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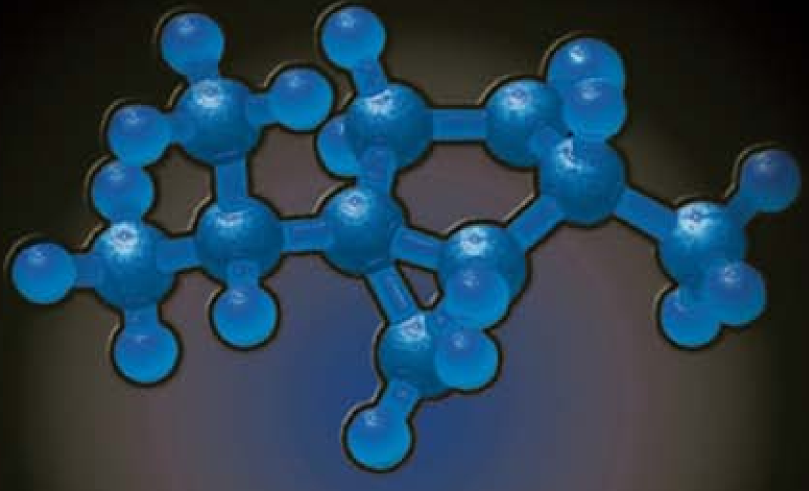

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Edited by
Gary A. Molander

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Library of Congress Cataloging-in-Publication Data

Handbook of reagents for organic synthesis.
p. cm.
Includes bibliographical references.
Contents: [1] Reagents, auxiliaries, and catalysts for C–C bond formation/edited by Robert M. Coates and Scott E. Denmark [2] Oxidising and reducing agents/edited by Steven D. Burke and Riek L. Danheiser [3] Acidic and basic reagents/edited by Hans J. Reich and James H. Rigby [4] Activating agents and protecting groups/edited by Anthony J. Pearson and William R. Roush [5] Chiral Reagents for Asymmetric Synthesis/edited by Leo A. Paquette [6] Reagents for high-throughput solid-phase and solution-phase organic synthesis / edited by Peter Wipf [7] Reagents for glycoside, nucleotide and peptide synthesis / edited by David Crich [8] Reagents for direct functionalization of C–H bonds/edited by Philip L. Fuchs [9] Fluorine-Containing Reagents/edited by Leo A. Paquette [10] Catalyst Components for Coupling Reactions / edited by Gary A. Molander

ISBN 0-471-97924-4 (v. 1) ISBN 0-471-97926-0 (v. 2)
ISBN 0-471-97925-2 (v. 3) ISBN 0-471-97927-9 (v. 4)
ISBN 0-470-85625-4 (v. 5) ISBN 0-470-86298-X (v. 6)
ISBN 0-470-02304-X (v. 7) ISBN 0-470-01022-3 (v. 8)
ISBN 978-0-470-02177-4 (v. 9) ISBN 978-0-470-51811-3 (v.10)

1. Chemical tests and reagents. 2. Organic compounds–Synthesis.
QD77.H37 1999
547′.2 dc 21
98-53088
CIP

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 13: 978-0-470-51811-3 (Hb)

Typeset in 9½/11½ pt Times Roman by Thomson Press (India) Ltd., New Delhi.
Printed and bound in Great Britain by Antony Rowe, Chippenham, Wiltshire
This book is printed on acid-free paper responsibly manufactured from sustainable forestry in which at least two trees are planted for each one used for paper production.

e-EROS Editorial Board

Contents

General Abbreviations

Preface

As stated in its preface, the major motivation for our undertaking the publication of the *Encyclopedia of Reagents for Organic Synthesis* was "to incorporate into a single work a genuinely authoritative and systematic description of the utility of all reagents used in organic chemistry." By all accounts, this reference compendium succeeded admirably in approaching this objective. Experts from around the globe contributed many relevant facts that define the various uses characteristic of each reagent. The choice of a masthead format for providing relevant information about each entry, the highlighting of key transformations with illustrative equations, and the incorporation of detailed indexes serve in tandem to facilitate the retrieval of desired information.

Notwithstanding these accomplishments, the editors came to recognize that the large size of this eight-volume work and prohibitive cost often deterred the placement of copies of the *Encyclopedia* in or near laboratories where the need for this type of information is most critical. In an effort to meet this demand in a cost-effective manner, the decision was made to cull from the major work that information with the highest probability for repeated consultation and to incorporate the same into a set of handbooks. The latter would also be purchasable on a single unit basis.

The ultimate result of these deliberations was the publication of the *Handbook of Reagents for Organic Synthesis*, the first four volumes of which appeared in 1999:

Reagents, Auxiliaries and Catalysts for C–C Bond Formation
Edited by Robert M. Coates and Scott E. Denmark

Oxidizing and Reducing Agents
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Activating Agents and Protecting Groups
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Since then, the fifth, sixth, seventh, eighth, and ninth members of this series listed below have made their appearance:

Chiral Reagents for Asymmetric Synthesis
Edited by Leo A. Paquette

Reagents for High-Throughput Solid-Phase and Solution-Phase Organic Synthesis
Edited by Peter Wipf

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Fluorine-Containing Reagents
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Each of the volumes contains a selected compilation of those entries from the original *Encyclopedia* that bear on the specific topic. The coverage of the last five handbooks also extends to the electronic sequel *e-EROS*. Ample listings can be found to functionally related reagents contained in the original work. For the sake of current awareness, references to recent reviews and monographs have been included, as have relevant new procedures from *Organic Syntheses*.

The present volume, entitled *Catalyst Components for Coupling Reactions*, constitutes the tenth entry in a continuing series of utilitarian reference works. As with its predecessors, this handbook is intended to be an affordable, enlightening compilation that will hopefully find its way into the laboratories of all practicing synthetic chemists. Every attempt has been made to be of the broadest possible relevance and it is hoped that our colleagues will share this opinion.

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Introduction

Among the myriad new methodological strategies developed over the past 50 years, none has impacted the construction of organic molecules as much as those transformations categorized as cross-coupling reactions. From the synthesis of pharmacologically active agents and natural products to all manner of new materials, the various synthetic methods established under the cross-coupling umbrella have revolutionized the manner in which novel molecular architectures are assembled. Recognizing the well-known limitations of classical S_N1 and S_N2 reactions, in the 1970s chemists began their search for catalyzed reactions that were able to overcome the energy barriers to substitution at sp- and sp^2-hybridized centers. Most of the processes derived from these investigations rapidly assumed their current status as ''name reactions,'' including the Suzuki–Miyaura, Negishi, Kumada–Tamao/Corriu, Stille/Migita–Kosugi, Tamao–Kumada/Hiyama–Hatanaka, and Sonogashira cross-couplings, as well as the Mizoroki–Heck, Tsuji–Trost, and Buchwald–Hartwig reactions.

Each of these cross-coupling processes is associated with a different set of reagents (e.g., organoborons, organozincs, etc.) that are vast in their scope and thus difficult to assemble in reasonable encyclopedic form. However, all cross-couplings are inextricably linked by one common theme—they employ catalyst systems comprised of various metal complexes and ligands that promote the reactions through catalytic cycles in which many of the individual steps are identical or related by analogy. As a consequence, familiarity with the properties and capabilities of the various catalyst components in one regime often opens diverse opportunities for application across the entire spectrum of cross-coupling transformations. For this reason, the current volume serves as a departure from its progenitors in that it focuses not on specific reagents, but rather on the individual components of catalyst systems.

The various precatalysts, catalysts, and ligands highlighted herein were selected from three different sources. The first set of these ''reagents'' appeared in the original *Encyclopedia of Reagents for Organic Synthesis* (*EROS*), which was published in 1995. Importantly, the vast majority of these have been subsequently updated by leading experts and appear in the continually expanding online encyclopedia *eEROS*. This supplemental information, so critical in the rapidly developing field of cross-coupling, is found herein in the form of extensions to the original article. Finally, entirely new compounds to *EROS*, again contributed by skilled practitioners in the art who have outlined the latest developments, comprise nearly 20% of the entries.

Readers will recognize that among the thousands of new ligand systems that have been developed during the past few decades, many may be organized into ''superfamilies'' of compounds that are constituted from similar molecular platforms. An attempt has been made to group these under a single, parent compound, but this effort in some cases has been thwarted by the historical, organic manner in which *EROS* has evolved, and it has not always been possible to accomplish this ideal.

A list of recent review articles and monographs concerning various aspects of cross-coupling reactions has been included, which appears directly after this Introduction. These articles and authoritative books detail both synthetic and mechanistic aspects of these important transformations. The list is divided into several sections. The first includes articles and books on general aspects of cross-coupling, broadly defined. The remainder of the reviews are organized according to the specific type of cross-coupling reaction involved, arranged by their now-familiar monikers. Subsequently, the various catalyst components are listed in alphabetical order in keeping with the *EROS* and *eEROS* format.

Because cross-coupling reactions play such an integral role in virtually all aspects of modern synthetic organic chemistry, we hope that this compilation will prove useful as a first reference source to those seeking a comprehensive, authoritative single volume for information on the catalyst components for various cross-coupling protocols.

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Recent Review Articles and Monographs

General Cross-Coupling

Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995.

Diederich, F.; Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998.

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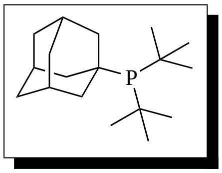
A

1-Adamantyl-di-*tert*-butylphosphine



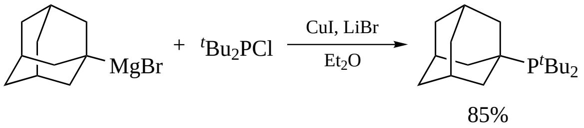
[338799-92-1] $C_{18}H_{33}P$ (MW 280.83)

(ligand used for palladium-catalyzed cross-coupling reactions)

Physical Data: not reported.
Solubility: soluble in ether, benzene, toluene, THF.
Form Supplied in: white solid.
Analysis of Reagent Purity: ^{31}P NMR (C_6D_6): δ 63.0.
Preparative Methods: prepared from the cuprate-mediated addition of 1-adamantyl Grignard reagent to $Bu^t{}_2PCl$.
Purification: distillation at 159–165 °C at 1 Torr under nitrogen atmosphere.
Handling, Storage, and Precautions: it is prone to oxidation in air and should be kept under inert atmosphere.

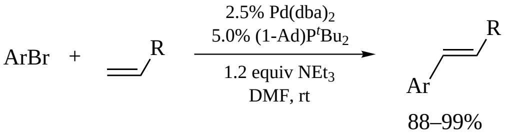
Overview. 1-Adamantyl di-*tert*-butylphosphine is a slightly more hindered variant of tri-*tert*-butylphosphine that emerged from the synthesis of a library of phosphines, work on catalytic coupling, and work on synthesis of organometallic intermediates in cross-coupling processes. Certain coupling processes have occurred in higher yields or under milder conditions with this ligand than with t-Bu_3P. In addition, some palladium catalyst precursors containing this ligand are significantly more stable to air and moisture than those containing t-Bu_3P, and arylpalladium(II) halide complexes of this ligand are more thermally stable than those containing t-Bu_3P.

Ligand Synthesis. 1-Adamantyl di-*tert*-butylphosphine is prepared from the cuprate-mediated addition of 1-adamantyl Grignard reagent to $Bu^t{}_2PCl$ as shown in eq 1.[1]

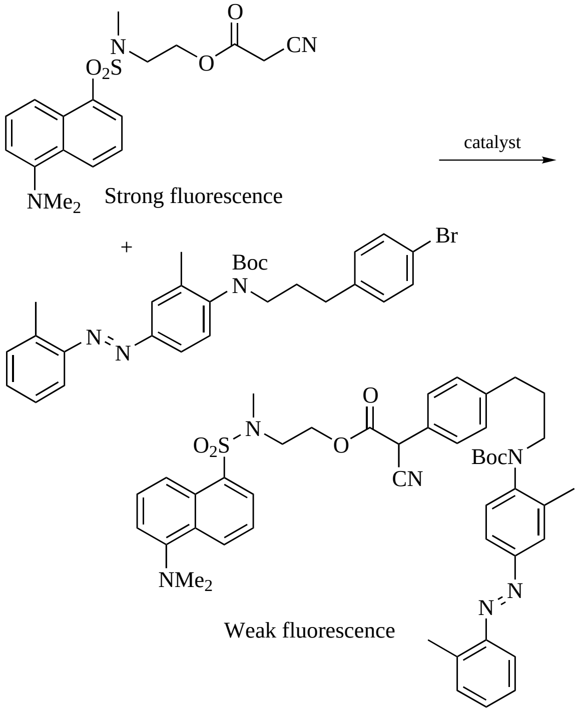


(1)

Preparation of 1-AdMgBr from 1-bromoadamantane is somewhat challenging on large scale because of competing radical coupling of the adamantyl groups[2–4] and is best conducted without stirring.[4,5] 1-Adamantyl di-*tert*-butylphosphine was first prepared as part of a library of sterically hindered monophosphines tested using a qualitative fluorescence assay for room-temperature Heck reactions of bromoarenes[1] (eq 2) and later a fluorescence resonance energy transfer system for the coupling of aryl halides with cyanoesters (eq 3).[6]



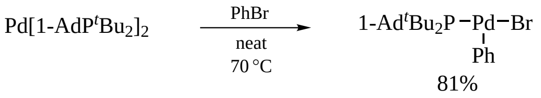
(2)



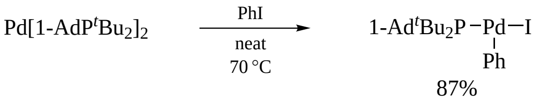
(3)

Catalysis with Palladium Complexes of 1-Adamantyl-di-*tert*-butylphosphine. The combination of adamantyl di-*tert*-butylphosphine and a palladium precursor typically reacts with similar rates and yields to those of tri-*tert*-butylphosphine.[6–8] However, the precatalyst with the general formula $(LPdBr)_2$ was more active when L = 1-adamantyl di-*tert*-butylphosphine than when L = $P(t\text{-}Bu)_3$.[9] Table 1 provides a series of aminations of aryl halides using the dimeric Pd(I) species containing t-Bu_3P and 1-adamantyl di-*tert*-butylphosphine as ligand. On the practical side, the dinuclear complex $\{[(1\text{-}Ad)P(t\text{-}Bu)_2]PdBr\}_2$was stable to air indefinitely as a solid, whereas $[(t\text{-}Bu)_3PPdBr]_2$can be weighed in air, but should be stored under nitrogen.

Organometallic Complexes of 1-Adamantyl-di-*tert*-butylphosphine. Differences in the stability of palladium complexes of 1-adamantyl di-*tert*-butylphosphine and tri-*tert*-butylphosphine were observed when conducting the synthesis of arylpalladium(II) complexes. As shown in eqs 4 and 5, the unusual three-coordinate arylpalladium halide complexes ligated by 1-adamantyl di-*tert*-butylphosphine are formed in good yield, whereas the analogous reaction with $Pd(Pt\text{-}Bu_3)_2$ occurs in yields less than 50%. In addition, the arylpalladium halide complexes ligated by 1-adamantyl di-*tert*-butylphosphine complex are more thermally stable and crystallize more readily, due to stabilization by an agostic interaction of a methylene hydrogen with the Pd(II) center.[10,11]

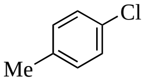
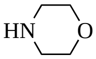
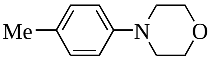
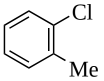
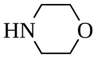
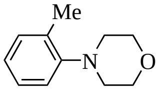
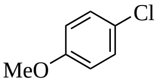
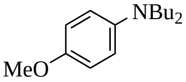
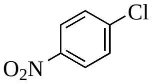
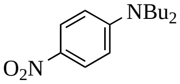
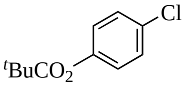
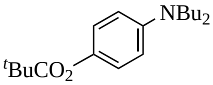
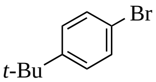
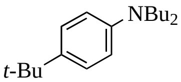
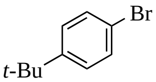
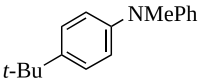
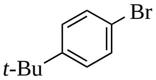
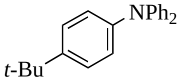
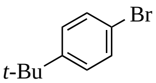
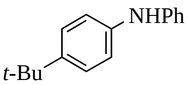


$$\mathrm{Pd[1\text{-}AdP^{\mathit{t}}Bu_2]_2} \xrightarrow[\text{neat, 70 °C}]{\mathrm{PhBr}} \mathrm{1\text{-}Ad^{\mathit{t}}Bu_2P{-}\underset{Ph}{Pd}{-}Br}\quad 81\% \qquad (4)$$



$$\mathrm{Pd[1\text{-}AdP^{\mathit{t}}Bu_2]_2} \xrightarrow[\text{neat, 70 °C}]{\mathrm{PhI}} \mathrm{1\text{-}Ad^{\mathit{t}}Bu_2P{-}\underset{Ph}{Pd}{-}I}\quad 87\% \qquad (5)$$

Table 1 Amination of aryl halides with $\{[(1\text{-Ad})\mathrm{P}(t\text{-Bu})_2]\mathrm{PdBr}\}_2$ as catalyst[a]

Entry	Aryl halide	Amine	Product	Yield[b]
1				88%
2				68%
3		$\mathrm{HNBu_2}$		87%
4		$\mathrm{HNBu_2}$		97%
5		$\mathrm{HNBu_2}$		>99%
6		$\mathrm{HNBu_2}$		96%
7		HNMePh		98%
8		$\mathrm{HNPh_2}$		96%
9		$\mathrm{H_2NPh}$		82%

[a] Reaction were conducted on 1 mmol scale in THF (1 mL) at room temperature for 15 min or 1 h (entry 8). The relative amounts of arly halide, amine, NaO*t*-Bu, and $[(\mathrm{R_3P})\mathrm{PdBr}]_2$ was 200:210:300:1.

[b] Yields of isolated products are an average of two runs.

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11. Stambuli, J. P.; Incarvito, C. D.; Buhl, M.; Hartwig, J. F., *J. Am. Chem. Soc.* **2004**, *126*, 1184.

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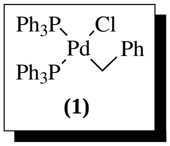
B

Benzylchlorobis(triphenylphosphine)-palladium(II)[1]



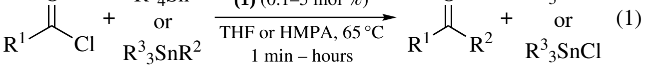
(1)

[22784-59-4] $C_{43}H_{37}ClP_2Pd$ (MW 757.59)

(catalyst for the cross coupling[1] of alkyl-, vinyl-, alkynyl-, and allylstannane groups with acyl chlorides,[2] allyl halides,[3] vinyl triflates, and iodides[4])

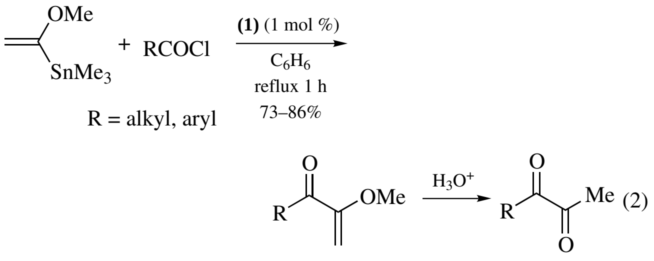
Physical Data: mp 166–170 °C.
Solubility: sol THF, benzene, and other organic solvents.
Form Supplied in: crystalline; commercially available.
Preparative Methods: may be prepared from benzyl chloride and $(Ph_3P)_4Pd$ in benzene at room temperature, washed with Et_2O, and dried under vacuum.[5]
Handling, Storage, and Precautions: is an air-stable solid and remains stable in solution. Irritant.

Cross Coupling Reactions with Organostannane Compounds. Palladium catalysis of cross coupling reactions is well established in organic chemistry.[1] Benzylchlorobis(triphenylphosphine)palladium(II) (**1**), first reported in 1969,[2] is used extensively for these reactions. Other palladium complexes, such as dichlorobis(triphenylphosphine)palladium(II) and tetrakis-(triphenylphosphine)palladium(0), catalyze cross coupling reactions; however, the title compound generally provides higher yields in shorter reaction times. Most common is the coupling of an organotin compound with an acyl halide to produce ketone products (eq 1), which has many advantages over existing methods of preparing ketones from acyl chlorides. The yields are high, and in many cases, nearly quantitative. Both the organotin compound and the catalyst are air stable. The reaction tolerates a wide variety of functional groups; ester, alkene, nitro, nitrile, halo, methoxy, silyloxy, vinyl ether, and even aldehyde remain intact during the reaction. Sterically hindered acid chlorides will react, and conjugate addition with α,β-unsaturated acid chlorides does not occur. Further, if a vinyl-, aryl-, or alkynyl-trialkylstannane is used, only the vinyl, aryl, or alkynyl group is transferred. With stannanes as substituents on a stereogenic center, the reaction stannanes as substituents on a stereogenic center, the reaction proceeds with stereochemical inversion of the stereogenic center.[6] Acylstannanes can be prepared by the coupling of acyl halides and distannyl species.[7]

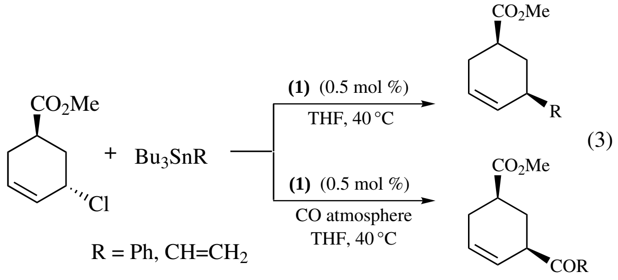


R^1 = alkyl, aryl, vinyl, alkynyl, allyl, -OR, $-NR_2$
R^2 = alkyl, aryl, vinyl, alkynyl, allyl
R^3 = Bu, Me

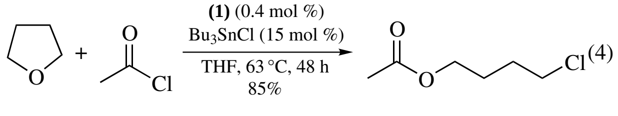
Aldehydes can be prepared from acid chlorides and tri-*n*-butyltin hydride in the presence of (**1**).[8] While this reduction can be performed by mixing the substrate and Bu_3SnH, ester byproducts and other products resulting from radical reactions occur without the palladium catalyst. 1,2-Diketones can be made easily by the reaction of a 1-methoxyvinylstannane and an acid chloride, followed by hydrolysis (eq 2).[9] A similar 2-methoxyvinylstannane was employed in the synthesis of agglomerin A and (±)-carolinic acid.[10] Vinylstannanes and acyl chlorides have been coupled intramolecularly to provide 11-, 12-, 14-, 16-, and 20-membered macrocycles in 32–72% yields.[11]

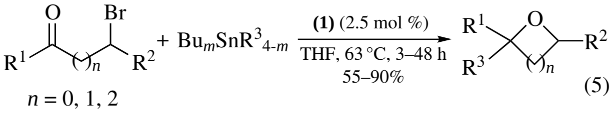


Allylic halides can be coupled with organostannanes without allylic transposition.[3b] The reaction takes place with inversion of stereochemistry at the allylic carbon, and double bond geometry remains intact for acyclic substrates (eq 3).[3c] In addition, carbon monoxide can be inserted during the course of the reaction to provide ketone products.[3a,12] Vinyl iodides couple in a similar fashion,[4a] and the coupling of vinyl triflates was used in the synthesis of pleraplysillin.[4b]



Ether Cleavage and Formation Reactions. While the cross coupling reactions of organotin compounds in the presence of (**1**) tolerate a great deal of functionality, cyclic (5-membered or less), allylic and benzylic ethers can be cleaved upon reaction with an acid chloride catalyzed by the presence of trialkyltin chloride (eq 4).[13] Aliphatic and phenolic ethers are not consumed. Complementary to this method of ether substrate cleavage, epoxides, oxetanes, and tetrahydrofurans can be formed by the reaction of bromo ketones and allylic stannanes or α-ketostannanes (eq 5).[14] Other alkylstannanes fail to give cyclic ethers.





(5)

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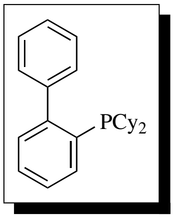
[1,1′-Biphenyl]-2-yldicyclohexylphosphine



[247940-06-3] $C_{24}H_{31}P$ (MW 350.48)

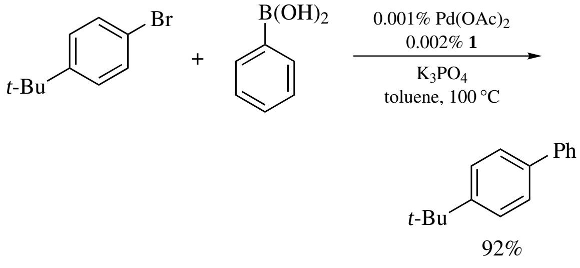
(reagent used as a ligand for a variety of palladium-catalyzed reactions)

Alternate Name: 2-(dicyclohexylphosphino)biphenyl.
Physical Data: mp 103 °C.
Solubility: soluble in most organic solvents.
Form Supplied in: white crystalline solid.
Purification: recrystallized from hot methanol.
Handling, Storage, and Precautions: stable to air and moisture.

Introduction. 2-(Dicyclohexylphosphino)biphenyl (**1**) is a monodentate phosphine ligand that is prepared via lithiation of 2-bromobiphenyl followed by phosphinylation with dicyclohexylchlorophosphine.[1] Ligand **1** was developed by Buchwald and first described in 1999 for use in Pd-catalyzed Suzuki–Miyaura couplings and N-arylation reactions of aryl bromides and chlorides. The high activity of catalysts supported by ligand **1** is believed to be due to a combination of steric and electronic properties. The ligand is electron rich, which facilitates oxidative addition of aryl halides to Pd(0), and is sterically bulky, which promotes carbon–carbon and carbon–heteroatom bond-forming reductive elimination. Unlike many electron-rich phosphines, **1** is air-stable at room temperature in crystalline form and in solution.[2] Ligand **1** has been used extensively in various palladium-catalyzed cross-coupling reactions,[3] which are described in this article.

Suzuki–Miyaura Couplings. The palladium-catalyzed cross coupling of organoboron reagents with aryl/alkenyl halides (Suzuki coupling) is one of the most common methods used for the formation of Csp^2–Csp^2 bonds.[4–7] Ligand **1** has been frequently employed in these transformations.

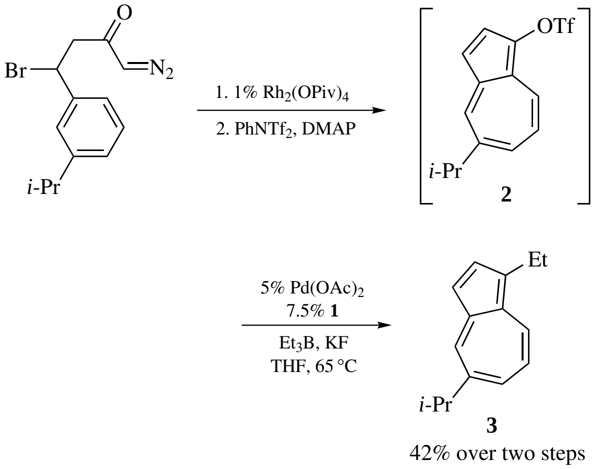
The high activity of catalysts supported by **1** allows Suzuki coupling reactions to be conducted with relatively low catalyst loadings. For example, the coupling of 4-bromo-*tert*-butyl benzene with phenylboronic acid was achieved using only 0.001 mol % palladium (eq 1).[1,8] The Suzuki coupling of unactivated aryl chlorides can also be effected, although slightly higher catalyst loadings are typically required (0.05–1 mol % Pd).[1,8] High turnover numbers have also been obtained using a palladium(0) monophosphine complex composed of diallyl ether and **1**.[9]



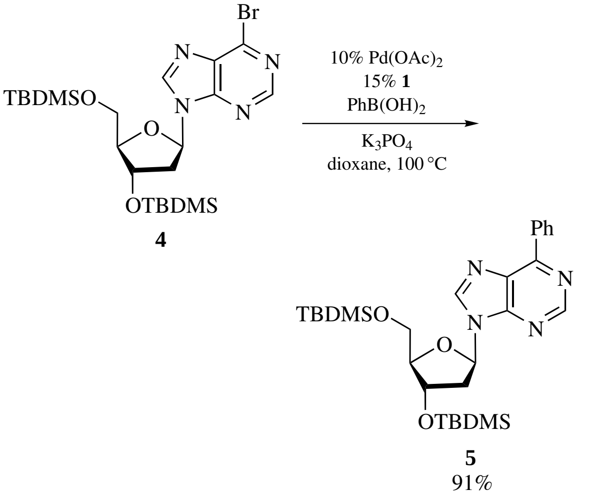
(1)

The $Pd(OAc)_2$/**1** catalyst system has also been employed for the Suzuki coupling of sensitive substrates. For example, the cross coupling of unstable 1-azulenyl triflate **2** with triethylborane was achieved using this catalyst (eq 2). The product of this transformation (**3**) is a key intermediate in Danheiser's synthesis of the antiulcer drug egualen sodium (KT1-32).[10,11] This catalyst operates efficiently under sufficiently mild conditions such that a broad array of functional groups are tolerated.[12–15]

Catalysts supported by **1** are often used for cross-coupling reactions of heteroaryl halides. In a representative example, C-6 arylpurine 2′-deoxyriboside analog **5** was prepared from the corresponding C-6 bromopurine substrate **4** (eq 3).[16] A similar strategy allowed the construction of C-6 aryl 2′-deoxyguanosine derivatives from the corresponding O^6-aryl sulfonates.[17] A broad array of heterocycles can be generated using this chemistry, including arylpyridines, arylquinolines,[18] and C-4 aryl coumarins.[19] Resin-bound chlorotriazines have also been used as coupling partners in these transformations.[20]



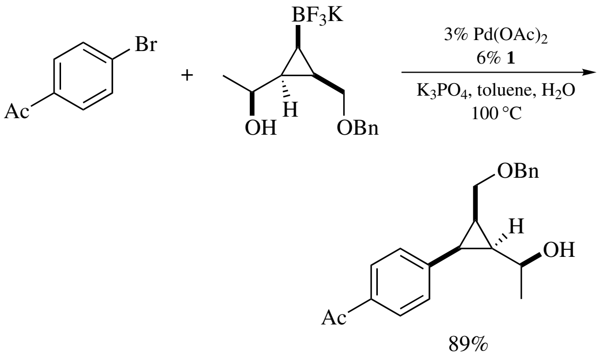
(2)



(3)

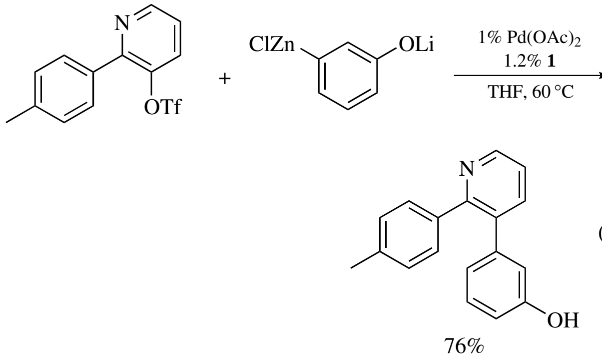
Although most Suzuki coupling reactions use boronic acids as the nucleophilic coupling partner, these reagents can be difficult to purify, and the boronic acid moiety is usually too sensitive to tolerate multistep sequences of reactions. In contrast aryl, alkyl, and alkenyl potassium trifluoroborates have much better physical and chemical properties and are finding many applications in Pd-catalyzed cross-coupling reactions.[21] These reagents can be prepared in highly pure form through recrystallization, and the trifluoroborate moiety is tolerant of conditions used in many common organic transformations. As shown below (eq 4), the $Pd(OAc)_2$/**1** catalyst system provides good results in Suzuki coupling reactions of cyclopropyl potassium trifluoroborates with aryl bromides.[22] However, in many cross-coupling reactions of organotrifluoroborate reagents, superior results are obtained with other ligands.[21]

Although **1** provides excellent results in a number of Pd-catalyzed Suzuki coupling reactions, related biaryl(dialkyl)-phosphine derivatives bearing substituents at the 2′- and 6′-positions often show higher reactivity and are effective with a broader array of substrates.[23–25] These ligands have found applications in transformations that were not efficiently catalyzed by Pd/**1**.



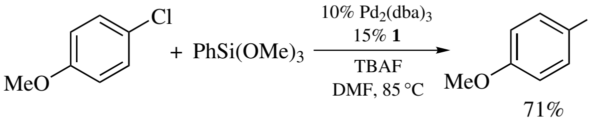
(4)

Other Pd-catalyzed Cross-coupling Reactions. In addition to the Suzuki coupling reactions described above, Pd/**1** catalysts have been used in several other Pd-catalyzed cross-coupling reactions of aryl halides with main-group organometallic reagents. For example, a catalyst composed of $Pd(OAc)_2$/**1** was shown to be optimal in Negishi coupling[26,27] reactions of aryl triflates with arylzinc phenoxides that afford biaryl phenols (eq 5).[28] This method can be employed for the synthesis of oligoarene products via an iterative sequence of cross coupling followed by triflation of the resulting phenol product.



(5)

Several examples of $Pd_2(dba)_3$/**1**-catalyzed Hiyama coupling reactions of organosilicon reagents with aryl, alkenyl, or alkynyl halides have been reported.[29] As shown below (eq 6), this catalyst provided excellent results in couplings of phenyltrimethoxysilane with aryl halides[30] and triflates.[31]

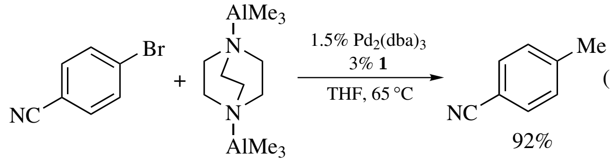


(6)

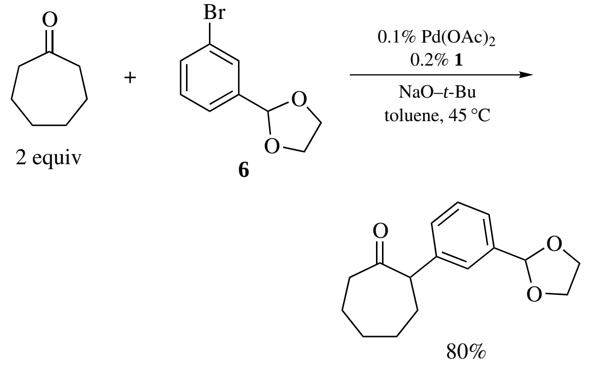
The methylation of aryl and vinyl halides with an air stable DABCO adduct of trimethylaluminum was achieved using a Pd/**1** catalyst.[32] As shown in eq 7, the methylation of 4-bromobenzonitrile with $(AlMe_3)_2$(DABCO) provided 4-cyanotoluene in 92% yield. These conditions are sufficiently mild that substrates bearing nitriles, hydroxyl groups, esters, aldehydes, and nitro groups are efficiently transformed without degradation of the functional group.

A few examples of the use of ligand **1** in Pd-catalyzed α-arylation of ketones have been described. For example, the coupling of cycloheptanone with aryl bromide **6** proceeded in 80% yield with the $Pd(OAc)_2$/**1** catalyst system (eq 8),[33] and ligand **1** was also optimal for Pd-catalyzed α-arylations of ethyl

N-diphenylmethylideneglycinate with iodopurines under mildly basic conditions (K_3PO_4).[34] However, other biaryl-derived phosphine ligands typically provide superior results in the majority of Pd-catalyzed ketone α-arylation reactions.[33]

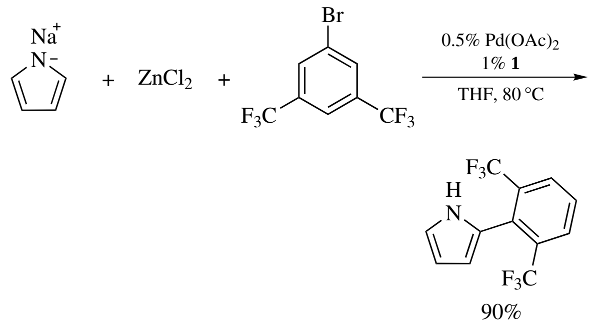


(7)



(8)

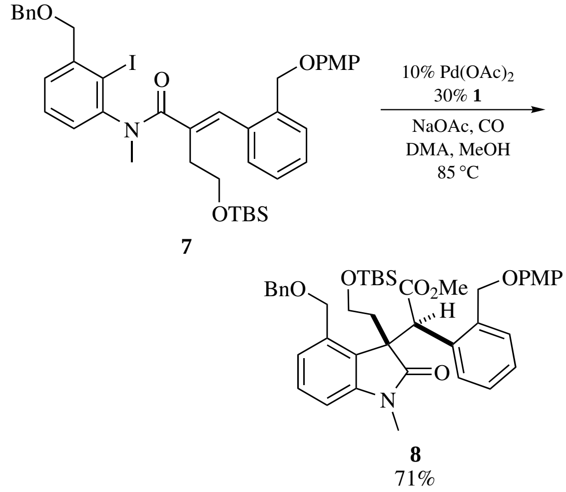
The C-2 arylation of pyrrole anions with aryl bromides can be accomplished under relatively mild conditions with the use of a Pd/**1** catalyst and stoichiometric amounts of zinc chloride (eq 9).[35] Ligand **1** was also shown to facilitate regioselective phenylation of 4-oxazolecarboxylate with iodobenzene in the presence of Cs_2CO_3.[36]



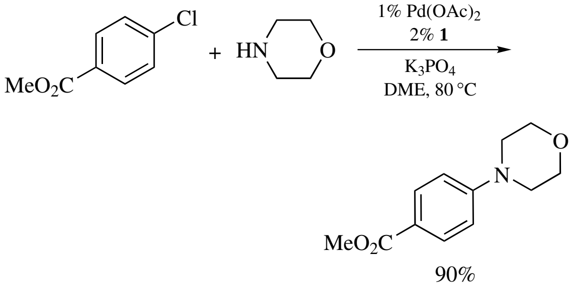
(9)

A single example of use of ligand **1** in a stereoselective palladium-catalyzed tandem Heck arylation/carbonylation reaction has been reported in the total synthesis of perophoramidine. As shown in eq 10, **7** was converted to **8** in 71% yield as a single diastereomer.[37]

Palladium-catalyzed Carbon–Heteroatom Bond Formation. The palladium-catalyzed amination of aryl halides is a powerful method for the synthesis of substituted or functionalized arylamines,[38,39] which are of particular importance in the pharmaceutical industry.[40,41] Ligand **1** is highly effective for palladium-catalyzed N-arylation reactions of aryl bromides,[42] chlorides,[42] and iodides (eq 11).[43] Other related biaryl(dialkylphosphine) ligands also provide excellent results in these transformations, and ligands bearing substituents at the 2′ and 6-positions are frequently more active than **1**.[42,44] The catalytic activity of **1** diminishes as reactions progress, which results from the formation of catalytically inactive palladacycles via competing intramolecular C–H activation of a 2′-aromatic hydrogen atom on the proximal ring.[45,46] In contrast, biaryl bearing substituents that block these positions do not undergo this side reaction and are more effective at low catalyst loadings.[46]



(10)



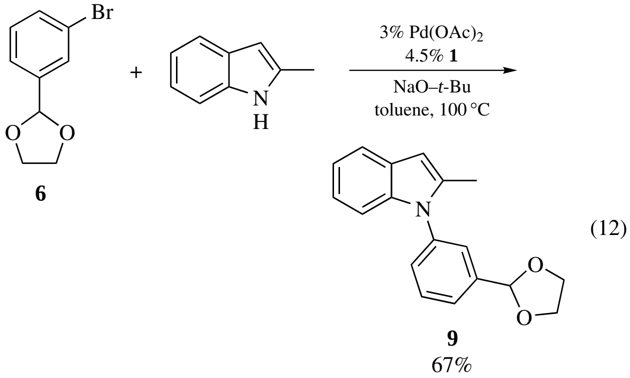
(11)

Ligand **1** has been employed in a variety of other Pd-catalyzed N-arylation or N-alkenylation reactions of aliphatic or aromatic amines. For example, use of **1** allows selective monoarylation of dichloropyridines with aniline derivatives,[47] and has been used in N-arylation reactions of bromoporphyrin derivatives.[48] Primary anilines can be easily obtained from reactions of aryl halides with ammonia equivalents (LiHMDS or Ph_3SiNH_2),[49,50] and enamines have been prepared via Pd/**1**-catalyzed reactions of vinyl triflates with secondary amines.[51] The Pd/**1** catalyst system has also been used in microwave-promoted coupling reactions of azaheteroaryl chlorides with various amines.[52,53]

Although a number of different phosphine ligands are suitable for Pd-catalyzed N-arylation reactions involving aliphatic or aromatic amine substrates,[38–41] the N-arylation of heterocycles is much more difficult, and relatively few palladium catalysts effectively promote this transformation.[54] As shown below, ligand **1** is a useful ligand for the N-arylation of indoles.[55] For example, aryl bromide **6** was coupled with 2-methylindole to afford N-aryl indole product **9** in 67% yield (eq 12). Despite the utility of **1** in these transformations, the Pd-catalyzed N-arylation of heterocycles remains challenging. However, highly effective copper catalysts have been developed for heterocycle N-arylation reactions that function well with a broad array of substrate combinations.[56,57]

Palladium-catalyzed aryl carbon–boron bond forming reactions are useful methods for the synthesis of organoboron reagents under mild conditions. The selective borylation of aryl bromides in the presence of a primary amine functionality has been achieved using a catalyst composed of $Pd(OAc)_2$/**1**. As shown in eq 13, 2-bromoaniline was coupled with pinacolborane to afford **10** in

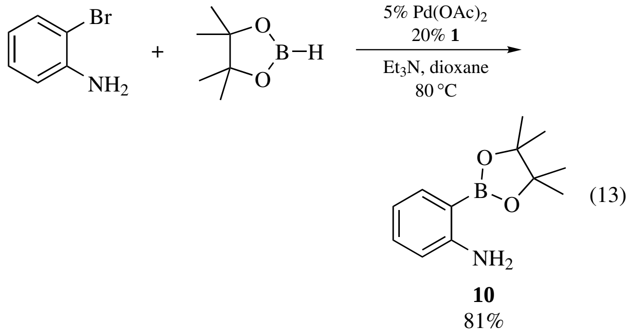
81% yield.[58] Borylation of bromoindoles with pinacolborane was effected using similar reaction conditions.[59]



6

9
67%

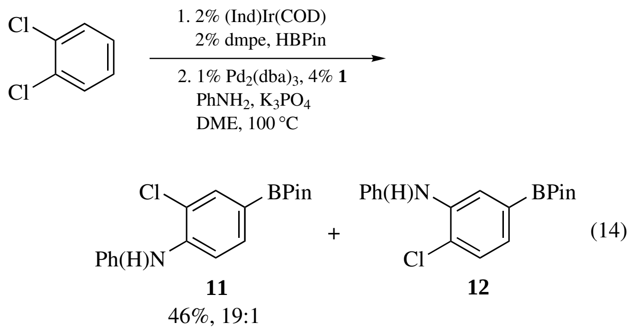
(12)



(13)

10
81%

Tandem reactions or one-pot sequences of reactions involving Pd-catalyzed N-arylation are useful ways to build complex and functionalized products rapidly. Ligand **1** is effective in several transformations of this type. For example, the tandem one-pot borylation/amination reaction of dichlorobenzene provided a 19:1 mixture of borylated chloroaniline derivatives **11** and **12** (eq 14).[60] The Pd/**1** catalyst has been employed in one-pot borylation/Suzuki coupling reactions of aryl halides,[58] which have been utilized for the synthesis of biologically active biaryl lactams,[61] β-benzo[*b*]thienyldehydrophenylalanine derivatives,[62] and the natural products hippadine and pratosine.[63] Ligand **1** has also been used in the synthesis of carbazole natural product murrastifoline-A via tandem intermolecular/intramolecular N-arylation of a 2,2′-dibromobiphenyl precursor.[64,65]

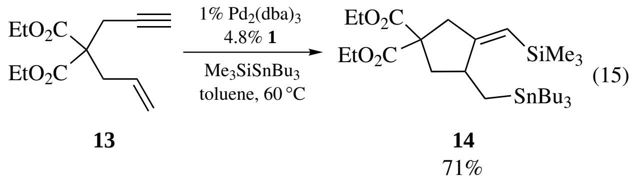


(14)

11
46%, 19:1

12

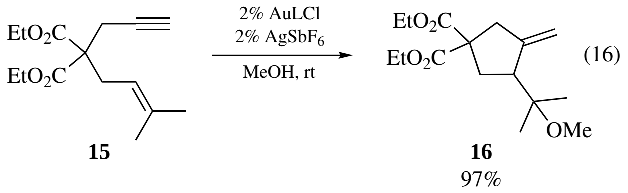
Enyne Cyclizations. Catalysts supported by ligand **1** have shown utility in several cyclization/addition reactions of enyne substrates. For example, silylstannation–cyclization of 1,6-enyne **13** was effected by treatment with tributyl(trimethylsilyl)stannane and catalytic amounts of $Pd_2(dba)_3$ and ligand **1**. This reaction provided a five-membered carbocyclic product (**14**) bearing (tributylstannyl)methyl- and alkylidenesilane moieties in 71% yield (eq 15).[66] A related enyne cyclization/addition reaction of **15** was achieved using a Au(L)Cl/$AgSbF_6$ catalyst (L = **1**). This transformation occurs with net 1,7-addition of methanol to afford **16** in 97% yield (eq 16).[67,68] Under similar reaction conditions, alkyne substrates bearing aromatic substituents were transformed to tricyclic products. Ligand **1** also provides satisfactory results in Pd-catalyzed cycloisomerization reactions of functionalized 1,6-dienes; although PCy_3 or $P(cyclopentyl)_3$ are more frequently employed as ligands in these transformations.[69]



(15)

13

14
71%

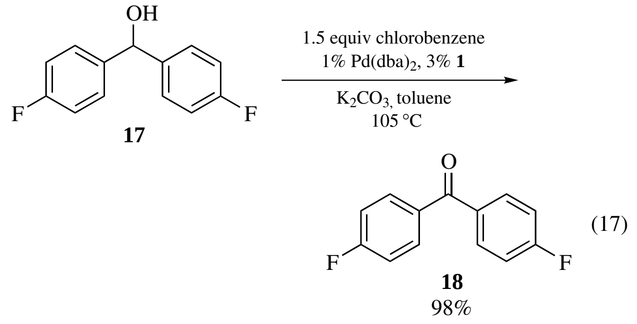


(16)

15

16
97%

Oxidation. The oxidation of alcohols to ketones or aldehydes under mild and environmentally sound conditions has been achieved using catalytic amounts of $Pd(dba)_2$ and ligand **1**, with chlorobenzene serving as the stoichiometric oxidant.[70,71] For example, alcohol **17** was converted to ketone **18** in 98% yield under these conditions (eq 17).



17

(17)

18
98%

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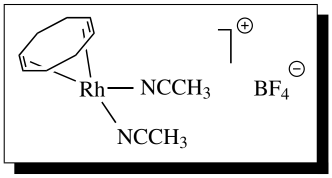
Bis(acetonitrile)[(1,2,5,6-η)-1,5-cyclooctadiene]-rhodium(1+),tetrafluoroborate(1-)



[32679-02-0] $C_{12}H_{18}BF_4N_2Rh$ (MW 379.99)

(catalyst for the formation of C–C bonds between various organic electrophiles and organometallic reagents. Also used as a catalyst for hydroformylation and hydrogenation reactions)

Physical Data: mp 188–190 °C (dec).[2]

Solubility: soluble in most organic solvents; insoluble in H_2O.

Form Supplied in: yellow crystals, commercially available from Aldrich (cat. #640360).

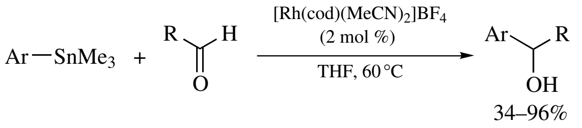
Analysis of Reagent Purity: melting point, IR.[2]

Preparative Methods: can be prepared by reaction of $[RhCl(cod)]_2$ and $AgBF_4$ in CH_2Cl_2 and CH_3CN, followed by filtration, concentration of the reaction solution, and precipitation of the product using Et_2O.[3] A similar synthesis has also been performed using Ph_3CBF_4 instead of $AgBF_4$.[2]

Purification: recrystallization can be done from acetonitrile with slow addition of diethyl ether.

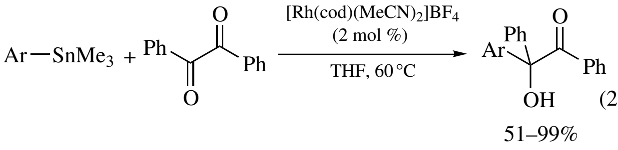
Handling, Storage, and Precautions: store in a cool, dry place in a tightly sealed container. Handle and store under an inert atmosphere of nitrogen or argon. May cause mild to severe irritation of the eyes, skin, nose, mucous membrane, or respiratory tract. Avoid ingestion, inhalation, or direct contact with skin or clothing. The toxicological effects of this reagent have not been thoroughly tested; unknown hazards may be present. Chemical-safety goggles and appropriate gloves are highly recommended. Use only in a chemical fume hood and near safety shower and eye bath. Do not breathe dust. Compound is incompatible with oxidizing agents and active metals and decomposes to carbon dioxide, carbon monoxide, boron oxides, hydrogen fluoride, and rhodium salts.

1,2-Additions to Carbonyls. Bis(acetonitrile) (η^4-1,5-cyclooctadiene) rhodium(I) tetrafluoroborate has been shown by Oi to catalyze addition of organometallic reagents to aldehydes. Under mild conditions, aromatic organostannanes undergo reaction with aromatic and aliphatic aldehydes in the presence of 2 mol % catalyst to generate secondary alcohols in excellent yields (eq 1).[4]



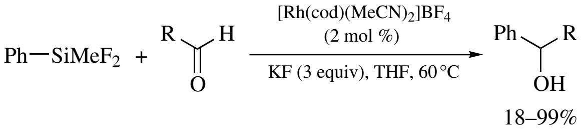
(1)

Despite the fact that this reaction is not compatible with ketones, α-dicarbonyl compounds also prove to be viable electrophiles.[3] For example, under the same conditions as those employed above, benzil treated with aryltrimethylstannanes in the presence of $[Rh(cod)(MeCN)_2]BF_4$ provides the monoaddition product (eq 2). Glyoxylic acid esters as well as α-ketoesters are also compatible under the reaction conditions.



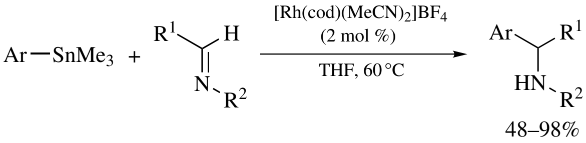
(2)

As well as organostannanes, phenylmethyldifluorosilane has been shown to add to aryl-, heteroaryl-, and alkyl-aldehydes in the presence of KF using $[Rh(cod)(MeCN)_2]BF_4$ as catalyst (eq 3).[5]



(3)

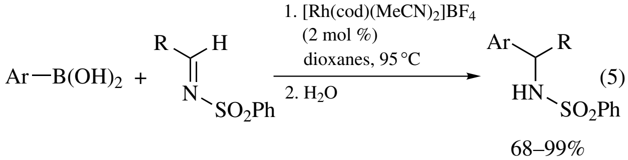
1,2-Additions to Imines. The addition of organometallic reagents to imines is a useful method of synthesizing amines. $[Rh(cod)(MeCN)_2]BF_4$ has been employed in the arylation of aldimines with *N*-electron-withdrawing groups. It was initially shown that addition of organostannanes, providing the corresponding sulfonamines in good to excellent yields (eq 4).[3,6,7] In almost concurrent reports Oi and Miyaura demonstrated that aryl organostannanes and sodium tetraphenylborate[7] are viable coupling partners in additions to *N*-tosylimines. Also, arylmethyldifluorosilanes react in the presence of $[Rh(cod)(MeCN)_2]BF_4$ and KF to provide *N*-tosylamines.[8]



(4)

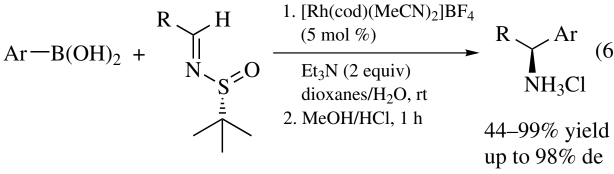
R^1 = aryl, heteroaryl, COOEt
R^2 = tosyl, $PO(OEt)_2$, COPh, COO^tBu

Subsequent reports have shown that boron-based coupling agents other than sodium tetraphenylborate can be employed in rhodium-catalyzed addition to imines.[9] Miyaura has shown that the coupling of aryl boronic acids with *N*-sulfonylimines in the presence of $[Rh(cod)(MeCN)_2]BF_4$ provides *N*-protected amines in excellent yields (eq 5).



(5)

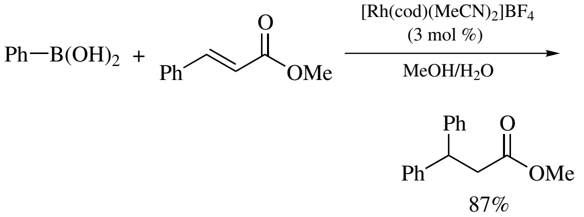
Of particular note is the diastereoselective addition of aryl boronic acids to sulfinimines in dioxanes and water.[10] Batey has shown that a range of aryl-, heteroaryl-, and alkyl-sulfinimines will react with arylboronic acids with high diastereoselectivities under rhodium(I) catalysis, which, following acidic hydrolysis, generate α-chiral primary amine salts (eq 6).



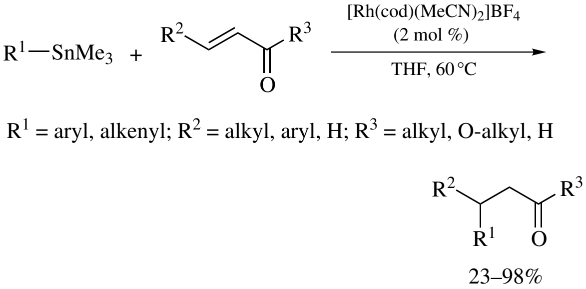
(6)

1,4-Additions to Carbonyl-containing Compounds. When contrasted to the number of reports involving rhodium(I)-catalyzed 1,4-additions to carbonyl-containing compounds,[11] the use of $[Rh(cod)(MeCN)_2]BF_4$ as either the catalyst or as a precatalyst for generation of a chiral complex is somewhat limited. However, there remain selected examples where this catalyst is the rhodium source of choice for conjugate addition to enones and related species. For example, Miyaura has shown that phenylboronic acid will react with α,β-unsaturated aldehydes and esters in the presence of $[Rh(cod)(MeCN)_2]BF_4$, providing the 1,4-addition product in excellent yield (eq 7).[12,13] This reaction can be performed in the presence of (*S*)-BINAP, generating enantioenriched products. However, neutral rhodium complexes were more effective catalysts in this reaction.

Aryl- and alkenylstannanes are also effective coupling partners in 1,4-additions to α,β-unsaturated carbonyl compounds with $[Rh(cod)(MeCN)_2]BF_4$ as catalyst.[14,15] Oi has shown that a wide range of unsaturated aldehydes, ketones, and esters are compatible under the mild reaction conditions (eq 8).

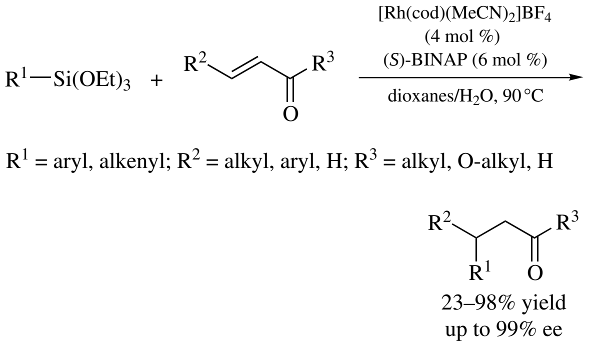


(7)



(8)

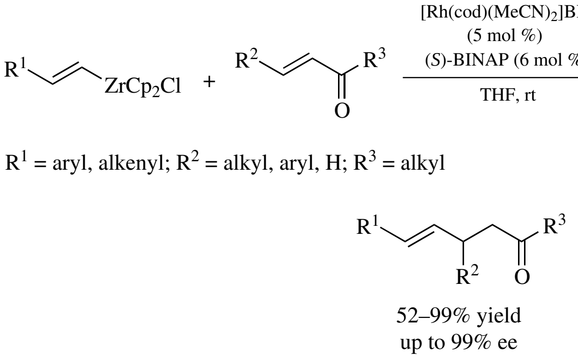
The same group has also demonstrated that organosiloxanes will perform conjugate addition to a number of α,β-unsaturated carbonyl compounds. While the initial studies generated racemic products,[16] subsequent investigations have shown that using 4 mol % $[Rh(cod)(MeCN)_2]BF_4$ with 6 mol % (*S*)-BINAP, aryl- and alkenylsiloxanes will perform highly asymmetric 1,4-addition to α,β-unsaturated ketones, esters, and amides (eq 9).[17,18] Unsaturated aldehydes and nitriles are compatible in the racemic arylation and alkenylation chemistry, but have not been shown to be compatible under asymmetric catalysis.



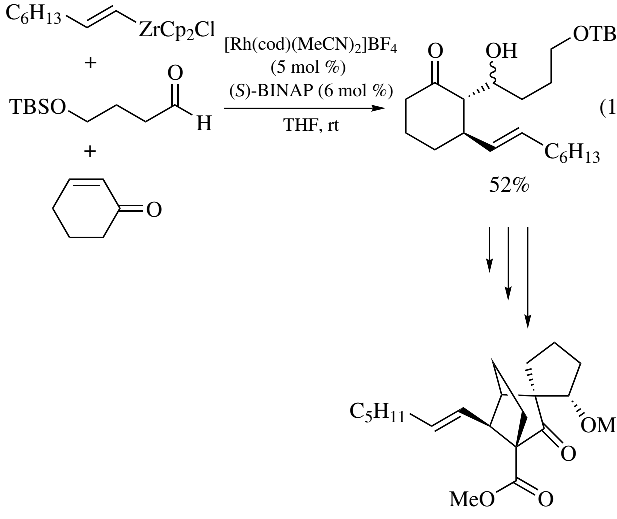
(9)

Additionally, alkenylzirconium reagents will undergo catalytic, asymmetric 1,4-addition to α,β-unsaturated ketones, catalyzed by $[Rh(cod)(MeCN)_2]BF_4$ in the presence of (*S*)-BINAP.[19] Both cyclic and acyclic ketones provide the substituted enone products, though enantioselectivities tend to be higher with cyclic species (eq 10).

This work has been elegantly exploited by Nicolaou in the synthesis of the spirocyclic system of Vannusal A.[20] By trapping the in situ-generated rhodium(I) enolate with an aldehyde, the result is an asymmetric three-component reaction of α,β-unsaturated ketones, alkenylzirconium reagents, and aldehydes through a 1,4-addition/aldol reaction sequence (eq 11).

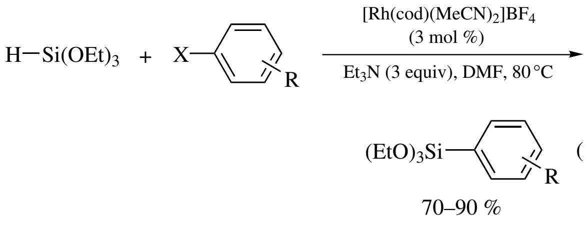


(10)



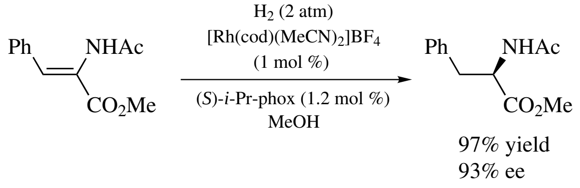
(11)

Synthesis of Organosilanes. $[Rh(cod)(MeCN)_2]BF_4$ has also been employed as a catalyst in the synthesis of silane organometallics from aryl halides and triethoxysilane.[21] Organosilanes provide a useful alternative to organoboron or organotin reagents in cross-coupling reactions. Thus, the rhodium(I)-catalyzed reaction of triethoxysilane and aromatic iodides and bromides provides a useful route to prepare aryltriethoxysilanes (eq 12), which were previously shown to be viable substrates in asymmetric 1,4-addition to α,β-unsaturated carbonyl compounds. This method has also been employed in the synthesis of 3,6-bis(triethoxysilyl)carbazoles, toward the generation of mesoporous materials.[22]



(12)

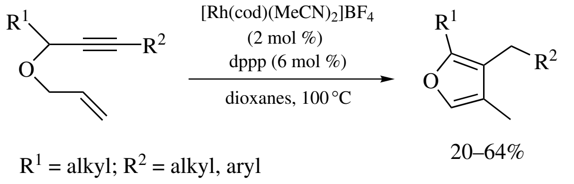
Hydrogenation. $[Rh(cod)(MeCN)_2]BF_4$ has not been extensively used as a hydrogenation catalyst. In the original communication of its synthesis, Green and co-workers demonstrated that when 1,5-cyclooctadiene is employed as a hydrogenation substrate, it is monohydrogenated to generate cyclooctene. They also demonstrated that 1,3-cyclooctadiene is not hydrogenated at all by this catalyst.[23] This metal complex, though, has been used as a precursor for asymmetric hydrogenation in combination with chiral phosphines.[24] For example, using silica gel-immobilized (*S*)-*i*-Pr-phox as a ligand in combination with $[Rh(cod)(MeCN)_2]BF_4$, the hydrogenation of methyl (*Z*)-α-(acetamido)cinnamate is accomplished in 97% yield with 93% enantioselectivity (eq 13).



(13)

Hydroformylation. $[Rh(cod)(MeCN)_2]BF_4$ itself has not been employed as a catalyst for hydroformylation. However, in combination with phosphine ligands, it has been shown to be effective in the hydroformylation of styrene using a solid-supported catalyst.[25] For example, a silica-supported diphenylphosphinoethane-derived phosphine in combination with $[Rh(cod)(MeCN)_2]BF_4$ catalyzes the hydroformylation of styrene and has been employed in mechanistic studies thereof.

Cycloisomerization. Interestingly, $[Rh(cod)(MeCN)_2]BF_4$ enables cycloisomerization of allyl propargyl ethers directly into substituted furans in one step (eq 14).[26] This reaction was found to be enhanced in the presence of catalytic quantities of carboxylic acids, for example, acetic acid. While the report reveals little functional group compatibility, it demonstrates a potential for use of related cycloisomerizations to other heterocyclic targets, such as pyrroles.



(14)

Related Reagents. Other related rhodium compounds [usually Rh(I)] include $[Rh(cod)_2]BF_4$, $[RhCl(cod)]_2$, Rh/C, $RhCl_3$, $[Rh(OAc)_2]_2$, $Rh(acac)(CH_2CH_2)_2$, $Rh(CO)_2(acac)$, $[RhCl(cod)]_2$, $RhH(CO)(PPh_3)_3$, $RhCl(CO)(PPh_3)_2$, $RhI(PPh_3)_3$, $RhBr(PPh_3)_3$, $RhCl(PPh_3)_3$, $Rh(acac)(coe)_2$, $Rh_2(OAc)_2$.

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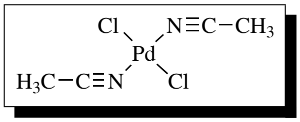
Bis(acetonitrile)dichloropalladium(II)



[14592-56-4] $C_4H_6Cl_2N_2Pd$ (MW 259.43)

Main Applications:

- Pd^{II}-catalyzed oxidative functionalization of alkenes, alkynes, and related unsaturated compounds.
- Pd^{II}-catalyzed sigmatropic rearrangements.
- Precursor of Pd^0 catalyst in a wide array of cross-coupling reactions.
- Precursor of other Pd^{II} dichloride complexes by acetonitrile ligand exchange.

Physical Data: mp 129–131 °C (decomp).

Solubility: sol CH_2Cl_2, THF, acetone, CH_2Cl_2/CH_3CN. Insol water and aqueous solutions.

Form Supplied in: orange solid; commercially available.

Preparation and Purification: $PdCl_2(CH_3CN)_2$ is easily prepared by stirring $PdCl_2$ in CH_3CN at room temperature for 24 h (or 18 h at reflux) under nitrogen. The resulting orange solid is filtered, washed with Et_2O, and dried. The dried product can be used without further purification. Recrystallization from CH_3CN/CH_2Cl_2/hexane or CH_3CN/Et_2O gives $PdCl_2(CH_3CN)_2$ as bright yellow crystals.

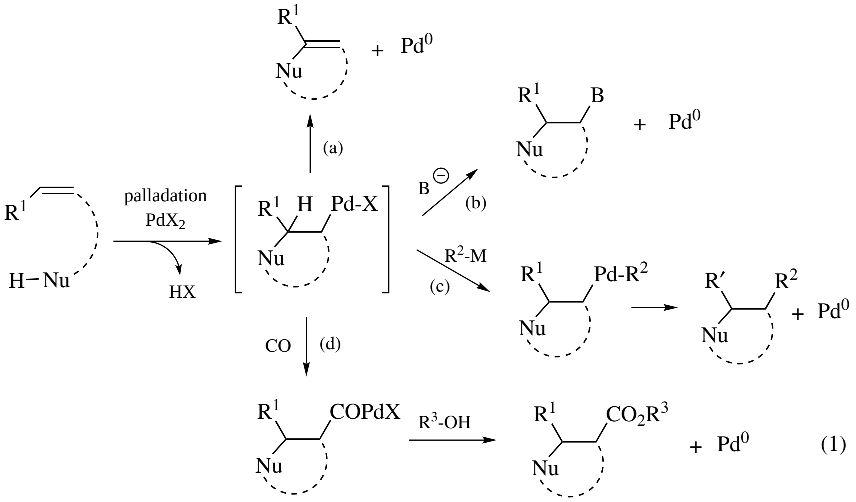
Handling, Storage, and Precautions: This complex, kept in a closed vessel is stable for months at room temperature. $PdCl_2$ $(CH_3CN)_2$ is harmful by inhalation, in contact with skin and if swallowed.

General Considerations. The ability of palladium to act both as a nucleophilic (Pd^0) and electrophilic (Pd^{II}) catalyst has made palladium chemistry an indispensable tool for synthetic organic chemists.[1] Pd^0-catalysis has dominated the landscape of catalyst development for the past several decades. In particular, Pd-catalyzed cross-coupling reactions are among the most efficient carbon–carbon and carbon–heteroatom bond-forming reactions in organic synthesis.[2] Although to a lesser extent, Pd^{II} oxidation catalysis has also experienced great development, leading to synthetically useful protocols and providing organometallic chemists with a platform to investigate fundamental processes.[3] In contrast to Pd^0-catalysis, in Pd^{II}-catalyzed oxidation reactions the functionalization of the organic substrate occurs with concomitant reduction of Pd^{II} to Pd^0, which requires the in situ oxidation of Pd^0 back to Pd^{II} to make the reaction catalytic with respect to Pd^{II}. Inorganic oxidants (such as Cu^{II} salts, HNO_3, H_2O_2) or MnO_2, and organic compounds (such as benzoquinone or alkyl hydroperoxides) are typically used for regenerating the active Pd^{II} species. More recently efficient reoxidation of Pd^0 with molecular oxygen, the most practical oxidant, has been achieved in DMSO.[4] It was found that DMSO, which is a favorable ligand for Pd^0, promotes direct oxidation to Pd^{II} with O_2. This and other recent achievements in this field have led to a re-emergence of Pd^{II}-catalyzed oxidation chemistry.

Palladium(II) compounds such as $PdCl_2$, $Pd(OAc)_2$, or $Pd(acac)_2$ are stable and commercially available. $PdCl_2$ has low solubility in water and organic solvents, but it becomes soluble in organic solvents by forming solvates such as $PdCl_2(CH_3CN)_2$ or $PdCl_2$ $(PhCN)_2$. They can be used in two important ways: as unique oxidizing agents and as sources of Pd^0 catalysts. Stable Pd^{II} salts are easily reduced to Pd^0 complexes with several reducing agents such as phosphines, metal hydrides, or organometallic reagents. In contrast to Pd^0-chemistry, which is dominated by the use of phosphanes and other soft donor ligands to stabilize Pd^0 species, most of these ligands decompose rapidly under oxidizing reaction conditions required in most Pd^{II}-catalyzed processes, and therefore palladium oxidation chemistry has been dominated by the use of simple palladium salts.

Palladium(II)-Catalyzed/Promoted Addition of Nucleophiles across the C=C Bond of Alkenes. Fast and reversible coordination of electrophilic Pd^{II} complexes to alkenes produces π-complexes that are activated toward addition of heteroatom- and carbon-nucleophiles. The nucleophilic attack on the π-olefin species is called palladation and generally occurs *anti* to the metal (*trans*-heteropalladation or carbopalladation) at the more substituted vinylic carbon, to give a σ-alkylpalladium(II) complex that is usually unstable and may then undergo a variety of processes (eq 1). Depending on the reaction conditions this Pd^{II} intermediate can evolve by a palladium β-hydride elimination (path a), resulting in nucleophilic substitution of the olefinic proton, or displacement of the Pd by another nucleophile (path b) to give formally the nucleophilic addition product. Another possibility is transmetallation with other organometallic reagents followed by reductive elimination (path c), or various insertion processes to the σ-alkylpalladium species, such as carbon monoxide insertion followed by alcoholysis of the resulting acylpalladium intermediate (path d). In all these transformations, the oxidation of the organic substrate occurs with concomitant reduction of Pd^{II} to Pd^0, therefore consuming a stoichiometric amount of expensive Pd^{II} salts. Sometimes, but not always, the reduced Pd^0 can be reoxidized in situ to Pd^{II}, making feasible the development of a truly useful synthetic method catalytic with regard to Pd^{II}. Typical Pd^{II} salts known to promote Lewis acid activation of alkenes, allowing the nucleophilic addition, are $PdCl_2$, $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$, and M_2PdCl_4 (M = Li, Na), the latter used especially for aqueous or alcohol reaction media.

After palladation of the alkene, the σ-alkylpalladium(II) complex intermediate may also evolve to form other Pd^{II} species. In such a case, no reoxidant is required for efficient catalytic reaction. An important Pd^{II}-generation step in Pd^{II}-catalyzed reactions is the elimination of heteroatom groups such as Cl, Br, OAc, and OH at the β-position to palladium (eq 2), which is faster



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