

# TM-Catalyzed Cross-Coupling Reactions

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Relevant references:

*Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**.

*Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, **2002**.

Cross-Coupling Reactions. A Practical Guide; Miyaura, N., Ed. *Top. Curr. Chem.* **2002**, 219.

Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int.* **2005**, 44, 4442-4489

Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, 106, 2651-2710.

<http://pubs.acs.org/JACSbeta/jvi/issue15.html>

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## Cross-Coupling Reactions

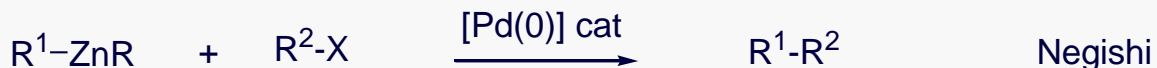
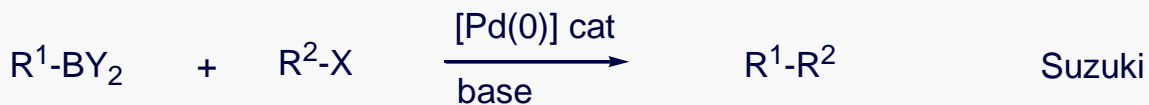
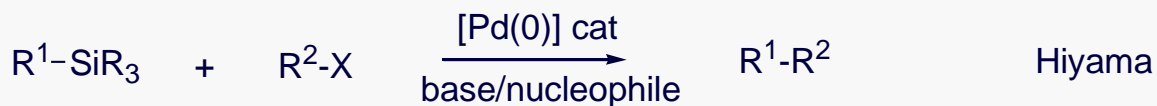
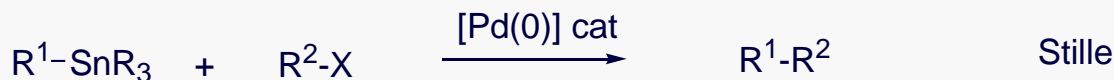
In 1989, OMCOS V<sup>1</sup> took place in Florence and being a major conference featuring new discoveries achieved with organometallic reagents in organic synthesis, it left me with the impression that *all* important transformations could—now or in the future—be performed with the aid of adequately fine-tuned metal catalysts. Today, it is safe to say that those early findings were key discoveries for a conceptual revolution that occurred in organic chemistry in recent years. Metal catalysts can be found everywhere, and many synthetic advances are directly linked to scientific progress and developments in catalytic chemistry.

In those early days, the seminal work by Heck, Negishi, and Suzuki on palladium-catalyzed cross-coupling reactions that led to their Nobel Prize in Chemistry in 2010<sup>2</sup> had already been known. Evidently, it was important for the formation of new

couplings with aryl halides has been provided by Bilodeau and Forgiione.<sup>5</sup> The substrate scope and the effects of various parameters such as solvent, base, and additives on the reaction efficiency have been studied and mechanistic considerations have revealed possible reaction pathways. The fact that this study was conducted at a pharmaceutical company shows the importance of such cross-coupling reactions in the synthesis of new drug candidates.

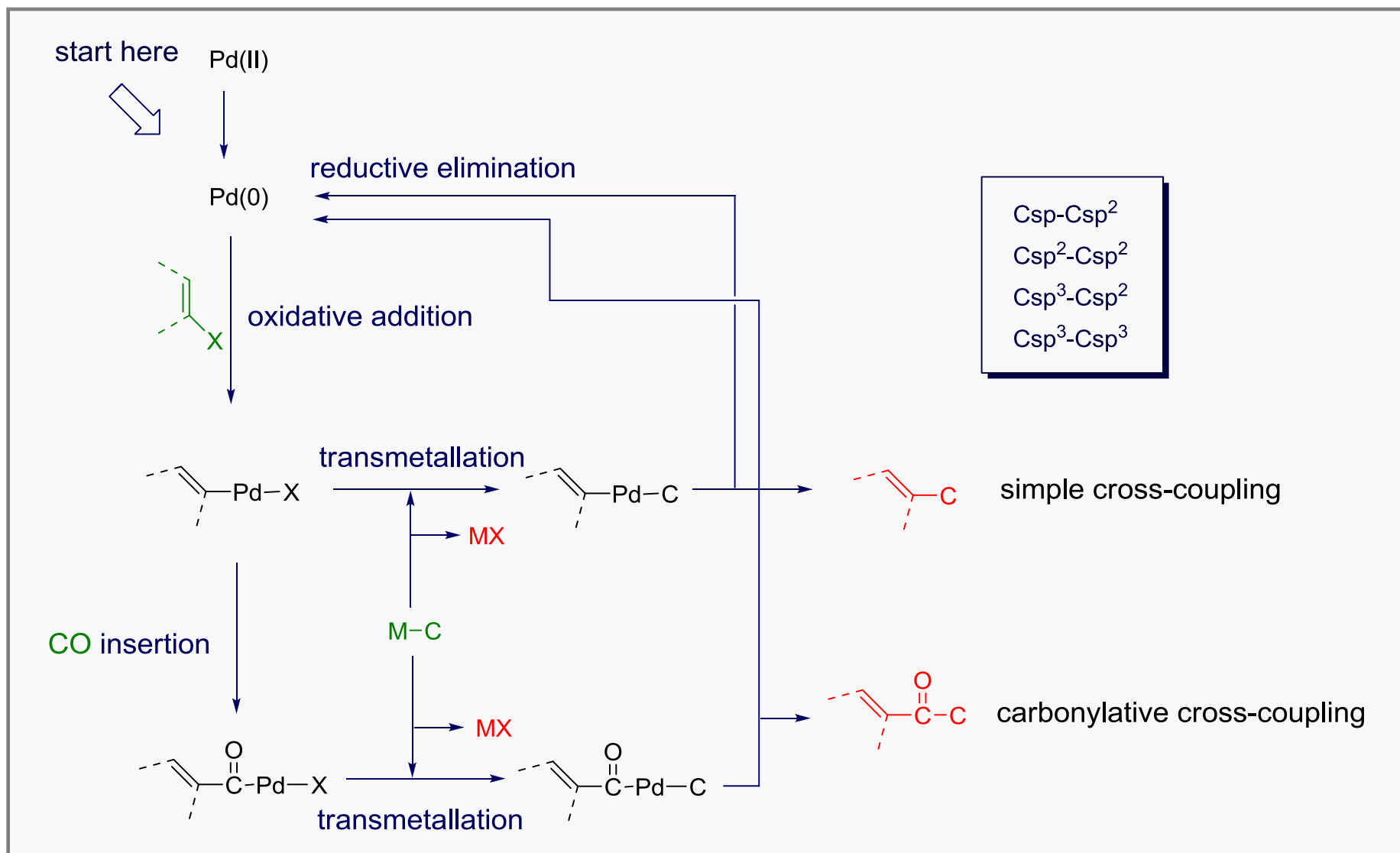
Many cross-coupling reactions lead to biaryl structures. However, the analogous approach can also be used for the synthesis of substituted olefins. Along those lines, Barluenga and Valdés described palladium-catalyzed cross-coupling reactions between tosyl hydrazones and aryl nonaflates.<sup>6</sup> The process provides access to di-, tri-, and tetrasubstituted alkenes. The exclusive *E*-stereochemistry in the formation of trisub-

# TM-Catalyzed Cross-Coupling Reactions

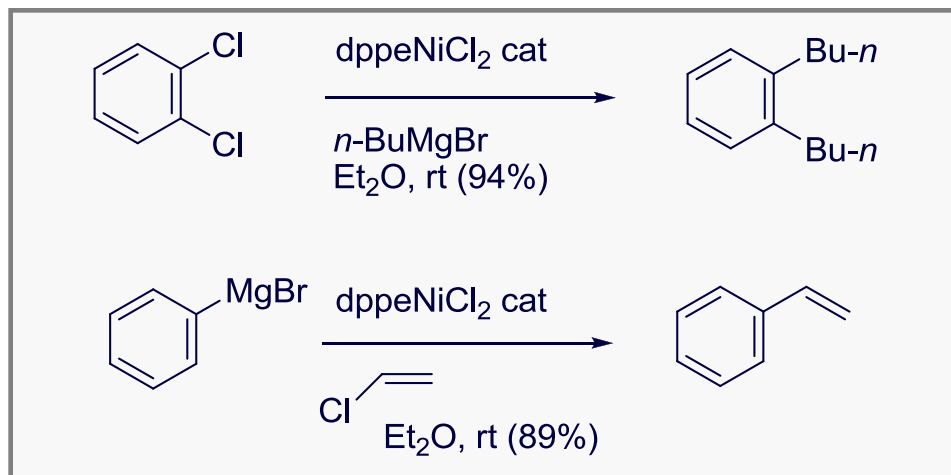


In the presence of CO atmosphere these reactions can be carbonylative

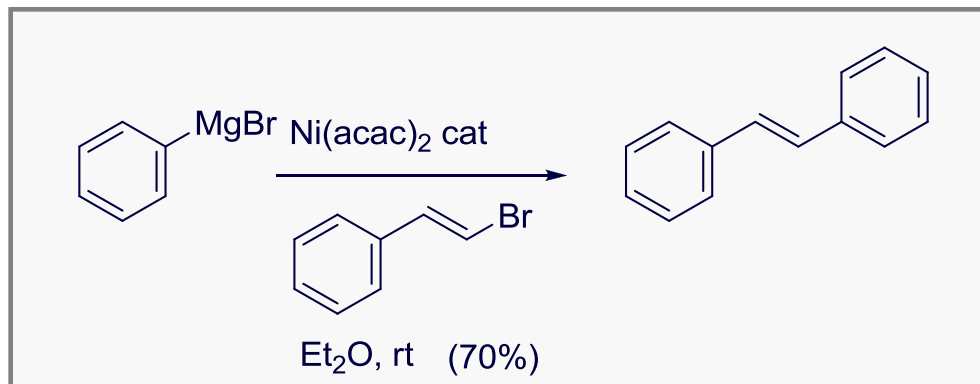
# General Mechanism



# The Kumada-Corriu Coupling



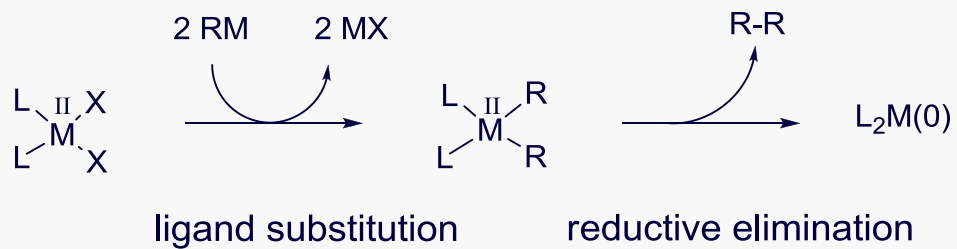
Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376.



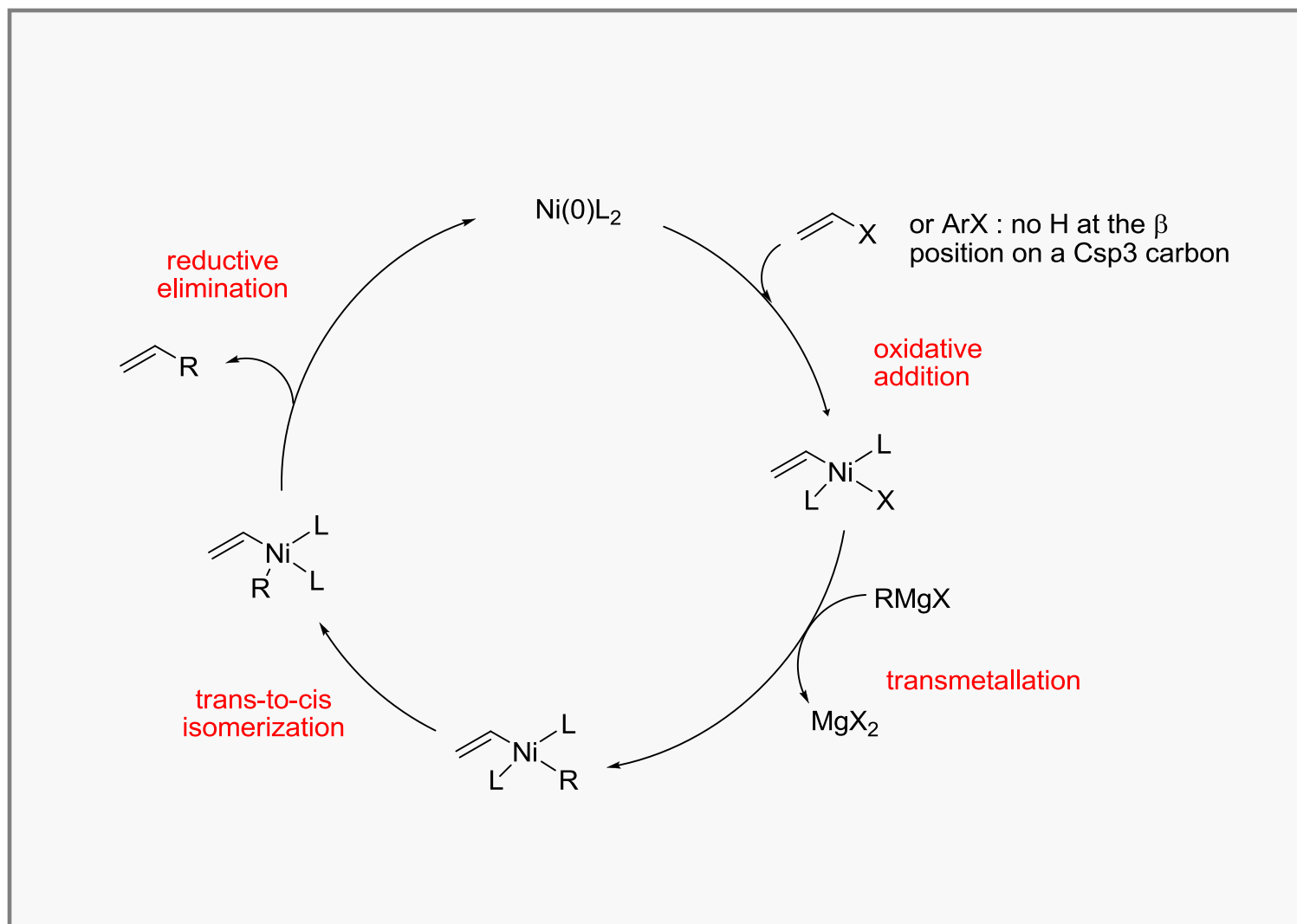
Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144.

# The Pd(II) Reduction

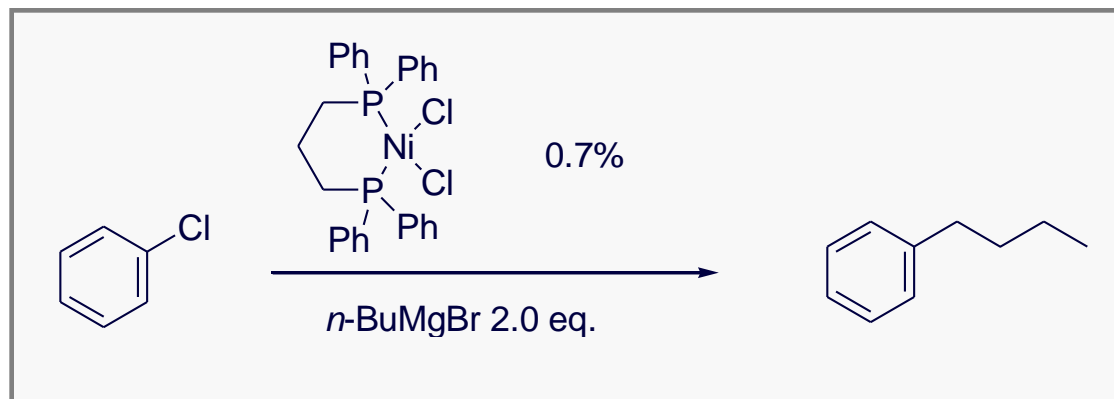
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# Mechanism



# The Kumada Corriu Coupling

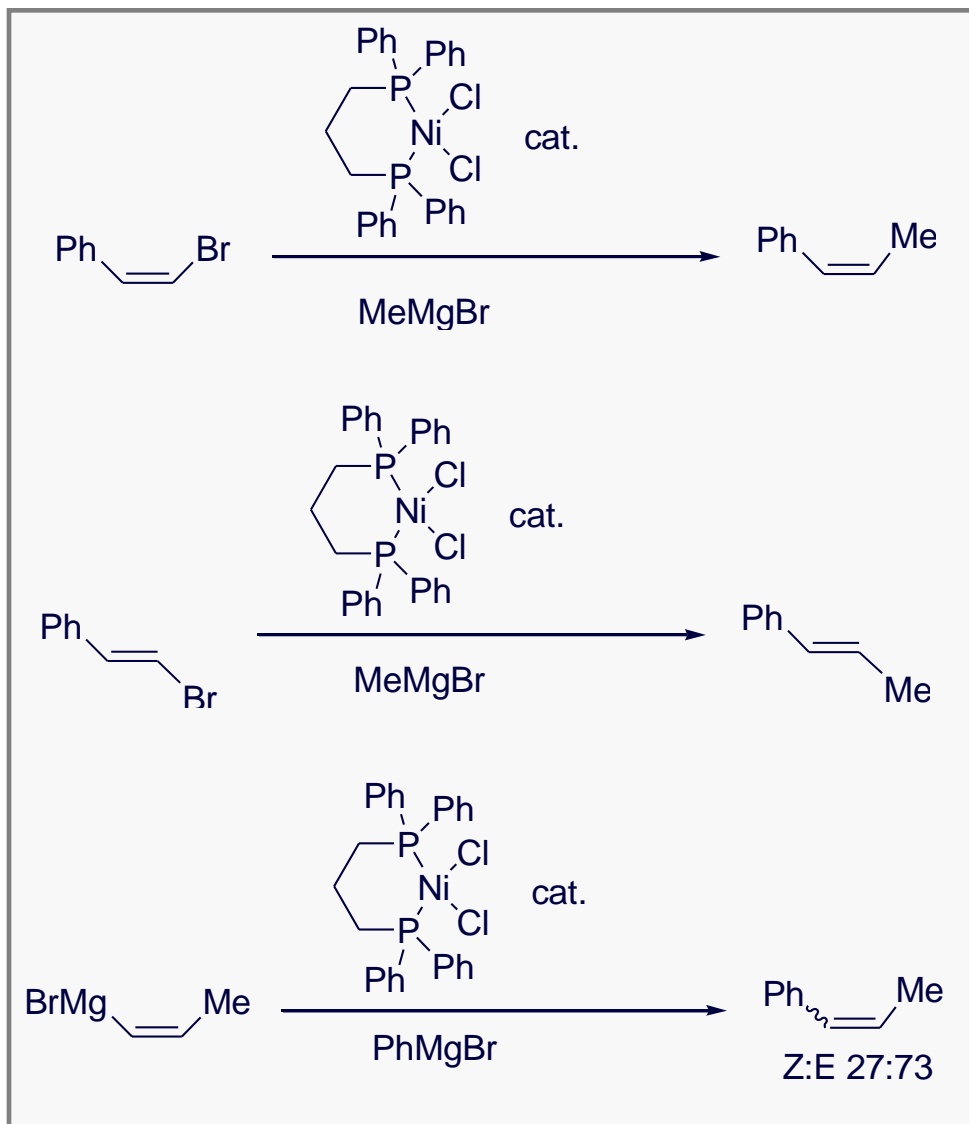


Kumada, M.  
*Bull. Chem. Soc. Jpn.* **1976**,  
49, 1958.

- Best results with diphosphine ligands (best dppp) and aryl or vinyl chlorides.
- The Ni pre-catalyst is commercially available
- Steric hindrance is acceptable only on the Grignard component
- The reaction is limited to halide partners that do not react with organomagnesium compounds.
- Typically used in the industrial-scale production of styrene derivatives and the synthesis of unsymmetrical biaryls.
- Alkynyl Grignard (with Pd cat.) can also be cross coupled *Org. Lett.*, **2004**, 6, 1461-1463
- Under particular and mild conditions [ $\text{Pd}(\text{OAc})_2/\text{PCy}_3$  cat, NMP/THF, rt] coupling of alkyl halides is also possible: Frisch, A. C. Shaikh, N. Zapf, A. Beller, M. *Angew. Chem.*, **2002**, 114, 4218-4221



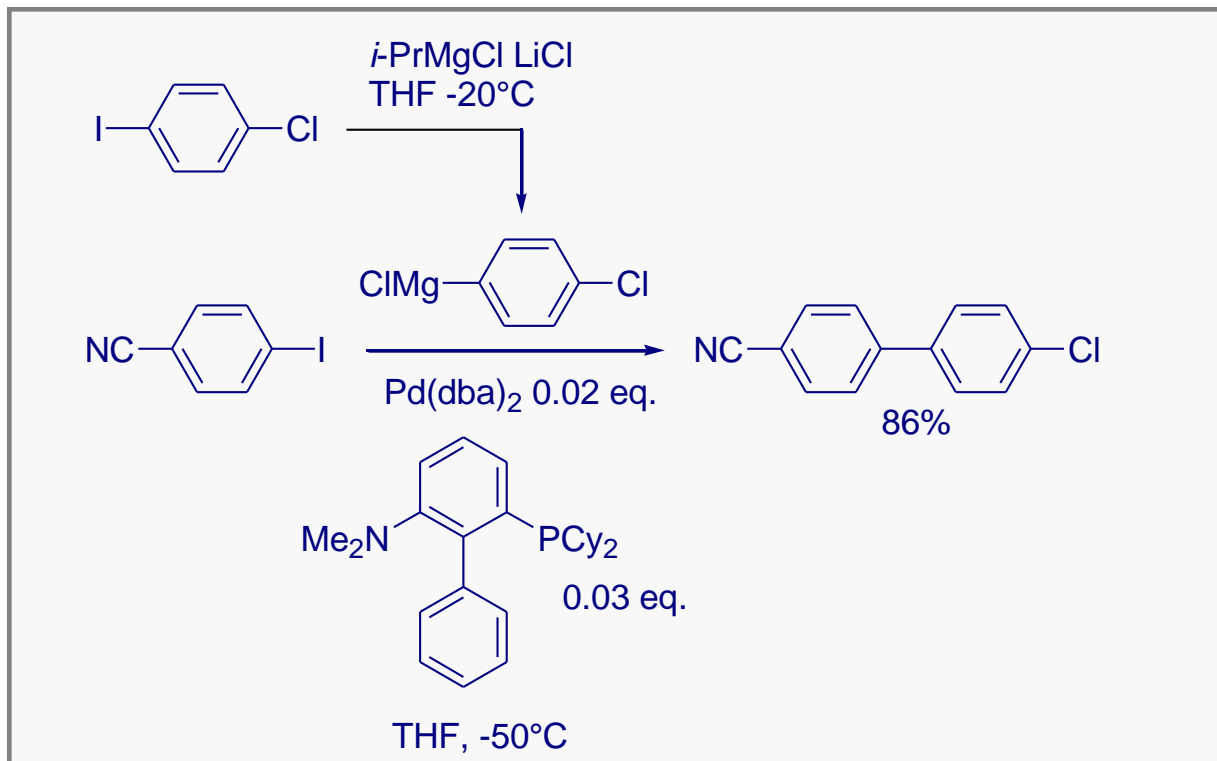
# Configuration of the Vinyl Residues



Vinyl halides cross couple with total retention of configuration.

In contrast, alkenyl Grignard reagents lose their configuration in the coupling

# Improved Functional Group Tolerance



The Grignard reagent is prepared in situ via the **Knochel method** (**I/Mg exchange** between an aryl iodide and isopropylmagnesium chloride/ lithium chloride).

Martin, R.; Buchwald S. L. *J. Am. Chem. Soc.*, **2007**, 129, 3844–3845A.

Krasovskiy, A.; Knochel, P. **2004**, *Angew. Chem. Int. Ed. Engl.*, 43, 3333–3336

# The Negishi Coupling

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In the seventies, Negishi's group published several seminal papers on the Pd- or Ni-catalyzed cross-coupling disclosing:

- The **Pd-** or **Ni-**catalyzed coupling between **alkenylalanes** and aryl **halides**, and the related alkenyl-alkenyl coupling.
- The **Pd-**catalyzed coupling of **organozinc chlorides** with alkenyl and aryl **halides**.
- The **Pd-** or **Ni-**catalyzed coupling of **organozirconiums** with aryl or alkenyl **halides**
- The **Pd-**catalyzed **carboalumination-cross-coupling tandem** reaction in the presence of  $\text{ZnCl}_2$  or  $\text{ZnBr}_2$  for the coupling step.

These findings established for the first time that the Pd- or Ni-catalyzed cross-coupling could be achieved with main group organometals less electropositive than Li or Mg such as Zn, B, and Sn. Subsequently, Negishi focused his studies on the coupling of organozincs, whereas coupling of organoboranes and organostannanes was subsequently developed by Suzuki and Stille, respectively.

The major drawback of the Negishi coupling is the incompatibility of the organozinc reagents with many common functional groups, together with their relative sensitivity towards oxygen and water.

Negishi, E-I.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G.; *Aldrichimica Acta*, **2005**, *38*, 71-88.  
Lessene, G. *Aust. J. Chem.* **2004**, *57*, 107-117.

# The Seminal Paper

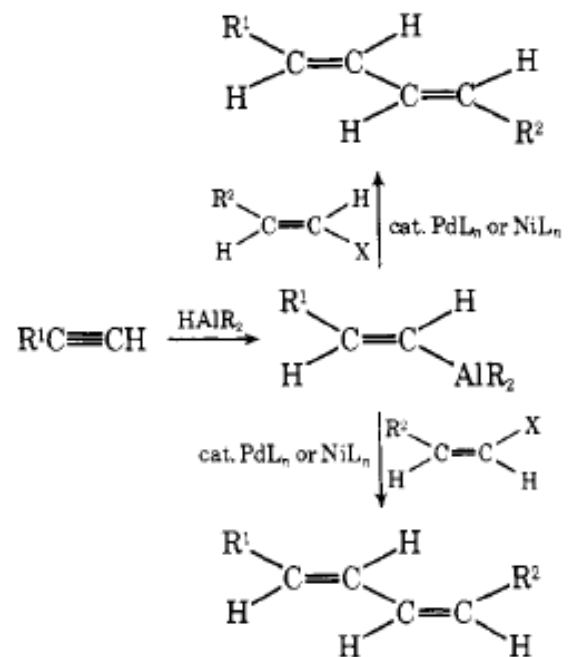
*Journal of the American Chemical Society* / 98:21 / October 13, 1976

## A Novel Stereospecific Alkenyl-Alkenyl Cross-Coupling by a Palladium- or Nickel-Catalyzed Reaction of Alkenylalanes with Alkenyl Halides

*Sir:*

Direct and selective coupling of two unlike alkenyl groups by the reaction of an alkenylmetal derivative with an alkenyl halide has been difficult. None of the known alkenylmetals of the main group elements appears to undergo satisfactorily a stereospecific substitution reaction with an alkenyl halide.<sup>1</sup> Although the reaction of alkenylcuprates with alkenyl halides is promising, it does not appear to have been well developed.<sup>2</sup>

We wish to report that a general and selective procedure for the synthesis of conjugated (*E,E*)- and (*E,Z*)-dienes can now be provided by the reaction of (*E*)-alkenylalanes, readily obtainable via hydroalumination of alkynes,<sup>3</sup> with alkenyl halides in the presence of suitable palladium or nickel complexes (eq 1).



$R^1, R^2 = \text{alkyl}; R = i\text{-Bu}; X = \text{Br or I}; L = PPh_3$

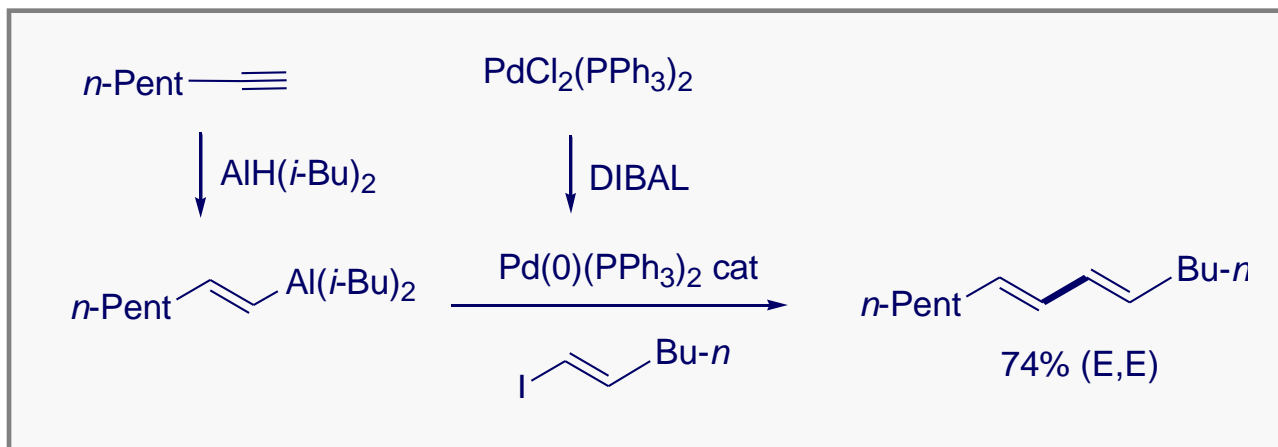
**Shigeru Baba, Ei-ichi Negishi\***

*Department of Chemistry, Syracuse University  
Syracuse, New York 13210*

*Received June 21, 1976*

# The 1<sup>st</sup> Report

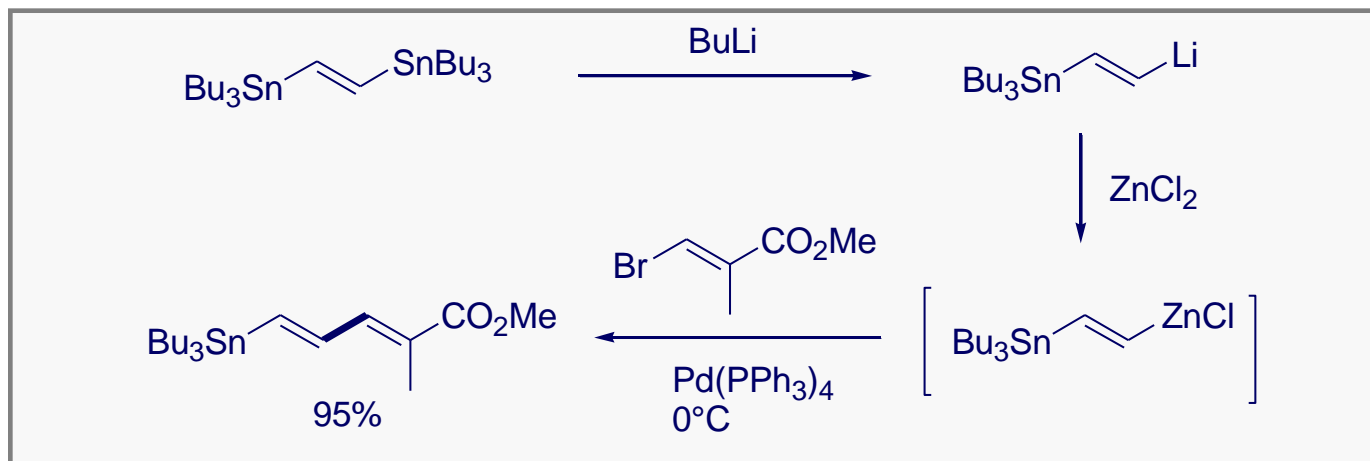
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Baba S.; Negishi, E.-i. *J. Am. Chem. Soc.*, **1976**, *98*, 6729-6731

Cross coupling via alkenylZr, in turn obtained via hydrozirconation of terminal alkynes, tolerates more functional groups

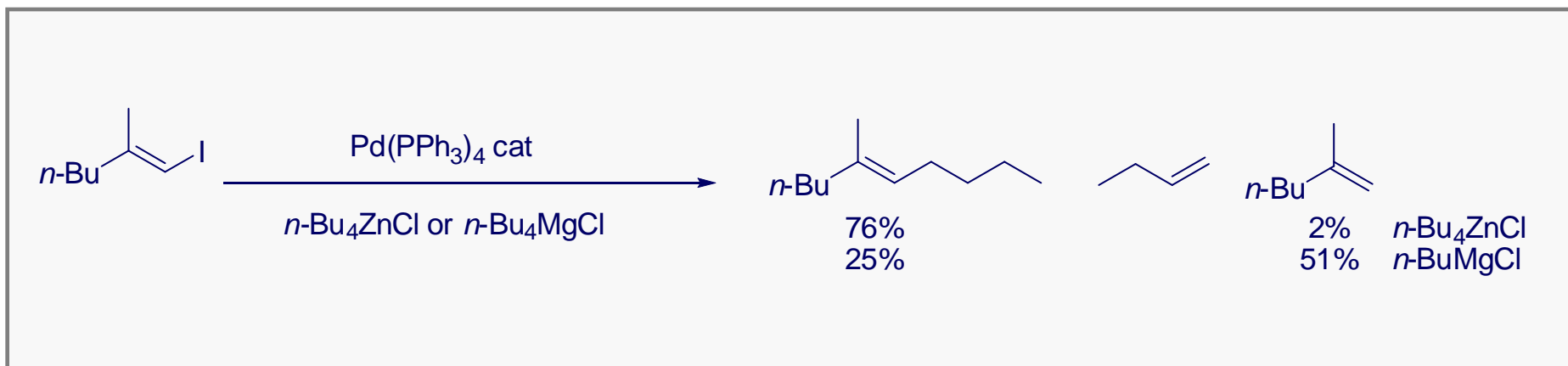
# Organozincs



Pihko, P. M.; Koskinen, A. M. P. *Synlett* **1999**, 1966-1968

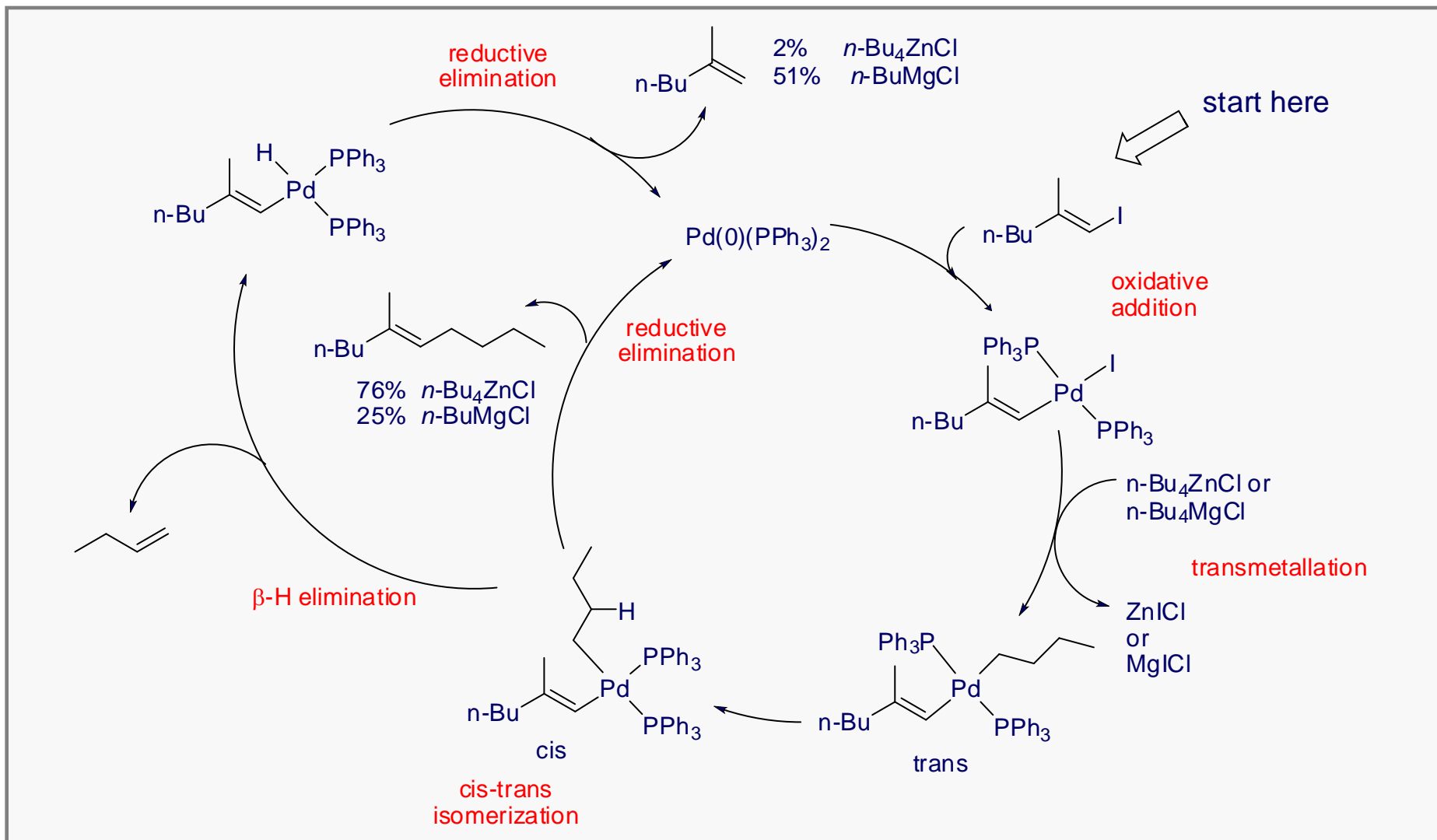
Organozincs are the most reactive organometals for TM-catalyzed cross-coupling reactions. They are usually generated via transmetalation from other organometals (Li, Mg, Al, Zr...) in the presence of  $\text{ZnCl}_2$  or  $\text{ZnBr}_2$ .

# Csp<sup>2</sup>-Csp<sup>3</sup> Couplings



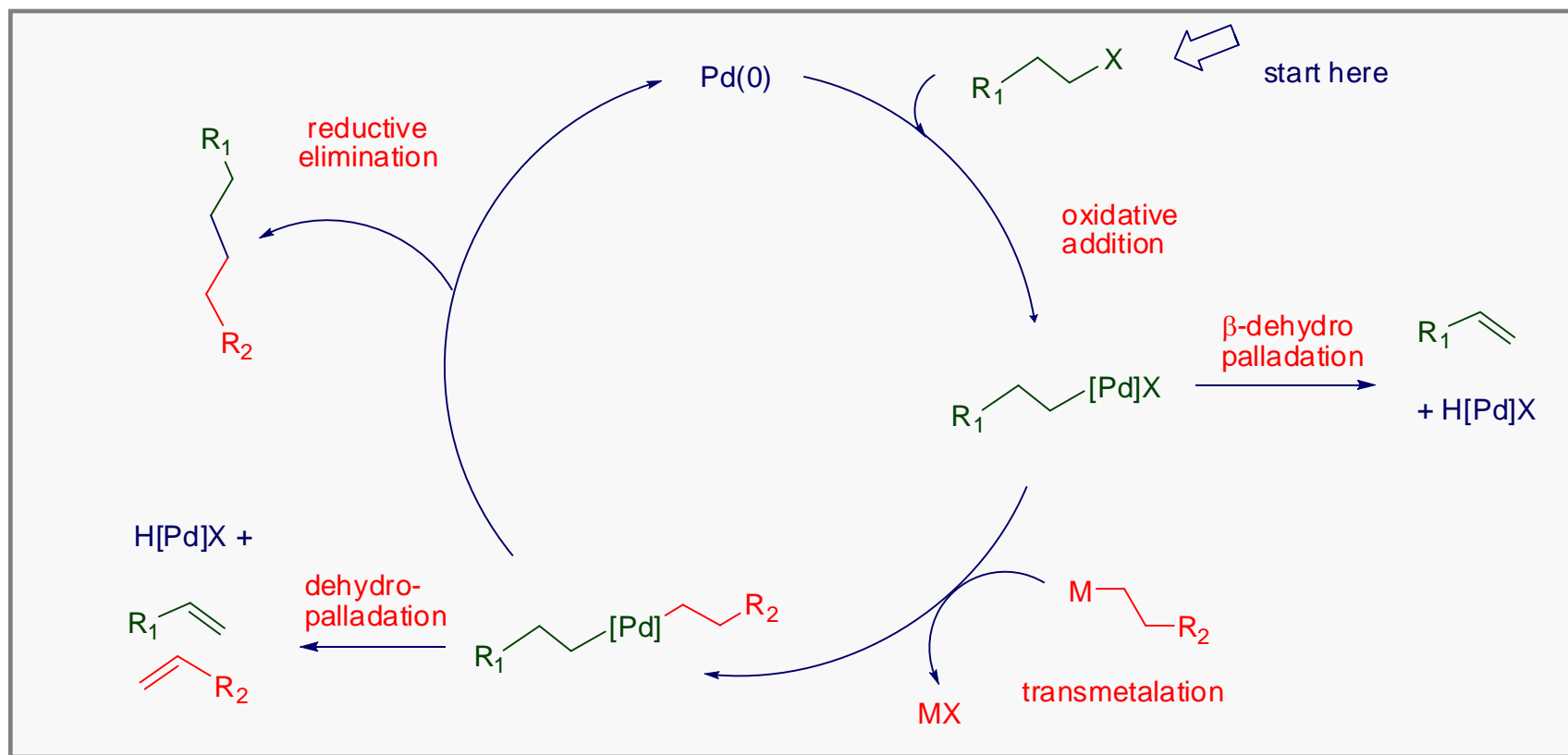
In contrast to what happens with Grignard reagents, when using  $\beta$ -H containing organozincs dehydropalladation does not compete with reductive elimination.

# Csp<sup>2</sup>-Csp<sup>3</sup> Couplings





# Csp<sup>3</sup>-Csp<sup>3</sup> Couplings



Coupling of Csp<sup>3</sup> residues, especially from the halide partner, is a great challenge, since dehydropalladation can become competitive. The solution: inhibition of the β-elimination using appropriate ligands that fill the vacant coordination site needed for the β-elimination, or speeding up the transmetalation and reductive elimination step..

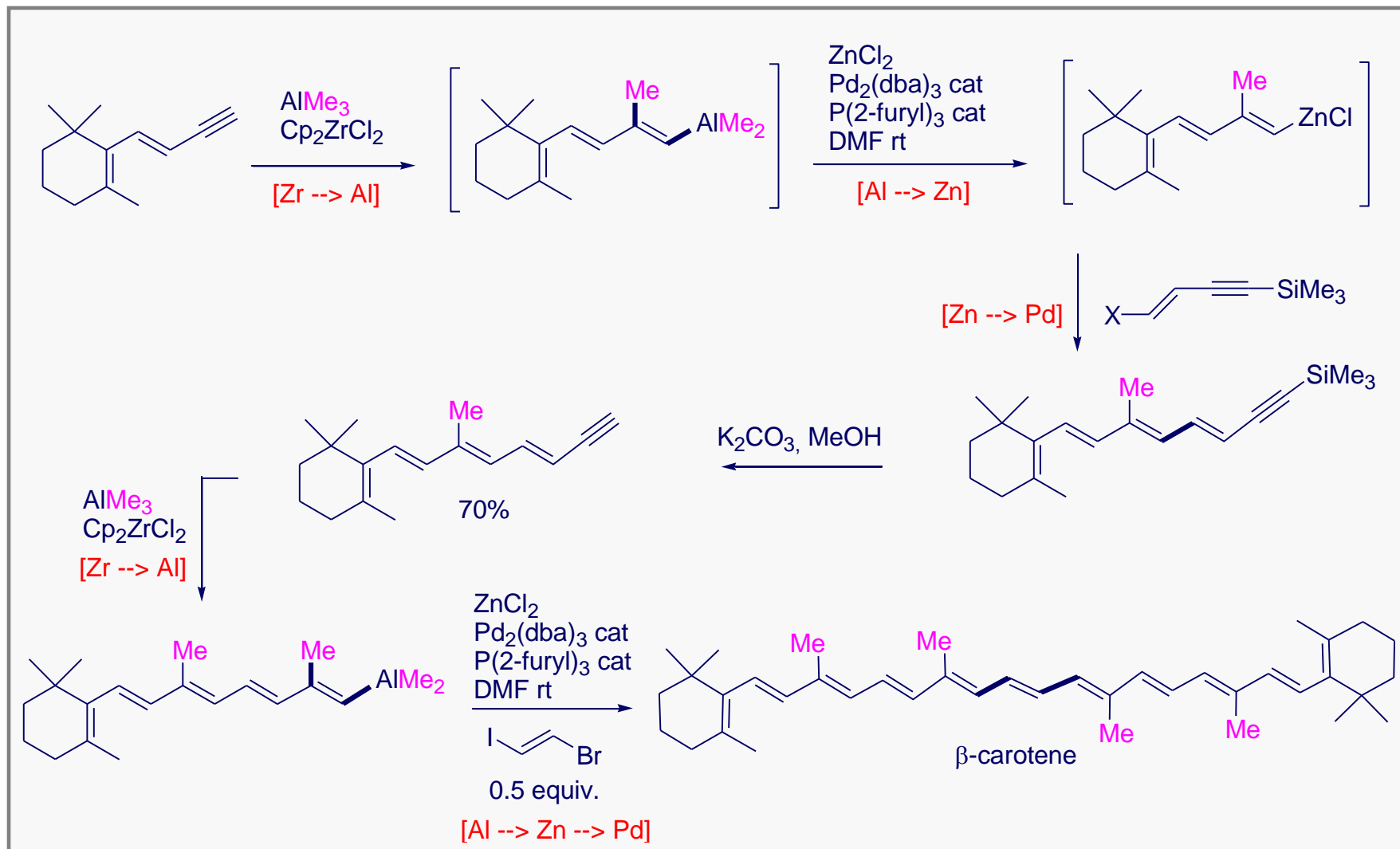
Cardenas, D. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3018-3020.

Luh, T.-Y.; Leung, M.-k.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187-3204.

Cardenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384-387.

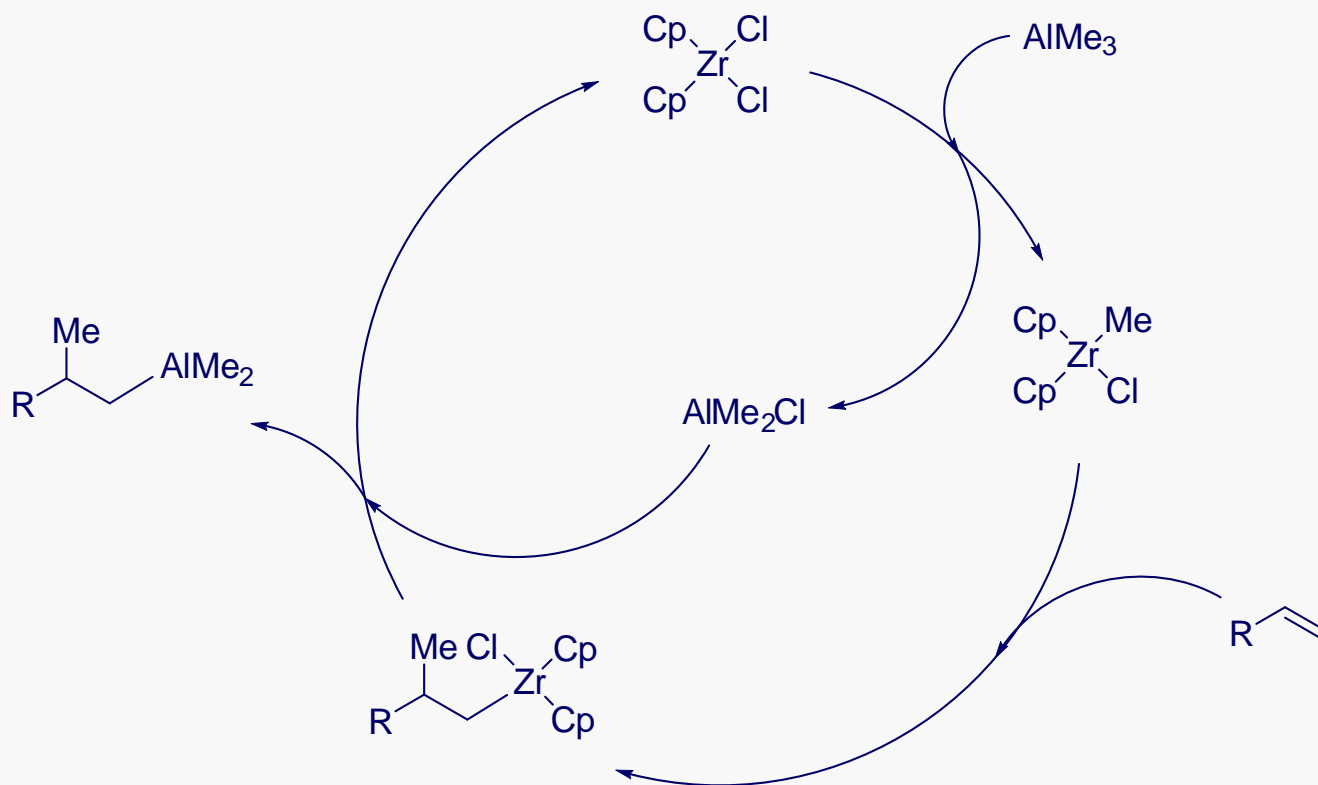
Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674-688.

# Synthesis of $\beta$ -Carotene



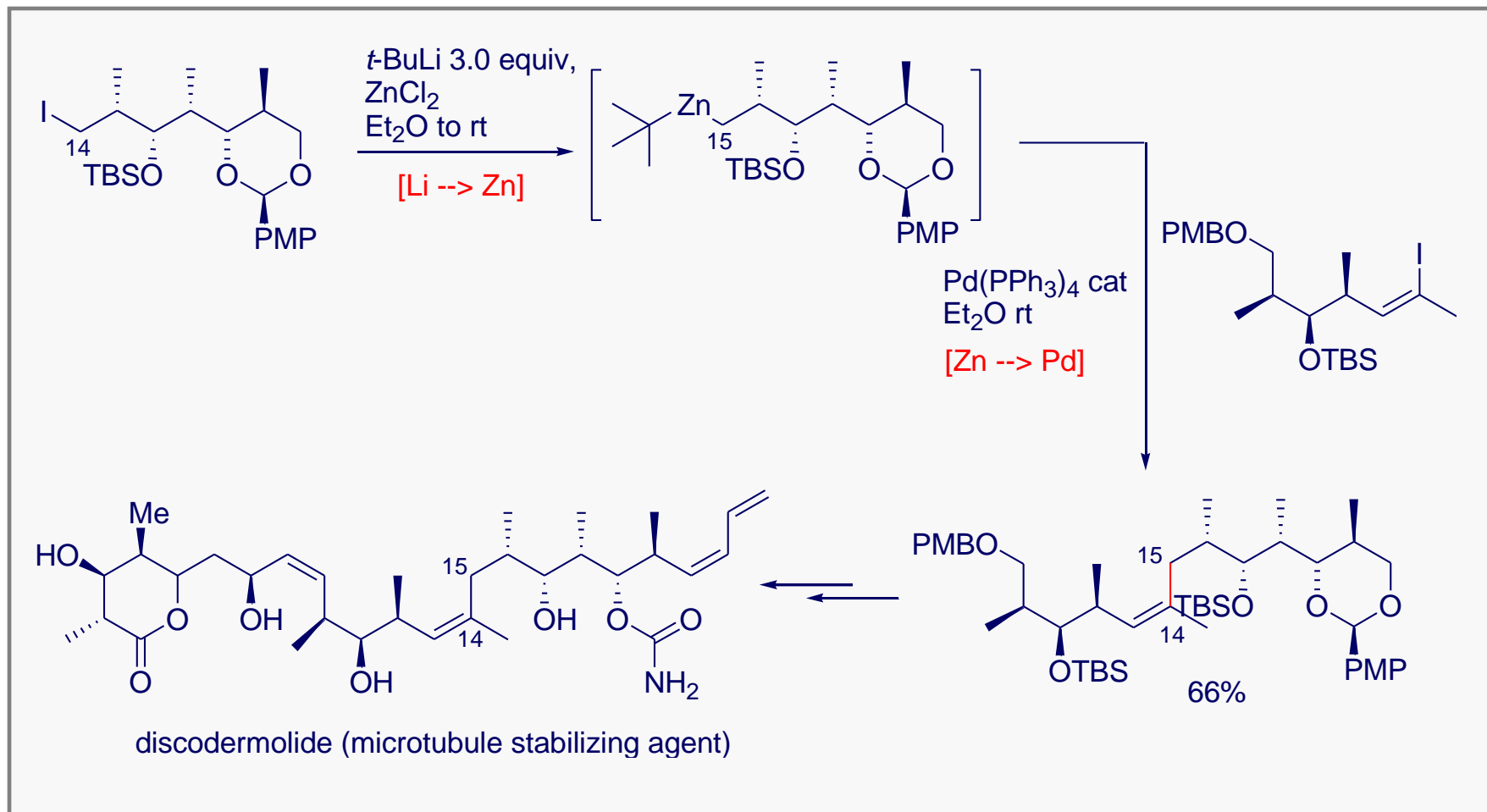
Negishi, E.-I.; Xeng, F. *Org. Lett.*, **2001**, 3, 719-722.

# Zr-Catalyzed Alkene Carboalumination



Negishi Ei-i, et al *J. Am. Chem. Soc.*, **1996**, 118 (40), 9577–9588

# Synthesis of Discodermolide

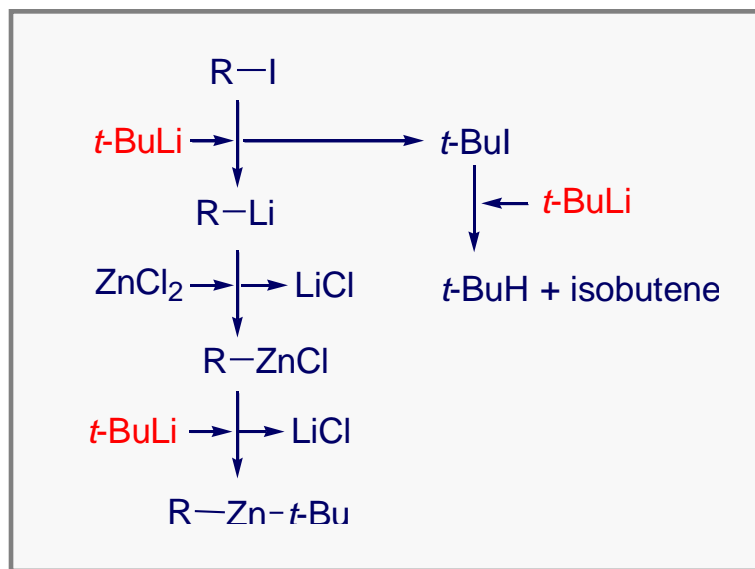


Smith III, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654 - 8664;

Smith III, A. B.; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823 - 1826.

# Li $\rightarrow$ Zn Transmetalation with *t*-BuLi

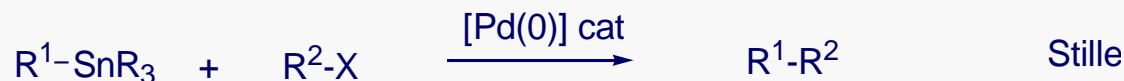
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This sequence would account for the need of 3.0 equivalents of *t*-BuLi

# The Migita-Kosugi-Stille Coupling

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The Stille Coupling is a flexible C-C bond forming reaction between stannanes and halides or pseudohalides.

The main drawback is the toxicity of the tin compounds, and their low polarity, which makes them poorly soluble in water.

Stannanes are stable, functional group tolerant and readily synthesizable.

Me and Bu groups are normally the non-transferable groups.

Transfer scale : alkynyl > alkenyl > aryl > benzyl > alkyl

Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1-652.

# The Seminal Paper

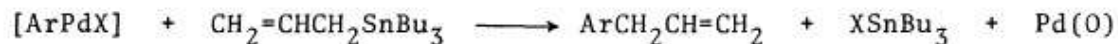
CHEMISTRY LETTERS, pp. 301-302, 1977. Published by the Chemical Society of Japan

REACTIONS OF ALLYL TIN COMPOUNDS III<sup>1)</sup>  
ALLYLATION OF AROMATIC HALIDES WITH ALLYLTRIBUTYL TIN  
IN THE PRESENCE OF TETRAKIS(TRIPHENYLPHOSPHINE)PALLADIUM(0)

Masanori KOSUGI, Kazuo SASAZAWA, Yutaka SHIMIZU, and Toshihiko MIGITA  
Department of Chemistry, Faculty of Technology, Gunma University,  
Kiryu, Gunma 376

Catalytic allylation of aryl halides with allyltributyltin in the presence of tetrakis(triphenylphosphine)palladium(0) was investigated. The reaction with aryl bromides proceeded efficiently to yield allylbenzenes.

We wish to report novel catalytic allylation of aromatic halides with allyltributyltin in the presence of tetrakis(triphenylphosphine)palladium(0).

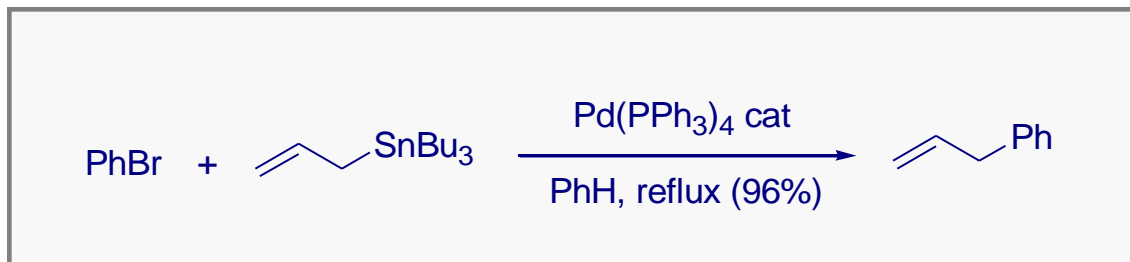


# The First Reports

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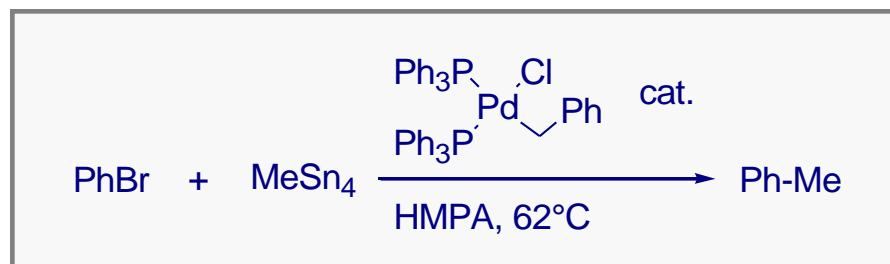
Kosugi and his group pioneered the coupling

The seminal papers



Kosugi, M. ; Sasazawa, K. ; Shimizu, Y. Migita, T. *Chem. Lett.* **1977**, 301 - 302.

Kosugi, M. Sasazawa, K. Migita, T. *Chem. Lett.* **1977**, 1423 - 1424.

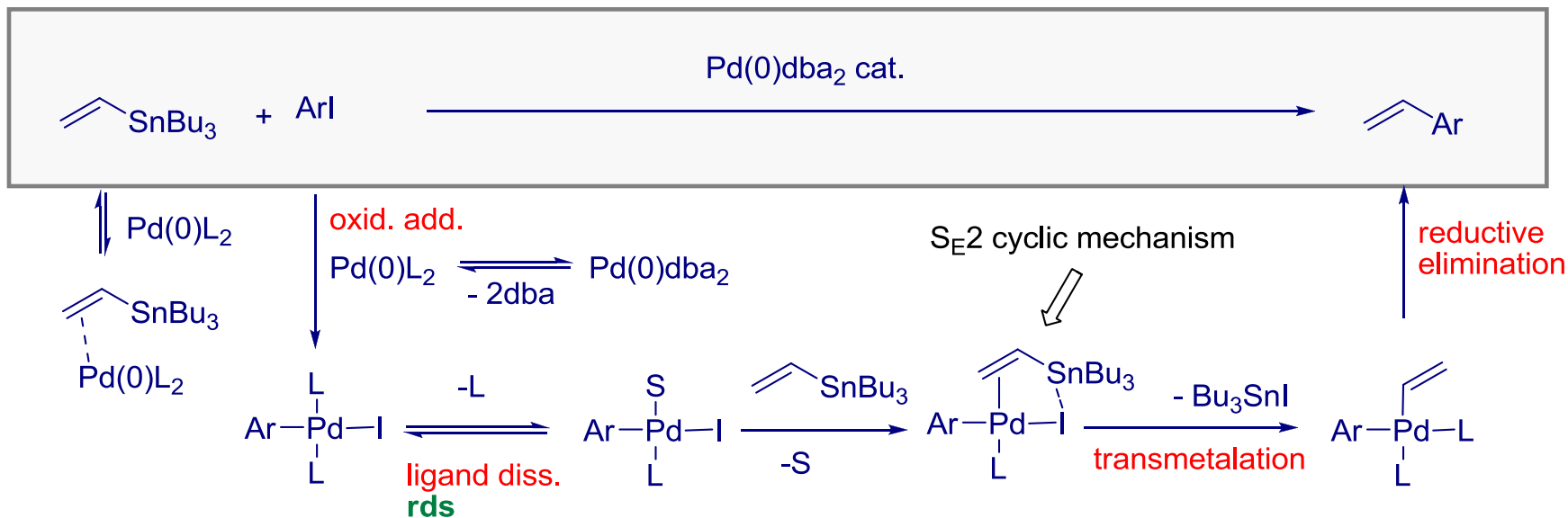


Milstein, D.; Stille J. K. *J. Am. Chem. Soc.* **1978**, 100:3636-3638.

Milstein, D.; Stille J. K. *J. Am. Chem. Soc.* **1979**, 101:4992-4998



# Mechanism of the Migita-Kosugi-Stille Coupling



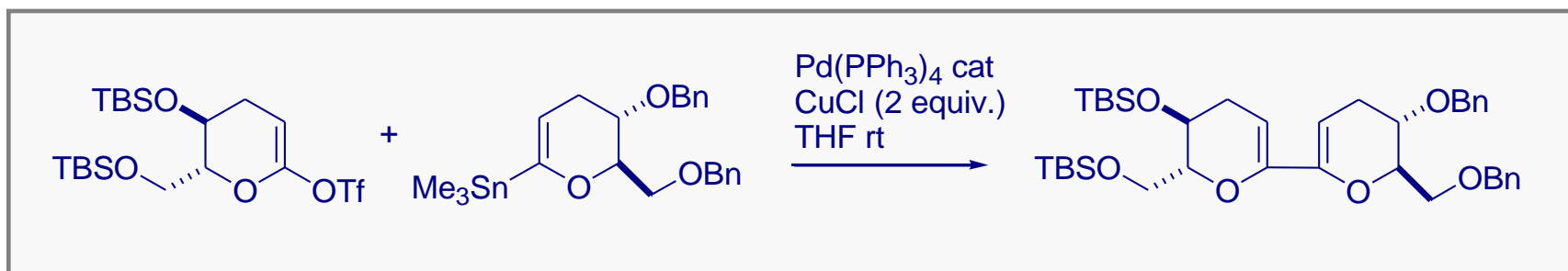
Amatore, C.; Jutand, et al. *Chem.Eur.J.* **2001**, 2134; *J. Am. Chem. Soc.* **2003**, 125, 4212

As the rds is the ligand dissociation, Ph<sub>3</sub>As, a weaker donor than phosphines, gives faster rates and generally better yields. V. Farina, *J.Am.Chem.Soc.* **1991**, 113, 9585.

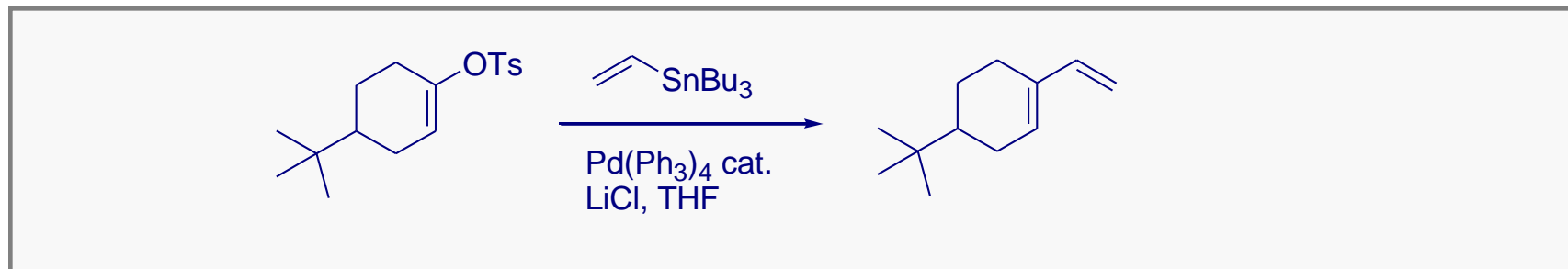
For a different interpretation see: Espinet, *J.Am.Chem.Soc.* **2000**, 122, 11771; *J.Am.Chem.Soc.* **1998**, 120, 8978.

# Examples

## The copper and the LiCl effect



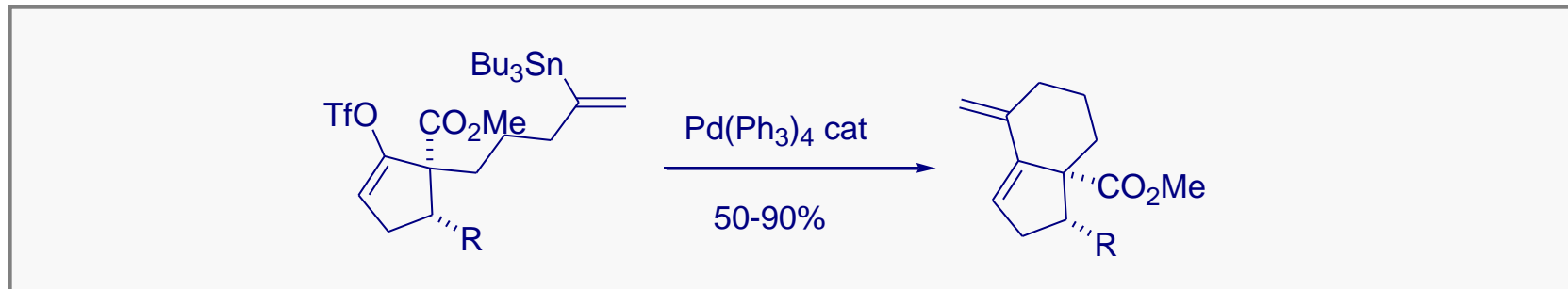
Nicolaou, K. C. et al. *Angew. Chem. Ed. Engl.* **1996**, *36*, 889-891



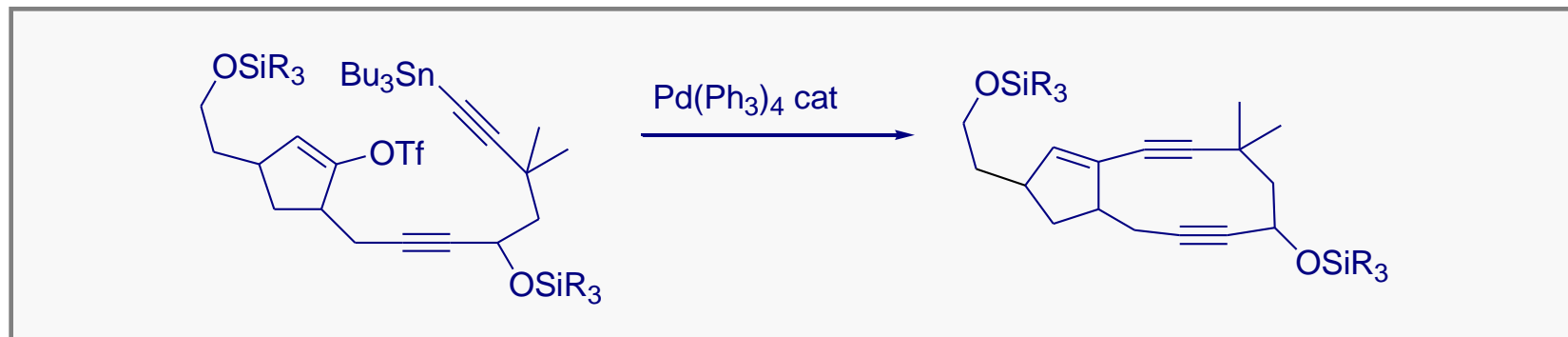
V. Farina, *J. Am. Chem. Soc.* **1991**, *113*, 9585

The presence of Cu(I) salts (CuCl better than CuI) is beneficial, especially when phosphines (instead of arsines) are used. It is believed that a first transmetalation from the organostannane to the organocuprate takes place, followed by a more facile transmetalation of the alkenylcuprate with the palladium catalyst. Also LiCl is beneficial and is believed to accelerate the transmetalation step.

# Examples

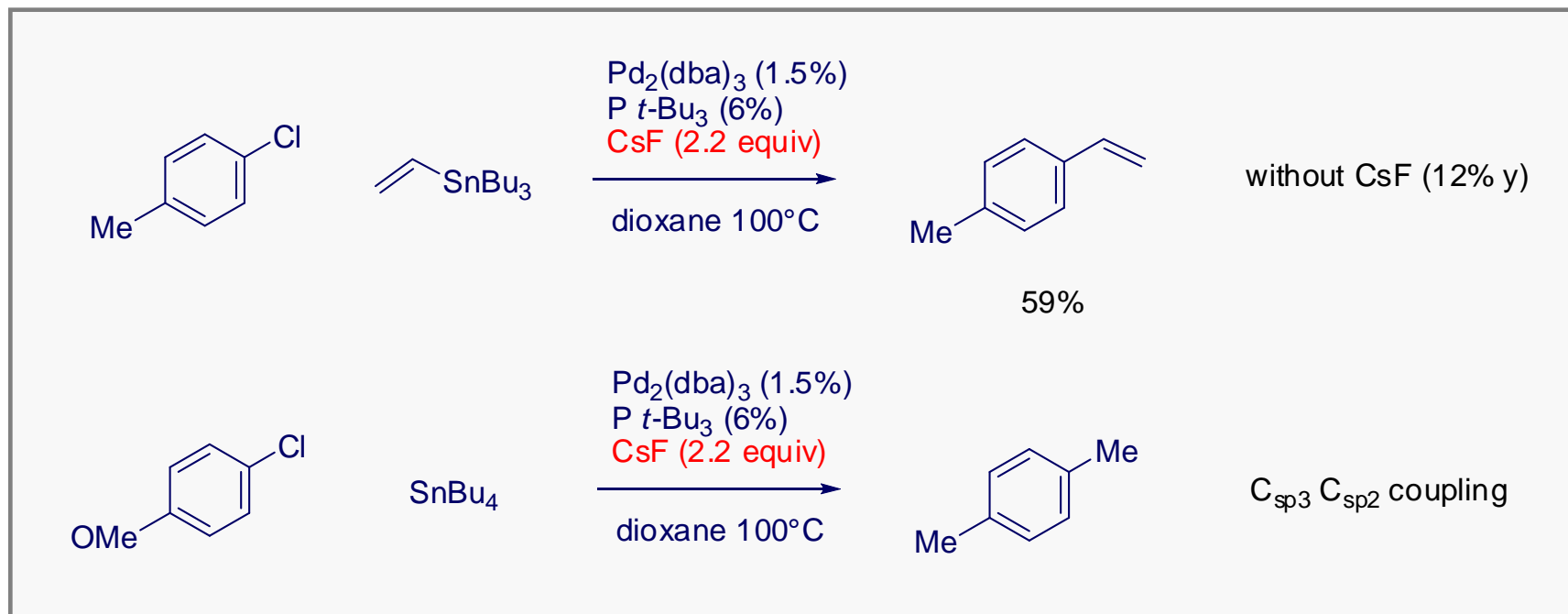


Piers, E. *Tetrahedron*, **1991**, *47*, 4555.



Hirama, M. *Synlett*, **1991**, 651

# Use of Aryl Chlorides

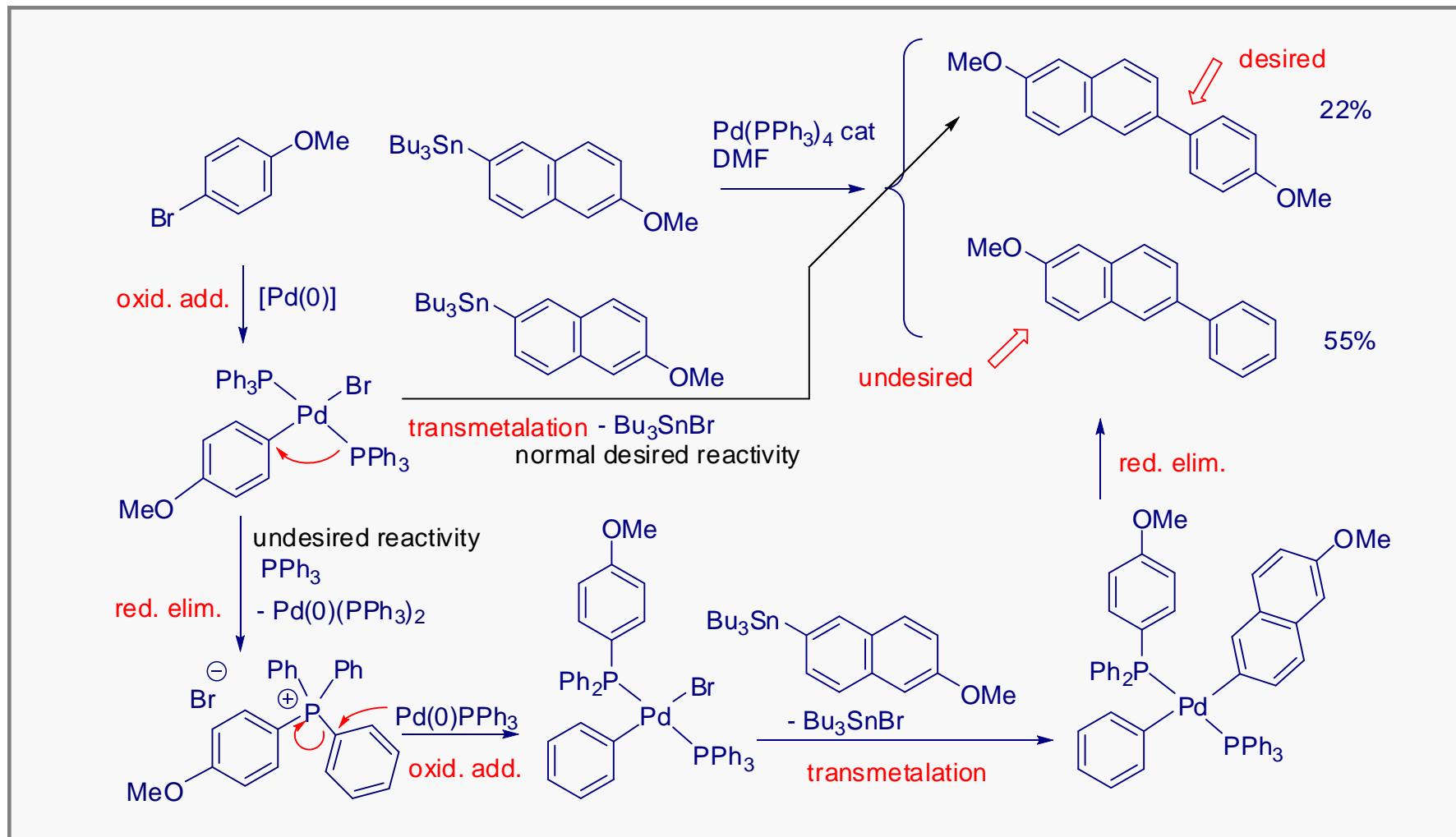


In difficult cases, addition of a fluoride salt can enhance the reactivity. Since these salts are expected to enhance the reactivity of the stannanes, it was postulated that, at least in these cases, the transmetalation is the slow step.

Fu, G., et al. *ACIE*. **1999**, 38, 2411; *J.Am.Chem.Soc.* **2002**, 124, 6343

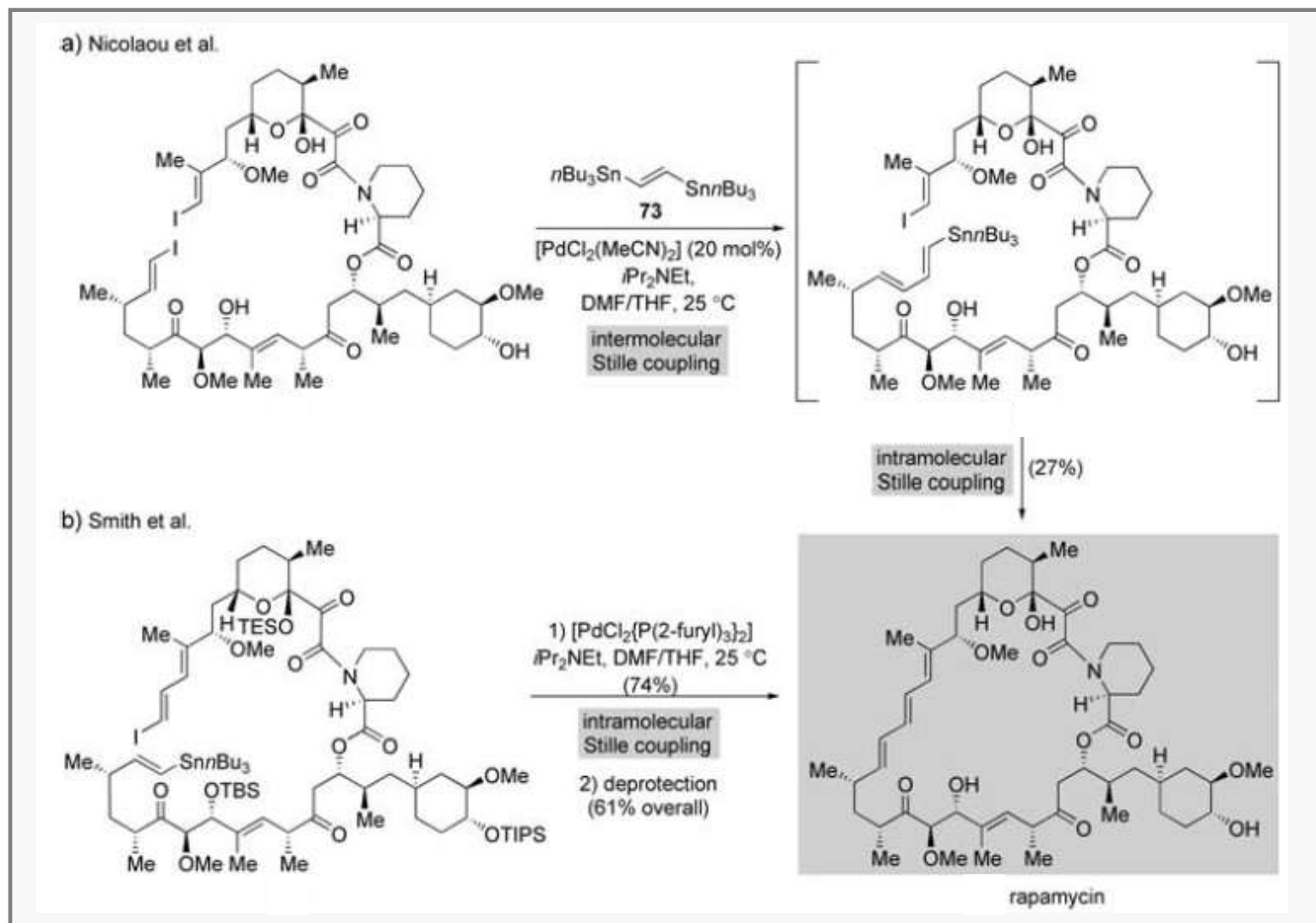
# Problems with Electron Rich Components

If there is not a special phosphine, problems may arise in coupling electron rich components



Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313-6315;  
Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12-13.

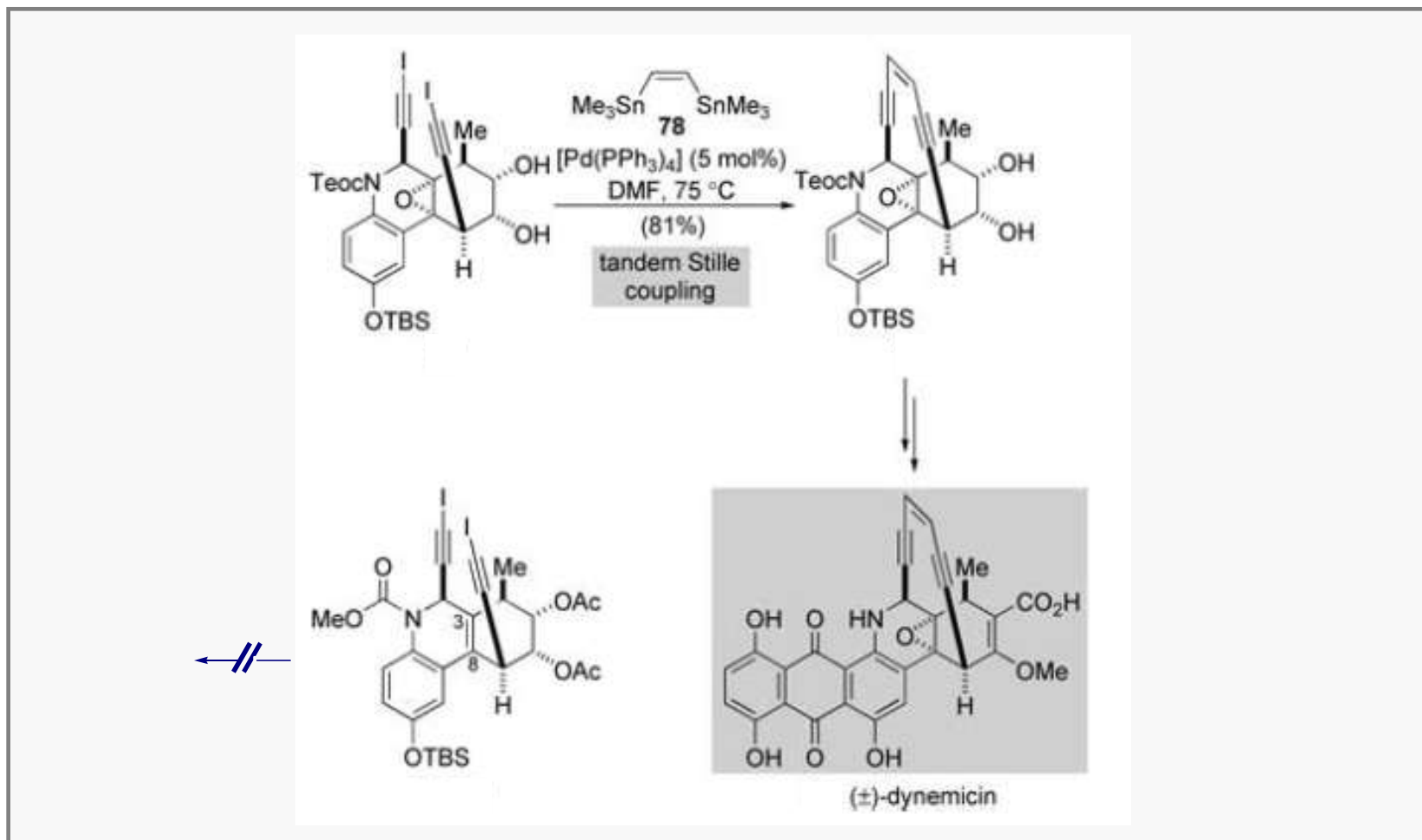
# Application to Rapamycin Synthesis



K. C. Nicolaou, et al. *Chem. Eur. J.* **1995**, 1, 318-333.

A. B. Smith III, et al. *J. Am. Chem. Soc.* **1995**, 117, 5407-5408.

# Application to Dynemicin Synthesis



S. J. Danishefsky et al., *J. Am. Chem. Soc.* **1996**, *118*, 9509-9525;