Sebald, F.; Voerckel, V. *J. Prakt. Chem.* **1988**, *330*, 671-673.

(153 mg, 2.63 mmol), $Pd_2(dba)_3$ (11.4 mg, 0.012 mmol), P(*t*-Bu)$_3$ (0.19 M stock solution; 0.15 mL, 0.029 mmol), and THF (1.4 mL). After 12 hours at 60 °C, workup and column chromatography (hexane) yielded 138 mg (95%) of the title compound as a colorless liquid, which was identical to authentic material (TCI) by ^{1}H NMR, GC, and TLC.

2,6,2'-Trimethylbiphenyl (Table 3, entry 2) [10273-87-7].[46] Procedure A was followed, using 2-chloro-*m*-xylene (115 mg, 0.818 mmol), *o*-tolylboronic acid (125 mg, 0.918 mmol), KF (159 mg, 2.73 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.012 mmol), PCy_3 (0.20 M stock solution; 0.17 mL, 0.034 mmol), and THF (1.4 mL). After 48 hours at 60 °C, workup and column chromatography (hexane) yielded 143 mg (89%) of the title compound as a colorless liquid, which was contaminated with 4% (by ^{1}H NMR and GC) of 2,2'-dimethylbiphenyl, the product of homocoupling of the boronic acid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31–7.09 (m, 6H), 7.03–6.99 (m, 1H), 1.97 (s, 3H), 1.94 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.2, 140.7, 136.0, 135.8, 130.1, 129.0, 127.4, 127.1, 127.1, 126.2, 20.6, 19.7.

2,4,6,2'-Tetramethylbiphenyl (Table 3, entry 3) [89970-02-5].[11] Procedure A was followed, using 2-chlorotoluene (98.9 mg, 0.781 mmol), 2,4,6-trimethylphenylboronic acid (195 mg, 1.18 mmol), K_3PO_4 (331 mg, 1.56 mmol), $Pd_2(dba)_3$ (10.6 mg, 0.012 mmol), PCy_3 (0.20 M stock solution; 0.17 mL, 0.035 mmol), and toluene (1.4 mL). After 37 hours at 90 °C, workup and column chromatography (hexane) yielded 148 mg (90%) of the title compound as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29–7.19 (m, 3H), 7.02–6.99 (apparent t, 1H), 6.94 (s, 2H), 2.33 (s, 3H), 1.97 (s, 3H), 1.91 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.7, 138.3, 136.5, 136.0, 135.9, 130.0, 129.3, 128.1, 127.0, 126.1, 21.4, 20.5, 19.8.

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[46] Kamikawa, T.; Hayashi, T. *Synlett* **1997**, 163-164.

4-Chlorobiphenyl (Table 4, entry 1) [2051-62-9].[47] Procedure A was followed, using 4-iodochlorobenzene (274 mg, 1.15 mmol), phenylboronic acid (140 mg, 1.15 mmol), KF (207 mg, 3.56 mmol), $Pd_2(dba)_3$ (5.3 mg, 0.0058 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.070 mL, 0.014 mmol), and THF (2.2 mL). After 48 hours at room temperature, workup and column chromatography (hexane) yielded 210 mg (97%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56–7.32 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.1, 139.7, 133.5, 129.0, 129.0, 128.5, 127.7, 127.1.

4-Chlorobiphenyl (Table 4, entry 2). Procedure A was followed, using 4-bromochlorobenzene (215 mg, 1.12 mmol), phenylboronic acid (136 mg, 1.11 mmol), KF (193 mg, 3.33 mmol), $Pd_2(dba)_3$ (5.1 mg, 0.0056 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.065 mL, 0.013 mmol), and THF (2.2 mL). After 3 hours at room temperature, workup and column chromatography (hexane) yielded 205 mg (97%) of the title compound as a white solid. Spectroscopic data were the same as that reported for Table 4, entry 1.

4-Trifluoromethanesulfonyloxybiphenyl (Table 4, entry 3) [17763-78-9].[48] Procedure A was followed, using 4-bromophenyl trifluoromethanesulfonate (232 mg, 0.759 mmol), phenylboronic acid (92.2 mg, 0.756 mmol), KF (131 mg, 2.26 mmol), $Pd_2(dba)_3$ (3.5 mg, 0.0038 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.045 mL, 0.0090 mmol), and THF (1.5 mL). After 3 hours at room temperature, workup and column chromatography (3% Et_2O/hexane) yielded 227 mg (99%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64–7.31 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.0, 141.8, 139.4, 129.1, 129.0, 128.2, 127.3, 121.8, 118.9 (q, $J_{C\text{-}F}$ = 318 Hz).

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47 Klement, I.; Rottlander, M.; Tucker, C. E.; Majid, T. N.; Knochel, P. *Tetrahedron* **1996**, *52*, 7201-7220.

48 Kamikawa, T.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 7087-7090.

4'-Trifluoromethanesulfonyloxy-2-methylbiphenyl (Table 4, entry 4). Procedure A was followed, using 4-chlorophenyl trifluoromethanesulfonate (276 mg, 1.06 mmol), *o*-tolylboronic acid (146 mg, 1.07 mmol), KF (186 mg, 3.20 mmol), $Pd_2(dba)_3$ (14.4 mg, 0.016 mmol), P(*t*-Bu)$_3$ (0.19 M stock solution; 0.165 mL, 0.031 mmol), and THF (2.0 mL). After 24 hours at room temperature, workup and column chromatography (3% Et_2O/hexane) yielded 319 mg (95%) of the title compound as a clear, colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.44–7.36 (m, 2H), 7.33–7.17 (m, 6H), 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.6, 142.5, 140.0, 135.3, 131.1, 130.6, 129.8, 128.1, 126.1, 121.1, 118.9 (q, J_{C-F} = 318 Hz), 20.6. IR (neat, cm^{-1}): 3064, 3022, 2957, 2928, 2865, 1595, 1506, 1483, 1426, 1213, 1178, 1140, 1103, 1091, 1021, 1010, 886, 845, 810, 780, 762, 732, 683. HRMS Calcd for $C_{14}H_{11}F_3SO_3$: 316.0381. Found: 316.0375.

4'-Chloro-2-methylbiphenyl (Table 4, entry 5) [89346-57-6].[49] Procedure A was followed, using 4-chlorophenyl trifluoromethanesulfonate (272 mg, 1.04 mmol), *o*-tolylboronic acid (145 mg, 1.06 mmol), KF (182 mg, 3.13 mmol), $Pd(OAc)_2$ (7.1 mg, 0.032 mmol), PCy_3 (0.20 M stock solution; 0.31 mL, 0.062 mmol), and THF (0.75 mL). After 48 hours at room temperature, workup and column chromatography (hexane) yielded 190 mg (90%) of the title compound as a colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37 (d, *J* = 8.7 Hz, 2H), 7.28–7.16 (m, 6H), 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.8, 140.4, 135.4, 132.9, 130.6, 130.5, 129.8, 128.4, 127.7, 126.0, 20.7.

Competition experiment between an aryl bromide and an aryl triflate (eq 1). In a glove box, $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), phenylboronic acid (151 mg, 1.24 mmol), and KF (214 mg, 3.69 mmol) were added to a 4 mL screw-cap vial equipped with a stir bar. 4-ethylbromobenzene (228 mg, 1.23 mmol), *p*-tolyltriflate (0.22 mL, 1.23 mmol) and THF (2.4 mL) were added to a separate 20

[49] Ikoma, Y.; Ando, K.; Naoi, Y.; Akiyama, T.; Sugimori, A. *Synth. Commun.* **1991**, *21*, 481-487.

mL screw-cap vial. This solution was then added via pipette to the 4 mL vial. PCy_3 (0.20 M stock solution in THF; 0.075 mL, 0.015 mmol) was then added via syringe. The reaction mixture was stirred at room temperature and monitored by GC. After 46 hours GC analysis indicated > 95% conversion with respect to the aryl bromide and the only product that could be detected was 4-ethylbiphenyl; 4-phenyltoluene, which would arise from coupling with the aryl triflate, was not observed.

Competition experiment between an aryl chloride and an aryl triflate (eq 2). In a glove box, $Pd_2(dba)_3$ (6.3 mg, 0.0069 mmol), phenylboronic acid (171 mg, 1.40 mmol), and KF (249 mg, 4.29 mmol) were added to a 4 mL screw-cap vial equipped with a stir bar. 4'-Chloroacetophenone (217 mg, 1.40 mmol), 4-acetylphenyltriflate (366 mg, 1.37 mmol), 2-phenyltoluene (internal standard; 114 mg, 0.68 mmol), and THF (2.8 mL) were added to a separate 20 mL screw-cap vial. This solution was then added via pipette to the 4 mL vial. P(*t*-Bu)$_3$ (0.21 M stock solution in THF; 0.065 mL, 0.014 mmol) was then added via syringe. The reaction mixture was stirred at room temperature for 25 hours, at which time GC analysis showed no further progress. The reaction was worked up in the usual way. ^{1}H NMR analysis of the unpurified mixture showed 4'-chloroacetophenone, 4-acetylphenyltriflate, 4-acetylbiphenyl, and the internal standard 2-phenyltoluene in a ratio of 2.77 : 37.14 : 40.20 : 19.89, respectively. This corresponds to a 7% recovery of the aryl chloride, a 93% recovery of the aryl triflate, and a 98% yield of 4-acetylbiphenyl.

2-Cyano-4'-methylbiphenyl (Table 5, entry 1). Procedure A was followed, using 2-chlorobenzonitrile (772 mg, 5.61 mmol), *p*-tolylboronic acid (867 mg, 6.37 mmol), KF (1.09 g, 18.8 mmol), $Pd_2(dba)_3$ (2.6 mg, 0.0028 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.028 mL, 0.0056 mmol), and THF (11 mL). After 24 hours at room temperature, workup and column chromatography (10% Et_2O/hexane)

yielded 1.06 g (98%) of 2-cyano-4'-methylbiphenyl as a white solid, which was identical to authentic material (Alfa-Aesar) by ^{1}H NMR, GC, and TLC.

2-Cyano-4'-methylbiphenyl (Table 5, entry 2). Procedure A was followed, using 2-chlorobenzonitrile (4.19 g, 30.4 mmol), *p*-tolylboronic acid (4.65 g, 34.2 mmol), KF (5.87 g, 101 mmol), $Pd_2(dba)_3$ (1.4 mg, 0.0015 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.015 mL, 0.0030 mmol), and dioxane (30 mL). After 25 hours at 90 °C, workup and column chromatography (10% Et_2O/hexane) yielded 5.73 g (97%) of 2-cyano-4'-methylbiphenyl as a white solid, which was identical to authentic material (Alfa-Aesar) by ^{1}H NMR, GC, and TLC.

4-Phenyltoluene (Table 5, entry 3). Procedure A was followed, using chlorobenzene (831 mg, 7.38 mmol), *p*-tolylboronic acid (1.10 g, 8.12 mmol), KF (1.42 g, 24.4 mmol), $Pd_2(dba)_3$ (3.4 mg, 0.0037 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.043 mL, 0.0086 mmol), and dioxane (7.4 mL). After 43 hours at 100 °C, workup and column chromatography (hexane) yielded 1.14 g (92%) of 4-phenyltoluene as a white solid, which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

1-*p*-Tolylcyclopentene (Table 6, entry 1) [827-56-5].[50] Procedure A was followed, using 1-chlorocyclopentene (91 mg, 0.89 mmol), *p*-tolylboronic acid (138 mg, 1.02 mmol), KF (174 mg, 3.00 mmol), $Pd_2(dba)_3$ (12.2 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.155 mL, 0.032 mmol), and THF (1.6 mL). After 44 hours at 50 °C, workup and column chromatography (hexane) yielded 131 mg (93%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.12 (apparent quintet, 1H), 2.73–2.65 (m, 2H), 2.55–2.48 (m, 2H), 2.33 (s, 3H), 2.00 (apparent quintet, 2H). ^{13}C

[50] Kamigata, N.; Fukushima, T.; Satoh, A.; Kameyama, M. *J. Chem. Soc., Perkin. Trans. 1* **1990**, 549-553.

NMR ($CDCl_3$, 75 MHz): δ 142.5, 136.7, 134.2, 129.2, 125.7, 125.3, 33.5, 33.4, 23.6, 21.4.

1-*o*-Tolyl-4-*t*-butylcyclohexene (Table 6, entry 2). Procedure B was followed, using 1-chloro-4-*t*-butylcyclohexene (180 mg, 1.04 mmol), *o*-tolylboronic acid (154 mg, 1.13 mmol), KF (196 mg, 3.38 mmol), $Pd_2(dba)_3$ (14.3 mg, 0.016 mmol), P(*t*-Bu)$_3$ (0.19 M stock solution; 0.195 mL, 0.037 mmol), and THF (1.9 mL). After 40 hours at 60 °C, workup and column chromatography (hexane) yielded 225 mg (95%) of the title compound as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16–7.04 (m, 4H), 5.57–5.53 (m, 1H), 2.32–2.14 (m, 3H), 2.28 (s, 3H), 2.00–1.88 (m, 2H), 1.44–1.25 (m, 2H), 0.92 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.4, 138.7, 135.2, 130.1, 128.4, 126.5, 126.0, 125.6, 44.1, 32.6, 31.9, 27.6, 27.4, 24.8, 20.2. IR (neat, cm^{-1}): 3058, 3014, 2946, 2838, 1663, 1479, 1434, 1393, 1378, 1365, 836, 754, 726. HRMS Calcd for $C_{17}H_{24}$: 228.1878. Found: 228.1883.

2-Methyl-1-*o*-tolylpropene (Table 6, entry 3) [5916-21-2].[51] Procedure A was followed, using 1-chloro-2-methylpropene (0.10 mL, 1.0 mmol), *o*-tolylboronic acid (147 mg, 1.08 mmol), KF (194 mg, 3.35 mmol), $Pd_2(dba)_3$ (13.6 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.18 mL, 0.036 mmol), and THF (1.8 mL). After 48 hours at 50 °C, workup and column chromatography (hexane) yielded 114 mg (77%) of the title compound as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14–7.12 (m, 4H), 6.21 (br s, 1H), 2.23 (s, 3H), 1.91 (d, J = 1.5 Hz, 3H), 1.70 (d, J = 1.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 136.5, 135.2, 129.7, 129.5, 126.3, 125,4, 124.2, 26.4, 20.2, 19.6.

Competition experiment between an aryl chloride and a vinyl chloride (eq 3). Procedure A was followed, using chlorobenzene (132 mg, 1.17 mmol), 1-chlorocyclopentene (0.115 mL, 1.16 mmol), *o*-tolylboronic acid (157 mg, 1.16

[51] Rottendorf, H.; Sternhell, S.; Wilmshurst, J. R. *Aust. J. Chem.* **1965**, *18*, 1759-1773.

mmol), KF (201 mg, 3.46 mmol), $Pd_2(dba)_3$ (16.1 mg, 0.018 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.205 mL, 0.042 mmol), and THF (2.2 mL). After 14 hours at 60 °C, workup and column chromatography (hexane) yielded 0.184 g of a mixture of 2-phenyltoluene and 1-(*o*-tolyl)cyclopentene. ^{1}H NMR showed a 64.3 : 35.7 ratio of 2-phenyltoluene : 1-(*o*-tolyl)cyclopentene, which corresponds to a 62% yield of 2-phenyltoluene and a 34% yield of 1-(*o*-tolyl)cyclopentene.

^{1}H and ^{31}P NMR studies of $Pd_2(dba)_3$/P(*t*-Bu)$_3$. In a glove box, $Pd_2(dba)_3$ (11.3 mg, 0.012 mmol) and THF-d_8 (~0.5 mL) were added to a resealable NMR tube, resulting in a dark-red, heterogenous solution. P(*t*-Bu)$_3$ (0.20 M stock solution in THF-d_8; 0.06 mL, 0.012 mmol) was added to the NMR tube, and the NMR tube was sealed with a teflon screw cap, removed from the glove box, and examined by NMR. The ^{31}P NMR spectrum showed a single resonance for Pd(P(*t*-Bu)$_3$)$_2$ at δ 85.6. The ^{1}H NMR spectrum showed a 1:2:1 triplet for Pd(P(*t*-Bu)$_3$)$_2$ at δ 1.48 and a tiny unidentified doublet at δ 1.27 (J = 12 Hz), along with bound and unbound dba. The NMR tube was then taken back into the glove box, and more P(*t*-Bu)$_3$ (0.06 mL, 0.012 mmol) was added. The ^{31}P and ^{1}H NMR spectra showed no change from before, except that there was more free dba in the ^{1}H NMR spectrum. The NMR tube was then taken back into the glove box, and more P(*t*-Bu)$_3$ (0.06 mL, 0.012 mmol) was added. The ^{31}P and ^{1}H NMR spectra again showed no change from before, except that there was more free dba in the ^{1}H NMR spectrum. The reaction mixture in the NMR tube had become essentially homogenous and was lighter red than before. The NMR tube was then taken back into the glove box, and more P(*t*-Bu)$_3$ (0.06 mL, 0.012 mmol) was added (P(*t*-Bu)$_3$:Pd = 2:1). The ^{31}P NMR spectrum now showed for the first time the presence of a small amount of free P(*t*-Bu)$_3$ at δ 63.4, in addition to Pd(P(*t*-Bu)$_3$)$_2$ at δ 85.6. The ^{1}H NMR spectrum also showed free P(*t*-Bu)$_3$ (δ 1.30, J = 10 Hz); the tiny doublet at δ 1.27 was gone, and essentially all of the dba

was unbound. The reaction mixture was lime-green, and a small amount of a black solid had formed. Addition of 2 more equivalents of P(*t*-Bu)$_3$ resulted in no new phosphorus-containing species.

^{1}H and ^{31}P NMR studies of the Suzuki cross-coupling of 3-chloropyridine and *o*-tolylboronic acid. In a glove box, $Pd_2(dba)_3$ (6.1 mg, 0.0067 mmol), *o*-tolylboronic acid (45.4 mg, 0.33 mmol), and KF (58.9 mg, 1.01 mmol) were placed into a resealable NMR tube. THF-d_8 (0.74 mL), 3-chloropyridine (0.025 mL, 29.8 mg, 0.26 mmol), and P(*t*-Bu)$_3$ (0.20 M stock solution in THF; 0.065 mL, 0.013 mmol) were then added, and the NMR tube was sealed with a teflon screw cap and examined by ^{31}P and ^{1}H NMR over the course of several days. The progress of the reaction could be monitored by ^{1}H NMR by the decrease in intensity of the signal for the methyl group of the boronic acid and the increase in intensity of the signal for the methyl group of the product. During this time, essentially the only species detectable by ^{31}P NMR was Pd(P(*t*-Bu)$_3$)$_2$ at δ 85.6 [At short reaction times (i.e., 0.5-6.0 h), a very small peak at δ 90.7 could be observed, but it was not be detectable at longer reaction times.].

Suzuki coupling of 3-chloropyridine and *o*-tolylboronic acid using 3.0% Pd(P(*t*-Bu)$_3$)$_2$ as catalyst (eq 4). Procedure A was followed, using 3-chloropyridine (80 mg, 0.70 mmol), *o*-tolylboronic acid (106 mg, 0.78 mmol), KF (136 mg, 2.34 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (10.5 mg, 0.021 mmol), undecane (internal standard; 37.0 mg, 0.24 mmol), and THF (1.4 mL). After 23 hours at room temperature, GC analysis showed 7% conversion with respect to 3-chloropyridine.

Suzuki coupling of 3-chloropyridine and *o*-tolylboronic acid using 1.5% Pd(P(*t*-Bu)$_3$)$_2$/0.75% $Pd_2(dba)_3$ as catalyst (eq 4). Procedure A was followed, using 3-chloropyridine (95 mg, 0.84 mmol), *o*-tolylboronic acid (121 mg, 0.89 mmol), KF (157 mg, 2.70 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (6.6 mg, 0.013 mmol), $Pd_2(dba)_3$

(5.9 mg, 0.0064 mmol), undecane (internal standard; 32.5 mg, 0.21 mmol), and THF (1.7 mL). After 23 hours at room temperature, GC analysis showed 91% conversion with respect to 3-chloropyridine.

4-Trifluoromethanesulfonyloxybiphenyl (Table 7, entry 1). Procedure A was followed, using 4-chlorophenyl trifluoromethanesulfonate (239 mg, 0.916 mmol), phenylboronic acid (115 mg, 0.940 mmol), KF (167 mg, 2.87 mmol), $Pd_2(dba)_3$ (12.7 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.21 M stock solution; 0.065 mL, 0.014 mmol), and THF (1.8 mL). After 24 hours at room temperature, workup and column chromatography (3% Et_2O/hexane) yielded 268 mg (97%) of the title compound as a white solid. Spectroscopic data were the same as that reported for Table 4, entry 3.

4-Trifluoromethanesulfonyloxybiphenyl (Table 7, entry 2). Procedure A was followed, using 4-chlorophenyl trifluoromethanesulfonate (234 mg, 0.897 mmol), phenylboronic acid (109 mg, 0.891 mmol), KF (164 mg, 2.83 mmol), $Pd_2(dba)_3$ (12.4 mg, 0.0135 mmol), P(*t*-Bu)$_3$ (0.21 M stock solution; 0.026 mL, 0.0055 mmol), and THF (1.8 mL). After 32 hours at room temperature, workup and column chromatography (3% Et_2O/hexane) yielded 252 mg (93%) of the title compound as a white solid. Spectroscopic data were the same as that reported for Table 4, entry 3.

4-Acetyl-2'-methylbiphenyl (Table 7, entry 3). Procedure A was followed, using 4'-chloroacetophenone (154 mg, 0.993 mmol), *o*-tolylboronic acid (146 mg, 1.07 mmol), KF (190 mg, 3.26 mmol), $Pd_2(dba)_3$ (4.7 mg, 0.0050 mmol), P(*t*-Bu)$_3$ (0.074 M stock solution; 0.028 mL, 0.0020 mmol), and THF (2.0 mL). After 8 hours at room temperature, workup and column chromatography (10% Et_2O/ hexane) yielded 206 mg (99%) of the title compound as a pale-yellow liquid. Spectroscopic data were the same as that reported for Table 1, entry 1.

4-Methoxy-2'-methylbiphenyl (Table 7, entry 4). Procedure A was followed, using 4-chloroanisole (138 mg, 0.969 mmol), *o*-tolylboronic acid (151 mg, 1.11 mmol), KF (207 mg, 3.56 mmol), $Pd_2(dba)_3$ (13.5 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.21 M stock solution; 0.07 mL, 0.015 mmol), and THF (1.8 mL). After 10 hours at 70 °C, workup and column chromatography (1% Et_2O/hexane) yielded 144 mg (75%) of the title compound as a clear, colorless liquid. Spectroscopic data were the same as that reported for Table 2, entry 1.

Part 2:

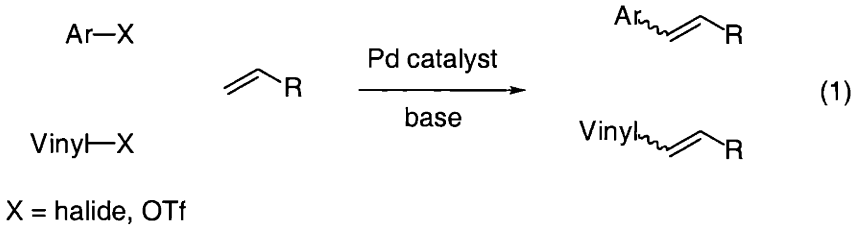
Heck Coupling using Pd/P(*t*-Bu)$_3$ Catalyst Systems

Chapter 3:

Heck Coupling of Aryl Chlorides using Pd/P(*t*-Bu)$_3$/Cs_2CO_3

Introduction

The Heck reaction, first discovered by Mizoroki and Heck in the early 1970's,[1] is the palladium-catalyzed coupling of aryl and vinyl halides and triflates with olefins (eq 1).[2] In contrast to many cross-coupling reactions, nickel-based catalysts are usually ineffective for the Heck reaction.[3] "Ligandless" palladium catalysts such as simple $Pd(OAc)_2$ are commonly employed for reactive substrates such as aryl iodides, while for Heck reactions of less reactive aryl bromides, triarylphosphines such as PPh_3 or more commonly $P(o\text{-tol})_3$ are usually used together with an appropriate palladium source. Like many palladium-catalyzed coupling reactions, such as the Suzuki and Stille reaction, the Heck reaction is a very functional-group tolerant reaction. The ready availability and low cost of simple olefins also contribute to the exceptional utility of the Heck reaction.



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1 (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320-2322.

2 For reviews of the Heck reaction, see: (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; Chapter 3. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009-3066. (c) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3. (d) Heck R. F. *Org. React.* **1982**, *27*, 345-390. (e) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427-436. (f) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379-2411. (g) Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1996; Vol. 5, pp. 153-260. (h) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2-7.

3 (a) Geissler, H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: New York, 1998; p. 166 (b) Beller, M.; Riermeier, T. H.; Stark, G. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: New York, 1998; p 214. (c) Herrmann, W. A. In *Applied Homogeneous Catalysis with Organometallic Compounds. A Comprehensive Handbook*; Cornils, B., Herrmann, W. A., Eds.; VCH: New York, 1996; p 713. (d) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, p 834.

All of the above-mentioned considerations make the Heck reaction a very powerful tool for carbon-carbon bond formation, and as such it has been widely used in areas such as natural products synthesis,[4,5] materials science,[6] bioorganic chemistry,[7] and pharmaceuticals.[8] Industrial applications include the production of the non-steroidal anti-inflammatory drug, Naproxen™,[9] the herbicide Prosulfuron™,[10] and octylmethoxycinnamate, which is the most common UV-B sunscreen on the market (eq 2).[11,12]

The mechanism of the Heck reaction is quite different from that of cross-coupling reactions, although the first step, the oxidative addition of an aryl or vinyl halide/triflate to Pd(0), is the same (Figure 1). Thus, the poor reactivity of aryl chlorides is a serious limitation that the Heck reaction shares with cross-

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4 For example, see: (a) Taxol: Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843-2859. (b) Scopadulcic acid: Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042-2044.

5 For overviews of applications of the Heck reaction in natural products synthesis, see: (a) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 6. (b) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; Chapter 3.6. (c) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: New York, 1996; Chapter 31. These authors refer to the Heck reaction as "one of the true power tools" of contemporary organic synthesis" (p. 566).

6 For example, see: (a) *Step-Growth Polymers for High-Performance Materials*; Hedrick, J. L., Labadie, J. W., Eds.; ACS Symp. Ser. 624; American Chemical Society: Washington, DC, 1996; Chapters 1, 2, and 4. (b) DeVries, R. A.; Vosejpka, P. C.; Ash, M. L. *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, 1998; Chapter 37. (c) Tietze, L. F.; Kettschau, G.; Heuschert, U.; Nordmann, G. *Chem. Eur. J.* **2001**, *7*, 368-373.

7 For some recent examples, see: (a) Haberli, A.; Leumann, C. J. *Org. Lett.* **2001**, *3*, 489-492. (b) Burke, T. R., Jr.; Liu, D.-G.; Gao, Y. *J. Org. Chem.* **2000**, *65*, 6288-6292.

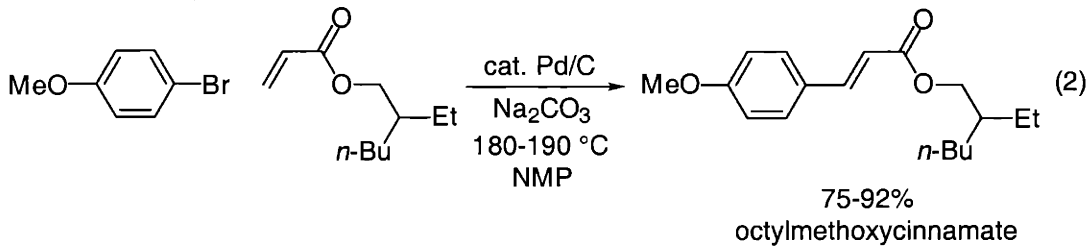
8 (a) Shinkai, I.; King, A. O.; Larsen, R. D. *Pure & Appl. Chem.* **1994**, *66*, 1551-1556. (b) Larsen, R. D.; Corley, E. G.; King, A. O.; Carrol, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398-3405. (c) Kehr, C.; Neidlein, R.; Engh, R. A.; Brandstetter, H.; Kucznierz, R.; Leinert, H.; Marzenell, K.; Strein, K.; von der Saal, W. *Helv. Chem. Acta* **1997**, *80*, 892-896.

9 Stinson, S. C. *Chem. Eng. News* January 18, 1999, p 81.

10 Baumeister, P.; Meyer, W.; Oertle, K.; Seifert, G.; Siegrist, U.; Steiner, H. In *Heterogenous Catalysis and Fine Chemicals IV.;* Blaser, H. U.; Baiker, A.; Prins, R., Eds.; Elsevier Science: Amsterdam, 1997; p 37.

11 Eisenstadt, A. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, 1998; Chapter 33.

12 For a recent overview of the application of the Heck reaction towards the production of fine chemicals, see: de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086-1092.



coupling reactions. In contrast to many cross-coupling reactions, prior to 1999 a significant amount of progress had already been made regarding the use of aryl chlorides in Heck reactions.

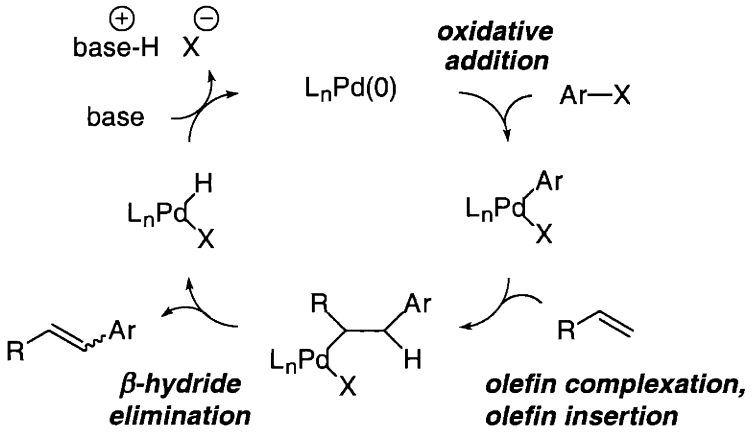


Figure 1. Outline of the catalytic cycle for the Heck coupling reaction.

In 1984, Spencer had reported modest success in Heck couplings of activated aryl chlorides with electron-deficient alkenes at 150 °C using catalytic $Pd(OAc)_2/PPh_3$ (23-45% yield).[13] Davison was the first to observe some success in Heck reactions of electron-neutral aryl chlorides using the chelating bisphosphine 1,2-bis(diphenylphosphino)ethane, which allowed for couplings of chlorobenzene with styrene in modest (44-56%) yields at 130 °C.[14]

[13] Spencer, A. *J. Organomet. Chem.* **1984**, *270*, 115-120.
[14] Davison, J. B.; Simon, N. M.; Sojka, S. A. *J. Mol. Cat.* **1984**, 22, 349-352.

Subsequently, Milstein and coworkers demonstrated that the bulky, electron-rich chelating bisphosphines 1,4-bis(diisopropylphosphino)butane and 1,3-bis(diisopropylphosphino)propane could be used to effect arylations of styrene at 140-150 °C using aryl chlorides; noteworthy is that even electron-rich 4-chloroanisole could participate in these couplings, albeit in modest (49%) yield.[15] Some success in Heck couplings of 4-chloroanisole (with *n*-butyl acrylate) had also been noted by Herrmann (up to 48% yield) using simple triarylphosphines, such as PPh_3, at 160 °C.[16] Other important contributions in this area have included the use of phosphapalladacycles,[17] *N*-heterocyclic carbenes,[18] phosphites,[19] and tetraphenylphosphonium salts,[20] although all of these systems, with the exception of tetraphenylphosphonium salts (electron-neutral aryl chlorides), are limited to electron-deficient aryl chlorides.[21,22,23]

Prior to our studies, the use of bulky, electron-rich monodentate trialkylphosphines in Heck reactions of aryl chlorides had been briefly explored by other groups with very little success. In Milstein's aforementioned studies, the use of P(*i*-Pr)$_3$ and P(*n*-Bu)(*i*-Pr)$_2$ instead of 1,4-

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15 (a) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995-1996. (b) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734-4735. (c) Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465-3479.

16 Herrmann, W. A.; Brossmer, C.; Ofele, K.; Beller, M.; Fischer, H. *J. Mol. Catal. A* **1995**, *103*, 133-146.

17 (a) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844-1848. (b) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Reirmeier, T. H.; Ofele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357-1364.

18 Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371-2374.

19 Beller, M.; Zapf, A. *Synlett* **1998**, 792-793.

20 Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 481-483.

21 For an example of a tricarbonyl(η^6-arylchloride)chromium complex undergoing Heck reaction, see: Scott, W, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1755-1756.

22 For examples of heterogeneously-catalyzed Heck reactions of aryl chlorides, see: (a) Kaneda, K.; Higuchi, M.; Imanaka, T. *J. Mol. Cat.* **1990**, *63*, L33-L36. (b) Reetz, M. T.; Lohmer, G. *Chem. Commun.* **1996**, 1921-1922.

23 For examples of heteroaryl chlorides participating in Heck reactions, see: Lie, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry;* Pergamon: Amsterdam, 2000 and references therein.

bis(diisopropylphosphino)butane and 1,3-bis(diisopropylphosphino)propane under identical conditions failed to yield significant amounts of desired product. This was primarily attributed to promotion of olefin insertion by the chelating bisphosphine. In 1995, Herrmann conducted an extensive investigation on Heck reactions of aryl chlorides using various monodentate phosphines and observed low conversions when P(*i*-Pr)$_3$ and PCy$_3$ were used as ligands.[16] Interestingly, in neither of these studies was P(*t*-Bu)$_3$ examined.

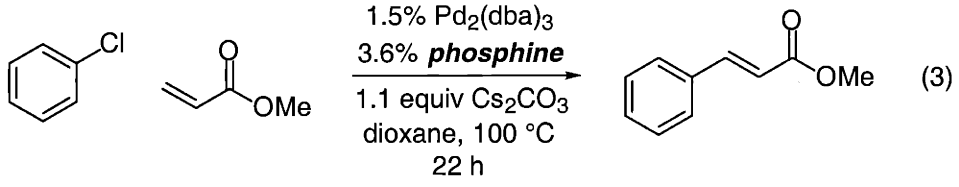
Despite the notable advances mentioned above, several challenges still remained. First, the development of protocols that operate under milder conditions is an important goal; in general, all of the above-mentioned catalyst systems require reaction temperatures of 130 °C or greater. Significant progress had been made regarding electron-deficient and electron-neutral aryl chlorides. However, with the exception of the two previously mentioned Heck reactions involving 4-chloroanisole from the Milstein and Herrmann groups (49 and 48% yield, respectively), electron-rich aryl chlorides had not proven to be viable substrates. In addition, only one example of a Heck reaction of a sterically hindered aryl chloride had been described.[24] Finally, the scope with respect to olefin was severely limited, as no examples of Heck reactions of aryl chlorides with olefins other than styrene and acrylic acid derivatives had been described. It was these limitations that we sought to address when we began our investigations into Pd/P(*t*-Bu)$_3$-catalyzed Heck reactions of aryl chlorides.

Results and Discussion

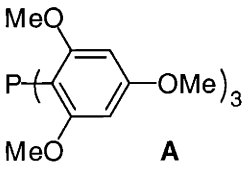
A screening of a variety of commonly used and commercially available phosphines for the Heck coupling of chlorobenzene and methyl acrylate

[24] Coupling of 2-chloro-5-nitrotoluene and *n*-butyl acrylate: reference 19.

revealed that P(*t*-Bu)$_3$ was *uniquely* effective for this transformation (eq 3); 56% GC yield was observed after 22 hours. Triarylphosphines such as P(*o*-tol)$_3$, which is a particularly efficacious ligand for aryl bromides, were totally ineffective. Other trialkylphosphines were also ineffective, including PCy$_3$, which had proven to be reasonably effective in Suzuki couplings of aryl chlorides. Most surprising was that essentially no reaction was observed in the presence of triarylphosphine **A** (eq 3), which has steric and electronic properties that are quite similar to P(*t*-Bu)$_3$ (cone angles: P(*t*-Bu)$_3$, 182°; **A**, 184°) (pK_a of conjugate acid: P(*t*-Bu)$_3$, 11.40; **A**, 11.02).



(3)



A

	% yield (GC)
P(*t*-Bu)$_3$	***56%***
PPh$_3$, P(*o*-tol)$_3$, BINAP, dppf, **A**	***<2%***
P(*n*-Bu)$_3$, Cy$_2$P(CH$_2$)$_2$PCy$_2$, PCy$_3$	***<2%***
no phosphine	***<2%***

Further optimization studies revealed that dioxane was the most suitable solvent. THF and toluene were also reasonable solvents, while commonly used solvents for the Heck reaction such as acetonitrile, DMF, and NMP were considerably poorer choices. In an initial screening of bases for the reaction illustrated in equation 3, Cs_2CO_3 proved to be optimal. Subsequent studies revealed that catalyst stability and overall conversions were considerably improved by using a P(*t*-Bu)$_3$:Pd ratio of 2:1 rather than 1.2:1; under these conditions both K_3PO_4 and NEt$_3$ were also quite effective bases.

Having optimized the reaction conditions, the scope of the $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cs_2CO_3$-catalyzed Heck coupling of aryl chlorides was examined (Table 1). Electron-neutral chlorobenzene reacted smoothly with both methyl acrylate (100 °C; Table 1, entry 1) and styrene (120 °C; Table 1, entry 3). Most significant was that the electron-rich 4-chloroanisole also reacted with either methyl acrylate (Table 1, entry 2) or styrene (Table 1, entry 5) at 120 °C to furnish the desired trans olefin in good yield. While electron-deficient 4'-chloroacetophenone underwent a high-yielding reaction with styrene (Table 1, entry 4), attempts to couple this aryl chloride with methyl acrylate resulted in only a 45% isolated yield of desired product, due to the formation of numerous unidentified side products. A 70% isolated yield could be obtained from the reaction of 2-chlorotoluene and styrene (Table 1, entry 6), albeit at the expense of a reaction time of 114 hours. However, the reaction of 2-chlorotoluene with methyl acrylate resulted in only a modest 45% yield. The use of olefins other than styrene and methyl acrylate such as acrylonitirile and 2,3-dihydrofuran were briefly examined but quickly abandoned, as low conversions and/or messy reactions were observed.

Preliminary investigations into obtaining high turnover numbers revealed that the coupling of chlorobenzene and styrene could be conducted at a catalyst loading of only 0.2% Pd, resulting in an 80% isolated yield of *trans*-stilbene and a turnover number of ~400 (eq 4).

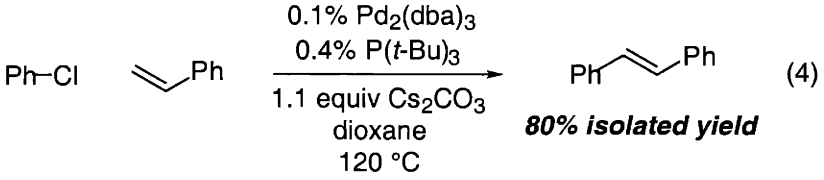


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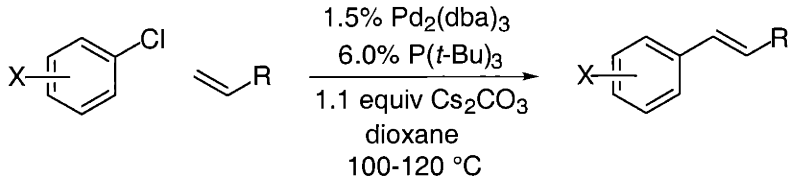
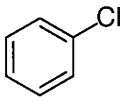
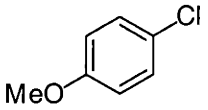
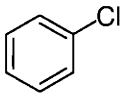
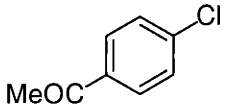
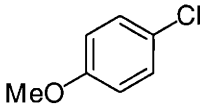
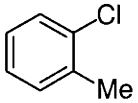
Table 1. Scope of the Heck Coupling of Aryl Chlorides Catalyzed by $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cs_2CO_3$



Entry	Aryl Chloride	R	Temp/Time	Isolated Yield[a,b]
1		CO_2Me	100 °C/42 h	76%
2		CO_2Me	120 °C/24 h	82%
3		Ph	120 °C/21 h	83%
4		Ph	100 °C/37 h	74%
5		Ph	120 °C/30 h	84%
6		Ph	120 °C/114 h	70%

[a]Average of two runs. [b]Only the trans product was detected by ^1H NMR, except for entry 6, which was a ~15:1 trans:cis mixture.

In conclusion, Heck reactions of aryl chlorides with styrene and methyl acrylate can be accomplished in good yields using $Pd_2(dba)_3/P(t\text{-}Bu)_3$ as catalyst as Cs_2CO_3 as base. Among a number of phosphine ligands screened, including similarly bulky and electron-rich phosphines, only $P(t\text{-}Bu)_3$ exhibits the desired high activity, with other phosphines displaying essentially no activity. Relatively high reaction temperatures of 100-120 °C are required, but nonetheless these conditions represent an improvement in terms of mildness over previously reported catalyst systems. The scope of the reaction with respect to aryl chloride

also compares favorably with other systems, as typically unreactive electron-rich aryl chlorides undergo efficient coupling in good yield at 120 °C. Preliminary studies indicate that lower catalyst loadings may be used for these Heck couplings.

While this first-generation protocol represents a significant advance, some limitations still exist. With respect to the scope of the olefin component, $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cs_2CO_3$ does not offer any improvement over existing protocols, as only the activated substrates styrene and methyl acrylate appear to be viable coupling partners. In addition, hindered aryl chlorides are still relatively challenging substrates. The development of a more active and general catalyst for Heck reactions of aryl chlorides was needed to address these and other issues.

Experimental Section

General Considerations. The general considerations are the same as the previous chapters with the following exceptions. Styrene (Aldrich) was purified by distillation. Methyl acrylate (Aldrich) was purified by vacuum transfer.

All yields that are reported in Table 1 are isolated yields and the average of two runs; the yields reported below for a specific experiment may differ from those values.

General Procedure for the $Pd_2(dba)_3/P(t\text{-}Bu)_3$-catalyzed Heck Coupling of Aryl Chlorides. In a Vacuum Atmospheres Glovebox, a dioxane solution of the aryl chloride and a dioxane solution of $P(t\text{-}Bu)_3$ are added in turn to a Schlenk tube charged with $Pd_2(dba)_3$, Cs_2CO_3, and a magnetic stir bar. The olefin (1.10 eq with respect to aryl chloride in the case of styrene; 2.00 eq with respect to aryl chloride in the case of methyl acrylate) is then added by syringe. The Schlenk

tube is sealed with a teflon stopcock, removed from the glovebox, and placed in a 100 or 120 °C oil bath and stirred for the indicated amount of time. At the conclusion of the reaction, the mixture was diluted with Et_2O or EtOAc, filtered through a pad of silica gel with copious washings, concentrated, and purified by column chromatography.

Methyl *trans*-cinnamate (Table 1, entry 1). The general procedure was followed using chlorobenzene (101 mg, 0.898 mmol), methyl acrylate (0.16 mL, 1.78 mmol), Cs_2CO_3 (329 mg, 1.01 mmol), $Pd_2(dba)_3$ (12.7 mg, 0.014 mmol), P(*t*-Bu)$_3$ (11.4 mg, 0.056 mmol) and dioxane (0.90 mL). After 42 hours at 100 °C, workup and column chromatography (5% EtOAc/hexane) yielded 106 mg (73%) of the title compound as a slightly yellow oil which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

***trans*-4-Methoxycinnamaic acid methyl ester (Table 1, entry 2) [3901-07-3].**[25] The general procedure was followed using 4-chloroanisole (125 mg, 0.877 mmol), methyl acrylate (0.16 mL, 1.78 mmol), Cs_2CO_3 (316 mg, 0.969 mmol), $Pd_2(dba)_3$ (12.1 mg, 0.013 mmol), P(*t*-Bu)$_3$ (10.9 mg, 0.054 mmol) and dioxane (0.88 mL). After 24 hours at 120 °C, workup and column chromatography (5% EtOAc/ hexane) yielded 134 mg (79%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 16.0 Hz, 1H), 7.48 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 161.5, 144.7, 129.9, 127.3, 115.4, 114.5, 55.5, 51.7.

***trans*-stilbene (Table 1, entry 3).** The general procedure was followed using chlorobenzene (132 mg, 1.17 mmol), styrene (0.15 mL, 1.31 mmol), Cs_2CO_3 (417 mg, 1.28 mmol), $Pd_2(dba)_3$ (15.9 mg, 0.017 mmol), P(*t*-Bu)$_3$ (14.8 mg, 0.073 mmol) and dioxane (1.17 mL). After 21 hours at 120 °C, workup and column chromatography (hexane) yielded 173 mg (82%) of the title compound as a white

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[25] Nesmelova, E. F.; Sidyakin, G. P. *Chem. Nat. Compd. (Engl. Transl.)* **1973**, *9*, 512.

solid which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

***trans*-4-acetylstilbene (Table 1, entry 4) [20488-42-0].**[26] The general procedure was followed using 4-chloroacetophenone (148 mg, 0.955 mmol), styrene (0.12 mL, 1.05 mmol), Cs_2CO_3 (342 mg, 1.05 mmol), $Pd_2(dba)_3$ (13.0 mg, 0.014 mmol), P(*t*-Bu)$_3$ (11.5 mg, 0.057 mmol) and dioxane (0.96 mL). After 37 hours at 100 °C, workup and column chromatography (40% CH_2Cl_2/pentane) yielded 154 mg (73%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J*= 9.0 Hz, 2H), 7.54 (d, *J*= 7.5 Hz, 2H), 7.38 (t, *J*= 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 16.5 Hz, 1H), 7.13 (d, *J* = 16.5 Hz, 1H), 2.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.6, 142.1, 136.8, 136.1, 131.6, 129.0, 128.9, 128.5, 127.6, 127.0, 126.6, 26.7.

***trans*-4-methoxystilbene (Table 1, entry 5).** The general procedure was followed using 4-chloroanisole (142 mg, 0.994 mmol), styrene (0.125 mL, 1.09 mmol), Cs_2CO_3 (351 mg, 1.08 mmol), $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol), P(*t*-Bu)$_3$ (11.7 mg, 0.058 mmol) and dioxane (1.00 mL). After 30 hours at 120 °C, workup and column chromatography (2% EtOAc/hexane) yielded 184 mg (88%) of the title compound as a white solid which was identical to authentic material (Alfa Aesar) by ^{1}H NMR, GC, and TLC.

2-methylstilbene (Table 1, entry 6) [22257-16-5].[27] The general procedure was followed using 2-chlorotoluene (125 mg, 0.987 mmol), styrene (0.125 mL, 1.09 mmol), Cs_2CO_3 (362 mg, 1.11 mmol), $Pd_2(dba)_3$ (13.4 mg, 0.015 mmol), P(*t*-Bu)$_3$ (12.3 mg, 0.061 mmol) and dioxane (1.00 mL). After 114 hours at 120 °C, workup and column chromatography (hexane) yielded 135 mg (71%) of the title compound as a slightly yellow liquid which ^{1}H NMR analysis revealed to be a

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[26] Bezou, P.; Hilberer, A.; Hadziioannou, G. *Synthesis* **1996**, 449-451.

[27] Lapouyade, R.; Veyres, A.; Hanafi, N.; Couture, A.; Lablache-Combier, A. *J. Org. Chem.* **1982**, *47*, 1361-1364.

15:1 mixture of trans:cis isomers. ^{1}H NMR (300 MHz, $CDCl_3$) trans isomer: 7.59 (d, *J*= 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.38-7.17 (m, 7H), 7.00 (d, *J* = 16.0 Hz, 1H), 2.43 (s, 3H). ^{1}H NMR (300 MHz, $CDCl_3$) cis isomer: δ 6.62 (d, *J* = 8.0 Hz, 1H), 2.27 (s, 3H). All other resonances for the cis isomer are obscured by the resonances for the trans isomer. ^{13}C NMR (75 MHz, $CDCl_3$) trans isomer: δ 137.9, 136.6, 136.0, 130.6, 130.2, 128.9, 127.8, 127.7, 126.8, 126.7, 126.4, 125.6, 20.1.

Heck coupling of chlorobenzene with styrene using 0.2% Pd (eq 4). The general procedure was followed using chlorobenzene (630 mg, 5.59 mmol), styrene (0.70 mL, 6.11 mmol), Cs_2CO_3 (2.00 g, 6.14 mmol), $Pd_2(dba)_3$ (5.1 mg, 0.006 mmol), P(*t*-Bu)$_3$ (4.5 mg, 0.022 mmol) and dioxane (5.50 mL). After 120 hours at 120 °C, workup and column chromatography (hexane) yielded 811 mg (80%) of the *trans*-stilbene as a white solid which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

Chapter 4:

Development of Milder and More General Reaction Conditions for the Heck Coupling of Aryl Chlorides and Bromides using Cy_2NMe as Base

Introduction

Like the Suzuki coupling, the Heck reaction is typically performed at elevated temperatures. As discussed in Chapter 2, the ability to perform reactions at room temperature offers significant benefits over elevated temperatures. Room-temperature Heck reactions are very rare and essentially limited to reactive substrates. Aryl and vinyl iodides can be coupled with olefins at room temperature using the Jeffery system ($Pd(OAc)_2$, HCO_3^-, R_4NX);[1] in a recent review, this development has been characterized as "a major achievement."[2] Jeffery has documented how the mildness of this procedure provides significant advantages over other catalyst systems with regard to selectivity issues and reactions of thermally labile compounds. Unfortunately, these conditions are not effective for room-temperature Heck couplings of less reactive aryl bromides and chlorides. Certain aryl electrophiles, such as aryldiazonium salts[3] and hypervalent iodo compounds,[4] have been demonstrated to undergo Heck reactions at room temperature. However, these substrates are, in general, not commercially available, which severely limits the practical utility of these types of coupling partners.

Concurrent with our own work, Hartwig described the first examples of room-temperature Heck reactions of aryl bromides using 1-adamantyl-di-*t*-butyl phosphine and a ferrocenyl-di-*t*-butyl phosphine as ligands.[5] Despite the significance of this accomplishment, only reactions with the reactive olefins styrene and methyl acrylate were reported; thus, a truly general system for

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1 Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1996; Vol. 5, pp 153-260.

2 Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; p 106.

3 Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31-36.

4 Moriarty, R. M.; Epa, W. R.; Awasthi, A. K. *J. Am. Chem. Soc.* **1991**, *113*, 6315-6317.

5 Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677-2678.

room-temperature Heck reactions of aryl bromides is still needed. Not surprisingly, examples of aryl chlorides participating in Heck reactions at room temperature are non-existent.

Another challenge that existed that was not addressed in our first-generation $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cs_2CO_3$ protocol was the limited scope with respect to olefin when aryl chlorides are used as substrates. Prior to and including our initial work, only styrenes and acrylic acid derivatives had been demonstrated to be competent coupling partners in Heck reactions with aryl chlorides. Subsequent to our initial report, Hartwig also reported that $Pd/P(t\text{-}Bu)_3$ was a uniquely active catalyst for Heck reactions of aryl chlorides with *n*-butyl acrylate at 110 °C.[6] In addition, Herrmann reported that $Pd_2(dba)_3/P(t\text{-}Bu)_3$ was the most effective catalyst, among a number surveyed, for Heck couplings of electron-neutral and electron-rich aryl chlorides with styrene at 150 °C in nonaqueous ionic liquids as solvent.[7] A number of other groups also described homogenous catalyst systems for effecting Heck reactions of unactivated aryl chlorides;[8] however, with the exception of one isolated case using cyclopentene (which furnished an undetermined mixture of isomeric arylated products),[9] all of these examples utilized styrene and acrylic acid derivatives.

Results and Discussion

The high reactivity that $Pd/P(t\text{-}Bu)_3$ exhibited toward aryl chlorides suggested to us that it might serve as a very versatile catalyst, under mild conditions, for Heck couplings of other substrates, in particular, aryl bromides. In fact, studies

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6 Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123-2132.
7 Bohm, V. P. W.; Herrmann, W. A. *Chem. Eur. J.* **2000**, *6*, 1017-1025.
8 (a) Herrmann, W. A.; Bohm, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141-145. (b) Morales-Morales, D.; Redon, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619-1620.
9 Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, *11*, 1589-1592.

by DeVries and coworkers at Dow Chemical Company revealed that P(*t*-Bu)$_3$ was the most active ligand, among a large number screened, for the Heck coupling of an aryl bromide with a vinyl silane (95 °C).[10]

In initial studies, we were pleased to observe that $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cs_2CO_3 did indeed effect the room-temperature coupling of a wide array of aryl bromides, including very electron-rich aryl bromides such as 4-bromo-*N*,*N*-dimethylaniline, with styrene and methyl acrylate. Similar to our observations regarding the Suzuki reaction, a 1:1 Pd:P(*t*-Bu)$_3$ ratio was important for high activity at room temperature. Unfortunately, little or no reaction was observed with more challenging monosubstituted olefins such as 1-hexene or disubstituted olefins such as methyl methacrylate or methyl *trans*-cinnamate. With the goal of an extremely versatile catalyst for room-temperature Heck couplings of aryl bromides, we were forced to conclude that our first-generation system was inadequate.

The choice of base can have a crucial effect on the rate and the product distribution of Heck reactions.[11] Prompted by a recent report from the Buchwald laboratory that described the unusual effectiveness of the bulky tertiary amine base, Cy_2NMe, in Heck couplings aryl bromides with disubstituted olefins at 85-100 °C,[12] we decided to investigate the replacement of Cs_2CO_3 with Cy_2NMe. We were delighted to observe that the use of Cy_2NMe leads to a significantly more active catalyst, permitting the room-temperature coupling of a wide array of aryl bromides with a broad spectrum of olefins

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[10] DeVries, R. A.; Vosejpka, P. C.; Ash, M. L. *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, 1998; Chapter 37.

[11] For some recent examples, see: (a) Morales-Morales, D.; Grause, C.; Kasaoka, K.; Redon, R.; Cramer, R. E.; Jensen, C. M. *Inorg. Chim. Acta* **2000**, *300-302*, 958-963. (b) Hartung, C. G.; Köhler, K.; Beller, M. *Org. Lett.* **1999**, *1*, 709-711. (c) Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29-35. (d) Beller, M.; Riermeier, T. H. *Tetrahedron Lett.* **1996**, *37*, 6535-6538.

[12] Gürtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107-3112.

(Table 1). Among other tertiary amine bases screened, N(*i*-Pr)$_2$Et (Hunig's base) was also reasonably effective. Secondary amines (Cy$_2$NH, *i*-Pr$_2$NH), cyclic amines (DBU, 1,2,2,6,6-pentamethylpiperidine), and aromatic amines (1,8-bis(dimethylamino)naphthalene) were all inferior, as were inorganic bases such as K_3PO_4. THF and toluene were only slightly worse than dioxane as solvent. Pd(II) sources such as Pd(OAc)$_2$ and Pd(MeCN)$_2$Cl$_2$ were briefly examined, but proved inferior to Pd$_2$(dba)$_3$.

Olefins with electron-donating groups are considered to be relatively challenging substrates for Heck reactions, as one often obtains mixtures of α- and β-arylated products. Arylations of alkyl vinyl ethers with electron-rich aryl halides usually furnish mixtures favoring the α-arylated product,[13] although the use of additives such as AgOTf or TlOAc[14] or the use of ionic liquids as solvents[15] can be employed in order to obtain high α:β selectivities. In our system we observe the expected regioselectivity for the Heck reaction of 4-bromo-*N*,*N*-dimethylaniline with *n*-butyl vinyl ether (Table 1, entry 1); the rather modest regioselectivity nonetheless compares favorably with other catalysts[7,16] and may be due to the lower reaction temperature (*vide infra*).

In order to fully examine the scope of the reaction with respect to the aryl bromide, methyl methacrylate was chosen as the coupling partner for a variety of reasons. Disubstituted olefins are typically less reactive than monosubstituted olefins, and arylations of methyl methacrylate can furnish mixtures of products. There are two possible pathways for β-hydride elimination, one leading to a 1,1-disubstituted olefin, which is susceptible to further Heck arylation,[11a,c,d] and the

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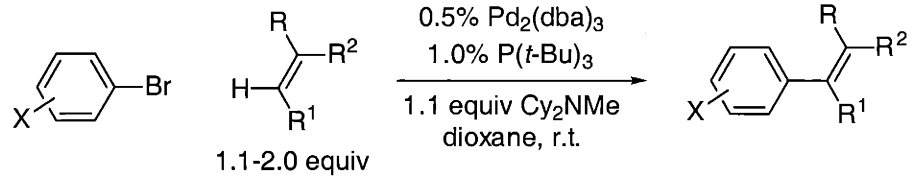
13 (a) Andersson, C.-M.; Hallberg, A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529-3536. (b) Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433-1445.

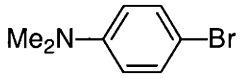
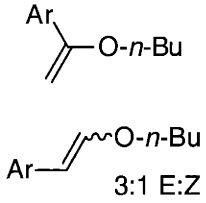
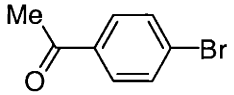
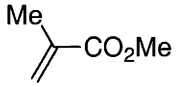
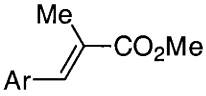
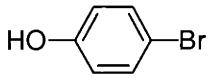
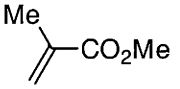
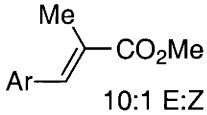
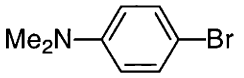
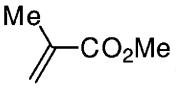
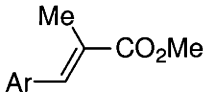
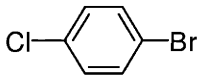
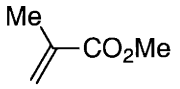
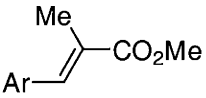
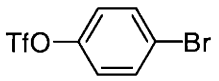
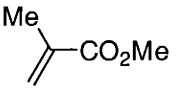
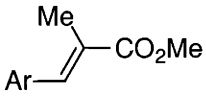
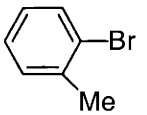
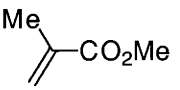
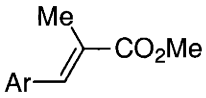
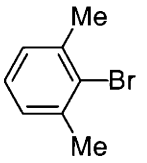
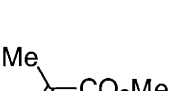
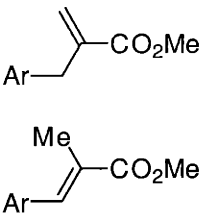
14 Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481-1486.

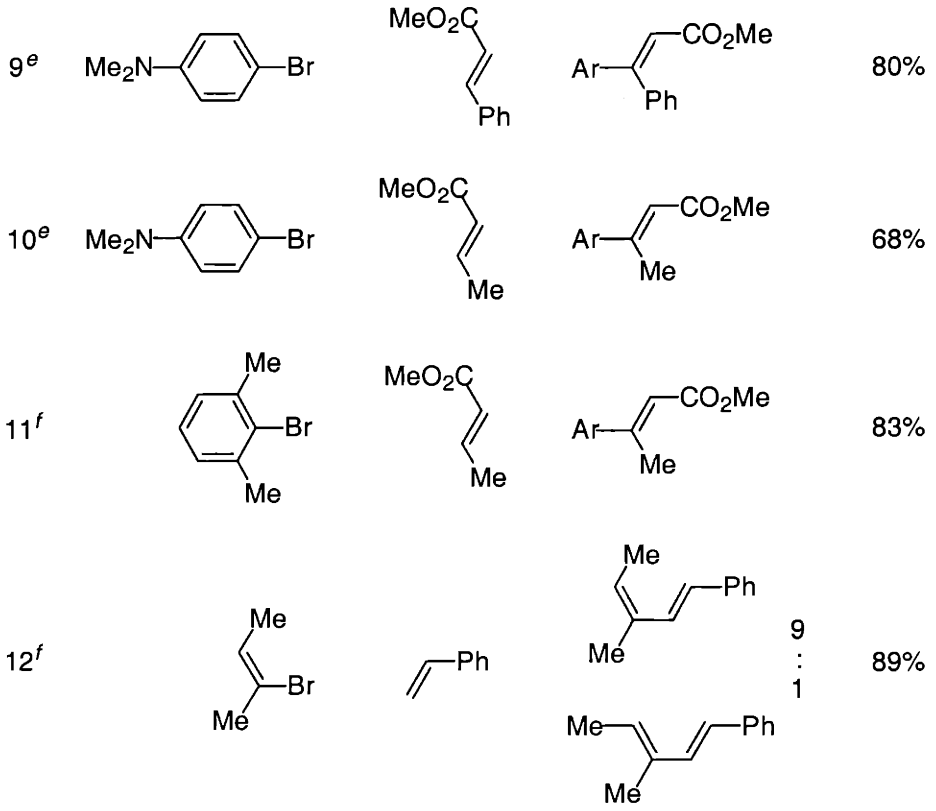
15 Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett.* **2001**, *3*, 295-297.

16 Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Reirmeier, T. H.; Ofele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357-1364.

Table 1. Heck Couplings of Aryl and Vinyl Bromides at Room Temperature

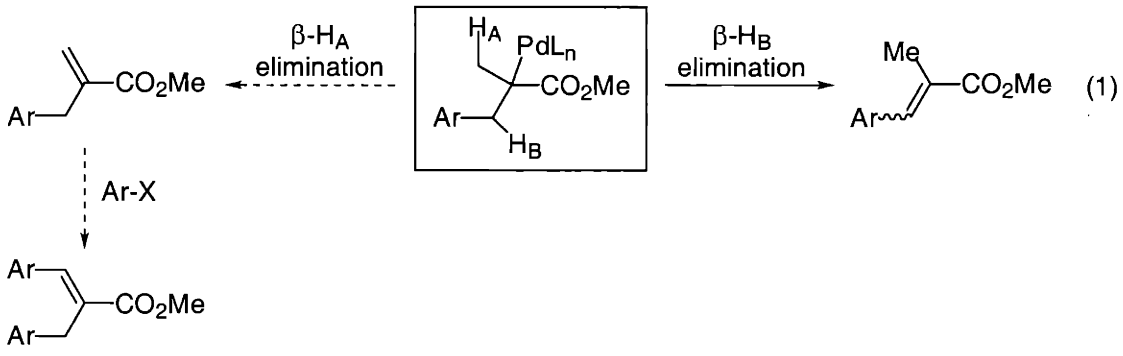


Entry	Aryl Bromide	Olefin	Product	Yield[a,b]
1			 4 : 1 3:1 E:Z	97%
2				74%
3			 10:1 E:Z	77%
4				96%
5				70%[c]
6				64%[c]
7				86%[d]
8			 6 : 1	97%



[a]Isolated yield, average of two runs. [b]Unless otherwise indicated, the E:Z ratio is >20:1, as determined by ^{1}H NMR. [c]16:1 ratio of internal:terminal olefin. [d]20:1 ratio of internal:terminal olefin. [e]1.0% $Pd_2(dba)_3$, 2.0% P(*t*-Bu)$_3$ was used. [f]1.5% $Pd_2(dba)_3$, 3.0% P(*t*-Bu)$_3$ was used.

other leading to the desired trisubstituted olefin, for which there is an *E*/*Z* stereochemical issue (eq 1).[17]



(1)

[17] We do not intend to imply that product formation in these Heck couplings must be under kinetic control. In fact, for one reaction we have evidence that an appreciable quantity of disubstituted olefin is generated initially, and that it is converted to the trisubstituted olefin under the coupling conditions (eq 9).

In addition, Heck reactions of aryl halides with methyl methacrylate can produce α-methylcinnamic acid derivatives, an important family of compounds that both possess biological activity (e.g., hypolipidemic[18] and antiobiotic[19]) and serve as intermediates in the synthesis of pharmaceuticals (e.g., Sulindac, a non-steroidal anti-inflammatory drug[20]).

$Pd_2(dba)_3/P(t\text{-}Bu)_3/Cy_2NMe$ is indeed a very effective and general system for room-temperature Heck arylations of methyl methacrylate (Table 1, entries 2-7). In all cases the ratio of trisubstituted:disubstituted olefin is >15:1, with the trisubstituted olefin displaying excellent *E*:*Z* selectivity (> 20:1, except for Table 1, entry 3). Electron-deficient (Table 1, entry 2), electron-rich (Table 1, entries 3 and 4), and hindered aryl bromides (Table 1, entry 7) all undergo smooth reaction with only 1% $Pd/P(t\text{-}Bu)_3$. Certain ortho substituents, however, were not tolerated. Attempts to couple 2-bromophenol or 2-bromobenzoic acid with methyl methacrylate resulted in no reaction; in both cases it is possible that coordination of oxygen to the palladium after oxidative addition may result in an inactive complex. No attempts were made to try these unsuccessful reactions at elevated temperatures.

Highly chemoselective Heck couplings are also possible, as a bromide can be coupled in the presence of a chloride (Table 1, entry 5) or a triflate (Table 1, entry 6). In both these cases, the product(s) arising from coupling at the other reactive site are not detected; however, small amounts of the diarylated product resulting from Heck reaction with the initially formed disubstituted olefin (eq 1) are

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18 For example, see: Watanabe, T.; Hayashi, K.; Yoshimatsu, S.; Sakai, K.; Takeyama, S.; Takashima, K. *J. Med. Chem.* **1980**, *23*, 50-59.

19 For example, see: Buchanan, J. G.; Hill, D. G.; Wightman, R. H.; Boddy, I. K.; Hewitt, B. D. *Tetrahedron* **1995**, *51*, 6033-6050.

20 Eisenstadt, A. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, 1998; Chapter 33.

observed. The use of 2 equiv of methyl methacrylate is beneficial from the standpoint of suppressing this undesired pathway.

The only example encountered where the trisubstituted olefin is *not* the major product is when a very bulky di-ortho-substituted aryl bromide is used (Table 1, entry 8). The steric demand of the two ortho methyl groups may disfavor β-hydride elimination to generate the trisubstituted olefin, instead furnishing the disubstituted olefin. However, when this reaction is conducted at 120 °C with 0.5% $Pd_2(dba)_3$/2.0% P(*t*-Bu)$_3$, an 87% yield (by NMR, versus an internal standard) is obtained of the *E* trisubstituted olefin, with no evidence of other isomers. Thus, by appropriate choice of conditions, either a di- or a trisubstituted olefin can be preferentially generated.

As noted in a recent review, the use of 1,2-disubstituted olefins in intermolecular Heck reactions is relatively uncommon, as these types of substrates usually exhibit low reactivity towards traditional catalyst systems.[21] Vigorous reaction conditions are often required, as in the case of Heck arylations of cinnamic acid esters, which produce β,β-diarylacrylates, useful intermediates for the synthesis of medicinally relevant compounds such as angiotension II receptor antagonists.[22] Particularly problematic is the use of electron-rich aryl halides, which often result in mixtures of *E* and *Z* olefin isomers due to isomerization of the olefin at the elevated temperatures that are typically required.[23] By being be able to conduct the reaction of 4-bromo-*N*,*N*-dimethylaniline with methyl *trans*-cinnamate at room temperature, the desired β,β-diarylacrylate is generated with >20:1 *E*:*Z* selectivity (Table 1, entry 9).

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21 Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; p 102.

22 For example: Almansa, C.; Gomez, L. A.; Cavalcanti, F. L.; de Arriba, A. F.; Rodriguez, R.; Carcellar, E.; Garcia-Rafanell, J.; Forn, J. *J. Med. Chem.* **1996**, *39*, 2197-2206.

23 For examples, see: (a) Moreno-Manas, M.; Perez, M.; Pleixats, R. *Tetrahedron Lett.* **1996**, *37*, 7449-7452. (b) Calo, V.; Nacci, A.; Monopoli, A.; Lopez, L.; Cosmo, A. -d. *Tetrahedron* **2001**, *57*, 6071-6077. (c) Reference 12

Another useful class of compounds, β-arylcrotonic esters, can also be accessed readily in high stereoselectivity through $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cy_2NMe$ by using methyl crotonate as the olefin (Table 1, entries 10 and 11). These types of products can be converted, for example, into biologically important 2(5*H*)-furanones.[24] Given the known sensitivity of the Heck reaction towards hindered substrates, an indication of the very high activity of this catalyst system is that a di-ortho-substituted aryl bromide can be coupled with a 1,2-disubstituted olefin at room temperature (Table 1, entry 11). Attempts to couple trisubstituted olefins with aryl bromides at room temperature resulted in negligible conversions.

Vinyl bromides may also be used for room-temperature Heck reactions (Table 1, entry 12), although they seem to be somewhat less reactive than their aryl counterparts, as a catalyst loading of 3% Pd is required despite the use of typically reactive styrene as the coupling partner.

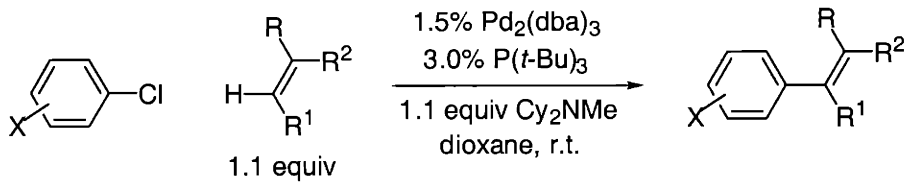
A wide variety of electron-deficient aryl chlorides may also be coupled with mono- and disubstituted olefins at room temperature using $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cy_2NMe$ (Table 2). The functional group tolerance of these Heck reactions is excellent, as ketones, esters, amides, nitriles, thiophenes, and alcohols are all compatible. In general, catalyst loadings of 3% $Pd/P(t\text{-}Bu)_3$ are required for these couplings to proceed at reasonable rates.

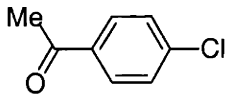
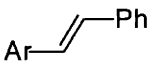
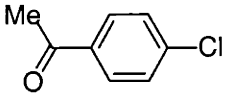
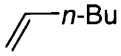
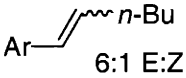
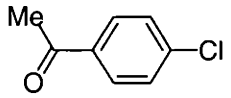
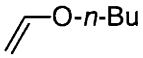
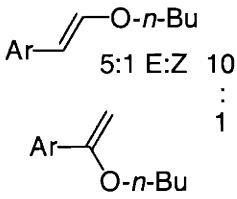
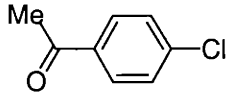
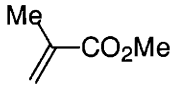
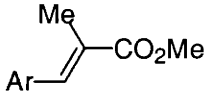
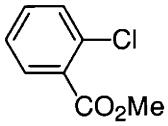
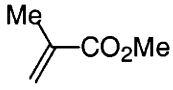
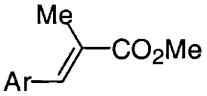
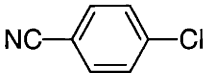
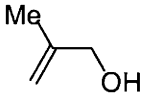
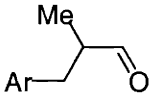
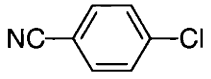
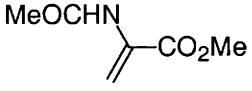
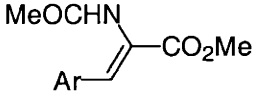
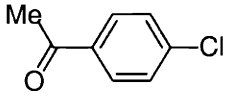
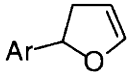
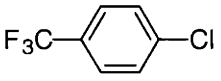
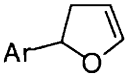
The coupling of styrene with 4'-chloroacetophenone previously required a reaction temperature of 100 °C using Cs_2CO_3 as base; now this coupling proceeds at room temperature in 78% yield using Cy_2NMe as base (Table 2, entry 1). Interestingly, room-temperature couplings of activated aryl chlorides with methyl acrylate, usually a very reactive substrate for Heck reactions, did not yield any desired product.

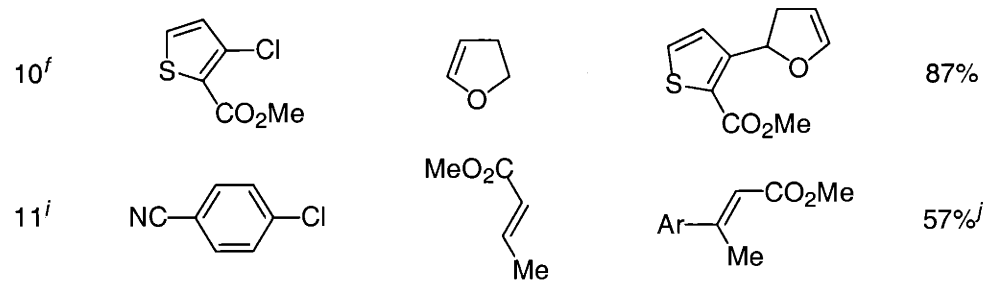
---

[24] For example, see: Kagabu, S.; Shimizu, Y.; Ito, C.; Moriya, K. *Synthesis* **1992**, 830-832.

Table 2. Heck Couplings of Activated Aryl Chlorides at Room Temperature



Entry	Aryl Chloride	Olefin	Product	Yield[a,b]
1				78%
2			 6:1 E:Z	70%
3			 5:1 E:Z 10 : 1	87%[c]
4				79%
5				90%
6				79%
7				57%[d]
8[e,f]				72%[g]
9[f]				76%[h]



[a]Isolated yield, average of two runs. [b]Unless otherwise indicated, the E:Z ratio is >20:1, as determined by ^{1}H NMR. [c]Product includes 5% 4'-chloroacetophenone. [d] Product from one run was a 10:1 Z:E mixture [e]0.5% $Pd_2(dba)_3$, 1.0% P(*t*-Bu)$_3$ was used. [f]3 equiv of olefin was used. [g] A small amount of the diarylated product was also generated, and it was removed by chromatography. [h]Product includes 6% diarylated product. [i]2 equiv of olefin was used. [j]Product includes 2% P(*t*-Bu)$_3$/OP(*t*-Bu)$_3$.

Electron-neutral alkyl-substituted olefins are another class of problematic substrates for Heck reactions due to modest regioselectivities and olefin isomerization.[25] Using $Pd_2(dba)_3$/P(*t*-Bu)$_3$/Cy_2NMe, the Heck reaction between 1-hexene and 4'-chloroacetophenone provides exclusively the 1,2-disubstituted product with a relatively good 6:1 *E*:*Z* selectivity (Table 2, entry 2).[26] As expected for an electron-deficient aryl halide, the reaction of 4'-chloroacetophenone and *n*-butyl vinyl ether yields primarily the β-arylated product (Table 2, entry 3);[13] the observed 10:1 β:α selectivity again compares favorably with other catalyst systems that require elevated temperatures.[27]

1,1-disubstituted olefins also undergo Heck coupling with a variety of electron-deficient aryl chlorides at room temperature (Table 2, entries 4-7). As in reactions with aryl bromides, arylations with methyl methacrylate furnish the *E* trisubstituted olefin with excellent selectivity (Table 2, entry 4), and ortho substituents are tolerated (Table 2, entry 5). Only 1.1 equiv of methyl

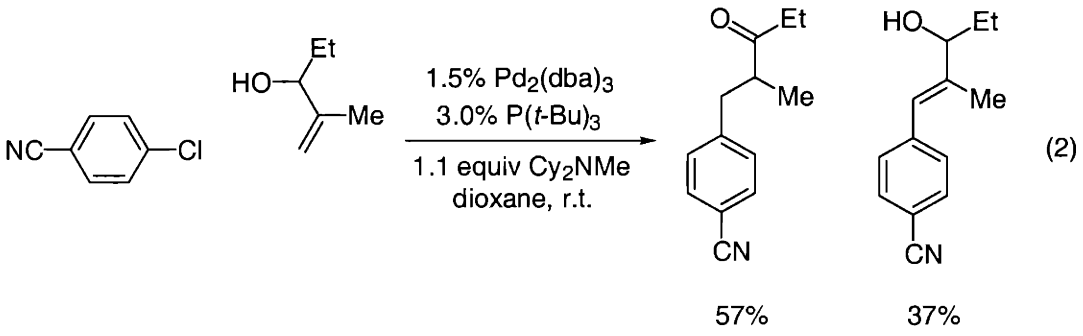
25 For recent examples, see: (a) Mabic, S.; Vaysse, L.; Benezra, C.; Lepoittevin, J.-P. *Synthesis* **1999**, 1127-1134. (b) Bräse, S.; Schroen, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 1071-1073.

26 With other catalysts, lower *E*:*Z* stereoselectivity is often observed. For example, see: Brunner, H.; de Courcy, N. L. C.; Genet, J.-P. *Tetrahedron Lett.* **1999**, *40*, 4815-4818.

27 Heck reactions of 4'-bromoacetophenone typically generate the β-arylated regioisomer preferentially, although the selectivity is often modest. For examples, see references 7 and 16.

methacrylate is required in these couplings as diarylation is *not* a significant side reaction.

A primary allylic alcohol, 2-methyl-2-propen-1-ol, undergoes Heck reaction with 4-chlorobenzonitrile to yield the aldehyde product exclusively over the allylic alcohol product due to regioselective β-hydride elimination (Table 2, entry 6).[28] Unfortunately, this high regioselectivity does not appear to be general. The reaction of this same primary allylic alcohol with 4-*tert*-butylbromobenzene resulted in a mixture of aldehyde and allylic alcohol products. The reaction of a *secondary* allylic alcohol with 4-chlorobenzonitrile resulted in a mixture comprised of 57% of the ketone and 37% of the allylic alcohol (eq 2).[29]



(2)

Methyl 2-acetamidoacrylate is a useful olefin for Heck couplings, allowing access to dehydroaminoacids (Table 2, entry 7),[30] an interesting class of compounds[31] that can be used to synthesize unnatural α-amino acids via asymmetric hydrogenation.[32]

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28 (a) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265-272. (b) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 1206-1209.

29 Others have also reported mixtures of products from Heck reactions with secondary allylic alcohols; for example, see: Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Namkoong, E.-Y.; Kim, T.-H. *Tetrahedron Lett.* **1995**, *36*, 6287-6290.

30 Carlstrom, A.-S.; Frejd, T. *Synthesis*, **1989**, 414-418.

31 Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159-172.

32 (a) Bozell, J. J.; Vogt, C. E.; Gozum, J. *J. Org. Chem.* **1991**, *56*, 2584-2587. (b) Dygos, J. H.; Yonan, E. E.; Scaros, M. G.; Goodmonson, O. J.; Getman, D. P; Periana, R. A.; Beck, G. R. *Synthesis* **1992**, 741-743.

1,2-Disubstituted olefins may also be arylated at room temperature with activated aryl chlorides (Table 2, entries 8-11). Reactions with a cyclic olefin, 2,3-dihydrofuran, lead exclusively to the thermodynamically favored 2-aryl-2,3-dihydrofuran, due to olefin isomerization subsequent to Heck arylation[33] (Table 2, entries 8-10); no trace of the isomeric 2-aryl-2,5-isomer is detected in these reactions. However, diarylation *is* a significant side reaction, and in order to suppress this, 3 equiv of the olefin is required although this side reaction still persists in certain cases despite the use of excess olefin (Table 2, entry 9). Certain heterocycles, such as a chlorothiophene (Table 2, entry 10), may also be used as substrates for room-temperature chemistry. More challenging acyclic 1,2-disubstituted olefins can be used to generate trisubstituted olefins in high stereoselectivity at room temperature, although yields are rather modest (Table 2, entry 11).

Reactions of the more bulky methyl *trans*-cinnamate with electron-poor aryl chlorides were exceedingly slow at room temperature and required heating (70 °C; Table 3, entry 1). The side product 4,4'-dicyanobiphenyl, arising from reductive homocoupling of the aryl chloride,[34] is observed in this reaction of 4-chlorobenzonitrile with methyl *trans*-cinnamate (Table 3, entry 1). Nonetheless, the high stereoselectivity and good yield for this coupling are noteworthy, as couplings of electron-deficient aryl bromides[12] and iodides[23a] with cinnamic acid esters have been reported to proceed in low yields and/or poor *E*:*Z* selectivities.

One functional group that did not appear to be well tolerated in these Heck couplings is nitro groups, as 4-nitrochlorobenzene failed to undergo reaction

---

[33] For leading references to isomerization reactions during Heck couplings of 2,3-dihydrofuran, see: Jeffery, T.; David, M. *Tetrahedron Lett.* **1998**, *39*, 5751-5754.

[34] This undesired pathway has been observed by others in Heck arylations of cinnamic acid esters with electron-deficient aryl iodides: Reference 23a

with a variety of olefins at room temperature, although no attempt to induce product formation by increasing the reaction temperature was attempted.[35]

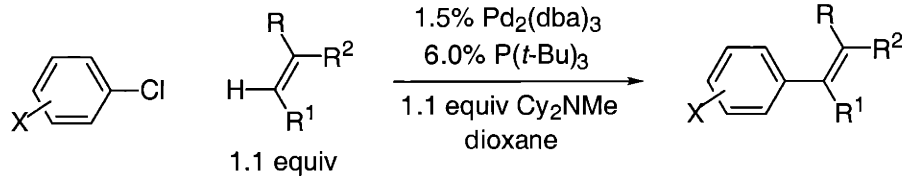
Attempts to selectively couple aryl chlorides in the presence of aryl triflates with olefins yielded mixtures of products arising from coupling at both reactive sites. For example, the attempted coupling of 4-chlorophenyltriflate with 2,3-dihydrofuran resulted in a 4.4:1.6:1.0 mixture (ratios uncorrected with response factors) of the product arising from reaction with the triflate, the product arising from reaction with the chloride and the product arising from reaction at *both* sites, respectively. Thus, in contrast to the remarkable results obtained in the Suzuki coupling (Chapter 2), Pd/P(*t*-Bu)$_3$ exhibits higher rectivity towards aryl triflates in the presence of aryl chlorides in the Heck reaction. A possible explanation for this observation is that Cy_2NMe may be bound to the palladium catalyst prior to oxidative addition which could affect the selectivity for chlorides versus triflates.

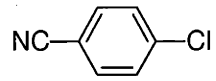
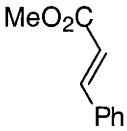
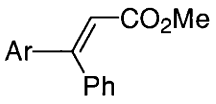
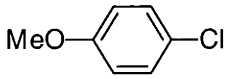
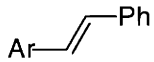
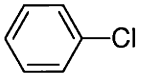
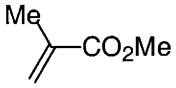
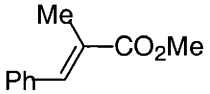
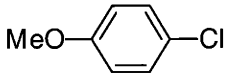
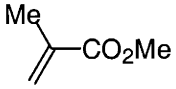
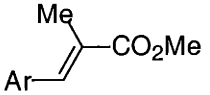
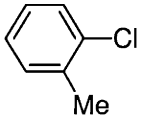
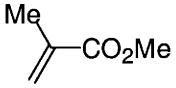
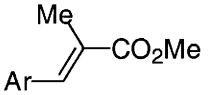
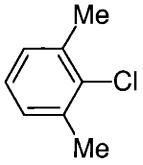
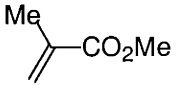
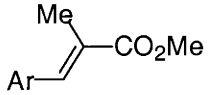
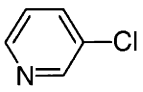
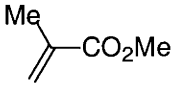
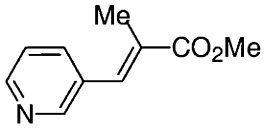
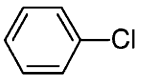
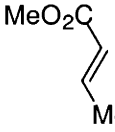
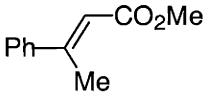
The dramatic decrease in reaction temperature that the use of Cy_2NMe as base allows for in Heck couplings of electron-deficient aryl chlorides was not observed in reactions of electron-neutral and electron-rich aryl chlorides, as temperatures of 100-120 °C are still required (Table 3, entries 2-10). However, the scope of the reaction with respect to both aryl chloride and olefin has improved considerably. Methyl methacrylate undergoes smooth Heck reaction with a variety of unactivated aryl chlorides to furnish the *E* trisubstituted olefin products in good yields (Table 3, entries 3-7). With regard to aryl chloride, electron-rich aryl chlorides are not a problem (Table 3, entries 2 and 4) as expected, but of primary significance is that hindered aryl chlorides (Table 3, entry 5), including a di-ortho-substituted aryl chloride (Table 3, entry 6), are

[35] The Heck reaction of 4-nitrobromobenzene with methyl methacrylate did proceed at room temperature although significant quantities of the disubstituted olefin were generated.

excellent substrates; reaction times are now quite reasonable (< 39 hours). 3-Chloropyridine is also a suitable substrate (Table 3, entry 7).

Table 3. Heck Couplings of Aryl Chlorides at Elevated Temperature



Entry	Aryl Chloride	Olefin	Temperature	Product	Yield[a,b]
1[c]			70 °C		67%[d]
2			120 °C		72%
3			100 °C		84%
4			120 °C		72%
5			110 °C		89%
6			120 °C		80%
7			100 °C		76%
8[e]			120 °C		52%

[a]Isolated yield, average of two runs. [b]E:Z ratio is >20:1, as determined by ^{1}H NMR. [c]3.6% P(*t*-Bu)$_3$ was used. [d]Product includes 2.5% P(*t*-Bu)$_3$/OP(*t*-Bu)$_3$. [e]2 equiv. of olefin was used.

Certain classes of substrates still do not give satisfactory results with this second-generation catalyst system. 2-Halopyridines are known to be problematic substrates in Heck reactions,[36] and, indeed, 2-chloropyridine is quite unreactive under the exact same conditions as for the coupling of 3-chloropyridine. Highly electron-rich aryl chlorides are also challenging substrates; although the reaction of 4-chloroaniline with methyl methacrylate proceeds with excellent (> 20:1) *E*:*Z* selectivity, the yield is rather modest (47%), primarily due to competing hydrodehalogenation, as aniline is generated in significant quantities. With respect to the olefin component, reactions of unactivated aryl chlorides with 1,2-disubstituted olefins suffer either from modest stereoselection or modest yield (e.g., Table 3, entry 8). Attempts to couple trisubstituted olefins with activated aryl chlorides at elevated temperatures did result in consumption of the aryl chloride, but reactions were not clean with multiple unidentified products being formed.

Certain unactivated monosubstituted olefins are also difficult substrates. Thus, the reaction of 4-chloroanisole with 1-hexene at 120 °C resulted in an extremely messy reaction (many peaks detected by GC), and reaction with *n*-butyl vinyl ether resulted in a nearly 1:1 mixture of α:β-arylated products. It is useful to contrast these results with the room-temperature coupling of these same olefins with activated aryl chlorides (Table 2, entries 2 and 3) and aryl bromides (Table 1, entry 1). For these room-temperature couplings, relatively high regio- and stereoselectivities were observed, and this is most certainly in part due to the lower reaction temperature.

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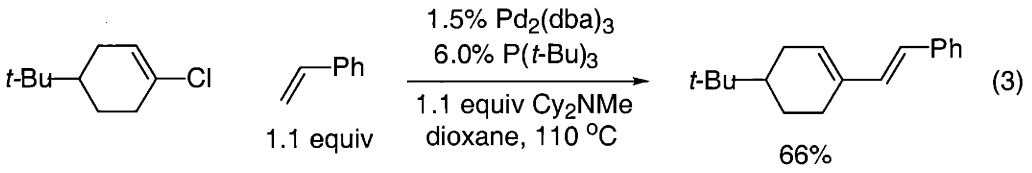
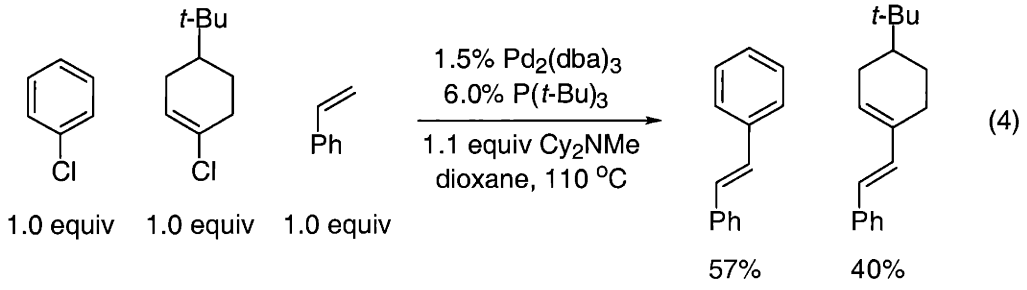
[36] This poor reactivity may be due to the formation, after oxidative addition, of an unreactive pyridyl-bridged palladium dimer (Nakatsu, K.; Kinoshita, K.; Kanda, H.; Isobe, K.; Nakamura, Y.; Kawaguchi, S. *Chem. Lett.* **1980**, 913-914). For reports of problems effecting Heck reactions of 2-halopyridines, see: (a) Frank, W. C.; Kim, Y. C.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2947-2949. (b) Basu, B.; Frejd, T. *Acta Chem. Scand.* **1996**, *50*, 316-322. (c) Reference 33a

Prior to our work, Heck reactions of vinyl chlorides had been restricted to activated vinyl chlorides.[37] This limitation can be overcome through the use of $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cy_2NMe$, as an unactivated vinyl chloride can be coupled with styrene in reasonable yield (eq 3).



(3)

As in Suzuki couplings catalyzed by $Pd_2(dba)_3/P(t\text{-}Bu)_3$, the rather unusual higher reactivity of aryl chlorides than vinyl chlorides is also observed in Heck reactions catalyzed by $Pd_2(dba)_3/P(t\text{-}Bu)_3$. In a competition experiment between chlorobenzene and 1-chloro-4-*tert*-butyl-cyclohexene for styrene, the aryl chloride couples preferentially (eq 4).



(4)

Intramolecular Heck reactions are a very powerful tool to generate complex carbo- and heterocycles as exemplified by the many applications in natural products synthesis. Such reactions are usually more facile than intermolecular variants; for example, while intermolecular Heck reactions with trisubstituted alkenes are very rare, there are quite a few examples of trisubstituted alkenes participating in intramolecular Heck reactions. Unfortunately, we obtained

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[37] (a) Horino, H.; Inoue, N.; Asao, T. *Tetrahedron Lett.* **1981**, *22*, 741-744. (b) Voigt, K.; Schick, U.; Meyer, F. E.; de Meijere, A. *Synlett* **1994**, 189-190.

disappointing results when a variety of substrates containing an aryl halide and pendent olefin were subjected to $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cy_2NMe$ either at room temperature (aryl bromides) or elevated temperatures (aryl chlorides) in an attempt to synthesize 5- and 6-membered carbocycles and heterocycles. In almost all cases, reactions were slow relative to intermolecular reactions, with multiple products being formed.

Lower catalyst loadings may also be used, and, in order to illustrate this, the relatively challenging coupling of unactivated chlorobenzene with the disubstituted olefin methyl methacrylate was examined in detail (eq 5). This coupling proceeds in 67% isolated yield using 0.1% $Pd_2(dba)_3$/0.4% $P(t\text{-}Bu)_3$, resulting in a turnover number of 335. An even higher turnover number can be achieved at the expense of lower conversion: with 0.05% $Pd_2(dba)_3$/0.2% $P(t\text{-}Bu)_3$ at 130 °C, a turnover number of 530, based on 53% isolated yield, is obtained. A turnover number comparable to that observed with 0.1% $Pd_2(dba)_3$/0.4% $P(t\text{-}Bu)_3$ can be obtained by using 0.2% $Pd(P(t\text{-}Bu)_3)_2$ (eq 5). As $Pd(P(t\text{-}Bu)_3)_2$ is a commercially available,[38] relatively air-stable, crystalline solid[39] it represents a very user-friendly alternative to $Pd_2(dba)_3/P(t\text{-}Bu)_3$ for this process.[40]

High turnover numbers can also be obtained in reactions with aryl bromides at room temperature. As mentioned in the introduction section of Chapter 3, the coupling of 4-bromoanisole and 2-ethylhexylacrylate is used on an industrial

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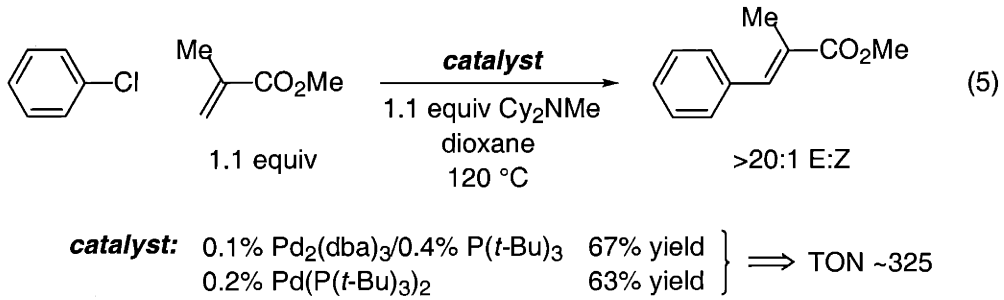
38 Strem Chemicals (Newburyport, MA), catalog number 46-0252.

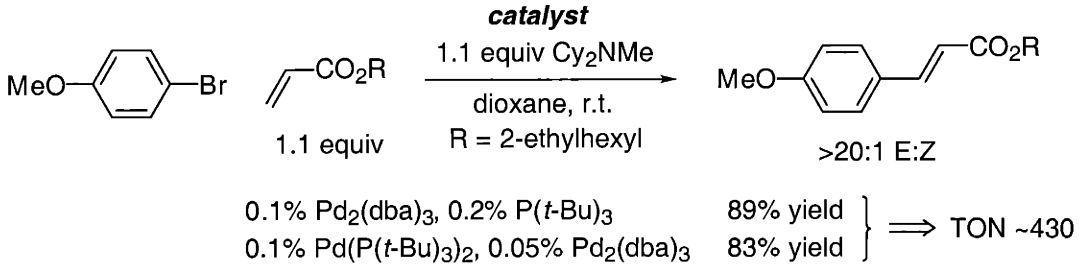
39 (a) Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. *J. Am. Chem. Soc.* **1976**, *98*, 5850-5858. (b) Yoshida, T.; Otsuka, S. *J. Am. Chem. Soc.* **1977**, *99*, 2134-2140. (c) Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1990**, *28*, 113-119. This report states that $Pd(P(t\text{-}Bu)_3)_2$ is "stable in air in the solid state." However, we recommend that $Pd(P(t\text{-}Bu)_3)_2$ be stored in a dessicator, preferably under argon or nitrogen.

40 Generally, for $Pd/P(t\text{-}Bu)_3$-catalyzed couplings that proceed at elevated temperature, a 1:2 Pd:phosphine ratio is preferred; for these applications, $Pd(P(t\text{-}Bu)_3)_2$ furnishes a user-friendly, one-component alternative to mixing $Pd_2(dba)_3$ and air-sensitive $P(t\text{-}Bu)_3$. For $Pd/P(t\text{-}Bu)_3$-catalyzed reactions that occur at room temperature, a 1:1 Pd:phosphine ratio is usually preferred; for these processes, a 2:1 mixture of $Pd(P(t\text{-}Bu)_3)_2$:$Pd_2(dba)_3$ provides the desired Pd:phosphine ratio and avoids the need to handle $P(t\text{-}Bu)_3$ (e.g., eqs 6 and 8).



(5)

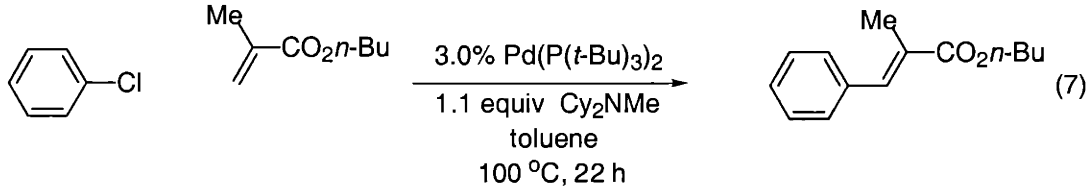
scale to produce octylmethoxycinnamate, the most common UV-B sunscreen on the market. With 0.1% $Pd_2(dba)_3$ (4.0 mg) and 0.2% P(*t*-Bu)$_3$, an 89% yield (1.1 g) of the desired compound is obtained, which corresponds to a turnover number of ~450 (eq 6). The more user-friendly protocol, a mixture of $Pd(P(t\text{-}Bu)_3)_2$ and $Pd_2(dba)_3$, provides a catalyst comparable to $Pd_2(dba)_3$/P(*t*-Bu)$_3$ (eq 6; % Pd and Pd:P(*t*-Bu)$_3$ are the same for the two reactions). Noteworthy is that even at low catalyst loadings, Pd/P(*t*-Bu)$_3$ is not highly sensitive to impurities such as hydroquinone and monomethyl ether hydroquinone, which are present in the 2-ethylhexylacrylate as inhibitors.



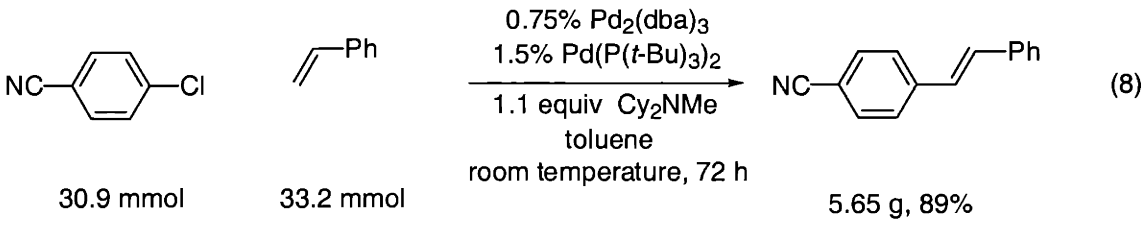
(6)

These Heck reactions can also be performed on relatively large scale to provide multigram quantities of product (eqs 7 and 8). For these large-scale reactions, minimal purification of reagents was performed and there was no use of a glovebox, high vacuum, or Schlenk tubes/flasks, in order to emphasize the robustness and practicality of Pd/P(*t*-Bu)$_3$/Cy_2NMe. Solid reagents were used as received, and liquid reagents were simply degassed by sparging with argon

for 5-10 minutes prior to use. Although dioxane is the most suitable solvent for Heck reactions catalyzed by Pd/P(*t*-Bu)$_3$/Cy$_2$NMe, this solvent may be unattractive for large-scale applications due to toxicity and/or cost issues. Toluene (anhydrous, Aldrich) from a Sure/Seal^{TM} bottle can be used as a very effective replacement for dioxane in these Heck couplings (eqs 7 and 8).



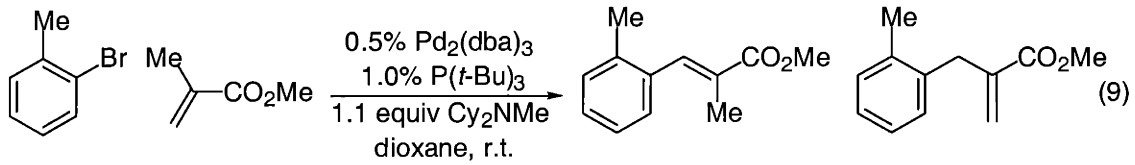
(7)



(8)

In order to gain some understanding as to the nature of the high stereoselectivity observed in many of the Heck reactions described thus far using Pd/P(*t*-Bu)$_3$/Cy$_2$NMe, a series of experiments were undertaken. In particular, we were interested in reactions involving methyl methacrylate, as this olefin has been known to give mixtures of regioisomers in arylations with other catalyst systems.[7,11a,c,d] In almost all the examples we have studied (Table 1, entries 2-7; Table 2, entries 4-5; Table 3, entries 3-7), the trisubstituted olefin is produced with high *E* selectivity with very little trace of the disubstituted olefin (eq 1). GC monitoring of many of these reactions, however, revealed significant quantities of another product being generated initially and gradually disappearing as the reaction proceeded to completion. Speculating that this "other" product was the disubstituted olefin, the Heck coupling of 2-bromotoluene with methyl

methacrylate was stopped prior to 100% conversion, and the crude reaction mixture analyzed by ^{1}H NMR after workup (eq 9). At 82% conversion, only a 1.6:1 ratio of trisubstituted:disubstituted olefin is observed; however, when this reaction is allowed to proceed to full conversion, a 20:1 ratio is obtained. These results suggest that the β-hydride elimination step is relatively non-selective, resulting in significant quantities of the disubstituted olefin being generated, which is then, under the reaction conditions, undergoing isomerization to the thermodynamically more stable trisubstituted olefin. Presumably, a palladium-hydride species undergoing re-addition to the olefin and subsequent β-hydride elimination of a different hydrogen is responsible for this isomerization process. In contrast, Beller has found that for Heck couplings of methyl methacrylate with aryl bromides at elevated temperatures catalyzed by phosphapalladacycles, the formation of the olefin occurs under *kinetic* control.[11c]



(9)

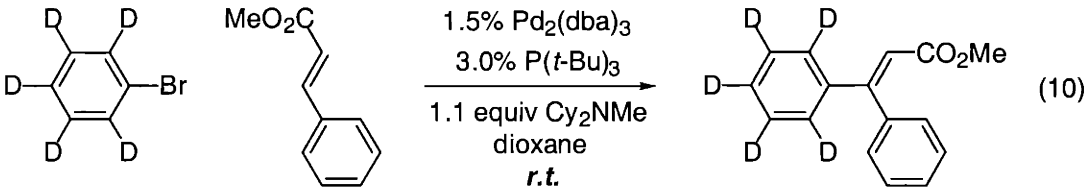
Stop reaction at 82% conversion (26 h): 1.6 : 1.0
68% combined yield

100% conversion (69 h, not optimized): 20.0 : 1.0
86% combined yield

We also studied reactions involving methyl *trans*-cinnamate; Heck arylations of this olefin with 4-bromo-*N*,*N*-dimethylaniline (Table 1, entry 9) and 4-chlorobenzonitrile (Table 3, entry 1) proceed with high stereoselectivity, generating the *E*-β,β-diarylacrylate products. These results strongly suggest that these processes are under kinetic control, and the data are consistent with a pathway that includes syn olefin insertion and syn β-hydride elimination (Chapter 3, Figure 1). By way of contrast, Buchwald has recently shown through

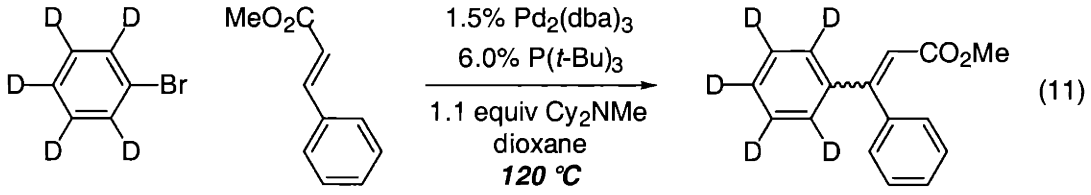
a study with C_6D_5Br that the product distribution of Heck reactions using his catalyst, which operates at elevated temperature (85-100 °C), is thermodynamic in origin.[12]

We have performed similar experiments with C_6D_5Br as described by Buchwald, and the results support our hypothesis that the above arylations using $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cy_2NMe$ are under kinetic control. The coupling of C_6D_5Br with methyl *trans*-cinnamate at room temperature exclusively generates the *E* trisubstituted olefin (eq 10). In contrast, Buchwald obtained a 1:1 mixture of olefin isomers using his catalyst system. Not surprisingly, when this same reaction using $Pd_2(dba)_3/P(t\text{-}Bu)_3/Cy_2NMe$ is conducted at elevated temperature, a 1:1 mixture of isomers is obtained (eq 11). Once again, the potential benefits offered by being able to perform Heck reactions under mild conditions is clearly demonstrated by these examples.



(10)

one isomer
94%



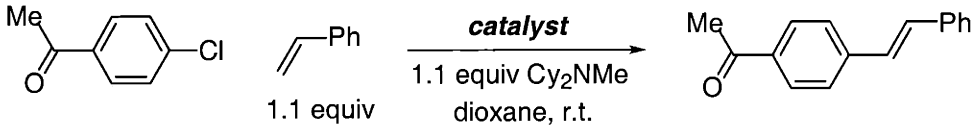
(11)

1:1 mixture of isomers
73%

^{31}P NMR and reactivity studies performed provide some insight into the reaction pathway. Essentially only $Pd(P(t\text{-}Bu)_3)_2$ is observed when room-temperature Heck reactions of aryl chlorides are monitored by ^{31}P NMR. Since a

1:1 ratio of Pd:P(t-Bu)$_3$ is employed for all room-temperature reactions, half of the palladium is in the form of Pd(P(t-Bu)$_3$)$_2$ and the other half is in the form of phosphine-free palladium complexes.

For couplings at room temperature, the use of a Pd:phosphine ratio of 1:2 leads to a marked decrease in the rate of the reaction (eq 12). This suggests that, although Pd(P(t-Bu)$_3$)$_2$ is the resting state of the system, it is not the catalytically active species in these Heck couplings. Similar to our hypothesis regarding the Suzuki coupling catalyzed by Pd/P(t-Bu)$_3$, a palladium monophosphine adduct is most probably the active catalyst, and the presence of phosphine-free palladium complexes leads to a higher concentration of this adduct. The use of either Pd$_2$(dba)$_3$/P(t-Bu)$_3$ or the more user-friendly Pd$_2$(dba)$_3$/Pd(P(t-Bu)$_3$)$_2$ leads to equally active catalysts as long as the Pd:P ratios are 1:1 (eq 12).



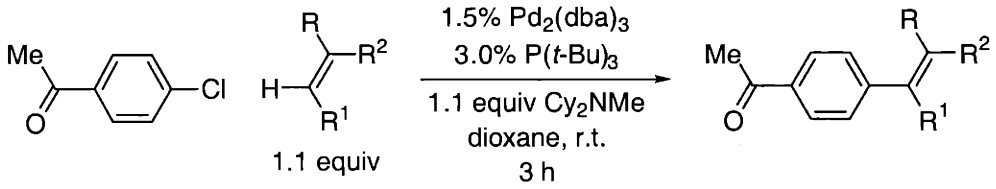
(12)

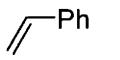
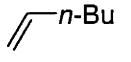
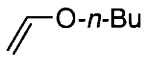
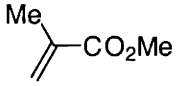
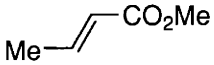
catalyst [Pd:phosphine ratio]	conversion after 3 hours
1.5% Pd$_2$(dba)$_3$/3.0% P(t-Bu)$_3$ [1:1]	30%
1.5% Pd(P(t-Bu)$_3$)$_2$/0.75% Pd$_2$(dba)$_3$ [1:1]	29%
3.0% Pd(P(t-Bu)$_3$)$_2$ [1:2]	<2%

In order to gain insight into which step of the catalytic cycle is turnover-limiting, a series of reactivity and kinetics studies were undertaken. The relative rate of arylation of a diverse set of olefins with 4'-chloroacetophenone was determined (Table 4), and, somewhat surprisingly, styrene, which is considered a fairly reactive olefin in Heck couplings using other catalyst systems, displayed similar reactivity to 1-hexene, n-butyl vinyl ether, and methyl methacrylate (Table 4, entries 1-4). The similar reactivities observed with

these sterically and electronically differentiated olefins suggests that the olefin is not playing a major role in the rate-limiting step.

Table 4. Effect of Olefin Structure on the Rate of Heck Coupling of 4'-Chloroacetophenone



Entry	Olefin	% Conversion (GC)
1		30
2		39
3		35
4		37
5		16

For the arylation of styrene with 4'-chloroacetophenone, a preliminary kinetics study indicates that the reaction rate is first order in aryl chloride and zero order in olefin, which is consistent with oxidative addition being the turnover-limiting step. In the coupling of 4'-chloroacetophenone with methyl crotonate (Table 4, entry 5), it is likely that a step after oxidative addition is turnover-limiting, presumably due to the steric demand of the olefin.

^{31}P NMR monitoring of the Heck reaction of 4-bromoanisole and styrene indicated a considerably more complex situation than was observed for the analogous reaction with 4'-chloroacetophenone, as more than one species was detected. Only a small amount of Pd(P(*t*-Bu)$_3$)$_2$ was evident by ^{31}P NMR, with

the major phosphorus-containing species resonating at δ ~64 (broad), accompanied by a minor compound at δ 92.

The peak at δ 92, which is not present in the absence of aryl halide, could also be observed in stoichiometric reactions between 4-bromoanisole and $Pd_2(dba)_3/P(t\text{-}Bu)_3$ (2:1:2). ^1H NMR analysis also indicated a set of resonances for a new compound derived from $P(t\text{-}Bu)_3$ and 4-bromoanisole. On the basis of these results, we speculate that the ^{31}P resonance at δ 92 arises from oxidative addition of the aryl bromide to a palladium monophosphine complex.

Attempts to isolate and further characterize this species have so far proven unsuccessful. In the stoichiometric experiments mentioned above, within several hours at room temperature, decomposition (precipitation of palladium metal) was observed, which may be due to a Heck reaction with the dba ligand. The use of aryl bromides with functional groups in the ortho position containing heteroatoms that could trap/stabilize an oxidative-addition adduct through coordination to Pd also failed to yield any desired complex. Such a strategy was recently successfully employed by Hartwig for the isolation of a $(PCy_3)Pd(Ar)Br$ species.[41]

NMR analysis of these stoichiometric reactions seemed to suggest that there is a weak driving force for the oxidative addition of aryl bromide to $P(t\text{-}Bu)_3$-ligated Pd(0) complexes, as considerable amounts of $Pd(P(t\text{-}Bu)_3)_2$ (^{31}P, ^1H) and unreacted aryl bromide (^1H) were always present, in addition to the peak at δ 92. These findings concur with recent studies by Hartwig on the reverse reaction, the reductive elimination of aryl halide from palladium phosphine (including $P(t\text{-}Bu)_3$) complexes.[42] The difficulty in obtaining an oxidative-addition adduct of a $(P(t\text{-}Bu)_3)$-Pd species was observed as early as 1989 by Osborn and coworkers.

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41 Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402-3415.
42 Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232-1233.

Although $Pd(PCy_3)_2(dba)$ underwent clean reaction with chlorobenzene at 60 °C to yield *trans*-$(Pd(PCy_3)_2(Ph)Cl)$, Pd(0) complexes with P(*t*-Bu)$_3$ did *not* undergo oxidative addition with chlorobenzene under identical conditions.[43]

In conclusion, we have developed exceptionally mild and general methods for effecting Heck reactions of aryl chlorides and bromides using Pd/P(*t*-Bu)$_3$ as catalyst and Cy_2NMe as base. In particular, coupling of electron-rich, electron-deficient, and sterically hindered aryl bromides with an array of olefins can be accomplished in high yields at room temperature. Pd/P(*t*-Bu)$_3$ also allows for the unprecedented room-temperature Heck coupling of electron-deficient aryl chlorides. Furthermore, for Heck couplings of unactivated aryl chlorides, in particular, electron-rich and hindered aryl chlorides, Pd/P(*t*-Bu)$_3$/Cy_2NMe currently represents the most general method. Essentially all reactions of aryl bromides and chlorides with disubstituted olefins proceed with a high degree of stereoselectivity, thus allowing the synthesis of stereodefined trisubstituted alkenes. Both unactivated vinyl chlorides and bromides also participate in these Heck couplings. Enhancing the utility of Pd/P(*t*-Bu)$_3$/Cy_2NMe is that relatively low catalyst loadings may be used and reactions can be performed on multigram scale. Mechanistic studies suggest that for room-temperature aryl chloride Heck couplings, oxidative addition is turnover-limiting. In terms of scope and mildness of conditions, we believe that this catalyst system represents a significant advance for the Heck reaction.[44]

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[43] Huser, M.; Youinou, M. -T.; Osborn, J. A. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1386-1388.

[44] For recent examples of Pd/P(*t*-Bu)3-catalyzed Heck reactions: (a) Allegretti, M.; Arcadi, A.; Marinelli, F.; Nicolini, L. *Synlett* **2001**, 609-612. (b) Early, T. R.; Gordon, R. S.; Carroll, M. A.; Holmes, A. B.; Shute, R. E.; McConvey, I. F. *Chem. Commun.* **2001**, 1966-1967. (c) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2002**, *124*, 754-755.

Experimental Section

General Considerations. The general considerations are the same as the previous chapters with the following exceptions. 1,4-Dioxane (anhydrous; Sure/Seal; Aldrich), toluene (anhydrous; Sure/Seal; Aldrich), chlorobenzene (anhydrous; Sure/Seal; Aldrich), $Pd_2(dba)_3$ (Aldrich), P(*t*-Bu)$_3$ (Strem), and P(*t*-Bu)$_3$ (10 wt% solution in hexane; Sure/Seal; Strem) were used as received. Pd(P(*t*-Bu)$_3$)$_2$ was either purchased from Strem and used as received or prepared according to the procedure below. DMF, (anhydrous, EM Science) was degassed under high vacuum for 10-15 min prior to use. MeOH, (lab grade, Mallinkrodt) was degassed via three freeze-pump-thaw cycles prior to use. The toluene that was used during the preparation of Pd(P(*t*-Bu)$_3$)$_2$ was purchased from J. T. Baker in CYCLE-TRAINER solvent delivery kegs and vigorously purged with argon for 2 hours followed by passage through two packed columns of neutral alumina and copper(II) oxide under argon pressure.[45] Cy_2NMe (Aldrich) was degassed (freeze-pump-thaw) prior to use with the exception of eqs 7 and 8 (degassing performed by sparging with argon). All aryl chlorides and bromides were purchased (Aldrich, Alfa-Aesar, and Lancaster) and degassed (freeze-pump-thaw) prior to use (if liquids) or used as received (if solids). All olefins were purchased from Aldrich. Methyl methacrylate, methyl crotonate, and *n*-butyl vinyl ether were vacuum transferred. Styrene and *n*-butyl methacrylate were degassed by gently sparging with argon for 5-10 minutes. 2,3-Dihydrofuran was distilled from calcium hydride. 1-Hexene was distilled from sodium. 2-Methyl-2-propen-1-ol and 2-ethylhexyl acrylate were degassed

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[45] (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520. (b) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. J. *J. Chem. Ed.* **2001**, *78*, 64-64.

(freeze-pump-thaw). Methyl *trans*-cinnamate and methyl 2-acetamidoacrylate were used as received.

E or *Z* olefin geometries were assigned on the basis of nOe studies or by analogy with known compounds.

All reactions were assembled under an inert atmosphere either in a screw-cap vial or in a resealable Schlenk tube (oven-dried), with the exception of eqs 7 and 8 (for specifics, please refer to experimental below for eqs 7 and 8). Because the yields that are reported in Tables 1-3 are the average of two runs (one with Procedure A and one with Procedure B), the yields that are reported below for a specific experiment may differ from those values.

Procedure for the preparation of Pd(P(*t*-Bu)$_3$)$_2$. In a nitrogen-filled Vacuum Atmospheres Glovebox, a 100 mL one-neck round-bottom flask equipped with a teflon-coated magnetic stir-bar and glass stopper is charged with $Pd_2(dba)_3$ (2.98 g, 3.25 mmol) . A solution of P(*t*-Bu)$_3$ (2.88 g, 14.2 mmol) in *N,N*-dimethylformamide (DMF) (43 mL) is then added to the reaction flask via a glass pipette and the resulting dark greenish-brown solution is stirred at room temperature in the glovebox for 23 hours. The reaction mixture is then filtered through a 30 mL medium porosity glass frit to collect the crude product Pd(P(*t*-Bu)$_3$)$_2$ as a gray solid. The reaction flask is successively rinsed with DMF (3 x 6 mL) and methanol (MeOH, 1 x 5 mL) and the rinses filtered through the glass frit. The crude product is then dissolved in toluene (100 mL) and filtered through a 3-cm diameter 0.45 um Gelman acrodisk into a 250 mL Schlenk tube to remove some black insoluble material, affording an orangish-yellow, homogenous solution. The Schlenk tube was then removed from the glovebox and the toluene solution concentrated via high vacuum to approximately 25 mL volume, at which point a white crystalline solid had begun to precipitate out of solution.

The Schlenk tube was brought back into the glovebox and the toluene solution and crystalline solid were transferred to a 250 mL Erlenmeyer flask via a glass pipette. MeOH (100 mL) was then added slowly via pipette over the course of 10 min which resulted in the precipitation of more white crystalline solid. The solution was allowed to stand for one hour at which point the mother liquor was decanted from the solid via pipette. The solid was washed with MeOH (2 x 10 mL) and transferred using a metal spatula to a tared 20 mL glass vial and dried under high vacuum to afford 1.50 g (45%) of desired $Pd(P(t\text{-}Bu)_3)_2$ as white, crystalline solid. A further 0.20 g (6%) of product could be obtained in a similar manner by concentrating the mother liquor, adding MeOH, decanting off the MeOH/toluene, washing with MeOH, and drying under vacuum. The bulk of $Pd(P(t\text{-}Bu)_3)_2$ is stored under nitrogen in a Vacuum Atmospheres Glovebox. Small portions (approximately 0.5-1.0 gram) were removed from the glovebox in glass vials and weighed in the air. $^{31}P\{^1H\}$ NMR (C_6D_6): 85.2; ^1H NMR (C_6D_6, 300 MHz): 1.53 (t, J = 5.7 Hz, 54H).

General Procedures for the $Pd_2(dba)_3/P(t\text{-}Bu)_3$-catalyzed Heck Coupling of Aryl Chlorides.

Procedure A. In a Vacuum Atmospheres Glovebox, $Pd_2(dba)_3$, the aryl or vinyl halide, Cy_2NMe, a solution of $P(t\text{-}Bu)_3$ in dioxane, dioxane, and the olefin (olefins that are solids were added prior to the addition of the halide) were added in turn to a reaction vessel equipped with a stir bar. The mixture was stirred at the indicated temperature for the indicated amount of time. At the conclusion of the reaction, the mixture was diluted with Et_2O or EtOAc, filtered through a pad of silica gel with copious washings, concentrated, and purified by column chromatography. For experiments in which an internal standard was used, the internal standard was added prior to the addition of the aryl or vinyl halide.

Procedure B (no glove box). $Pd_2(dba)_3$ was added (along with the aryl or vinyl halide and the olefin, if they are solids) to an oven-dried Schlenk tube equipped with a stir bar. The Schlenk tube was fitted with a rubber septum, evacuated, and then refilled with argon. The halide, Cy_2NMe, a solution of P(*t*-Bu)$_3$ in dioxane, the olefin, and then dioxane were added via syringe. The septum was replaced with a Teflon stopcock, and the reaction mixture was stirred at the indicated temperature for the indicated amount of time. At the conclusion of the reaction, the mixture was diluted with Et_2O or EtOAc, filtered through a pad of silica gel with copious washings, concentrated, and purified by column chromatography.

1-Butoxyethenyl-4-dimethylaminobenzene and (*E*)- and (*Z*)-(2-butoxyethenyl)-4-dimethylaminobenzene (Table 1, entry 1). Procedure B was employed, using 4-bromo-*N*,*N*-dimethylaniline (185 mg, 0.926 mmol), *n*-butyl vinyl ether (0.130 mL, 1.00 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (4.3 mg, 0.0047 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.096 mL, 0.0096 mmol), and dioxane (0.84 mL). After 48 hours at room temperature, workup and column chromatography (4% NEt_3/hexanes) yielded 202 mg (99%) of a slightly pale-yellow liquid, which on the basis of ^1H NMR analysis was determined to consist of the terminal olefin and the *E* and *Z* disubstituted olefins in a 13:3:1 ratio. ^1H NMR (C_6D_6, 300 MHz) terminal olefin: 7.83 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 9.0 Hz, 2H), 4.76 (d, *J* = 2.4 Hz, 1H), 4.16 (d, *J* = 2.4 Hz, 1H), 3.72 (t, *J* = 6.3 Hz, 2H), 2.48 (s, 6H), 1.18-1.81 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H). *E* olefin: 7.23 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 12.9 Hz, 1H), 6.02 (d, *J* = 12.9 Hz, 1H), 3.54 (t, *J* = 6.3 Hz, 2H), 2.54 (s, 6H). Other resonances are obscured by the resonances for the terminal olefin and the *Z* olefin. *Z* olefin: 6.70 (d, *J* = 9.0 Hz, 2H), 5.91 (d, *J* = 7.2 Hz, 1H), 5.35 (d, *J* = 7.2 Hz, 1H), 3.51 (t, *J* = 6.3 Hz, 2H), 2.52 (s, 6H). Other resonances are

obscured by the resonances for the terminal olefin and the *E* olefin. ^{13}C NMR (C_6D_6, 75 MHz) terminal olefin: 161.4, 151.2, 127.1, 126.1, 112.5, 79.5, 67.7, 40.5, 32.1, 20.4, 14.6. IR (neat, cm^{-1}): 2933, 1666, 1600, 1520, 1446, 1367, 1279, 947, 819. HRMS (EI, *m/z*) calcd. for $C_{14}H_{21}NO$ (M^+): 219.1623. Found: 219.1619.

(*E*)-3-(4-Acetylphenyl)-2-methyl acrylic acid methyl ester (Table 1, entry 2). Procedure B was employed, using 4-bromoacetophenone (185 mg, 0.927 mmol), methyl methacrylate (0.200 mL, 1.87 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (4.3 mg, 0.0047 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.095 mL, 0.0095 mmol), and dioxane (0.84 mL). After 26 hours at room temperature, workup and column chromatography (30% Et_2O/hexanes) yielded 155 mg (77%) of the title compound as a pale-yellow solid. ^1H NMR ($CDCl_3$, 300 MHz): 7.98 (d, *J* = 8.4 Hz, 2H), 7.70 (apparent s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H), 2.62 (s, 3H), 2.13 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 197.5, 168.7, 140.6, 137.7, 136.4, 130.5, 129.8, 128.4, 52.5, 26.9, 14.5. IR (CH_2Cl_2 solution, cm^{-1}): 2951, 1712, 1684, 1603, 1435, 1260, 1120, 737. HRMS (EI, *m/z*) calcd. for $C_{13}H_{14}O_3$ (M^+): 218.0943. Found: 218.0950.

(*E*)-and (*Z*)-3-(4-Hydroxyphenyl)-2-methyl acrylic acid methyl ester (Table 1, entry 3) [153773-39-8] [169237-15-4].[19] Procedure B was employed, using 4-bromophenol (157 mg, 0.910 mmol), methyl methacrylate (0.195 mL, 1.82 mmol), Cy_2NMe (0.21 mL, 0.98 mmol), $Pd_2(dba)_3$ (4.2 mg, 0.0046 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.094 mL, 0.0094 mmol), and dioxane (0.82 mL). After 26 hours at room temperature, workup and column chromatography (50% Et_2O/hexanes) yielded two sets of fractions: 114 mg (65%) of a white solid which based on ^1H NMR analysis was the *E* isomer and 24 mg (14%) of a yellow solid which based on ^1H NMR analysis was a 1.1:1 mixture of the *E* and *Z* isomers. Total yield: 79%; overall *E*:*Z* ratio = 11:1. ^1H NMR ($CDCl_3$, 300 MHz) *E* isomer: 7.64 (apparent s, 1H), 7.32 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.98 (broad

s, 1H), 3.82 (s, 3H), 2.13 (d, J = 1.5 Hz, 3H). *Z* isomer: 7.12 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 6.65 (apparent s, 1H), 3.69 (s, 3H), 2.07 (s, J = 1.5 Hz, 3H) (cannot detect phenolic hydrogen). ^{13}C NMR ($CDCl_3$, 75 MHz) *E* isomer: 170.0, 156.3, 139.3, 131.8, 128.4, 125.8, 115.6, 52.5, 14.4. ^{13}C NMR ($CDCl_3$, 75 MHz) *Z* isomer: 170.9, 155.7, 135.3, 129.9, 128.5, 127.4, 115.3, 52.0, 21.8.

(*E*)-3-(4-Dimethylaminophenyl)-2-methyl acrylic acid methyl ester (Table 1, entry 4) [50704-04-6].[46] Procedure B was employed, using 4-bromo-*N,N*-dimethylaniline (191 mg, 0.956 mmol), methyl methacrylate (0.205 mL, 1.92 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (4.4 mg, 0.0048 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.098 mL, 0.0098 mmol), and dioxane (0.86 mL). After 24 hours at room temperature, workup and column chromatography (20% Et_2O/hexanes) yielded 210 mg (100%) of the title compound as a yellow solid. ^1H NMR ($CDCl_3$, 300 MHz): 7.62 (apparent s, 1H), 7.38 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), 3.00 (s, 6H), 2.16 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 169.8, 150.3, 139.5, 131.7, 123.7, 123.1, 111.7, 52.0, 40.4, 14.5.

(*E*)-3-(4-Chlorophenyl)-2-methyl acrylic acid methyl ester (Table 1, entry 5) [53059-73-7].[47] Procedure B was employed, using 4-bromochlorobenzene (173 mg, 0.905 mmol), methyl methacrylate (0.195 mL, 1.82 mmol), Cy_2NMe (0.21 mL, 0.98 mmol), $Pd_2(dba)_3$ (4.2 mg, 0.0046 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.094 mL, 0.0094 mmol), and dioxane (0.82 mL). After 10 hours at room temperature, workup and column chromatography (5% Et_2O/hexanes) yielded 134 mg (70%) of the title compound as a slightly yellow liquid that contained 8% of the terminal olefin (based on NMR). ^1H NMR ($CDCl_3$, 300 MHz): 7.63 (m, 1H), 7.37 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H), 2.10 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 168.9, 137.7, 134.4, 134.3, 131.0, 129.0, 128.8, 52.4, 14.4.

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[46] El-Abbady, A. M.; Doss, A. M.; Ahmed, M. S. *J. Drug. Res.* **1972**, *4*, 123-134.
[47] Bottin-Strzalko, T. *Tetrahedron* **1973**, *29*, 4199-4204.

(*E*)-3-(4-Trifluoromethylsulfonylphenyl)-2-methyl acrylic acid methyl ester (Table 1, entry 6). Procedure B was employed, using 4-bromophenyl trifluoromethanesulfonate (311 mg, 1.02 mmol), methyl methacrylate (0.220 mL, 2.06 mmol), Cy_2NMe (0.240 mL, 1.12 mmol), $Pd_2(dba)_3$ (4.7 mg, 0.0051 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.10 mL, 0.010 mmol), and dioxane (0.92 mL). After 19 hours at room temperature, workup and column chromatography (20% Et_2O/hexanes) yielded 210 mg (63%) of the title compound as a yellow liquid that contained 7% of the terminal olefin (based on NMR). ^1H NMR ($CDCl_3$, 300 MHz): 7.65 (apparent s, 1H), 7.45 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H), 2.10 (d, J = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 168.6, 149.0, 136.7, 136.3, 131.4, 130.2, 121.5, 118.8 (q, J = 318 Hz), 52.5, 14.3. IR (neat, cm^{-1}): 2955, 1718, 1640, 1596, 1426, 1213. 1141, 888. HRMS (EI, m/z) calcd. for $C_{12}H_{11}F_3O_5S$ (M^+): 324.0279. Found: 324.0271.

(*E*)-3-(2-Methylphenyl)-2-methyl acrylic acid methyl ester (Table 1 entry 7). Procedure B was employed, using 2-bromotoluene (0.150 mL, 1.25 mmol), methyl methacrylate (0.270 mL, 2.52 mmol), Cy_2NMe (0.290 mL, 1.35 mmol), $Pd_2(dba)_3$ (5.7 mg, 0.0062 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.12 mL, 0.012 mmol), and dioxane (1.10 mL). After 69 hours at room temperature, workup and column chromatography (5% Et_2O/hexanes) yielded 205 mg (86%) of the title compound as a slightly yellow liquid that contained 5% of the terminal olefin (based on NMR). ^1H NMR ($CDCl_3$, 300 MHz): 7.74 (apparent s, 1H), 7.18-7.23 (m, 4H), 3.82 (s, 3H), 2.28 (s, 3H), 1.96 (d, J = 1.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 169.0, 138.5, 137.0, 135.2, 130.2, 129.1, 128.9, 128.3, 125.6, 52.3, 20.2, 14.3. IR (neat, cm^{-1}): 2950, 1714, 1637, 1435, 1257, 1120, 758, 742. HRMS (EI, m/z) calcd. for $C_{12}H_{14}O_2$ (M^+): 190.0994. Found: 190.0991.

2-(2,6-Dimethylphenylbenzyl)acrylic acid methyl ester and (*E*)-3-(2,6-dimethylphenyl)-2-methyl acrylic acid methyl ester (Table 1, entry 8).

Procedure B was employed, using 2-bromo-*m*-xylene (0.140 mL, 1.05 mmol), methyl methacrylate (0.125 mL, 1.17 mmol), Cy_2NMe (0.250 mL, 1.17 mmol), $Pd_2(dba)_3$ (4.9 mg, 0.0054 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.11 mL, 0.011 mmol), and dioxane (0.94 mL). After 12 hours at room temperature, workup and column chromatography (5% Et_2O/hexanes) yielded 208 mg (97%) of a colorless liquid that was an 8:1 mixture of 2-(2,6-dimethylphenylbenzyl)acrylic acid methyl ester and (*E*)-3-(2,6-dimethylphenyl)-2-methyl acrylic acid methyl ester (based on NMR). ^{1}H NMR ($CDCl_3$, 300 MHz) 2-(2,6-dimethylphenylbenzyl)acrylic acid methyl ester: 7.01-7.15 (m, 3H), 6.12 (dt, J = 3.3, 1.5 Hz, 1H), 4.92 (dt, J = 3.6, 1.5 Hz, 1H), 3.83 (s, 3H), 3.62 (apparent triplet, 2H), 2.21 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 167.8, 137.8, 137.1, 135.0, 128.1, 126.6, 124.4, 52.2, 31.5, 20.0. IR (neat, cm^{-1}): 3067, 3020, 2950, 1720, 1631, 1436, 1279, 1255, 1135, 770. HRMS (EI, m/z) calcd. for $C_{13}H_{16}O_2$: 204.1150 (M^+). Found: 204.1154. The ^{1}H and ^{13}C NMR data for the minor component, (*E*)-2-methyl-3-(2,6-dimethylphenyl)acrylic acid methyl ester, were the same as that reported in Table 3, entry 6.

(*E*)-3-(4-Dimethyaminophenyl)-3-phenyl acrylic acid methyl ester (Table 1, entry 9) [255054-06-9].[12] Procedure B was employed, using 4-bromo-*N,N*-dimethylaniline (196 mg, 0.978 mmol), methyl *trans*-cinnamate (172 mg, 1.06 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.010 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.20 mL, 0.020 mmol), and dioxane (0.78 mL). After 72 hours at room temperature, workup and column chromatography (70% CH_2Cl_2/hexanes $\rightarrow$ 85% CH_2Cl_2/hexanes) yielded 200 mg (73%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.36-7.41 (m, 3H), 7.18-7.22 (m, 4H), 6.61 (d, J = 9.3 Hz, 2H), 6.30 (s, 1H), 3.58 (s, 3H), 2.98 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 166.9, 157.7, 151.3, 139.6, 129.6, 129.1, 127.8, 127.7, 111.8, 111.5, 51.2, 40.4.

(*E*)-3-(4-Dimethylaminophenyl)-3-methyl acrylic acid methyl ester (Table 1, entry 10). Procedure B was employed, using 4-bromo-*N,N*-dimethylaniline (186

mg, 0.929 mmol), methyl crotonate (0.200 mL, 1.88 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (8.6 mg, 0.0094 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.19 mL, 0.019 mmol), and dioxane (0.74 mL). After 23 hours at room temperature, workup and column chromatography (20% Et_2O/hexanes) yielded 134 mg (66%) of the title compound as a yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.44 (d, J = 9.0 Hz, 2H), 6.67 (d, J = 9.0 Hz, 2H), 6.11 (q, J = 1.5 Hz, 1H), 3.73 (s, 3H), 2.99 (s, 6H), 2.57 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 167.9, 155.8, 151.2, 128.9, 127.5, 112.4, 111.8, 51.2, 40.5, 17.5. IR (CH_2Cl_2 solution, cm^{-1}): 3052, 2947, 1707, 1599, 1438, 1349, 1266, 1159, 817. HRMS (EI, m/z) calcd. for $C_{13}H_{17}O_2N$ (M^+): 219.1259. Found: 219.1265.

(*E*)-3-(2,6-Dimethylphenyl)-3-methyl acrylic acid methyl ester (Table 1, entry 11). Procedure B was employed, using 2-bromo-*m*-xylene (0.115 mL, 0.863 mmol), methyl crotonate (0.100 mL, 0.943 mmol), Cy_2NMe (0.200 mL, 0.934 mmol), $Pd_2(dba)_3$ (11.9 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.26 mL, 0.026 mmol), and dioxane (0.60 mL). After 49 hours at room temperature, workup and column chromatography (5% Et_2O/hexanes) yielded 150 mg (85%) of the title compound as a clear, colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.01-7.12 (m, 3H), 5.70 (q, J = 1.5 Hz, 1H), 3.76 (s, 3H), 2.39 (d, J = 1.5 Hz, 3H), 2.20 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): 167.1, 158.4, 143.2, 133.7, 127.6, 127.2, 119.2, 51.3, 20.3, 19.9. IR (neat, cm^{-1}): 3062, 3017, 2949, 2922, 1719, 1643, 1434, 1265, 1170, 1036, 771. HRMS (EI, m/z) calcd. for $C_{13}H_{16}O_2$ (M^+): 204.1145. Found: 204.1144.

(*E,Z*)- and (*E,E*)-3-Methyl-1-phenylpenta-1,3-diene (Table 1, entry 12) [104722-44-3] [20414-99-7].[48] Procedure B was employed, using 2-bromo-*trans*-2-butene (0.0800 mL, 0.789 mmol), styrene (0.100 mL, 0.873 mmol), Cy_2NMe (0.190 mL, 0.887 mmol), $Pd_2(dba)_3$ (11.1 mg, 0.012 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.25 mL, 0.025 mmol), and dioxane (0.54 mL). After 77 hours at room temperature,

[48] Uriac, P.; Bonnic, J.; Huet, J. *Tetrahedron* **1985**, *41*, 5051-5060.

workup and column chromatography (pentane) yielded 116 mg (93%) of the title compound as a yellow liquid, which by ^{1}H NMR analysis consisted of an 8:1 mixture of the (*E*,*Z*) and (*E*,*E*) isomers. ^{1}H NMR ($CDCl_3$, 300 MHz): (*E*,*Z*) isomer: 7.42-7.47 (m, 2H), 7.28-7.35 (m, 2H), 7.18-7.26 (m, 2H), 6.55 (d, *J* = 16.2 Hz, 1H), 5.54 (qq, *J* = 7.2, 1.5 Hz, 1H), 1.93 (apparent quintet, 3H), 1.82-1.87 (m, 3H). (*E*,*E*)-isomer: 6.81 (d, *J* = 15.9 Hz, 1H), 6.44 (d, *J* = 15.9 Hz, 1H), 5.67-5.75 (m, 1H), 1.77-1.81 (m, 3H) Other resonances are obscured by the major (*E*,*Z*) isomer. ^{13}C NMR ($CDCl_3$, 75 MHz): (*E*,*Z*) isomer: 138.1, 132.9, 128.7, 128.1, 127.3, 126.5, 126.2, 125.9, 20.8, 13.6.

***trans*-4-Acetylstilbene (Table 2, entry 1) [20488-42-0].**[49] Procedure B was employed, using 4'-chloroacetophenone (0.115 mL, 0.887 mmol), styrene (0.110 mL, 0.960 mmol), Cy_2NMe (0.210 mL, 0.980 mmol), $Pd_2(dba)_3$ (12.3 mg, 0.013 mmol), P(*t*-Bu)$_3$ (10 wt% solution in hexane; 0.080 mL, 0.029 mmol), and dioxane (0.80 mL). After 32 hours at room temperature, workup and column chromatography (15% Et_2O/hexanes) yielded 149 mg (76%) of the title compound as a pale-yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.94 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.24-7.40 (m, 3H), 7.22 (d, *J* = 16.5 Hz, 1H), 7.11 (d, *J* = 16.5 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 197.5, 142.1, 136.8, 136.0, 131.5, 129.0, 128.9, 128.4, 127.5, 126.9, 126.6, 26.9.

(*E*)- and (*Z*)-1-[4-(Hex-1-enyl)phenyl]ethanone (Table 2, entry 2) [137365-00-5].[50] Procedure B was employed, using 4'-chloroacetophenone (0.125 mL, 0.964 mmol), 1-hexene (0.135 mL, 1.08 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (13.4 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.20 mL, 0.030 mmol), and dioxane (0.76 mL). After 47 hours at room temperature, workup and column chromatography (8% Et_2O/hexanes) yielded 136 mg (70%) of a

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[49] Bezou, P.; Hilberer, A.; Hadziioannou, G. *Synthesis* **1996**, 449-451.
[50] Kauffmann, T.; Laarmann, B.; Menges, D.; Neiteler, G. *Chem. Ber.* **1992**, *125*, 163-169.

slightly pale-yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) *E* isomer: 7.88 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.37-6.45 (m, 2H), 2.58 (s, 3H), 2.19-2.28 (m, 2H), 1.30-1.60 (m, 4H), 0.90-1.00 (m, 3H). *Z* isomer: 7.45 (d, *J* = 8.7 Hz, 2H), 5.85-5.98 (m, 2H), 2.59 (s, 3H). Other resonances for the *Z* isomer are obscured by the resonances for the *E* isomer. ^{13}C NMR ($CDCl_3$, 75 MHz) *E* isomer: 197.6, 142.8, 135.4, 134.6, 129.0, 128.8, 126.0, 33.1, 31.5, 26.8, 22.6, 14.2. IR (neat, cm^{-1}): 2958, 2927, 1682, 1602, 1357, 1267, 1181, 856. HRMS (EI, *m/z*) calcd. for $C_{14}H_{18}O$ (M^+): 202.1358. Found: 202.1361. The *E*:*Z* ratio was determined by GC.

(*E*)- and (*Z*)-(2-Butoxyethenyl)-4-acetylbenzene and 1-butoxyethenyl-4-acetylbenzene (Table 2, entry 3) [153390-96-6] [153390-95-5].[51] Procedure B was employed, using 4'-chloroacetophenone (0.110 mL, 0.848 mmol), *n*-butyl vinyl ether (0.120 mL, 0.927 mmol), Cy_2NMe (0.200 mL, 0.934 mmol), $Pd_2(dba)_3$ (11.6 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.17 mL, 0.025 mmol), and dioxane (0.68 mL). After 33 hours at room temperature, workup and column chromatography (7% NEt_3/hexanes) yielded 155 mg (84%) of a yellow liquid that was comprised of a mixture of the *E*, *Z*, and terminal olefin isomers in a ratio of 8.2:1.6:1.0 (according to ^{1}H NMR). The olefin mixture was contaminated with 4% of 4'-chloroacetophenone (by ^{1}H NMR). ^{1}H NMR (C_6D_6, 300 MHz) *E* isomer: 7.80 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 12.9 Hz, 1H), 5.75 (d, *J* = 12.9 Hz, 1H), 3.44 (t, *J* = 6.3 Hz, 2H), 2.15 (s, 3H), 1.16-1.50 (m, 4H), 0.81 (t, *J* = 7.2 Hz, 3H). *Z* isomer: 7.90 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 5.88 (d, *J* = 7.2 Hz, 1H), 5.15 (d, *J* = 7.2 Hz, 1H), 2.12 (s, 3H). Other resonances are obscured by the resonances for the E and terminal olefins. Terminal olefin: 4.70 (d, *J* = 2.7 Hz, 1H), 4.16 (d, *J* = 2.7 Hz, 1H), 3.56 (t, *J* = 6.6 Hz, 2H), 2.09 (s, 3H). Other resonances are obscured by the resonances for the *E* and *Z* isomers. ^{13}C

[51] Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1993**, *58*, 7421-7426.

NMR (C_6D_6, 75 MHz) *E* isomer: 196.0, 150.9, 142.3, 135.3, 129.6, 125.3, 105.7, 70.3, 32.0, 26.6, 19.9, 14.4.

(*E*)-3-(4-Acetylphenyl)-2-methyl acrylic acid methyl ester (Table 2, entry 4). Procedure B was employed, using 4'-chloroacetophenone (0.180 mL, 1.39 mmol), methyl methacrylate (0.165 mL, 1.54 mmol), Cy_2NMe (0.330 mL, 1.54 mmol), $Pd_2(dba)_3$ (19.0 mg, 0.021 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.28 mL, 0.042 mmol), and dioxane (1.10 mL). After 36 hours at room temperature, workup and column chromatography (30% Et_2O/hexanes) yielded 240 mg (79%) of the title compound as a slightly yellow solid. Spectral data were the same as that reported for Table 1, entry 2.

(*E*)-3-(2-Carbomethoxyphenyl)-2-methyl acrylic acid methyl ester (Table 2, entry 5). Procedure B was employed, using methyl 2-chlorobenzoate (0.125 mL, 0.873 mmol), methyl methacrylate (0.105 mL, 0.982 mmol), Cy_2NMe (0.21 mL, 0.980 mmol), $Pd_2(dba)_3$ (12.0 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.26 mL, 0.026 mmol), and dioxane (0.62 mL). After 24 hours at room temperature, workup and column chromatography (25% Et_2O/hexanes) yielded 186 mg (91%) of the title compound as a clear yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz): 8.11 (apparent s, 1H), 8.04 (dd, J = 7.8, 1.2 Hz, 1H), 7.52-7.57 (m, 1H), 7.37-7.43 (m, 1H), 7.27-7.30 (m, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 1.91 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 168.8, 166.9, 139.8, 137.9, 132.1, 130.8, 130.3, 129.1, 128.0, 127.9, 52.4, 52.3, 14.1. IR (neat, cm^{-1}): 3065, 2994, 2951, 1715, 1639, 1598, 1434, 1270, 1203, 1080, 763. HRMS (EI, m/z) calcd. for $C_{13}H_{14}O_4$ (M^+): 234.0887. Found: 234.0879.

3-(4-Cyanophenyl)-2-methylpropanal (Table 2, entry 6) [57918-88-4].[52] Procedure B was employed, using 4-chlorobenzonitrile (142 mg, 1.03 mmol), 2-methyl-2-propen-1-ol (0.0950 mL, 1.13 mmol), Cy_2NMe (0.240 mL, 1.12 mmol),

[52] Sunjic, V.; Majeric, M.; Hamersak, Z. *Croat. Chem. Acta.* **1996**, *69*, 643-660.

$Pd_2(dba)_3$ (14.3 mg, 0.016 mmol), P(*t*-Bu)$_3$ (10 wt% solution in hexane; 0.090 mL, 0.033 mmol), and dioxane (0.94 mL). After 48 hours at room temperature, workup and column chromatography (50% Et_2O/hexanes) yielded 127 mg (71%) of the title compound as a clear, slightly yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz): 9.70 (d, J = 1.2 Hz, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 3.10-3.21 (m, 1H), 2.62-2.79 (m, 2H), 1.12 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 203.2, 144.8, 132.4, 129.9, 118.9, 110.4, 47.8, 36.6, 13.6.

2-acetylamino-3-(4-cyanophenyl)-acrylic acid methyl ester (Table 2, entry 7). [43229-84-1][53] Procedure B was followed using 4-chlorobenzonitrile (148 mg, 1.07 mmol), methyl 2-acetamidoacrylate (170 mg, 1.19 mmol), dicyclohexylmethylamine (0.25 mL, 1.17 mmol), $Pd_2(dba)_3$ (14.9 mg, 0.016 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.22 mL, 0.033 mmol), and dioxane (0.86 mL). After 50 hours at room temperature, workup and column chromatography (75% EtOAc/hexanes) yielded 159 mg (61%) of the title compound (9.8:1 *Z*:*E* mixture) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): *Z* isomer: 7.62 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.35 (s, 1H), 7.28 (br s, 1H), 3.88 (s, 3H), 2.14 (s, 3H). *E* isomer: 8.11 (br s, 1H), 3.63 (s, 3H), 2.18 (s, 3H). Other resonances are obscured by the resonances for the *Z* isomer. ^{13}C NMR (DMSO-d_6, 75 MHz): 169.2, 165.0, 138.1, 132.2, 130.1, 129.0, 127.7, 118.5, 110.9, 52.4, 22.5. Assignment of the *Z* and *E* isomers was made by comparison with analogous compounds.[31]

2-(4-Acetylphenyl)-2,3-dihydrofuran (Table 2, entry 8) [131516-06-8].[57] Procedure B was employed, using 4'-chloroacetophenone (0.145 mL, 1.12 mmol), 2,3-dihydrofuran (0.250 mL, 3.31 mmol), Cy_2NMe (0.260 mL, 1.21 mmol), $Pd_2(dba)_3$ (5.1 mg, 0.0060 mmol), P(*t*-Bu)$_3$ (0.10 M solution; 0.115 mL, 0.012 mmol), and dioxane (1.00 mL). After 24 hours at room temperature, workup

[53] Richter, P.; Wagner, G. *Pharmazie* **1973**, *28*, 514-519.

and column chromatography (20% Et_2O/hexanes) yielded 144 mg (68%) of the title compound as a pale-yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz): 7.95 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.46 (q, J = 2.4 Hz, 1H), 5.56 (dd, J = 8.4, 11.1 Hz, 1H), 4.96 (q, J = 2.7 Hz, 1H), 3.14 (ddt, J = 15.3, 10.8, 2.4 Hz, 1H), 2.60 (s, 3H), 2.57 (ddt, J = 15.3, 8.1, 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 197.7, 148.5, 145.4, 136.5, 128.8, 125.7, 99.2, 81.7, 38.2, 26.9.

2-(4-Trifluoromethylphenyl)-2,3-dihydrofuran (Table 2, entry 9). Procedure B was employed, using 4-chlorobenzotrifluoride (0.130 mL, 0.974 mmol), 2,3-dihydrofuran (0.220 mL, 2.91 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (13.3 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.20 mL, 0.030 mmol), and dioxane (0.78 mL). After 26 hours at room temperature, workup and column chromatography (2% Et_2O/hexanes) yielded 163 mg (78%) of the title compound as a clear, colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): 7.61 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 7.8 Hz, 2H), 6.46 (q, J = 2.7 Hz, 1H), 5.56 (dd, J = 10.8, 8.1 Hz, 1H), 4.96 (q, J = 2.7 Hz, 1H), 3.14 (ddt, J = 15.6, 10.5, 2.4 Hz, 1H), 2.56 (ddt, J = 15.6, 7.8, 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 147.2, 145.4, 130.1, 129.7, 125.9, 125.6, 99.2, 81.6, 38.2. IR (neat, cm^{-1}): 3106, 2936, 2864, 1619, 1418, 1326, 1125, 843. HRMS (EI, m/z) calcd. for $C_{11}H_9F_3O$ (M^+): 214.0600. Found: 214.0604.

2-(2-Carbomethoxythiophene)-2,3-dihydrofuran (Table 2, entry 10). Procedure B was employed, using 2-carbomethoxy-3-chlorothiophene (167 mg, 0.946 mmol), 2,3-dihydrofuran (0.215 mL, 2.84 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (13.2 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.20 mL, 0.030 mmol), and dioxane (0.76 mL). After 23 hours at room temperature, workup and column chromatography (7% Et_2O/hexanes) yielded 172 mg (86%) of the title compound as a clear, colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): 7.44 (d, J = 5.1 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 6.45 (q, J = 2.7 Hz, 1H), 6.23 (dd, J = 10.8, 7.5 Hz, 1H), 4.94 (q, J = 2.7 Hz, 1H), 3.87 (s, 3H), 3.26 (ddt, J = 15.3, 10.8, 2.7

Hz, 1H), 2.41 (ddt, J = 15.3, 7.5, 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 162.6, 152.8, 145.1, 131.0, 127.4, 125.5, 99.5, 78.2, 52.2, 37.7. IR (cm^{-1}): 3104, 2994, 2950, 1711, 1620, 1532, 1436, 1256, 778. HRMS (EI, m/z) calcd. for $C_{10}H_{10}O_3S$ (M^+): 210.0351. Found: 210.0354.

(*E*)-3-(4-Cyanophenyl)-3-methyl acrylic acid methyl ester (Table 2, entry 11) [255054-11-6].[12] Procedure B was employed, using 4-chlorobenzonitrile (115 mg, 0.838 mmol), methyl crotonate (0.180 mL, 1.70 mmol), Cy_2NMe (0.200 mL, 0.934 mmol), $Pd_2(dba)_3$ (11.8 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.18 mL, 0.026 mmol), and dioxane (0.66 mL). After 60 hours at room temperature, workup and column chromatography (25% Et_2O/hexanes) yielded 88.4 mg (52%) of the title compound as a pale-yellow solid. ^1H NMR ($CDCl_3$, 300 MHz): 7.67 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 6.15 (q, J = 1.2 Hz, 1H), 3.77 (s, 3H), 2.57 (d, J = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 166.6, 153.5, 146.6, 132.5, 127.1, 119.3, 118.6, 112.6, 51.6, 18.1.

Heck reaction between 4-chlorobenzonitrile and 2-methyl-1-penten-3-ol (eq 2). Procedure A was employed, using 4-chlorobenzonitrile (109 mg, 0.789 mmol), 2-methyl-1-penten-3-ol (87.5 mg, 0.874 mmol), Cy_2NMe (0.185 mL, 0.864 mmol), $Pd_2(dba)_3$ (11.0 mg, 0.012 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.12 mL, 0.024 mmol), and dioxane (0.66 mL). After 25 hours at room temperature, workup and column chromatography (50% Et_2O/hexanes) yielded 91 mg (57%) of the ketone, 2-methyl-1-(4-cyanophenyl)-3-pentanone as a pale-yellow liquid and 59 mg (37%) of the allylic alcohol, 2-methyl-1-(4-cyanophenyl)-1-penten-3-ol as a pale yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz) 2-methyl-1-(4-cyanophenyl)-3-pentanone: 7.56 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 3.05 (dd, J = 13.5, 7.8 Hz, 1H), 2.85 (apparent sextet, J = 7.2 Hz, 1H), 2.62 (dd, J = 13.5, 6.9 Hz, 1H), 2.49 (dq, J = 17.7, 7.5 Hz, 1H), 2.25 (dq, J = 17.7, 7.2 Hz, 1H), 1.11 (d, J = 7.2 Hz, 3H),

0.98 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 213.7, 145.7, 132.3, 129.9, 119.0, 110.2, 47.6, 39.1, 35.3, 17.2, 7.9. HRMS (ESI, m/z) calcd. for $C_{13}H_{15}NO$ (M + Na): 224.1046. Found: 224.1053. ^1H NMR ($CDCl_3$, 300 MHz) 2-methyl-1-(4-cyanophenyl)-1-penten-3-ol: 7.60 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 6.50 (s, 1H), 4.12 (broad t, J = 6.3 Hz, 1H), 1.88-1.86 (m, 4H), 1.74-1.62 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) 2-methyl-1-(4-cyanophenyl)-1-penten-3-ol: 143.8, 142.6, 132.0, 129.6, 124.2, 119.2, 109.8, 79.0, 28.3, 13.9, 10.2. HRMS (ESI, m/z) calcd. for $C_{13}H_{15}NO$ (M + Na): 224.1046. Found: 224.1042.

(*E*)-3-(4-Cyanophenyl)-3-phenyl acrylic acid methyl ester (Table 3, entry 1). Procedure B was employed, using 4-chlorobenzonitrile (140 mg, 1.01 mmol), methyl *trans*-cinnamate (186 mg, 1.15 mmol), Cy_2NMe (0.240 mL, 1.12 mmol), $Pd_2(dba)_3$ (14.0 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.25 mL, 0.037 mmol), and dioxane (0.76 mL). After 70 hours at 70 °C, workup and column chromatography (30% Et_2O/hexanes) yielded 190 mg (71%) of the title compound as a pale-yellow solid. ^1H NMR ($CDCl_3$, 300 MHz): 7.61 (d, J = 8.1 Hz, 2H), 7.36-7.43 (m, 5H), 7.15-7.20 (m, 2H), 6.39 (s, 1H), 3.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 165.9, 154.7, 145.3, 137.6, 132.3, 129.1, 129.0, 128.9, 128.3, 119.6, 118.6, 113.0, 51.8. IR (CH_2Cl_2 solution, cm^{-1}): 3056, 2950, 2229, 1725, 1622, 1434, 1265, 1169, 841, 738. HRMS (EI, m/z) calcd. for $C_{17}H_{13}O_2N$ (M^+): 263.0941. Found: 263.0930.

***trans*-4-Methoxystilbene (Table 3, entry 2).** Procedure B was employed, using 4-chloroanisole (0.145 mL, 1.18 mmol), styrene (0.150 mL, 1.31 mmol), Cy_2NMe (0.280 mL, 1.31 mmol), $Pd_2(dba)_3$ (16.2 mg, 0.018 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.49 mL, 0.073 mmol), and dioxane (0.70 mL). After 26 hours at 120 °C, workup and column chromatography (1% Et_2O/hexanes) yielded 171 mg (69%) of the title compound as a white solid that was identical to authentic material (Alfa-Aesar) by GC, TLC, and ^1H NMR.

(*E*)-3-Phenyl-2-methyl acrylic acid methyl ester (Table 3, entry 3) [22946-43-6].[54] Procedure B was employed, using chlorobenzene (0.105 mL, 1.03 mmol), methyl methacrylate (0.120 mL, 1.12 mmol), Cy_2NMe (0.245 mL, 1.14 mmol), $Pd_2(dba)_3$ (14.1 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.14 M stock solution; 0.43 mL, 0.060 mmol), and dioxane (0.60 mL). After 60 hours at 100 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 158 mg (87%) of the title compound as a slightly red solid. ^1H NMR ($CDCl_3$, 300 MHz): 7.70 (q, J = 1.5 Hz, 1H), 7.29-7.40 (m, 5H), 3.82 (s, 3H), 2.12 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 169.2, 139.0, 135.9, 129.7, 128.4, 128.4, 128.3, 52.3, 14.3.

(*E*)-3-(4-Methoxyphenyl)-2-methyl acrylic acid methyl ester (Table 3, entry 4) [126356-04-5].[55] Procedure B was employed, using 4-chloroanisole (0.110 mL, 0.898 mmol), methyl methacrylate (0.105 mL, 0.982 mmol), Cy_2NMe (0.210 mL, 0.980 mmol), $Pd_2(dba)_3$ (12.2 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.14 M stock solution; 0.37 mL, 0.052 mmol), and dioxane (0.52 mL). After 53 hours at 120 °C, workup and column chromatography (20% Et_2O/hexanes) yielded 123 mg (66%) of the title compound as a clear, yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz): 7.64 (apparent s, 1H), 7.38 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.13 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 169.5, 159.7, 138.8, 131.5, 128.5, 126.1, 114.0, 55.5, 52.2, 14.4.

(*E*)-3-(2-Methylphenyl)-2-methyl acrylic acid methyl ester (Table 3, entry 5). Procedure B was employed, using 2-chlorotoluene (0.110 mL, 0.941 mmol), methyl methacrylate (0.110 mL, 1.03 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (12.9 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.38 mL, 0.057 mmol), and dioxane (0.56 mL). After 24 hours at 110 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 158 mg (88%) of the title compound

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54 van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron* **1996**, *52*, 12313-12322.
55 Mitra, J.; Mitra, A. K. *Indian J. Chem.* **1992**, *31B*, 613-616.

as a clear, colorless liquid. Spectroscopic data were the same as that reported for Table 1, entry 7.

(*E*)-3-(2,6-Dimethylphenyl)-2-methyl acrylic acid methyl ester (Table 3, entry 6) [124317-09-5].[56] Procedure B was employed, using 2-chloro-*m*-xylene (0.120 mL, 0.905 mmol), methyl methacrylate (0.110 mL, 1.03 mmol), Cy_2NMe (0.210 mL, 0.980 mmol), $Pd_2(dba)_3$ (12.3 mg, 0.013 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.36 mL, 0.054 mmol), and dioxane (0.54 mL). After 39 hours at 120 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 134 mg (72%) of the title compound as a clear, colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz): 7.62 (apparent s, 1H), 7.03-7.15 (m, 3H), 3.83 (s, 3H), 2.16 (s, 6H), 1.68 (d, J = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 168.4, 139.2, 135.5, 135.2, 130.5, 127.5, 127.4, 52.2, 20.4, 14.1.

(*E*)-3-(3-Pyridyl)-2-methyl acrylic acid methyl ester (Table 3, entry 7). Procedure B was employed, using 3-chloropyridine (0.0950 mL, 0.999 mmol), methyl methacrylate (0.120 mL, 1.12 mmol), Cy_2NMe (0.240 mL, 1.12 mmol), $Pd_2(dba)_3$ (13.6 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.41 mL, 0.061 mmol), and dioxane (0.58 mL). After 26 hours at 100 °C, workup and column chromatography (60% Et_2O/hexanes) yielded 140 mg (79%) of the title compound as a clear, yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz): 8.65 (apparent s, 1H), 8.55-8.56 (m, 1H), 7.71 (apparent dt, 1H), 7.64 (s, 1H), 7.32-7.36 (m, 1H), 3.84 (s, 3H), 2.13 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 168.5, 150.6, 149.1, 136.5, 135.2, 131.8, 130.7, 123.4, 52.5, 14.4. IR (neat, cm^{-1}): 3027, 2994, 2951, 1709, 1638, 1566, 1435, 1260, 1192, 1118, 1024, 800. HRMS (EI, m/z) calcd. for $C_{10}H_{11}O_2N$ (M^+): 177.0790. Found: 177.0787.

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[56] Moormann, A. E.; Pitzele, B. S.; Jones, P. H.; Gullikson, G. W.; Albin, D.; Yu, S. S.; Bianchi, R. G.; Sanguinetti, E. L.; Rubin, B.; Grebner, M.; Monroy, M.; Kellar, P.; Casler, J. *J. Med. Chem.* **1990**, *33*, 614-626.

(*E*)-3-Phenyl-3-methyl acrylic acid methyl ester (Table 3, entry 8) [3461-50-5].[55] Procedure B was employed, using chlorobenzene (0.100 mL, 0.983 mmol), methyl crotonate (0.210 mL, 1.98 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (13.8 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.14 M stock solution; 0.42 mL, 0.059 mmol), and dioxane (0.56 mL). After 49 hours at 120 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 86.7 mg (50%) of the title compound as a slightly pale-yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz): 7.44-7.49 (m, 2H), 7.34-7.39 (m, 3H), 6.13 (q, J = 1.5 Hz, 1H), 3.75 (s, 3H), 2.58 (d, J = 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 167.3, 156.0, 142.2, 129.2, 128.6, 126.4, 116.8, 51.4, 18.3.

2-(4-*t*-Butyl-1-cyclohexenyl)styrene (eq 3) [96575-67-6].[57] Procedure B was employed, using 1-chloro-4-*t*-butyl-cyclohexene (202 mg, 1.17 mmol), styrene (0.145 mL, 1.26 mmol), Cy_2NMe (0.280 mL, 1.31 mmol), $Pd_2(dba)_3$ (16.5 mg, 0.018 mmol), P(*t*-Bu)$_3$ (0.15 M stock solution; 0.50 mL, 0.075 mmol), and dioxane (0.66 mL). After 46 hours at 110 °C, workup and column chromatography (hexanes) yielded 188 mg (67%) of the title compound as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): 7.38-7.40 (m, 2H), 7.24-7.31 (m, 2H), 7.14-7.20 (m, 1H), 6.78 (d, J = 16.2 Hz, 1H), 6.41 (d, J = 16.2 Hz, 1H), 5.88-5.90 (m, 1H), 2.43-2.50 (m, 1H), 2.10-2.30 (m, 2H), 1.88-2.04 (m, 2H), 1.14-1.38 (m, 2H), 0.89 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 138.1, 135.8, 132.2, 131.2, 128.6, 126.9, 126.2, 124.9, 44.5, 32.5, 28.0, 27.5, 26.2, 24.1.

Competition experiment between an aryl chloride and a vinyl chloride (eq 4). Procedure A was employed, using chlorobenzene (0.0750 mL, 0.738 mmol), 1-chloro-4-*t*-butylcyclohexene (125 mg, 0.723 mmol), styrene (0.0850 mL, 0.742 mmol), Cy_2NMe (0.170 mL, 0.794 mmol), $Pd_2(dba)_3$ (10.0 mg, 0.011 mmol), P(*t*-

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[57] Scott, W. J.; Pena, M. R.; Sward, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302-2308.

$Bu)_3$ (0.10 M solution; 0.43 mL, 0.043 mmol), and dioxane (0.30 mL). After 26 hours at 110 °C, workup and column chromatography (hexanes) yielded 76.6 mg (58%) of a white solid that consisted of a 37:1 mixture of stilbene:diene and 68.1 mg (39%) of a white solid that consisted of a 32:1 mixture of diene:stilbene (ratios determined by ^{1}H NMR). The "diene" includes ~10% of an isomer of the expected diene in which both double bonds are part of the six-membered ring.

Heck coupling of chlorobenzene with methyl methacrylate at low catalyst loading (eq 5; typical procedure). $Pd(P(t\text{-}Bu)_3)_2$ (3.1 mg, 0.0060 mmol) was added to an oven-dried Schlenk tube equipped with a stir bar. A rubber septum was then attached to the reaction vessel, which was evacuated and refilled with argon. Next, chlorobenzene (0.310 mL, 3.05 mmol), Cy_2NMe (0.720 mL, 3.36 mmol), methyl methacrylate (0.360 mL, 3.37 mmol), and dioxane (1.50 mL) were added successively via syringe through the rubber septum. The rubber septum was removed, and the Schlenk tube was sealed with a Teflon stopcock. After stirring for 48 hours at 120 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 339 mg (63%) of the title compound as a colorless liquid that solidified on standing. Spectroscopic data were the same as that reported for Table 3, entry 3.

Room-temperature Heck coupling of 4-bromoanisole with 2-ethylhexyl acrylate catalyzed at low catalyst loading (eq 6; typical procedure). $Pd(P(t\text{-}Bu)_3)_2$ (3.2 mg, 0.0060 mmol) and $Pd_2(dba)_3$ (3.0 mg, 0.0030 mmol) were added to an oven-dried Schlenk tube equipped with a stir bar. A rubber septum was then attached to the reaction vessel, which was evacuated and refilled with argon. Next, 4-bromoanisole (0.800 mL, 6.39 mmol), Cy_2NMe (1.50 mL, 7.00 mmol), 2-ethylhexyl acrylate (1.45 mL, 6.96 mmol), and dioxane (2.05 mL) were added successively via syringe through the rubber septum. The rubber septum was removed, and the Schlenk tube was sealed with a Teflon stopcock. After stirring

for 148 hours at room temperature, workup and column chromatography (15% Et_2O/hexanes) yielded 1.54 g (83%) of the title compound as a colorless liquid that was identical to authentic material (Aldrich) by GC, TLC, and ^1H NMR.

***(E)*-2-methyl-3-phenyl-acrylic acid butyl ester [215111-00-5] (eq 7).** An oven-dried 250 mL three-necked round-bottom flask equipped with a reflux condenser fitted with an argon inlet adapter, a teflon-coated magnetic stir-bar and one glass stopper is cooled to room temperature under an argon purge. A rubber septum is attached to the other side neck of the flask and the glass stopper is removed followed by charging the flask with bis(tri-*tert*-butylphosphine)palladium ($Pd(P(t\text{-}Bu)_3)_2$) (482 mg, 0.943 mmol, 3.0 mol% Pd). The glass stopper is placed back on the flask and the flask is purged with argon for 15 min. The glass stopper is removed and toluene (32 mL) is added through the neck of the flask. The glass stopper is again placed on the flask and the mixture is gently stirred at room temperature resulting in a brownish-orange, homogenous solution. Chlorobenzene (3.2 mL, 31.5 mmol), Cy_2NMe, (7.5 mL, 35.0 mmol) and butyl methacrylate (5.5 mL, 34.6 mmol) were then successively added via syringe through the rubber septum. The resulting mixture was then allowed to stir at room temperature for 5 min resulting in a light orange homogenous solution. The rubber septum is then removed and replaced with a glass stopper and the flask is placed in a 100 °C oil bath and stirred at this temperature under a positive pressure of argon for 22 hours. Upon inital heating of the reaction mixture, the solution became bright canary yellow in color. Within 10-15 min, the formation of a white precipitate (the amine hydrochloride salt) can be observed. Upon reaction completion, shiny palladium metal deposits can be observed on the sides of the flask and a large amount of white precipitate has formed. The reaction mixture is removed from the oil bath and allowed to cool to room temperature. Diethyl ether (100 mL) is added to the flask and the resulting

solution is filtered through a 7 cm diameter Buchner funnel packed with silica gel (7 cm diameter x 1.8 cm height). The flask is then rinsed with diethyl ether (3 x 100 mL) and the rinses are filtered through the pad of silica gel. The pad of silica gel is further washed with diethyl ether (200 mL). The combined organic extracts are concentrated via rotary evaporation and the residual solvent is removed from the crude product, a dark brown oil, under high vacuum. The crude product was then purified via flash column chromatography (5% diethyl ether/hexane) to afford 6.55 g (95%) of the title compound as a reddish-orange liquid. Although this liquid exhibited favorable spectroscopic properties, the discoloration was removed by filtering the product through a small column of silica gel (3 cm diameter x 10 cm height) to furnish 6.51 g (95%) of the title compound as a clear, colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.68 (apparent d, J = 1.5 Hz, 1H), 7.40-7.28 (m, 5H), 4.22 (t, J = 6.6 Hz, 2H), 2.12 (d, J = 1.5 Hz, 3H), 1.76-1.66 (m, 2H), 1.52-1.39 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 168.9, 138.8, 136.1, 129.8, 128.8, 128.5, 128.4, 64.9, 30.9, 19.4, 14.2, 13.9; IR (neat, cm^{-1}): 3058, 3026, 2960, 1709, 1635, 1448, 1254, 1114, 765, 703; Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.28; H, 8.34.

***(E)*-4-(2-Phenylethenyl)-benzonitrile [13041-79-7] (eq 8).**[58] An oven-dried 250 mL three-necked round-bottom flask equipped with an argon inlet adapter, a teflon-coated magnetic stir-bar and one glass stopper is cooled to room temperature under an argon purge. A rubber septum is attached to the middle neck of the flask and the glass stopper is removed followed by charging the flask with bis(tri-*tert*-butylphosphine)palladium (Pd(P(*t*-Bu)$_3$)$_2$) (238 mg, 0.466 mmol, 1.5 mol% Pd), $Pd_2(dba)_3$, (213 mg, 0.233 mmol, 1.5 mol% Pd), and 4-chlorobenzonitrile (4.25 g, 30.9 mmol).[59] The glass stopper is placed back on the

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[58] Gusten, H.; Salzwedel, M. *Tetrahedron* **1967**, *23*, 173-185.

[59] 4-Chlorobenzonitrile, 99%, was purchased from Avocado Research Chemicals Ltd. and used as received. We discovered that one batch of this aryl chloride from the same supplier did

flask and the flask is purged with argon for 15 min. The glass stopper is removed and toluene (62 mL)[60] is added through the neck of the flask. The glass stopper is again placed on the flask and the mixture is gently stirred at room temperature resulting in a dark reddish-purple solution. Cy_2NMe (7.5 mL, 35.0 mmol) and styrene (3.8 mL, 33.2 mmol) were then successively added via syringe through the rubber septum. The reaction mixture was then allowed to stir at room temperature under a positive pressure of argon for 72 hours. Within the first 1-2 hours, the color changes from deep red-purple to dark brown and precipitate (the amine hydrochloride salt) begins to form. Ethyl acetate (100 mL) is added to the flask and the resulting solution is filtered through a 7 cm diameter Buchner funnel packed with silica gel (7 cm diameter x 1.8 cm height). The flask is then rinsed with ethyl acetate (3 x 100 mL) and the rinses are filtered through the pad of silica gel. The pad of silica gel is further washed with ethyl acetate (200 mL). The combined organic extracts are concentrated via rotary evaporation and the residual solvent is removed from the crude product, a yellow solid, under high vacuum. The crude product is then purified via flash column chromatography (20% hexane/toluene)[61] to afford 5.65 g (89%) of the title compounds as a white solid. mp (uncorr.) 116-118 °C (lit. mp 115 °C); ^1H NMR ($CDCl_3$, 300 MHz): 7.64 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 7.55-7.52 (m, 2H), 7.42-7.29 (m, 3H), 7.22 (d, J = 16.5 Hz, 1H), 7.09 (d, J = 16.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 142.0, 136.4, 132.7, 132.6, 129.1, 128.8, 127.1, 127.1, 126.9,

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not give satisfactory results in these Heck couplings. TLC analysis (20% hexane/toluene) revealed a small amount of a polar impurity (R_f = 0.29) which was not evident by ^1H NMR. Once the impurity was removed by flash column chromatography, this batch of aryl chloride performed satisfactorily in subsequent Heck couplings.

60 It was found to be beneficial to run this reaction at half the concentration (2 mL solvent per mmol ArCl) vs. the general procedure (1 mL solvent per mmol ArCl) due to more efficient stirring.

61 A small amount of unreacted aryl chloride remained after 72 hours reaction time and could be removed by flash column chromatography at the expense of approximately 4-5% of desired product.

119.3, 110.7; IR (CH_2Cl_2 solution, cm^{-1}): 3055, 2225, 1602, 1504, 1265, 966, 873, 824, 738; Anal. Calcd for $C_{15}H_{11}N$: C, 87.78; H, 5.40; N, 6.82 Found: C, 87.73; H, 5.44; N, 6.82.

(*E*)-2-methyl-3-(2-methylphenyl)-acrylic acid methyl ester and 2-(2-methyl-benzyl)-acrylic acid methyl ester (eq 9). Procedure A was used using 2-bromotoluene (171 mg, 0.998 mmol), methyl methacrylate (0.215 mL, 2.01 mmol), dicyclohexylmethylamine (0.23 mL, 1.07 mmol), $Pd_2(dba)_3$ (4.7 mg, 0.005 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.05 mL, 0.010 mmol), and dioxane (0.94 mL). After 26 hours at room temperature, 1-methylnapthalene (52.5 mg, 0.37 mmol) was added to the reaction mixture as an internal standard and the reaction was worked up in the usual fashion. ^{1}H NMR analysis of the crude reaction mixture revealed 82% conversion with respect to 2-bromotoluene, 42% yield of the internal olefin, (*E*)-2-methyl-3-(2-methylphenyl)-acrylic acid methyl ester and 26% yield of the terminal olefin, 2-(2-methyl-benzyl)-acrylic acid methyl ester. GC/MS confirmed that these two olefins are indeed isomers with the same molecular weight. Spectral data of (*E*)-2-methyl-3-(2-methylphenyl)-acrylic acid methyl ester matched that reported for entry 1, table 7. ^{1}H NMR ($CDCl_3$, 300 MHz) 2-(2-methyl-benzyl)-acrylic acid methyl ester: 7.10-7.20 (m, 4H), 6.21 (apparent quartet, 1H), 5.17 (apparent quartet, 1H), 3.77 (s, 3H), 3.61 (m, 2H), 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) 2-(2-methyl-benzyl)-acrylic acid methyl ester: 167.6, 139.2, 136.8, 136.7, 130.4, 130.1, 126.8, 126.2, 126.0, 52.2, 35.5, 19.6.

Heck coupling of bromobenzene-d_5 with methyl *trans*-cinnamate at room temperature (eq 10). Procedure A was employed, using bromobenzene-d_5 (148 mg, 0.914 mmol), methyl *trans*-cinnamate (161 mg, 0.993 mmol), Cy_2NMe (0.220 mL, 1.03 mmol), $Pd_2(dba)_3$ (12.7 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.14 mL, 0.028 mmol), and dioxane (0.78 mL). After 14 hours at room

temperature, workup and column chromatography (5% Et_2O/hexanes) yielded 209 mg (94%) of (*E*)-3-(phenyl-d_5)-3-phenyl acrylic acid methyl ester as a pale-yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz): 7.35-7.40 (m, 3H), 7.18-7.22 (m, 2H), 6.36 (s, 1H), 3.61 (s, 3H).

Heck coupling between bromobenzene-d_5 and methyl *trans*-cinnamate at 120 °C (eq 11) Procedure A was employed, using bromobenzene-d_5 (149 mg, 0.922 mmol), methyl *trans*-cinnamate (167 mg, 1.03 mmol), Cy_2NMe (0.22 mL, 1.03 mmol), $Pd_2(dba)_3$ (12.6 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.27 mL, 0.054 mmol), and dioxane (0.65 mL). After 13 hours at 120 °C, workup and column chromatography (5% Et_2O/hexanes) yielded 165 mg (73%) of a 1:1 mixture of (*E*)- and (*Z*)-3-(phenyl-d_5)-3-phenyl acrylic acid methyl ester as a pale-yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz): 7.26-7.40 (m, 4H), 7.18-7.22 (m, 1H), 6.36 (s, 1H), 3.61 (s, 3H).

^{31}P NMR study of the Heck coupling of 4'-chloroacetophenone with styrene. Procedure A was employed, using 4'-chloroacetophenone (0.130 mL, 1.00 mmol), styrene (0.125 mL, 1.09 mmol), Cy_2NMe (0.240 mL, 1.12 mmol), $Pd_2(dba)_3$ (14.0 mg, 0.015 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.15 mL, 0.030 mmol), and dioxane (0.84 mL). The reaction was stirred for 10 minutes at room temperature, and then it was transferred via pipette to an NMR tube equipped with a teflon screwcap. The tube was sealed and removed from the glove box, and then the reaction was monitored by ^{31}P NMR. Essentially the only phosphorus-containing species observed during the course of the reaction was Pd(P(*t*-Bu)$_3$)$_2$ at δ 86 (a trace of free P(*t*-Bu)$_3$ was also present).

Heck coupling of 4'-chloroacetophenone with styrene as a function of Pd: phosphine ratio (eq 12; typical procedure). In a Vacuum Atmospheres Glovebox, $Pd_2(dba)_3$ (6.6 mg, 0.0070 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (7.1 mg, 0.014 mmol), *n*-tridecane (internal standard; 38.7 mg, 0.206 mmol), 4'-chloroacetophenone (149

mg, 0.962 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), dioxane (0.96 mL), and styrene (0.120 mL, 1.05 mmol) were added in turn to a 4-mL vial equipped with a stir bar. The reaction mixture was stirred at room temperature; after 3 hours, GC revealed 29% conversion.

Rate of Heck coupling of 4'-chloroacetophenone as a function of olefin (Table 4; typical procedure). Procedure A was employed, using 4'-chloroacetophenone (149 mg, 0.964 mmol), styrene (0.120 mL, 1.05 mmol), Cy_2NMe (0.230 mL, 1.07 mmol), $Pd_2(dba)_3$ (13.0 mg, 0.014 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.14 mL, 0.028 mmol), dioxane (0.82 mL), and *n*-tridecane (internal standard; 42.5 mg, 0.230 mmol). After 3 hours at room temperature, GC revealed 30% conversion.

^{31}P NMR study of the Heck coupling of 4-bromoanisole with styrene. Procedure A was employed, using 4-bromoanisole (0.0950 mL, 0.759 mmol), styrene (0.0950 mL, 0.829 mmol), Cy_2NMe (0.180 mL, 0.840 mmol), $Pd_2(dba)_3$ (10.6 mg, 0.012 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.12 mL, 0.024 mmol), and dioxane (0.65 mL). The reaction was stirred for 2-3 minutes at room temperature, and then it was transferred via pipette to an NMR tube equipped with a teflon screwcap. The tube was sealed and removed from the glove box. The reaction was then monitored by ^{31}P NMR, which showed the major phosphorus-containing species to be a broad peak at δ ~64. In addition, resonances at δ 86 (Pd(P(*t*-Bu)$_3$)$_2$) and δ 92 (small) were observed.

^{31}P NMR study of the stoichiometric reaction of 4-bromoanisole with $Pd_2(dba)_3$/P(*t*-Bu)$_3$. In a Vacuum Atmospheres Glovebox, $Pd_2(dba)_3$ (17.3 mg, 0.019 mmol), 4-bromoanisole (0.0050 mL, 0.040 mmol), P(*t*-Bu)$_3$ (0.20 M stock solution; 0.19 mL, 0.038 mmol), and dioxane-d_8 (0.54 mL) were added successively to an NMR tube equipped with a teflon screwcap. The tube was sealed and removed from the glove box. The initial ^{31}P NMR spectrum showed

an ~1:1 ratio of two species at δ 86 ($Pd(P(t\text{-}Bu)_3)_2$) and δ 92. The initial ^1H NMR spectrum revealed a new doublet at δ 1.12 (J = 11.7 Hz; $P(t\text{-}Bu)_3$ group), a new singlet at δ 3.65 (MeO group), and a new doublet at δ 6.52 (J = 8.4 Hz; aromatic group); in addition, unreacted 4-bromoanisole and $Pd(P(t\text{-}Bu)_3)_2$ were present.

Part 3:

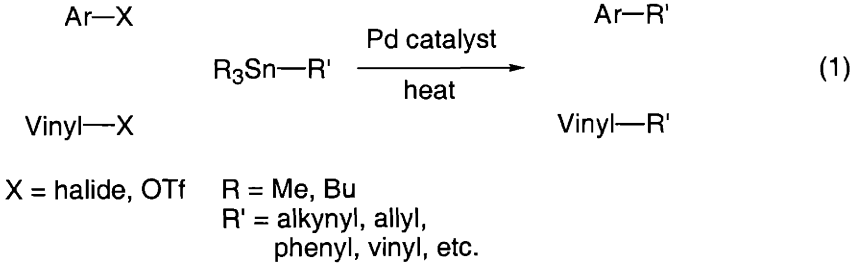
Stille Coupling using Pd/P(*t*-Bu)$_3$ Catalyst Systems

Chapter 5:

Stille Coupling of Aryl Chlorides using Pd/P(t-Bu)$_3$/CsF

Introduction

The Stille cross-coupling refers to the palladium-catalyzed coupling of aryl and vinyl halides and triflates with organotin compounds (eq 1).[1,2] The organic group to be transferred is usually an unsaturated moiety such as vinyl, aryl, alkynyl, and allyl. Alkyl groups are the least reactive groups to transfer in Stille couplings, and as such they (typically Bu or Me) are commonly used as non-transferable ligands on the organostannane component.



Additives, such as bases that are normally required for the Suzuki coupling, are not usually needed for the Stille coupling, as under typical reaction conditions the organostannane is reactive enough by itself to undergo transmetalation with Pd (Figure 1). This factor, combined with the excellent functional-group compatibility of the process and the air- and moisture-stability of organotin reagents, makes the Stille coupling a very powerful and popular tool for carbon-carbon bond formation. This is perhaps most evident in the numerous applications in natural products synthesis where the Stille coupling has often played a pivotal role.[3]

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[1] (a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301-302. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636-3638.

[2] For reviews of the Stille reaction, see: (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1-652. (b) Mitchell, T. N. *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 4.

[3] (a) For a discussion of applications of the Stille reaction in natural products synthesis (e.g., lepicidin aglycon and rapamycin), see: Nicolaou, K. C.; Sorensen, E. J. *Classics in Total*

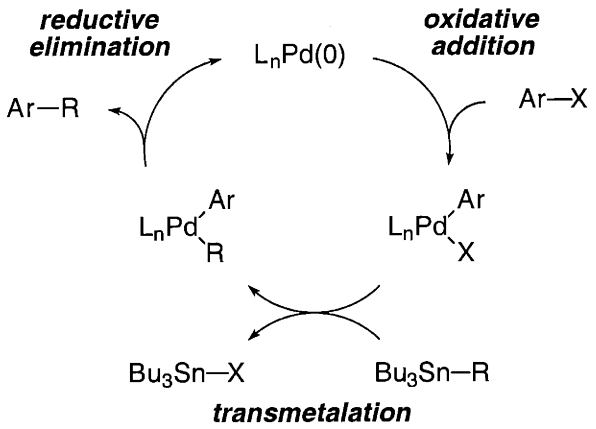

Figure 1. Outline of the catalytic cycle for the Stille cross-coupling reaction.

A serious drawback of the Stille coupling is the toxicity of organotin compounds. Organostannanes that contain butyl groups are less toxic than those that contain methyl groups,[4] hence, tributyltin compounds are more commonly employed in Stille couplings than trimethyltin compounds despite the lower reactivity of the former. In addition, the separation of the organotin-containing byproducts from the desired product is usually a non-trivial procedure.[5] These considerations render the Stille reaction less attractive for pharmaceutical applications than the Suzuki coupling, although under certain circumstances, the Stille coupling can be a valuable tool for the synthesis of medicinally relevant compounds.[6]

Synthesis; VCH: New York, 1996; Chapter 31. (b) For some very recent examples, see: Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765-766. White, J. D.; Carter, R. G.; Sundermann, K. F.; Wartmann, M. *J. Am. Chem. Soc.* **2001**, *123*, 5407-5413. Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918-5924. Hannessian, S.; Ma, J.; Wang, W. *J. Am. Chem. Soc.* **2001**, *123*, 10200-10206. Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942-10953.

4 Smith, P. J. *Toxicological Data on Organotin Compounds*; ITRI Publication #538; International Research Institute: Perivale, UK, 1977.

5 For a discussion, see: Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200-7201.

6 For a recent example, see: Jensen, M. S.; Yang, C.; Hsiao, Y.; Rivera, N.; Walls, K. M.; Chung, J. Y. L.; Yasuda, N.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2000**, *2*, 1081-1084.

With regard to scope, one of the most glaring limitations in the palladium-catalyzed Stille reaction has been the inability to couple electron-neutral and electron-rich aryl chlorides.[7] In 1977 Migita reported that the $Pd(PPh_3)_4$-catalyzed Stille coupling of allyltributyltin with the highly activated 4-nitrochlorobenzene proceeded in a modest 59% yield at 120 °C.[1a] Under the same conditions, both 1,4-dichlorobenzene and chlorobenzene yielded <5% desired product. As in the Suzuki and Heck reactions, tricarbonyl(η^6-arylchloride)chromium complexes are known to undergo Stille coupling,[8] even at room temperature if $AsPh_3$ is used as ligand.[9] Subsequent to our initial communication (*vide infra*), Nolan reported that a Pd/imidazolium salt-based catalyst in conjunction with *n*-Bu_4NF was quite effective for Stille couplings of electron-deficient aryl chlorides with aryl- and vinyltin reagents; unfortunately, electron-neutral and electron-rich aryl chlorides could only be coupled in poor to moderate (15-54%) yields.[10] Nickel-based catalysts have been used with some success for Stille couplings of unactivated aryl chlorides; yields up to 66% have been demonstrated in couplings with electron-rich aryl chlorides.[11] Given the importance of the Stille reaction as a valuable method for carbon-carbon bond formation, we felt that the development of a general method for effecting Stille couplings of aryl chlorides based on Pd/P(*t*-Bu)$_3$ was an important goal.

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[7] For examples of Stille couplings of heteroaryl chlorides, see: Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, 2000 and referenes therein.

[8] (a) Scott, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1755-1756. (b) Clough, J. M.; Mann, I. S.; Widdowson, D. A. *Tetrahedron Lett.* **1987**, *28*, 2645-2648. (c) Mitchell, T. N.; Kwekat, K.; Rutschow, D.; Schneider, U. *Tetrahedron* **1989**, *45*, 969-978. (d) Wright, M. E. *Organometallics* **1989**, *8*, 407-411. d) Wright, M. E. *Macromolecules* **1989**, *22*, 3256-3259. (e) Uemura, M.; Nishimura, H.; Hayashi, T. *J. Organomet. Chem.* **1994**, *473*, 129-137.

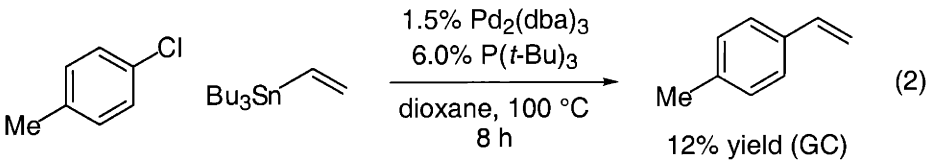
[9] Prim, D.; Tranchier, J. –P.; Rose-Munch, F.; Rose, E.; Vaissermann, J. *Eur. J. Inorg. Chem.* **2000**, 901-905.

[10] Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119-122.

[11] (a) Shirakawa, E.; Yamasaki, K.; Hiyama, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2449-2450. (b) Shirakawa, E.; Yamasaki, K.; Hiyama, T. *Synthesis* **1998**, 1544-1549.

Results and Discussion

At the time that we began our investigations into Stille couplings of aryl chlorides catalyzed by Pd/P(*t*-Bu)$_3$, there were no examples of palladium-catalyzed Stille reactions in which an unactivated aryl chloride served as a coupling partner. Initial studies focused on the coupling of 4-chlorotoluene and vinyltributyltin catalyzed by 1.5% $Pd_2(dba)_3$/6.0% P(*t*-Bu)$_3$ (eq 2); unfortunately, only a small amount of 4-vinyltoluene was obtained after eight hours at 100 °C. Given our earlier success in accomplishing Suzuki and Heck reactions of a wide array of aryl chlorides using $Pd_2(dba)_3$/P(*t*-Bu)$_3$ as catalyst, we reasoned that the problem should not be the oxidative addition step and that a subsequent step in the catalytic cycle, perhaps transmetalation, may be impeding effective catalysis (Figure 1).



(2)

Hypervalent organotin species are usually more reactive (nucleophilic) than their neutral precursors.[12] In order to enhance the reactivity of the organostannane through hypercoordinate intermediates and accelerate the sluggish transmetalation step, we decided to investigate the addition of various potential activators for the organotin species. Such a strategy has been successfully applied to Stille couplings on a number of occasions, for example, many groups have demonstrated that organotin species can be activated through intramolecular coordination of a Lewis base such as an amine.[6,13]

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12 *Chemistry of Tin*; Smith, P. J., Ed.; Blackie: New York, 1998.

13 (a) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556-6558. (b) Brown, J. M.; Pearson, M.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1440-1441. (c) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73-78. (d) Fouquet, E.;

A variety of additives were thus screened in the aforementioned Stille coupling of 4-chlorotoluene and vinyltributyltin (Table 1). While the use of NEt_3 yielded only a modest enhancement of rate (Table 1, entry 1 versus entry 2), both Cs_2CO_3[14] (Table 1, entry 3) and NaOH[15,16] (Table 1, entry 4) provided significant acceleration. Fluoride additives are very effective in promoting both Suzuki[17] and organosilicon (Hiyama) couplings,[18] and a fluoride activation strategy has used by a number of groups to enhance the reactivity of organotin reagents in Stille couplings.[19] However, such a strategy had not been successfully applied towards Stille couplings of aryl chlorides; in fact Kosugi has reported that $Pd(dba)_2/PPh_3/n\text{-}Bu_4NF$ does *not* effect Stille couplings of aryl chlorides.[20] A variety of fluoride sources were examined (Table 1, entries 5-7), with CsF proving to be particularly efficient. A further acceleration in rate was observed when an excess of CsF was employed (2.2 equiv relative to 4-chlorotoluene; Table 1, entry 8), although 100% conversion with respect to aryl chloride could be obtained with only 1.1 equiv of CsF.

Having discovered CsF as a very effective additive for Stille couplings of aryl chlorides, other reaction parameters were briefly examined. Aryl chloride coupling still proceeded when replacing $P(t\text{-}Bu)_3$ with PCy_3, although slower reaction rates were observed. No coupling was observed with the use of the

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Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242-5243.

14 Both Ag_2CO_3 and K_2CO_3 have been shown to promote the intramolecular transmetalation of alkylsilanes with aryl palladium complexes: Mateo, C.; Fernandez-Rivas, C.; Cardenas, D. J.; Echavarren, A. M. *Organometallics* **1998**, *17*, 3661-3669.

15 For Stille cross-couplings of aryl bromides and aryl iodides in the presence of hydroxide, see: Roshchin, A. I.; Bumagin, N. A.; Beletskaya, I. P. *Tetrahedron Lett.* **1995**, *36*, 125-128.

16 For Hiyama cross-couplings in the presence of hydroxide, see: Hagiwara, E.; Gouda, K.-i.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439-442.

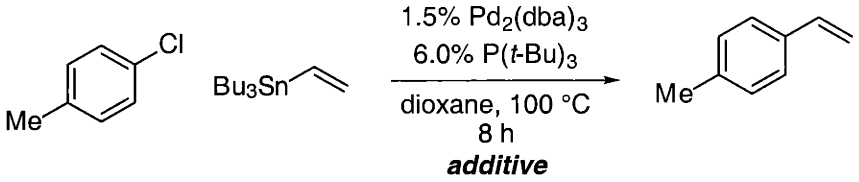
17 Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095-6097.

18 Gouda, K.-i.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232-7233.

19 (a) Martinez, A. G.; Barcina, J. O.; Cerezo, A. de F.; Subramanian, L. R. *Synlett* **1994**, 1047-1048. (b) Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242-5243. (c) Fouquet, E.; Rodriguez, A. L. *Synlett* **1998**, 1323-1324. (d) Martinez, A. G.; Barcina, J. O.; Heras, M. del R. C.; Cerezo, A. de F. *Org. Lett.* **2000**, *2*, 1377-1378.

20 Fugami, K.; Ohnuma, S.-y.; Kameyama, M.; Saotome, T.; Kosugi, M. *Synlett* **1999**, 63-64.

Table 1. Effect of Additives on the Rate of Pd/P(*t*-Bu)$_3$-Catalyzed Stille Cross-Coupling of 4-Chlorotoluene with Vinyltributyltin



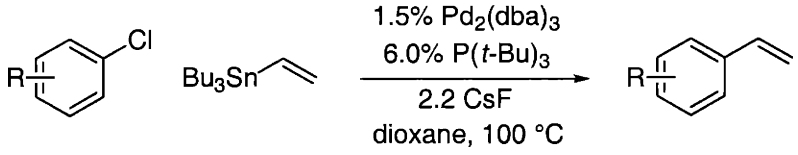
entry	***additive*** (1.1 equiv)	% yield after 8 h (GC)[a]
1	none	12
2	NEt_3	16
3	Cs_2CO_3	40
4	NaOH	42
5	TBAF•3H_2O	24
6	KF	28
7	CsF	50
8	CsF (2.2 equiv)	59

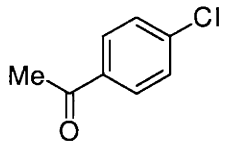
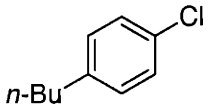
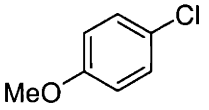
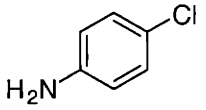
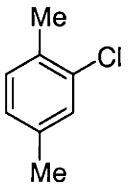
[a]Average of two runs.

bulky, electron-rich tri*aryl*phosphine tris(2,4,6-trimethoxyphenyl)phosphine. THF was a comparable solvent to dioxane, while toluene was only slightly worse. The use of $Pd(OAc)_2$ instead of $Pd_2(dba)_3$ resulted in a significantly slower reaction. Finally, the use of a P(*t*-Bu)$_3$:Pd ratio of 1.2:1 instead of 2:1 also resulted in sluggish reactions, although high conversions could still be obtained at these low P:Pd ratios.

Under the optimized conditions (1.5% $Pd_2(dba)_3$/6.0% P(*t*-Bu)$_3$/2.2 equiv CsF), a variety of aryl chlorides could be coupled with vinyltributyltin in moderate to good yield (Table 2). Electron-deficient (Table 2, entry 1) and electron-neutral (Table 2, entry 2) aryl chlorides furnished the desired styrene derivatives in ≥80% yield. Electron-rich aryl chlorides (Table 2, entries 3 and 4) could also undergo reaction with vinyltributyltin at 100 °C; even very electron-rich 4-chloroaniline could be used, albeit in modest (61%) yield. Hindered aryl chlorides (Table 2, entry 5) also participate in these $Pd_2(dba)_3$/P(*t*-Bu)$_3$-catalyzed Stille couplings.

Table 2. Scope of the $Pd_2(dba)_3/P(t\text{-}Bu)_3$-Catalyzed Stille Cross-Coupling of Aryl Chlorides



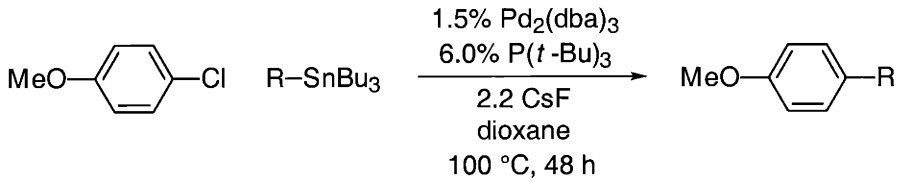
entry	aryl chloride	yield (%)[a]
1		87%[b]
2		80%
3		82% (90%)
4		61%
5		71% (84%)

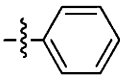
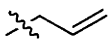
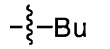
[a]Isolated yields (average of two runs). Values in parentheses are yields measured by GC for reaction products that are volatile. [b]Reaction temperature: 80 °C.

A variety of organostannanes undergo reaction with aryl chlorides using $Pd_2(dba)_3/P(t\text{-}Bu)_3/CsF$ (Table 3). The relatively challenging substrate 4-chloroanisole couples in high yield with phenyl-, 1-ethoxyvinyl-, and allyltributyltin (Table 3, entries 1-3). Even typically unreactive alkyl groups can be transferred efficiently under these conditions (Table 3, entry 4). Given this surprising result, it is worth mentioning that in the couplings with other organostannanes illustrated in Table 3, virtually no (< 2%) butyl transfer is

observed. However, one limitation with respect to the tin reagent is that alkynylstannanes did not undergo efficient coupling with aryl chlorides either in the presence or absence of CsF.

Table 3. Scope of the $Pd_2(dba)_3/P(t\text{-}Bu)_3$-Catalyzed Stille Cross-Coupling of Aryl Chlorides: Variation in the Tin Reagent



entry	R	yield (%)[a]
1		94
2		98
3		87
4		82

[a]Isolated yields (average of two runs).

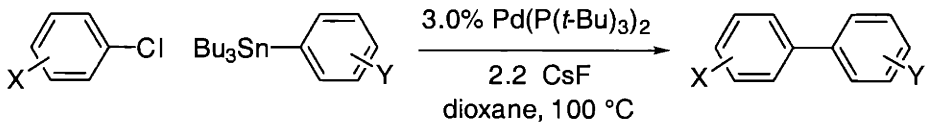
As mentioned in the Introduction, one of the drawbacks of the Stille coupling is that the separation of the organotin byproducts from the desired product is often quite difficult. This is not an issue using $Pd_2(dba)_3/P(t\text{-}Bu)_3/CsF$, due to the in-situ generation of the relatively insoluble Bu_3SnF. Thus, most of the organotin byproducts can be removed by simple filtration of the crude reaction mixture through a plug of silica gel during the workup procedure.[21]

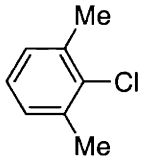
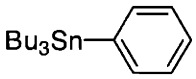
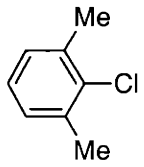
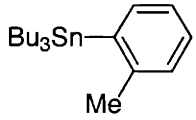
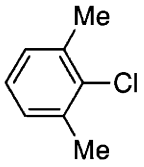
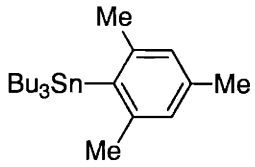
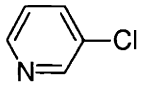
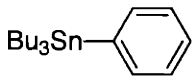
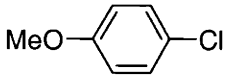
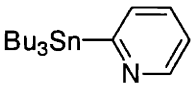
In order to avoid the need to handle air-sensitive $P(t\text{-}Bu)_3$ and develop a more user-friendly protocol, the use of commercially available $Pd(P(t\text{-}Bu)_3)_2$ as a

[21] Addition of fluoride (e.g., KF) after a reaction is complete is a common method for removing organotin impurities: (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636-3638. (b) Liebner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449-450.

catalyst for Stille couplings of aryl chlorides was investigated (Table 4). As the results in Table 4 indicate, $Pd(P(t\text{-}Bu)_3)_2$ is indeed a very efficient catalyst for several relatively challenging Stille couplings.

Table 4. Stille Cross-Couplings of Aryl Chlorides Catalyzed by $Pd(P(t\text{-}Bu)_3)_2$



entry	aryl chloride	Bu_3Sn—R	yield (%)[a]
1			94
2			96
3			89
4[b]			76
5			47

[a]All yields are isolated yields (average of two runs).
[b]Reaction run at 60 °C

Traditional Pd/triarylphosphine-based catalysts for the Stille reaction are known to be relatively sensitive to couplings of hindered substrates, in particular with respect to the organostannane component.[22] In light of this fact, we were

[22] For example, see: (a) Saa, J. M.; Martorell, G.; Garcia-Raso, A. *J. Org. Chem.* **1992**, *57*, 678-685. (b) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434-5444. (c) Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940-7942. (d) Anderson, J. C.;

interested in examining the synthesis of highly hindered biaryls using Pd(P(*t*-Bu)$_3$)$_2$ as catalyst. Sterically demanding 2-chloro-*m*-xylene couples efficiently with phenyltributyltin (Table 4, entry 1) and even hindered *o*-tolyltributyltin (Table 4, entry 2) to furnish a di- and tri-ortho-substituted biaryl, respectively, in excellent yields.

Most remarkable is that a *tetra*-ortho-substituted biaryl may be synthesized in good yield from 2-chloro-*m*-xylene and mesityltributyltin (Table 4, entry 3). The synthesis of tetra-ortho-substituted biaryls, in particular unsymmetrical ones, is a challenging task, and there are few examples of successful syntheses of this class of compounds via cross-coupling methodology.[23,24] Dr. Chaoyang Dai demonstrated the successful synthesis of a tetra-ortho-substituted biaryl via a Negishi coupling of an aryl chloride and an arylzinc reagent using Pd(P(*t*-Bu)$_3$)$_2$ as catalyst.[25] Very recently, Buchwald has described a general catalyst system for the synthesis of tetra-ortho-substituted biaryls via Suzuki coupling.[26] To the best of our knowledge, entry 3 in Table 4 represents the first successful synthesis of a tetra-ortho-substituted biaryl via a Stille coupling. Noteworthy is that side products that are typically observed with other catalysts, such as products arising from butyl transfer or homocoupling of either the aryl chloride or stannane, are not detected using Pd(P(*t*-Bu)$_3$)$_2$.

Namli, H.; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123-15134.

23 For examples of difficulties in synthesizing tetra-ortho-substituted biaryls via cross-coupling methodology, see: (a) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207-210. (b) Johnson, M. G.; Foglesong, R. J. *Tetrahedron Lett.* **1997**, *38*, 7001-7002. (c) Yamada, I.; Yamazaki, N.; Yamaguchi, M.; Yamagishi, T. *J. Mol. Catal. A* **1997**, *120*, L13-L15. (d) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889-9890. (e) Bohm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 1602-1604. (f) Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* **2000**, *56*, 9655-9662. (g) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 6667-6670.

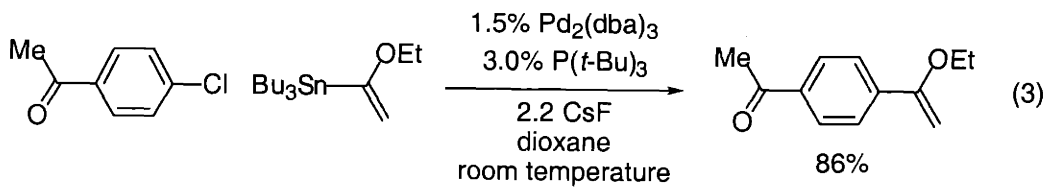
24 For an example of a successful synthesis of a tetra-ortho-substituted biaryl via a Suzuki cross-coupling, see: Cammidge, A. N.; Crepy, K. V. L. *Chem. Commun.* **2000**, 1723-1724.

25 Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719-2724.

26 Yin, J.; Rainka, M. P.; Zhang, X. -X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162-1163.

Stille couplings of heteroaromatic substrates have a long and rich history.[7] $Pd(P(t\text{-}Bu)_3)_2$ may be used to catalyze the coupling between 3-chloropyridine and phenyltributyltin at 60 °C to furnish the desired heterobiaryl in good yield (Table 4, entry 4). However, only a modest yield is obtained when a 2-stannylpyridine is employed (Table 4, entry 5); in this case several side products are formed including the dehalogenated arene, anisole, in addition to the homocoupled product of the aryl chloride, 4,4'-dimethoxybiphenyl, as well as 4-*n*-butylanisole arising from butyl transfer from tetrabutyltin.[27]

With the exception of the coupling of a $Cr(CO)_3$-complexed aryl chloride,[9] there are no examples of Stille couplings of aryl chlorides that proceed at room temperature. $Pd/P(t\text{-}Bu)_3$ can serve as an effective catalyst for this purpose as illustrated by the coupling of 4'-chloroacetophenone and 1-ethoxyvinyltributyltin (eq 3). As with room-temperature Suzuki and Heck couplings catalyzed by $Pd/P(t\text{-}Bu)_3$, the use of a Pd:phosphine ratio of 1:1, rather than 1:2, leads to a significantly faster reaction. In addition, the use of the more user-friendly catalyst system 0.75% $Pd_2(dba)_3$/1.5% $Pd(P(t\text{-}Bu)_3)_2$ (same amounts of Pd and $P(t\text{-}Bu)_3$ as in eq 3) provides a similar result.



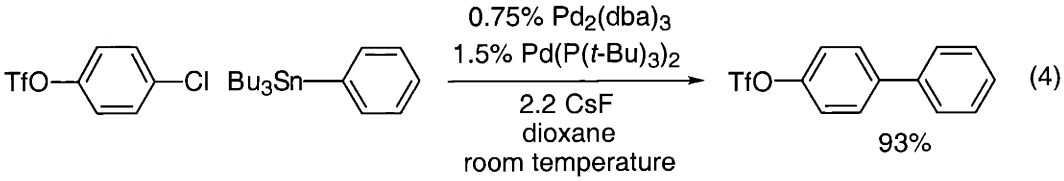
(3)

The scope of room-temperature Stille couplings of aryl chlorides is, as of yet, quite limited. Although electron-neutral aryl chlorides do undergo reaction at room temperature, these couplings are not practical as conversions are very slow. For example, 14 days are required for the coupling of 4-chlorotoluene with phenyltributyltin to furnish 4-methylbiphenyl in 78% isolated yield (0.75%

[27] Commercially availiable 2-pyridyltributyltin is contaminated with 5-15% tetrabutyltin.

$Pd_2(dba)_3$/1.5% $Pd(P(t\text{-}Bu)_3)_2$). In addition, preliminary studies seem to indicate that only phenyltributyltin and 1-ethoxyvinyltributyltin are viable stannanes for room-temperature couplings. Attempts to couple electron-deficient aryl chlorides at room temperature with other organotin reagents, such as vinyltributyltin, allyltributyltin, 2-furyl or 2-thienyltributyltin, resulted mostly in recovery of starting materials.

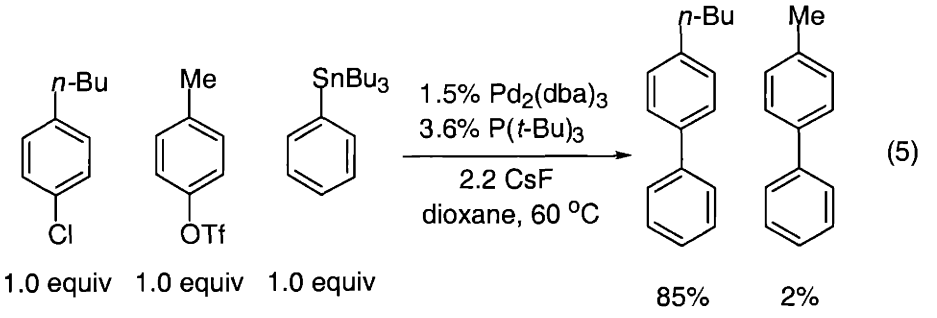
As discussed in Chapter 2, triflates are invariably much more reactive substrates for palladium-catalyzed coupling reactions than are chlorides. The only exception to this rule is the $Pd/P(t\text{-}Bu)_3$-catalyzed Suzuki coupling (Chapter 2); we speculated that this remarkable selectivity may extend to the Stille reaction. This turned out to be the case, as $Pd/P(t\text{-}Bu)_3$ activates the C–Cl bond of 4-chlorophenyltriflate, in preference to the C–OTf bond, with excellent selectivity (eq 4). Interestingly, when this reaction is conducted in NMP as solvent, coupling at *both* the chloride and triflate sites are observed, with the major product arising from coupling at the triflate site. Not surprisingly, the diarylated product, *p*-terphenyl is also formed in this reaction. Thus, the rather unique reactivity that $Pd/P(t\text{-}Bu)_3$ exhibits for coupling chlorides in the presence of triflates seems to be dependent on the solvent to a certain degree.



(4)

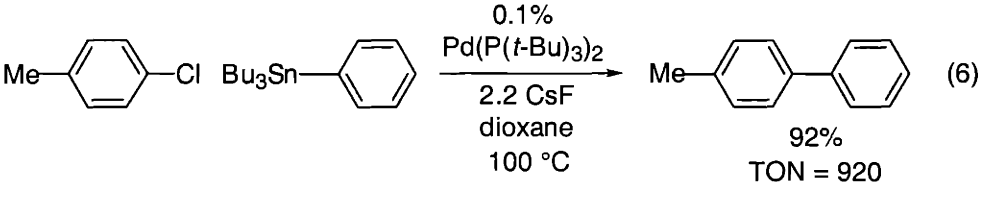
To establish the generality of this unprecedented selectivity in a Stille coupling for a chloride over a triflate, an intermolecular competition experiment was performed (eq 5). When 4-*n*-butylchlorobenzene and 4-methyphenyltriflate are allowed to compete for phenyltributyltin, almost exclusively the product that

arises is that from coupling with the aryl chloride (85% yield); only a trace of the biaryl that originates from reaction with the triflate (2% yield) is observed.



(5)

The use of lower catalyst loadings than the standard 3% Pd that has been universally applied thus far should be feasible. For example, for the coupling of unactivated 4-chlorotoluene and phenyltributyltin (eq 6), the catalyst loading can simply be decreased to 0.1% $Pd(P(t\text{-}Bu)_3)_2$ without otherwise modifying the reaction conditions, resulting in a 92% isolated yield of 4-phenyltoluene. The turnover number of 920 for this process is the highest that has been observed for a Stille coupling of an aryl chloride.

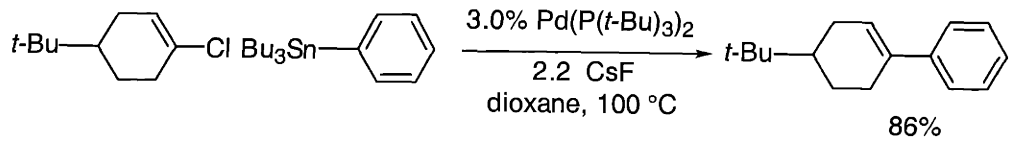


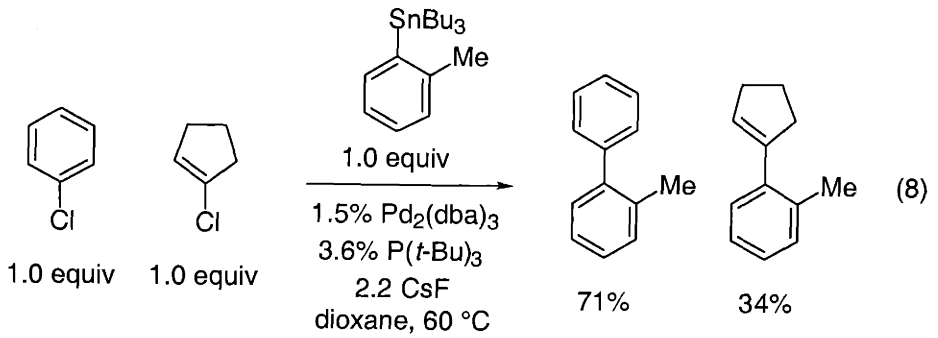
(6)

Examples of Stille couplings of vinyl chlorides have been limited to activated vinyl chlorides.[28] $Pd/P(t\text{-}Bu)_3$ does in fact serve as an effective catalyst for the

[28] For some examples of Stille couplings of activated vinyl chlorides, see: (a) Peet, W. G.; Tam, W. *J. Chem. Soc., Chem. Commun.* **1983**, 853-854. (b) Kobayashi, Y.; Kato, N.; Shimazaki, T.; Sato, F. *Tetrahedron Lett.* **1988**, *29*, 6297-6300. (c) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293-4296. (d) Rubin, Y.; Knobler, C. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 1607-1617. (e) Farina, V.; Hauck, S. I. *J. Org. Chem.* **1991**, *56*, 4317-4319. (f) Liebeskind, L. S.; Yu, M. S.; Yu, R. H.; Wang, J.; Hagen, K. S. *J. Am. Chem. Soc.* **1993**, *115*, 9048-9055. (g) May, P. D.; Larsen, S. D. *Synlett* **1997**, 895-896.

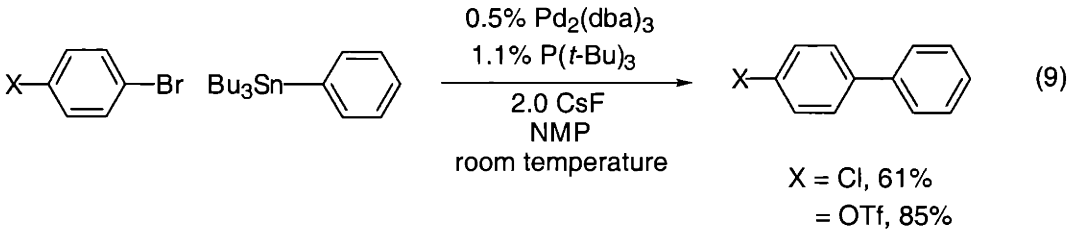
coupling of unactivated vinyl chlorides (eq 7). As we have previously observed for Pd/P(*t*-Bu)$_3$-catalyzed Suzuki and Heck reactions, for Pd/P(*t*-Bu)$_3$-catalyzed Stille processes, aryl chlorides couple in preference to vinyl chlorides (eq 8).





Highly chemoselective couplings of bromides over chlorides and triflates were achieved in both Suzuki and Heck couplings catalyzed by Pd/P(*t*-Bu)$_3$, and as such we were interested in knowing if this same high degree of selectivity would be observed for Stille reactions. A postdoctoral associate, Dr. Lothar Schwarz, demonstrated that a wide variety of sterically and electronically diverse aryl bromides could be coupled at room temperature with a range of organotin reagents using Pd/P(*t*-Bu)$_3$/CsF and NMP as solvent. These conditions were applied towards substrates with more than one reactive site (eq 9). For the room-temperature coupling of 4-bromophenyltriflate with phenyltributyltin, the triflate-substituted biaryl is isolated in good (85%) yield. However, GC analysis of the crude reaction mixture did indicate the presence of the diarylated product, *p*-terphenyl. Thus, Pd/P(*t*-Bu)$_3$ does exhibit a certain degree of reactivity towards triflates in the presence of bromides in NMP as solvent. Coupling at both reactive sites is a particularly deleterious side reaction observed in the

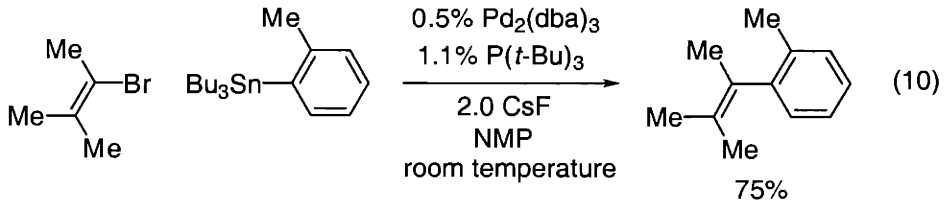
coupling of 4-bromochlorobenzene and phenyltributyltin (eq 9) and accounts for the rather modest 61% isolated yield.



(9)

It is also worth mentioning that both of these reactions were somewhat cleaner when using 0.5% $Pd_2(dba)_3$/1.1% P(*t*-Bu)$_3$ as catalyst rather than 0.25% $Pd_2(dba)_3$ /0.5% Pd(P(*t*-Bu)$_3$)$_2$. Although our results regarding Heck couplings of aryl chlorides and bromides (Chapter 4) seemed to indicate that $Pd_2(dba)_3$/P(*t*-Bu)$_3$ and $Pd_2(dba)_3$ /Pd(P(*t*-Bu)$_3$)$_2$ are completely interchangeable catalyst systems, the same may not hold true for Stille couplings of aryl bromides and for any given substrate pair it may be prudent to try both systems.

Finally, we have briefly examined the applicability of Pd/P(*t*-Bu)$_3$ to the Stille coupling of vinyl bromides. Equation 10 illustrates that this catalyst system can couple even very sterically demanding substrates in good yield at room temperature.



(10)

Due to the heterogeneous nature of many of these Stille couplings, detailed mechanistic and/or kinetic studies were not performed. Pd(P(*t*-Bu)$_3$)$_2$ does appear to be the resting state in Stille couplings with aryl chlorides as this was the

major species detected by ^{31}P NMR in the reaction of 4-chloroanisole and vinyltributyltin (1.5% $Pd_2(dba)_3$/6.0% P(*t*-Bu)$_3$/2.2 eq CsF, dioxane, 100 °C); a small amount of free P(*t*-Bu)$_3$ was also observed.

In conclusion, Pd/P(*t*-Bu)$_3$ serves as an unusually versatile catalyst for Stille reactions of aryl chlorides, and it currently represents the only effective catalyst for Stille couplings of unactivated aryl or vinyl chlorides. A broad array of organotin reagents can participate in these couplings to transfer a variety of groups, including alkyl groups. These Stille couplings are also very tolerant of hindered substrates and can be used for the synthesis of tetra-ortho-substituted biaryls. In addition, Pd/P(*t*-Bu)$_3$ allows for very selective reactions of aryl chlorides in the presence of aryl triflates and can be used at low catalyst loadings. Finally, Pd/P(*t*-Bu)$_3$/CsF constitutes a user-friendly and practical method for Stille couplings, as Pd(P(*t*-Bu)$_3$)$_2$ is commercially available and purification of the desired products is straightforward due to the in-situ generation of Bu_3SnF, which can be easily filtered off at the end of the reaction. This catalyst system has already been used by other groups for a number of interesting applications[29] and should find further use given the popularity of the Stille coupling.

Experimental Section

General Considerations. The general considerations are the same as the previous chapters with the following exceptions. NMP (anhydrous; Sure/Seal; Aldrich), and Pd(P(*t*-Bu)$_3$)$_2$ (Strem) were used as received. CsF (Strem) was ground to a fine powder using a mortar and pestle and then dried under high

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[29] (a) Kraxner, J.; Arlt, M.; Gmeiner, P. *Synlett* **2000**, 125-127. (b) Zhu, J.; Price, B. A.; Zhao, S. X.; Skonezny, P. M. *Tetrahedron Lett.* **2000**, *41*, 4011-4014. (c) Zhang, N.; Thomas, L.; Wu, B. *J. Org. Chem.* **2001**, *66*, 1500-1502. (d) Pereira, R.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **2001**, *57*, 7871-7881. (e) Okujima, T.; Ito, S.; Morita, N. *Tetrahedron Lett.* **2002**, *43*, 1261-1264.

vacuum at 100 °C for 2-4 hours. Mesityltributylstannane and *o*-tolyltributylstannane were prepared by reaction of the corresponding Grignard reagent with tributyltin chloride and purified by distillation under reduced pressure. All other organotin reagents were purchased (Aldrich, Gelest or Frontier Scientific) and distilled under reduced pressure or simply degassed.

General Procedures for the Pd/P(*t*-Bu)$_3$-catalyzed Heck Coupling of Aryl Chlorides and Bromides.

Procedure A. In a Vacuum Atmospheres Glovebox, the palladium source, CsF, the aryl or vinyl chloride, the P(*t*-Bu)$_3$ source, the organotin reagent, and dioxane were added in turn to a reaction vessel equipped with a stir bar. The mixture was stirred at the indicated temperature for the indicated amount of time. At the conclusion of the reaction, the mixture was diluted with Et_2O or EtOAc, filtered through a pad of silica gel with copious washings (Et_2O or EtOAc), concentrated, and purified by column chromatography.

Procedure B (no glove box). Pd(P(*t*-Bu)$_3$)$_2$ (along with $Pd_2(dba)_3$, for room temperature reactions) and CsF were added to an oven-dried Schlenk tube equipped with a stir bar. The Schlenk tube was fitted with a rubber septum, evacuated, and then refilled with argon. The halide (halides that are solids were added prior to the evacuation and argon refill cycle), the organotin reagent, and then dioxane were added via syringe. The septum was replaced with a teflon stopcock, and the reaction mixture was stirred at the indicated temperature for the indicated amount of time. At the conclusion of the reaction, the mixture was diluted with Et_2O or EtOAc, filtered through a pad of silica gel with copious washings (Et_2O or EtOAc), concentrated, and purified by column chromatography.

4-Vinylacetophenone (Table 2, entry 1) [10537-63-0].[11b] Procedure A was followed, using 4-chloroacetophenone (140 mg, 0.908 mmol), vinyltributyltin (0.280 mL, 0.958 mmol), CsF (304 mg, 2.00 mmol), $Pd_2(dba)_3$ (12.4 mg, 0.014 mmol), P(*t*-Bu)$_3$ (11.2 mg, 0.055 mmol), and dioxane (0.91 mL). After 12 hours at 80 °C, workup and column chromatography (10% Et_2O/pentane) yielded 116 mg (88%) of the title compound as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.75 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.87 (dd, *J* = 17.7, 0.9 Hz, 1H), 5.39 (dd, *J* = 11.1, 0.9 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.8, 142.2, 136.4, 136.1, 128.9, 126.5, 116.9, 26.8.

4-*n*-Butylstyrene (Table 2, entry 2) [26206-42-8].[30] Procedure A was followed, using 4-*n*-butylchlorobenzene (169 mg, 1.00 mmol), vinyltributyltin (0.305 mL, 1.04 mmol), CsF (336 mg, 2.22 mmol), $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol), P(*t*-Bu)$_3$ (12.4 mg, 0.061 mmol), and dioxane (1.00 mL). After 23 hours at 100 °C, workup and column chromatography (pentane) yielded 126 mg (79%) of the title compound as a clear, colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.69 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.70 (dd, *J* = 17.4, 0.9 Hz, 1H), 5.18 (dd, *J* = 10.8, 0.9 Hz, 1H), 2.60 (t, *J* = 7.5 Hz, 2H), 1.54-1.62 (m, 2H), 1.30-1.40 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 136.8, 135.1, 128.7, 126.2, 112.9, 35.7, 33.9, 22.7, 14.3.

4-Vinylanisole (Table 2, entry 3). Procedure A was followed, using 4-chloroanisole (133 mg, 0.936 mmol), vinyltributyltin (0.290 mL, 0.992 mmol), CsF (314 mg, 2.07 mmol), $Pd_2(dba)_3$ (12.7 mg, 0.014 mmol), P(*t*-Bu)$_3$ (11.5 mg, 0.057 mmol), and dioxane (0.94 mL). After 48 hours at 100 °C, workup and column chromatography (1% Et_2O/pentane) yielded 104 mg (83%) of the title compound as a clear, colorless liquid, which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

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[30] Nakatani, H; Nitta, K.-h.; Takata, T.; Soga, K. *Polym. Bull.* **1997**, *38*, 43-48.

4-Aminostyrene (Table 2, entry 4). Procedure A was followed, using 4-chloroaniline (118 mg, 0.925 mmol), vinyltributyltin (0.290 mL, 0.992 mmol), CsF (316 mg, 2.08 mmol), $Pd_2(dba)_3$ (12.5 mg, 0.014 mmol), P(*t*-Bu)$_3$ (11.4 mg, 0.056 mmol), and dioxane (0.93 mL). After 48 hours at 100 °C, workup and column chromatography (20% Et_2O/pentane) yielded 67.2 mg (61%) of the title compound as a yellow-orange liquid, which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

2,5-Dimethylstyrene (Table 2, entry 5). Procedure A was followed, using 2,5-dimethylchlorobenzene (132 mg, 0.941 mmol), vinyltributyltin (0.290 mL, 0.992 mmol), CsF (313 mg, 2.06 mmol), $Pd_2(dba)_3$ (12.8 mg, 0.014 mmol), P(*t*-Bu)$_3$ (11.3 mg, 0.056 mmol), and dioxane (0.94 mL). After 36 hours at 100 °C, workup and column chromatography (pentane) yielded 90.4 mg (73%) of the title compound as a clear, colorless liquid, which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

4-Methoxybiphenyl (Table 3, entry 1). Procedure A was followed, using 4-chloroanisole (130 mg, 0.911 mmol), phenyltributyltin (0.310 mL, 0.950 mmol), CsF (302 mg, 1.99 mmol), $Pd_2(dba)_3$ (12.7 mg, 0.014 mmol), P(*t*-Bu)$_3$ (11.4 mg, 0.056 mmol), and dioxane (0.91 mL). After 48 hours at 100 °C, workup and column chromatography (1% Et_2O/pentane) yielded 155 mg (92%) of the title compound as a white solid, which was identical to authentic material (Aldrich) by ^{1}H NMR, GC, and TLC.

1-(1-Ethoxyvinyl)-4-methoxybenzene (Table 3, entry 2) [66821-19-0].[31] Procedure A was followed, using 4-chloroanisole (149 mg, 1.05 mmol), 1-ethoxyvinyltributyltin (0.370 mL, 1.09 mmol), CsF (349 mg, 2.29 mmol), $Pd_2(dba)_3$ (14.4 mg, 0.016 mmol), P(*t*-Bu)$_3$ (13.1 mg, 0.065 mmol), and dioxane (1.05 mL). After 48 hours at 100 °C, workup and column chromatography (2.5%

[31] Quelet, R.; Allard, J. *Bull. Soc. Chim. Fr.* **1940**, *7*, 215-226.

NEt_3/hexanes) yielded 182 mg (97%) of the title compound as a clear, slightly yellow liquid. ^1H NMR (300 MHz, C_6D_6): δ 7.72 (d, J = 9 Hz, 2H), 6.78 (d, J = 9 Hz, 2H), 4.66 (d, J = 2.4 Hz, 1H), 4.09 (d, J = 2.4 Hz, 1H), 3.61 (q, J = 6.9 Hz, 2H), 3.26 (s, 3H), 1.16 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ 160.7, 160.6, 130.2, 127.5, 114.2, 81.0, 63.6, 55.1, 15.1.

4-Allylanisole (Table 3, entry 3). Procedure A was followed, using 4-chloroanisole (149 mg, 1.04 mmol), allyltributyltin (0.340 mL, 1.10 mmol), CsF (351 mg, 2.31 mmol), $Pd_2(dba)_3$ (14.2 mg, 0.016 mmol), P(*t*-Bu)$_3$ (12.5 mg, 0.062 mmol), and dioxane (1.04 mL). After 48 hours at 100 °C, workup and column chromatography (1% Et_2O/pentane) yielded 137 mg (89%) of the title compound as a clear, slightly pale-yellow liquid, which was identical to authentic material (Aldrich) by ^1H NMR, GC, and TLC.

4-*n*-Butylanisole (Table 3, entry 4) [18272-84-9].[32] Procedure A was followed, using 4-chloroanisole (135 mg, 0.948 mmol), tetrabutyltin (0.330 mL, 1.00 mmol), CsF (317 mg, 2.09 mmol), $Pd_2(dba)_3$ (13.0 mg, 0.014 mmol), P(*t*-Bu)$_3$ (11.6 mg, 0.057 mmol), and dioxane (0.95 mL). After 48 hours at 100 °C, workup and column chromatography (1% Et_2O/pentane) yielded 131 mg (84%) of the title compound as a yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 2.54 (t, J = 7.2 Hz, 2H), 1.51-1.61 (m, 2H), 1.30-1.40 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 135.2, 129.5, 113.8, 55.5, 34.9, 34.1, 22.5, 14.2.

2,6-Dimethylbiphenyl (Table 4, entry 1) [3976-34-9].[33] Procedure B was followed, using 2-chloro-*m*-xylene (0.115 mL, 0.868 mmol), phenyltributyltin (0.300 mL, 0.919 mmol), CsF (292 mg, 1.92 mmol), Pd(P(*t*-Bu)$_3$)$_2$ (13.5 mg, 0.026 mmol), and dioxane (0.86 mL). After 24 hours at 100 °C, workup and column

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[32] Adamska, G.; Dabrowski, R.; Dziabuszek, J. *Mol. Cryst. Liq. Cryst.* **1981**, *76*, 93-99.
[33] Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561.

chromatography (hexane) yielded 150 mg (95%) of the title compound as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.45 (m, 2H), 7.30-7.36 (m, 1H), 7.09-7.19 (m, 5H), 2.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 141.3, 136.3, 129.2, 128.6, 127.5, 127.2, 126.8, 21.1.

2,6,2'-Trimethylbiphenyl (Table 4, entry 2) [10273-87-7].[34] Procedure B was followed, using 2-chloro-*m*-xylene (0.110 mL, 0.830 mmol), *o*-tolyltributyltin (0.300 mL, 0.874 mmol), CsF (280 mg, 1.84 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (12.7 mg, 0.025 mmol), and dioxane (0.84 mL). After 24 hours at 100 °C, workup and column chromatography (hexane) yielded 152 mg (93%) of the title compound as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09-7.30 (m, 6H), 6.99-7.03 (m, 1H), 1.97 (s, 3H), 1.95 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 140.7, 136.1, 135.8, 130.2, 129.0, 127.4, 127.2, 127.1, 126.2, 20.5, 19.6.

2,2',4,6,6'-Pentamethylbiphenyl (Table 4, entry 3) [76411-12-6].[35] Procedure B was followed, using 2-chloro-*m*-xylene (0.100 mL, 0.755 mmol), mesityltributylstannane (323 mg, 0.789 mmol), CsF (257 mg, 1.69 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (11.7 mg, 0.023 mmol), and dioxane (0.76 mL). After 15 hours at 100 °C, workup and column chromatography (hexane) yielded 149 mg (88%) of the title compound as a slightly yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09-7.18 (m, 3H), 6.94 (s, 2H), 2.33 (s, 3H), 1.90 (s, 6H), 1.86 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.2, 137.2, 136.3, 135.9, 135.4, 128.4, 127.6, 126.9, 21.3, 20.1, 20.0.

3-Phenylpyridine (Table 4, entry 4). Procedure B was followed, using 3-chloropyridine (0.080 mL, 0.84 mmol), phenyltributyltin (0.290 mL, 0.889 mmol), CsF (280 mg, 1.84 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (12.7 mg, 0.025 mmol), and dioxane (0.84 mL). After 72 hours at 60 °C, workup and column chromatography (50%

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[34] Kamikawa, T.; Hayashi, T. *Synlett* **1997**, 163-164.
[35] Brotzeller, U.; Nyitrai, J.; Musso, H. *Chem. Ber.* **1980**, *113*, 3610-3620.

Et_2O/hexane) yielded 91.2 mg (70%) of the title compound as a colorless liquid, which was identical to authentic material (Aldrich) by ^1H NMR, GC, and TLC.

2-(4-Methoxyphenyl)pyridine (Table 4, entry 5) [5957-90-4].[36] Procedure B was followed, using 4-chloroanisole (0.105 mL, 0.857 mmol), 2-pyridyltributyltin (388 mg, 1.05 mmol), CsF (292 mg, 1.92 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (13.1 mg, 0.026 mmol), and dioxane (0.86 mL). After 48 hours at 100 °C, workup and column chromatography (30% Et_2O/hexane) yielded 70.5 mg (44%) of the title compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 8.64-8.66 (m, 1H), 7.95 (d, J = 9.0 Hz, 2H), 7.64-7.74 (m, 2H), 7.15-7.19 (m, 1H), 7.00 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.6, 157.3, 149.8, 136.8, 132.2, 128.4, 121.6, 120.0, 114.3, 55.6.

1-(1-Ethoxyvinyl)-4-acetylbenzene (eq 3). Procedure A was followed, using 4'-chloroacetophenone (0.120 mL, 0.925 mmol), 1-ethoxyvinyltributyltin (0.330 mL, 0.977 mmol), CsF (314 mg, 2.06 mmol), $Pd_2(dba)_3$ (12.6 mg, 0.014 mmol), P(t-Bu)$_3$ (0.21 M solution; 0.130 ml, 0.027 mmol), and dioxane (0.80 mL). After 75 hours at room temperature, workup and column chromatography (7% NEt_3/hexanes) yielded 151 mg (86%) of the title compound as a clear, slightly yellow liquid. ^1H NMR (300 MHz, C_6D_6): δ 7.79 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 4.68 (d, J = 2.7 Hz, 1H), 4.11 (d, J = 2.7 Hz, 1H), 3.51 (q, J = 6.9 Hz, 2H), 2.08 (s, 3H), 1.11 (t, J = 6.9 Hz, 3H). ^{13}C NMR (C_6D_6, 75 MHz): δ 196.4, 159.6, 141.3, 137.7, 128.8, 126.0, 84.5, 63.8, 26.5, 14.8. IR (thin film): 2981, 2931, 2883, 1684, 1607, 1404, 1359, 1311, 1267, 1128, 1056, 974, 846, 808, 591 cm^{-1}. HRMS (EI) calcd. for $C_{12}H_{14}O_2$: 190.0988. Found: 190.0981.

4-Trifluoromethanesulfonyloxybiphenyl (eq 4) [17763-78-9].[37] Procedure B was followed, using 4-chlorophenyl trifluoromethanesulfonate (256 mg, 0.983

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[36] Shigyo, H.; Sato, S.; Shibuya, K.; Takahashi, Y.; Yamaguchi, T.; Sonoki, H.; Ohta, T. *Chem. Pharm. Bull.* **1993**, *41*, 1573-1582.

[37] Kamikawa, T.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 7087-7090.

mmol), phenyltributyltin (0.320 mL, 0.981 mmol), CsF (320 mg, 2.11 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (7.4 mg, 0.014 mmol), $Pd_2(dba)_3$ (6.6 mg, 0.0072 mmol), and dioxane (0.98 mL). After 72 hours at room temperature, workup and column chromatography (3% Et_2O/hexane) yielded 277 mg (93%) of the title compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.33-7.67 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1, 141.9, 139.5, 129.2, 129.1, 128.3, 127.4, 121.8, 119.0 (q, $J_{C\text{-}F}$ = 319 Hz).

Competition experiment between an aryl chloride and an aryl triflate (eq 5). A modification of Procedure A was used. In a Vacuum Atmospheres Glovebox, $Pd_2(dba)_3$ (10.3 mg, 0.011 mmol), CsF (255 mg, 1.68 mmol), 4-*n*-butylchlorobenzene (127 mg, 0.753 mmol), 4-methylphenyltrifluoromethanesulfonate, (0.135 mL, 0.754 mmol), $P(t\text{-}Bu)_3$ (0.20 M solution; 0.140 mL, 0.028 mmol), phenyltributyltin (0.250 mL, 0.766 mmol), and dioxane (0.62 mL) were successively added to a Schlenk tube equipped with a stir bar. The tube was sealed with a teflon stopcock, removed from the glove box, and placed in a 60 °C oil bath. After 22 hours, the reaction was worked up in the usual fashion, and the products were purified by column chromatography (hexane), which yielded 135 mg (85%) of 4-*n*-butylbiphenyl and 2.8 mg (2%) of 4-methylbiphenyl. Both products were identical to authentic material (Alfa Aesar) by ^1H NMR, GC, and TLC.

4-Phenyltoluene (eq 6). Procedure B was followed, using 4-chlorotoluene (0.350 mL, 2.96 mmol), phenyltributyltin (1.00 mL, 3.06 mmol), CsF (1.00 g, 6.58 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (1.5 mg, 0.0029 mmol), and dioxane (3.00 mL). After 78 hours at 100 °C, workup and column chromatography (hexane) yielded 440 mg (88%) of the title compound as a white solid, which was identical to authentic material (Alfa Aesar) by ^1H NMR, GC, and TLC.

1-Phenyl-4-*t*-butyl-cyclohex-1-ene (eq 7) [3419-73-6].[38] Procedure B was followed, using 1-chloro-4-*t*-butyl-cyclohex-1-ene (131 mg, 0.757 mmol), phenyltributyltin (0.260 mL, 0.797 mmol), CsF (264 mg,1.74 mmol), $Pd(P(t\text{-}Bu)_3)_2$ (12.0 mg, 0.023 mmol), and dioxane (0.76 mL). After 21 hours at 100 °C, workup and column chromatography (hexane) yielded 142 mg (87%) of the title compound as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.36-7.40 (m, 2H), 7.27-7.33 (m, 2H), 7.17-7.23 (m, 1H), 6.11-6.14 (m, 1H), 2.36-2.56 (m, 2H), 2.20-2.30 (m, 1H), 1.90-2.02 (m, 2H), 1.22-1.42 (m, 2H), 0.91 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 136.5, 128.4, 126.7, 125.1, 125.1, 44.0, 32.4, 29.0, 27.7, 27.4, 24.6.

Competition experiment between an aryl chloride and a vinyl chloride (eq 8). A modification of Procedure A was used. In a Vacuum Atmospheres Glovebox, $Pd_2(dba)_3$ (14.2 mg, 0.016 mmol), CsF (341 mg, 2.24 mmol), chlorobenzene (0.105 mL, 1.03 mmol), 1-chlorocyclopentene, (0.105 mL, 1.06 mmol), $P(t\text{-}Bu)_3$ (0.13 M solution; 0.290 mL, 0.037 mmol), *o*-tolyltributyltin (395 mg, 1.04 mmol), and dioxane (0.74 mL) were successively added to a Schlenk tube equipped with a stir bar. The tube was sealed with a teflon stopcock, removed from the glove box, and placed in a 60 °C oil bath. After 20 hours, the reaction was worked up in the usual fashion, and the products were purified by column chromatography (hexane), which yielded 124 mg (71%) of 2-phenyltoluene and 55 mg (34%) of 1-(*o*-tolyl)cyclopentene. The 2-phenyltoluene was identical to authentic material (Aldrich) by ^1H NMR, GC, and TLC. 1-(*o*-Tolyl)cyclopentene [37438-00-9]:[39] ^1H NMR (300 MHz, $CDCl_3$): δ 7.12-7.22 (m, 4H), 5.76 (apparent quintet, 1H), 2.63-2.70 (m, 2H), 2.49-2.57 (m, 2H), 2.36 (s, 3H), 1.99 (apparent quintet, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 138.4, 135.7, 130.6, 129.5, 128.2, 126.7, 125.7, 36.9, 33.8, 23.9, 21.4.

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[38] Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunishima, M.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095-4112.

[39] Baddeley, G.; Chadwick, J.; Taylor, H. T. *J. Chem. Soc.* **1956**, 451-456.

4-Chlorobiphenyl (eq 9) [2051-62-9].[40] Procedure B was followed, using 4-bromochlorobenzene (287 mg, 1.50 mmol), phenyltributyltin (0.490 mL, 1.50 mmol), CsF (462 mg, 3.04 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), P(*t*-Bu)$_3$ (0.13 M solution; 0.130 mL, 0.017 mmol) and NMP (1.35 mL). After 3 hours at room temperature, workup and column chromatography (hexane) yielded 173 mg (61%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.56 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.1, 139.8, 133.5, 129.1, 129.1, 128.6, 127.8, 127.1.

4-Trifluoromethanesulfonyloxybiphenyl (eq 9). Procedure B was followed, using 4-bromophenyl trifluoromethanesulfonate (341 mg, 1.12 mmol), phenyltributyltin (0.360 mL, 1.10 mmol), CsF (347 mg, 2.29 mmol, $Pd_2(dba)_3$ (5.1 mg, 0.0056 mmol), P(*t*-Bu)$_3$ (0.13 M solution; 0.095 mL, 0.012 mmol) and NMP (1.02 mL). After 3 hours at room temperature, workup and column chromatography (3% Et_2O/hexane) yielded 264 mg (78%) of the title compound as a white solid. Spectroscopic properties were the same as that listed for eq 4.

3-Methyl-2-*o*-tolyl-2-butene (eq 10) [273937-89-6].[41] Procedure B was followed, using 2-bromo-3-methyl-2-butene (0.240 mL, 2.07 mmol), *o*-tolyltributylstannane (522 mg, 1.37 mmol), CsF (407 mg, 2.68 mmol), $Pd_2(dba)_3$ (6.4 mg, 0.0070 mmol), P(*t*-Bu)$_3$ (0.13 M stock solution; 0.120 mL, 0.016 mmol), and NMP (1.25 mL). After 71 hours at room temperature, workup and column chromatography (pentane) yielded 154 mg (70%) of the title compound as a slightly yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10-7.20 (m, 3H), 6.96-7.00 (m, 1H), 2.16 (s, 3H), 1.85-1.88 (m, 3H), 1.80 (s 3H), 1.39-1.41 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2, 135.4, 129.9, 129.5, 128.6, 127.1, 126.2, 125.8, 21.8, 20.3, 20.0, 19.3.

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[40] Klement, I.; Rottlander, M.; Tucker, C. E.; Majid, T. N.; Knochel, P. *Tetrahedron* **1996**, *52*, 7201-7220.

[41] Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.

Curriculum Vitae

EDUCATION

Ph.D., Organic Chemistry, Massachusetts Institute of Technology, MA, June 2002

- Thesis title: "Application of a Palladium/Tri-*tert*-butylphosphine Catalyst System Towards Mild and General Methods for Carbon-Carbon Bond Formation" Advisor: Professor Gregory C. Fu

Bachelor of Science, Honors, Chemistry (summa cum laude), University of Ottawa, Ontario, Canada, May 1997

- Thesis title: "Group (IV) Transition Metal Alkylamidinate Complexes: Synthesis and Structure of a New Class of Ziegler-Natta Olefin Polymerization Catalysts" Advisor: Professor Darrin Richeson

AWARDS AND SCHOLARSHIPS

2001	Roche Award for Excellence in Organic Chemistry
2001	MIT Wyeth-Ayerst Scholar
2000-2001	Boehringer-Ingelheim Graduate Fellowship
2000-2002	Julie-Payette Natural Sciences and Engineering Research Council of Canada (NSERC) Postgraduate Scholarship
1999-2000	Pharmacia Graduate Fellowship
1998-2000	NSERC Postgraduate Scholarship (PGS A)
1997	Merck-Frosst Prize for Outstanding Honors Thesis
1997	University of Ottawa Silver Medal
1996-1997	Ottawa Section of the Petroleum Society of the C.I.M. Award
1996	University of Ottawa Undergraduate Summer Research Scholarship
1995	NSERC Undergraduate Summer Research Scholarship
1994-1995	3M Canada Inc. Annual Bursary
1993-1997	Canada Scholarship in Science and Engineering
1993-1997	University of Ottawa Excellence (A+) Scholarship
1993-1997	Dean's Honor List

PUBLICATIONS

1) Littke, A. F.; Schwarz, L.; Fu, G. C. "Pd/P(*t*-Bu)$_3$: A Mild and General Catalyst for Stille Reactions of Aryl Chlorides and Aryl Bromides" *submitted for publication.*
2) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989-7000.
3) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.
4) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729-1731.
5) Leblanc, Y.; Dufresne, C.; Dhawan, R.; Ollerenshaw, J.; Littke, A.; Trimble, L. A.; Tsou, N. N. *Can. J. Chem.* **2000**, *78*, 784-790.
6) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 2411-2413.
7) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10-11.
8) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387-3388.
9) Littke, A.; Sleiman, N.; Benisom, C.; Richeson, D.; Yap, G.; Brown, S. *Organometallics* **1998**, *17*, 446-451.