Transition Metal Catalyzed C-C Cross Coupling Reactions: An Introduction

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Crosscoupling reactions refer to reactions that couple two different organic fragments with the aid of metal catalysts (Wikipedia).
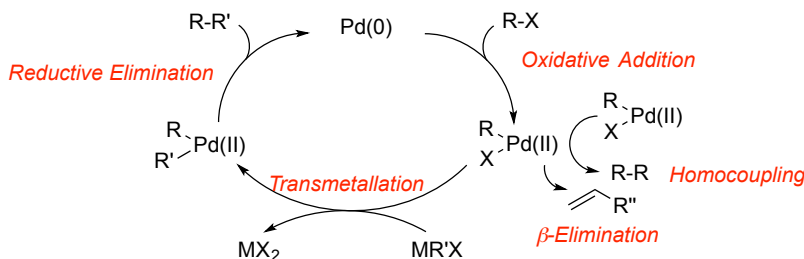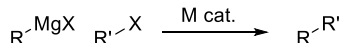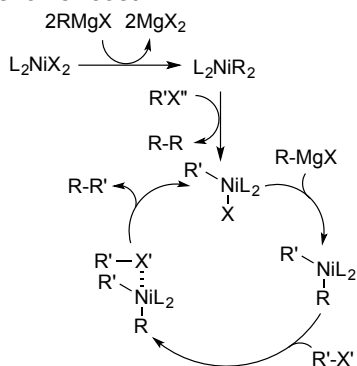

Table of Contents

1. Kumada Coupling

The Kumada coupling connects the organic fragments of a Grignard reagent and a halide to produce the product. This coupling was first found to be catalyzed by a nickel complex and is still used because of its ease of oxidative addition and its lower cost.[1]


The diagram shown above is the proposed catalytic cycle for Kumada coupling. After entering the cycle, the alkyl group from the Grignard reagent is transmetalated onto the nickel. Then reductively elimination of the R groups produces a Nickel (0) species. Oxidative addition of the alkyl halide reproduces the nickel (II) species. Major side reactions are homocoupling or β-hydride elimination.[2]
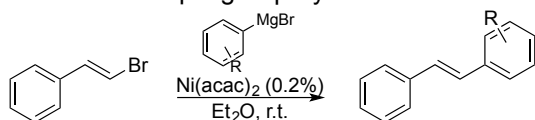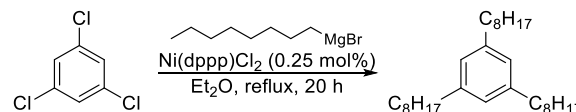

R=OMe, Me, Br, e.t.c   50-75%

Diphosphine ligands enhance the yield of the Kumada coupling and therefore became common ligands.[3]
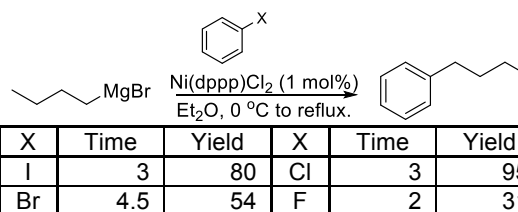

X	Time	Yield	X	Time	Yield
I	3	80	Cl	3	95
Br	4.5	54	F	2	31

There is no clear trend in the yield of Kumada coupling using different halides, but the rates of dehalogenation follow the order I>Br>>Cl>F.[4]

If there is more than one halogen group in the substrate, all of these are potential reactive sites unless steric hindrance blocks a halide.[5] However, selective coupling can be achieved by modulating the catalyst activity.
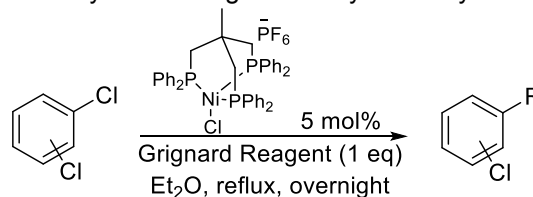

| Cl	Grignard	Yield	
		1x R	2x R
ortho	EtMgBr	71	11
	sec-BuMgBr	45	5
Meta	n-BuMgBr	68	23
	sec-BuMgBr	21	11
para	EtMgBr	75	9
	sec-BuMgBr	31	13

For example, use of a tri-dentate ligand, triphos, is able to stop the reaction at the stage of monoalkylation.

The table above also shows a characteristic of Kumada coupling that more substituted Grignard reagents tend to give poorer yield.[6]

Directing groups such as OH are often exploited to selectively couple halide substrate at the *ortho* halide.[7]
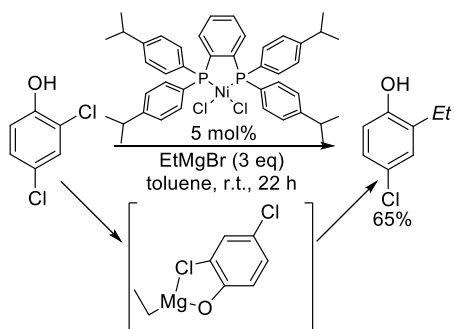
Although Kumada coupling with nickel complexes is common, palladium complexes sometimes have advantages. Shown below is the first Pd catalyzed Kumada coupling. The strong NHC-Pd bond that is formed *in situ* protects the palladium from oxidation.[8]
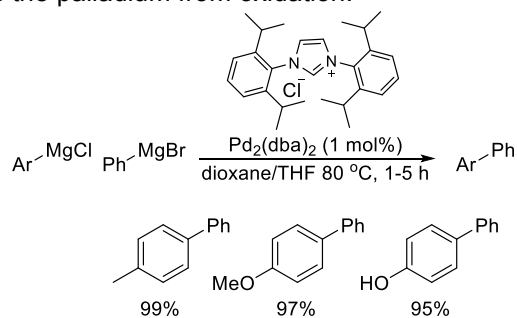
Kumada couplings with vinyl Grignard reagents are possible but may be tricky because the vinyl fragment is prone to isomerization to give an unwanted side product.[9]
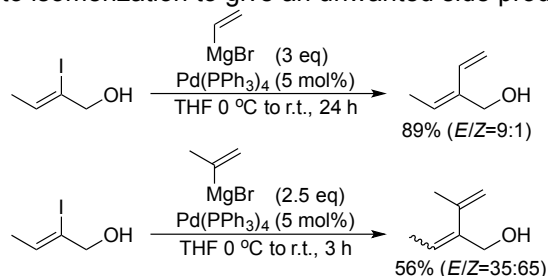

Alkynyl magnesium bromide reagents readily undergo Kumada couplings. Some recent Kumada couplings use LiBr to break down oligometric magnesium halides. A OTf group on benzene is usually stable under coupling conditions, but it is activated for this reaction.[10]
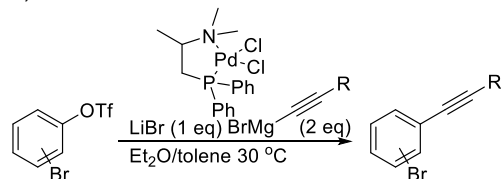
Entry	Br	R	Temp	Time	Yield
1		Et$_3$Si	20	1	99
2	para	n-C$_5$H$_{11}$	30	12	92
3		t-Bu	30	20	90
4	ortho	Ph	20	4	92
5		Et$_3$Si	30	4	91
6	meta	Ph	20	1	99
7		Et$_3$Si	20	1	93

Alkyl halides are seldom used in Kumada coupling successfully.
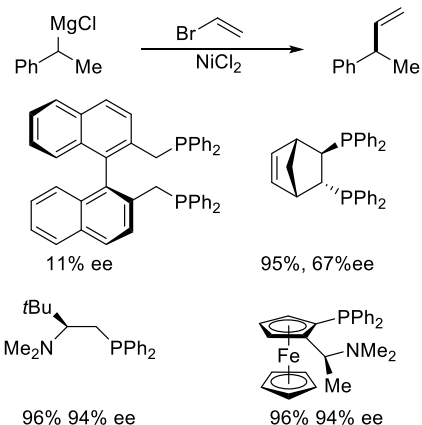
Stereoselective Kumada couplings initially focused on the Pd and Ni complexes ligated by a PP ligand with modest enantiomeric excesses, but the effort has now shifted to PN ligands, which deliver higher ee's.

Compared to the other coupling reactions, the Kumada coupling is superior in terms of the ample availability of Grignard reagents, but many functional groups are incompatible with the conditions, and the reaction is often limited to ether solvents. These limitations have driven a search for alternative coupling reactions.[11]

•References for Kumada Couplings:
1. C. E. I. Knappke and A. J. von Wangelin, *Chem. Soc. Rev.*, **2011**, 40, 4948
2. Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, 111, 1417.
3. R. J. P. Corriu and J. P. Masse, *J. Chem. Soc., Chem. Commun.*, **1972**, 144a
4. Tamao, K.; Kumada, M. et al. *Bull, Chem. Soc. Jpn.* **1976**. *49*, 1958.
5. Eapen, K. C.; Dua, S. S.; Tamborski, C. *J. Org. Chem.* **1984**, 49, 478.
6. Reddy, G. S.; Tam, W. *Organometallics* **1984**, 3, 630.
7. Wang, J.-R.; Manabe, K. *Org. Lett.* **2009**, 11, 741.
8. J. Huang and S. P. Nolan, *J. Am. Chem. Soc.*, **1999**, 121, 9889
9. P. Gamez, C. Ariente, J. Goré and B. Cazes, *Tetrahedron.* **1998**, 54, 14825
10. Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, 115, 9587
11. T. Kamikawa and T. Hayashi, *J. Org. Chem.*, **1998**, 63, 8922

2. Negishi Coupling

The Negishi coupling is similar to the Kumada coupling, except that the reaction is between zinc compounds and a halide. Because the C-Zn bond is stronger than the Mg-C interaction, organozinc reagents are less reactive, and therefore organozinc reagents don't react with other functional groups such as ester and nitriles.

An organozinc reagent was prepared by allowing an organohalide to react with powdered zinc in the presence of lithium chloride, which removes the oxide impurities.[1]
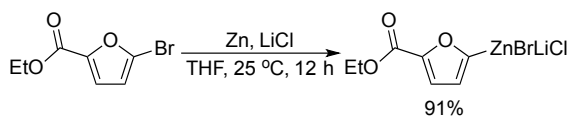

Sometimes, the organozinc reagent is prepared via transmetallation from a Grignard reagent. The example shown below combines regioselective Mg/Br exchange and a mild Negishi coupling that does not influence the nitrile. Only the bromide on the less crowded side of the pyridine readily couples with the aryl partner.[2]
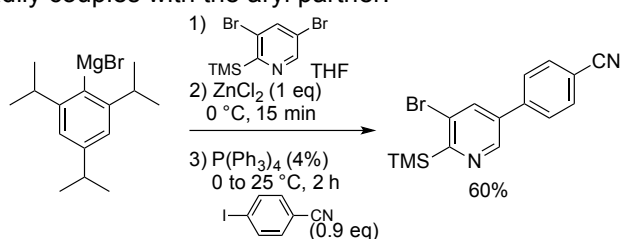
Sometimes, *n*-butyllithium is added to the mixture for lithium/halogen exchange followed by transmetallation with zinc. Butyllithium can also deprotonate the substrate directly to make a precursor for the transmetallation.
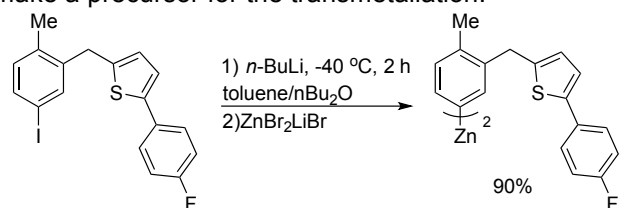

Tetrabutylammonium iodide is known to be a promoter of some Negishi couplings.[4] One hypothesis is that iodide coordination on Zn creates an active zincate intermediate, whereas another attributes the enhancement to increased ionic strength.[5] However, the effect of the Bu_4NI is not perfectly clear.
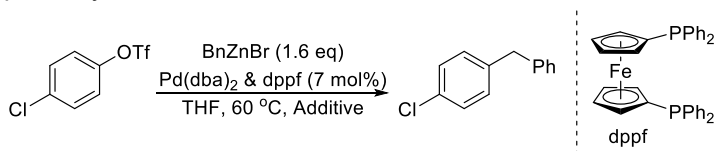

| Entry	Additive	Eq	Time	Conversion
1	None	1	1	0.5%
2	Bu_4NF	1	1	0.7%
3	Bu_4NBr	1	1	23%
4	Bu_4NI	0.1	1.5	2.4%
5	Bu_4NI	1	1.5	38%
6	Bu_4NI	3	1.5	90%

In contrast to Kumada couplings, palladium is used in Negishi coupling most commonly. In addition, the mechanisms for these metals are different. Oxidative addition of alkyl or aryl halides by Pd(0) produces Pd(II) onto which the alkyl zinc transmetallates. The coupling partners on palladium are then released in a reductive elimination.[6]
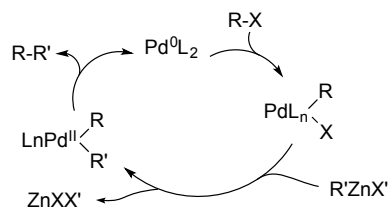
By understanding the traits of each step of the coupling, the product yields can be improved. To increase the relative speed of oxidative addition, strong electron donating ligands such as electron rich phosphines or NHC ligands are used. These ligands increase the electron density of the metal center, and therefore facilitate the oxidative addition.[7]
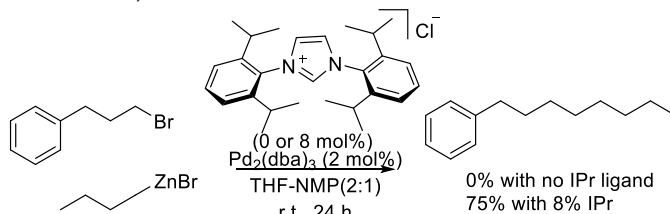

Once oxidative addition of the alkyl halide and transmetallation are completed, there are two possible pathways: reductive elimination that produces the desired product or β-elimination leading to an alkene by-product. To obtain the desired product, a ligand with a large bite angle is used. In the second example below, the angle of P-Pd-P, 99°, pushes the coupling partners closer and encourages the reductive elimination process.[8]
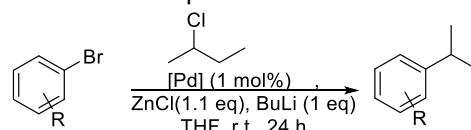
Catalyst	R=H	R=*p*-OMe	R=*o*-Me
$PdCl_2$(dppf)	1h, 95%	18 h, 3%	20 h, 0%
$PdCl_2(PPh_3)_2$	24 h, 5%	19 h, 75%	19 h, 58%

The mechanism of the nickel catalyzed Negishi coupling is postulated to involve an electron transfer reaction after the oxidative addition.
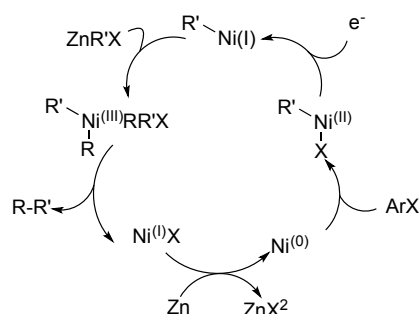

The relative readiness of R groups to be transferred was investigated. The result is as shown below. The table

shows that a phenyl group is transferred fastest and an *i*-Pr group (branched alkane) is slowest. Because zinc parts with aryl groups quickly, this creates a problem when a stereoselective Negishi coupling is the goal.
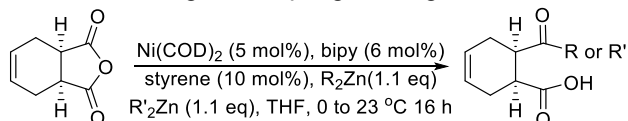

Entry	R	R'	R:R'	Yield%
1	Ph	Et	19:1	91
2	Ph	Me	9:1	89
3	Me	Et	3:1	75
4	Ph	*i*Pr	>20:1	90
5	Me	*i*Pr	>20:1	90
6	Et	TMSCH$_2$	>20:1	78

Recently, a successful enantioselective Negishi coupling involving an alkyl halide was reported.[9]


90% yield
92% ee
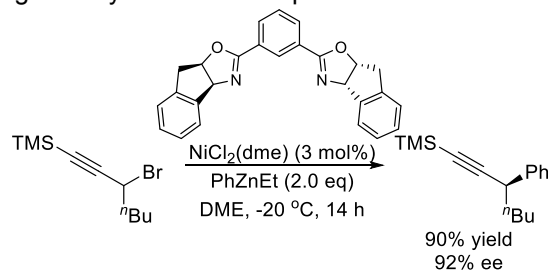
Another challenging situation involves the use of a secondary zinc alkyl substrate because it can isomerize. A handful of successful couplings are known. The reaction below achieved an enantioselective Negishi coupling with a cyclic nucleophile using an N,N ligand.[10]
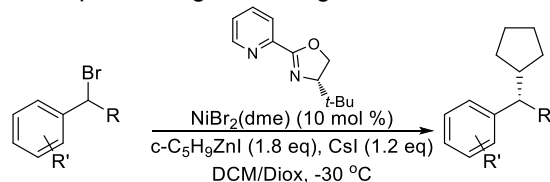
Entry	R	R'	ee	Yield
1	H	Me	95	91
2	H	Et	93	84
3	H	CH$_2$CH$_2$Ph	95	72
4	H	*i*-Bu	93	75
5	*o*-F	Me	87	48
6	*m*-OMe	Me	95	86
7	*p*-Br	Et	92	68

Even using this ligand, the methodology fails when acyclic substrates are used because of branched/unbranched isomerization.


59% ee   9% ee
76:24
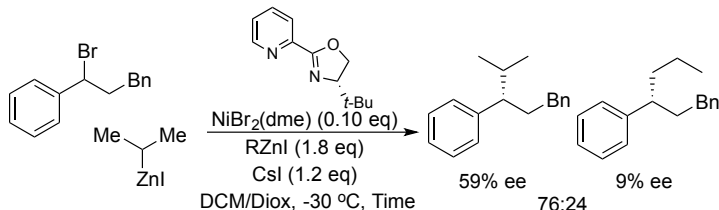
A major drawback of zinc reagents is that they are sensitive to moisture and air. For this reason, more stable coupling reagents have been sought.

•References for Negishi Coupling:
1. Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, 45, 6040
2. Saemann, C.; Haag, B.; Knochel, P. *Chem. Eur. J.* **2012**, 18, 16145
3. Lemaire, S.; Houpis, I. N.; Xiao, T.; Li, J.; Digard, E.; Gozlan, C.; Liu, R.; Gavryushin, A.; Diene, C.; Wang, Y.; Farina, V.; Knochel, P. *Org. Lett.* **2012**, 14, 1480
4. Piber, M.; Jensen, A. E.; Rottl€ander, M.; Knochel, P. *Org. Lett.* **1999**, 1, 1323.
5. Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, 111, 1417
6. Casares, J. A.; Espinet, P.; Fuentes, B.; Salas, G. *J. Am. Chem. Soc.* **2007**, 129, 3508
7. Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, 7, 3805.
8. A. Klein, Y. H. Budnikova and O. G. Sinyashin, *J. Organomet. Chem.*, **2007**, 692, 3156.
9. Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, 130, 12645.
10. Binder, J. T.; Cordier, C. J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, 134, 17003

3. Stille Coupling
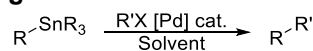
A Stille coupling is the reaction between an organotin and an alkyl halide, traditionally catalyzed by PdCl$_2$(PPh$_3$)$_2$, Pd(PPh$_3$)$_4$, or Pd(dba)$_2$Cl$_2$. The relatively strong and less polar Sn-C bond makes this species stable under air or moisture.[1]

Sn transfers only one R group in the transmetallation step in the Stille coupling. Therefore, having 4 substituents of the same R group is clearly a waste. Because the rate of transmetalltion for sp^3 R groups is far slower than sp^2 R groups (Aryl>Alkenyl>Alkynyl>Benzyl>Allyl>Alkyl), trialkyltin is chosen for the precursor.[2] This tin species is made in a variety of ways, with the typical species being SnBu$_3$R$_{sp2}$.
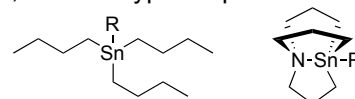

Sometimes, N-ligated polycyclic trialkyl stannyl chloride is used. The lone pair from nitrogen coordinates the Sn, and the nucleophilicity of the organotin reagent improves, as nucleophilic Sn readily undergoes transmetallation. This reagent also is stable under air.[3]

Lithiation of an acidic proton and subsequent stannylation produces an organotin reagent.[4] This method, however, does not tolerate some functional groups.
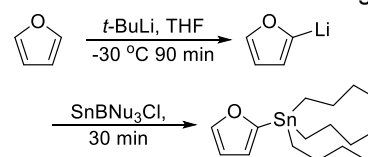

Organotin reagents can also be prepared by the hydrastannation of alkynes.[5] However, the addition of metal catalysts is often needed to obtain high regioselectivity, stereoselectivity, and yield.


89%
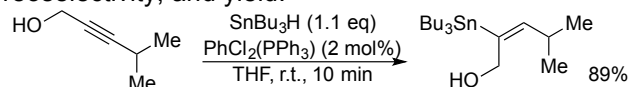
A sp[2]-triflate group also undergoes Stille couplings. This offers a strategy for a connection at the carbonyl carbon.[6]
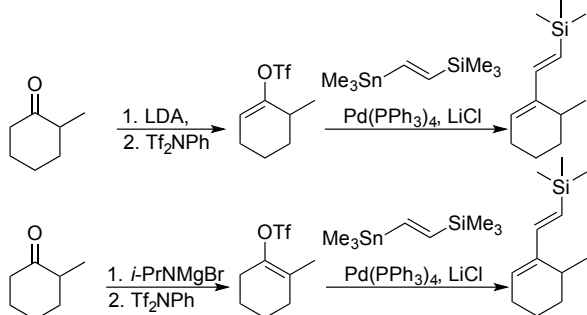

The mechanism of Stille couplings is similar to those described previously. However, discussion of diastereo-selective Stille couplings requires a detailed description of the transmetallation step. Because reductive elimination is always accompanied with retention of configuration, it is sufficient to consider the open and closed transition states for transmetallation. The closed transition state is favored when a non-coordinating solvent such as toluene is used, resulting in the retention of configuration.[7] If a strongly coordinating solvent such as HMPA is used instead, solvent coordination will replace a negatively charged Pd ligand to produce an ionic complex, which induces transmetallation from backside attack, giving inverted stereochemistry.[8]
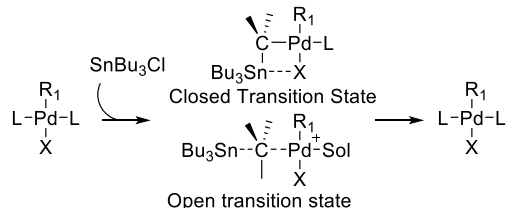

When a Stille coupling takes place in the presence of carbon monoxide, CO inserts between the coupling partners.[9] This carbonylative Stille coupling is thought to operate with CO insertion after the oxidative addition of RX. The stereochemistry of the product is not changed.
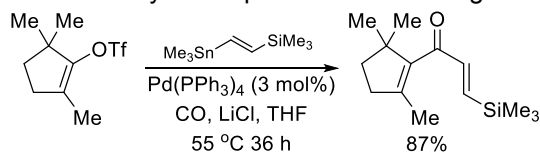
Some researchers noticed that copper alone can catalyze the Stille reaction.[10]
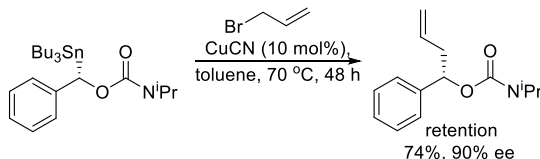
Copper(I) was originally added as an additive to improve the product yield.[11] This so-called "Copper Effect" is caused by the copper capturing the triphenylphosphine ligand dissociated from the palladium catalyst.[1]
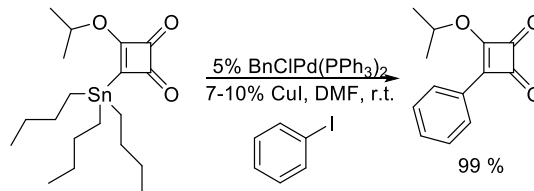
Although the Stille reaction is intriguing in terms of educational benefit, Stille coupling nowadays is not often used due to the toxicity of alkyl tin. The Suzuki coupling (next section) can achieve a similar transformation using more available boron reagents.

References for Stille Couplings:
1. Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, 43, 4704
2. J. W. Labadie, J. K Stille, *J. Am Chem. Soc* **1987**, 105, 6129.
3.E. Vedejs, A. R. Haigt, W. O. Moss, *J. Am. Chem. Soc.* **1992**, 114, 6556
4. J. T. Pinhey and E. G. Roche, J. *Chem. SOC., Perkin Trans.* **1988**, 1, 2415
5. Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, 115, 11393
6. Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, 106, 4630.
7. J. Ye, R. K. Bhatt, J. R. Falck, *J. Am. Chem. Soc.* **1994**, 116, 1
8. J. W. Labadie, J. K. Stille, *J. Am. Chem. Soc.* **1983**, 105, 6129
9. Grisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, 106, 7500
10. Lange, H.; Fröhlich, R.; Hoppe, D. *Tetrahedron*. **2008**, 64, 9123
11. L. S. Liebeskind, R.W. Fengl, *J. Org. Chem.* **1990**, 55, 5359

4. Suzuki Coupling

Suzuki coupling is significantly more popular than other cross coupling reactions because boron reagents are relatively benign and stable, and available in a larger variety than organotin reagents.[1] Organoboranes are also very easy to prepare. However, their drawback is that they may be sensitive to air. For this reason, handling is sometimes tricky, and incomplete degassing will result in low yields.

Boronic esters are somewhat more stable than organoboranes and are less sensitive to oxygen than organoboronates sometimes. This class of compounds is relatively easy to prepare and an entry point to other boron species. Boronic acids are very reactive in the transmetallation step of the Suzuki coupling. A high concentration of the boronic acid therefore is thought to result in side-reactions that reduces the yield.
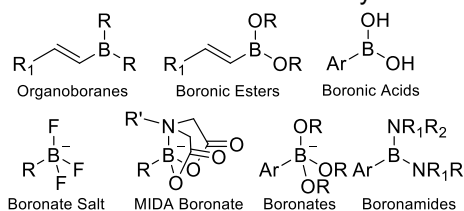

Organotrifluoroborate salts are often easier to handle since they are crystalline. Unless it is hydrolyzed, it is relatively stable (when hydrolyzed, it gives HF, which destroys the glassware). During reaction, it maintains a low boronic acid concentration for transmetallation to minimize

the by-products. *N*-coordinated boronates are very stable because boron's p-orbital is masked by the lone pair from the nitrogen and can be activated by hydrolysis. The properties of boronates and boronamides are somewhat similar to trifluoroborates and *N*-coordinated boranes.
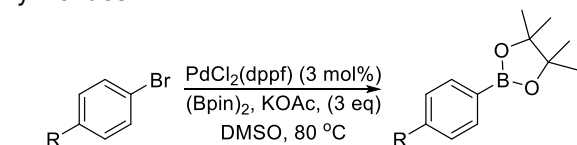
Facile preparation of boron reagents is accomplished via the hydroboration of a double or triple bond.[2, 3]
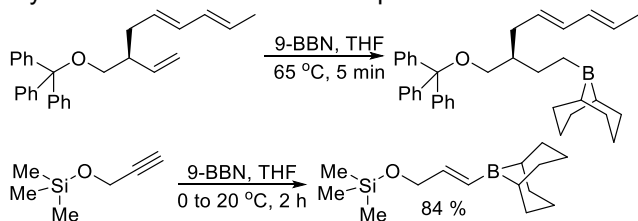
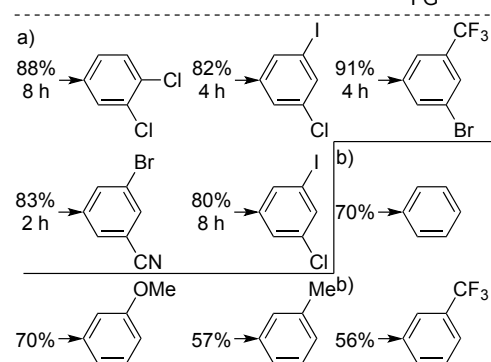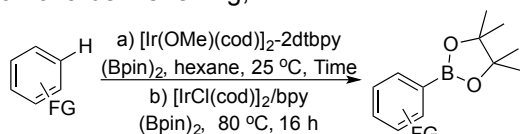An alkynylboronate is prepared by treating a terminal alkyne with butylithium followed by addition of a borate.[4]
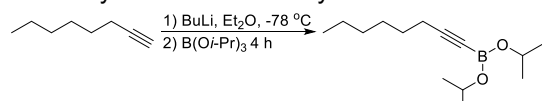
Phenylboronates can be prepared by *ipso*-substitution of phenyl halides.[5]

PdCl$_2$(dppf) (3 mol%)
(Bpin)$_2$, KOAc, (3 eq)
DMSO, 80 °C

Entry	R	Time	Yield	Entry	R	Time	Yield
1	H	2	98	5	COCH$_3$	1	80
2	NMe$_2$	24	23	6	CN	1	76
3	OMe	24	69	7	NO$_2$	2	86
4	CO$_2$Me	1	86				

Phenylboronates can also be prepared by direct borylation of a benzene ring,[6, 7]

a) [Ir(OMe)(cod)]$_2$-2dtbpy
(Bpin)$_2$, hexane, 25 °C, Time
b) [IrCl(cod)]$_2$/bpy
(Bpin)$_2$, 80 °C, 16 h

a)
88% 8 h — Cl, Cl
82% 4 h — I, Cl
91% 4 h — CF$_3$, Br
83% 2 h — Br, CN
80% 8 h — I, Cl
b) 70% — benzene
70% — OMe
57% — Me b)
56% — CF$_3$

Three features of the catalysts for the Suzuki coupling required to give good yields are high electron density on Pd by having good electron donor ligands to foster oxidative addition, coordination of basic phosphine ligands to avoid the precipitation of Pd catalyst, and the steric bulkiness of the ligand for faster reductive elimination.[8]

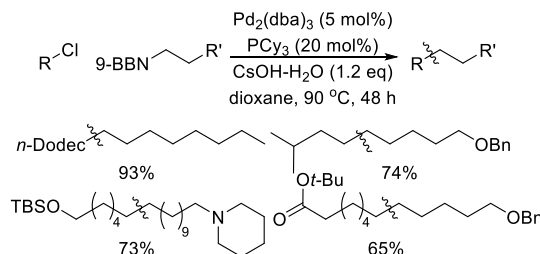Most Suzuki couplings are catalyzed by Pd(PPh$_3$)$_4$ and Pd(dppf)Cl$_2$.[9] However, these complexes are very sensitive to air. Hence, there have been efforts to develop easier to handle palladium complexes. Below are representative ligands of the NHC, PN, palladacycle, and pincer ligand classes. Most of them contain a phosphine ligand, which is a good σ-donor that increases the electron density on the Pd. The NHC motif plays the same role. They contain a bulky backbone that facilitate the reductive elimination.

NHC Ligand   PN Ligand

Palladacycle Ligand   Pincer Ligand
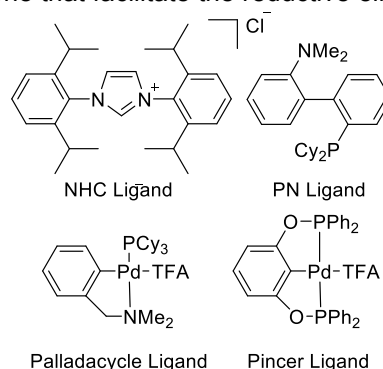
A unique feature of Suzuki reaction is the acceleration of the reaction by the addition of Brønsted base. It is postulated that the hydroxide ion coordinates either to the boron (top) to increase the nucleophilicity of the alkyl group or to palladium to activate it (bottom).[10] Typical bases are NaOH and NaOMe for THF, and K$_2$CO$_3$ and K$_3$PO$_4$ for DMF.
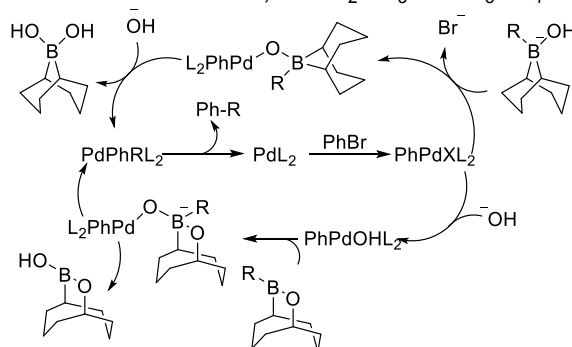
Suzuki coupling not only gives products from sp^2 hybridized coupling partners in good yields but also form primary C(sp^3)-C(sp^3) bonds in moderate yields by preventing β-elimination by the use of a bulky PCy$_3$ ligand.[11] Still, the Suzuki coupling using secondary aliphatic halides is not well established.

Pd$_2$(dba)$_3$ (5 mol%)
PCy$_3$ (20 mol%)
CsOH-H$_2$O (1.2 eq)
dioxane, 90 °C, 48 h

R-Cl   9-BBN   R'

n-Dodec — 93%
Ot-Bu — 74% OBn
TBSO — 73%
65% — OBn

Stereoselective coupling in the Suzuki reaction is similar to that of the Stille coupling; diastereoselective Suzuki reactions are regularly reported, but enantioselective versions are rare.

References for Suzuki Couplings:
1. A. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, **2014**, 43, 412.

2. M. Gärtner, D. Kossler, D. Pflästerer, G. Helmchen, *J. Org. Chem.* **2012**, 77, 4491
3. G. Y. Fang and V. K. Aggarwal, *Angew Chem., Int. Ed.*, **2007**, 46, 359;
4. H. C. Brown, N. G. Bhat and M. Srebnik, *Tetrahedron Lett.*, **1988**, 29, 2631
5. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, 60, 7508.
6. Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, 3, 271.
7. Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390.
8. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, 58, 9633.
9. Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, 111, 1417.
10. Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, 63, 461.
11. Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, 41, 1945.

5. Hiyama Couplings

Hiyama couplings use organosilicate substrates in lieu of organoboron reagents. The stability of organosilicates is comparable to organoborates, but Suzuki coupling is more commonly used. The Hiyama coupling was first discovered using hexacoordinate silicates.[1] However, the use of organopentafluorosilicate has been discontinued since its preparation is troublesome. Organosilicate reagents used now are tetra-coordinated.
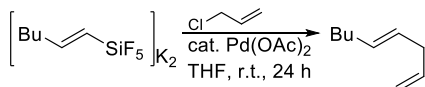

Soon after, organosilanols were found to be good coupling partners as they are stable with air and moisture.[2]
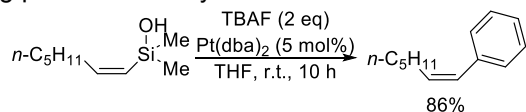
These reagents are usually activated upon the coordination of fluoride ion before the transmetallation.
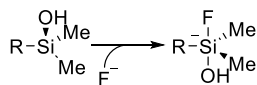

Organosilanol reagents can easily be prepared similarly to organoboron reagents. An alkenylsilanol reagent can be prepared by lithium halogen exchange followed by the treatment with hexamethylcyclotrisiloxane.[2] A silylated benzene ring was prepared in the same way.[3] Ruthenium catalysis furnishes alkynosilanes.[4]
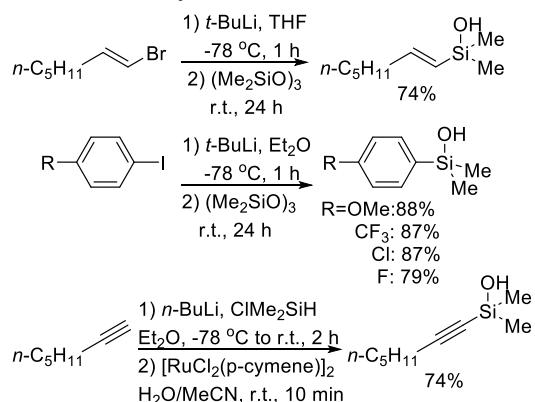
Fluoride activation of oganosilicon reagents for Hiyama couplings is a drawback of the coupling; silyl protected functional groups are deprotected in the process. Thus, fluoride free activation is sometimes desirable. Ag$_2$O was identified as a promoter to activate the silicates.[5]
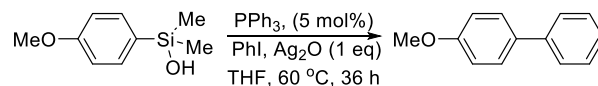

Following this finding, bases were used as promoters of Hiyama coupling. TMSOK recorded a fast coupling rate.[6]
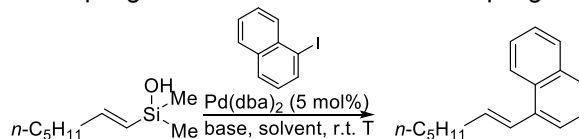

Entry	Base	Solvent	Time	Yield
1	MeLi	THF	24 h	40
2	NaH	THF	8 h	85
3	NaH	DMF	1.5 h	78
4	NaH	DME	1 h	81
5	KH	THF	2 h	85
6	KH	DME	15 min	82
7	KOt-Bu	DME	3 h	90

The base deprotonates the silanol, which then attacks the palladium to produce a penta-coordinated silicate. This mechanism activates the silicon and accelerate the reaction rate. However, the use of base may cause undesirable dehydration of the silanol or protodesilylation.[7] For this reason, the organosiliocon reagent was prepared as the silanolate salt form to avoid using base. The salt form is convenient for handling and storage as it is a solid and insensitive to air and moisture in general.[8]
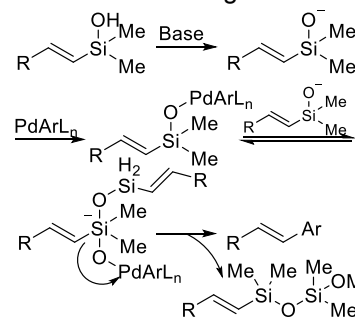
An interesting adaptation is the intramolecular Hiyama coupling. Intramolecular cross coupling is possible if the substrate contains a hydroxyl group. For example, a propargylic alcohol is treated with disiloxane. The following hydrosilylation will produce a cyclic intermediate, which undergoes Hiyama coupling to produce the product and release the hydroxyl group after workup.[9]
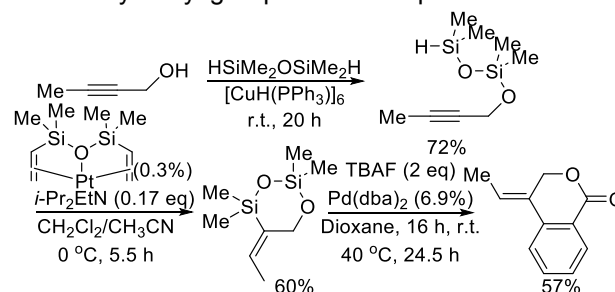
As described above, the Hiyama coupling is as fascinating as the Suzuki coupling in terms of the mild reaction conditions. However, the unavailability of sp³-sp³ coupling makes the Suzuki coupling popular.

References for Hiyama Couplings:
1. J. I. Yoshida, K. Tamao, M. Takahashi and M.Kumada, *Tetrahedron Lett.*, **1978**, 19, 2161
2. Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, 2, 565.
3. Denmark, S. E.; Smith, R. C.; Chang, W.-T. T.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2009**, 131, 3104
4. Denmark, S. E.; Tymonko, S. A. *J. Org. Chem.* **2003**, 68, 9151
5. Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, 65, 5342
6. Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, 123, 6439.
7. Denmark, S. E.; Baird, J. D. *Chem. Eur. J.* **2006**, 12, 4954
8. Denmark, S. E. *J. Org. Chem.* **2009**, 74, 2915
9. Denmark, S. E.; Pan, W. *Org. Lett.* **2003**, 5, 1119
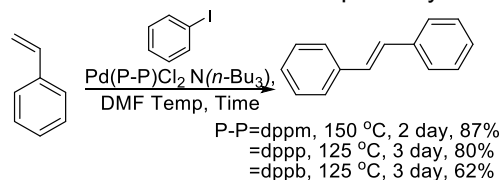
6. Heck Reaction
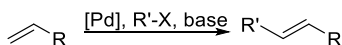
The Heck reaction is a coupling between an alkene and vinyl halide or aryl halide. A major difference between the Heck reaction and the coupling reactions in the previous sections is that this reaction does not need a "leaving group" on the partner. The yield tends to be higher with a less substituted alkene, whereas Heck reactions with more substituted alkenes are more challenging.

There is also a big difference in the mechanism of the Heck reaction. After oxidative addition, palladium needs to open a coordination site for the incoming alkene by dissociation because there is no transmetallation possible. Palladium gives up either the halogen or a neutral ligand. Palladium becomes positively charged if the halogen dissociates from the metal, and it will insert into the olefin in a way that the coordinated alkyl group inserts at the more positively charged carbon to give the product having the alkyl groups on the same carbon (1,1-insertion).[1] If the neutral ligand dissociates instead, it will lead to the neutral palladium complex. In most cases, the neutral ligand is one of the phosphines because the rate of oxidative addition relies on the σ-donicity of the phosphine. However, the strong coordination of electron rich phosphine ligands will lower the concentration of the complex with an open coordination site.[2] To overcome the problem, mono-phosphine is usually added in excess. The neutral pathway favors 1,2-insertion, giving the *E*-alkene product.
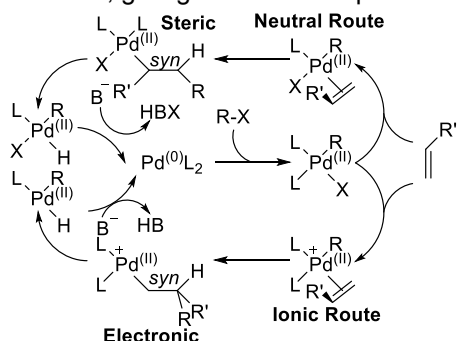
P-P chelated palladium complexes also can catalyze the Heck reaction.[3] Because the chelating ligand reluctantly dissociates from the palladium, it is likely that halides leave the palladium to give a positively charged intermediate. The reaction then would choose the ionic pathway.

Pd(P-P)Cl₂ N(*n*-Bu₃), DMF Temp, Time

P-P=dppm, 150 °C, 2 day, 87%
=dppp, 125 °C, 3 day, 80%
=dppb, 125 °C, 3 day, 62%

As explained above, loss of a phosphine ligand (neutral pathway) is slow. One solution is a stable palladacycle complex, which will disassemble *in situ* to a catalytically active species that undergoes oxidative addition.[4] As a result, the entire complex is negatively charged, and therefore the halogen easily exchanges with the olefin.

Palladacycle   Carbene
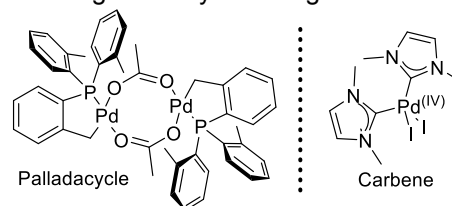
Carbene ligands are as strong electron donors as phosphines, and therefore they can replace phosphorus in catalysts.[5] Each carbene ligand imparts one negative charge to the metal and can lead to the ionic pathway. One drawback of the phosphine catalysts is that they are very unstable, giving palladium precipitate over time.

The asymmetric Heck reaction is counter-intuitive because a double bond is restored after the addition of the alkyl group. However, if the β-elimination occurs at the opposite carbon, a new chiral center could be made.
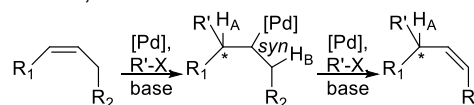
Chiral ligands are usually bidentate and have to remain coordinated throughout the reaction for it to be asymmetric. Therefore, only the halide can dissociate before olefin coordination The reaction must follow the ionic pathway. A "privileged ligand", BINAP ligand works well in this reaction.[6] BINAP had been the best ligand for years.

PPh₃ PPh₃ (6 mol%)
Pd(OAc)₂ (3 mol%)
ArOTf, *i*-Pr₂NEt
benzene, 40 °C
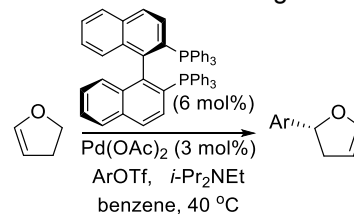
Ar	Time	Yield %	ee %
p-Cl	22 h	71	91
m-Cl	29 h	67	93
p-COMe	1 day	61	93
p-CN	26 h	61	93
p-OMe	3 days	52	73

Eventually, phosphinooxazoline P-N ligands were developed. Palladium ligated by this oxazoline-based ligand

showed a much improved yield and enantiomeric excess.[7] Importantly, the double bond migration that is observed with BINAP is suppressed. The stereochemical result is directly correlated with the chirality of the ligand.
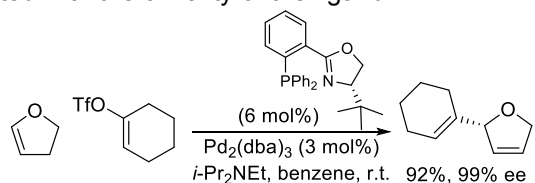
Nonoxazoline based P-N ligands and N-N ligands were found to catalyze the Heck reaction with moderate yield and enantiomeric excess.[8,9] The fused benzene keeps the oxazine flat.
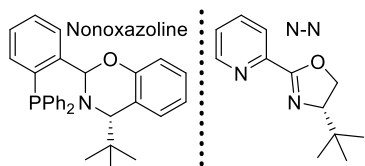

A quaternary carbon center can be created by a Heck reaction. The success is limited to intramolecular reactions, but enantioselective versions of these are reported.[10]
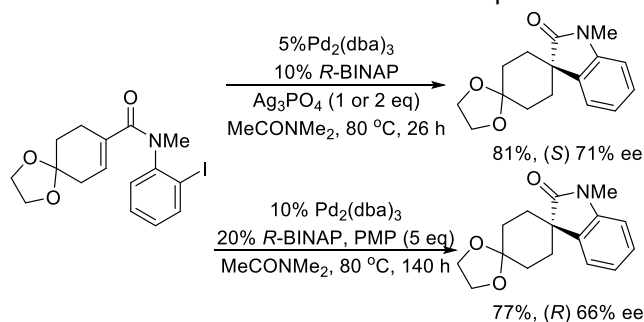
References for Heck Reaction

1. D. Mc Cartney and P. J. Guiry, *Chem. Soc. Rev.*, **2011**, 40, 5122
2. Amatore, C.; Jutand, A.; Meyer, G. *Inorg. Chim. Acta.* **1998**, 273, 76.
3. Shaw, B. L.; Perera, S. D. *Chem. Commun.* **1998**, 1863
4. Herrmann, W. A.; Brossmer, C.; O¬ fele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1844.
5. Herrmann, W. A.; Elison, M.; Fischer, J.; Koecher, C.; Artus, G. R. J. *Angew. Chem.* **1995**, 107, 2602.
6. F. Ozawa, A. Kubo and T. Hayashi, *J. Am. Chem. Soc.,* **1991**, 113, 1417
7. O. Loiseleur, M. Hayashi, N. Schmees and A. Pfaltz, *Synthesis.,* **1997**, 1338
8. E. P. Ku¨ ndig and P. Meier, *Helv. Chim. Acta.,* **1999**, 82, 1360
9. C. Bolm, K. Weickhardt, M. Zehnder and T. Ranff, Chem. Ber., **1991**, 124, 1173
10. A. Ashimori and L. E. Overman, *J. Org. Chem.*, **1992**, 57, 4571
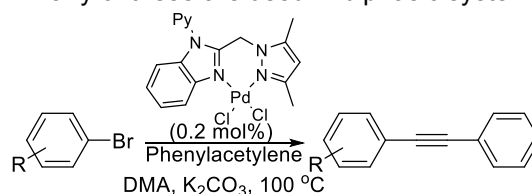
7. Sonogashira Coupling
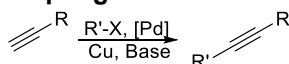
The Sonogashira coupling is a C-C bond forming reaction between a terminal alkyne and alkenyl or aryl halide. This reaction often is catalyzed by palladium and is facilitated by copper and base. Palladium catalysts are typically $Pd(PPh_3)_4$ or $Pd(PPh_3)_2$. The general mechanism is basically the same as Kumada, Negishi, Stille, Suzuki, and Hiyama couplings: oxidative addition, transmetallation and reductive elimination. However important roles played by the copper and base should be considered.

The role of the copper in the catalytic cycle is to activate the alkyne for transmetallation.[1] Copper is also activated by the coordination of the base. However, Sonogashira reactions that do not require copper have been reported. Because the base is not strong enough to deprotonate the terminal alkyne, palladium is believed to assist by the coordination to the triple bond.[2] Copper free reactions are advantageous in that trace amounts of oxygen do not trigger copper-mediated Hay/Glacer reactions.[3]
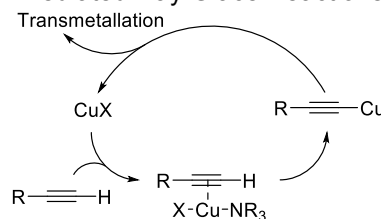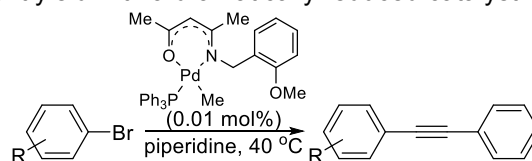

N-N ligands were developed that show good catalytic activity.[4] Many of these are used in biphasic systems.

| E	R	Time (h)	yield %
1	p-Ac	4	99
2	p-CHO	4	99
3	H	20	99
4	p-Me	19	97
5	o-CHO	20	98

A PNO type complexes, β-oxoiminatophosphane coordinated palladium, catalyzes Sonogashira couplings in excellent yield with a dramatically reduced catalyst loading.


| E	R	T (h)	Y%	E	R	T (h)	Y%
1	p-NO2	1	94	7	p-NO2	2	98
2	p-OMe	2	93	8	p-OMe	3	91
3	o-OMe	3	94	9	o-OMe	4	95
4	p-Me	2	96	10	p-Me	3.5	92
5	o-Me	3	94	11	o-Me	4	93
6	H	3	93	12	H	3	91

For entry 1-6, X=I, 7-12, X=Br

NHC ligated and palladacycle complexes were used in Sonogashira couplings too. The former is stable under the reaction conditions, and the latter maintains a balance between stability and high catalytic activity.
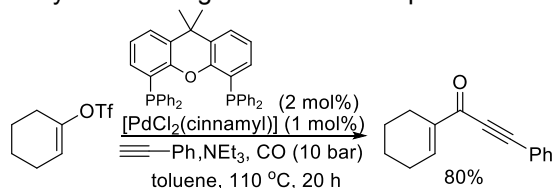
NHC ligated Pd

Palladacycle
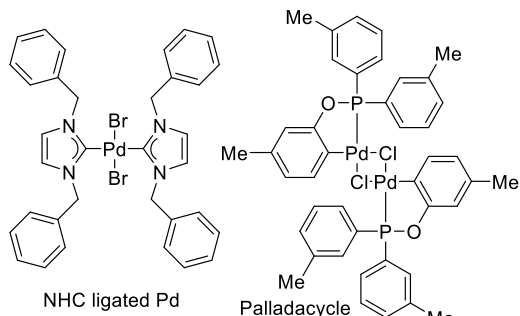
The coupling with a silylated terminal alkyne is called a sila-Sonogashira coupling.[8]
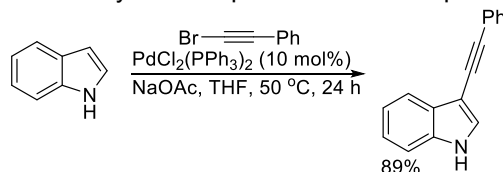

89%
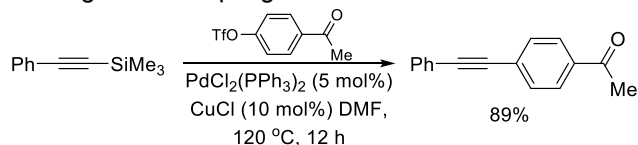
Sonogashira coupling can be carried out while a silyl group remains intact. Desilylation followed by another Sonogashira coupling furnishes an internal alkyne.[9]


85%
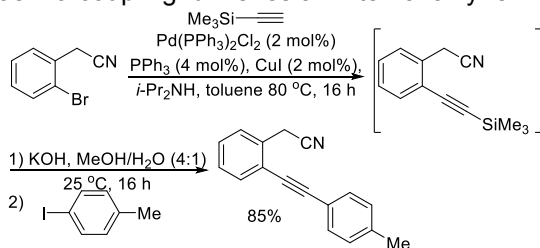
Carbonylative Sonogashira reactions produce ketones.[10]

80%

The formal inverse of the Sonogashira coupling between a halogenated alkyne and sp[2] carbons was reported.[11]

89%

Some "palladium-free Sonogashira reactions were reported.[12] However, it is suspected that minute amount of a palladium impurity in the copper reagent catalyzes the reaction,[13] and an investigation of the effect of ppb level of palladium was made.[14]
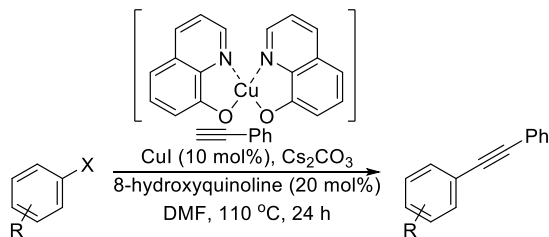
E	R	Yield	E	R	Yield
1	H	92	5	H	85
2	p-OMe	86	6	p-OMe	70
3	p-NO$_2$	90	7	p-NO$_2$	71
4	p-Cl	90			

For entry 1-4, X=I, 5-7, X=Br

References for Sonogashira Reaction:
1. Meunier and J.-C. Hierso, *Organometallics*, **2010**, 29, 2815.
2. Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, 5, 4191.
3. G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, **2008**, 108, 3054
4. F. Li and T. S. A. Hor, *Adv. Synth. Catal.*, **2008**, 350, 2391
5. D.-H. Lee, H. Qiu, M.-H. Cho, I.-M. Lee and M.-J. Jin, *Synlett*, **2008**, 1657
6. L. Ray, S. Barman, M. M. Shaikh and P. Ghosh, *Chem.–Eur. J.*, **2008**, 14, 6646
7. I. B"aszczyk, A. M. Trzeciak and J. J. Zio"kowski, *Catal. Lett.*, **2009**, 133, 262
8. Y. Nishihara, K. Ikegashira, A. Mori and T. Hiyama, *Chem. Lett.*, **1997**, 1233
9. R. Severin, J. Reimer and S. Doye, *J. Org. Chem.*, **2010**, 75, 3518
10. X. F. Wu, B. Sundararaju, H. Neumann, P. H. Disneuf and M. Beller, *Chem.–Eur. J.*, **2011**, 17, 106
11. Y. Gu, X. Wang, *Tetrahedron Lett.* **2009**, 50, 763.
12. M. Wu, J. Mao, J. Guo and S. Ji, *Eur. J. Org. Chem.*, **2008**, 4050
13. H. Plenio, Angew. *Chem., Int. Ed.*, **2008**, 47, 6954
14. Z. Gonda, G. L. Tolasi and Z. Nova´ k, *Chem.–Eur. J.*, **2010**, 16, 11822