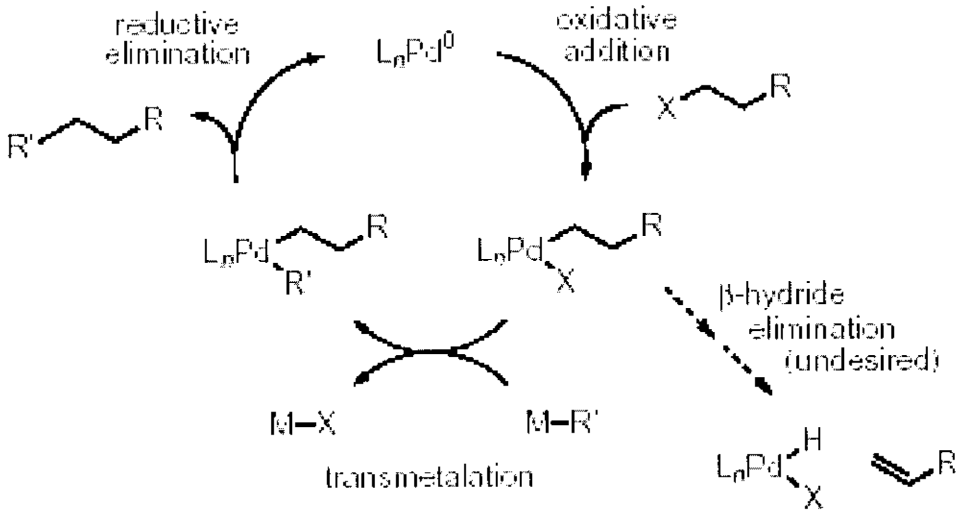
Suzuki Cross-Couplings of Unactivated Secondary Alkyl Bromides and Iodides

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

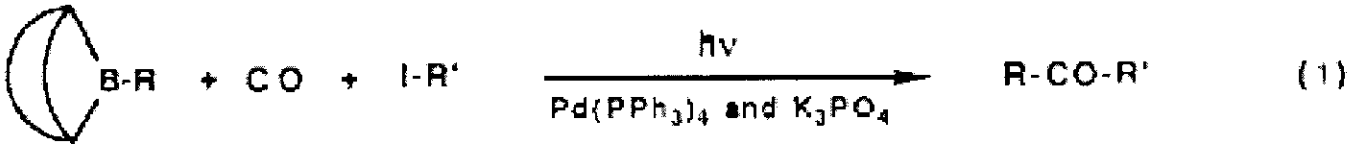
Rob Halter
February 21st, 2004

Perceived Difficulties

- Oxidative addition to sp^3-I bond thought to be slow
- β-elimination presumed to be fast and the dominant pathway if oxidative addition did indeed occur.



First sp³-X Suzuki Type Coupling



$$\text{B-R} + CO + \text{I-R'} \xrightarrow[\text{Pd(PPh}_3)_4 \text{ and } K_3PO_4]{h\nu} \text{R-CO-R'} \quad (1)$$

R=primary, R'= primary, secondary, and tertiary

- 1 atm CO
- Reaction is greatly accelerated by light (24 h vs 52 h)
- Radical formation is thought to be important

$$Pd(PPh_3)_4 + CO \longrightarrow Pd(CO)(PPh_3)_3 \xrightarrow{h\nu} Pd(CO)(PPh_3)_2 \longrightarrow Pd^{i}\text{-}X + R^{\cdot} \longrightarrow X\text{-}Pd\text{-}R$$

Ishiyama, T., Miyaura, N., Suzuki, A. *Tetrahedron Lett.* **1991**, *32*, 6923c

Scope of Reaction

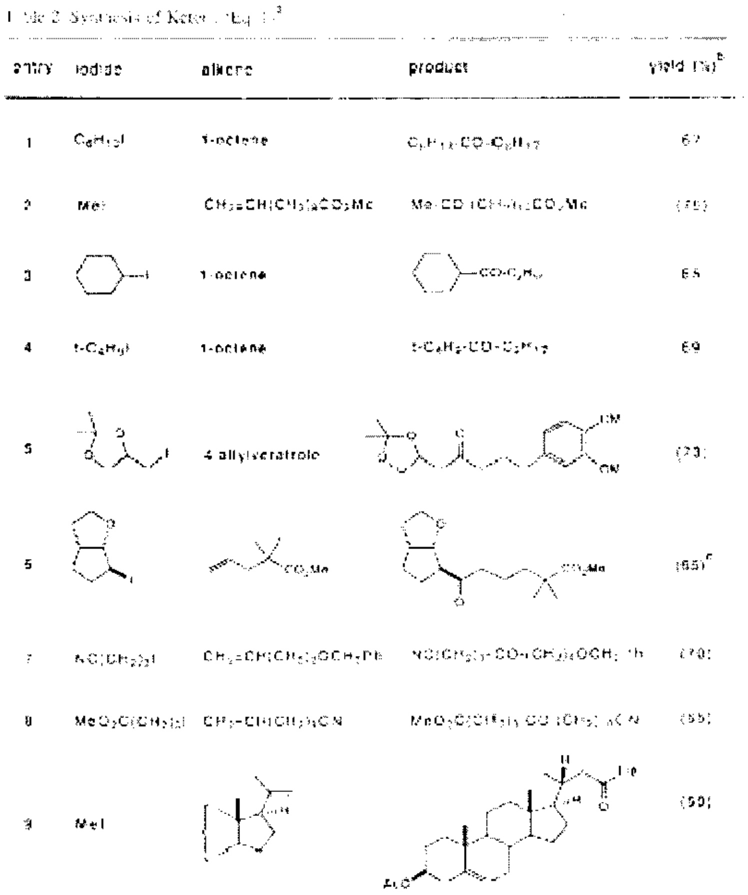


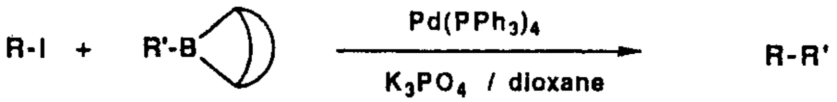
Table 2. Synthesis of Ketones (Eq. 1)^a

entry	iodide	alkene	product	yield (%)^b
1	$C_8H_{17}I$	1-octene	C_8H_{17}-CO-C_8H_{17}	67
2	MeI	$CH_2=CH(CH_2)_8CO_2Me$	Me-CO-$(CH_2)_{10}CO_2Me$	(75)
3		1-octene	—CO-C_8H_{17}	65
4	t-C_4H_9I	1-octene	t-C_4H_9-CO-C_8H_{17}	69
5		4-allylveratrole		(73)
6				(65)^c
7	$NC(CH_2)_3I$	$CH_2=CH(CH_2)_3OCH_2Ph$	$NC(CH_2)_3$-CO-$(CH_2)_4OCH_2Ph$	(70)
8	$MeO_2C(CH_2)_3I$	$CH_2=CH(CH_2)_3CN$	$MeO_2C(CH_2)_3$-CO-$(CH_2)_5CN$	(55)
9	MeI			(59)

- Tertiary iodides are activated by electron withdrawing groups (entries 8 & 9)
- Bromides and sp^2 boronates were not attempted
- Only 9-BBN couple, no esters or boronic acids coupled

Ishiyama, T., Miyaura, N., Suzuki, A. *Tetrahedron Lett.* **1991**, *32*, 6923c

First Suzuki Alkyl-Alkyl Cross-Coupling



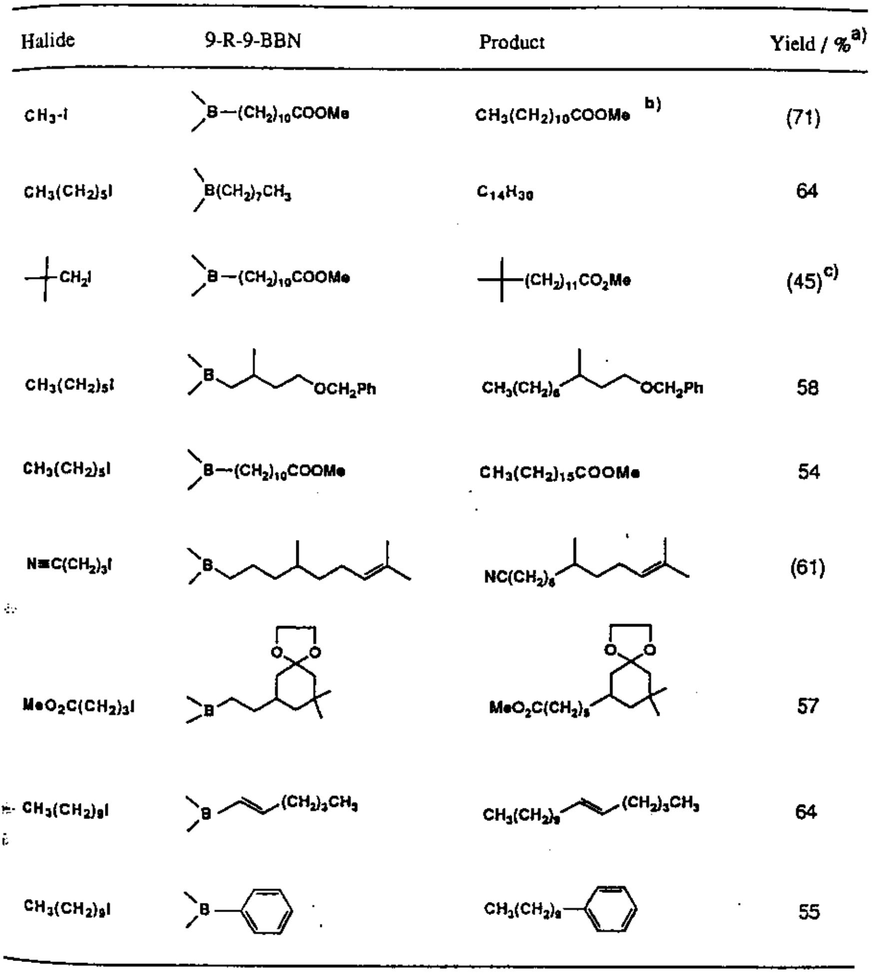
R, R' = alkyl

- Bidentate ligands give low yield of coupling products
    - Thought to slow down the reductive elimination (ie., coupling)
- Oxidative addition was the slow step
- Light does not accelerate the reaction
- Only 9-BBN is successful as a ligand
    - Mg, Zn, Al, Sn, Zr and Hg were tried
    - β-elimination major reaction pathway

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

Scope of Reaction

Table 1. Cross-Coupling Reaction of 9-Alkyl-9-BBN Derivatives with Alkyl Iodides



Halide	9-R-9-BBN	Product	Yield / %[a)]
CH_3-I	B—$(CH_2)_{10}$COOMe	$CH_3(CH_2)_{10}$COOMe [b)]	(71)
$CH_3(CH_2)_5$I	B$(CH_2)_7CH_3$	$C_{14}H_{30}$	64
CH_2I	B—$(CH_2)_{10}$COOMe	$(CH_2)_{11}CO_2$Me	(45)[c)]
$CH_3(CH_2)_5$I	B OCH$_2$Ph	$CH_3(CH_2)_6$ OCH$_2$Ph	58
$CH_3(CH_2)_5$I	B—$(CH_2)_{10}$COOMe	$CH_3(CH_2)_{15}$COOMe	54
N≡C$(CH_2)_3$I	B	NC$(CH_2)_6$	(61)
MeO$_2$C$(CH_2)_3$I	B	MeO$_2$C$(CH_2)_5$	57
$CH_3(CH_2)_9$I	B $(CH_2)_3CH_3$	$CH_3(CH_2)_9$ $(CH_2)_3CH_3$	64
$CH_3(CH_2)_9$I	B	$CH_3(CH_2)_9$	55

- Only primary iodides
- No primary bromides
- Reaction mechanism obviously different from the CO insertion mechanism

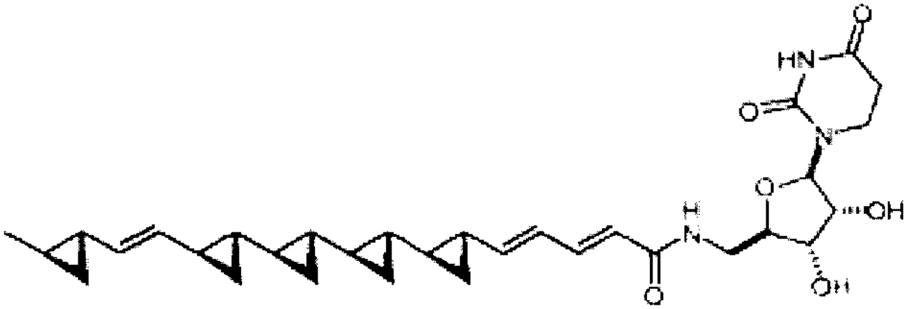
ki, A. *Chem. Lett.*, **1992**, 691.

Coupling to "Secondary" Iodides

- Choice of base very important
  - Best results obtained with Bu_4NCl as phase transfer catalyst in DMF-H_2O

Charette, A. B., Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718-8719

Cyclopropyl Coupling in Total Synthesis



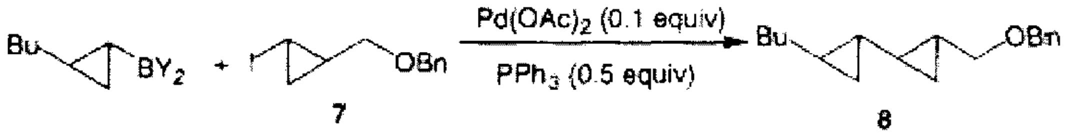
(-)-FR-900848 (1)

(-)-U-106305 (2)

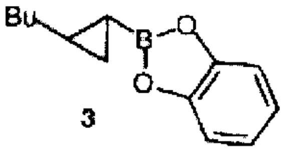
- Wanted to use the coupling they developed for a synthesis of these molecules

Charette, A. B., Freitas-Gil, R. P. D. *Tetrahedron Letters*, **1997**, *38*, 2809

Cyclopropyl Coupling in Total Synthesis



Entry	Y	Conditions	Time (h)	Yield (%)[b]
1	**3**	DMF, H_2O, K_2CO_3, Bu_4NCl	48	---[c]
2	**4**	DMF, H_2O, K_2CO_3, Bu_4NCl	48	---[c]
3	**5**	DMF, H_2O, K_2CO_3, Bu_4NCl	20	---[d]
4	**4**	DME, K_2CO_3, 80 °C	90	---[d]
5	**4**	DME, NaOH[e], 80 °C	90	10
6	**4**	DME, NaOEt[f], 80 °C	90	30
7	**4**	DME, KO*t*-Bu[g], 80 °C	36	65[h]
8	**5**	Toluene, $K_3PO_4 \cdot 3H_2O$, 100 °C	48	---[d]
9	**5**	DME, $K_3PO_4 \cdot 3H_2O$, 80 °C	48	---[d]
10	**3**	DME, KO*t*-Bu[g], 80 °C	90	50
11	**5**	DME, KO*t*-Bu[g], 80 °C	36	69
12	**6**	DME, KO*t*-Bu[g], 80 °C	48	54



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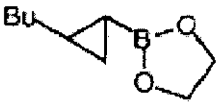

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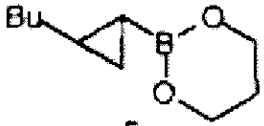

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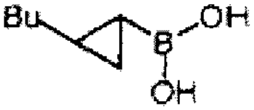
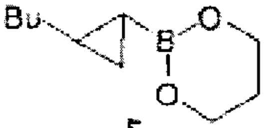
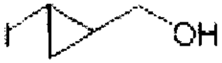


6

- Initial conditions didn't work
- Use of strong base (entry 7) led to good yields
- Size of boronate ester also mattered, **5** giving the best results

Charette, A. B., Freitas-Gil, R. P. D. *Tetrahedron Letters*, **1997**, *38*, 2809

Extension Toward Natural Products

Entry	Boronate ester	Iodocyclopropane	time (h)	Product[a]	Yield (%)[b]
1	 **5**	 **9**	36	 **11**	64
2	 **12**	**7**	48	 **13**	60
3	 **14**	**7**	48	 **15**	71

Charette, A. B., Freitas-Gil, R. P. D. *Tetrahedron Letters*, **1997**, *38*, 2809

Suzuki Couplings of Tosylates

$$R_{alkyl}\text{—OTs} + \underset{\text{1.2 equiv}}{\text{9-BBN—R'}} \xrightarrow[\text{1.2 equiv NaOH, dioxane, 50 °C}]{\text{4\% Pd(OAc)}_2\text{, 16\% P}t\text{Bu}_2\text{Me}} R_{alkyl}\text{—R'} \qquad (1)$$

- Condition previously used for alkyl bromides ineffective
- Reaction is very senstive to phosphine size

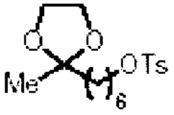
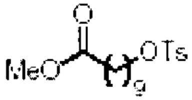
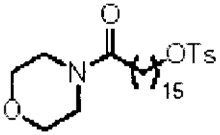
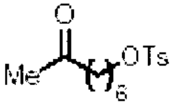
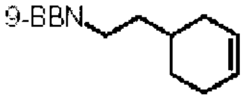
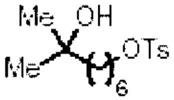
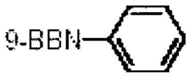
$$n\text{Dodec—OTs} + \underset{\text{1.2 equiv}}{\text{9-BBN—}n\text{Oct}} \xrightarrow[\text{1.2 equiv NaOH, dioxane, 50 °C}]{\text{4\% Pd(OAc)}_2\text{, 16\% trialkyl phosphane}} n\text{Dodec—}n\text{Oct}$$

for PCy_3: 46% yield

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

Netherton, M. R. and Fu, G. C. *Angew. Chem. I.E.* **2002**, *41*, 3910

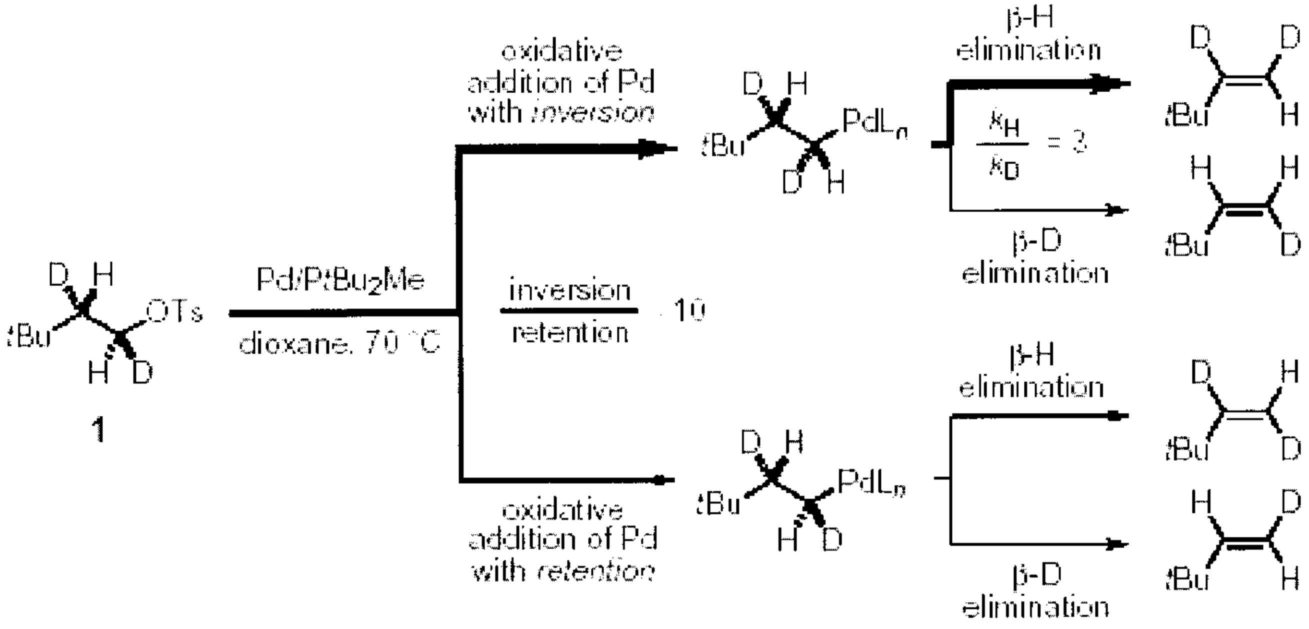
Tosylate Coupling Scope is Good

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–$(CH_2)_4$OBn	61[c]
4		9-BBN–$(CH_2)_4$OBn	60
5		9-BBN–*n*Oct	76
6		9-BBN–$(CH_2)_{11}$OTES[b]	55
7	$NC(CH_2)_6$–OTs		64
8			63
9[d]	TsO–$(CH_2)_{12}$–OTs	9-BBN–*n*Oct	73

- Functionality is tolerated
- Both alkyl and aryl/vinyl boronic esters tolerated
- Do not describe boronic acids in any couplings

Netherton, M. R. and Fu, G. C. *Angew. Chem. I.E.* **2002**, *41*, 3910

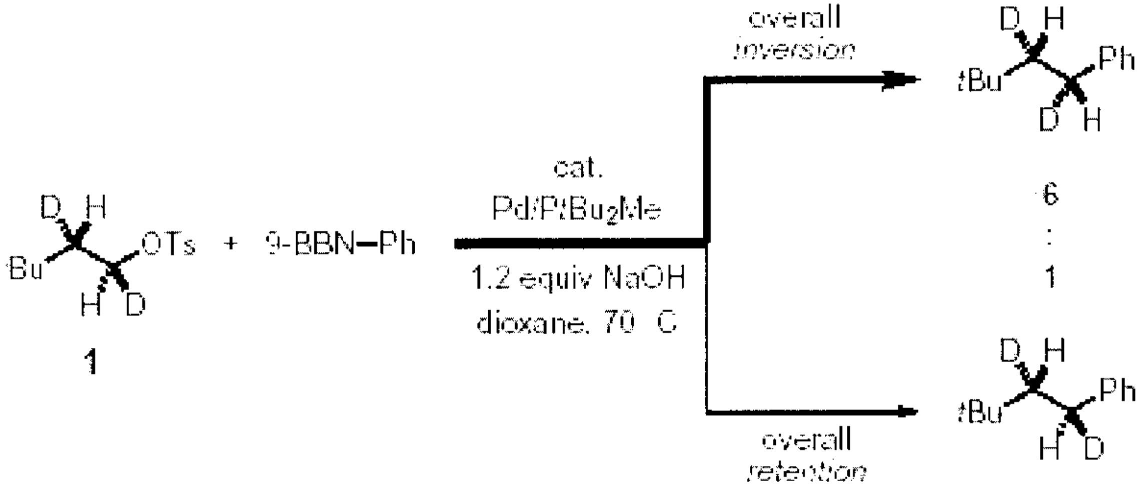
Stereochemistry of Addition



- Ratio not reported, but oxidative addition occurs primarily with retention of configuration.

Netherton, M. R. and Fu, G. C. *Angew. Chem. I.E.* **2002**, *41*, 3910

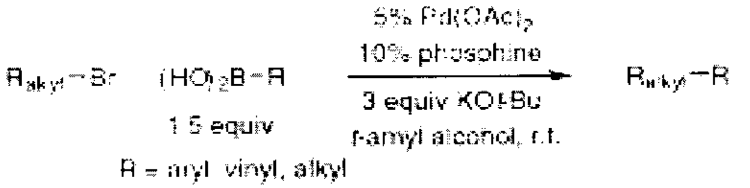
Stereochemistry of Addition



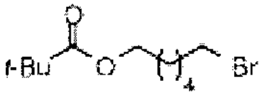
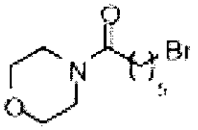
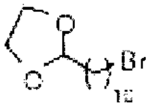
Scheme 4. Examination of the stereochemistry of a Pd/PtBu$_2$Me-catalyzed Suzuki cross-coupling of an alkyl tosylate.

Netherton, M. R. and Fu, G. C. *Angew. Chem. I.E.* **2002**, *41*, 3910

Coupling of Boronic Acids with Alkyl Bromides



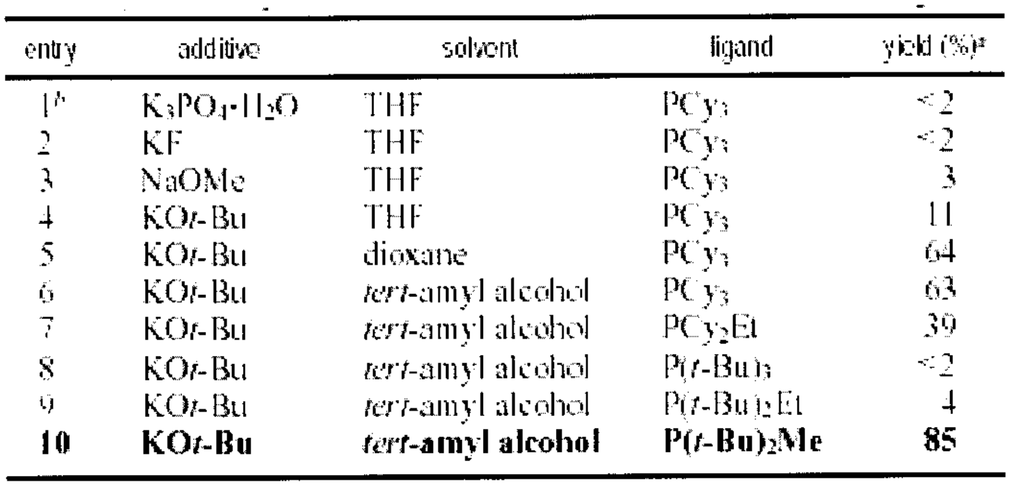
$$R_{alkyl}-Br \quad \underset{\substack{1.5\ equiv \\ R\ =\ aryl,\ vinyl,\ alkyl}}{(HO)_2B-R} \xrightarrow[\substack{3\ equiv\ KOt\text{-}Bu \\ t\text{-}amyl\ alcohol,\ r.t.}]{\substack{5\%\ Pd(OAc)_2 \\ 10\%\ phosphine}} R_{alkyl}-R \qquad (1)$$

entry	$R_{alkyl}-Br$	R	yield (%)[a]	
			$P(t\text{-}Bu)_2Me$	$[HP(t\text{-}Bu)_2Me]BF_4$
1	*n*-Oct–Br	Ph	87	90
2		$4\text{-}(MeS)C_6H_4$	68	66
3	$BnO-(CH_2)_6-Br$	$4\text{-}(MeO)C_6H_4$	85	84
4	$TBSO-(CH_2)_6-Br$	$4\text{-}(F_3C)C_6H_4$	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

- Coupling occurs at room temperature!!
- Good reactivity
- Reacts with boronic acids
- Extremely sensitive to phosphine ligand
- Base, solvent and ligand are different from boronate ester reactions

Kirchhoff, J. K., Netherton, M. R., Hills, I. D., Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662

Sensitivity to Phosphine Ligand

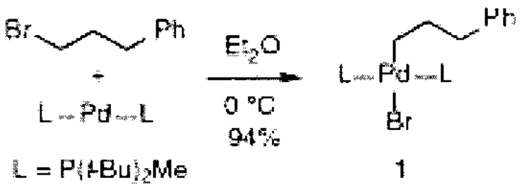


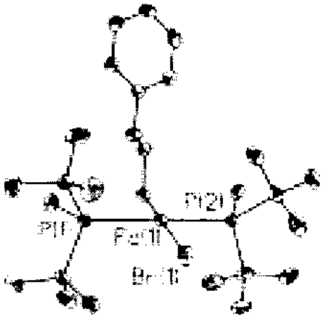
entry	additive	solvent	ligand	yield (%)[a]
1[b]	$K_3PO_4 \cdot H_2O$	THF	PCy_3	<2
2	KF	THF	PCy_3	<2
3	NaOMe	THF	PCy_3	3
4	KO*t*-Bu	THF	PCy_3	11
5	KO*t*-Bu	dioxane	PCy_3	64
6	KO*t*-Bu	*tert*-amyl alcohol	PCy_3	63
7	KO*t*-Bu	*tert*-amyl alcohol	PCy_2Et	39
8	KO*t*-Bu	*tert*-amyl alcohol	$P(t\text{-}Bu)_3$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

- Difference between ethyl and methyl is huge (85 % vs 4 % yield)
- Methyl gives oxidative addition, ethyl primarily give β-elimination

Kirchhoff, J. K., Netherton, M. R., Hills, I. D., Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662

Oxidative Addition is Easy

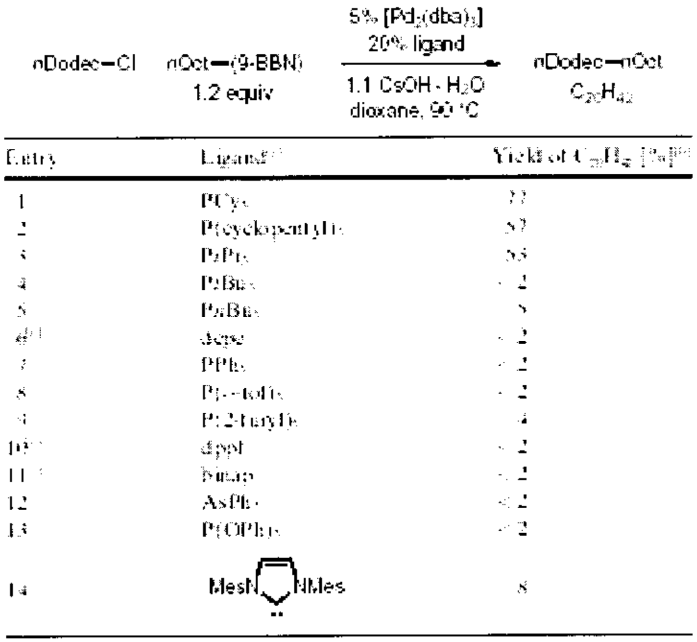




- β-hydride elimination does not occur until heating to 50 ^{0}C
- The addition occurs at 0 ^{o}C

Kirchhoff, J. K., Netherton, M. R., Hills, I. D., Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662

Alkyl Chloride Coupling – Importance of the Ligand



$$\text{nDodec—Cl} \quad \underset{\text{1.2 equiv}}{\text{nOct—(9-BBN)}} \xrightarrow[\text{1.1 CsOH·H}_2\text{O, dioxane, 90 °C}]{\text{5\% [Pd}_2\text{(dba)}_3\text{], 20\% ligand}} \underset{C_{20}H_{42}}{\text{nDodec—nOct}}$$

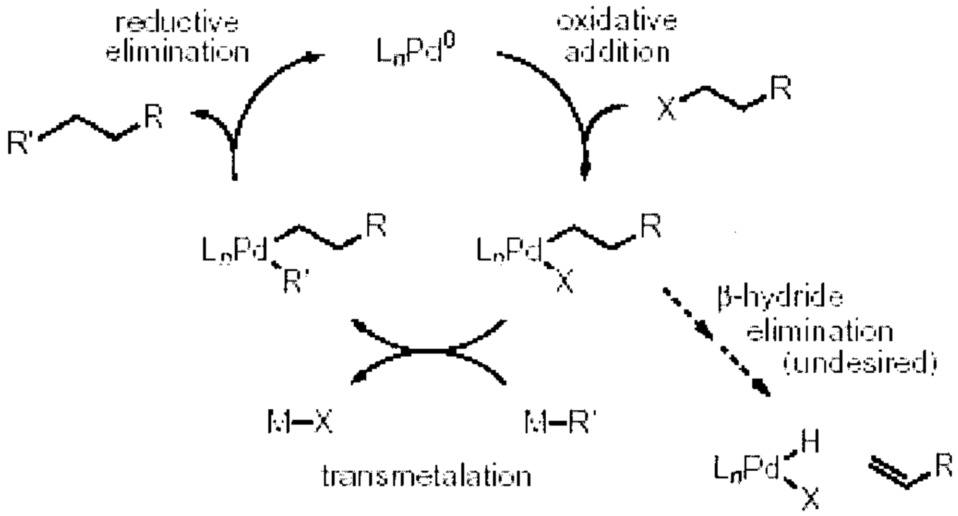
Entry	Ligand[a]	Yield of $C_{20}H_{42}$ [%][b]
1	PCy_3	77
2	$P(cyclopentyl)_3$	57
3	$P(iPr)_3$	53
4	$P(tBu)_3$	< 2
5	$P(nBu)_3$	5
6[c]	dcpe	< 2
7	PPh_3	< 2
8	$P(o\text{-}tol)_3$	< 2
9	$P(2\text{-}furyl)_3$	4
10[c]	dppf	< 2
11[c]	binap	< 2
12	$AsPh_3$	< 2
13	$P(OPh)_3$	< 2
14	MesN NMes	8

- Ligand size is extremely important
- Only mono-dentate ligands effective
- Conditions aren't quite as mild

Kirchhoff, J. H., Dai, C., Fu, G. C. *J. Am. Chem. Soc.* **2002**, *41*, 1945

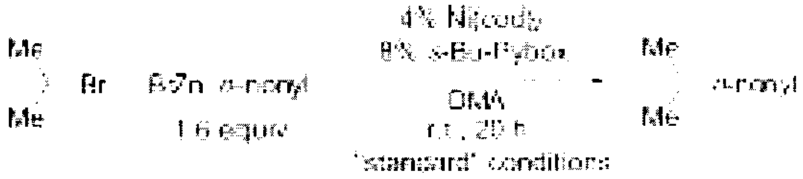
Why Only Monodentate Ligands?

- Reductive elimination requires a free coordination site
- β-elimination does not require a free coordination site
- The reductive elimination must be fast, to compete with β-elimination

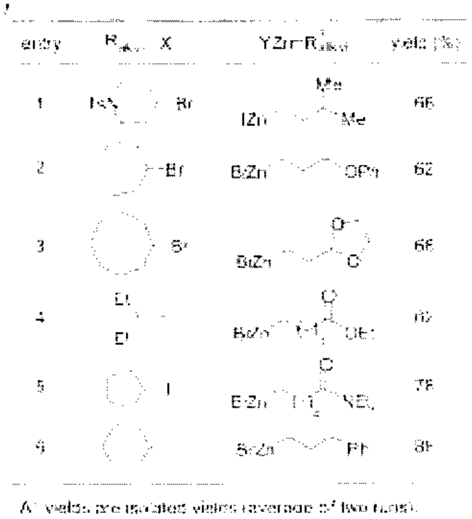


Ozawa, F., Ito, T., Yamamoto, A. *J. Am. Chem. Soc.*, **1980**, *102*, 6457

Negeshi Coupling of Secondary Alkyl Halides

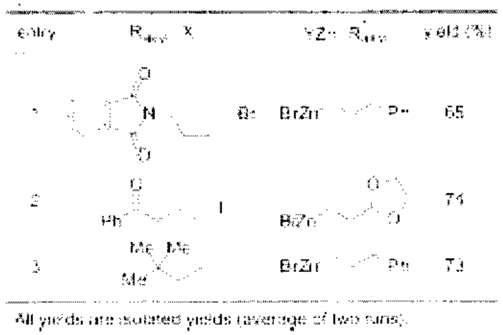


- Of the ligands surveyed, only Pybox ligands gave good yields, and yields were variable depending upon the properties of the ligand itself.
- Reaction also works for alkyl iodides



entry	R_{alkyl}–X	YZn–R'_{alkyl}	yield (%)
1	BocN, Br	IZn, Me, Me	66
2	Br	BrZn, OPh	62
3	Br	BrZn, O, O	68
4	Et, Et	BrZn, O, OEt	62
5	I	BrZn, O, NEt2	78
6		BrZn, Ph	81

All yields are isolated yields (average of two runs).

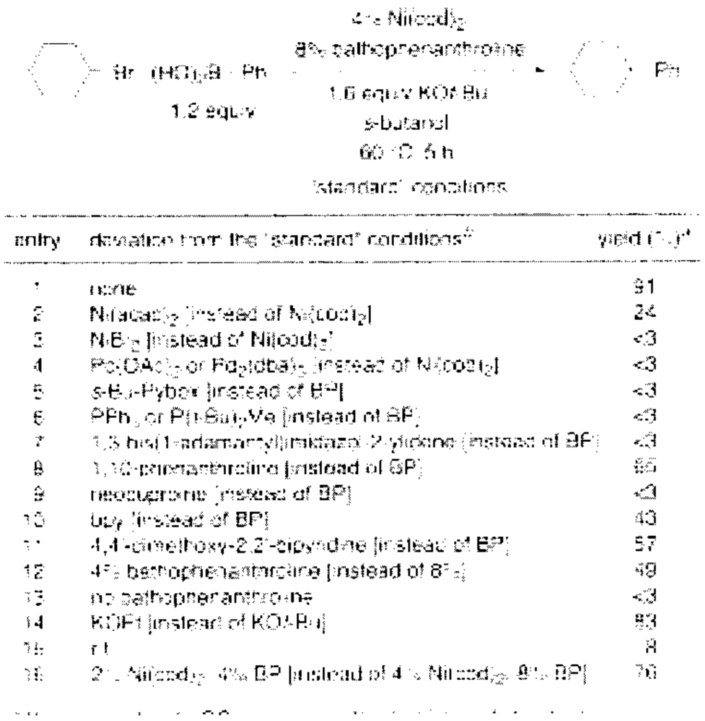


entry	R_{alkyl}–X	YZn–R'_{alkyl}	yield (%)
1	O, N, O, Br	BrZn, Ph	65
2	O, Ph, I	BrZn, O, O	71
3	Me, Me, Me	BrZn, Ph	73

All yields are isolated yields (average of two runs).

Zhou, J., Fu, G. C. *J. Am. Chem. Soc.*, **2003**, *125*, 14726

Suzuki Coupling of Secondary Alkyl Halides



Br + $(HO)_2B-Ph$ (1.2 equiv) → Ph

4% $Ni(cod)_2$
8% bathophenanthroline
1.6 equiv KO*t*-Bu
s-butanol
60 °C, 5 h
"standard" conditions

entry	deviation from the "standard" conditions[a]	yield (%)[b]
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 $P(t\text{-}Bu)_2Me$ [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]	70

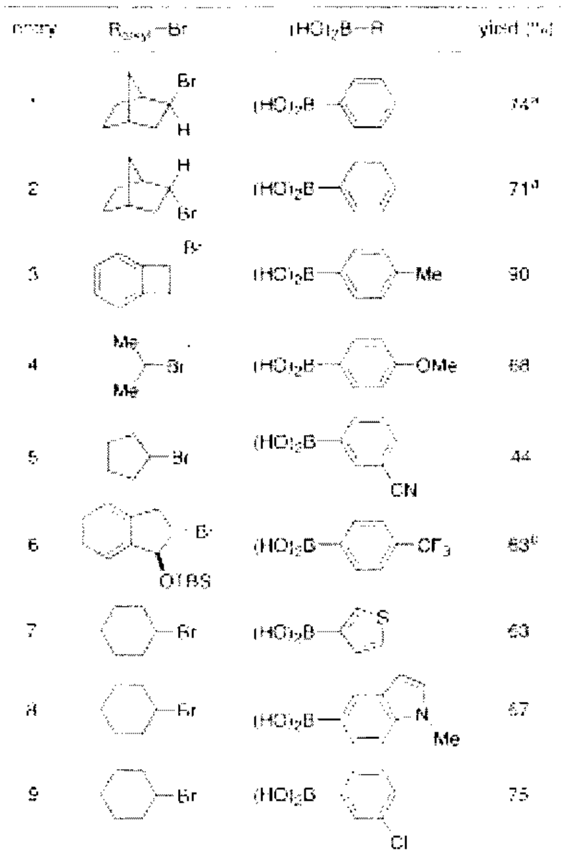
- As in all previous cases, the exact nature and size of the ligand is very important

- Ligands that were successful for the Negeshi coupling do not work here, entry 5.

- Surprisingly, bidentate ligands are necessary here

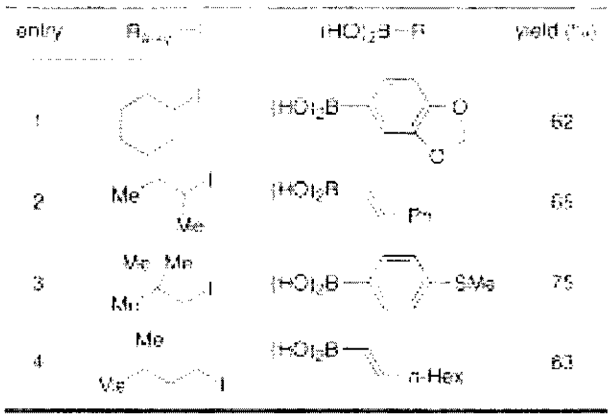
Zhou, J., and Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340

Scope of Reaction



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			66
3			75
4			63

- Reaction does not work with boronate esters
- Only works with secondary alkyl halides
- Does not work with ortho-substituted aryls.
- Does not work with alkyl boronic acids

Future Work

- Improve generality of each system to include both boronic acids and esters
- Improve generality of each system to include both alkyl and aryl boronates
- If possible, make system less dependent upon the exact conditions
- Gain an understanding of the role the phosphine (ligand) in the catalytic cycle
- Do the Ni and Pd catalyzed reactions proceed through the same sort of mechanism?
- Biggest problem: If a key step in a total synthesis you may need to optimize multiple variables in multiple ways to get the desired reaction -- and test reactions/substrates would be of little to no use