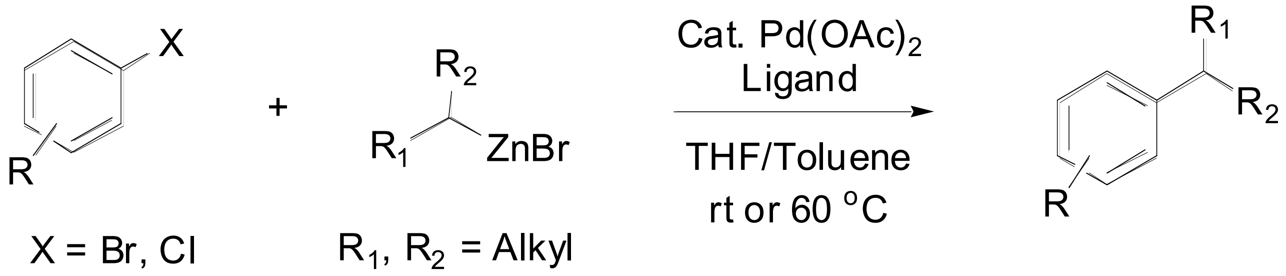
Negishi Coupling of Secondary Alkylzinc Halides with Aryl Bromides and Chlorides



J. Am. Chem. Soc. **2009**, ASAP Article

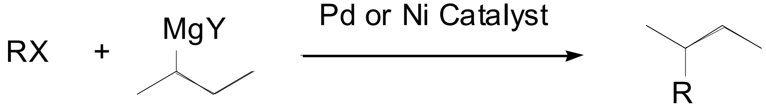
Chong Han and Stephen L. Buchwald

Current Literature: 5/21/09

David Arnold

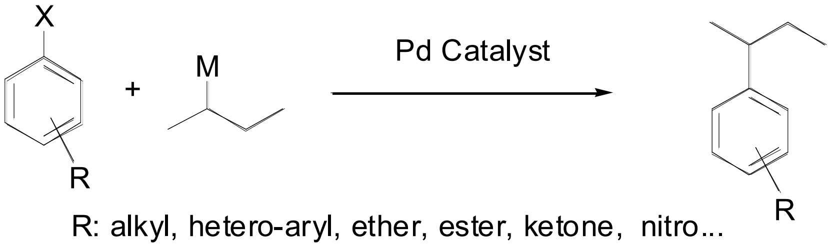
Common Strategies Utilized for the Cross-Coupling of Secondary Alkyl Organometallic Reagents with Aryl Halides

1. Kumada Coupling (1972):



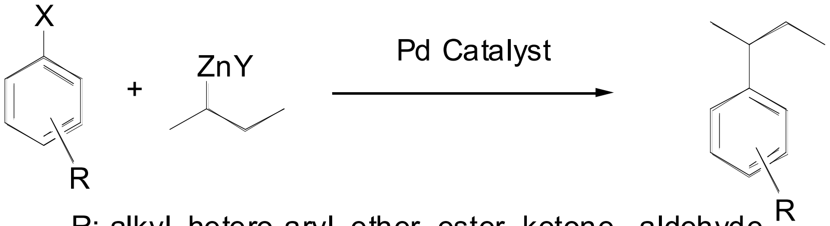
R: aryl, vinyl; X = Cl, Br or I; Y = Cl or Br

2. Suzuki Coupling (2000):



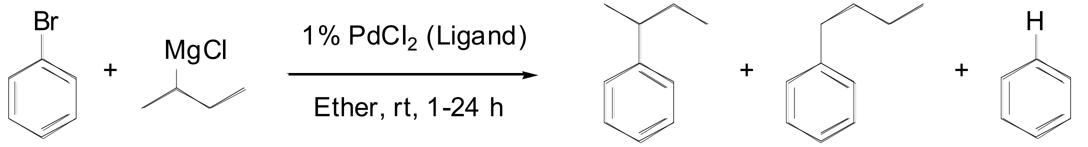
R: alkyl, hetero-aryl, ether, ester, ketone, nitro...
X: Cl, Br or I
M: $-B(OH)_2$, $-B(OR)_2$, $-BF_3K$

3. Negishi Coupling:

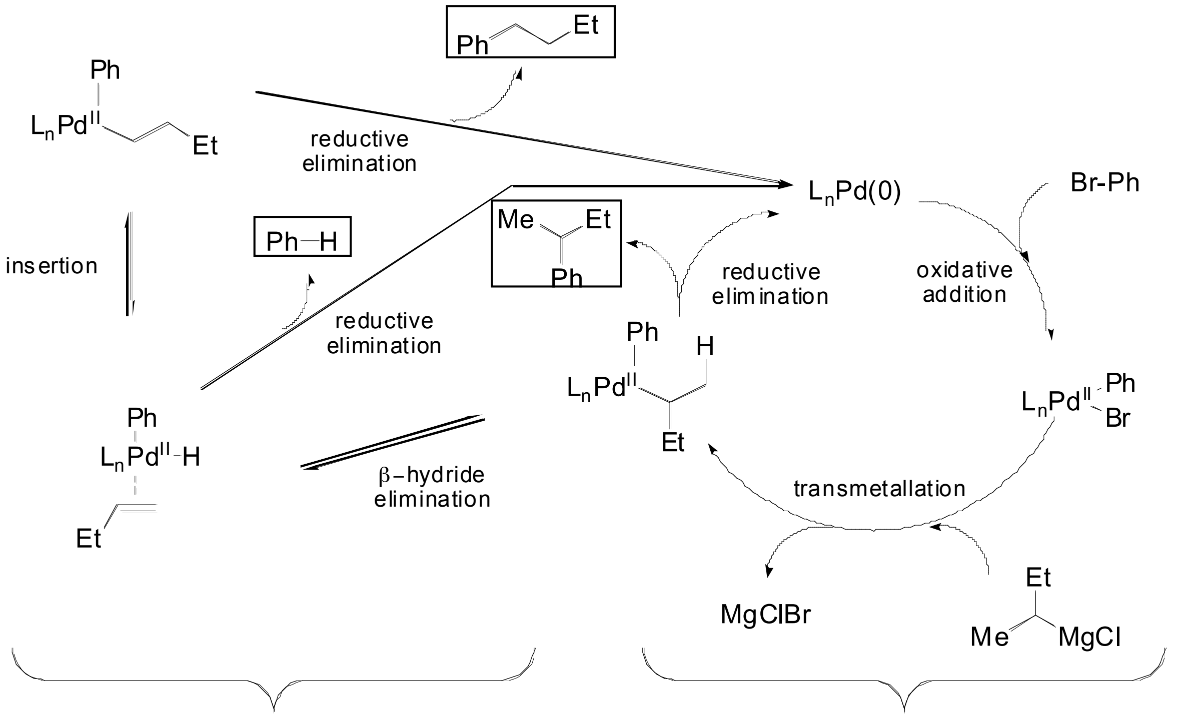


R: alkyl, hetero-aryl, ether, ester, ketone, aldehyde...
X or Y: Cl, Br or I

Pioneering Work by Kumada and Hayshi: Mechanistic Considerations for Kumada / Suzuki / Negishi Couplings



dppf / 1 h	95%	0%	0%
(PPh$_3$)$_2$ / 24 h	5%	6%	80%
dppp / 24 h	43%	19%	15%



Competing Pathways

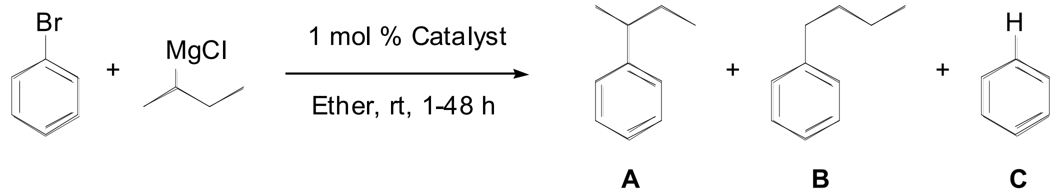
Desired Catalytic Cycle

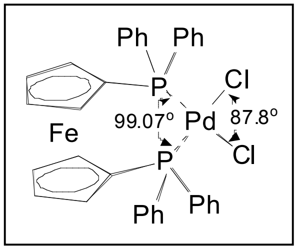
* **Proper Ligand Selection is Key!**

J. Am. Chem. Soc. **1984**, *106*, 158.

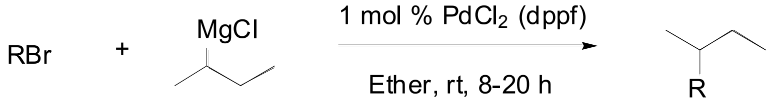
Kumada Coupling: Catalyst, Ligand and Scope

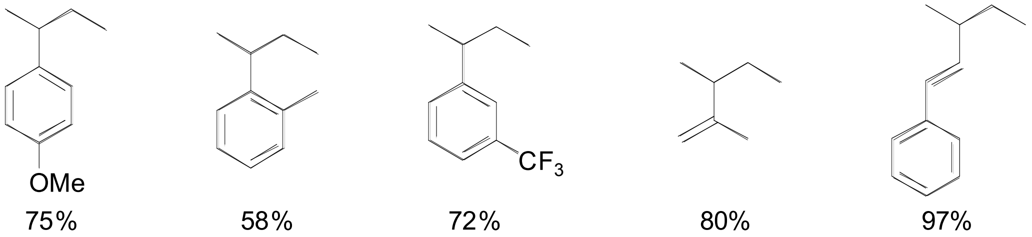
- Catalyst Screening:





				% Yield Determined by GC			Catalyst Bond Angles, deg	
Entry	Catalyst	Temp (°C)	Time (h)	A (%)	B (%)	C (%)	P-Pd-P	Cl-Pd-Cl
1	$PdCl_2$ (dppf)	rt	1	95	0	0	99.07	87.8
2	$PdCl_2$ (dppp)	rt	24	43	19	23	90.6	90.8
3	$PdCl_2$ (dppe)	rt	48	0	0	4	85.8	94.2
4	$PdCl_2$ $(PPh_3)_2$	rt	24	5	6	80	-	-
5	$NiCl_2$ (dppp)	rt	23	29	3	63	-	-
6	$NiCl_2$ $(PPh_3)_2$	rt	23	3	5	88	-	-



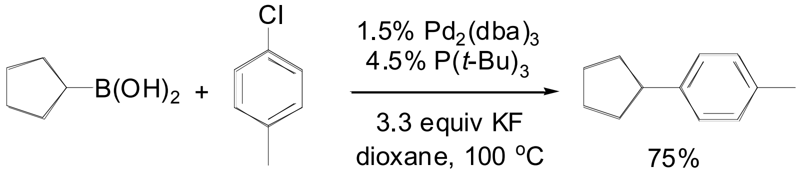


- Use of the $PdCl_2$ (dppf) catalyst successfully suppressed byproducts resulting from β-hydride elimination.
- Substrate scope is limited to halide coupling partners compatible with Grignard reagents.

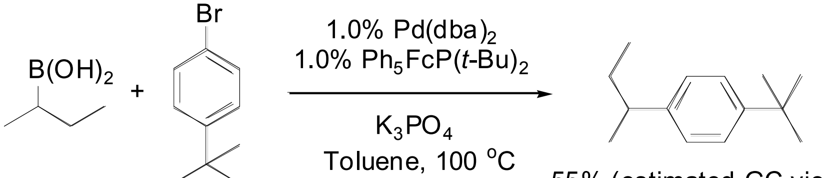
J. Am. Chem. Soc. **1984**, 106, 158.

Suzuki Cross-Coupling Reactions: Scope and Present Limitations

- Initial Reports:



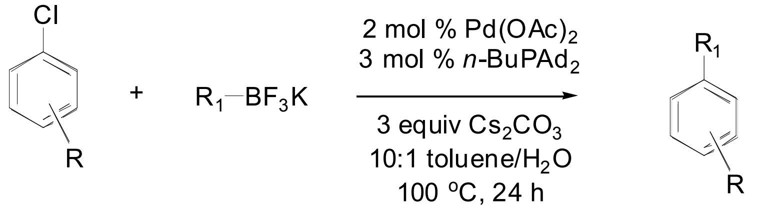
J. Am. Chem. Soc. **2000**, *122*, 4020.



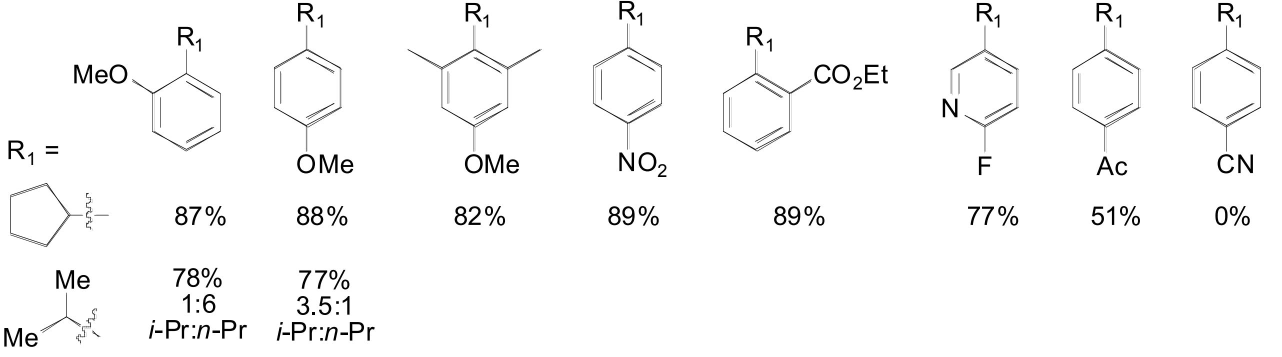
55% (estimated GC yield)
Mixture of *sec*- and *n*-butylaryl products

J. Org. Chem. **2002**, *67*, 5553.

- Recent Work by Molander:



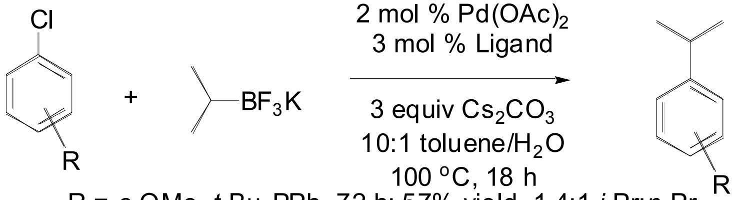
R = CH_3, OMe, Ac, CO_2Me, NO_2, CF_3, Het-Ar
R_1 = $c\text{-}C_5H_9$, *i*-Pr



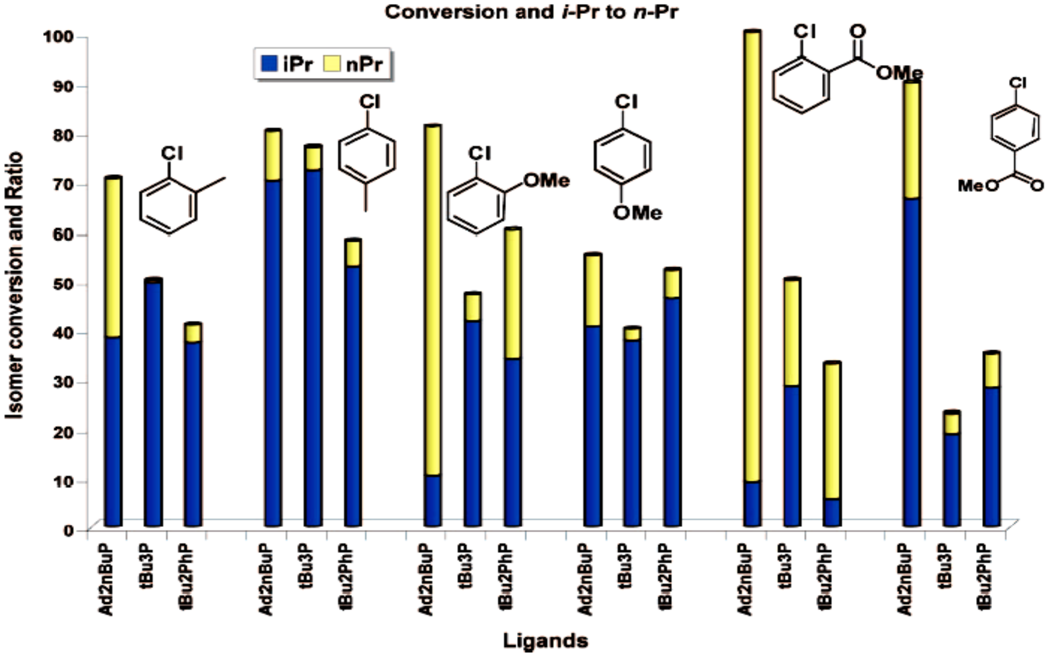
J. Am. Chem. Soc. **2008**, *122*, 4020.

Suzuki Cross-Coupling Reactions: Scope and Present Limitations

- 60 ligands were screened in parallel.
- The best 3 were further tested against diverse substrates.



R = *o*-OMe, *t*-Bu_2PPh, 72 h: 57% yield, 1.4:1 *i*-Pr:*n*-Pr
R = *p*-OMe, *t*-Bu_2PPh, 72 h: 79% yield, 8.2:1 *i*-Pr:*n*-Pr

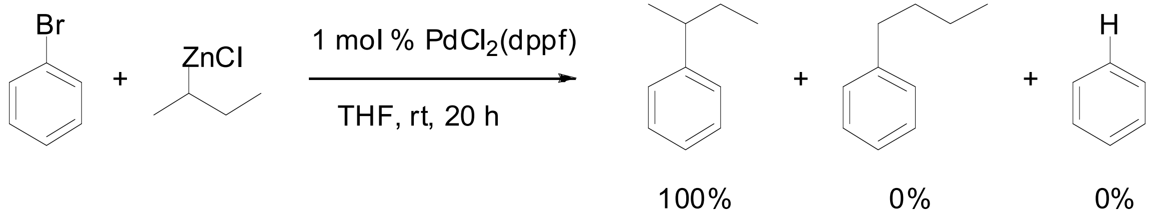


- Good Functional Group Compatibility: Alkyl, Aryl, Het-Aryl, Ether, Ester, Ketone, Nitro, and Trifluoromethyl; Does Not Work With Cyano Substituents
- Limitations: Moderate Selectivities for *i*-Pr vs. *n*-Pr, Sensitive to electronic and steric factors

J. Am. Chem. Soc. **2008**, *122*, 4020.

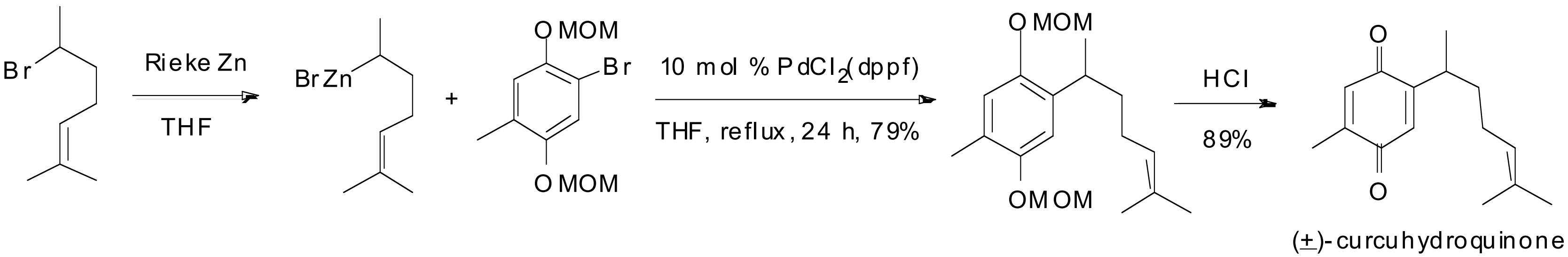
Negishi Coupling: New Uses for Old Ligands

- Early Reports from Kumada (1984):



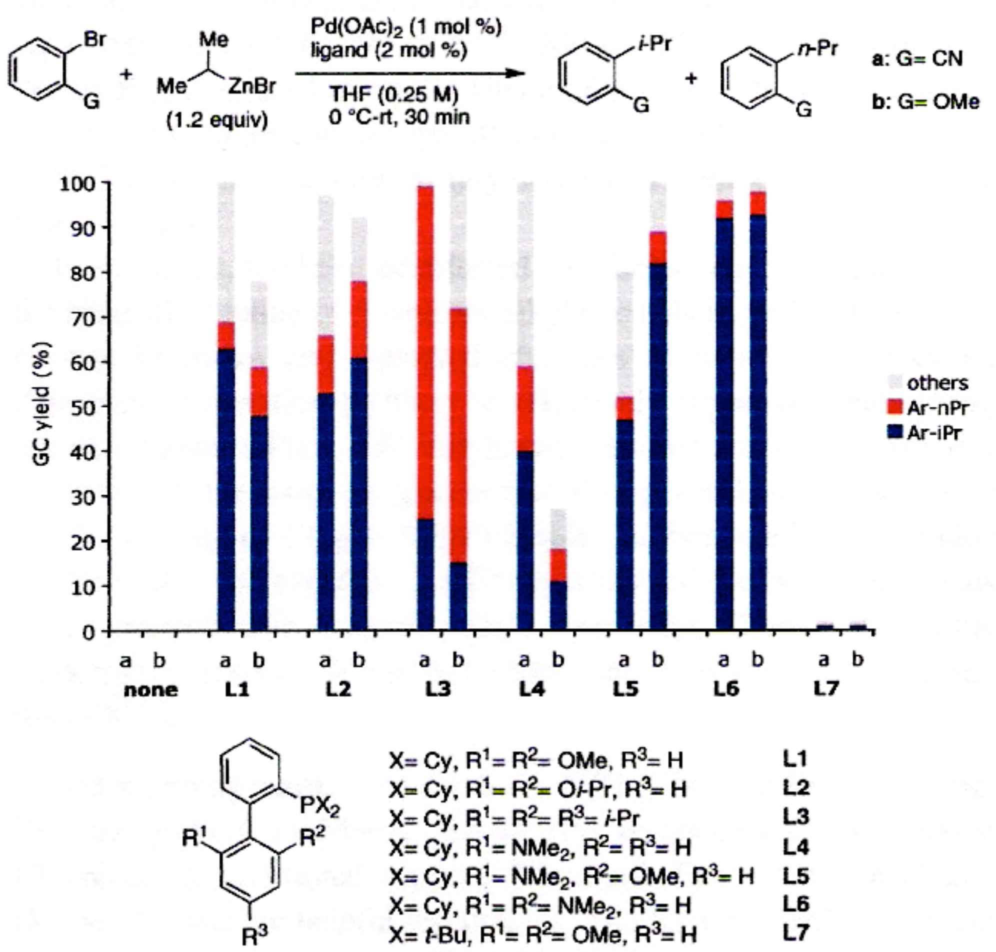
J. Am. Chem. Soc. **1984**, *106*, 158.

- 20 Years Later… the same methodology was applied to the racemic synthesis of bisabolene natural products which are components of many plant essential oils and many have been found to have a range of biological activities.

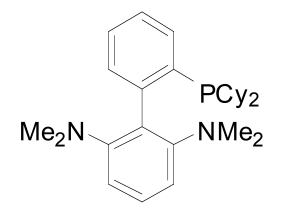


J. Org. Chem. **2004**, *7*, 2461.

Title Paper: Ligand Screening on Problematic Substrates



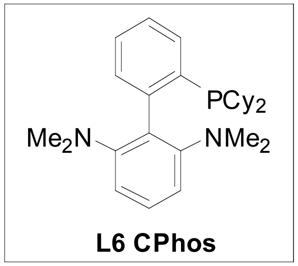
X= Cy, R^1= R^2= OMe, R^3= H L1
X= Cy, R^1= R^2= O*i*-Pr, R^3= H L2
X= Cy, R^1= R^2= R^3= *i*-Pr L3
X= Cy, R^1= NMe$_2$, R^2= R^3= H L4
X= Cy, R^1= NMe$_2$, R^2= OMe, R^3= H L5
X= Cy, R^1= R^2= NMe$_2$, R^3= H L6
X= *t*-Bu, R^1= R^2= OMe, R^3= H L7



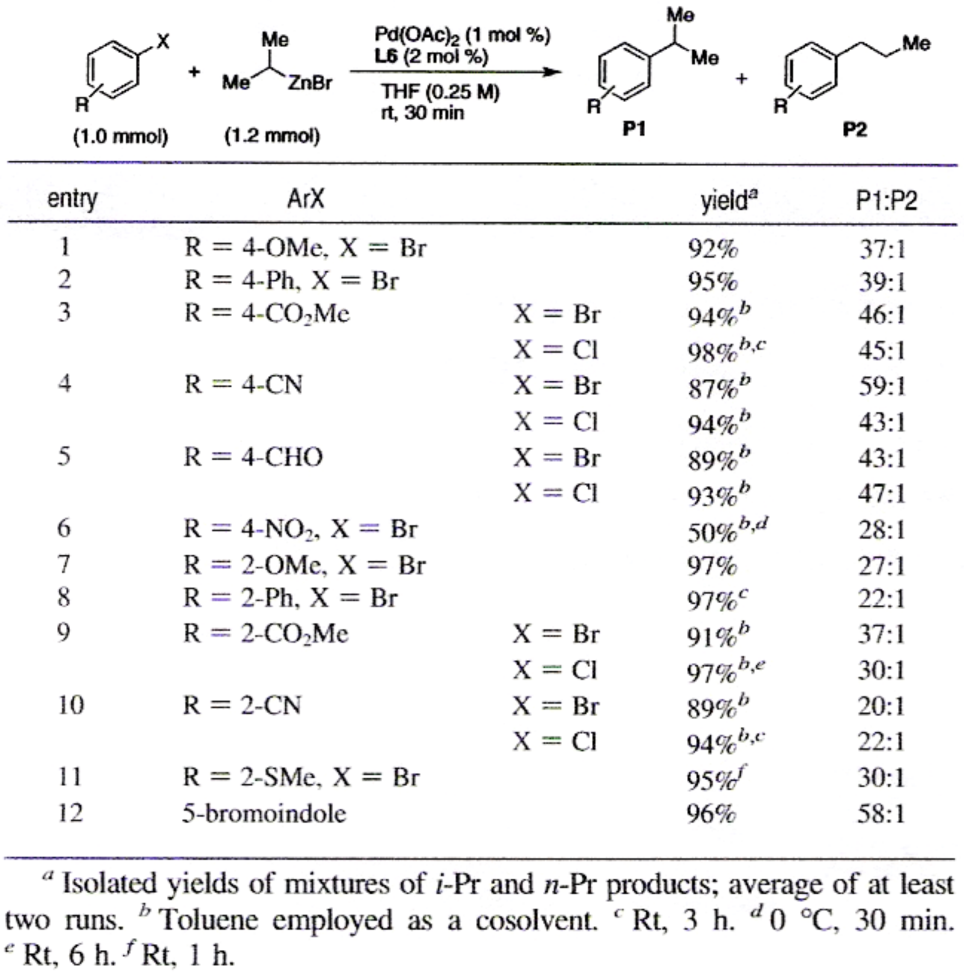
L6 CPhos

- The new CPhos ligand showed excellent conversions and selectivity for the desired branched products.

Title Paper: Substrate Scope and Isomeric Product Ratios Employing the CPhos Ligand



L6 CPhos

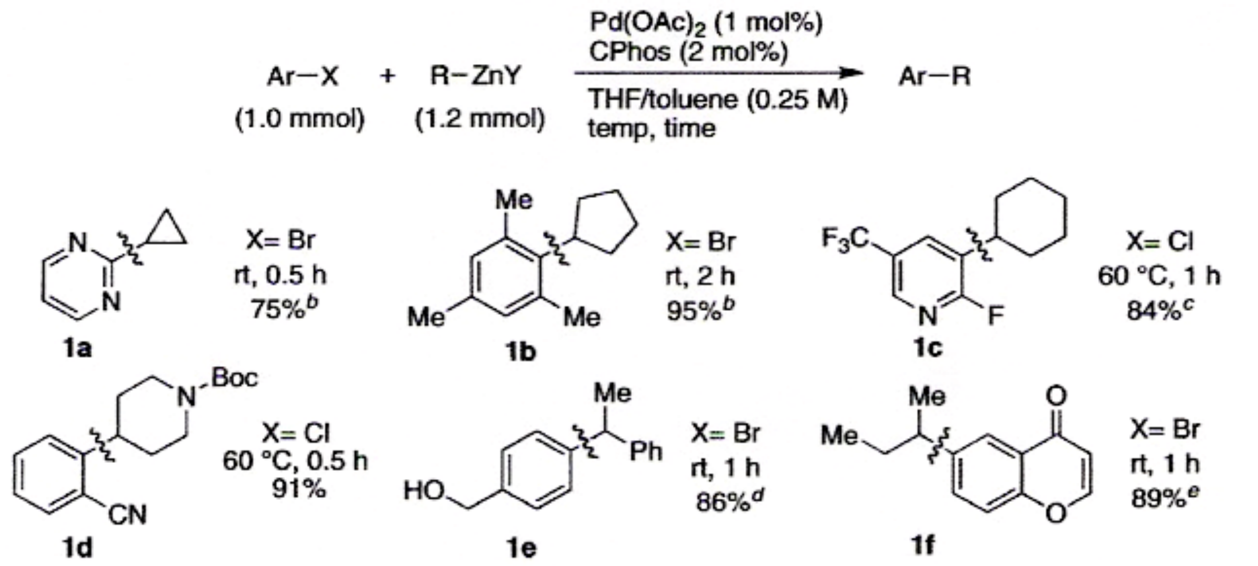


entry	ArX		yield[a]	P1:P2
1	R = 4-OMe, X = Br		92%	37:1
2	R = 4-Ph, X = Br		95%	39:1
3	R = 4-CO_2Me	X = Br	94%[b]	46:1
		X = Cl	98%[b,c]	45:1
4	R = 4-CN	X = Br	87%[b]	59:1
		X = Cl	94%[b]	43:1
5	R = 4-CHO	X = Br	89%[b]	43:1
		X = Cl	93%[b]	47:1
6	R = 4-NO_2, X = Br		50%[b,d]	28:1
7	R = 2-OMe, X = Br		97%	27:1
8	R = 2-Ph, X = Br		97%[c]	22:1
9	R = 2-CO_2Me	X = Br	91%[b]	37:1
		X = Cl	97%[b,e]	30:1
10	R = 2-CN	X = Br	89%[b]	20:1
		X = Cl	94%[b,c]	22:1
11	R = 2-SMe, X = Br		95%[f]	30:1
12	5-bromoindole		96%	58:1

[a] Isolated yields of mixtures of *i*-Pr and *n*-Pr products; average of at least two runs. [b] Toluene employed as a cosolvent. [c] Rt, 3 h. [d] 0 °C, 30 min. [e] Rt, 6 h. [f] Rt, 1 h.

- Excellent yields and selectivities for branched products
- Good functional group tolarance

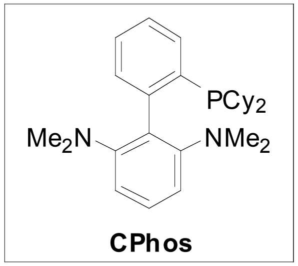
Title Paper: Substrate Scope Continued



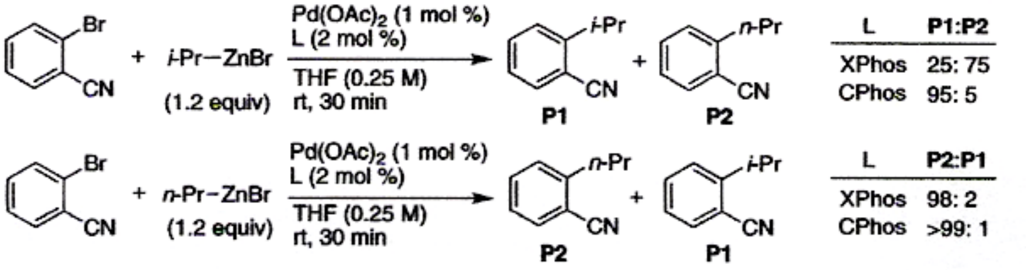
[a] Isolated yields; average of two runs. [b] Reaction conducted in THF. [c] 2 mol % $Pd(OAc)_2$ and 4 mol % CPhos. [d] The alkylzinc reagent (1.5 equiv) was slowly added over 30 min. [e] 23:1 branched/linear.

- The optimized reaction works well with sterically hindered, electron deficient and heteroaromatic aryl bromides and chlorides.
- Cyclic and acyclic zinc reagents were demonstrated to be good coupling partners.

Mechanistic Considerations

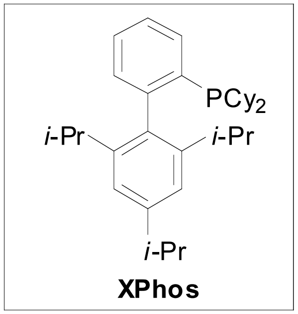


CPhos

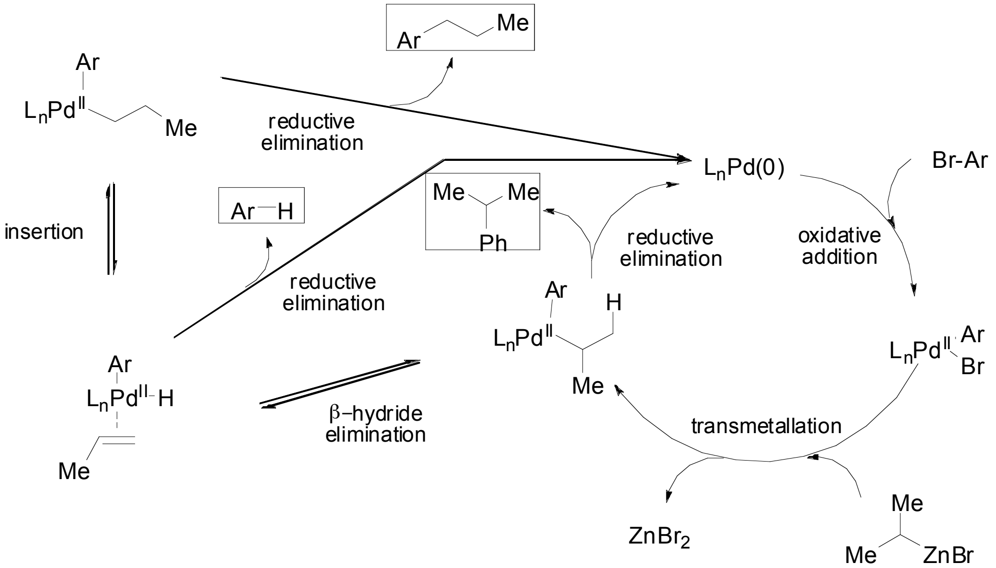


L	P1:P2
XPhos	25: 75
CPhos	95: 5

L	P2:P1
XPhos	98: 2
CPhos	>99: 1



XPhos



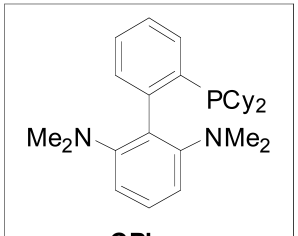
- Since different product ratios are observed between the coupling of *i*-PrZnBr and *n*-PrZnBr to the aryl bromide for each ligand, the product ratio of branched to linear products is determined by the relative rates of reductive elimination vs. β-hydride elimination – reinsertion.

Conclusion

- The authors have designed a new and efficient catalytic system for Negishi couplings of secondary alkylzinc halides with aryl bromides and activated chlorides.

- The coupling reaction shows good functional group tolerance and wide substrate scope.

- The introduction of the new CPhos ligand has allowed for excellent reaction selectivity for branched vs. linear coupling products by suppressing the undesired β-hydride elimination pathway competitive in these reactions.



CPhos