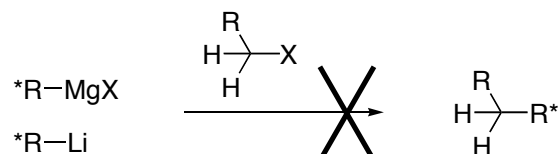


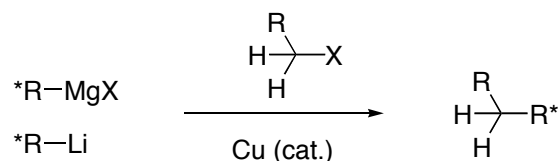
**Recent Advances in
sp³-sp³ Cross-
coupling Reactions**

*Amran A. Gowani
Crimmins Group Meeting
8/18/04*

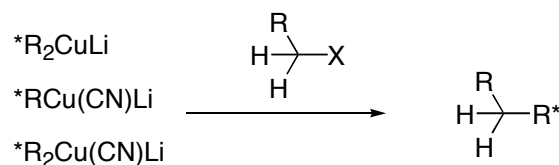
Why is There a Need for Transition Metal Catalysis?



- Grignard reagents do not generally undergo direct reaction with alkyl electrophiles



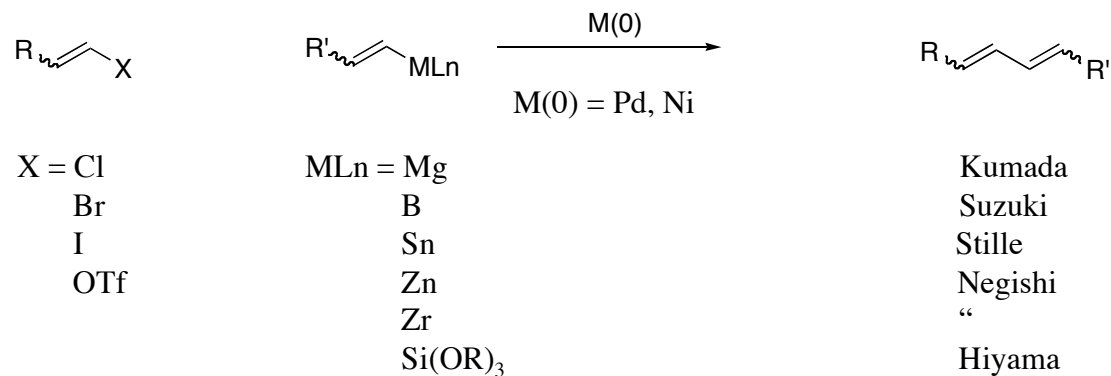
- Addition of Cu salts catalyzes these transformations
- A lack of functional group compatibility still exists



- Cuprates are milder, however, require two equivalents of nucleophile, which is not amenable to precious synthons

See: B.H. Lipshultz, S. Sengupta, *Organic Reactions* **1992**, 41, 135-631

Useful Transition-Metal Catalyzed Cross-coupling Reactions



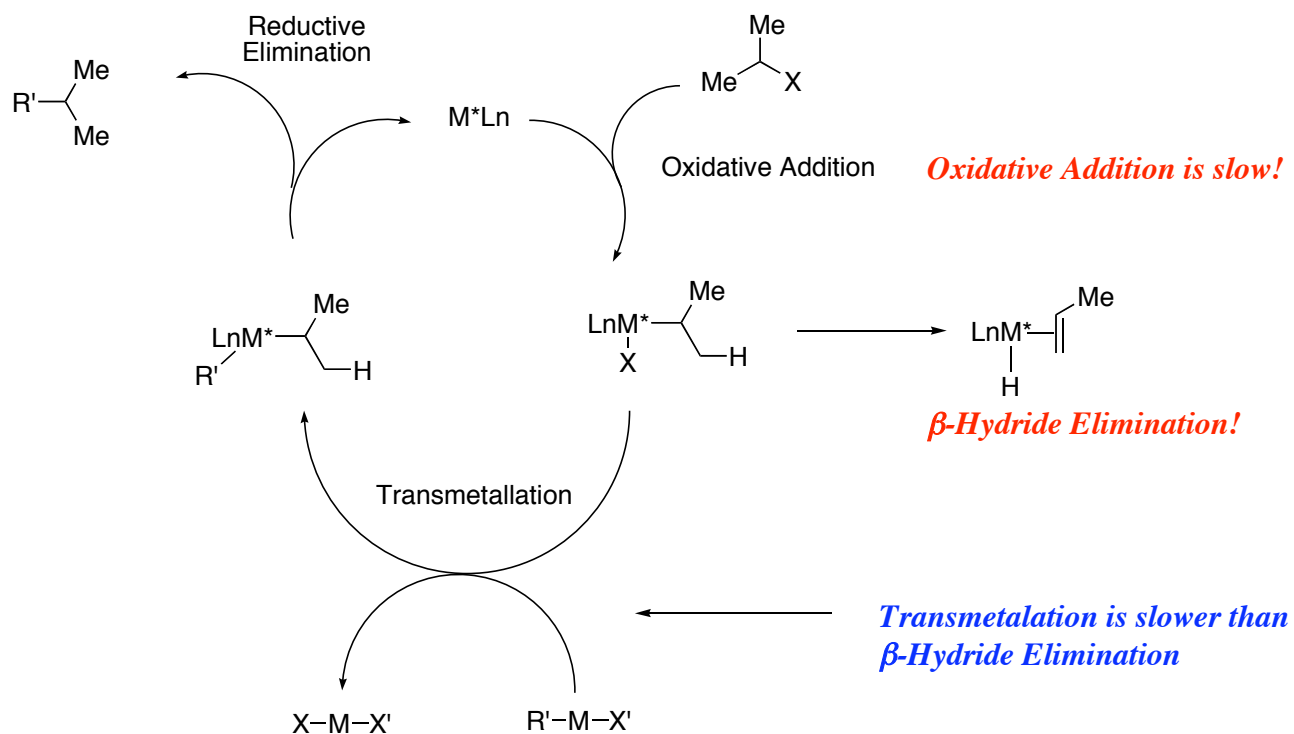
- All of these methods have found broad application for sp²-sp², sp-sp² and sp-sp cross-couplings
- These methods are typically very mild, display functional group tolerance and do not lead to formation of extraneous byproducts
- The staggering limitation of these methods is their inability to utilize sp³ (C-X) bonds as electrophilic coupling partners
- The ability to effect such a transformation would greatly lend to organic synthesis

For Reviews, see: *Angew. Chem. Int. Ed.* **1998**, 38, 3018
Chem. Rev. **2000**, 100, 3187
Angew. Chem. Int. Ed. **2003**, 42, 384

sp³-sp³ Couplings: A Field in its Infancy

- First Report by Suzuki in 1992
- Nickel Catalyzed Cross-couplings by Knochel and Coworkers (ca. 1995)
- Nickel Catalyzed Kumada-like Cross-couplings by Kambe in 2002
- Advent of Palladium Catalyzed Methods by Fu et. al. Beginning in 2001
- Other Recent Examples

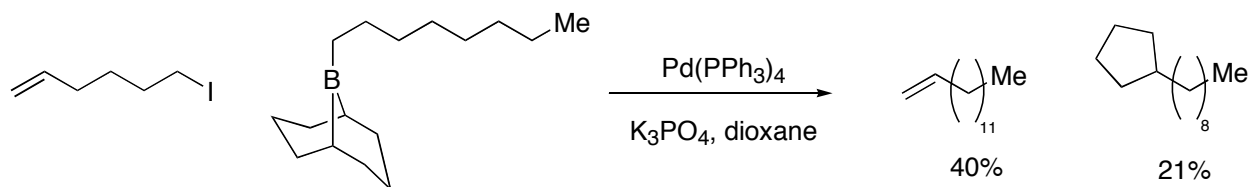
Problematic Aspects of sp³ Electrophiles



- Slow Oxidative Addition Makes for a Sluggish Catalytic Cycle
- β -Hydride Elimination Interrupts Catalytic Cycle

For Reviews, see: *Angew. Chem. Int. Ed.* **1998**, 38, 3018
Chem. Rev. **2000**, 100, 3187
Angew. Chem. Int. Ed. **2003**, 42, 384

Pioneering Work by Suzuki



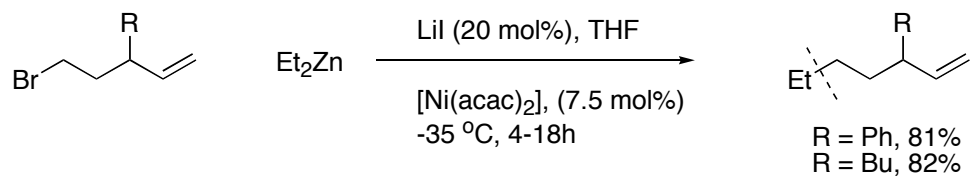
| Alkyl Iodide | 9-R-9-BBN | Yield of Coupled Product |
|--------------|-----------|--------------------------|
| Me-I | | 71 |
| | | 64 |
| | | 45 |
| | | 58 |
| | | 54 |
| | | 61 |
| | | 57 |
| | | 64 |
| | | 55 |

- Suzuki reports that PPh_3 is most effective ligand for the alkyl-alkyl coupling

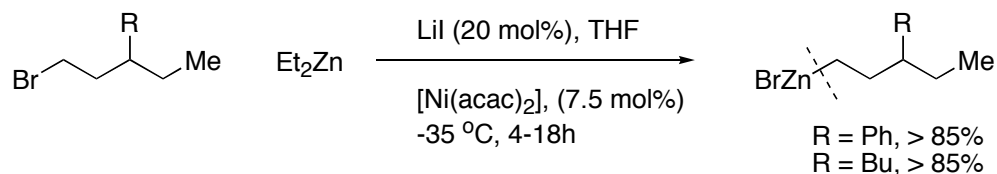
- Bidentate ligands do not effect cross-coupling, e.g. $\text{Pd}(\text{dppf})\text{Cl}_2$

- Only 9-BBN derivatives effectively couple; trialkyl boranes, borates, grignards, alkyl zincs, aluminum, tin, zirconium and mercury failed

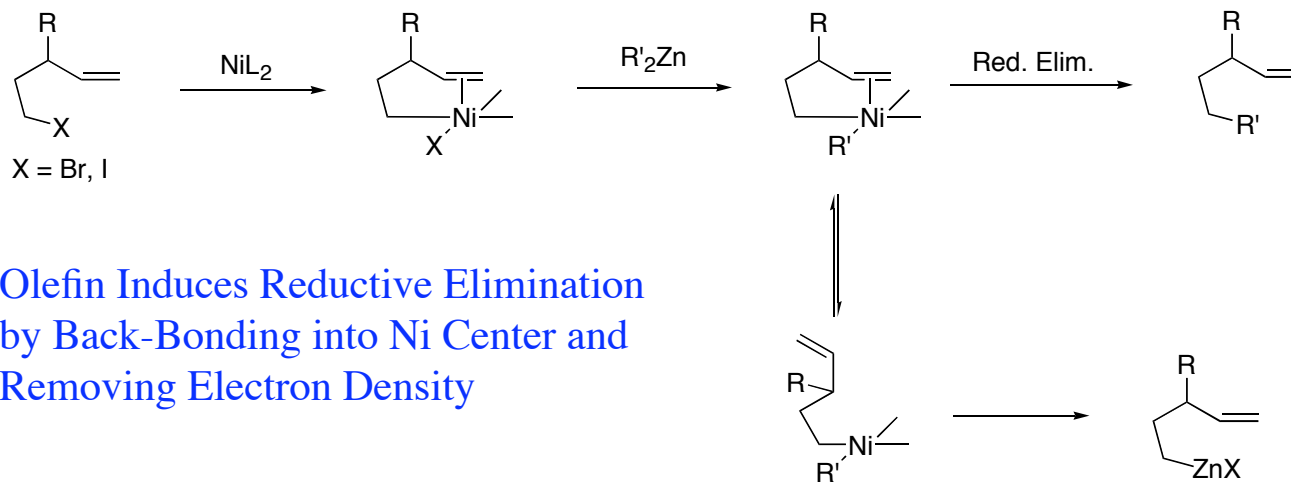
A Series of Communications by Knochel



Cross Coupling Only Occurs in the Presence of an Unsaturated Group

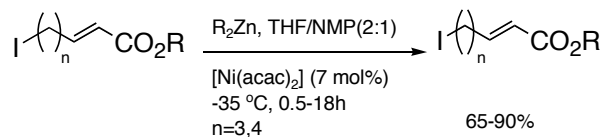


Proposed Mechanism Based on Unsaturated Unit



Olefin Induces Reductive Elimination by Back-Bonding into Ni Center and Removing Electron Density

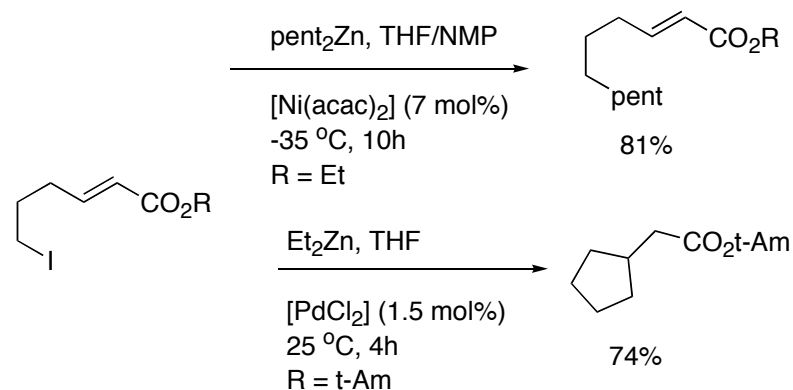
Preliminary Results by Knochel



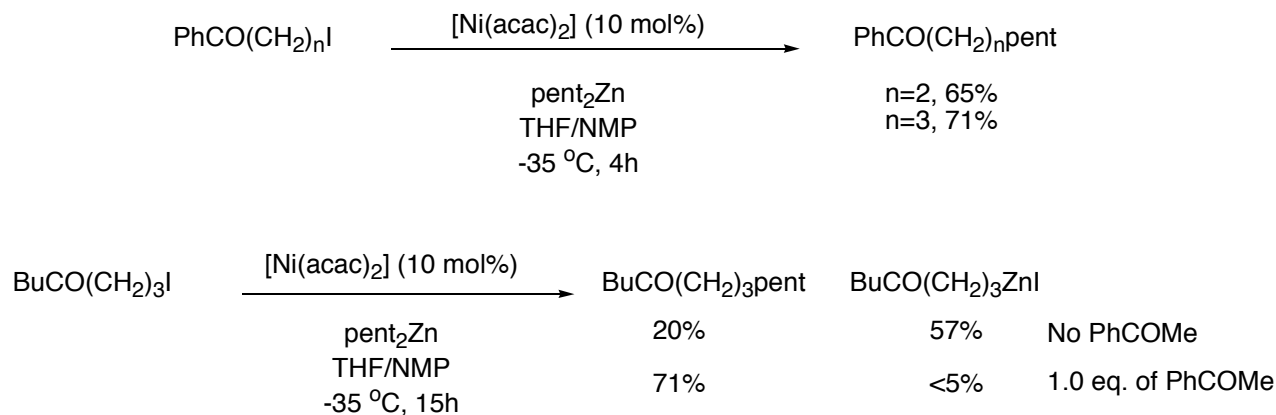
| Alkyl Iodide | Diorganozinc | Product | Yield |
|--------------|--|---------|--------|
| | pent ₂ Zn | | 80(73) |
| | pent ₂ Zn | | 72 |
| | (PivO(CH ₂) ₃) ₂ Zn | | 90(77) |
| | (PivO(CH ₂) ₃) ₂ Zn | | 70(32) |
| | pent ₂ Zn | | 83 |
| | Et ₂ Zn | | 84 |
| | (PivO(CH ₂) ₃) ₂ Zn | | 79 |
| | (AcO(CH ₂) ₅) ₂ Zn | | 78 |
| | (PivO(CH ₂) ₆) ₂ Zn | | 73 |
| | | | 65 |

Parentheses indicate yield in THF only.

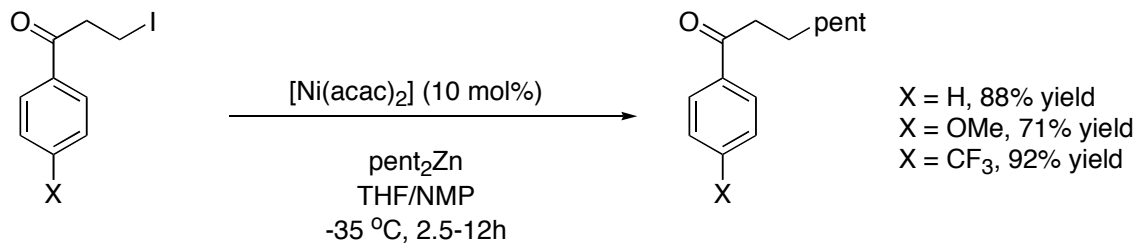
- Yield and reaction rate are greatly increased by adding NMP as co-solvent
- Position of olefin relative to iodine (n=3,4) affects reaction rate, where n=3 is faster
- Coupling is tolerant of ester functional groups
- Proceeds readily at -35 °C
- Pd (0) does not effect coupling



Expanding the Scope



The nature of the unsaturated unit affects the reactivity

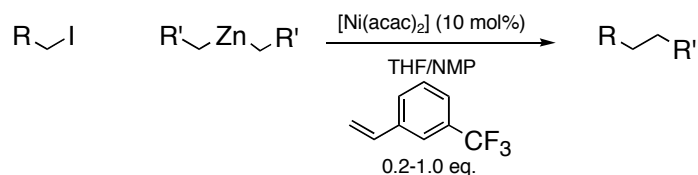







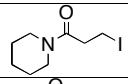
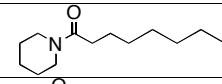

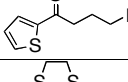
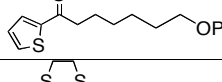

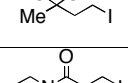
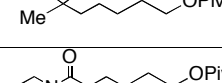

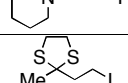
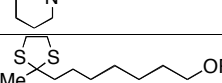

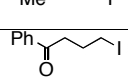
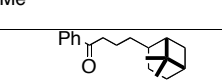


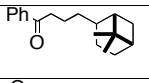


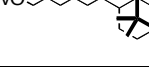

Electron poor aromatic ketones give increased yields

Angew. Chem. Int. Ed. Engl. **1998**, 37, 2387

J. Org. Chem. **1999**, 64, 3544

Expanding the Scope (Continued)

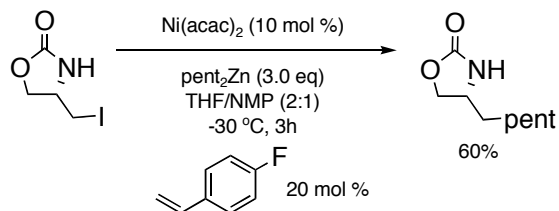
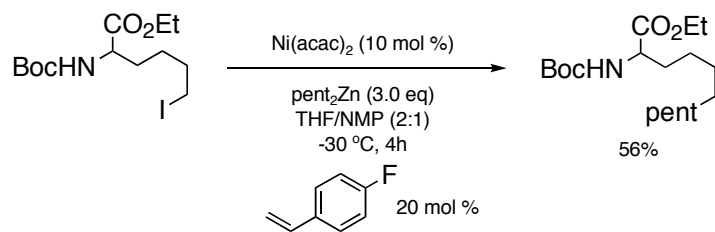
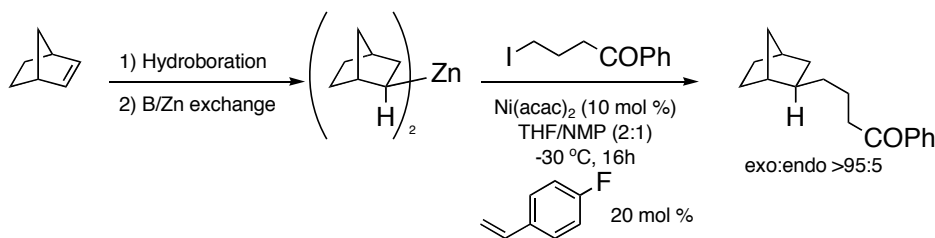
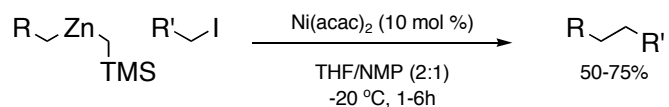
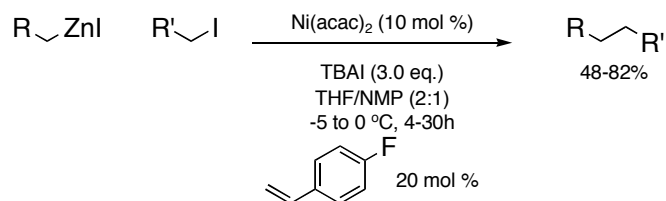


| Iodoalkane | Diorganozinc (R ₂ Zn, R=) | Product | Yield (%) | Co-Catalyst |
|---|---|---|-----------|--|
| PhS-CH ₂ -CH ₂ -CH ₂ -I | pent | PhS-CH ₂ -CH ₂ -CH ₂ -pent | 71 |  |
| PivO-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -I | pent | PivO-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -pent | 78 |  |
| Ph-C(=O)-CH ₂ -CH ₂ -CH ₂ -I | CH ₃ -CH ₂ -CH ₂ -OPiv | Ph-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -OPiv | 76 |  |
| Bu-C(=O)-CH ₂ -CH ₂ -CH ₂ -I | CH ₃ -CH ₂ -CH ₂ -OPiv | Bu-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -OPiv | 68 |  |
| BnO-C(=O)-CH ₂ -CH ₂ -CH ₂ -I | pent | BnO-C(=O)-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -pent | 76 |  |
|  | pent |  | 70 |  |
|  | CH ₃ -CH ₂ -CH ₂ -OPiv |  | 70 |  |
|  | CH ₃ -CH ₂ -CH ₂ -OPiv |  | 70 |  |
|  | CH ₃ -CH ₂ -CH ₂ -OPiv |  | 68 |  |
|  | CH ₃ -CH ₂ -CH ₂ -CH ₂ -OPiv |  | 67 |  |
| Ph-C(=O)-CH ₂ -CH ₂ -CH ₂ -I |  |  | 66 |  |
| PivO-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -I |  |  | 74 |  |

- Addition of Co-catalyst allows for coupling of species without an unsaturated moiety
- Cross-coupling is highly tolerant of a variety of functional groups
- No loss in reactivity or yield is observed
- Conditions can be extended to cross couplings of aryl zinc species
See: *J. Am. Chem. Soc.* **1998**, *120*, 11186
- Addition of TBAI also facilitates coupling of benzylic zinc nucleophiles
See: *Org. Lett.* **1999**, *1*, 1323

Angew. Chem. Int. Ed. Engl. **1998**, *37*, 2387
J. Org. Chem. **1999**, *64*, 3544

Knochel's Optimized Coupling Conditions

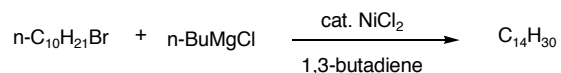


- Addition of TBAI effects coupling of primary alkyl zinc iodides
- TBAI also enhances the rate of the reaction
- *p*-F-styrene operates as the most effective mediator of the cross-coupling
- Substituting the halide for CH₂TMS allows coupling to proceed in absence of TBAI

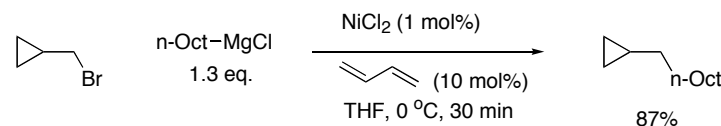
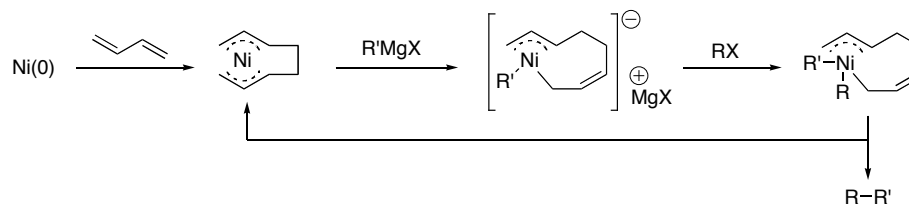
- Transmetalation proceeds with retention of configuration

- Alkyl couplings proceed in the presence of free NH groups
- Potential for diverse chiral auxiliary synthesis

Kambe's Nickel Catalyzed System



Proposed Mechanism



- Radical mechanism eliminated
- No coupling without diene additives

Table 1. Cross-Coupling Reaction of $n\text{-C}_{10}\text{H}_{21}\text{Br}$ with $n\text{-BuMgCl}$

| entry | catalyst | additive | GC yield (%) ^a | | |
|-------|-----------------------|----------------------------|--------------------------------|--------|----------------------|
| | | | $n\text{-C}_{14}\text{H}_{30}$ | decane | decenes ^b |
| 1 | NiCl ₂ | | 92 | <1 | 2 |
| 2 | NiCl ₂ | none | 2 | 49 | 27 |
| 3 | Ni(acac) ₂ | | 90 | <1 | 2 |
| 4 | Ni(COD) ₂ | | 92 | <1 | 3 |
| 5 | PdCl ₂ | | 38 | 1 | 3 |
| 6 | NiCl ₂ | | 99 | <1 | 0 |
| 7 | NiCl ₂ | | 5 | 14 | 9 |
| 8 | NiCl ₂ | COD ^c | 10 | 18 | 38 |
| 9 | NiCl ₂ | Ph—Et | 3 | 7 | 23 |
| 10 | NiCl ₂ | 3-CF ₃ -styrene | 15 | 25 | 14 |

^a Conditions: $n\text{-C}_{10}\text{H}_{21}\text{Br}$ (2 mmol), catalyst (3 mol %), $n\text{-BuMgCl}$ (1.3 equiv, 0.9 M), additive (1 equiv, 0.7 M); 25 °C; 3 h. ^b A mixture of 1-decene and 2-decenes. ^c 1,5-Cyclooctadiene.

- High yields of coupled products
- Scope of coupling not yet fully explored

J. Am. Chem. Soc. **2002**, *124*, 4223

Table 2. Ni-Catalyzed Cross-Coupling Reaction of Alkyl Halides and a Tosylate with Grignard Reagents

| entry | R-X | R'-MgX' (equiv to R-X) | NiCl ₂ (mol %) | 1,3-butadiene (mol %) ^a | temp. (°C) | time (h) | product | yield (%) ^b |
|-------|--|---------------------------|------------------------------|---------------------------------------|---------------|-------------|--------------------------------|------------------------|
| 1 | $n\text{-C}_{10}\text{H}_{21}\text{-Br}$ | $n\text{-Bu-MgCl}$ (1.3) | 1 | 10 (0.07 M) | 0 | 0.5 | $n\text{-C}_{14}\text{H}_{30}$ | 100 |
| 2 | | $n\text{-Bu-MgCl}$ (1.3) | 1 | 10 (0.07 M) | 0 | 0.5 | | 100 |
| 3 | Ph-CH ₂ -OTs | Et-MgBr (1.3) | 3 | 30 (0.23 M) | 0 | 3 | Ph-CH ₂ -Et | 87 |
| 4 | $n\text{-Bu-OTs}$ | $n\text{-Bu-MgCl}$ (1.3) | 3 | 100 (0.69 M) | 0 | 3 | $n\text{-C}_8\text{H}_{18}$ | 100 |
| 5 | Et-OTs | Ph-MgBr (1.3) | 3 | 100 (0.77 M) | 0 | 6 | Et-Ph | 56 |
| 6 | $n\text{-Oct-Br}$ | Ph-MgBr (1.3) | 3 | 30 (0.23 M) | 25 | 3 | $n\text{-Oct-Ph}$ | 90 |
| 7 | $n\text{-Oct-Br}$ | (3.0) | 3 | 30 (0.07 M) | 0 | 0.5 | $n\text{-Oct-}$ | 72 |
| 8 | $n\text{-Oct-Cl}$ | $n\text{-Bu-MgCl}$ (2.0) | 3 | 50 (0.23 M) | 25 | 20 | $n\text{-C}_{12}\text{H}_{26}$ | 96 |

^a Based on R-X (concentration is in parentheses). ^b Determined by GC.

Alkyl-Fluoride Couplings by Kambe

Table 1. Cross-Coupling Reaction of ${}^n\text{C}_8\text{H}_{17}\text{-F}$ with ${}^n\text{C}_3\text{H}_7\text{-MgBr}^{\text{a}}$

| entry | catalyst | additive (mol %) | product yield (%) ^b | | |
|-------|--|--------------------------------|--------------------------------|--------|----------------------|
| | | | undecane | octane | octenes ^c |
| 1 | NiCl ₂ | none | 0 | 0 | 0 |
| 2 | (PPh ₃) ₂ NiCl ₂ | none | 0 | 0 | 0 |
| 3 | (dppp)NiCl ₂ | none | 0 | 0 | 0 |
| 4 | NiCl ₂ | 1,3-butadiene (10) | 9 | 1 | 0 |
| 5 | NiCl ₂ | 1,3-butadiene (50) | 44 | 2 | 1 |
| 6 | NiCl ₂ | 1,3-butadiene (70) | 50 | 2 | 2 |
| 7 | NiCl ₂ | 1,3-butadiene (100) | 64 | 4 | 2 |
| 8 | NiCl ₂ | 1,3-butadiene (200) | 67 | 3 | 1 |
| 9 | NiCl ₂ | isoprene (100) | 47 | 0 | 0 |
| 10 | NiCl ₂ | 2,3-methyl-1,3-butadiene (100) | 0 | 0 | 0 |
| 11 | NiCl ₂ | 1,5-cyclooctadiene (100) | 0 | 0 | 0 |
| 12 | NiCl ₂ | diphenylacetylene (100) | 0 | 0 | 0 |
| 13 | (PPh ₃) ₂ NiCl ₂ | 1,3-butadiene (100) | 8 | 3 | 2 |
| 14 | (dppp)NiCl ₂ | 1,3-butadiene (100) | 57 | 3 | 2 |
| 15 | FeCl ₂ | 1,3-butadiene (100) | 0 | 0 | 0 |
| 16 | CoCl ₂ | 1,3-butadiene (100) | 0 | 0 | 0 |
| 17 | PdCl ₂ | 1,3-butadiene (100) | 23 | 1 | 4 |
| 18 | CuCl ₂ | 1,3-butadiene (100) | 97 | 0 | 0 |
| 19 | CuCl | 1,3-butadiene (100) | 94 | 0 | 0 |
| 20 | Li ₂ CuCl ₄ | 1,3-butadiene (100) | 30 | 0 | 0 |

^a Conditions: ${}^n\text{Oct-F}$ (2 mmol), 3 mol % catalyst, additive (mol % based on the substrate), and ${}^n\text{Pr-MgBr}$ (2 equiv, 1 M), in THF, 25 °C, 3 h.

^b Determined by GC. ^c A mixture of 1-octene and 2-octenes.

- Nickel catalysts with diene additives displayed decent reactivity
- Sterically demanding dienes reduced reactivity and resulted in diminished yields
- Fe, Co, Pd did not effect coupling
- Surprisingly, Cu salts led to excellent yields of coupled products

J. Am. Chem. Soc. **2003**, *125*, 5646.

Coupling of Various Unfunctionalized Partners

Table 2. Cu-Catalyzed Cross-Coupling Reaction of ${}^n\text{Oct-F}$ with Grignard Reagents

| ${}^n\text{Oct-F}$ 2 mmol | | + | R-MgX 2.6 mmol | $\xrightarrow[\text{THF}]{\text{CuCl}_2 (3 \text{ mol } \%)}$ | ${}^n\text{Oct-R}$ | |
|------------------------------|--|---|------------------------|---|--------------------|-----------------|
| entry | R-MgX | | additive (0.2 mmol) | temp (${}^\circ\text{C}$) | time (h) | GC yield (%) |
| 1 | ${}^n\text{C}_3\text{H}_7\text{-MgBr}$ | | 1,3-butadiene | 25 | 6 | 94 |
| 2 | | | isoprene | 25 | 6 | 34 |
| 3 | | | none | 25 | 6 | 20 |
| 4 | | | 1,3-butadiene | -20 | 6 | 38 |
| 5 | | | none | -20 | 6 | 36 |
| 6 | | | none | -20 | 48 | 68 |
| 7 | | | none | -40 | 6 | 3 |
| 8 | ${}^i\text{C}_3\text{H}_7\text{-MgBr}$ | | 1,3-butadiene | 25 | 6 | 81 |
| 9 | | | none | 25 | 6 | 35 |
| 10 | ${}^n\text{C}_4\text{H}_9\text{-MgCl}$ | | 1,3-butadiene | 25 | 6 | 99 |
| 11 | | | none | 25 | 6 | 99 |
| 12 | Ph-MgBr | | 1,3-butadiene | 25 | 6 | 38 |
| 13 | | | none | 25 | 6 | 53 |
| 14 | | | none | 67 (reflux) | 1 | 99 |

- 1,3-butadiene assists the room temperature cross coupling of $n\text{PrMgBr}$
- In the absence of additive, reaction takes place slowly even at $-20\text{ }^\circ\text{C}$
- Coupling of $i\text{PrMgBr}$ is facilitated by 1,3-butadiene
- Authors suggest that the diene additive is playing a role in the stabilizing the active Cu catalyst
- Grignard's sans β -hydrogens do not require diene additives for cross-coupling

Initial Studies on Suzuki Couplings with Alkyl Bromides

Table 1. Suzuki Coupling of an Alkyl Bromide: Ligand Survey^a

| entry | ligand ^a | % yield after 16 h (by GC) | |
|-------|--|----------------------------|----|
| | | | |
| 1 | PCy ₃ | 85 | <2 |
| 2 | PPh ₃ | <2 | <2 |
| 3 | P(2-furyl) ₃ | <2 | <2 |
| 4 | P(o-tol) ₃ | <2 | 14 |
| 5 | P(2,4,6-trimethoxyphenyl) ₃ | <2 | 31 |
| 6 | dppf | <2 | 12 |
| 7 | binap | <2 | <2 |
| 8 | P(OPh) ₃ | <2 | <2 |
| 9 | AsPh ₃ | <2 | <2 |
| 10 | P(<i>t</i> -Bu) ₃ | <2 | 21 |
| 11 | P(<i>n</i> -Bu) ₃ | 9 | 27 |
| 12 | dcpe | <2 | 21 |
| 13 | P(<i>i</i> -Pr) ₃ | 68 | 6 |

^a In the case of bidentate ligands, 4% of the ligand was used.

- Previous work with aryl-chlorides as electrophiles has demonstrated that *electron-rich phosphine ligands* are required

See: *J. Am. Chem. Soc.* **2001**, *123*, 2719

- Triaryl phosphines do not couple alkyl bromides or chlorides, which is in accord with Suzuki's 1992 report
- Of the trialkyl phosphines tested, PCy₃ performs optimally
- Bidentate ligands effect no cross-couplings

Alkyl Bromide Suzuki Coupling Results

- Unfunctionalized substrates cross-couple most effectively
- Numerous functional groups are tolerated: amines, olefins, alkynes
- Selective cross coupling of an alkyl-bromide occurs in the presence of an alkyl-chloride

Mechanistic Implications

- Reactions are not moisture sensitive
- Water is required for coupling
- ^{11}B experiments demonstrate a significant upfield shift upon addition of water indicating the formation of a boron 'ate' complex

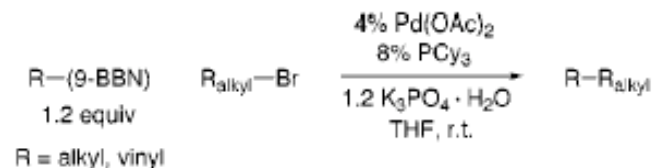


Table 2. Room-Temperature Suzuki Cross-Coupling of Alkyl Bromides (eq 3): Reaction Scope

| entry | R-(9-BBN) ^a | R _{alkyl} -Br | yield (%) ^b |
|-------|---|------------------------|------------------------|
| 1 | <i>n</i> -Hex-(9-BBN) | <i>n</i> -Dodec-Br | 93 |
| 2 | | <i>n</i> -Dodec-Br | 78 ^c |
| 3 | | <i>n</i> -Dodec-Br | 85 |
| 4 | <i>n</i> -Bu-C≡C-(CH ₂) ₄ -9-BBN | | 58 |
| 5 | TESO-(CH ₂) ₆ -9-BBN | | 72 |
| 6 | | <i>n</i> -Hex-Br | 80 |
| 7 | MeO-C(=O)-(CH ₂) ₁₀ -9-BBN | | 81 |
| 8 | TESO-(CH ₂) ₆ -9-BBN | | 81 |
| 9 | | <i>n</i> -Dodec-Br | 66 |

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

Palladium Catalyzed Cross-Coupling of Alkyl Chlorides

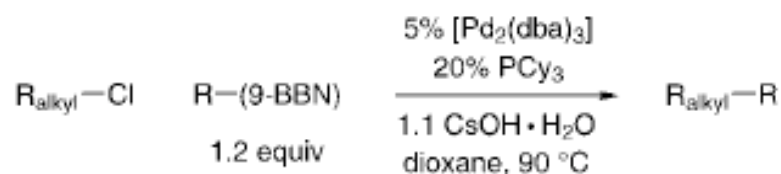
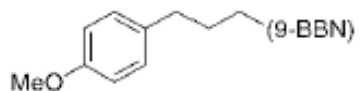
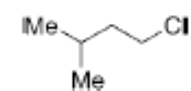
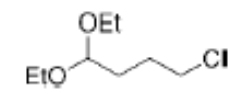
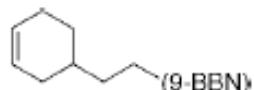
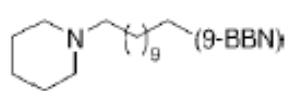
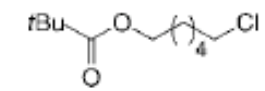


Table 2. Suzuki cross-couplings of alkyl chlorides [Eq. (1)].

| Entry | $R_{\text{alkyl}}-\text{Cl}$ | $R-(9\text{-BBN})^{[a]}$ | Yield [%] ^[b] |
|------------------|---|---|--------------------------|
| 1 | <i>n</i> -Dodec-Cl | <i>n</i> -Oct-(9-BBN) | 83 |
| 2 | <i>n</i> -Pent-Cl |  (9-BBN) | 82 |
| 3 |  -Cl | BnO-(CH ₂) ₃ -(9-BBN) | 74 |
| 4 |  -Cl | BnO-(CH ₂) ₃ -(9-BBN) | 70 |
| 5 | TBSO-(CH ₂) ₄ -Cl |  (9-BBN) | 72 |
| 6 ^[c] | TBSO-(CH ₂) ₄ -Cl |  (9-BBN) | 73 |
| 7 | NC-(CH ₂) ₄ -Cl | <i>n</i> -Oct-(9-BBN) | 73 |
| 8 ^[d] |  -Cl | BnO-(CH ₂) ₃ -(9-BBN) | 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 · H₂O.

- Conditions for alkyl bromide couplings were not amenable to alkyl chlorides

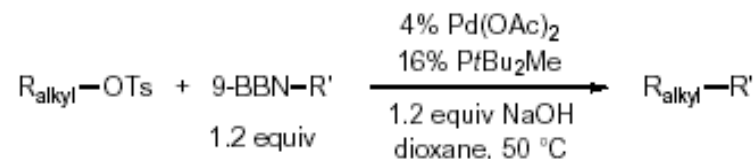
- Results of a ligand screen again demonstrated the necessity for trialkyl phosphine ligands, e.g. triaryl phosphines, arsines, bidentate phosphine ligands and imidazolium carbenes all proved ineffective

- Pd₂(dba)₃ functioned most effectively

- Increased temperature was required

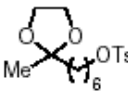

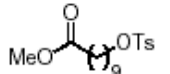
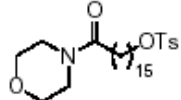
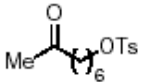
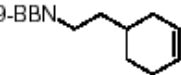
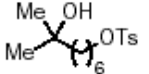

- This cross-coupling is also tolerant of numerous functional groups

Suzuki Cross-Couplings of Alkyl Tosylates



- Conditions for alkyl bromides and alkyl chlorides do not achieve cross-coupling for alkyl tosylates (naturally)
- **PCy₃ gives poor yields < 50%**
- **PtBu₃ is not effective**
- **PCy₂Et works well (70% for Entry 1)**
- **PtBu₂Et works optimally**
- Again the coupling conditions are tolerant of multiple functional groups
- Couplings can be conducted at rt at the expense of long reaction times (~ 1 week)

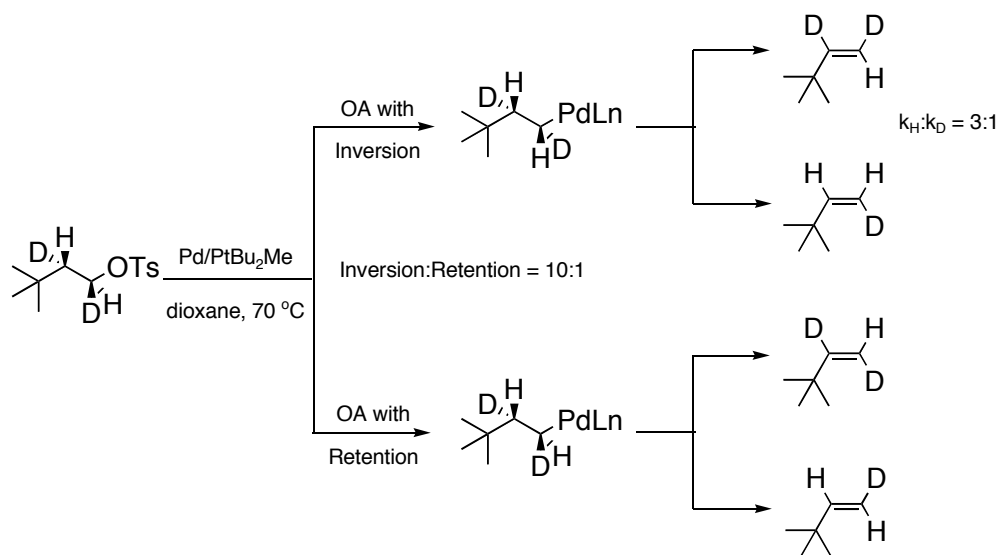
Table 1. Examples of Pd/PtBu₂Me-catalyzed Suzuki cross-couplings of alkyl tosylates

| Entry | R _{alkyl} -OTs | 9-BBN-R' | Yield [%] ^[a] |
|------------------|---|--|--------------------------|
| 1 | <i>n</i> Dodec-OTs | 9-BBN- <i>n</i> 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- <i>n</i> Oct | 76 |
| 6 |  | 9-BBN-(CH ₂) ₁₁ OTES ^[b] | 55 |
| 7 | NC(CH ₂) ₈ -OTs | 9-BBN-  | 64 |
| 8 |  | 9-BBN-  | 63 |
| 9 ^[d] | TsO-(CH ₂) ₁₂ -OTs | 9-BBN- <i>n</i> Oct | 73 |

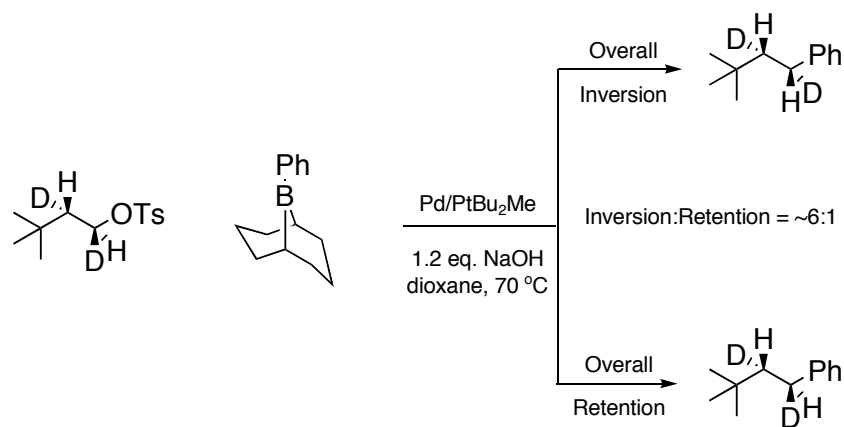
Angew. Chem. Int. Ed. **2002**, *41*, 3910

[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% PtBu₂Me, and 2.4 equiv of NaOH were used.

Mechanistic Features of Alkyl Tosylate Cross Couplings



Oxidative Addition Occurs with Predominate Inversion of Configuration



Reductive Elimination Occurs with Predominate Retention of Configuration

Boronic Acids as Coupling Partners with Alkyl Bromides

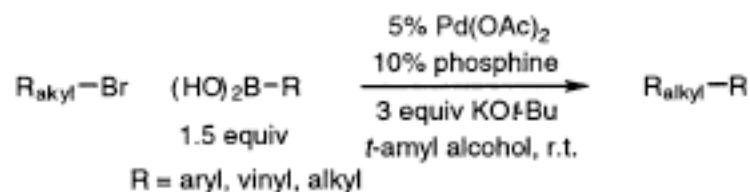


Table 2. Pd/P(*t*-Bu)₂Me-Catalyzed Suzuki Cross-Couplings of Alkyl Bromides with Boronic Acids

| entry | R _{alkyl} -Br | R | yield (%) ^a | |
|-------|---|---|----------------------------------|--|
| | | | P(<i>t</i> -Bu) ₂ Me | [HP(<i>t</i> -Bu) ₂ Me]BF ₄ |
| 1 | <i>n</i> -Oct-Br | Ph | 87 | 90 |
| 2 | | 4-(MeS)C ₆ H ₄ | 68 | 66 |
| 3 | BnO ⁻ (CH ₂) ₆ -Br | 4-(MeO)C ₆ H ₄ | 85 | 84 |
| 4 | TBSO ⁻ (CH ₂) ₆ -Br | 4-(F ₃ C)C ₆ H ₄ | 63 | 67 |
| 5 | | <i>o</i> -tolyl | 71 | 76 |
| 6 | | 1-naphthyl | 97 | 93 |
| 7 | Cy-Br | mesityl | 89 | 91 |
| 8 | NC ⁻ (CH ₂) ₆ -Br | (<i>E</i>)-1-hexenyl | 85 | 87 |
| 9 | <i>n</i> -Dodec-Br | <i>n</i> -Hex | 66 | 62 |

^aIsolated yield.

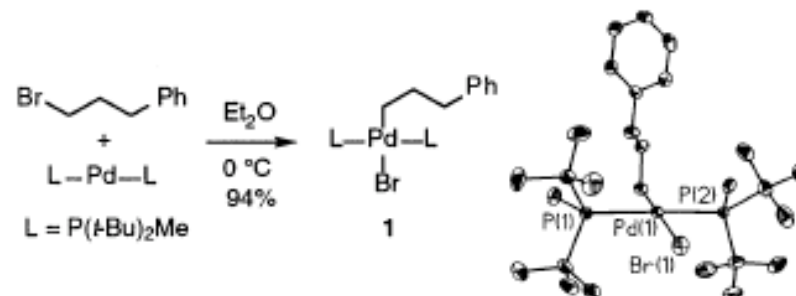
- Optimization reveals that *t*-amyl alcohol is the best solvent; THF affords poor yields

- P(*t*Bu)₂Me is the ligand of choice

- The use of *air stable phosphonium salts* as ligands proves equally effective

See: *Org. Lett.* **2001**, 3, 4295

- An oxidative addition intermediate was isolated and characterized

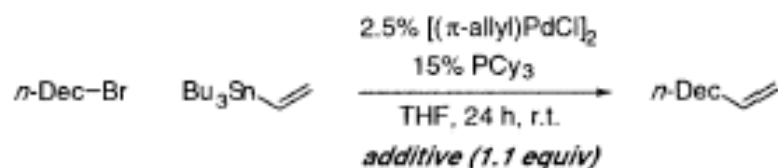


- This species is chemically competent and undergoes cross-coupling upon introduction of a nucleophile

J. Am. Chem. Soc. **2002**, 124, 13662

First Stille Cross-coupling Utilizing Alkyl Electrophiles

Table 1. Effect of Lewis-Basic Additives on the Stille Coupling of an Alkyl Bromide



| entry | additive | yield (%) ^a |
|-------|--|------------------------|
| 1 | none | <2 |
| 2 | N(<i>i</i> -Pr) ₂ Et | <2 |
| 3 | CsOH·H ₂ O | 7 |
| 4 | NaOMe | 4 |
| 5 | KF | <2 |
| 6 | CsF | <2 |
| 7 | Bu ₄ NF·3H ₂ O | 32 |
| 8 | Me ₄ NF (1.9 equiv), 3 Å molec. sieves | 73 |

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

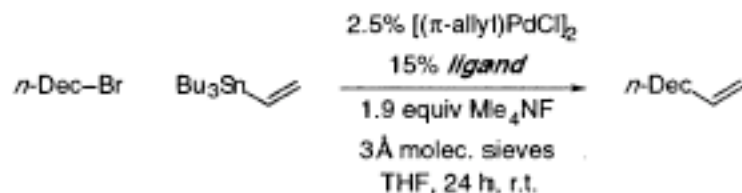
- Utilizing the identical conditions previously optimized for Suzuki couplings proved ineffective

- Prior evidence suggests that oxidative addition is facile in this catalyst system, therefore it was conjectured that transmetalation was the inhibitory step

- Addition of TBAF effected good conversion most likely via the tin ‘ate’ species, accelerating transmetalation

Ligand Screening for Stille Cross-couplings

Table 2. Effect of Ligand Structure on the Stille Coupling of an Alkyl Bromide



| entry | ligand | yield (%) ^a |
|----------|-------------------------------------|------------------------|
| 1 | PCy ₃ | 73 |
| 2 | PCy ₂ Et | 17 |
| 3 | PCy ₂ Me | <2 |
| 4 | PCy ₂ (<i>t</i> -Bu) | 9 |
| 5 | P(<i>t</i> -Bu) ₃ | <2 |
| 6 | P(<i>t</i> -Bu) ₂ Et | <2 |
| 7 | P(<i>t</i>-Bu)₂Me | 86 ← |
| 8 | P(OPh) ₃ | <2 |
| 9 | PPh ₃ | <2 |
| 10 | P(<i>o</i> -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.

- Screening was carried out under conditions optimized for PCy₃
- Cross-Coupling reactions are extremely sensitive to steric changes at phosphine
- The source of this extreme sensitivity is not currently well understood
- **P(*t*Bu)₂Me** was found to be the most effective ligand

Scope of the Alkyl Stille Cross-Coupling

$$\text{R-Br} + \text{Bu}_3\text{Sn-CH=CH-R}^1 \xrightarrow[\text{THF, r.t.}]{\begin{array}{l} 2.5\% [(\pi\text{-allyl})\text{PdCl}]_2 \\ 15\% \text{P}(\text{t-Bu})_2\text{Me or [HP}(\text{t-Bu})_2\text{Me]BF}_4 \\ 1.9 \text{equiv Me}_4\text{NF} \\ 3\text{\AA} \text{ molec. sieves} \end{array}} \text{R-CH=CH-R}^1$$

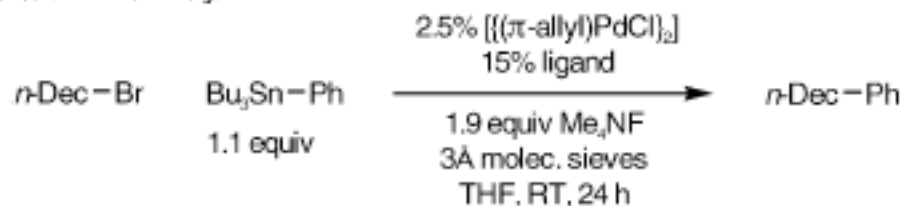
| entry | R-Br | tin reagent | yield (%) ^a | |
|-------|------|---|-------------------------|---|
| | | | P(t-Bu) ₂ Me | [HP(t-Bu) ₂ Me]BF ₄ |
| 1 | | Bu ₃ Sn-CH=CH- <i>n</i> -Hept | 96 | 92 |
| 2 | | Bu ₃ Sn-CH=CH-CH ₂ (OTHP)-CH ₃ | 71 | 70 |
| 3 | | Bu ₃ Sn-CH=CH-CH ₂ (OTHP)-CH ₃ | 62 | 64 |
| 4 | | Bu ₃ Sn-CH=CH-CH ₂ (OTHP)-CH ₃ | 60 | 66 |
| 5 | | Bu ₃ Sn-CH=CH- <i>n</i> -Hept | 59 | 59 |
| 6 | | Bu ₃ Sn-CH=CH-CH ₂ CH ₂ -Ph | 74 | 77 |
| 7 | | Bu ₃ Sn-CH=CH-CH ₂ CH ₂ -Ph | 58 | 65 |
| 8 | | Bu ₃ Sn-CH=CH-CH ₂ CH ₂ -Ph | 55 | 53 |
| 9 | | Bu ₃ Sn-CH=CH-C(Me)=CH-OTHP | 55 | 53 |

^a Isolated yield, average of two runs.

- Under optimized conditions good yields of cross-coupled adducts are obtained
- These conditions are again amenable to a diverse array of organic functional groups
- Phosphonium salts can be used in place of trialkyl phosphines with no diminishment in yield or reactivity
- Presently, only alkenyl tin species can be cross-coupled
- Only alkyl bromides react under these conditions

New Ligands for Alkyl-Aryl Stille Cross-Couplings

Table 1: Effect of ligand structure on the cross-coupling of 1-bromodecane with PhSnBu_3 .



| Entry | Ligand | Yield [%] ^[a] |
|-------|--|--------------------------|
| 1 | $\text{P}(\text{tBu})_2\text{Me}$ | 12 |
| 2 | PCy_3 | 22 |
| 3 | $\text{PMe}(\text{pyrrolidinyl})_2$ | 9 |
| 4 | $\text{PEt}(\text{pyrrolidinyl})_2$ | 32 |
| 5 | $\text{PCy}(\text{pyrrolidinyl})_2$ | 45 |
| 6 | $\text{P}(\text{tBu})(\text{pyrrolidinyl})_2$ | 4 |
| 7 | $\text{PPh}(\text{pyrrolidinyl})_2$ | 7 |
| 8 | $\text{P}(\text{iBuNCH}_2\text{CH}_2)_3\text{N}$ | <2 |
| 9 | PPh_3 | <2 |
| 10 | no ligand | <2 |

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

- Utilizing diaminophospane ligands significantly expands the scope of cross-couplings

- Diaminophosphanes are readily synthesized from PRCl_2 and amines

See: *Chem. Comm.* **2000**, 2065

J. Chem. Soc. Dalton Trans. **2002**, 1093

- Almost certainly attempts at asymmetric variants are underway

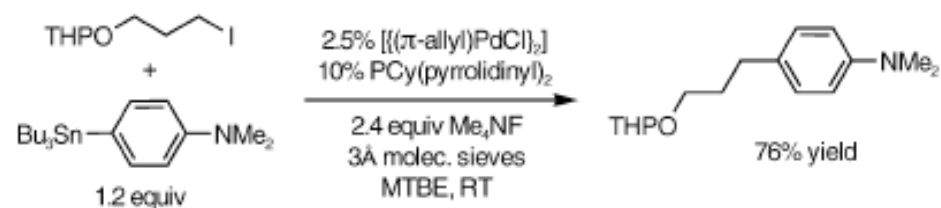
Extension of Stille Methodology

Table 2: Room-temperature Stille cross-couplings of functionalized alkyl bromides with aryl stannanes catalyzed by Pd/PCy(pyrrolidinyl)₂.

| Entry | R-Br | Aryl stannane | Yield [%] ^[a] |
|------------------|---|--|--------------------------|
| 1 | <i>n</i> -Dec-Br | Bu ₃ Sn-Ph | 72 |
| 2 | EtO-C(=O)-(CH ₂) ₄ -Br | Bu ₃ Sn-Ph-Me | 63 |
| 3 | EtO-C(=O)-(CH ₂) ₄ -Br | Bu ₃ Sn-Ph-OMe | 71 |
| 4 | EtO-C(=O)-(CH ₂) ₄ -Br | Bu ₃ Sn-Ph-CF ₃ | 57 |
| 5 | EtO-C(=O)-(CH ₂) ₄ -Br | Bu ₃ Sn-Ph-OMe | 61 |
| 6 | EtO-C(=O)-(CH ₂) ₄ -Br | Bu ₃ Sn-Ph-Me | 62 |
| 7 | NC-(CH ₂) ₄ -Br | Bu ₃ Sn-Ph-NMe ₂ | 68 |
| 8 ^[b] | THPO-(CH ₂) ₄ -Br | Bu ₃ Sn-Ph-F | 64 |
| 9 | CH ₂ =CH-(CH ₂) ₄ -Br | Bu ₃ Sn-Pyridine | 53 |

[a] Yield of isolated product (except for entry 1, which is a yield by GC versus a calibrated internal standard), average of two runs. [b] THP=tetrahydropyran.

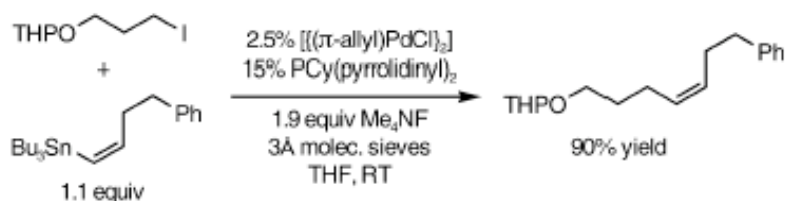
- PCy(pyrrolidinyl)₂ was found to be the best ligand
- MTBE was found to be a more effective solvent than THF
- An electronically diverse set of aromatic species undergo cross coupling with high functional group tolerance
- These conditions are extendable to alkyl iodides



Angew. Chem. Int. Ed. **2003**, *42*, 5079

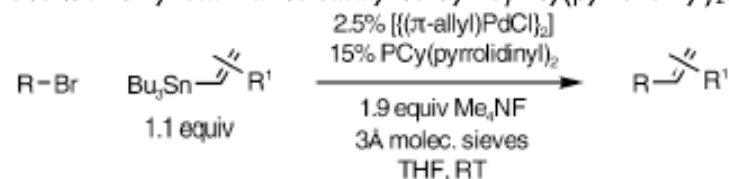
Optimized Conditions are Extended to Alkenyl Stannanes

- Alas, one set of conditions is suitable for aryl and alkenyl stannanes
- These conditions also allow for coupling of vinyl stannanes and alkyl iodides



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Table 3: Room-temperature Stille cross-couplings of functionalized alkyl bromides with vinyl stannanes catalyzed by $\text{Pd}/\text{PCy}(\text{pyrrolidinyl})_2$.

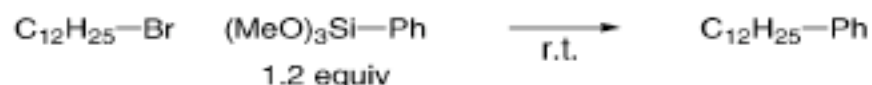


| Entry | R-Br | Vinyl stannane | Yield [%] ^[a] |
|-------|---------------------------------------|-----------------------------------|--------------------------|
| 1 | <chem>BnO-CH2-CH2-CH2-CH2-Br</chem> | <chem>Bu3Sn-CH=CH-CH2-OTHP</chem> | 74 |
| 2 | <chem>THP-CH2-CH2-CH2-Br</chem> | <chem>Bu3Sn-CH=CH-CH2-OTHP</chem> | 60 |
| 3 | <chem>NC-CH2-CH2-CH2-Br</chem> | <chem>Bu3Sn-CH=CH-CH2-OAc</chem> | 68 |
| 4 | <chem>EtO-C(=O)-CH2-CH2-Br</chem> | <chem>Bu3Sn-CH=CH-CH2-Ph</chem> | 89 |
| 5 | <chem>EtO-C(=O)-N(CH2)2-CH2-Br</chem> | <chem>Bu3Sn-CH=CH-CH2-Ph</chem> | 79 |
| 6 | <chem>CH2=CH-CH2-CH2-CH2-Br</chem> | <chem>Bu3Sn-CH=CH-CH2-Ph</chem> | 78 |
| 7 | <chem>THP-CH2-CH2-CH2-Br</chem> | <chem>Bu3Sn-CH=CH-CH2-OTHP</chem> | 54 |
| 8 | <chem>EtO-C(=O)-CH2-CH2-Br</chem> | <chem>Bu3Sn-CH=CH-CH2-OTHP</chem> | 73 |

[a] Yield of the isolated product, average of two runs.

Hiyama Cross-couplings of Organosilicon Reagents

Table 1. Effect of Reaction Parameters on the Hiyama Cross-Coupling of an Alkyl Bromide



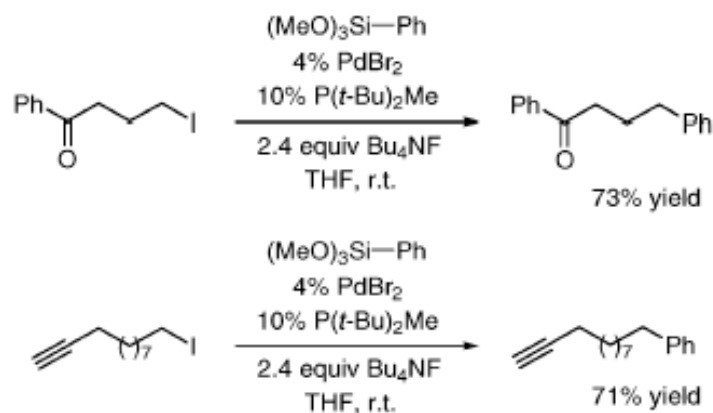
| entry | conditions | yield (%) ^a |
|----------|---|------------------------|
| 1 | 4% Pd(OAc) ₂ , 8% PCy ₃ , K ₃ PO ₄ ·H ₂ O | 0 |
| 2 | 5% Pd(OAc) ₂ , 10% P(<i>t</i> -Bu) ₂ Me, KO <i>t</i> -Bu | 0 |
| 3 | 2.5% [(π -allyl)PdCl] ₂ , 15% P(<i>t</i> -Bu) ₂ Me, Me ₄ NF, 3 Å molec. sieves | 0 |
| 4 | 4% PdBr₂, 10% P(<i>t</i>-Bu)₂Me, 2.4 equiv of Bu₄NF | 81 ← |
| 5 | 10% P(<i>t</i> -Bu) ₂ Me, 2.4 equiv of Bu ₄ NF | 0 |
| 6 | 4% PdBr ₂ , 2.4 equiv of Bu ₄ NF | 0 |
| 7 | 4% PdBr ₂ , 10% PPh ₃ , 2.4 equiv of Bu ₄ NF | 8 |
| 8 | 4% PdBr ₂ , 10% P(<i>t</i> -Bu) ₃ , 2.4 equiv of Bu ₄ NF | 0 |
| 9 | 4% PdBr ₂ , 10% P(<i>i</i> -Pr) ₂ Me, 2.4 equiv of Bu ₄ NF | 23 |
| 10 | 4% PdBr ₂ , 10% IMesHCl, 2.4 equiv of Bu ₄ NF ^b | 36 |

^a Determined by GC versus a calibrated internal standard (average of two runs). ^b IMesHCl: 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride.

- *Not surprisingly*, conditions for Suzuki and Stille couplings proved unsatisfactory
- PdBr₂ was the most effective Pd source
- TBAF was required to activate the organosilicon species
- P(*t*Bu)₂Me was again the best ligand
- IMes demonstrated some cross-coupling efficiency

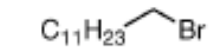
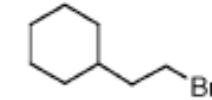

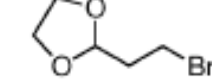


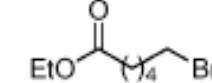
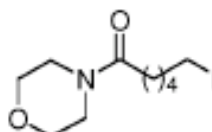
Variation of Alkyl Bromide Electrophiles

- Cross-coupling occurs with a variety of functionalized electrophiles
- Phosphonium salts can be used in place of free phosphines with marginal drops in yield
- Alkyl iodides can be used as electrophiles



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Table 2. Palladium-Catalyzed Hiyama Cross-Couplings of Alkyl Bromides at Room Temperature

| R-Br | | (MeO) ₃ Si-Ph 1.2 equiv | | 4% PdBr ₂ 10% P(<i>t</i> -Bu) ₂ Me 2.4 equiv Bu ₄ NF THF, r.t. | | R-Ph | |
|-------|---|---------------------------------------|--|---|--|------|--|
| entry | R-Br | yield (%) ^a | | | | | |
| | | P(<i>t</i> -Bu) ₂ Me | [HP(<i>t</i> -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.

Exploring the Scope of the Aryl-Si(OMe)₃ Coupling Partner

Table 3. Room-Temperature Hiyama Cross-Couplings of Alkyl Bromides with Arylsilanes

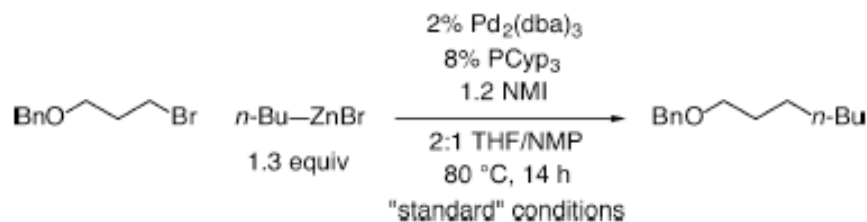
| | R-Br | (MeO) ₃ Si-Ar | 1.2 equiv | $\xrightarrow[\text{THF, r.t.}]{\begin{array}{l} 4\% \text{ PdBr}_2 \\ 10\% \text{ P}(t\text{-Bu})_2\text{Me} \\ 2.4 \text{ equiv Bu}_4\text{NF} \end{array}}$ | R-Ar |
|-------|------|--------------------------|-----------|--|------------------------|
| entry | R-Br | Ar | | | yield (%) ^a |
| 1 | | <i>p</i> -anisyl | | | 66 |
| 2 | | <i>p</i> -fluorophenyl | | | 55 |
| 3 | | <i>o</i> -tolyl | | | 59 |
| 4 | | 2-naphthyl | | | 67 |
| 5 | | <i>p</i> -anisyl | | | 69 |
| 6 | | <i>p</i> -fluorophenyl | | | 36 |
| 7 | | <i>o</i> -tolyl | | | 76 |
| 8 | | 2-naphthyl | | | 70 |
| 9 | | <i>p</i> -anisyl | | | 82 |
| 10 | | <i>p</i> -fluorophenyl | | | 50 |
| 11 | | <i>o</i> -tolyl | | | 72 |
| 12 | | 2-naphthyl | | | 84 |

^a Isolated yield, average of two runs.

- Electronically dissimilar aryl groups are coupled in good yields
- Diverse functionality is tolerated with regard to the electrophilic partner
- Scope is limited to aryl organosilicates

Negishi Couplings of Alkyl Electrophiles

Table 1. Effect of Various Reaction Parameters on the Efficiency of a Negishi Cross-Coupling



| entry | change from the standard conditions | yield (%) ^a |
|-------|---|------------------------|
| 1 | none | 70 |
| 2 | without 2% Pd ₂ (dba) ₃ | 0 |
| 3 | without 8% PCyp ₃ | 0 |
| 4 | without NMI | 54 |
| 5 | without NMP | 48 |
| 6 | at 30 °C | 43 |
| 7 | with 4% PCyp ₃ | 55 |
| 8 | with 1% Pd ₂ (dba) ₃ , 4% PCyp ₃ | 65 |

^a Yield according to GC, versus a calibrated internal standard.

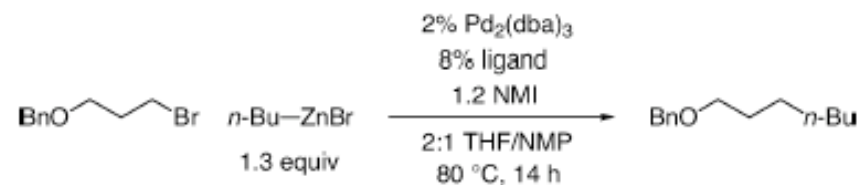
- Extensive investigation led to the use of PCyp₃ as the ligand of choice
- 2:1 THF/NMP was the optimum solvent
- High temperature was required

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- A ligand screen demonstrated that trialkyl phosphines are required for reactivity

- PCyp₃ emerged as the ligand of choice; unpublished in Suzuki/Stille reactions

Table 2. Effect of the Ligand on the Efficiency of a Negishi Cross-Coupling



| entry | ligand | yield (%) ^a |
|-------|---|------------------------|
| 1 | PCyp ₃ | 70 |
| 2 | PCy ₃ | 65 |
| 3 | P(<i>i</i> -Pr) ₃ | 59 |
| 4 | P(<i>t</i> -Bu) ₂ Me | 55 |
| 5 | P(<i>t</i> -Bu) ₃ | 3 |
| 6 | P(<i>n</i> -Bu) ₃ | 9 |
| 7 | PPh ₃ | 5 |
| 8 | P(<i>o</i> -tol) ₃ | 1 |
| 9 | P(2,4,6-trimethoxyphenyl) ₃ | 0 |
| 10 | P(2-furyl) ₃ | 2 |
| 11 | Cy ₂ P(CH ₂) ₂ PCy ₂ | 0 ^b |
| 12 | 1,3-bis(mesityl)-4,5-dihydroimidazolium tetrafluoroborate | 4 |
| 13 | P(OPh) ₃ | 0 |

^a Yield according to GC, versus a calibrated internal standard. ^b Ligand loading: 4%.

Generality of the Negishi Coupling Method

Table 3. Negishi Cross-Couplings of Alkyl Bromides with Alkylzinc Reagents

| entry | R-Br | R ¹ -ZnBr 1.3 equiv | 2% Pd ₂ (dba) ₃ 8% PCyp ₃ 1.2 NMI 2:1 THF/NMP 80 °C, 14 h | R-R ¹ | yield (%) ^a |
|-------|------------------|-----------------------------------|--|------------------|------------------------|
| 1 | <i>n</i> -Dec-Br | <i>n</i> -Bu-ZnBr | | | 90 |
| 2 | <i>n</i> -Dec-Br | | | | 89 |
| 3 | | | | | 76 |
| 4 | | | | | 83 |
| 5 | <i>n</i> -Dec-Br | | | | 52 |
| 6 | | | | | 68 |
| 7 | | | | | 67 |
| 8 | | | | | 65 |

^a Isolated yield (average of two runs).

Table 4. Negishi Cross-Couplings of Alkyl Iodides, Tosylates, and Chlorides with Alkylzinc Reagents

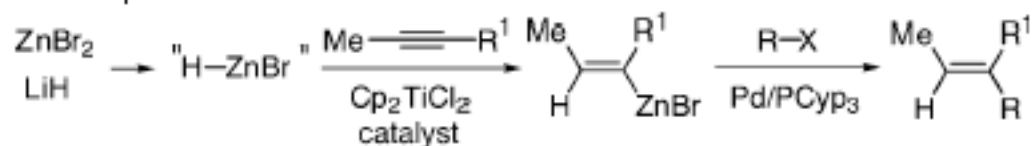
| entry | R-X | R ¹ -ZnBr 1.3 equiv | 2% Pd ₂ (dba) ₃ 8% PCyp ₃ 1.2 NMI 2:1 THF/NMP 80 °C, 14 h | R-R ¹ | yield (%) ^a |
|-------|---------------------|-----------------------------------|--|------------------|------------------------|
| 1 | <i>n</i> -Dec-I | <i>n</i> -Bu-ZnBr | | | 87 |
| 2 | | <i>n</i> -Bu-ZnBr | | | 48 |
| 3 | <i>n</i> -Dodec-OTs | <i>n</i> -Bu-ZnBr | | | 86 |
| 4 | | | | | 64 |
| 5 | <i>n</i> -Dec-Cl | <i>n</i> -Bu-ZnBr | | | 97 |
| 6 | | <i>n</i> -Bu-ZnBr | | | 77 |
| 7 | | <i>n</i> -Bu-ZnBr | | | 70 ^b |



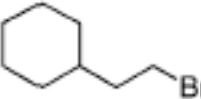
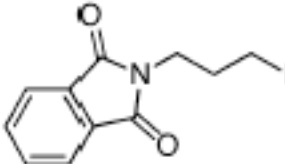
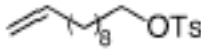
^a Isolated yield (average of two runs). ^b Alkyl halide:organozinc = 1:2:6. Product: double Negishi cross-coupling.

- A variety of alkyl bromides serve as cross-coupling partners in good yields
- This Negishi method is general for alkyl bromides, chlorides and tosylates!!

One-Pot Negishi Couplings with Alkenyl/Aryl Zinc Reagents

Table 6. One-Pot Hydrozincation/Negishi Cross-Coupling of Alkyl Electrophiles



| entry | Me—C≡C—R ¹ | R—X | yield (%) | |
|----------------|-----------------------|---|-------------------|--------------------------------------|
| | | | PCyp ₃ | [HPCyp ₃]BF ₄ |
| 1 | Me—C≡C—Me |  | 63 | 48 |
| 2 | Me—C≡C—Me |  | 53 | 51 |
| 3 ^a | Me—C≡C—Ph |  | 61 | 63 |
| 4 | Me—C≡C—Me |  | 69 | 72 |
| 5 ^a | Me—C≡C—Ph |  | 59 | 62 |

^a The product is an ~95:5 mixture of regioisomers.

- Simple, one-pot procedure demonstrates the utility and functional group compatibility of the method

- Coupling occurs with decent yields with free phosphines or with air-stable phosphonium salts

- For extended scope of alkenyl zinc cross couplings, see ‘Table 5’ in Full Paper

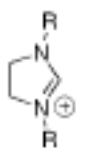

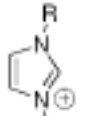
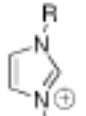
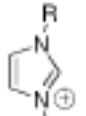
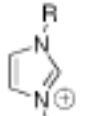
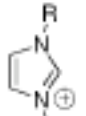
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Sonogashira Couplings Featuring N-Heterocyclic Carbenes

Table 1. Effect of Ligand Structure on the Sonogashira Coupling of an Unactivated Alkyl Bromide

$n\text{-Non-Br} \quad \equiv \quad n\text{-Hex} \xrightarrow[\text{DMF/Et}_2\text{O (1:2), 45 }^\circ\text{C, 16 h}]{\text{ligand}}$
 $n\text{-Non} \equiv n\text{-Hex}$

1.3 equiv
 2.5% $[(\pi\text{-allyl})\text{PdCl}]_2$
 7.5% CuI, 1.4 equiv Cs_2CO_3

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

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

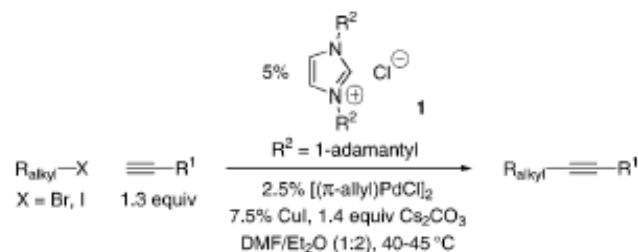
- Interestingly, trialkyl phosphines do not furnish coupling adducts

- Imidazolium carbenes that are sterically undemanding fail to yield cross-coupled adducts in appreciable quantity

- Increasing the steric bulk of the R-groups leads to increased yields and reactivity

- Unsurprisingly, in the absence of either Pd or Cu, no reaction occurs

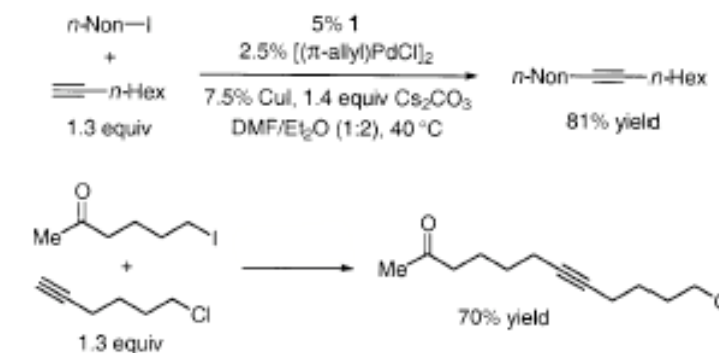
Scope and Reactivity of Sonogashira Cross-coupling



- Numerous functional groups are tolerated
- Coupling is limited to alkyl bromides
- **Allows for selective coupling of alkyl bromides in the presence of alkyl chlorides**
- Exact conditions are suitable for cross-coupling of alkyl iodides

Table 2. Sonogashira Couplings of Unactivated Alkyl Bromides

| entry | R-Br | $\equiv-R^1$ | yield (%) ^a |
|-------|--|---|------------------------|
| 1 | <i>n</i> -Non-Br | \equiv - <i>n</i> -Hex | 77 |
| 2 | AcO-CH ₂ (CH ₂) ₄ -Br | \equiv - <i>n</i> -Hex | 71 |
| 3 | NC-CH ₂ (CH ₂) ₄ -Br | \equiv - <i>n</i> -Hex | 79 |
| 4 | Cl-CH ₂ (CH ₂) ₄ -Br | \equiv - <i>n</i> -Dec | 50 |
| 5 | HO-CH ₂ (CH ₂) ₄ -Br | \equiv - <i>n</i> -Bu | 59 |
| 6 | NC-CH ₂ (CH ₂) ₄ -Br | \equiv - <i>t</i> -Bu | 70 |
| 7 | Ph-CH ₂ (CH ₂) ₄ -Br | \equiv -CH ₂ (CH ₂) ₄ -Cl | 74 |
| 8 | NC-CH ₂ (CH ₂) ₄ -Br | \equiv -CH ₂ (CH ₂) ₄ -Cl | 74 |
| 9 | AcO-CH ₂ (CH ₂) ₄ -Br | \equiv -CH ₂ (CH ₂) ₄ -Cl | 73 |
| 10 | Cyclohexyl-CH ₂ (CH ₂) ₄ -Br | \equiv -CH ₂ (CH ₂) ₄ -OTHP | 67 |
| 11 | CH ₂ =CH-CH ₂ (CH ₂) ₄ -Br | \equiv -CH ₂ (CH ₂) ₄ -OTHP | 69 |
| 12 | 2-(2-oxo-1,3-dioxolane-5-yl)-CH ₂ (CH ₂) ₄ -Br | \equiv -CH ₂ (CH ₂) ₄ -OAc | 58 ^b |
| 13 | 2-(2-oxo-1,3-dioxolane-5-yl)-CH ₂ (CH ₂) ₄ -Br | \equiv -CH ₂ (CH ₂) ₄ -OAc | 51 ^b |
| 14 | NC-CH ₂ (CH ₂) ₄ -Br | \equiv -Ph | 61 ^c |

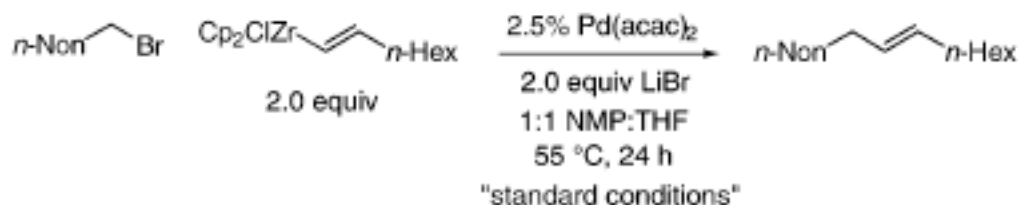


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^a Isolated yield, average of two runs. ^b Reaction was conducted at 60 °C. ^c 7.5% [(π -allyl)PdCl]₂, 22.5% CuI, and 15% ligand were employed.

Zirconium-Negishi Couplings Under 'Ligandless' Conditions

Table 1. Effect of Reaction Parameters on the Cross-Coupling of an Alkyl Bromide with an Organozirconium Reagent



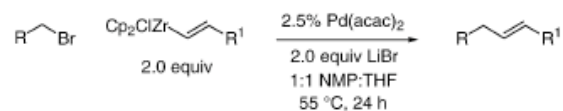
| entry | change from the "standard conditions" | yield (%) ^a |
|-------|---------------------------------------|------------------------|
| 1 | none | 99 |
| 2 | PdBr ₂ | 100 |
| 3 | Pd ₂ (dba) ₃ | 100 |
| 4 | NiBr ₂ | 57 |
| 5 | Ni(cod) ₂ | 62 |
| 6 | no Pd(acac) ₂ | 0 |
| 7 | LiI | 100 |
| 8 | no 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).

- Cross-coupling proceeds in excellent yields despite the nature of the Pd source
- Ni species do not efficiently catalyze the reaction under these conditions
- Poorer yield is obtained under reduced temperatures
- Lower catalyst loading reduces yield
- 'Ligandless' conditions reduce cost and simplify purification

'Ligandless' Negishi (Continued)

Table 2. Zirconium-Negishi Cross-Couplings of Alkyl Bromides under Ligandless Conditions^a



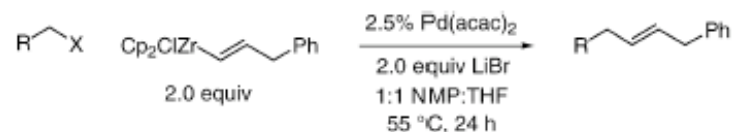
| entry | alkyl bromide | zirconium reagent | yield (%) |
|-------|---------------|---------------------------------------|-----------------|
| 1 | | $\text{Cp}_2\text{ClZr-CH=CH-Ph}$ | 99 |
| 2 | | $\text{Cp}_2\text{ClZr-CH=CH-t-Bu}$ | 86 |
| 3 | | $\text{Cp}_2\text{ClZr-CH=CH-OEt}$ | 96 |
| 4 | | $\text{Cp}_2\text{ClZr-CH=CH-OTHP}$ | 72 |
| 5 | | $\text{Cp}_2\text{ClZr-CH=CH-OTBDPS}$ | 99 |
| 6 | | $\text{Cp}_2\text{ClZr-CH=CH-OTHP}$ | 73 ^b |
| 7 | | $\text{Cp}_2\text{ClZr-CH=CH-n-Hex}$ | 82 |
| 8 | | $\text{Cp}_2\text{ClZr-CH=CH-Ph}$ | 97 |
| 9 | | $\text{Cp}_2\text{ClZr-CH=CH-Ph}$ | 68 |
| 10 | | $\text{Cp}_2\text{ClZr-CH=CH-Ph}$ | 77 |
| 11 | | $\text{Cp}_2\text{ClZr-CH=CH-Ph}$ | 77 |
| 12 | | $\text{Cp}_2\text{ClZr-CH=CH-Ph}$ | 74 |
| 13 | | $\text{Cp}_2\text{ClZr-CH=CH-Ph}$ | 60 ^b |
| 14 | | $\text{Cp}_2\text{ClZr-CH=CH-Et}$ | 85 |
| 15 | | $\text{Cp}_2\text{ClZr-CH=CH-t-Bu}$ | 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.

- Notably high yields are obtained for many diverse coupling partners

- The conditions are general and may be applied to alkyl iodides, tosylates and chlorides (in lower yield)

Table 3. Zirconium-Negishi Cross-Couplings of Other Alkyl Electrophiles under Ligandless Conditions^a



| entry | alkyl halide | yield (%) |
|-------|--------------|-----------|
| 1 | | 82 |
| 2 | | 83 |
| 3 | | 46 |

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

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Conclusions

- Cross-coupling reactions of alkyl electrophiles have only recently become feasible (first report 1992)
- Preliminary studies by Suzuki and Knochel demonstrated the viability of these types of transformations
- Recently Fu and coworkers have extended this reaction type to Suzuki, Stille, Negishi, Hiyama, and Kumada cross-couplings

Other Communications

For Pd catalyzed Kumada-like couplings, see: Beller, et. al. *Angew. Chem. Int. Ed.* **2002**, 41, 4056

For Ni catalyzed Negishi couplings of secondary alkyl halides, see: Fu, et. al. *J. Am. Chem. Soc.* **2003**, 125, 14726

For Ni catalyzed Suzuki couplings of secondary alkyl halides, see: Fu, et. al. *J. Am. Chem. Soc.* **2004**, 126, 1340

For Fe catalyzed Kumada-like couplings, see: Hayashi, et. al. *Org. Lett.* **2004**, 6, 1297

For Kumada-Corriu like couplings of alkyl halides and alkynes, see: Luh, et. al. *Org. Lett.* **2004**, 6, 1461