Alkyl Electrophiles in Pd-Catalyzed Cross-Coupling Reactions

Frontiers of Chemistry
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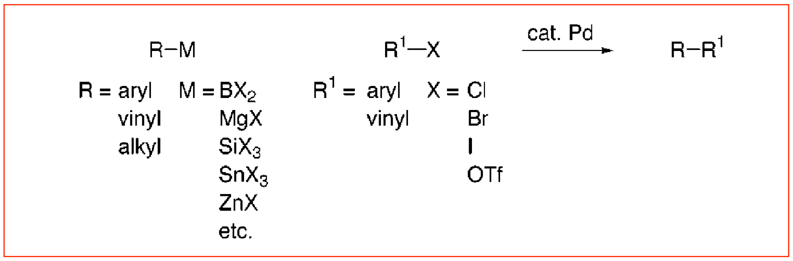
April 16, 2005

General Ref.:
-Diederich, F., Stang, P.J., Eds. *Metal-catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, 1998.
-de Meijere, A., *Organopalladium Chemistry for Organic Synthesis;* Negishi, E Ed.; Wiley: New York, Vol. 1.
Difficulty with Csp^3-X couplings:
-Cardenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384.

Metal Mediated-Cross Couplings

- 1st reports in the mid 1970's
- Transition mediated cross-coupling reactions are important methods for forming new C-C bonds.
  - -Pd(0) catalysis, Cu(I) mediated reactions, Ni-and Fe-complexes
- Advances using aryl-and alkenyl- electrophiles have seen tremendous growth, alkyl electrophiles have lagged behind.



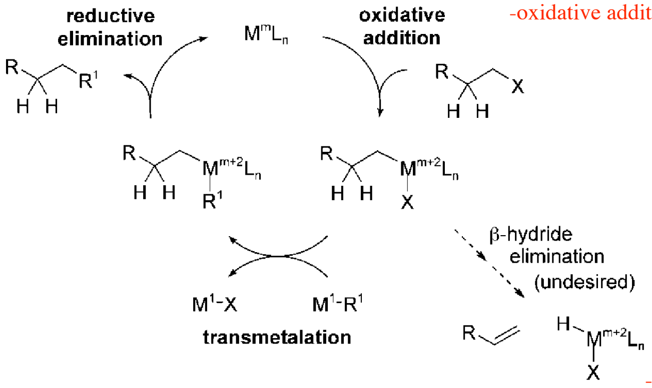
$$R{-}M \qquad R^1{-}X \xrightarrow{\text{cat. Pd}} R{-}R^1$$

R = aryl, vinyl, alkyl
M = BX_2, MgX, SiX_3, SnX_3, ZnX, etc.
R^1 = aryl, vinyl
X = Cl, Br, I, OTf

Overview

- Alkyl Electrophiles
- Suzuki Reaction (1° -Br, -Cl, -OTs; 2° -I, -Br)
  - Alkyl boranes
  - Boronic Acids
- Stille Reaction
  - Improved Stille
- Sonigashira Reaction
- Hiyama
- Negishi Coupling
- Mechanistic Work
- Future Work

Lack of Success



-oxidative addition is slow

-may undergo intramolecular β-hydride elimination faster than intermolecular transmetalation

Fu, G.; Netherton, M. *Adv. Synth. Catal.* **2004**, *346*, 1525.

Oxidative Addition into C-X Bond

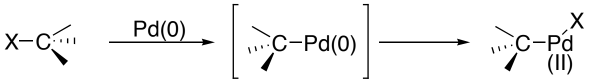
- Most cross-coupling reactions require a good leaving group which is directly attatched or adjacent to a carbon atom with sp^2(allylic or benzylic) or sp(propargylic) hybridization. Coordination at these centers facilitate cleavage of the C-X bond.

Allyl > Benzyl, Acyl > Alkenyl > Aryl >> Alkyl
Propargyl Alkynyl

- Order of reactivity

I > OTf > Br > Cl >> F

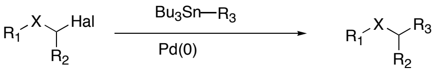
- Oxidative addition of C(sp^3)-X to Pd(0) via a bimolecular S$_N$2 process



de Meijere, A., *Organopalladium Chemistry for Organic Synthesis;* Negishi, E Ed.; Wiley: New York, Vol. 1, p.134.

Activation of C-X Bond

α-Heteroatom-Substituted C-X Bond Activation

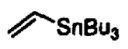
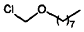
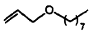
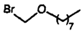
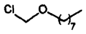
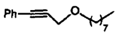
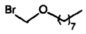
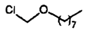
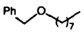
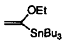
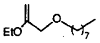
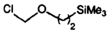
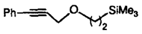
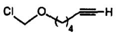
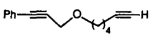
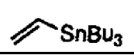
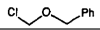
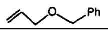


61-86%

presence of the α-heteroatom may weaken the C-X bond.

X = O,S

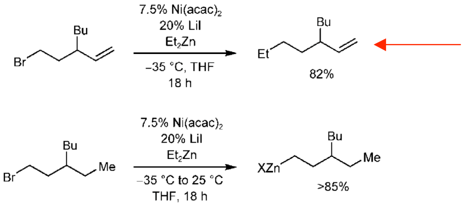
Shimizu, R.; Fuchikami, T. *Tetrahedron Lett.* **2001,** *42*, 6891.

Entry	Organotin	α-Haloether	Adduct	Temp (°C)/ Time(h)	Isolated Yield(%)
1				24/1.5^a	82
2	"		"	24/10^a	84
3	Ph—≡—SnBu$_3$			80/1.5^b	71
4	"		"	40/8^c	55
5	PhSnBu$_3$			80/2^b	86
6		"		80/12^b	81
7	Ph—≡—SnBu$_3$			80/12^d	61
8	"			65/12^b	61
9				80/4^b	75

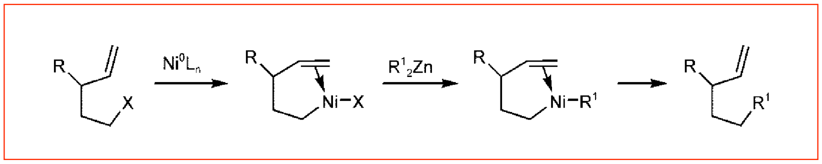
Activation of C-X Bond

Chelation Assisted Activation of a Proximal C-X bond

- 1995- P.Knochel-Negishi Rxn.

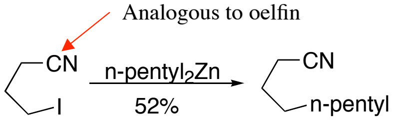


Remote C=C double bond is a critical element for the cross-coupling



π-acidity of the oelfin facilitates reductive elimination

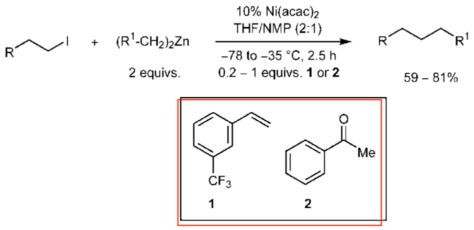
Analogous to oelfin

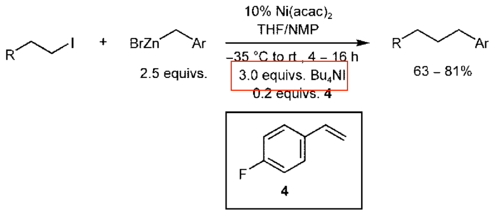


- 3-4 carbon tethers b/n oelfin and halogen are allowed

Knochel, P.; Studemann, T.; Devasagayaraj, A. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2723.

Expanded Scope



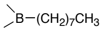
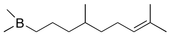
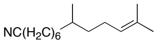
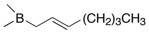
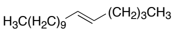
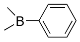
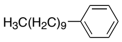


What about unactivated alkyl haildes?

Knochel, P.; Studemann, T.;Giovannini, R.; Dussin, G. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2387.

First Examples

- 1992- A. Suzuki
  - $Pd(PPh_3)_4$ catalyzed couplings of alkyl iodides with alkyl-, alkenyl-, and aryl-9-BBN reagents

Halide	9-R-9-BBN	Product	Yield %
$CH_3(CH_2)_5I$		$C_{14}H_{30}$	64
$NC(CH_2)_3I$			61
$CH_3(CH_2)_9I$			64
$CH_3(CH_2)_9I$			55

conditions: $Pd(PPh_3)_4$, K_3PO_4 in dioxane

- Alkyl bromides or secondary alkyl iodides never provided the corresponding coupling product

- Also looked at the reaction of various butyl metals: Bu_3B, Bu_4BLi, $BuMgBr$, $BuZnCl$, Et_3Al, Bu_4Sn, $Cp_2Zr(Bu)Cl$..all were ineffective, major product obtained was the β-hydride elimination product

Suzuki, A.; Ishiyama, T.; Abe, S.; Miyaura, N. *Chem. Lett.* **1992**, 691.

Suzuki Rxn-alkyl bromides

$$\underset{\text{1.2 equiv}}{R-(9\text{-BBN})} \quad R_{alkyl}-Br \xrightarrow[\substack{1.2\ K_3PO_4\cdot H_2O \\ \text{THF, r.t.}}]{\substack{4\%\ Pd(OAc)_2 \\ 8\%\ PCy_3}} R-R_{alkyl}$$

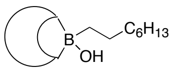
R = alkyl, vinyl

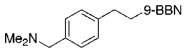
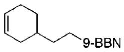
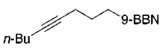
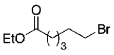
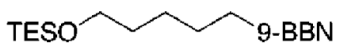
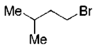
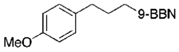
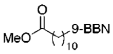
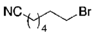
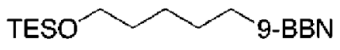
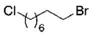
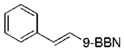
- Use of bulky, e-rich phosphines aid in the cross coupling of aryl chlorides: variety of phospine ligands-triaryl-, bidentate, phosphite, and arsines(AsPh)
- Not moisture sensitive, rm. temp
- Anhydrous K_3PO_4 - No reaction

$$\text{B-n-hexyl-9-BBN} \xrightarrow[\text{THF}]{\text{anhy. }K_3PO_4} \text{no change in }^{11}\text{B NMR (}\delta\text{ 78)}$$

$$\text{B-n-hexyl-9-BBN} \xrightarrow[\text{THF}]{K_3PO_4.H_2O\ (1:1)} \text{change in }^{11}\text{B NMR (}\delta\text{ 4)}$$

hydroxyl bound "ate" complex



entry	R−(9-BBN)[a]	R_{alkyl}−Br	yield (%)[b]
1	*n*-Hex−(9-BBN)	*n*-Dodec−Br	93
2		*n*-Dodec−Br	78[c]
3		*n*-Dodec−Br	85
4			58
5			72
6		*n*-Hex−Br	80
7			81
8			81
9		*n*-Dodec−Br	66

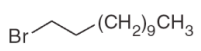
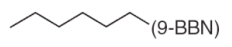
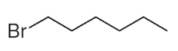
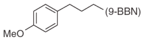
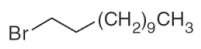
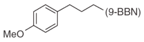
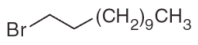
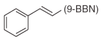
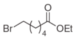
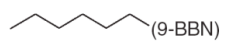
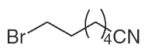
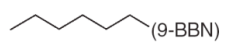
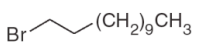
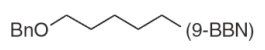
[a] Prepared by hydroboration with 9-BBN of the corresponding kene/alkyne and used without purification. [b] Isolated yield, average two runs. [c] 1.05 equiv of R-(9-BBN) was used.

Fu, G.; Netherton, M.; Dai, C.; Neuschutz, K. *J. Am. Chem. Soc.* **2001**, *123*, 10099.

Suzuki Rxn-alkyl bromides

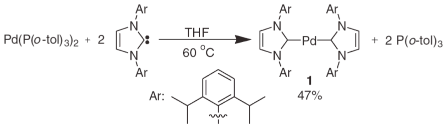
- N-Heteocyclic carbenes (NHC) are considered phosphine mimics

$$\text{R–Br} + \text{R}^1\text{—(9-BBN)} \xrightarrow[\substack{\text{KO}t\text{-Bu (1.2 eq.)} \\ \text{AgOTf (4 mol\%)} \\ \text{THF, 40 °C, 24 h}}]{\substack{\text{Pd(dba)}_2\text{ (4 mol\%)} \\ \text{IPr.HCl (8 mol\%)}}} \text{R–R}^1$$

Entry	R–Br	R^1–(9-BBN)[a]	Yield (%)[b]
1			56
2			46
3			39
4			37
5			53
6			52
7			28

[a] Organoboranes prepared from 9-BBN dimer (0.6 equiv) and terminal alkene/alkyne (1.2 equiv), not isolated or purified prior to use.

[b] Isolated yield.



Using 1 in rxn yielded only 20% of cross-coupling product

Caddick, S.; Arensten, K.; Cloke, G.;Herring, A.; Hitchcock, P. *Tetrahedron Lett*. **2004**, *45*, 3511.

Boronic Acids

$$\text{R}_{\text{akyl}}\text{–Br} \quad \underset{\text{1.5 equiv}}{(\text{HO})_2\text{B–R}} \xrightarrow[\substack{\text{3 equiv KO}t\text{-Bu} \\ t\text{-amyl alcohol, r.t.}}]{\substack{\text{5\% Pd(OAc)}_2 \\ \text{10\% phosphine}}} \text{R}_{\text{alkyl}}\text{–R}$$

R = aryl, vinyl, alkyl

- Air stable
- Commercially available
- Only one previous report 1999-β-(perfluoroalkyl)ethyl iodides

$$\text{n-Oct—Br} + \text{PhB(OH)}_2 \xrightarrow{\substack{\text{5\% Pd(OAc)}_2 \\ \text{10\% ligand}}} \text{n-Oct—Ph}$$

entry	additive	solvent	ligand	yield (%)[a]
1[b]	$K_3PO_4 \cdot H_2O$	THF	PCy_3	<2
2	KF	THF	PCy_3	<2
3	NaOMe	THF	PCy_3	3
4	KO*t*-Bu	THF	PCy_3	11
5	KO*t*-Bu	dioxane	PCy_3	64
6	KO*t*-Bu	*tert*-amyl alcohol	PCy_3	63
7	KO*t*-Bu	*tert*-amyl alcohol	PCy_2Et	39
8	KO*t*-Bu	*tert*-amyl alcohol	$P(t\text{-Bu})_3$	<2
9	KO*t*-Bu	*tert*-amyl alcohol	$P(t\text{-Bu})_2Et$	4
10	**KO*t*-Bu**	***tert*-amyl alcohol**	$\mathbf{P(t\text{-Bu})_2Me}$	**85**

[a] Average of two runs. Determined by GC versus a calibrated internal standard. [b] Conducted according to the procedure in ref 4b.

Solubility improved

Fu, G.; Kirchhoff, J.; Netherton, M.; Hills, I. *J. Am. Chem. Soc.* **2002**, *124*, 13662.
Ding, Y.; Yang, G.; Xie, X.; Zhao, G. *J. Fluorine Chem.* **1999**, *2*, 159.

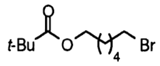
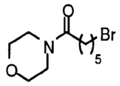
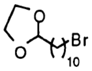
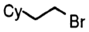
Boronic Acids

$$R_{akyl}{-}Br \quad (HO)_2B{-}R \xrightarrow[\text{3 equiv KO}t\text{-Bu, }t\text{-amyl alcohol, r.t.}]{\text{5\% Pd(OAc)}_2\text{, 10\% phosphine}} R_{alkyl}{-}R$$

1.5 equiv

R = aryl, vinyl, alkyl

- In the presence of 1 equiv. of H_2O, the rxn proceeds in comparable yield.
- Heteroaryl- and e- deficient arylboronic acids have not been successful.

entry	R_{alkyl}–Br	R	yield (%)[a]	
			P(*t*-Bu)$_2$Me	[HP(*t*-Bu)$_2$Me]BF$_4$
1	*n*-Oct–Br	Ph	87	90
2		4-(MeS)C_6H_4	68	66
3	BnO-$(CH_2)_6$–Br	4-(MeO)C_6H_4	85	84
4	TBSO-$(CH_2)_6$–Br	4-(F_3C)C_6H_4	63	67
5		*o*-tolyl	71	76
6		1-naphthyl	97	93
7		mesityl	89	91
8	NC-$(CH_2)_6$–Br	(*E*)-1-hexenyl	85	87
9	*n*-Dodec–Br	*n*-Hex	66	62

[a] Isolated yield.

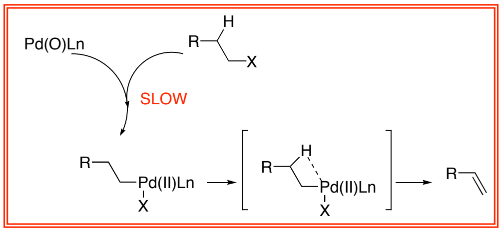
$$\text{n-OctBr} + (OH)_2B{-}Ph \xrightarrow{\substack{0.5\%\ Pd(OAc)_2 \\ 1.0\%\ P(t\text{-}Bu)_2Me}} \text{n-Oct—Ph}$$

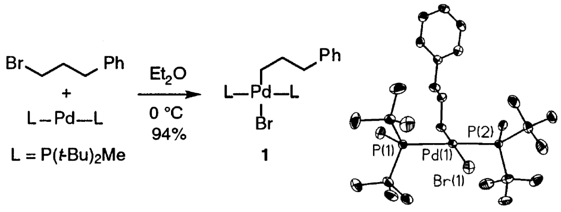
81%

TON ~160

Suzuki, A.; Ishiyama, T.; Abe, S.; Miyaura, N. *Chem. Lett.* **1992**, 691.
Fu, G.; Kirchhoff, J.; Netherton, M.; Hills, I. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

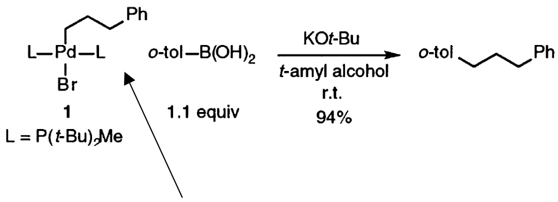
Oxidative Addition





when warmed to 50 °C,β-elimination occurs

Cross-Coupling



also serves as a catalyst for the coupling of alkyl bromides to boronic esters @ rm. temp.

Fu, G.; Kirchhoff, J.; Netherton, M.; Hills, I. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

Alternative to Trialkylphosphines

- Trialkylphosphines (P(*n*-Bu)$_3$) can furnish reactivities that are not acessible with more commonly used triarylphosphines (PPh$_3$)
  - Electron richness
  - Shape/steric

- air-sensitive- readily undergo oxidation
  - "Improperly stored bottles of Bu$_3$P are invariably contaminated with tributylphosphine oxide and butylphosphinate..Oxygen should be rigorously excluded to avoid free radical chain oxidation. Tributylphosphine is pyrophoric.."

- Strategy:

Use conjugate acid---> use as the phosphonium salt and a weak base in the reaction mixture would form the phosphine *in situ*

1991-Whitesides applied tris(2-carboxyethyl)phosphine hydrochloride as a water soluble reducing agent for disulfides.

Fu, G.; Netherton, M. *Org. Lett.* **2001**, *3(26)*, 4295.
Whitesides, G.; Burns, J.; Butler, J.; Moran, J. *J. Org. Chem.* **1991**, *56*, 2648.
Diver, S.T. In Encyclopedia of Reagents for Organic Synthesis; Paquette, L.A., Ed.; Wiley: New York, 1995; Vol. 7, pp 5014-5016.

Phosphonium Salts

P(*n*-Bu)$_3$ pK_a 8.4
P(*t*-Bu)$_3$ pK_a 11.4

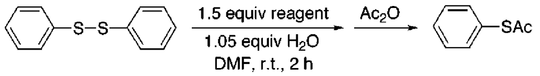
To maximize the likelihood that the chemistry of the phosphine salt would mimic that of the free phosphine a non-coordinating counterion was chosen.

$$\begin{matrix}[(n\text{-Bu})_3\text{PH}]\text{BF}_4 \\ \\ [(t\text{-Bu})_3\text{PH}]\text{BF}_4\end{matrix} \Longrightarrow \begin{matrix}\text{P}(n\text{-Bu})_3 \\ + \\ \text{HBF}_4\end{matrix}$$

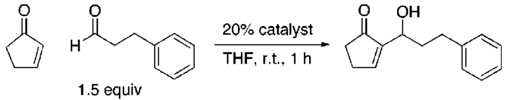
Stable to oxygen, moisture, and can be stored in air (4 months) without any deterioration---heating @ 120 C for 24 h in air also reveals no decomposition
Salts are not hygroscopic.

Fu, G.; Netherton, M. *Org. Lett.* **2001**, *3(26)*, 4295.

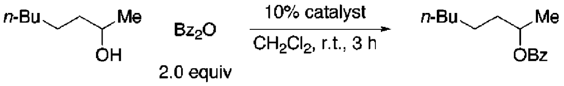
Phosphonium Salts



Reagent	Yield
$(n\text{-Bu})_3P$	91%
$[(n\text{-Bu})_3PH]BF_4$ / $(i\text{-Pr})_2NEt$ (1:1)	91%



Catalyst	Yield
$(n\text{-Bu})_3P$ / PhOH (1:1)	96%
$[(n\text{-Bu})_3PH]BF_4$ / PhONa (1:1)	94%



Catalyst	Yield
$(n\text{-Bu})_3P$	96%
$[(n\text{-Bu})_3PH]BF_4$ / NaOBz (1:1)	97%
$[(n\text{-Bu})_3PH]BF_4$ / $(i\text{-Pr})_2NEt$ (1:1)	98%

Fu, G.; Netherton, M. *Org. Lett.* **2001**, *3(26)*, 4295.

Suzuki Rxn.- Alkyl Chlorides

- One examples of simple alkyl chlorides in lit.

$$^{n}\text{Oct-Cl} + {}^{n}\text{BuMgCl} \xrightarrow[\text{1,3 -butadiene}]{\text{cat. NiCl}_2} {}^{n}C_{12}H_{26}$$

96%

- Lower reactivityof alkyl chlorides
  - Decreased leaving group ability
  - Higher strength of the C-Cl bond

C-Cl ~79 kcałmol

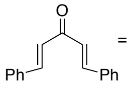
C-Br ~66 kcałmol

C-I ~52 kcałmol

Kambe, N.; Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H. *J. Am. Chem. Soc.* **2002**, *124*, 4222.

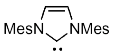
J. March, *Advanced Organic Chemistry*, Wiley, New York, **1992**, p.24.

Fu, G.; Kirchhoff, J.; Dai, C. *Angew. Chem. Int. Ed.* **2002**, *41(11),* 1945.



= dba

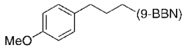
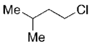
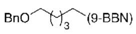
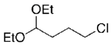
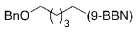
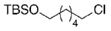
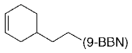
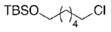
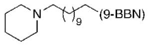
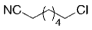
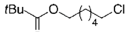
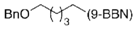
$$n\text{Dodec}{-}\text{Cl} \quad \underset{\text{1.2 equiv}}{n\text{Oct}{-}(\text{9-BBN})} \xrightarrow[\text{1.1 CsOH}\cdot H_2O\text{, dioxane, 90 °C}]{\text{5\% }[Pd_2(\text{dba})_3]\text{, 20\% ligand}} \underset{C_{20}H_{42}}{n\text{Dodec}{-}n\text{Oct}}$$

Entry	Ligand[a]	Yield of $C_{20}H_{42}$ [%][b]
1	PCy_3	77
2	$P(\text{cyclopentyl})_3$	57
3	$PiPr_3$	53
4	$PtBu_3$	< 2
5	$PnBu_3$	5
6[c]	dcpe	< 2
7	PPh_3	< 2
8	$P(o\text{-tol})_3$	< 2
9	$P(2\text{-furyl})_3$	4
10[c]	dppf	< 2
11[c]	binap	< 2
12	$AsPh_3$	< 2
13	$P(OPh)_3$	< 2
14		8

[a] dcpe = 1,2-bis(dicyclohexylphosphanyl)ethane, tol = tolyl, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, Mes = mesityl. [b] Determined by GC versus a calibrated internal standard. [c] For bidentate ligands, 10% of the ligand was used.

Suzuki Rxn.- Alkyl Chlorides

$$R_{alkyl}-Cl \quad \underset{1.2\ \text{equiv}}{R-(9\text{-BBN})} \xrightarrow[\substack{1.1\ CsOH \cdot H_2O \\ \text{dioxane, } 90\ ^\circ C}]{\substack{5\%\ [Pd_2(dba)_3] \\ 20\%\ PCy_3}} R_{alkyl}-R$$

Entry	R_{alkyl}–Cl	R–(9-BBN)[a]	Yield [%][b]
1	*n*-Dodec–Cl	*n*-Oct–(9-BBN)	83
2	*n*-Pent–Cl		82
3			74
4			70
5			72
6[c]			73
7		*n*-Oct–(9-BBN)	73
8[d]			65

[a] Prepared by hydroboration with 9-BBN of the corresponding alkene and used without purification. [b] Yield of isolated product, average of two runs. [c] 1.05 equiv of R–(9-BBN) was used. [d] KOH was used instead of $CsOH \cdot H_2O$.

If no phosphane is present, no coupling product is observed

No products observed for 2° alkyl chlorides or 2° alkyl bromides

KOH was used to decrease the amount of hydrolysis

Fu, G.; Kirchhoff, J.; Dai, C. *Angew. Chem. Int. Ed.* **2002**, *41(11),* 1945.

Suzuki Rxn.- Alkyl Tosylates

$$nDodec-OTs \ + \ \underset{1.2\ \text{equiv}}{9\text{-BBN}-nOct} \xrightarrow[\substack{1.2\ \text{equiv NaOH} \\ \text{dioxane, } 50\ ^\circ C}]{\substack{4\%\ Pd(OAc)_2 \\ 16\%\ \text{trialkyl phosphane}}} nDodec-nOct$$

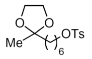
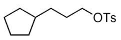
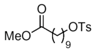
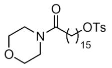
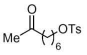
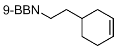
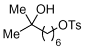
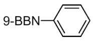
for PCy_3: 46% yield

	R =		
	*i*Pr	Et	Me
PCy_2R	44%	70%	48%
$PtBu_2R$	<2%	<2%	**78%**

- Can be run at room temperature with longer reaction times
- Coupling is noteworthy while aryl tosylates are not sutiable substrates for Pd-catalyzed cross-couplings
- Analogues mesylate in entry 1--> 51% yield
- Cannot be coupled with boronic acids

Fu, G.; Netherton, M. *Angew. Chem. Int. Ed.* **2002**, *41(20),* 3910.

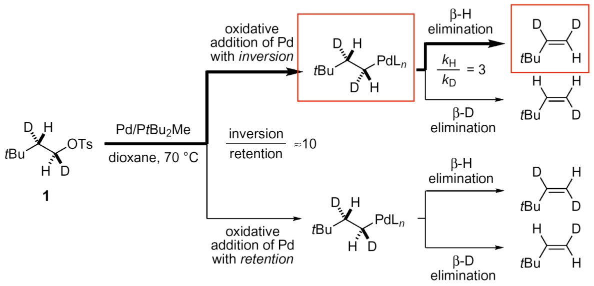
$$R_{alkyl}-OTs \ + \ \underset{1.2\ \text{equiv}}{9\text{-BBN}-R'} \xrightarrow[\substack{1.2\ \text{equiv NaOH} \\ \text{dioxane, } 50\ ^\circ C}]{\substack{4\%\ Pd(OAc)_2 \\ 16\%\ PtBu_2Me}} R_{alkyl}-R'$$

Entry	R_{alkyl}–OTs	9-BBN–R′	Yield [%][a]
1	*n*Dodec–OTs	9-BBN–*n*Oct	80
2		9-BBN–$(CH_2)_{11}$OTES[b]	67
3		9-BBN–$(CH_2)_5$OBn	61[c]
4		9-BBN–$(CH_2)_5$OBn	60
5		9-BBN–*n*Oct	76
6		9-BBN–$(CH_2)_{11}$OTES[b]	55
7	$NC(CH_2)_8$–OTs		64
8			63
9[d]	TsO–$(CH_2)_{12}$–OTs	9-BBN–*n*Oct	73

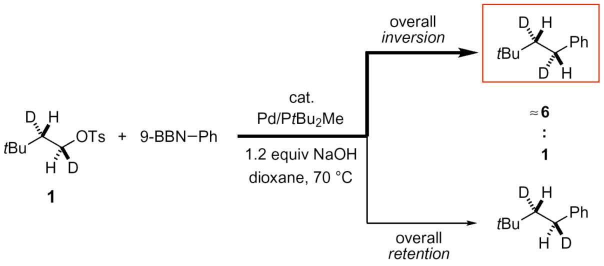
[a] Yield of isolated product, average of two runs. [b] TES = triethylsilyl. [c] Isolated as 8-cyclopentyl-octan-1-ol (after hydrogenolysis). [d] 2.4 equiv of 9-BBN–R′, 8% $Pd(OAc)_2$, 32% $PtBu_2Me$, and 2.4 equiv of NaOH were used.

Suzuki Rxn.- Alkyl Tosylates

Mechanistic Work:
stereochemistry
of process



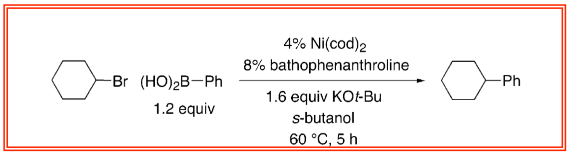
Inversion during
Oxidation addition



Retention during
Reductive elimination

Fu, G.; Netherton, M. *Angew. Chem. Int. Ed.* **2002**, *41(20),* 3910.

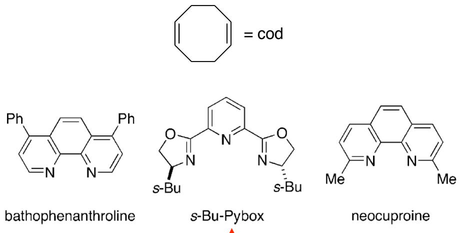
Suzuki Rxn.- Secondary alkyl bromides and iodides



"standard" conditions

entry	deviation from the "standard" conditions[b]	yield (%)[a]
1	none	91
2	Ni(acac)$_2$ [instead of Ni(cod)$_2$]	24
3	NiBr$_2$ [instead of Ni(cod)$_2$]	<3
4	Pd(OAc)$_2$ or Pd$_2$(dba)$_3$ [instead of Ni(cod)$_2$]	<3
5	*s*-Bu-Pybox [instead of BP]	<3
6	PPh$_3$ or P(*t*-Bu)$_2$Me [instead of BP]	<3
7	1,3-bis(1-adamantyl)imidazol-2-ylidene [instead of BP]	<3
8	1,10-phenanthroline [instead of BP]	65
9	neocuproine [instead of BP]	<3
10	bpy [instead of BP]	43
11	4,4'-dimethoxy-2,2'-bipyridine [instead of BP]	57
12	4% bathophenanthroline [instead of 8%]	49
13	no bathophenanthroline	<3
14	KOEt [instead of KO*t*-Bu]	83
15	r.t.	8
16	2% Ni(cod)$_2$, 4% BP [instead of 4% Ni(cod)$_2$, 8% BP]	76

[a] Yield according to GC, versus a calibrated internal standard (average of two runs). [b] BP = bathophenanthroline.



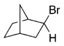
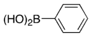
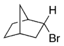
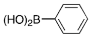
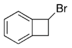
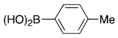
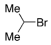
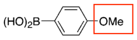
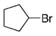
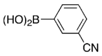
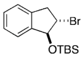
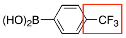
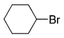
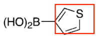
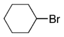
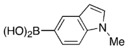
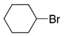
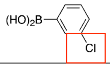
Used in 2003 in the Negishi reaction of secondary halides

Fu, G.; Zhou, *J. Am. Chem. Soc.* **2004**, *126*, 1340.

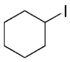
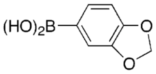
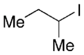
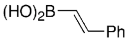
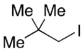
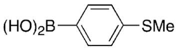
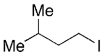
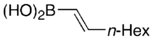
Suzuki Rxn.- Secondary alkyl bromides and iodides

$$R_{alkyl}-X \quad (HO)_2B-R \xrightarrow[\substack{1.6\ \text{equiv KO}t\text{-Bu} \\ s\text{-butanol} \\ 60\ °C}]{\substack{4\%\ \text{Ni(cod)}_2 \\ 8\%\ \text{bathophenanthroline}}} R_{alkyl}-R$$

X = Br, I   1.2 equiv

entry	R_{alkyl}—Br	$(HO)_2B$—R	yield (%)
1			74[a]
2			71[a]
3			90
4			68
5			44
6			63[b]
7			63
8			67
9			75

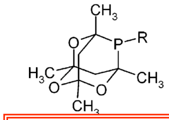
[a] The exo product is formed. [b] The trans product is formed.

entry	R_{alkyl}—I	$(HO)_2B$—R	yield (%)
1			62
2			65
3			75
4			63

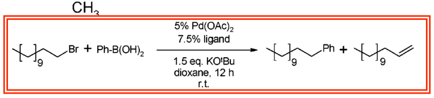
- 1° and 3° alkyl bromides, alkyl chlorides, 3° alkyl iodides, alkylboronic acids, and ortho substituted arylboronic acids are not suitable substrates.

Fu, G.; Zhou, *J. Am. Chem. Soc.* **2004**, *126*, 1340.

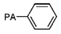
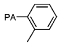
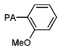
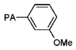
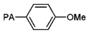
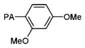
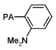
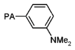
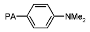
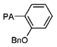
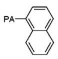
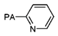
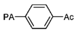
Library Synthesis



1: R = H
2: R = Ph



"One size fits all ligand"

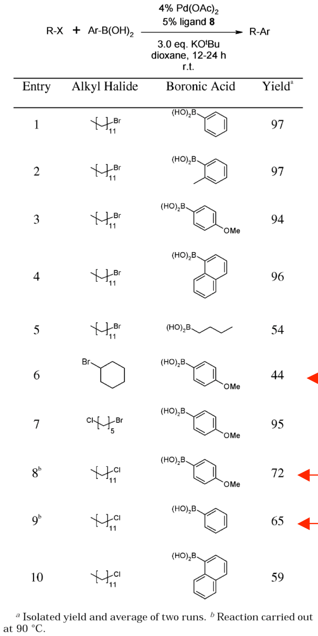
Ligand[a]	Yield (%)[b]	
	Coupled Product	Elimination
2 	5	23
3 	6	17
4 PA—$C_{14}H_{29}$	2	7
5 	71	15
6 	34	5
7 	64	26
8 	96	4
9 	40	33
10 	23	45
11 	51	17
12 	34	37
13 	44	21
14 	6	23
15 	3	45

[a] PA = phosphaadamantane. [b] Percent coupled product and percent elimination product determined by GC/MS.

- Air stable, crystalline, easily prepared and handled

Capretta, A. *et al. J. Org. Chem.* **2004**, *69*, 7635.

Library Synthesis



Entry	Alkyl Halide	Boronic Acid	Yield[a]
1			97
2			97
3			94
4			96
5			54
6			44
7			95
8[b]			72
9[b]			65
10			59

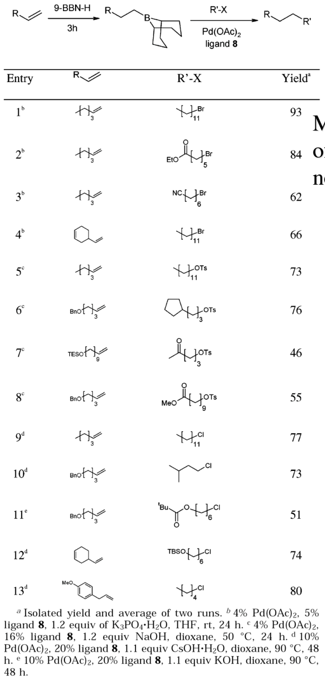
[a] Isolated yield and average of two runs. [b] Reaction carried out at 90 °C.

Capretta, A. *et al. J. Org. Chem.* **2004**, *69*, 7635.

- Dioxane- best solvent to minimize elimination product

Rapid β-H elimination

Elevated temperatures, 90 °C

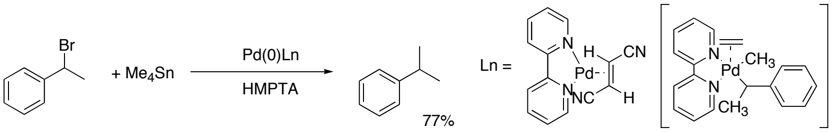


Entry		R'-X	Yield[a]
1[b]			93
2[b]			84
3[b]			62
4[b]			66
5[c]			73
6[c]			76
7[c]			46
8[c]			55
9[d]			77
10[d]			73
11[e]			51
12[d]			74
13[d]			80

[a] Isolated yield and average of two runs. [b] 4% $Pd(OAc)_2$, 5% ligand **8**, 1.2 equiv of $K_3PO_4 \cdot H_2O$, THF, rt, 24 h. [c] 4% $Pd(OAc)_2$, 16% ligand **8**, 1.2 equiv NaOH, dioxane, 50 °C, 24 h. [d] 10% $Pd(OAc)_2$, 20% ligand **8**, 1.1 equiv $CsOH \cdot H_2O$, dioxane, 90 °C, 48 h. [e] 10% $Pd(OAc)_2$, 20% ligand **8**, 1.1 equiv KOH, dioxane, 90 °C, 48 h.

Manipulation of bases necessary

Stille Rxn.-Earlier Work



Sustmann, R.; Lau, J.; Zipp, M. *Tetrahedron Lett.* **1986,** *27*, 5207.

$$R{-}I \xrightarrow[\text{cat. } Pd(PPh_3)_4 \text{ (10 mol\%)} \text{, benzene, 120 C, 16 h}]{Ph{-}C{\equiv}C{-}SnBu_3 \text{ (3.0 equiv.)}} R{-}C{\equiv}C{-}Ph$$

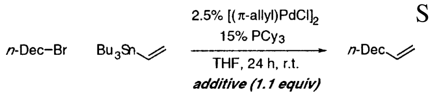
R = C_6H_{13}-CF_2-$(CH_2)_3$- 33%
C_7H_{15}-CF_2-$(CH_2)_2$- 36%

Mioskowski, C.; Bhatt, R.K.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1992,** *33*, 4885.

All either activated towards oxidative addition or stabalized against β-H elimination

Stille Rxn.

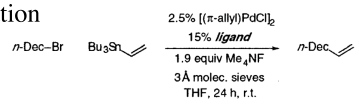
- 1976



Slow transmetalation

entry	additive	yield (%)[a]
1	none	<2
2	$N(i\text{-}Pr)_2Et$	<2
3	$CsOH{\cdot}H_2O$	7
4	NaOMe	4
5	KF	<2
6	CsF	<2
7	$Bu_4NF{\cdot}3H_2O$	32
8	Me_4NF (1.9 equiv), 3 Å molec. sieves	73

[a] Determined by GC versus a calibrated internal standard (average of two runs).

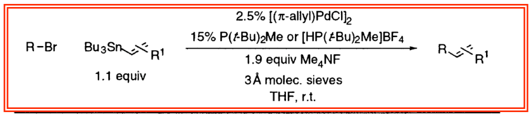


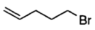
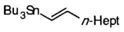
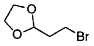
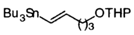
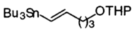
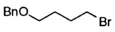
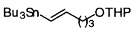
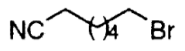
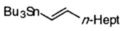
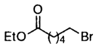
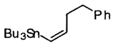
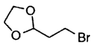
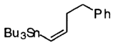
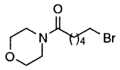
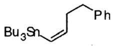
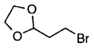
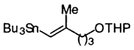
entry	ligand	yield (%)[a]
1	PCy_3	73
2	PCy_2Et	17
3	PCy_2Me	<2
4	$PCy_2(t\text{-}Bu)$	9
5	$P(t\text{-}Bu)_3$	<2
6	$P(t\text{-}Bu)_2Et$	<2
7	$\mathbf{P(}t\text{-}\mathbf{Bu)_2Me}$	**86** ⟸
8	$P(OPh)_3$	<2
9	PPh_3	<2
10	$P(o\text{-}tol)_3$	<2
11	P(2-furyl)$_3$	<2
12	$AsPh_3$	<2
13	IMesHCl[b]	<2

[a] Determined by GC versus a calibrated internal standard (average of two runs). [b] 1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride.

Fu, G.; Menzel K. *J. Am. Chem. Soc.* **2003**, *125*, 3718.

Stille Rxn.



entry	R-Br	tin reagent	yield (%)[a] P(t-Bu)$_2$Me	yield (%)[a] [HP(t-Bu)$_2$Me]BF$_4$
1			96	92
2			71	70
3			62	64
4			60	66
5			59	59
6			74	77
7			58	65
8			55	53
9			55	53

[a] Isolated yield, average of two runs.

- Use of $[HP(t\text{-}Bu)_2Me]BF_4$ shows comparable yields.
- Allyl-, aryl-, alkynyltin reagents, and hindered alkyl bromides are not reactive under theses conditions.

Fu, G.; Menzel K. *J. Am. Chem. Soc.* **2003**, *125*, 3718.

Improved Stille Rxn.

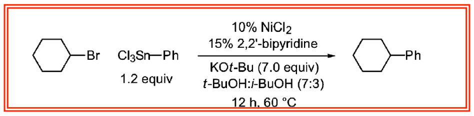
Problem:

- toxicity of organotin compounds
- seperation of Sn-byproduct from coupling adduct
  - Polymer supported Sn reagents
  - Fluorous Sn reagents
  - Catalytic hydrostannation/stille reactions

Solution:

- an organotin reagent that does not generate R_3SnX--> monoorganotin compounds

Improved Stille Rxn.-2° alkyl bromides



"standard conditions"

entry	variation from the "standard conditions"	yield[a] (%)
1	none	83
2	no $NiCl_2$	<5
3	10% $Pd(OAc)_2$ or $Pd_2(dba)_3$ [instead of $NiCl_2$]	<5
4	10% $Ni(cod)_2$, $NiBr_2$, or $NiBr_2$•diglyme [instead of $NiCl_2$]	82−86
5	no 2,2′-bipyridine	<5
6	15% bathophenanthroline [instead of 2,2′-bipyridine]	33
7	no KO*t*-Bu	<5
8	5.0 equiv of KO*t*-Bu [instead of 7.0 equiv]	55
9	*i*-BuOH [instead of *t*-BuOH/*i*-BuOH]	76
10	*t*-BuOH [instead of *t*-BuOH/*i*-BuOH]	<5
11	KO*i*-Bu in *i*-BuOH [instead of KO*t*-Bu in *t*-BuOH/*i*-BuOH]	61
12	5% $NiCl_2$, 7.5% 2,2′-bipyridine [instead of 10% $NiCl_2$, 15% 2,2′-bipyridine]	69
13	room temperature [instead of 60 °C]	<5

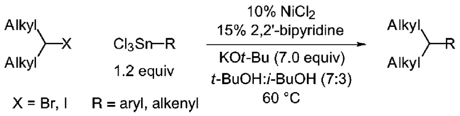
[a] Determined by GC analysis versus a calibrated internal standard (average of two experiments).

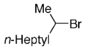
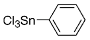
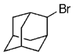
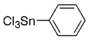
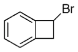
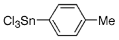
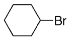
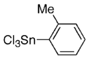
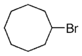
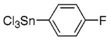
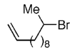
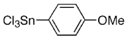
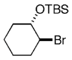
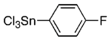
Air stable
less expensive

Role of KOt-Bu maybe to generate a hypervalent tin species which would undergo efficient transmetalation.

Fu, G.;Powell, D.; Maki, Toshide. *Am. Chem. Soc*. **2005**, *127*, 510.

Improved Stille Rxn.-2° alkyl bromides



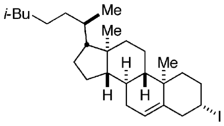
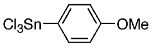
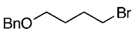
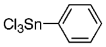
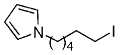
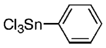
entry	$R_{alkyl}–Br$	$Cl_3Sn–R$	yield (%)[a]
1			72
2			74
3			83
4			47
5			67
6			68
7			48[b]

[a] Isolated yield (average of two experiments). [b] Catalyst: 20% $NiCl_2$/30% 2,2′-bipyridine. The unpurified product was a 96:4 *trans*/*cis* mixture. The reported yield is for the diastereomerically pure trans isomer.

- 2° alkyl tosylates and chlorides are unreactive
- Functional groups on the alkyl halide diminsh reactivity
- Moisture sensitive
- After chromatography less than 5 ppm of Sn contamination

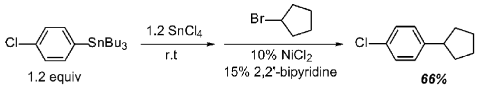
Fu, G.;Powell, D.; Maki, T. *J. Am. Chem. Soc*. **2005**, *127*, 510.

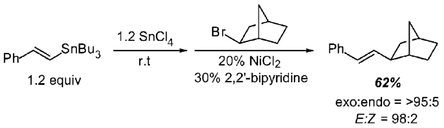
Improved Stille Rxn.-2°alkyl bromides

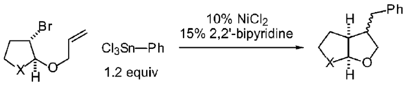
entry	$R_{alkyl}–X$	$Cl_3Sn–R$	yield (%)[a]
1			55[b]
2			61
3			62

[a] Isolated yield (average of two experiments). [b] Only the 3*S* isomer is observed.

Commercially available alkylstannanes---> trichlorotin







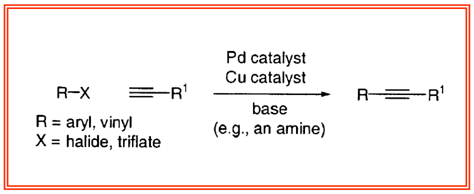
(4)

1, X = CH_2
2, X = O

3, X = CH_2: ***67%*** (2:1 endo:exo)
4, X = O: ***57%*** (>20:1 endo:exo)

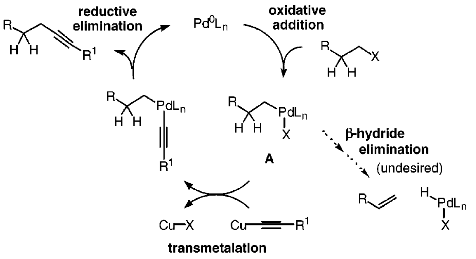
Fu, G.;Powell, D.; Maki, Toshide. *Am. Chem. Soc*. **2005**, *127*, 510.

Sonogashira Rxn - alkyl bromides and iodides



- 1975

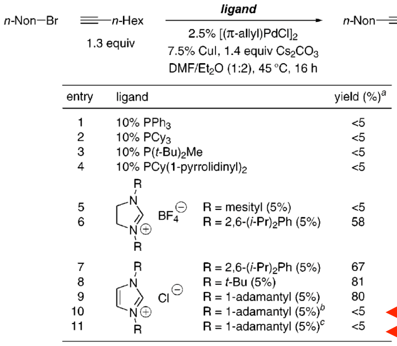
Experimental simplicity
High atom-economy
FG tolerant



- most coupling reactions of alkyl halide with a terminal alkyne require strong base
- catalytic amount of copper to generate copper acetylide

Fu, G.; Eckhardt, M. *J. Am. Chem. Soc.* **2003**, *125*, 13642.

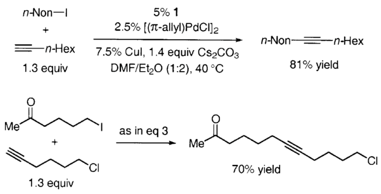
Sonogashira - alkyl bromides and iodides



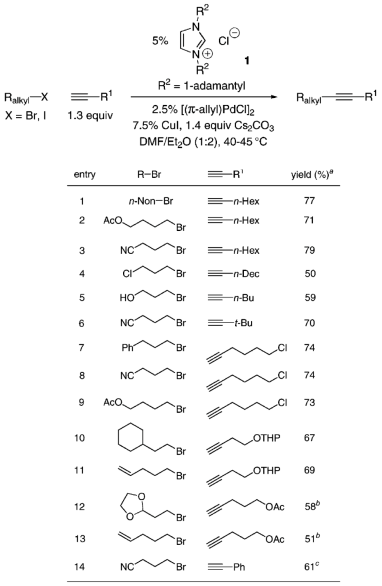
entry	ligand		yield (%)[a]
1	10% PPh_3		<5
2	10% PCy_3		<5
3	10% $P(t\text{-}Bu)_2Me$		<5
4	10% PCy(1-pyrrolidinyl)$_2$		<5
5	BF_4^-	R = mesityl (5%)	<5
6		R = 2,6-(i-Pr)$_2$Ph (5%)	58
7	Cl^-	R = 2,6-(i-Pr)$_2$Ph (5%)	67
8		R = t-Bu (5%)	81
9		R = 1-adamantyl (5%)	80
10		R = 1-adamantyl (5%)[b]	<5
11		R = 1-adamantyl (5%)[c]	<5

w/o Pd
w/o Cu

[a] Determined by GC versus a calibrated internal standard (average of at least two runs). [b] Reaction was conducted without [(π-allyl)PdCl]$_2$. [c] Reaction was conducted without CuI.



Fu, G.; Eckhardt, M. *J. Am. Chem. Soc.* **2003**, *125*, 13642.

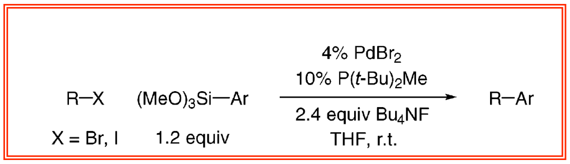


entry	R–Br	≡–R¹	yield (%)[a]
1	n-Non–Br	≡–n-Hex	77
2	AcO Br	≡–n-Hex	71
3	NC Br	≡–n-Hex	79
4	Cl Br	≡–n-Dec	50
5	HO Br	≡–n-Bu	59
6	NC Br	≡–t-Bu	70
7	Ph Br	Cl	74
8	NC Br	Cl	74
9	AcO Br	Cl	73
10	Br	OTHP	67
11	Br	OTHP	69
12	O O Br	OAc	58[b]
13	Br	OAc	51[b]
14	NC Br	≡–Ph	61[c]

[a] Isolated yield, average of two runs. [b] Reaction was conducted at 60 °C. [c] 7.5% [(π-allyl)PdCl]$_2$, 22.5% CuI, and 15% ligand were employed.

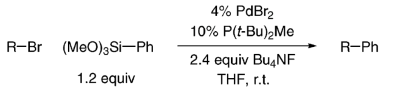
1st example of a nonphosphine-based palladium catalyst for cross-coupling unactivated alkyl electrophiles

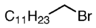
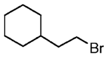
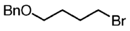
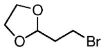
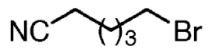
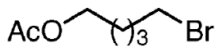
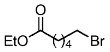
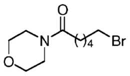
Hiyama



- Organosilicon compounds are attractive due to their ease of handling and low toxicity.
- 1st. example of Hiyama cross-coupling of unactivated alkyl electrophiles.
- Absence of PdBr$_2$ or P(t-Bu)$_2$-no product observed
- Increasing or decreasing the steric demand of the trialkylphosphine shows a substantial drop in yield.

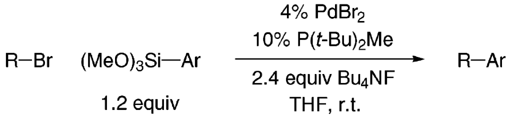
Fu, G.; Lee, J. *J. Am. Chem. Soc.* **2003**, *125*, 5616.

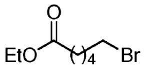
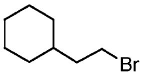


entry	R–Br	yield (%)[a]	
		P(t-Bu)$_2$Me	[HP(t-Bu)$_2$Me]BF$_4$
1		75	88
2		81	85
3		68	46
4		71	69
5		70	47
6		65	42
7		79	66
8		73	66

[a] Isolated yield, average of two runs.

Hiyama-arylsilanes

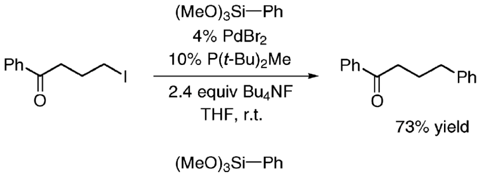


entry	R–Br	Ar	yield (%)[a]
1		*p*-anisyl	66
2		*p*-fluorophenyl	55
3		*o*-tolyl	59
4		2-naphthyl	67
5		*p*-anisyl	69
6		*p*-fluorophenyl	36
7		*o*-tolyl	76
8		2-naphthyl	70
9		*p*-anisyl	82
10		*p*-fluorophenyl	50
11		*o*-tolyl	72
12		2-naphthyl	84

[a] Isolated yield, average of two runs.

- e- poor arylsilanes are the least suitable reaction partners.

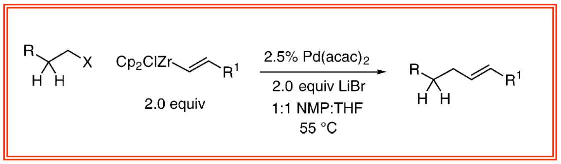
- Conditions are not effective for alkyl chlorides or tosylates and ally- or vinyl-silanes



73% yield

Fu, G.; Lee, J. *J. Am. Chem. Soc.* **2003**, *125*, 5616.

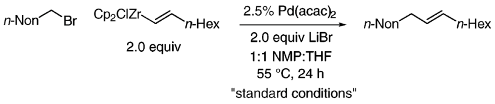
Negishi Reaction of Organozirconium Reagents



- 1977

- “ligandless” palladium complexes - no phosphine present
  - Cost, simplicity, and ease of purification

- If the alkenylzirconium reagent is replaced with a zinc reagent,essentially no cross-coupling is observed. (<2%)

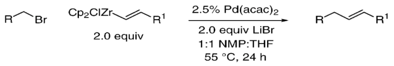


entry	change from the "standard conditions"	yield (%)[a]
1	none	99
2	PdBr$_2$	100
3	Pd$_2$(dba)$_3$	100
4	NiBr$_2$	57
5	Ni(cod)$_2$	62
6	no Pd(acac)$_2$	0
7	LiI	100
8	no LiBr	20
9	room temp	14
10	1.0% Pd(acac)$_2$	80

[a] Yield according to GC, versus a calibrated internal standard (average of two runs).

Fu, G.; Wiskur, S.; Korte, A. *J. Am. Chem. Soc*. **2004**, *126*, 82.

Negishi Reaction of Organozirconium Reagents



entry	alkyl bromide	zirconium reagent	yield (%)
1	EtO O ( )4 Br	Cp$_2$ClZr Ph	99
2	EtO O ( )4 Br	Cp$_2$ClZr t-Bu	86
3	EtO O ( )4 Br	Cp$_2$ClZr OEt	96
4	EtO O ( )4 Br	Cp$_2$ClZr OTHP	72
5	EtO O ( )4 Br	Cp$_2$ClZr OTBDPS	99
6	BnO Br	Cp$_2$ClZr OTHP	73[b]
7	BnO Br	Cp$_2$ClZr n-Hex	82
8	BnO Br	Cp$_2$ClZr Ph	97
9	NC Br	Cp$_2$ClZr Ph	68
10	O N O ( )4 Br	Cp$_2$ClZr Ph	77
11	THPO Br	Cp$_2$ClZr Ph	77
12	Br	Cp$_2$ClZr Ph	74
13	Br	Cp$_2$ClZr Ph	60[b]
14	EtO O ( )4 Br	Cp$_2$ClZr Et Et	85
15	EtO O ( )4 Br	Cp$_2$ClZr t-Bu Me	76[c]

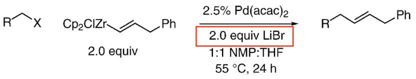
[a] All yields are isolated yields (average of two runs). [b] 5% Pd(acac)$_2$ was used. [c] 5% Pd(acac)$_2$ was used. Reaction time: 48 h.

Fu, G.; Wiskur, S.; Korte, A. *J. Am. Chem. Soc*. **2004**, *126*, 82.

- 2° alkyl bromides are not suitable substrates

- Conditions also effective for coupling of arylbromides

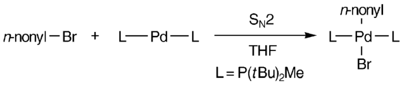
- Entry 1-under microwave condition(100 °C, 15 min, 30W) ---> 94% yield



entry	alkyl halide	yield (%)
1	EtO O ( )4 I	82
2	BnO OTs	83
3	BnO Cl	46

[a] All yields are isolated yields (average of two runs).

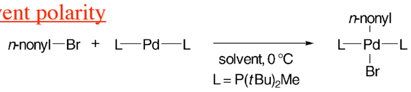
Rate of Oxidative Addition



$$n\text{-nonyl}{-}\mathrm{Br} + \mathrm{L{-}Pd{-}L} \xrightarrow[\text{THF}\ \ \mathrm{L = P(}t\mathrm{Bu)_2Me}]{\mathrm{S_N2}} \mathrm{L{-}Pd(}n\text{-nonyl}\mathrm{)(Br){-}L}$$

ΔG = 20.8 kcal/mol; ΔH = 2.4 kcal/mol; ΔS = -63 eu.

Solvent polarity

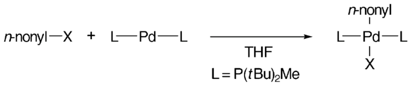


$$n\text{-nonyl}{-}\mathrm{Br} + \mathrm{L{-}Pd{-}L} \xrightarrow[\text{solvent, 0 °C}\ \ \mathrm{L = P(}t\mathrm{Bu)_2Me}]{} \mathrm{L{-}Pd(}n\text{-nonyl}\mathrm{)(Br){-}L}$$

Entry	Solvent	Polarity	$\Delta G^{\ddagger}$ [kcal mol^{-1}]
1	hexane	0.68	> 23.0[b]
2	toluene	1.66	20.0
3	THF	2.08	19.5
4	*tert*-amyl alcohol	2.46[c]	18.1
5	NMP[d]	2.62	18.0
6	DMF[e]	2.80	17.8

[a] All data are the average of two runs. [b] No reaction at 0–60 °C. $\Delta G^{\ddagger}$ was calculated for 60 °C. [c] Value for *tert*-butanol. [d] NMP = *N*-methylpyrrolidinone. [d] DMF = dimethylformamide.

Leaving group ability



$$n\text{-nonyl}{-}\mathrm{X} + \mathrm{L{-}Pd{-}L} \xrightarrow[\text{THF}\ \ \mathrm{L = P(}t\mathrm{Bu)_2Me}]{} \mathrm{L{-}Pd(}n\text{-nonyl}\mathrm{)(X){-}L}$$

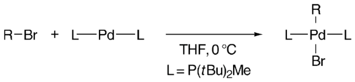
Entry	X	$t_{1/2}$
1	I	2.2 h at −60 °C
2	Br	2.3 h at 0 °C
3	Cl	2.0 d at 60 °C
4	F	< 2% reaction after 43 h at 60 °C
5	OTs[b]	10.4 h at 40 °C

[a] All data are the average of two runs. [b] Ts = toluenesulfonyl.

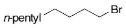
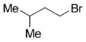
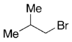
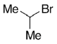
Fu, G.; Hills, I.; Netherton, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749.

Rate of Oxidative Addition

Steric demand

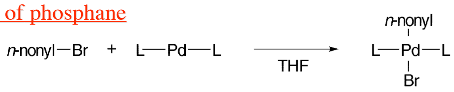


$$\mathrm{R{-}Br} + \mathrm{L{-}Pd{-}L} \xrightarrow[\text{THF, 0 °C}\ \ \mathrm{L = P(}t\mathrm{Bu)_2Me}]{} \mathrm{L{-}Pd(R)(Br){-}L}$$

Entry	R–Br	k_{rel}	$\Delta G^{\ddagger}$ [kcal mol^{-1}]
1		1.0	19.5
2		0.19	20.3
3		0.054	21.0
4		< 0.0001	> 24.0[b]

[a] All data are the average of two runs. [b] Extrapolated from a reaction run at 60 °C.

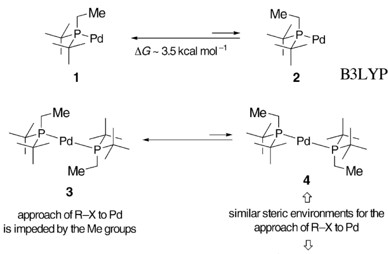
Effect of phosphane



$$n\text{-nonyl}{-}\mathrm{Br} + \mathrm{L{-}Pd{-}L} \xrightarrow[\text{THF}]{} \mathrm{L{-}Pd(}n\text{-nonyl}\mathrm{)(Br){-}L}$$

Entry	L	$\Delta G^{\ddagger}$ [kcal mol^{-1}][b]
1	P(tBu)$_2$Me	19.5 (0 °C)
2	PCy$_3$	20.0 (0 °C)
3	P(tBu)$_2$Et	25.4 (60 °C)
4	P(tBu)$_3$	> 28.4 (60 °C)

[a] All data are the average of two runs. [b] The temperature at which $\Delta G^{\ddagger}$ was measured is noted in parentheses.



B3LYP/LanL2DZ DFT

Fu, G.; Hills, I.; Netherton, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749.

Summary

- Variety of conditions are now available for the Pd cross coupling of alkyl halides and tosylates in Suzuki, Stille, Sonigashira, Hiyama, and Negishi reactions.

- Preliminary mechanistic work sheds light on the unusual reactivity of Pd^0/ trialkylphosphane catalysts.

Future Work

- Sterically hindered alkyl halide substrates

- Introduction of diverse functionality on the alkyl halide substrates

- Further elucidation of precise mechanism

- “one size fits all ligand”