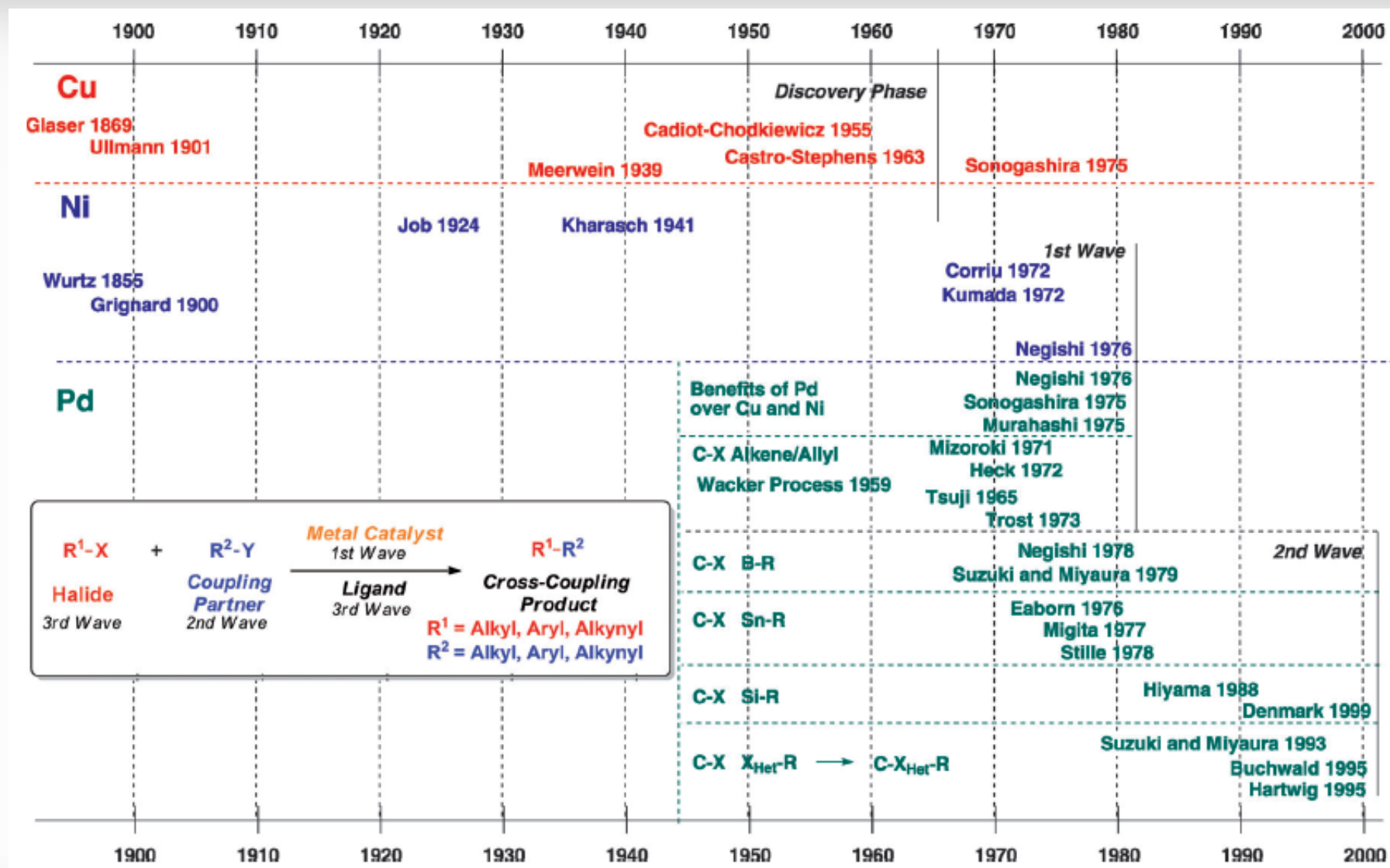


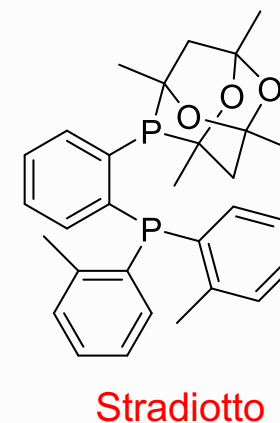
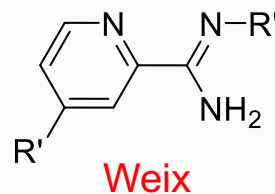
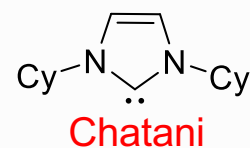
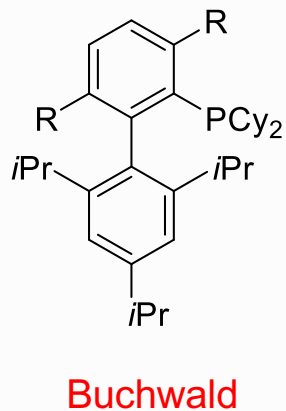
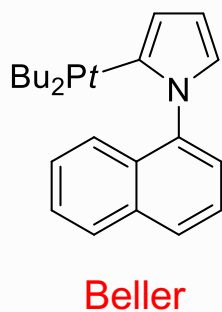
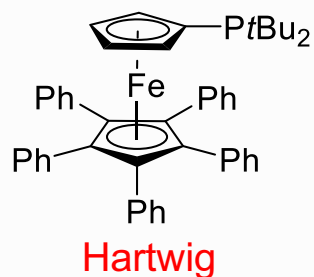
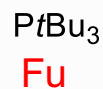
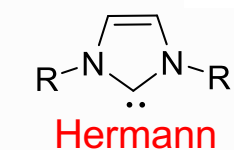
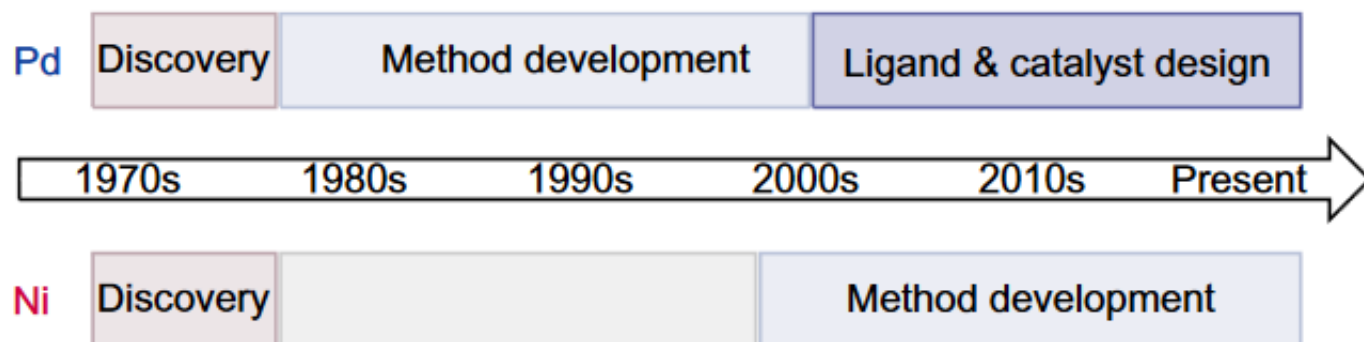
Kevin Wu and Abigail Doyle  
*Nat. Chem.*, **2017**, 9, 779-784

## Parameterization of Phosphine Ligands Demonstrates Enhancement of Nickel Catalysis via Remote Steric Effects

# Metal Catalysis History



# Ligand Development of Ni vs Pd

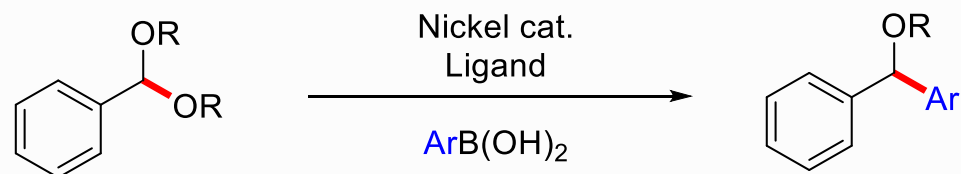


- \*Major advances in Pd cross coupling
- \*Expand substrate scope & catalyst compatibility

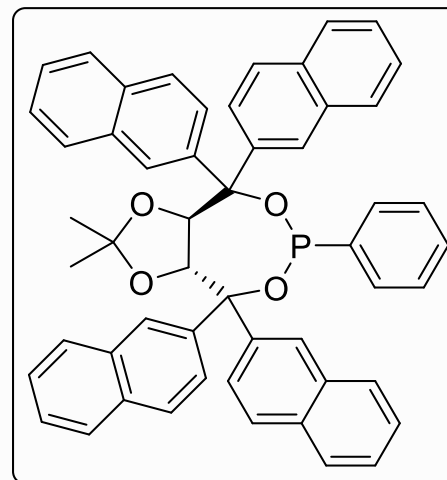
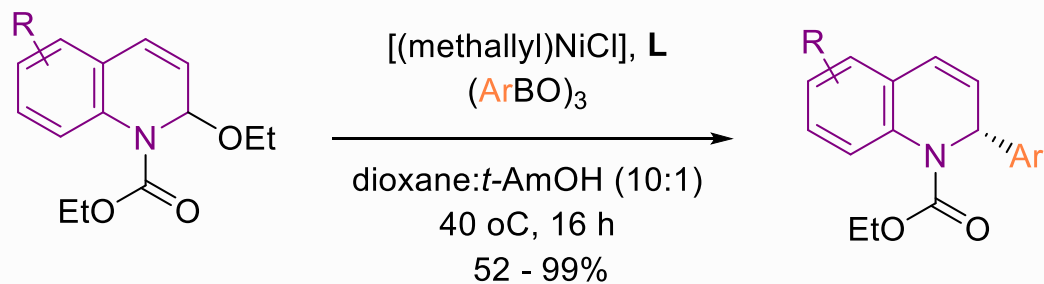
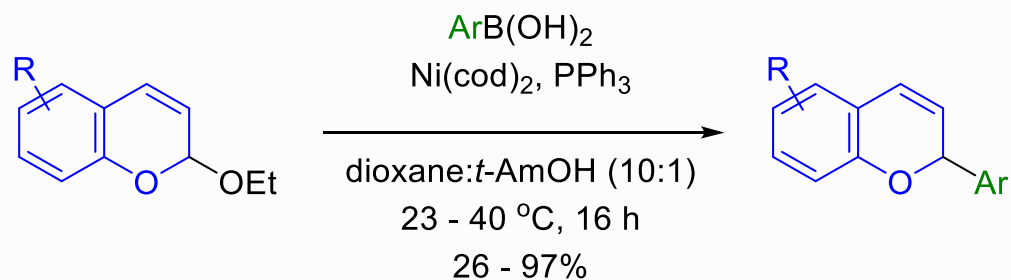
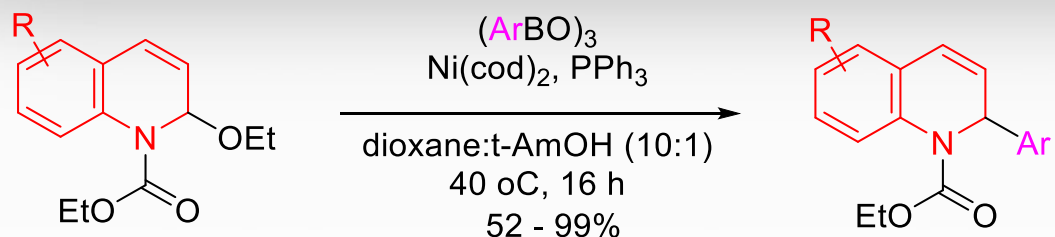
- \*Limited ligand set for Ni catalysis
- \*Narrow substrate scope

# Goal

Rational development of a new class of ligand tailored for Ni catalysis via molecular parameterization

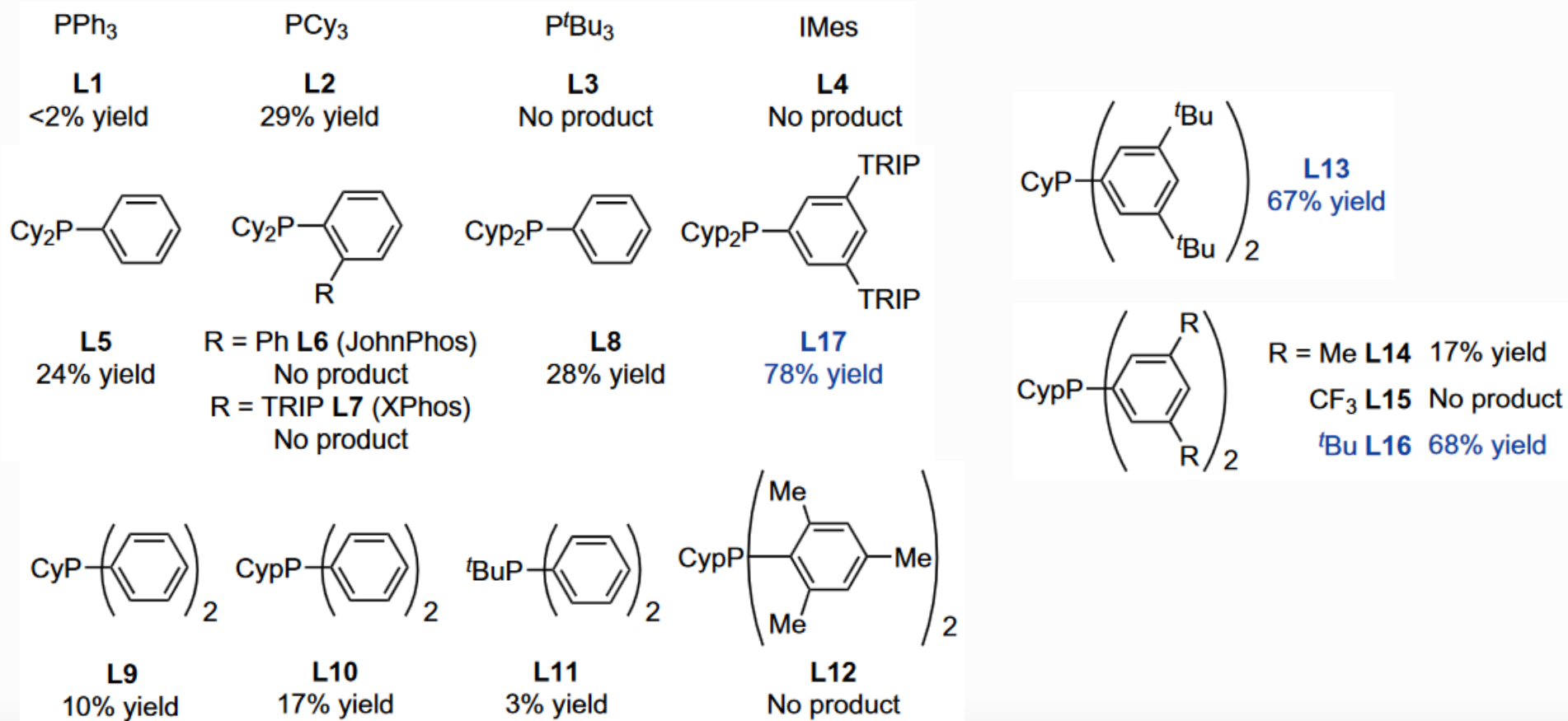
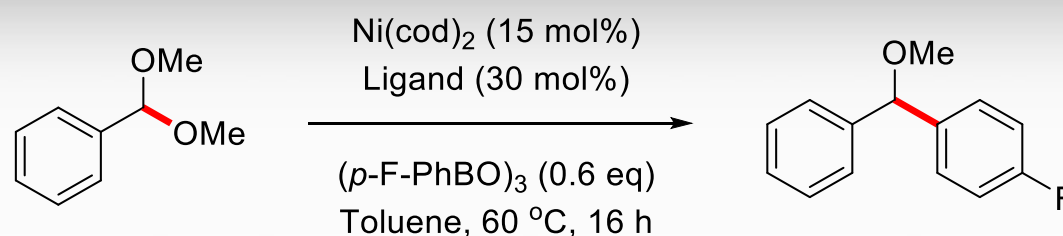


# Ni-catalyzed Suzuki Coupling of Acetals (Doyle Group)

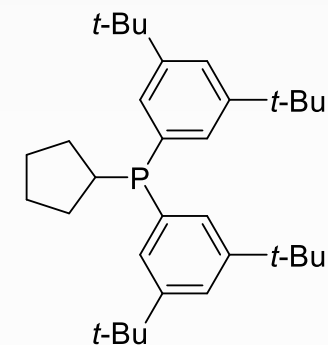
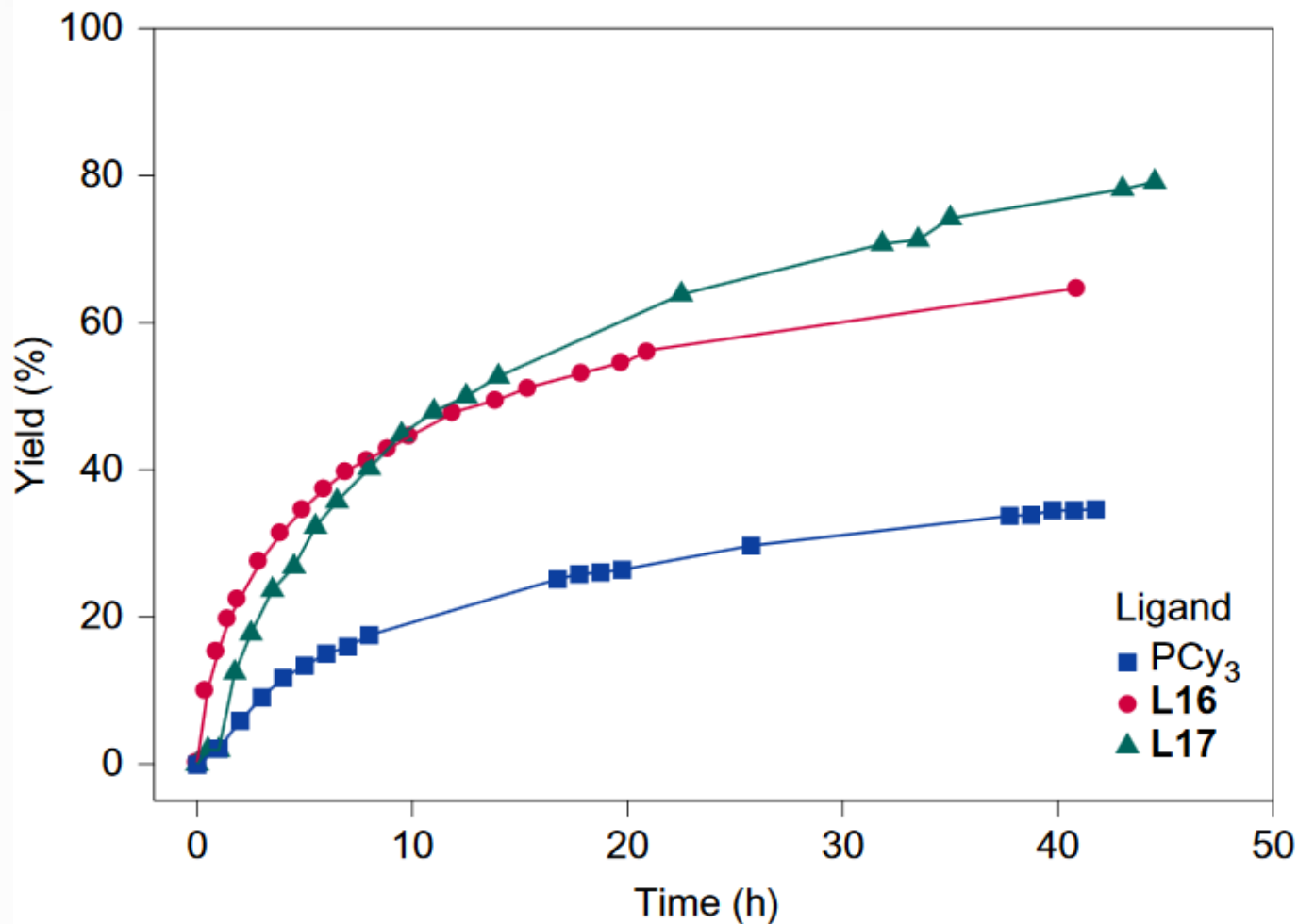


*Chem. Sci.*, **2011**, *2*, 980-984  
*Org. Lett.*, **2012**, *14*, 1616-1619  
*Org. Lett.*, **2014**, *16*, 142-145

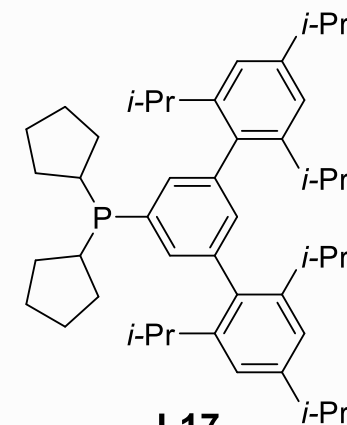
# Initial Ligand Evaluation



# NMR Timepoint Studies



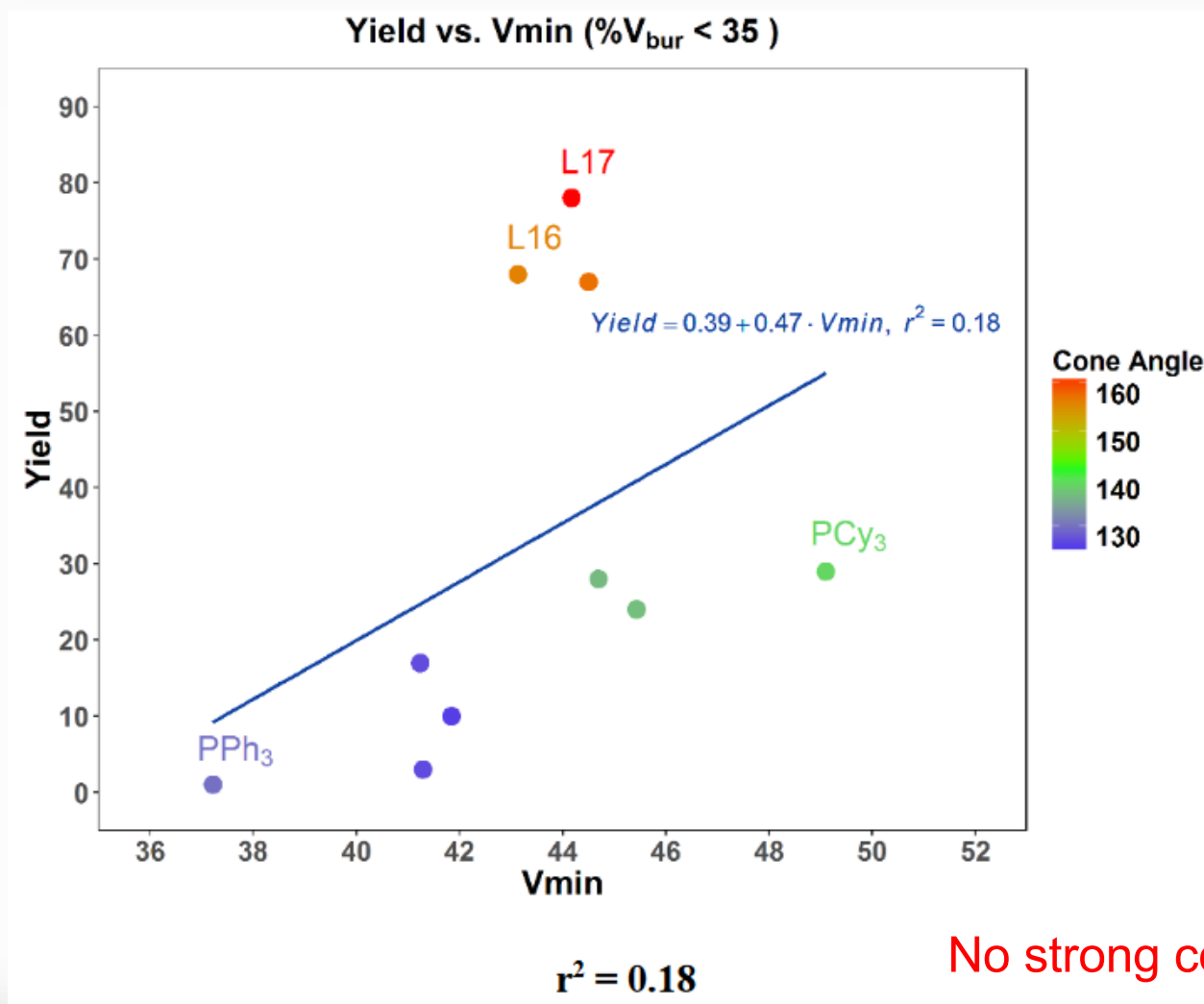
**L16**



**L17**

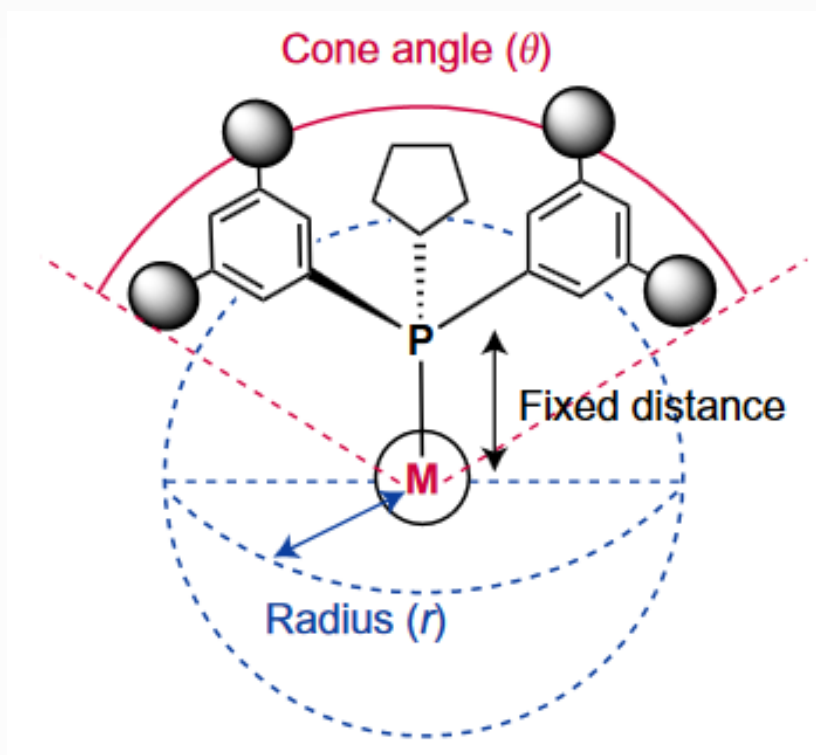
# Computational Evaluation of Ligand Electronic Properties

## ❖ Effect of minimum electrostatic potential on yield





# Sterics - Cone Angle vs $\%V_{bur}$



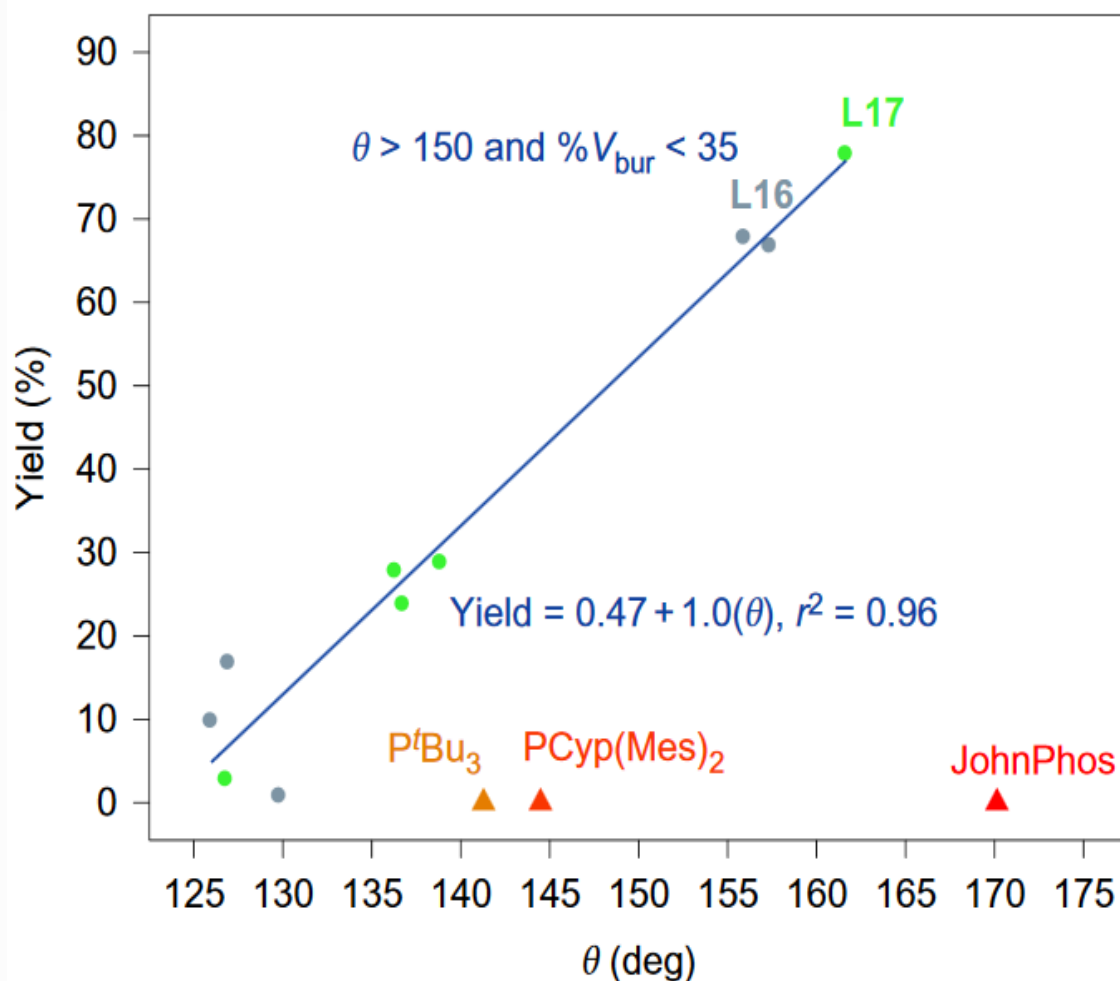
Cone angle: angle swept by cone that encloses all ligand groups

$\%V_{bur}$ : % volume of a sphere with radius  $r$  occupied by ligand – emphasizes steric hindrance proximal to metal

Pd–P distance = 2.28 Å  
Ni–P distance = 2.05 Å

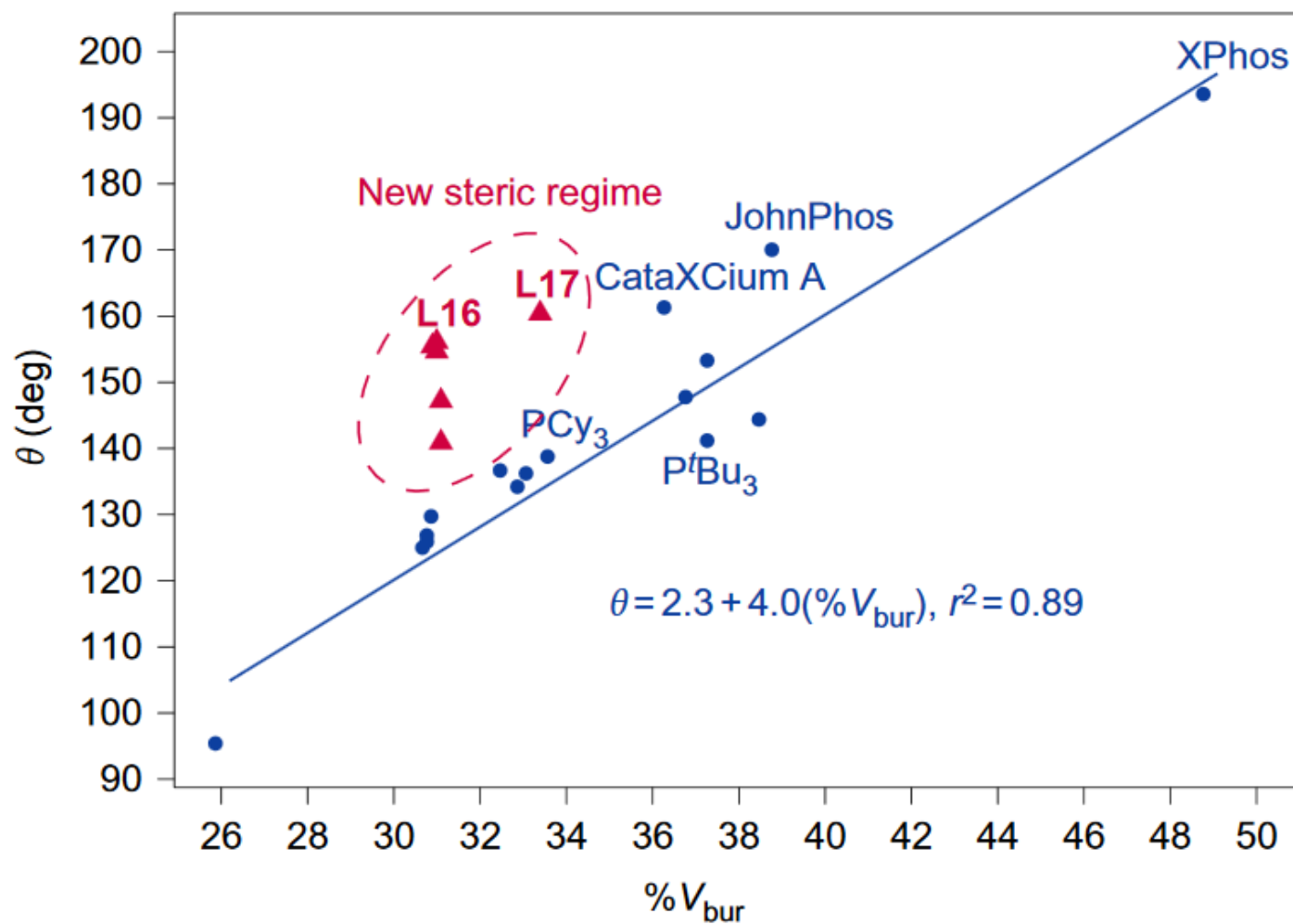
# Computational Evaluation of Ligand Steric Properties

## ❖ Effect of Tolman cone angle on yield



- Strong positive correlation between Tolman cone angle and yield ( $r^2 = 0.96$ )
- Outliers:  $P^tBu_3$ ,  $PCyp(Mes)_2$ , JohnPhos
- Ligands with large  $\%V_{bur}$  are ineffective

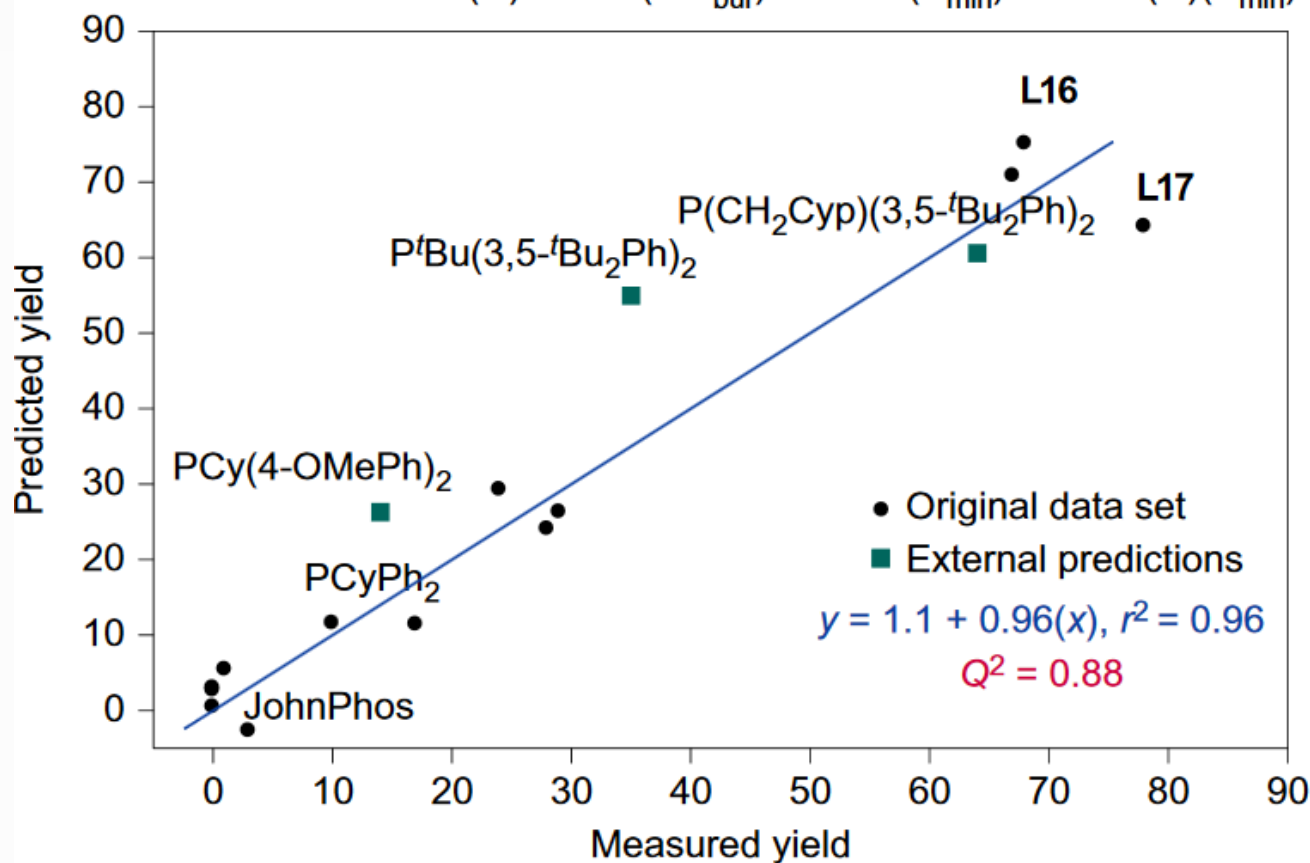
# Cone angle $\neq$ $\%V_{bur}$



# Remote Steric Effect Model

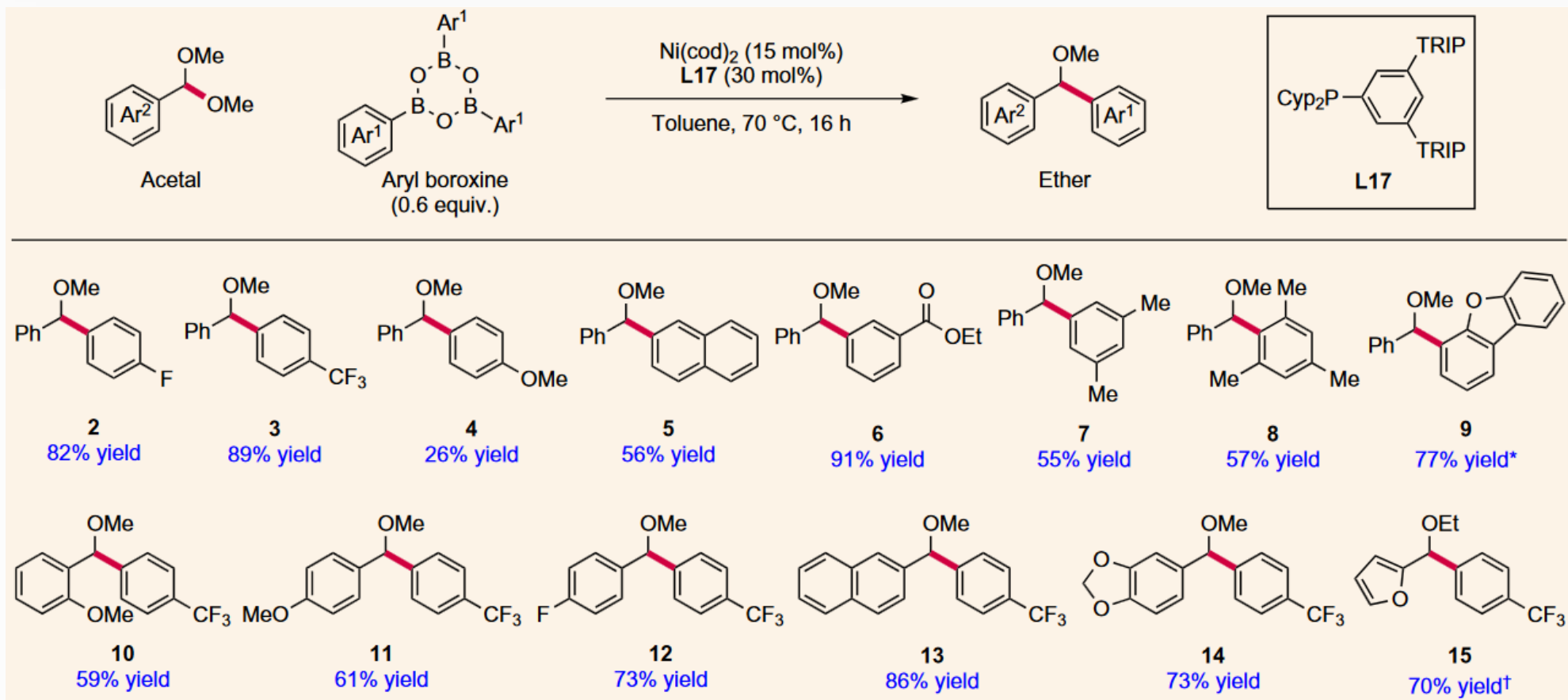
## Ligand parameter regression model

$$\text{Yield} = 0.24 + 0.82(\theta) - 0.67(\%V_{\text{bur}}) - 0.084(V_{\text{min}}) - 0.534(\theta)(V_{\text{min}})$$

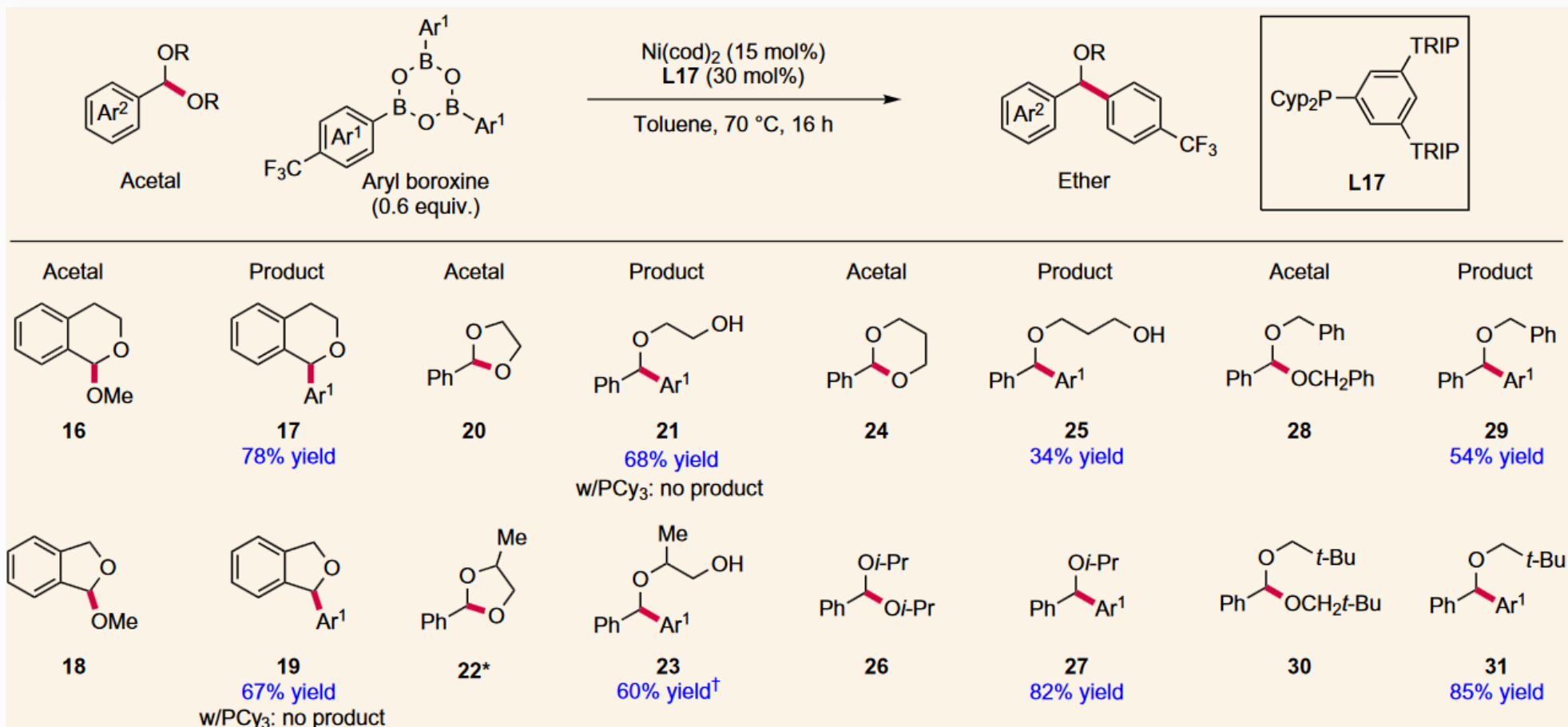


- Accurate and precise model
- Potential predictive ability on new data set
- Can predict ligands featuring unique structural motifs

# Suzuki Coupling of Acetals - Scope Investigation



# Suzuki Coupling of Acetals - Scope Investigation



# Conclusions

“It can be compared to a spirited horse, delicate, difficult to control, and incapable of sustainable work...” -Paul Sabatier (Nobel Laureate)

- ❖ New ligand class tailored for efficient Nickel catalysis was developed
- ❖ Cone angle and  $\%V_{bur}$  parameters are not always equivalent
- ❖ Remote steric hindrance concept developed from quantitative model to predict ligand reactivity