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Cross-Coupling Reaction Manual: Desk Reference

MilliporeSigma

Foreword

About the Author

Dr. Nick Bruno was born and raised in California, MD. He received his B.A. in 2010 from St. Mary's College of Maryland, working under Dr. Andrew Koch. In 2015 he received his Ph.D. from MIT in the lab of Dr. Steve Buchwald, where he worked on the development of palladium precatalysts for cross-coupling. Outside of chemistry, he is an amateur woodworker and avid fan of the Baltimore Orioles and Washington DC's NFL team.

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If any further evidence was needed, the 2010 Nobel Prize in Chemistry solidified palladium-catalyzed cross-coupling as one of the most versatile and powerful bond-forming methods in synthetic organic chemistry. Truly, the field of cross-coupling has matured to the point where nearly any two fragments can be coupled with the right catalyst system.

Despite the power and utility of cross-coupling, the proper choices in catalyst system and reaction optimization can be daunting to chemists without an extensive background in palladium chemistry. Having recently completed my Ph.D. in the Buchwald lab, developing the Pd G3 precatalysts, I became intimately familiar with many cross-couplings as well as the need to simplify cross-coupling reaction design and setup to maximize user-friendliness.

The desire to further the simplicity, reliability, and robustness of cross-coupling methods led to this guide. The guide is designed to be your go-to reference for planning and setting up cross-coupling reactions. Each reaction page contains the best initial set of reaction conditions and catalyst system, which are based on the most robust and broadly applicable methods in the literature. Additional viable ligands for each transformation are listed, as well as notes specific to each reaction, additional experimental conditions, and relevant references. This guide also outlines catalyst generation, reaction setup, and basic troubleshooting to help you streamline your cross-coupling method development.

In my experience, optimizing cross-coupling methods follows three basic principles:

1. There is no magic formula to know precisely what set of conditions or supporting ligand for palladium should be used. There are, however, reasonable starting points for both conditions and ligands that provide a solid starting point and will lead to developing an intuition for what will and will not work in cross-coupling chemistry.
2. Intelligent screening is vital. Whether to determine the proper base, ligand, solvent, concentration, etc., well-guided screening is the best way to find optimized conditions and further your intuition.
3. Efficient catalyst generation is crucial. Traditional palladium sources can work well but all have inherent issues. As substrates for cross-coupling reactions become more complex, the need for clean catalyst generation becomes more important. The advent of modern precatalysts, such as the Buchwald G3 palladacycles and PEPPSI™ catalysts are much more reliable and competitively priced.

Following this guide and the three principles outlined above, in conjunction with the Aldrich® Cross-Coupling Quick Guide: Bench Reference, should provide an excellent starting point and solid foothold to demystify palladium cross-coupling chemistry.

– Dr. Nick Bruno

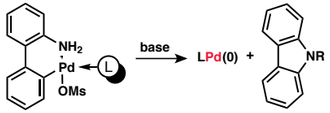
Catalyst Generation

Palladium Source + Ligand ⟶ LPd(0)

Efficient generation of the active catalyst species is often pivotal to the success of a cross-coupling reaction. Traditional palladium sources can have varying degrees of efficacy in generating the active catalyst. Recent advances in precatalyst development have led to the third-generation Buchwald palladium precatalysts (Pd G3) that quickly and quantitatively generate active LPd(0) catalysts with phosphine ligands. PEPPSI™ precatalysts are highly effective Pd sources for *N*-heterocyclic carbene (NHC) ligands.

Pd G3 Precatalysts

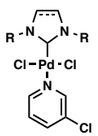
Third-generation palladium precatalysts are air- and moisture-stable*, phosphine-ligated palladium sources that release LPd(0) and a carbazole under basic conditions, activating at temperatures as low as -40°C with weak base.



Pd G3 Precatalyst

PEPPSI™ Precatalysts

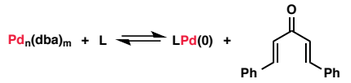
PEPPSI™ precatalysts are air- and moisture-stable*, NHC-ligated palladium sources. They activate similarly to Pd(II) salts, and do so cleanly and efficiently due to the stability of the NHC-Pd bond.



PEPPSI™ Precatalyst

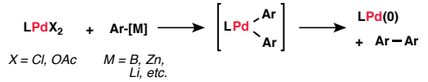
*Once activated, these catalysts become air-sensitive. Always run reaction under N_2 or Ar for best results.

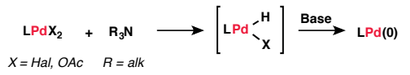
$Pd_n(dba)_m$

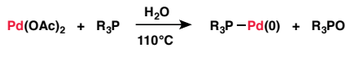


Pros	Easily handled; convenient; commercially available.
Cons	Loses activity over time, forming Pd nanoparticles and free dba; dba can inhibit some coupling reactions; premixing is sometimes necessary.

Pd(II) Salts

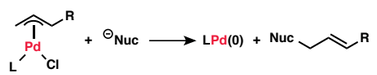






Pros	Easily handled; convenient; commercially available; least expensive Pd sources.
Cons	Can be inefficient; does not ensure clean, quantitative catalyst generation; excess ratio of L to Pd necessary; premixing is sometimes required.

π-Allyl Pd Chloride Dimers



Pros	High reactivity; convenient; commercially available.
Cons	Temperature-sensitive; less consistent commercial purity; can occasionally form inactive Pd(I) complexes.

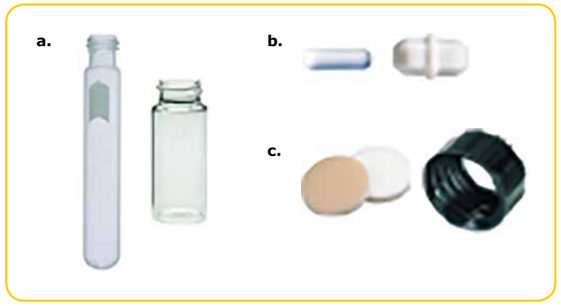
Setting Up a Cross-Coupling Reaction

Reaction Vessel

a. Screw-top test tube (for use with oil baths) or fitted screw-top vial (for use with heated aluminum blocks), oven- or flame-dried (except for Suzuki couplings and biphasic reactions when water is needed in the reaction).

b. Suitably sized magnetic stir bar (also oven-/flame-dried).

c. Open screw cap with PTFE insert.



Reagents

Aryl (pseudo)halide and nucleophile: Substrates need to be of suitable purity. Solid reagents can be recrystallized. Liquid reagents should be distilled or eluted through a short plug of activated alumina (this is particularly effective for amines).

Bulk bases: Should be stored in a drybox, with aliquots for bench-top use stored in a dessicator for 1 – 2 weeks. Aqueous-base solutions also require proper degassing.

Solvents: *Need to be free of oxygen*. Sure/Seal™ bottles are generally sufficiently degassed. The most rapid and efficient method for degassing other solvents is by evacuating a vessel containing the solvent under vacuum while sonicating for 1 minute, refilling with N_2 or Ar, and repeating this cycle 3 – 5 times. Sparging is generally not an efficient degassing method.

Reaction Setup

1. Weigh all solid reagents (e.g., base, catalyst, coupling partners) and transfer them to the chosen reaction vessel. Cap the reaction vessel with the screw-top septum.*
2. Put the reaction vessel under an inert environment. (Cross-coupling reactions are not immensely air-sensitive, but to obtain consistent and reliable results, the reactions cannot be run under air.) The most reliable method is to evacuate the vessel on a vacuum manifold and backfill with Ar or N_2, performing this cycle a total of three times. Purging the reaction vessel with N_2 or Ar for 5–10 min is also suitable.
3. Under N_2 or Ar, liquid reagents are added followed by solvent(s), both by syringe. If the reaction is being performed above the boiling point of the chosen solvent, at this time the PTFE cap insert should be replaced with one that is unpunctured, under a positive pressure of N_2 or Ar.
4. The reaction vessel is then placed into a preheated oil bath or fitted aluminum block with a high-enough stirring rate to ensure adequate mixing, but not so high as to splatter reagents above the level of the solvent. Cross-coupling reactions generally take anywhere from 15 minutes to 48 hours to reach full conversion.

Reaction Monitoring

The reaction progress can be monitored by removing a small aliquot with a nitrogen-flushed needle and syringe under a positive pressure of N_2 or Ar and observing the disappearance of starting material or emergence of product by GC, HPLC, TLC, etc. Cool the reaction first if running it at an elevated temperature above the boiling point of the solvent.

Work-up

After completion, the reaction mixture is removed from the oil bath or aluminum block and allowed to cool to room temperature. It is then diluted with solvent, and either filtered through silica, celite, cotton or a glass-fritted funnel or washed with water. This removes most of the inorganic material and insoluble organics, simplifying purification. The crude product is then purified by chromatography. Alternatively, an internal standard can be added directly into the crude reaction mixture, the mixture diluted, then an aliquot filtered and analyzed for conversion and yield by HPLC or GC.

*Never run reactions in a completely sealed system. Use screw caps fitted with PTFE inserts.

General Troubleshooting

Low Conversion

Catalyst Generation: Ensure that the active LPd(0) species is being generated. Ideal palladium sources are Pd G3 or G4 precatalysts for phosphine ligands and PEPPSI™ precatalysts for NHC ligands. If Pd(II) salts are used, preactivate* the Pd(II)/L mixture before adding to the reaction vessel. An extra equivalent of ligand relative to palladium can improve catalyst stability.

Impure Reagents: Assess the purity of the starting materials and purify or reacquire as necessary. Amines should generally be purified by distillation, crystallization, or filtration through a plug of activated alumina before use (See: *Setting Up a Cross-Coupling Reaction*).

Sluggish Reaction: Run the reaction under more forcing conditions, including higher temperatures, higher catalyst loadings, or with stronger bases. Screen ligands or solvents to improve the problematic step of the catalytic cycle or improve solubility, respectively.

Poor Mixing: Ensure the reaction is stirring vigorously, especially in the case of biphasic reaction mixtures. If efficient mixing cannot be obtained, use a bigger stir bar or stronger stir plate. In a drybox, finely grind inorganic bases using a mortar and pestle or in a coffee grinder. Smaller particle size maximizes surface interactions with the base.

High Conversion, Low Yield

Homocoupling: Usually results from the presence of an oxidant, generally oxygen. Ensure that the reaction vessel has been purged of air and that the solvents employed have been properly degassed (See: *Setting Up a Cross-Coupling Reaction*).

Functional Group Incompatibilities: Use a weaker base (e.g. carbonate, phosphate) with hydrolytically labile or reactive functional groups (e.g. -CN, $-CO_2R$, $-NO_2$, -CHO, etc.). Try decreasing the temperature or screening concentration. Consider protecting group strategies.

Unproductive Pathways: Identify side-products being formed in the reaction, such as competing β-hydride reduction, isomerization, amine over-arylation, alkoxide base coupling, or phenol/diaryl ether formation. Once identified, a judicious choice of supporting ligand will generally fix these problems. (For example, ligands such as CPhos and IPent minimize β-hydride reduction and isomerization in Negishi couplings. Ligands such as BrettPhos and JosiPhos SL-J009-1 prevent the over-arylation of primary amines. Phenol/diaryl ether formation can occur when water is present and the cross-coupling partner is weakly nucleophilic or undergoes a difficult transmetallation or reductive elimination.)

Setup and Scale-Up

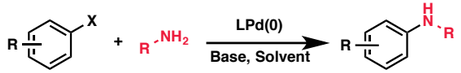
Stirring: Upon scale-up, stirring can become difficult. Overhead mechanical stirrers in place of a magnetic stir bar often provide more efficient stirring.

Concentration: Often when scaling up a cross-coupling reaction, the concentration can be increased†, which can improve the rate of reaction. When scaling up and changing the concentration, factors such as available headspace in the reaction vessel and possible pressure build-up need to be addressed.

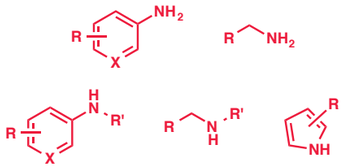
*Preactivation can be achieved by stirring the Pd(II) source and ligand in solution and may require elevated temperatures and/or base. A small amount of hydrazine or DIBAL can also be used to reduce Pd(II) to Pd(0).

†Upon scaling, catalyst load can often be decreased as well.

Buchwald-Hartwig Amination: Primary Amines

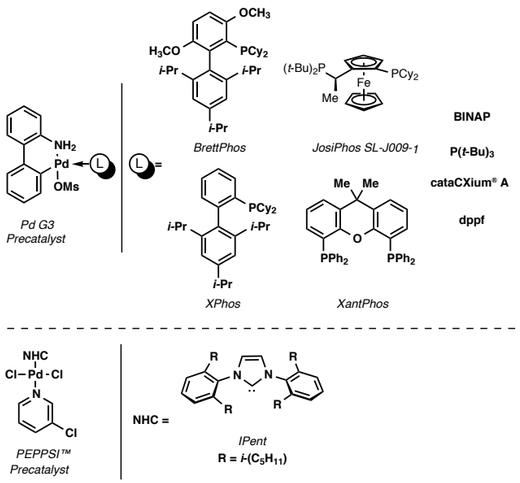


The Buchwald-Hartwig amination, the cross-coupling of an aryl (pseudo)halide and an amine, is a staple reaction for chemists across a wide range of disciplines. With the proper choice of catalyst and conditions, developments in the field allow for the selective arylation of primary over secondary amines and vice versa, as well as the incorporation of substrates containing heterocycles, sensitive functional groups, and steric hindrance. Aryl halides and phenol-derived aryl sulfonates both make suitable coupling partners.



Of the five general classes of amines (above), the nucleophilicity and steric properties of the amine, as well as the functional groups present, have a great impact on the proper choice of catalyst and optimal reaction conditions.

A Starting Point for Catalysis: Primary Amines

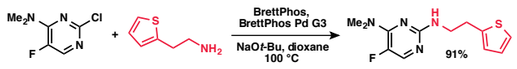


BrettPhos[1] shows excellent selectivity and scope as a supporting ligand for the arylation of primary amines and represents the best starting point. JosiPhos SL-J009-1[2] and IPent-based[3] systems are also efficient. For phosphine ligands, Pd G3 precatalysts[1] are the optimal palladium source, while PEPPSI™ is ideal for NHC ligands.[3]

Common Conditions

Solvent	Toluene, THF, Dioxane, *t*-BuOH, DMF, H20 (0.2–1 M)
Base	Cs_2CO_3, Na/KO*t*-Bu, LHMDS, Na/K_3PO_4, Na/K_2CO_3, Na/KOH (1.2–3 equiv)
Amines	(Hetero)anilines and alkylamines (1.2–2 equiv)
Pd Source	Palladium precatalyst or L+[Pd] (0.1–10 mol %)
Temperature	rt–110°C

Illustrative Example[1]



Solvent	Dioxane (1 M)
Base	NaO*t*-Bu (2 equiv)
Amine	(1.2 equiv)
Pd Source	(0.1 mol %)
Ligand	(0.1 mol %)
Temperature	100°C

Standard Conditions[1]

Solvent	Dioxane (1 M)
Base	NaO*t*-Bu (1.2 equiv)
Amine	(1.2 equiv)
Ligand	BrettPhos (10 mol %)
Pd Source	BrettPhos Pd G3 (10 mol %)
Temperature	100°C

Conditions for Protic Substrates[4]

Solvent	THF (1 M)
Base	LHMDS (2.4 equiv)
Amine	(1.2 equiv)
Ligand	BrettPhos (10 mol %)
Pd Source	BrettPhos Pd G3 (10 mol %)
Temperature	65–80°C

Conditions for Base-Sensitive Substrates

Solvent	*t*-BuOH (0.5 M)
Base	Cs_2CO_3 (2 equiv)
Amine	(1.2 equiv)
Ligand	BrettPhos (10 mol %)
Pd Source	BrettPhos Pd G3 (10 mol %)
Temperature	100°C

Troubleshooting: Amination Reactions

Since amines themselves can act as ligands for palladium, it is generally helpful to add an extra equivalent of ligand relative to palladium when using phosphine ligands to prevent catalyst deactivation.

When using aryl iodides as substrates it is generally ideal to run the reaction in less polar solvents, such as toluene, to prevent the iodide salt formed from inhibiting the reaction. This is presumably from the *in situ* formation of catalytically inactive M_2PdX_4 species.[5]

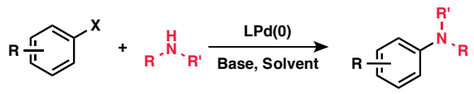
The purity of the amines used is EXCEEDINGLY IMPORTANT. Trace impurities in amines can cause a reaction to fail. Liquid amines should be purified by distillation or elution through a plug of activated alumina. Solid amines should be purified by crystallization or chromatography.

When using substrates with weakly acidic functional groups (N-H heterocycles, amides) LHMDS should be used in excess as the base (> 2 equiv).[1b,4] Solid LHMDS is very sensitive to moisture, but anhydrous solutions are stable for weeks if stored and handled under inert gas.

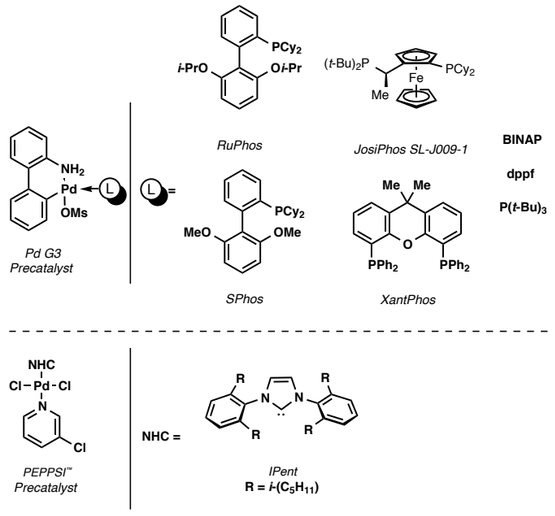
Materials List

Description	Cat. No.
BrettPhos	**718742**
BrettPhos Pd G3	**761605**
NaO*t*-Bu	**359270**
Dioxane (anhyd.)	**296309**
THF (anhyd.)	**401757**
LHMDS (neat)	**324620**
LHMDS/1 M in THF	**225770**
t-BuOH	**471712**
Cs_2CO_3	**202126**

Buchwald-Hartwig Amination: Secondary Amines



A Starting Point for Catalysis: Secondary Amines

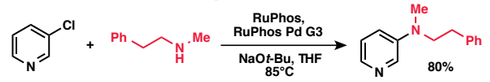


RuPhos[1] shows excellent selectivity and scope as a supporting ligand for the arylation of secondary amines and represents the best starting point. JosiPhos SL-J009-1[2] and IPent-[3] based systems are also efficient. For phosphine ligands, Pd G3 precatalysts[1] are the optimal palladium source, while PEPPSI™ is ideal for NHC ligands.[3]

Common Conditions

Solvent	Toluene, THF, Dioxane, *t*-BuOH, DMF, H_2O (0.2 – 1 M)
Base	Cs_2CO_3, Na/KO*t*-Bu, LHMDS, Na/K_3PO_4, Na/K_2CO_3, Na/KOH (1.2 – 3 equiv)
Amines	(Hetero)anilines and alkylamines (1.2 – 2 equiv)
Pd Source	Palladium precatalyst or L+[Pd] (0.1 – 10 mol %)
Temperature	rt–110°C

Illustrative Example[1]



Solvent	THF (1 M)
Base	NaO*t*-Bu (1.2 equiv)
Amine	(1.2 equiv)
Pd Source	(0.75 mol %)
Ligand	(0.75 mol %)
Temperature	85°C

Standard Conditions[1]

Solvent	THF (1 M)
Base	NaO*t*-Bu (1.2 equiv)
Amine	(1.2 equiv)
Ligand	RuPhos (10 mol %)
Pd Source	RuPhos Pd G3 (10 mol %)
Temperature	85°C

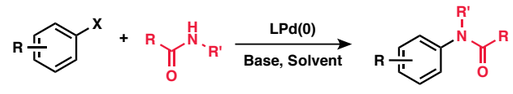
Base-Sensitive Substrates[1]

Solvent	*t*-BuOH (0.5 M)
Base	Cs_2CO_3 (2 equiv)
Amine	(1.2 equiv)
Ligand	RuPhos (10 mol %)
Pd Source	RuPhos Pd G3 (10 mol %)
Temperature	85°C

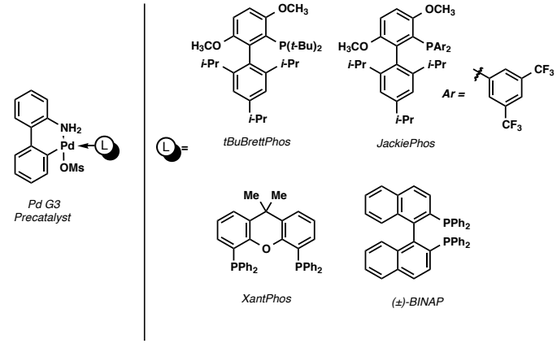
Materials List

Description	Cat. No.
RuPhos	**663131**
RuPhos Pd G3	**763403**
NaO*t*-Bu	**359270**
NaO*t*-Bu/2 M in THF	**702706**
THF (anhyd.)	**401757**
t-BuOH (anhyd.)	**471712**
Cs_2CO_3	**202126**

Buchwald-Hartwig Amidation: Amides



A Starting Point for Catalysis: Amides

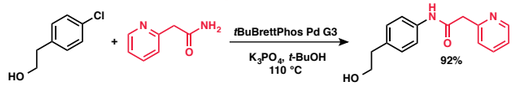


*t*BuBrettPhos[6] is an excellent supporting ligand for the arylation of primary amides. JackiePhos-based catalyst systems work well for arylation[7] of secondary amides. For X≠Cl, XantPhos-based[8] systems are highly effective. BINAP[9] is also a suitable supporting ligand.

Common Conditions

Solvent	Toluene, THF, Dioxane, *t*-BuOH, DMF, H_2O (0.2 – 1 M)
Base	Na/K_3PO_4, Na/K_2CO_3, Na/KOH (2 – 3 equiv)
Amines	Secondary Amides (1.2 – 2 equiv)
Pd Source	Palladium precatalyst or L+[Pd] (0.1 – 10 mol %)
Temperature	50 – 110°C

Illustrative Example[6b]



Solvent	*t*-BuOH (0.5 M)
Base	K_3PO_4 (1.4 equiv)
Amide:	(1.2 equiv)
Pd Source	Pd G3 complex (1 mol %)
Temperature	110°C

Standard Conditions

Solvent	*t*-BuOH (0.5 M)
Base	K_3PO_4 (1.4 equiv)
Amide	(1.2 equiv)
Ligand	*t*BuBrettPhos (10 mol %)
Pd Source	*t*BuBrettPhos Pd G3 (10 mol %)
Temperature	110°C

Materials List

Description	Cat. No.
t-BuOH (anhyd.)	**471712**
K_3PO_4	**RDD019**
*t*BuBrettPhos	**730998**
*t*BuBrettPhos Pd G3	**745979**

References

1. (a) Bruno, N. C., Tudge, M. T., Buchwald, S. L. *Chem. Sci*. **2013**, *4*, 916. (b) Maiti, D.; et al. *Chem. Sci*. **2011**, *2*, 57. (c) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **2010**, *132*, 15914.
2. (a) Shen, Q.; et al. *Angew. Chem., Int. Ed*. **2005**, *44*, 1371. (b) Ogata, T.; Hartwig, J.F. *J. Am. Chem. Soc.*, **2008**, *130*, 13848. (c) Shen, Q., Ogata, T., J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 6586.
3. Hoi, K. H.; et al. *Chem. Eur. J*. **2012**, *18*, 145.
4. Henderson, J. L.; Buchwald, S. L. *Org. Lett*. **2010**, *12*, 4442.
5. Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc*. **2009**, *131*, 5766.
6. (a) Fors, B. P. et al. *Tetrahedron*, **2009**, *65*, 6576. (b) Bruno, N. C.; Buchwald, S. L. *Org. Lett*. **2013**, *15*, 2876.
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8. Yin, J.; Buchwald, S. *J. Am. Chem. Soc.*, **2002**, *124*, 6043.
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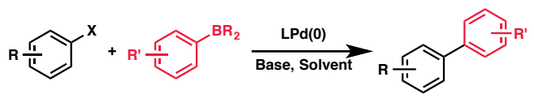
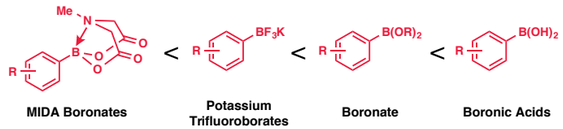
Suzuki-Miyaura Coupling



Suzuki-Miyaura Coupling (SMC), the cross-coupling of an aryl (pseudo)halide and organoborate, is a versatile reaction for carbon-carbon bond formation. Most commonly used to synthesize biaryl motifs, the SMC can also incorporate vinyl and alkyl fragments as coupling partners. With the proper choice of conditions, the cross-coupling of hindered substrates, heterocycles, and substrates with protic or sensitive functional groups can be accomplished. Aryl halides and phenol-derived aryl sulfonates both make suitable coupling partners.

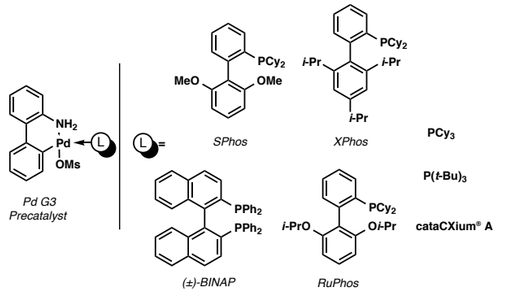


The reactivity of boronates (listed above in increasing rates of hydrolysis) can be tuned to the needs of a specific SMC reaction.

The Role of Water[1]

Water is necessary, in at least trace amounts, for nearly all SMC reactions. Water hydrolizes boronates to the active boronic acid and likely plays a role in transmetallation. This water can arise from biphasic conditions or adventitious water in the solvent or base. All water used as part of the solvent system must be properly degassed.

A Starting Point for Catalysis: Suzuki-Miyaura

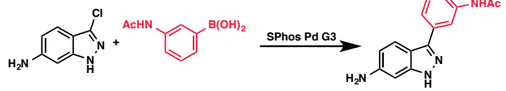


SPhos[2] and XPhos[2] show exceptional functional group compatibility and scope in the SMC reaction. The NHC IPent[3] has emerged as another excellent supporting ligand, especially for very hindered substrates. These ligands represent the most reliable starting point. CataCXium A[4], RuPhos[5], P(*t*-Bu)$_3$[6], and PCy$_3$[7] are also good starting points, the latter three of which are efficient ligands for the SMC reaction of sp^3 coupling partners.

Common Conditions

Solvent	Toluene, THF, Dioxane, BuOH, DMF, Water (0.2–1 M)
Base	Na/K$_3$PO$_4$, Na/K$_2$CO$_3$, Na/KOH, Na/KO*t*-Bu (1.5–3 equiv)
Boronate	Boronic Acid, Bpin Ester, BF$_3$K, MIDA Boronate (1.2–2 equiv)
Pd Source	Palladium Precatalyst or [L+Pd(OAc)$_2$] (0.1–10 mol %)
Temperature	rt–110°C

Illustrative Example[2]



Solvent	1:1 Dioxane:Water (0.2 M)
Base	K$_3$PO$_4$ (2 equiv)
Boronate	Boronic Acid (2 equiv)
Pd Source	(2 mol %)
Temperature	100°C

Standard Conditions[2]

Solvent	1:2 THF:Water (0.33 M)
Base	K$_3$PO$_4$ (2 equiv)
Boronate	Boronic Acid (1.5 equiv)
Pd Source	SPhos or XPhos Pd G3 (5–10 mol %)
Temperature	40°C

Substrates with Steric Hindrance[2-3]

For Pd G3 Complexes
(use conditions listed, except substitute 5–10 mol % SPhos or XPhos Pd G3 for PEPPSI™)

For PEPPSI Complexes	
Solvent	*t*-BuOH (0.25 M), 4A MS
Base	KO*t*-Bu or KOH (3 equiv)
Boronate	Boronic Acid (2 equiv)
Pd Source	PEPPSI™-IPent (5–10 mol %)
Temperature	65°C

Very Polar, Chelating, or N-H Het. Containing Substrates[1]

Solvent	1:1 Dioxane:Water or DMF (0.2 M)
Base	K$_3$PO$_4$ (2 equiv)
Boronate	Boronic Acid (2 equiv)
Pd Source	SPhos or XPhos Pd G3 (5–10 mol %)
Temperature	100°C

Troubleshooting: Protodeboronation

Protodeboronation is the formal hydrolysis of a boronic acid to the parent arene and boric acid. Some boronic acids are especially prone to protodeboronation, including 2-(hetero)arylboronic acids and perfluoroarylboronic acids. If protodeboronation is observed, first try less harsh reaction conditions (i.e., lower temperature, weaker base) or a different ligand. If this does not provide product, try a more stable boronate derivative (i.e., Bpin, BF$_3$K, MIDA, etc.). If none of these routes are successful, consider a different cross-coupling method such as the Negishi or Kumada coupling.

Materials List

Description	Cat. No.
SPhos Pd G3	**776246**
XPhos Pd G3	**763381**
PEPPSI™-IPent	**732117**
THF (anhyd.)	**401757**
K$_3$PO$_4$	**RDD019**
Toluene (anhyd.)	**244511**
K$_2$CO$_3$	**791776**
Dioxane (anhyd.)	**296309**
DMF (anhyd.)	**227056**

References

1. Lou, S.; Fu, G. C. *Adv. Synth. Catal.* **2010**, *352*, 2081.
2. (a) Düfert, A.; Billingsley, K. L.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2013**, *135*, 12877.
   (b) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2010**, *132*, 14073.
   (c) Walker, S. D.; et al. *Angew. Chem. Int. Ed.*, **2004**, *43*, 1871.
3. (a) Organ, M. G.; et al. *Angew. Chem. Int. Ed.*, **2009**, *48*, 2383.
   (b) Valente, C.; et al. *Angew. Chem. Int. Ed.*, **2012**, *51*, 3314.
4. Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.*, **2000**, *39*, 4153.
5. (a) Dreher, S. D.; et al. *J. Org. Chem.*, **2009**, *74*, 3626.
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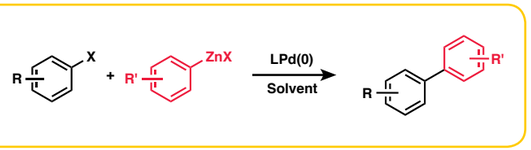
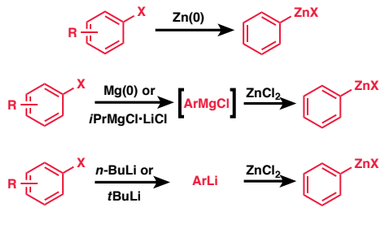
   (b) Das, S.; Abraham, S.; Sinha, S. C. *Org. Lett.*, **2007**, *9*, 2273.

Negishi Coupling

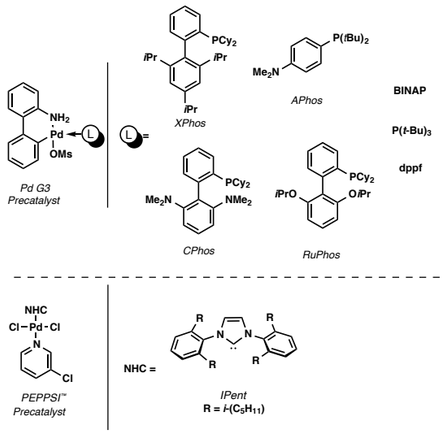


The Negishi coupling is the cross-coupling of an aryl (pseudo)halide and an organozinc nucleophile to form C-C bonds. Organozinc reagents are more reactive than their organoboron counterparts and provide more stability than organolithium or organomagnesium reagents. Advances in the Negishi coupling have made possible the use of substrates with base-sensitive functional groups and diverse arrays of heterocycles as substrates. The development of catalyst systems that suppress β-hydride elimination allows for the efficient coupling of alkylzinc nucleophiles.



Organozinc reagents can be accessed through a variety of means. Certain organozinc solutions are available commercially. They can be synthesized *in situ* (above) through direct insertion of activated zinc metal into an aryl-X bond or through transmetallation of a Grignard or organolithium reagent with a zinc salt. Organozinc solutions, if kept completely free of oxygen and moisture, are relatively stable over time.

A Starting Point for Catalysis: Negishi

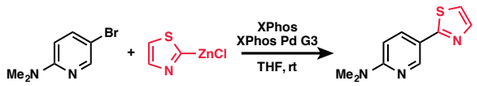


XPhos[1] is an excellent supporting ligand for Negishi couplings, showing great substrate compatibility and scope. IPent-[2] and RuPhos-based[3] systems are also very efficient. For the coupling of alkylzinc reagents, CPhos[4] is ideal, suppressing β-hydride elimination and isomerization. APhos[5] and IPent[6] also give highly efficient systems for alkylzinc coupling.

Common Conditions

Solvent	THF, Toluene, Dioxane, NMP, DMF (0.2–1 M)
Organozinc	(1.2–2 equiv)
Pd Source	Palladium Precatalyst or L+[Pd] (0.1–10 mol %)
Temperature	rt–80°C

Illustrative Example[1]

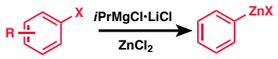


Solvent	THF (1 M)
Organozinc	(1.3 equiv)
Ligand	(2 mol %)
Pd Source	(2 mol %)
Temperature	rt

Standard Conditions[1]

Solvent	THF (1 M)
Organozinc	(1.3 equiv)
Ligand	XPhos (5–10 mol %)
Pd Source	XPhos Pd G3 (5–10 mol %)
Temperature	rt

Organozinc via Mg-Hal Exchange[1]



Solvent	THF or 2-MeTHF
ArBr or ArI	(1 equiv)
***i*PrMgCl•LiCl**	(1.3 equiv)
$ZnCl_2$	(1.4 equiv)
Temperature	0°C–rt

Secondary Alkylzinc Coupling

Solvent	2:1 THF:Toluene (0.33 M)
Organozinc	(1.3 equiv)
Ligand	CPhos (5–10 mol %)
Pd Source	CPhos Pd G3 (5–10 mol %)
Temperature	0°C–rt

Organozinc via Li-Hal Exchange[1]

Solvent	THF or 2-MeTHF
ArBr or ArI	(1 equiv)
***n*-BuLi:**	(1.1 equiv)
$ZnCl_2$	(1.2 equiv)
Temperature	0°C–rt

Note: $ZnCl_2$ is **EXTREMELY** hygroscopic and should only be handled in a glovebox or as a solution under inert gas to avoid introducing any water.

Materials List

Description	Cat. No.
XPhos	**638064**
XPhos Pd G3	**763381**
CPhos	**759171**
CPhos Pd G3	**763004**
THF (anhyd.)	**401757**
Toluene (anhyd.)	**244511**
2-MeTHF (anhyd.)	**673277**
i-PrMgCl•LiCl (1.3 M in THF)	**656984**
$ZnCl_2$ (anhyd. Redi-Dri™)	**793523**
n-BuLi (2.5 M in hexanes)	**230707**

References

1. Yang, Y.; Oldenhuis, N. J.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2013**, *52*, 615.
2. Çalimsiz, S.; et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 2014.
3. Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.
4. Yang, Y. et al. *Org. Lett.* **2014**, *16*, 4638.
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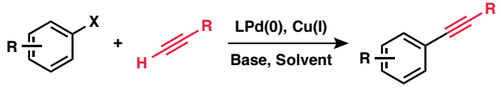
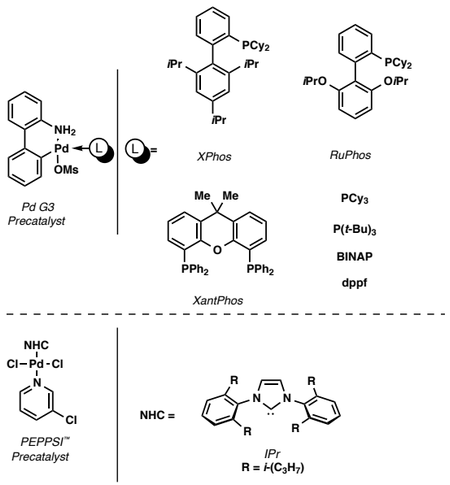
6. Çalimsiz, S.; Organ, M. G. *Chem. Comm.* **2011**, *47*, 5181.

Sonogashira Coupling



The Sonogashira coupling is the cross-coupling of an aryl (pseudo) halide with a terminal alkyne to give disubstituted acetylenes. Sonogashira coupling is a robust transformation, capable of being carried out on a range of substrates and under a myriad of mild reaction conditions. The reaction typically employs a Cu(I) co-catalyst to aid in the transmetallation of the acetylide to palladium, though copper-free methods have been reported in recent years.

A Starting Point for Catalysis: Sonogashira

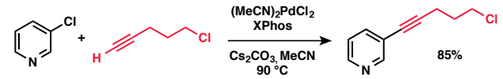


XPhos[1] is an excellent supporting ligand for Sonogashira couplings and obviates the need for a Cu(I) co-catalyst. RuPhos[2] and an IPr-Pd/ IPr-Cu[3] system have also been shown to be effective for Sonogashira couplings. dppf·Pd[4] is also effective. XantPhos[5] is a highly effective ligand for carbonylative Sonogashira couplings.

Common Conditions

Solvent	Toluene, THF, Dioxane, DMF, MeCN, DMSO, Water (0.2–1 M)
Base	Cs_2CO_3, Na/K_3PO_4, Na/K_2CO_3, Et_3N, $(i\text{-}Pr)_2NEt$ (1.2–3 equiv, as solvent if NR_3)
Alkyne	(1.2–2 equiv)
Copper	CuI (5–20 mol %, if used)
Pd Source	Palladium Precatalyst or L+[Pd] (0.1–10 mol %)
Temperature	rt–110°C

Illustrative Example[1]



Solvent	MeCN (0.5 M)
Base	Cs_2CO_3 (2.6 equiv)
Alkyne	(1.3 equiv)
Copper	(none)
Ligand	(3 mol %)
Pd Source	(1 mol %)
Temperature	90°C

Standard Conditions: Without Copper[1]

Solvent	MeCN (0.5 M)
Base	Cs_2CO_3 (2.6 equiv)
Alkyne	(1.3 equiv)
Copper	(none)
Ligand	XPhos (10 mol %)
Pd Source	XPhos Pd G3 (5 mol %)
Temperature	90°C

Standard Conditions: With Copper

Solvent	1:1 THF/NEt_3 (0.5 M)
Base	NEt_3 (co-solvent)
Alkyne	(1.3 equiv)
Copper	CuI (10 mol %)
Ligand	dppf (10 mol %)
Pd Source	dppf Pd G3 (10 mol %)
Temperature	80°C

Materials List

Description	Cat. No.
XPhos	**638064**
XPhos Pd G3	**763381**
MeCN	**271004**
Cs_2CO_3	**202126**
TEA	**T0886**
THF	**401757**
CuI	**792063**
dppf	**177261**
dppf Pd G3	**804983**

References

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4. Moon, J.; et al. *Org. Lett.* **2008**, *10*, 945.
5. Wu, X.-F.; et al. *Chem. Eur. J.* **2011**, *17*, 106.

Full Materials List

Description	Ligand Cat. No.	G3 Complex Cat. No.
Buchwald		
BrettPhos	**718742**	**761605**
*t*BuBrettPhos	**730998**	**745979**
RuPhos	**663131**	**763403**
SPhos	**638072**	**776246**
XPhos	**638064**	**763381**
Select Non-Buchwald Ligands		
rac-BINAP	**481084**	**804967**
P(*t*-Bu)$_3$	**570958**	—
P(*t*-Bu)$_3$ Pd G2	**756482**	—
cataCXium® A	**671479**	**761435**
dppf	**177261**	**804983**
JosiPhos SL-J009-1	**88733**	**747130**
XantPhos	**526460**	**763039**
PCy_3	**261971**	**764175**
APhos	**677264**	**764183**
JackiePhos	**731013**	**762830**
CPhos	**759171**	**763004**

Description	Cat. No.
Anhydrous Sure/Seal™ Solvents and Reagents	
Toluene	**244511**
THF	**401757**
1,4 Dioxane	**296309**
t-BuOH	**471712**
DMF	**227056**

Description	Cat. No.
BuOH (1-Butanol)	**281549**
NMP	**328634**
2-MeTHF	**673277**
MeCN	**271004**
DMSO	**D5879**
i-PrMgCl•LiCl (1.3 M in THF)	**656984**
$ZnCl_2$	**793523**
Bases	
n-BuLi (2.5 M in hexanes)	**230707**
NaO*t*-Bu	**359270**
NaO*t*-Bu/2 M in THF	**702706**
KO*t*-Bu	**156671**
LHMDS (neat)	**324620**
LHMDS/1 M in THF	**225770**
Na_3PO_4	**342483**
K_3PO_4	**RDD019**
Na_2CO_3	**791768**
K_2CO_3	**791776**
NaOH	**795429**
KOH	**484016**
Cs_2CO_3	**202126**
Et_3N (TEA)	**T0886**
$(i\text{-}Pr)_2NEt$ (DIEA)	**387649**
Other Catalysts	
CuI	**792063**
PEPPSI™ -IPent	**732117**
PEPPSI™-IPr	**669032**

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