# Palladium-Catalyzed Reactions of Arylindium Reagents Prepared Directly from Aryl Iodides and Indium Metal

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*JOC*, ASAP, 8/22/2008

Gary Davis, Current Literature Presentation, 8/30/08

# Introduction

- Why Indium?
  -Closely parallels chemistry of transition metals (Zn, Sn) without toxicity problems

  -Safe for the environment

  -Mild and selective without use of cryogenic or inert conditions

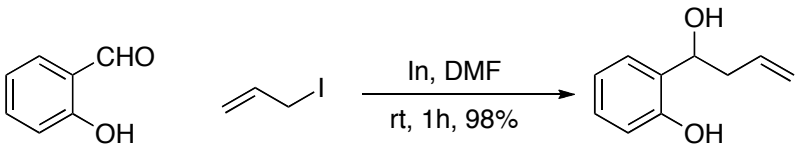
- Preparation of organoindium reagents:
  -Allylic halides and In(0) (*J. Organomet. Chem*. **1972**, *40*, C9.)

  -Transmetalation between $HgR_2$ and In(0) (*JACS*, **1934**, *56*, 1047.)

  -RLi or RMgBr and $InX_n$ n = 1-3 (most common)

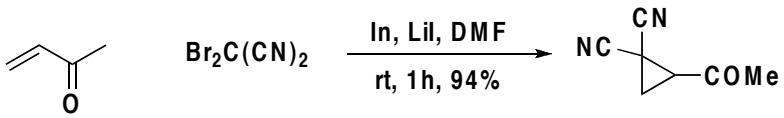
# Reactions of Organoindium Reagents

## Allylation



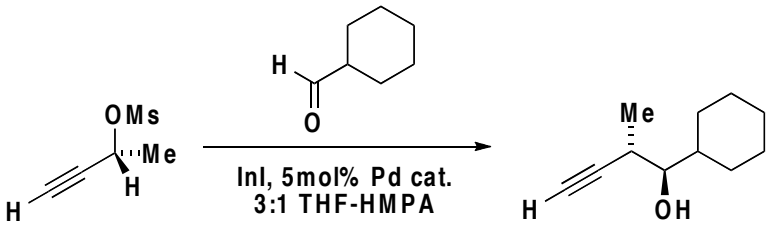

*J. Organomet. Chem*. **1972**, *40*, C9.
*J. Organomet. Chem*. **1974**, *81*, 329.

## Cyclopropanation of deactivated olefins




*J. Chem. Soc., Chem. Commun.* **1989**, 1286.

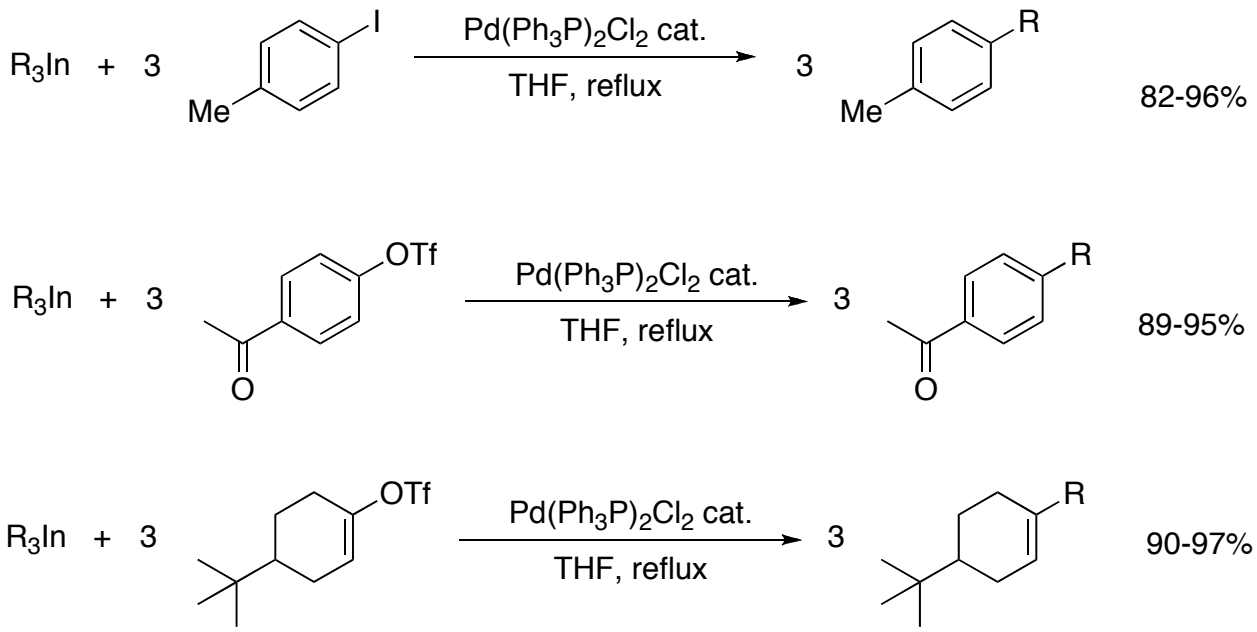
## Enantioenriched homopropargylic alcohols




**76%, 95:5 (anti:syn), 95%** *ee*

*JOC* **1999**, *64*, 696.

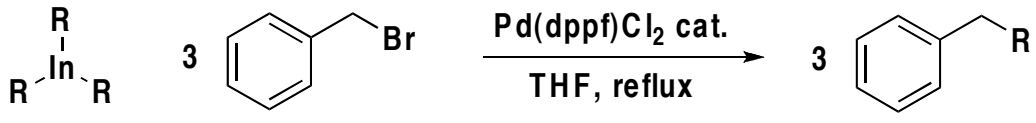
# Cross-couplings: General Cases




R = Ph, vinyl, Ph-acetylene, TMS-acetylene, *n*-Bu, Me, c-$C_3H_5$

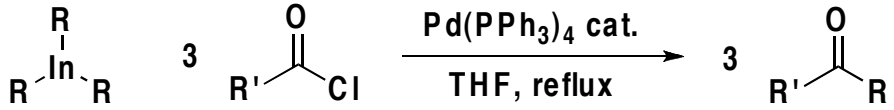
Sarandeses et al., *Org. Lett*. *1*(8), **1999**, 1267-69.

# Benzylic, Acyl Chloride Cross-Coupling




94-96%

R = Ph, vinyl, Ph-acetylene, TMS-acetylene

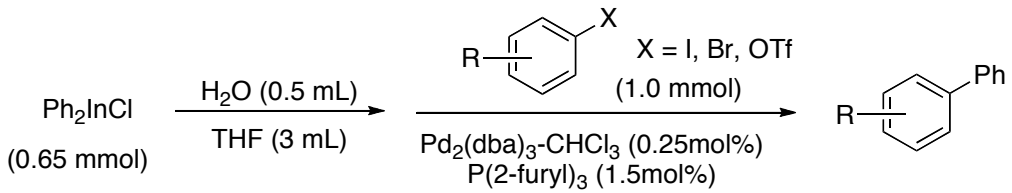



89-97%

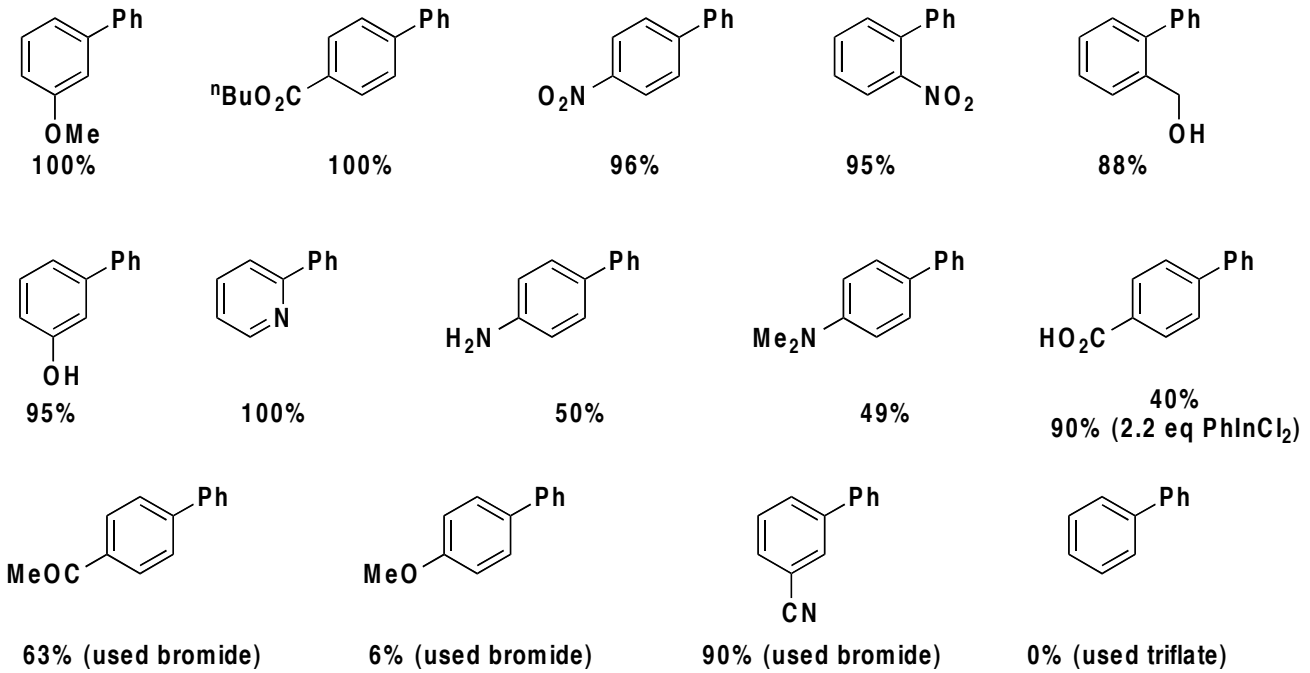
R = Ph, vinyl, Ph-acetylene, TMS-acetylene, Me

Sarandeses et al., *JACS* **2001**, *123*, 4155-4160.

# Cross-Coupling in Aqueous Media



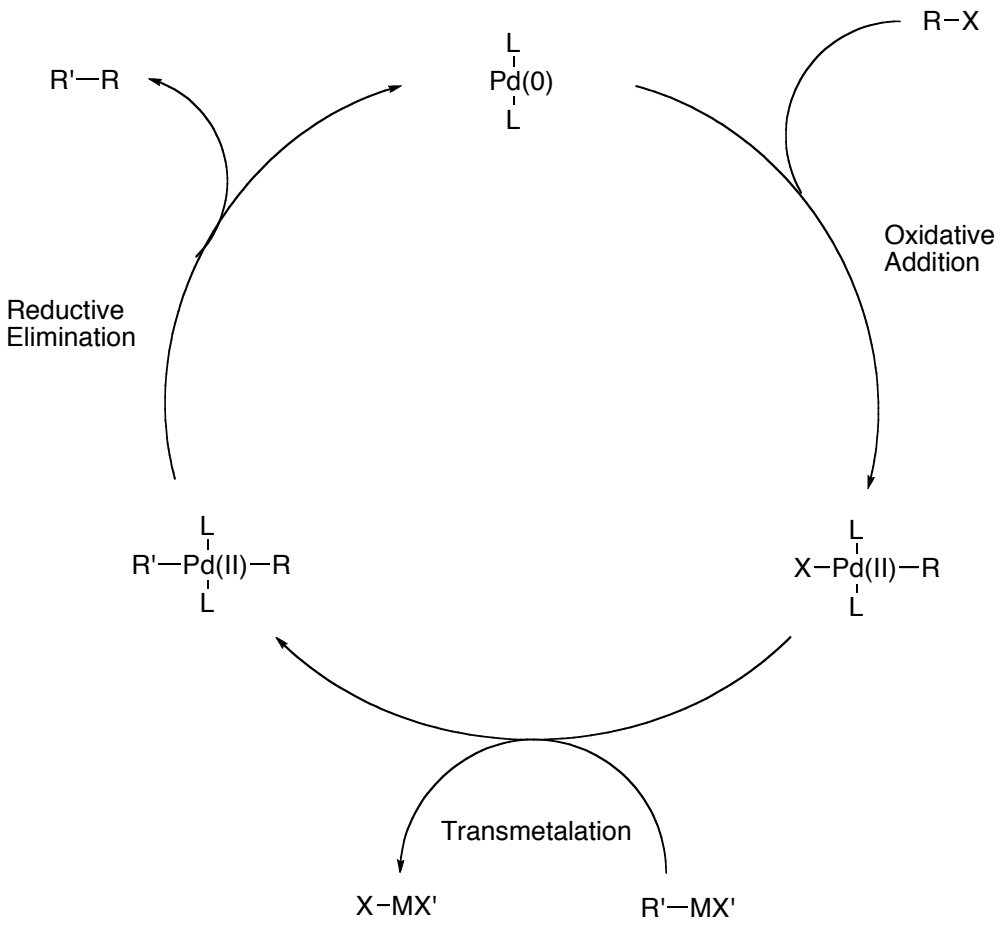

Product Scope:




Oshima et al., *OL* **2001**, *3*, 1997.

# Mechanistic Considerations

General Catalytic Cycle



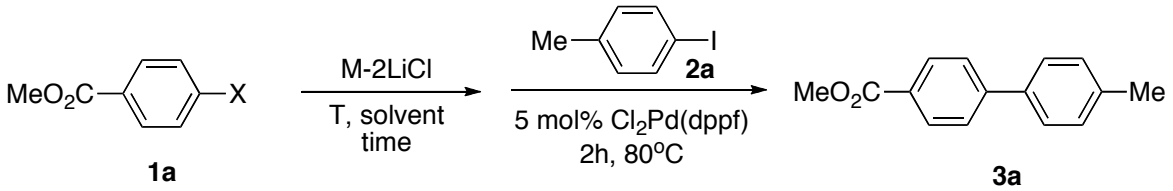

May also involve a transient Pd-In complex prior to transmetalation as proposed by Marshall and others.

*Chem. Rev*. **2000**, *100*, 3163-3185.

# Title Paper

- Preparation of organoindium reagents using In(0) and LiCl (As reported by Knochel for Zn, Mg, and Cu)
- Minimal activation of metal required
- Resulting organoindium reagents are air and moisture stable
- Indium can then be reduced with Zn to regenerate In(0)

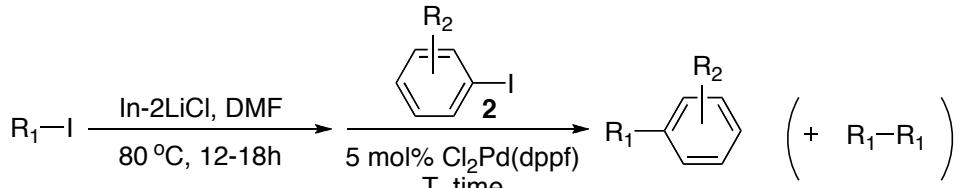
# Title Paper-Optimization




| entry | M | X | solvent | T (°C) | time (h) | % yield 3a[a] |
|---|---|---|---|---|---|---|
| 1 | In | I | DMF | 80 | 12 | 85 |
| 2 | In | I | THF | 65 | 12 | 20 |
| 3 | In | I | DME | 80 | 12 | 25 |
| 4 | In | I | DMF[b] | 80 | 12 | 83 |
| 5 | In | I | DMF | 100 | 2 | 80 |
| 6 | In | Br | DMF | 100 | 12 | 45 |
| 7 | InI | I | DMF | 80 | 12 | 42 |
| 8 | $InCl_2$ | I | DMF | 80 | 12 | <10 |

[a]Refers to isolated yields after column chromatography. [b]Methanol (10% by volume) was added to the DMF solution of the indium reagent just prior to the cross-coupling reaction.

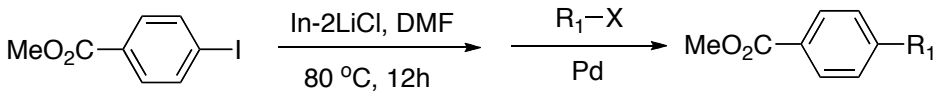
# Title Paper-Diversity of Aryl Iodides



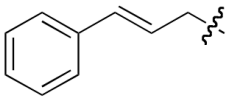
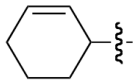

| entry | $R_1$ | % conv **1**[a] | $R_2$ | $T$ (°C) | time (h) | **3** | % yield **3**[b] |
|---|---|---|---|---|---|---|---|
| 1 | 4-$CO_2$Me-$C_6H_4$ | 97 | 4-OMe | 80 | 2 | b | 75 |
| 2 | 4-$CO_2$Me-$C_6H_4$ | | 4-Ac | 80 | 4 | c | 65 |
| 3 | 4-$CO_2$Me-$C_6H_4$ | | 4-CN | 80 | 3 | d | 59 |
| 4 | 4-$CO_2$Me-$C_6H_4$ | | 2-$CO_2$Me | 80 | 2 | e | 55 |
| 5 | 4-$CO_2$Me-$C_6H_4$ | | H | 80 | 3 | f | 63 |
| 6 | 4-Ac-$C_6H_4$ | 98 | 4-Me | 80 | 3 | g | 50[d,e] |
| 7 | 3-CN-$C_6H_4$ | 98 | 4-Ac | 80 | 6 | h | 89[d] |
| 8 | 3-CN-$C_6H_4$ | | 4-OMe | 80 | 6 | i | 75[d] |
| 9 | 3-CN-$C_6H_4$ | | 2-Me | 100 | 12 | j | 62[d] |
| 10 | 4-CN-$C_6H_4$ | 97 | 4-Cl | 80 | 6 | k | 50[d,e] |
| 11 | 4-CN-$C_6H_4$ | | 2-F | 80 | 3 | l | 88[d,f] |
| 12 | 4-CN-$C_6H_4$ | | 2-OMe | 100 | 3 | m | 37[e] |
| 13 | 4-Cl-$C_6H_4$ | 87 | 4-Ac | 80 | 12 | n | 61[d] |
| 14 | 2-Ac-$C_6H_4$ | 88 | 4-CN | 90 | 15 | o | 72[d] |
| 15 | 4-OMe-$C_6H_4$ | 94[c] | 4-Ac | 100 | 5 | p | 35[e] |

[a]For the insertion reaction, conversions were assayed by GC-MS analysis of an aliquot quenched with HCl/$H_2O$. [b]Refers to isolated yields after column chromatography, unless otherwise indicted. [c]Insertion reaction performed at 120 °C for 12 h. [d]Yield determined by GC-MS analysis. [e]Significant amounts of homodimer **4** also produced. [f]Catalyst for cross-coupling was $Cl_2Pd(PPh_3)_2$.

# Title Paper-Acyl and Allylic Electrophiles




**1** **7**

| Entry | $R_1$ | X | Pd[b] | **7** | % Yield **7**[e] |
|---|---|---|---|---|---|
| 1 | 4-Me-PhCO | Cl | A | **7a** | 40 |
| 2 | $PhCH_2CH_2CO$ | Cl | A | **7b** | 45 |
| 3 | $CH_2CH(CH_2)_3CO$ | Cl | A | **7c** | 40 |
| 4 |  | OAc | B | **7d** | 48 |
| 5 |  | $OCO_2Me$ | B | **7e** | 51 |

[a]Typical reaction conditions: a DMF solution of the indium reagent (~0.81 M) was added to $R_1$-X (1.0 equiv) and palladium catalyst (5-10 mol %) and heated to 80 C under argon for 2 h, at which time complete consumption of $R_1$-X was observed by TLC. [b]A = 5 mol % $Pd(PPh_3)_4$; B = 10 mol % $Pd(dba)_2$. [c]Refers to isolated yields after column chromatography.

# Limitations

- In in all forms is expensive when compared to Zn and Mg

| Metal Species | Quanitity (g) | Cost ($) |
|---|---|---|
| In (powder) | 5 | 125.50 |
| InCl | 2 | 132.50 |
| $InCl_2$ | 10 | 127.50 |
| $InCl_3$ | 5 | 82.60 |
| Zn (dust) | 1000 | 67.20 |
| Mg (turnings) | 1000 | 79.40 |

- Regeneration process from paper still under investigation

# Conclusions

- Demonstrated a wide variety of arylindium reagents can be prepared directly without transmetalation
- Pd cat. cross-coupling of arylindium reagents with aryl iodides proceeds in high yields
- Cross-coupling reactions can be done in the presence of protic solvents
- Reaction also occurs with acyl and allylic electrophiles