Literature Report

The Design of Ligands for Ni-catalysed Coupling Reaction

Reporter: Chang-Bin Yu
Checker: Mu-Wang Chen

January 2, 2018

Wu, K.; **Doyle, A. G.** *Nat. Chem.* **2017**, *9,* 779

CV of Prof. Abigail G. Doyle

Prof. A. G. Doyle

1998-2002 A.B. and A.M. (Harvard University)

2002-2003 MS, Prof. Justin Du Bois (Stanford University)

2003-2008 Ph.D Prof. Eric Jacobsen (Harvard University)

2008-2013 Assistant Professor (Princeton University)

2013- now Associate Professor (Princeton University)

Research Fields:

1. **Nucleophilic Fluorination**
2. **Ni-catalysed Cross Coupling**

Contents

- Introduction
- Ni-catalysed C(sp^2)–N Cross-coupling
- Ni-catalysed Suzuki Coupling of Benzylic Acetals
- Summary

Introduction

Nickel

1751: Nickel was isolated firstly from Kupfernickel

1775: Purified nickel obtained from Kupfernickel

1890: Mond observed and synthesized $Ni(CO)_4$

1900: Sabatier performed hydrogenation of ethylene with nickel

1970: Application in reactions: nucleophilic allylation oligomerization, cycloisomerization and reductive coupling

Tasker, S. Z.; Standley, E. A. *et al*. *Nature* **2014**, *509*, 299

Introduction

Periodic Table

	VIII		IB
4	27 Co	28 Ni	29 Cu
5	45 Rh	46 Pd	47 Ag
6	77 Ir	78 Pt	79 Au

Pd

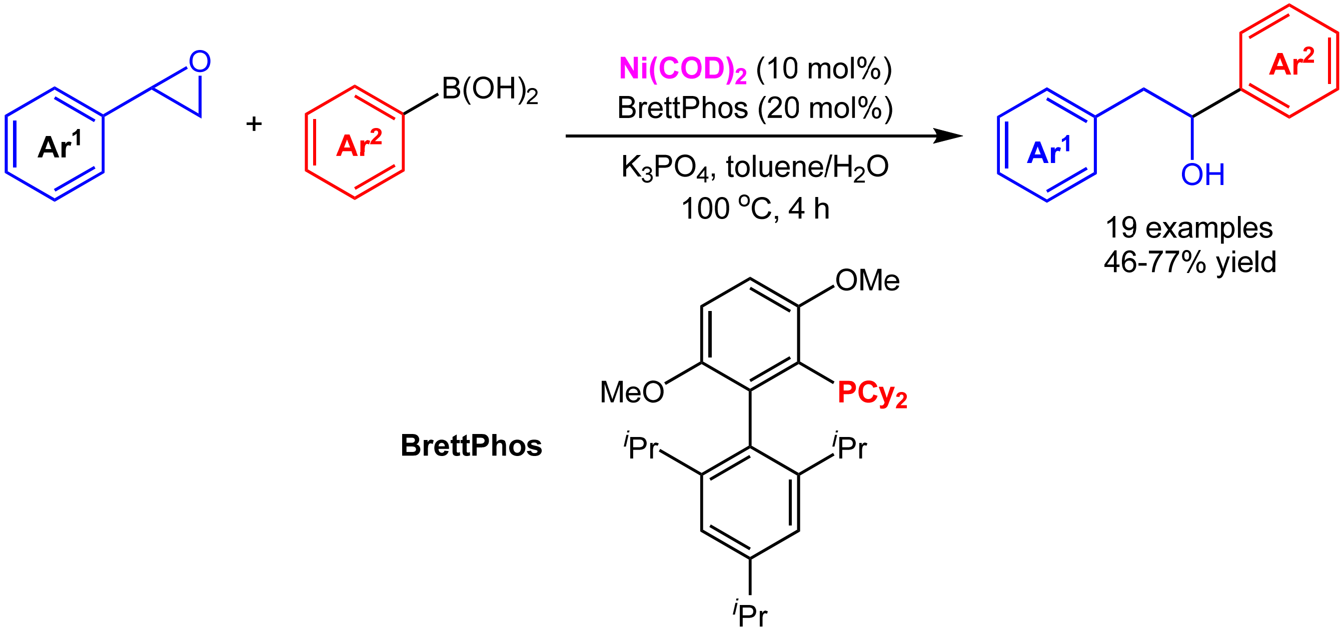
Larger atomic radius
More electronegative
Softer
Facile reductive elimination
Facile *β*-hydride elimination

Ni

Smaller atomic radius
Less electronegative
Harder
Facile oxidative addition
Facile migratory insertion
Radical pathways more accessible

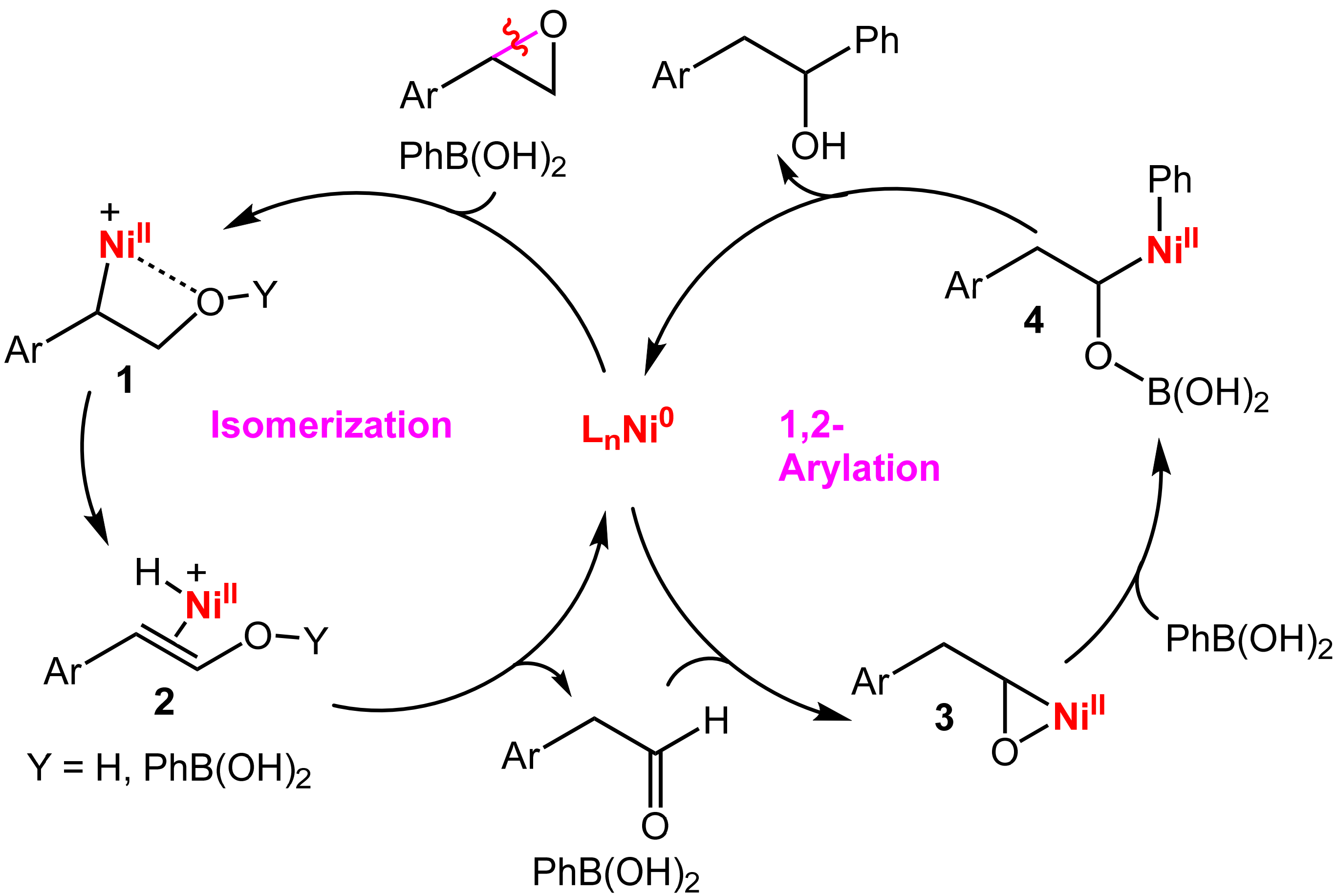
Tasker, S. Z.; Standley, E. A. *et al*. *Nature* **2014**, *509*, 299

Ni-catalysed Cross-coupling of Epoxides



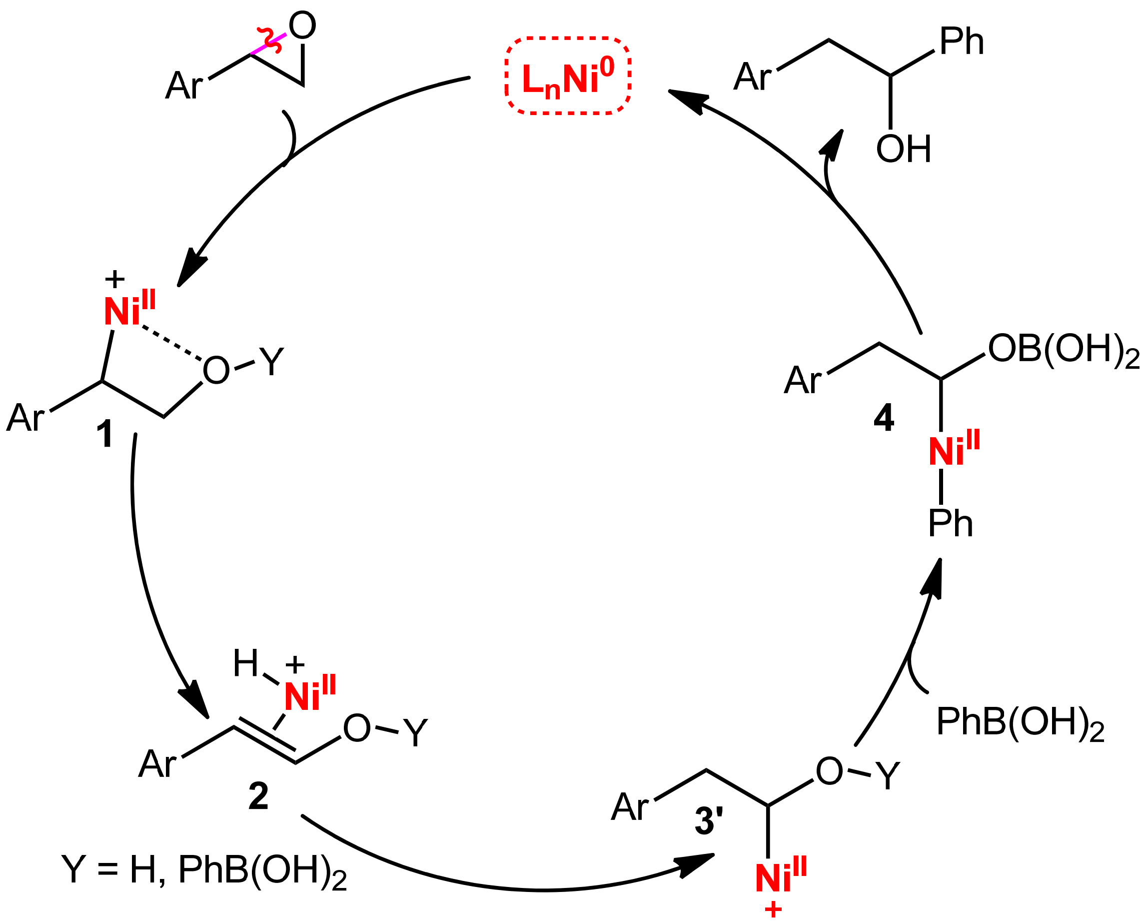
Nielsen, D. K.; **Doyle, A. G.** *et al*. *Angew. Chem. Int. Ed.* **2011**, *50,* 6056

Proposed Catalytic Cycle



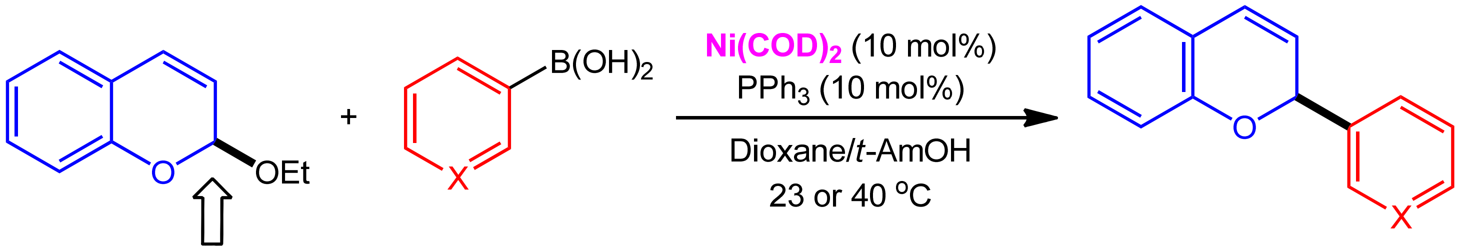
Nielsen, D. K.; **Doyle, A. G.** *et al*. *Angew. Chem. Int. Ed.* **2011**, *50,* 6056

Possible Catalytic Cycle



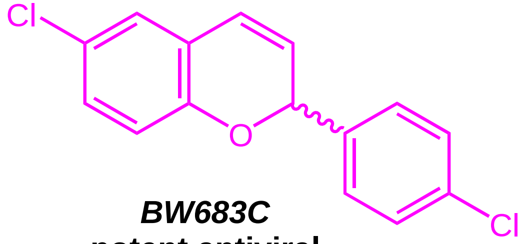
Nielsen, D. K.; **Doyle, A. G.** *et al*. *Angew. Chem. Int. Ed.* **2011**, *50,* 6056

Ni-catalysed Coupling of Chromene Acetals



multiple poorly reactive C-O bonds

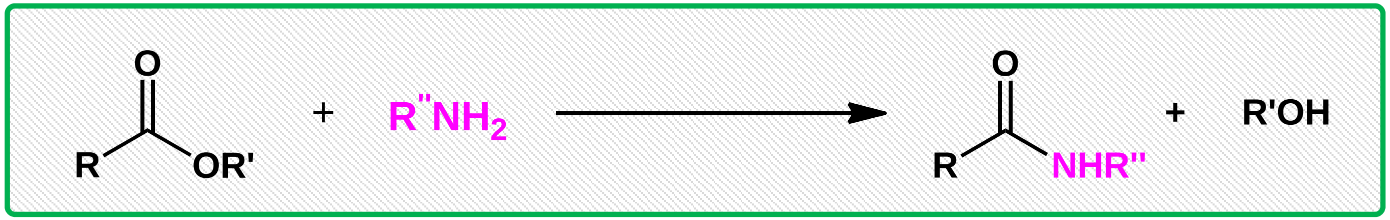
36 examples
Up to 97% yield

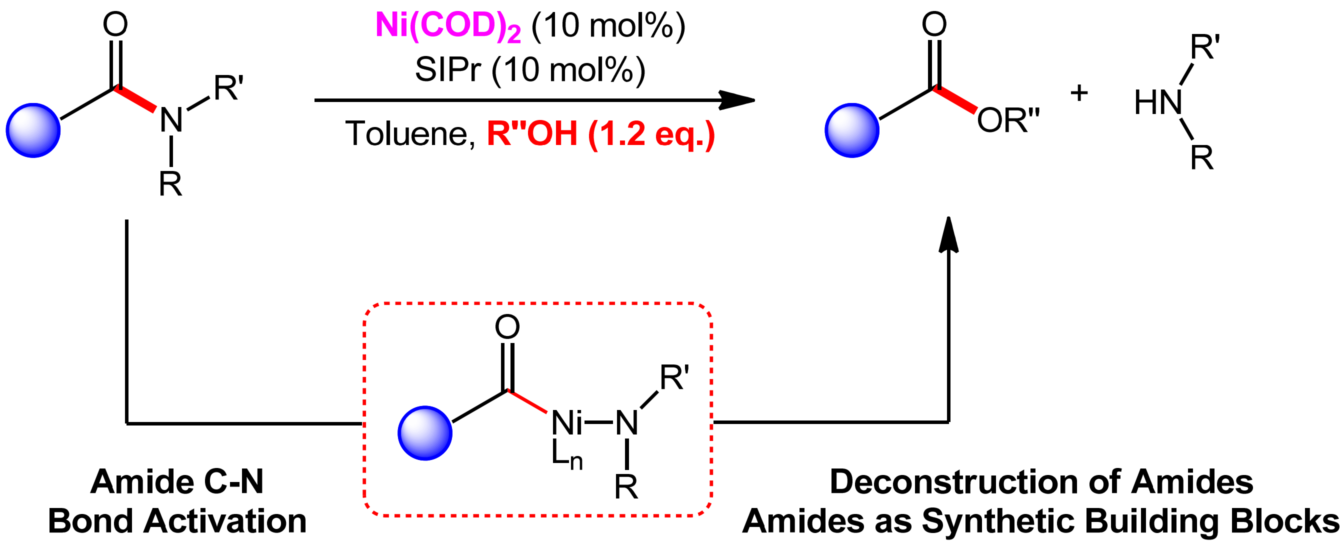


BW683C
potent antiviral

Graham, T. J. A.; **Doyle, A. G.** *et al*. *Org. Lett*. **2012**, *14*, 1616

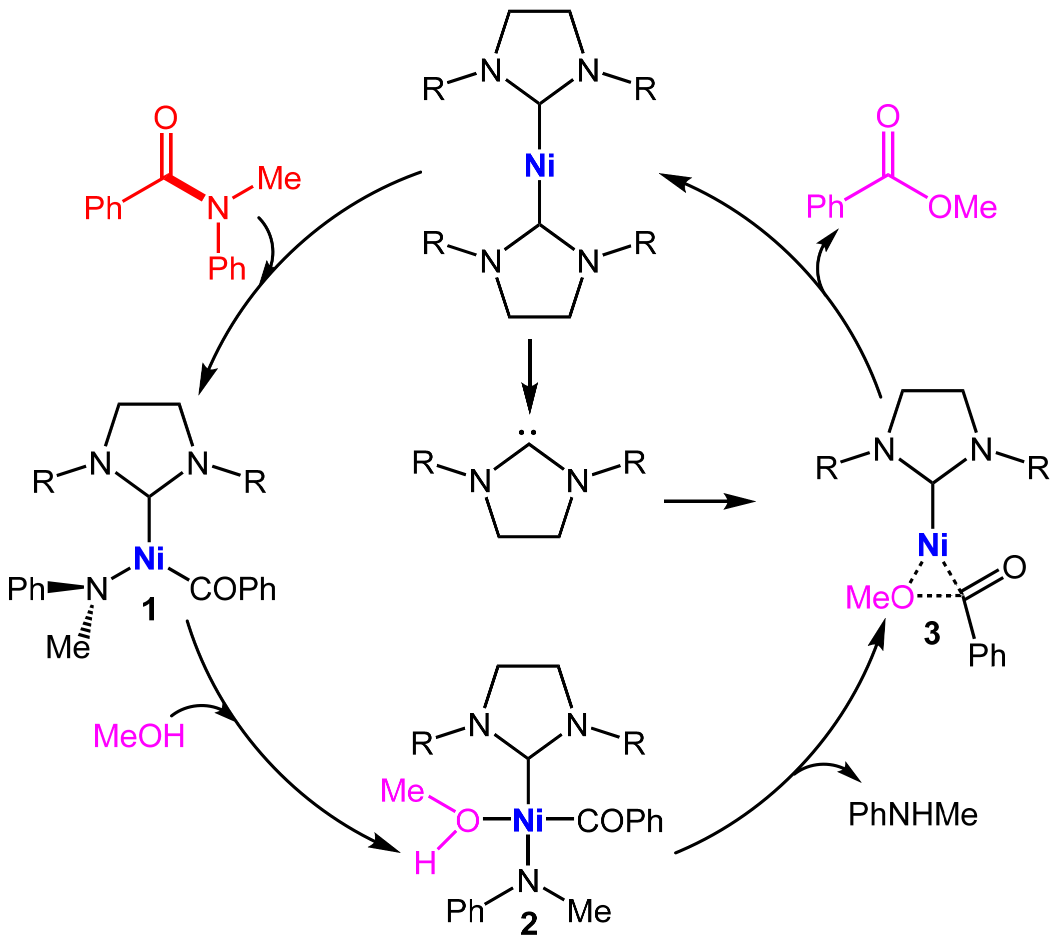
Ni-catalysed Activation of Amide C–N Bond





Hie, L.; Houk, K. N.; **Garg, N. K.** *et al*. *Nature* **2015**, *524*, 79

Proposed Catalytic Cycle



Hie, L.; Houk, K. N.; **Garg, N. K.** *et al*. *Nature* **2015**, *524*, 79

Ni-catalysed Amine Arylations

Buchwald-Hartwig Amination (BHA):

(Hetero)aryl-**X** + **R_2NH** —[M, Ligand]→ (Hetero)aryl-**NR_2**

Pd

Buchwald-Hartwig Amination (BHA)
- Broad substrate scope
- Pd expensive and rare

Ni

Comparatively not well explored
- Potential for broad substrate scope
- Ni inexpensive and abundant

Lavoie, C. M.; **MacQueen, P. M**. *et al*. *Nat. Commun*. **2016**, *7*, 11073

Ni-catalysed Amine Arylations

Pd

- Promote difficult aryl-X oxidative addition
- Want a **bulky electron-rich ligand**

⇩

Selected Noteworthy Examples:

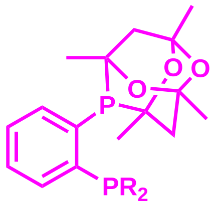
- Buchwald Biarylphosphines
  (e.g., BrettPhos)
- N-heterocyclic Carbenes
  (e.g., IPr, IPent)
- P,N and P,P Ligands
  (e.g., Mor-DalPhos, CyPF-^{t}Bu)

Ni

- Promote aryl-N reductive elimination
- Want a **bulky electron-poor ligand**

⇩

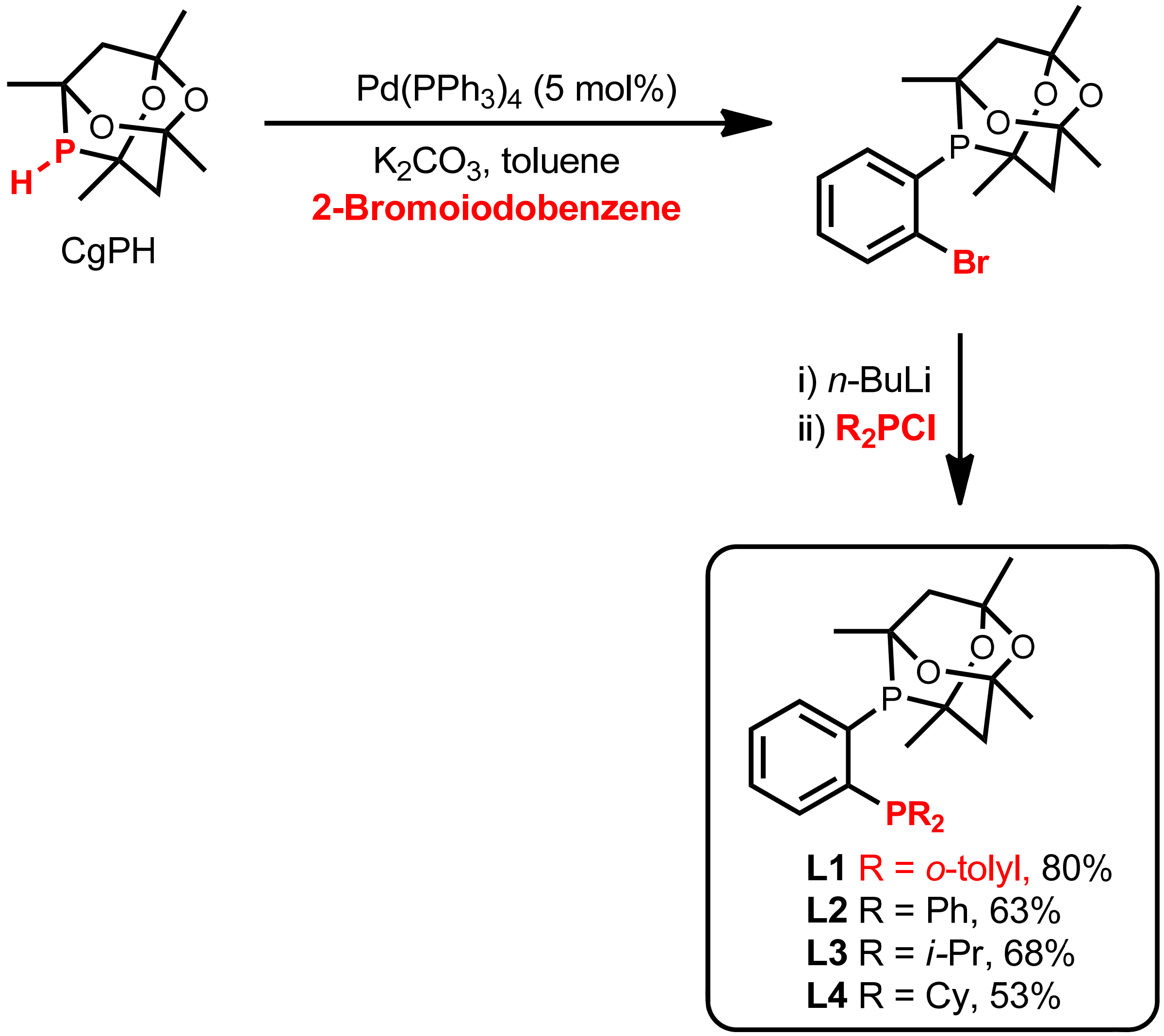
This Work: L1 (PAd-DalPhos)



L1 R = *o*-tolyl
L2 R = Ph
L3 R = ^{i}Pr
L4 R = Cy

- Inexpensive, air-stable ligand and derived pre-catalyst
- Unprecedented scope of NH substrates and electrophiles
- Room temperature cross couplings

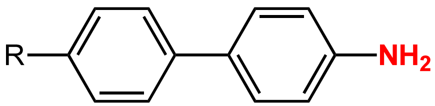
The Synthesis of Ligands



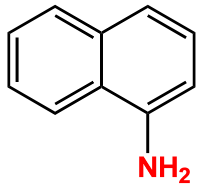
Substrate Scope

(Hetero)aryl-**X** + **NH_3** or **NH_4**OAc $\xrightarrow[\text{1,4-dioxane/toluene (1:3), MO}^t\text{Bu, 25-160 °C, 16 h}]{\textbf{Cat.}\text{ (1-5 mol\%)}}$ (Hetero)aryl-**NH_2**

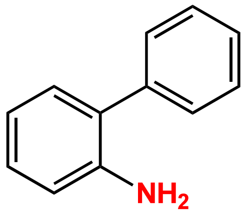
X = Cl, Br, I, OTf, OTs, OMs, imidazolylSO_3



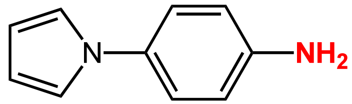
X = Br, R = H, 63%
X = Cl, R = H, 76%
X = Cl, R = CH_3, 78%
X = Cl, R = OMe, 86%



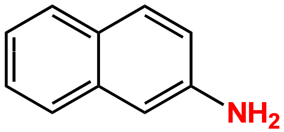
X = **Cl**, 89%
X = **Br**, 73%
X = **I**, 68%
X = **OTf**, 43%
X = **OMs**, 71%
X = **imidazolylSO_3**, 59%



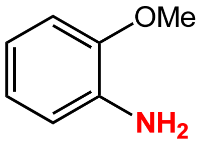
X = Br, 83%
X = OMs, 58%
X = imidazolylSO_3, 59%



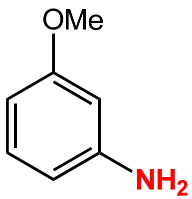
X = Cl, 76%



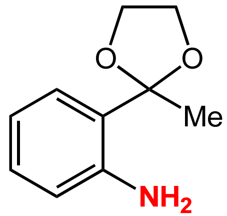
X = OTs, 76%



X = Cl, 80%

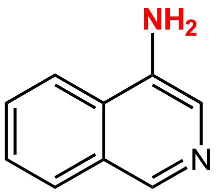


X = Cl, 60%

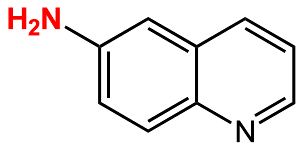


X = Cl, 83%

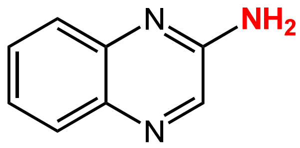
Substrate Scope



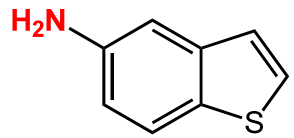
X = Br, 81%



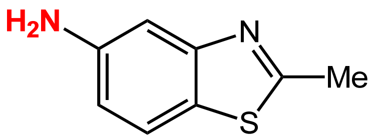
X = Cl, 82%



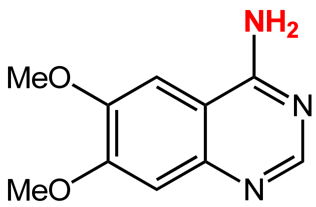
X = Cl, 76%



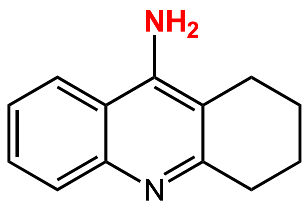
X = Cl, 68%



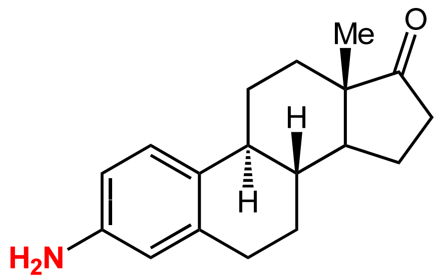
X = Cl, 68%



X = Cl, 90%

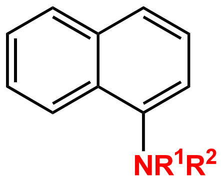


X = Cl, 87%

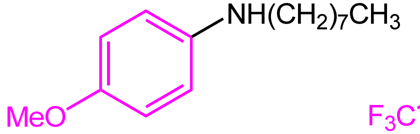


X = OTf, 58%

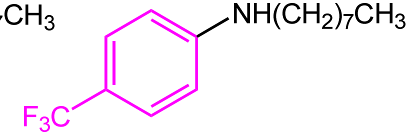
Substrate Scope



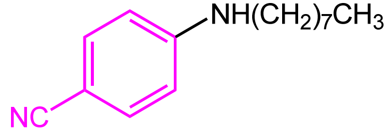
X = **Cl**, R^1 = H, R^2 = $(CH_2)_7CH_3$, 96%
X = **Br**, R^1 = H, R^2 = $(CH_2)_7CH_3$, 94%
X = **OMs**, R^1 = H, R^2 = $(CH_2)_7CH_3$, 91%
X = **Cl**, R^1 = H, R^2 = CH_3, 99%
X = Cl, R^1 = R^2 = CH_3, 57%



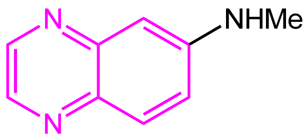
X = Cl, 85%



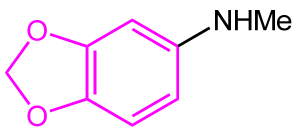
X = Cl, 70%



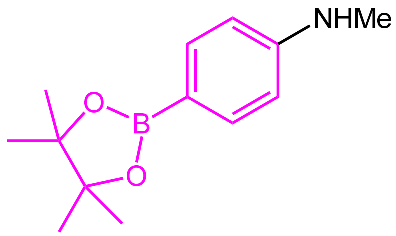
X = Cl, 80%



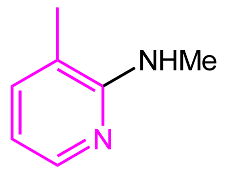
X = Cl, 81%



X = Cl, 80%

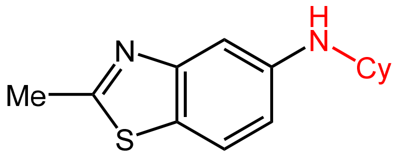


X = Cl, 69%

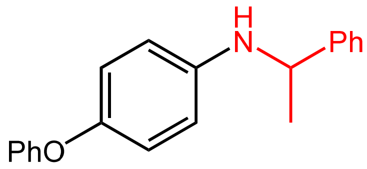


X = Cl, 73%

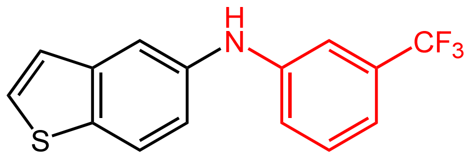
Substrate Scope



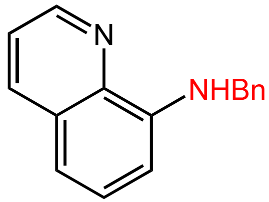
X = Cl, 98%



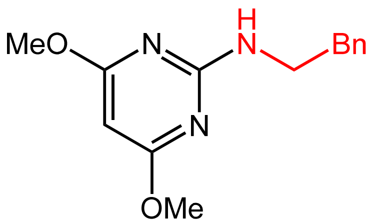
X = Cl, 70%



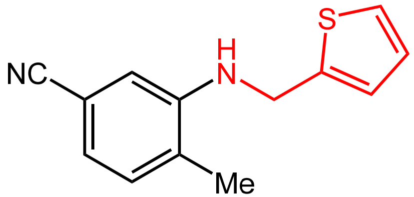
X = Cl, 94%



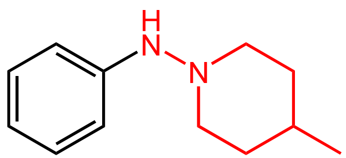
X = OTs, 60%



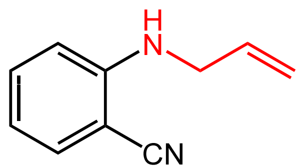
X = Cl, 67%



X = Br, 94%



X = Cl, 76%

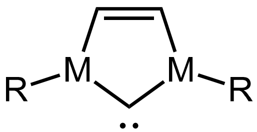


X = Cl, 70%

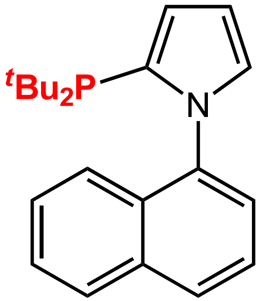
Design of Ligands for Ni-catalysed Reaction

$P^{t}Bu_3$

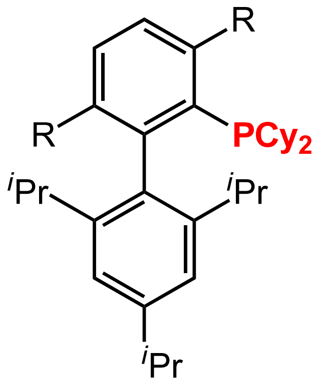
Fu



Hermann



Beller



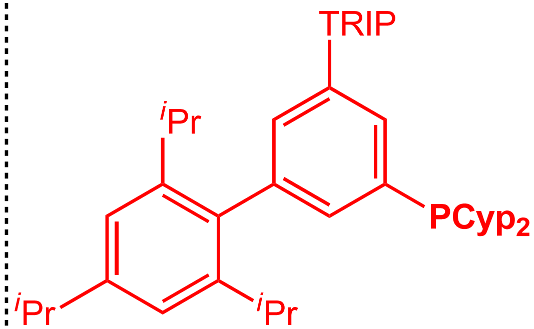
Buchwald

Pd

Major Advances in
Pd-catalysed
Cross-coupling

Phosphines
Designed for Pd
Mostly Ineffective

Few Efforts towards
Ni Ligand Development



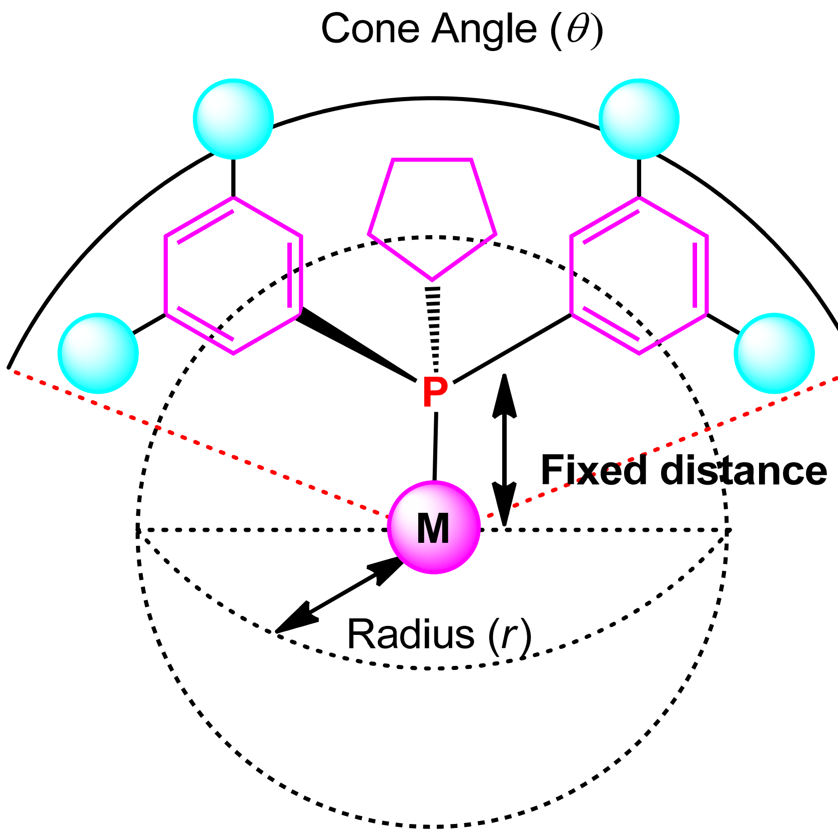
Novel Phosphine Ligand

Ni

New Reactions
Greater Efficiency
Expanded Scope

Wu, K.; **Doyle, A. G.** *Nat. Chem.* **2017**, *9,* 779

Ligand Design for Ni-catalysed Reactions



%V_{bur} = % Volume of Sphere of Radius *r* Occupied by Ligand; any Group beyond *r* is not Captured

θ = Angle Swept by Cone that Encloses all Ligand Groups

Remote Steric Hindrance = High θ and Low %V_{bur}

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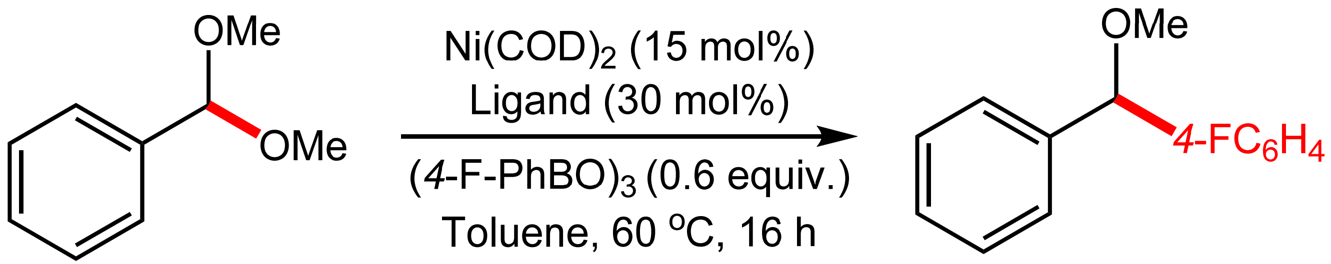
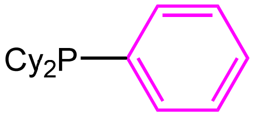
Ligand Evaluation



Classical Phosphine and Carbene Ligands：

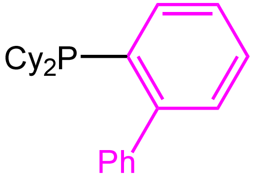
PPh_3	PCy_3	P^tBu_3	IMes
L_1	**L_2**	**L_3**	**L_4**
<2% yield	29% yield	No product	No product

Ligand Evaluation



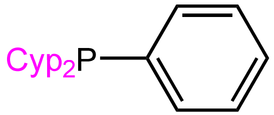
L5

24% yield



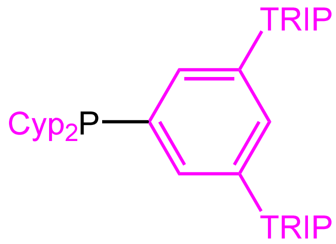
L6

No product



L7

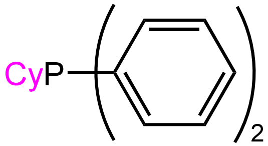
28% yield



L8

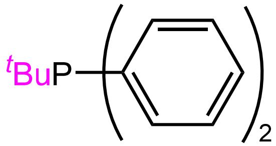
78% yield

Cyp = Cyclopentyl group



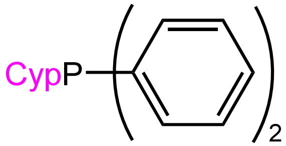
L9

10% yield



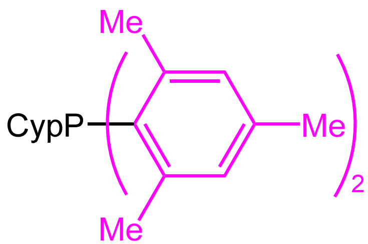
L10

3% yield



L11

17% yield

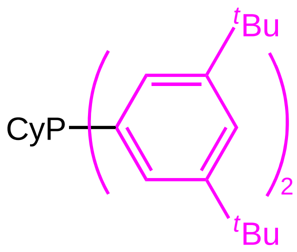


L12

No product

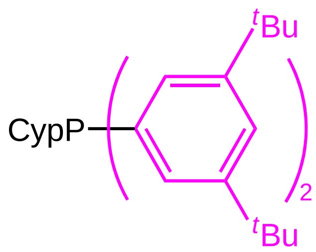
Conclusion: 1. Cyp > Cy > ^{t}Bu； 2. *meta* > *ortho* in aromatic ring

Ligand Evaluation



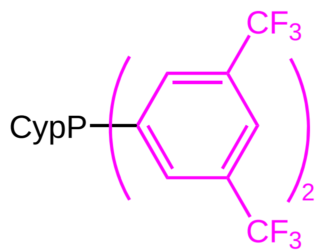
L_{13}

67% yield



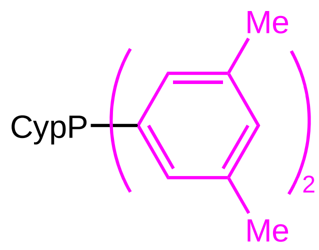
L_{14}

68% yield



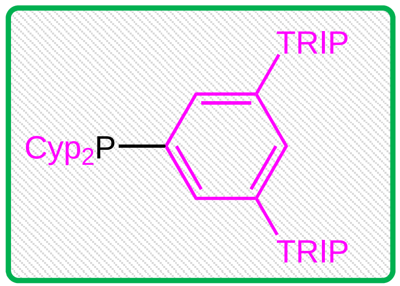
L_{15}

No product



L_{16}

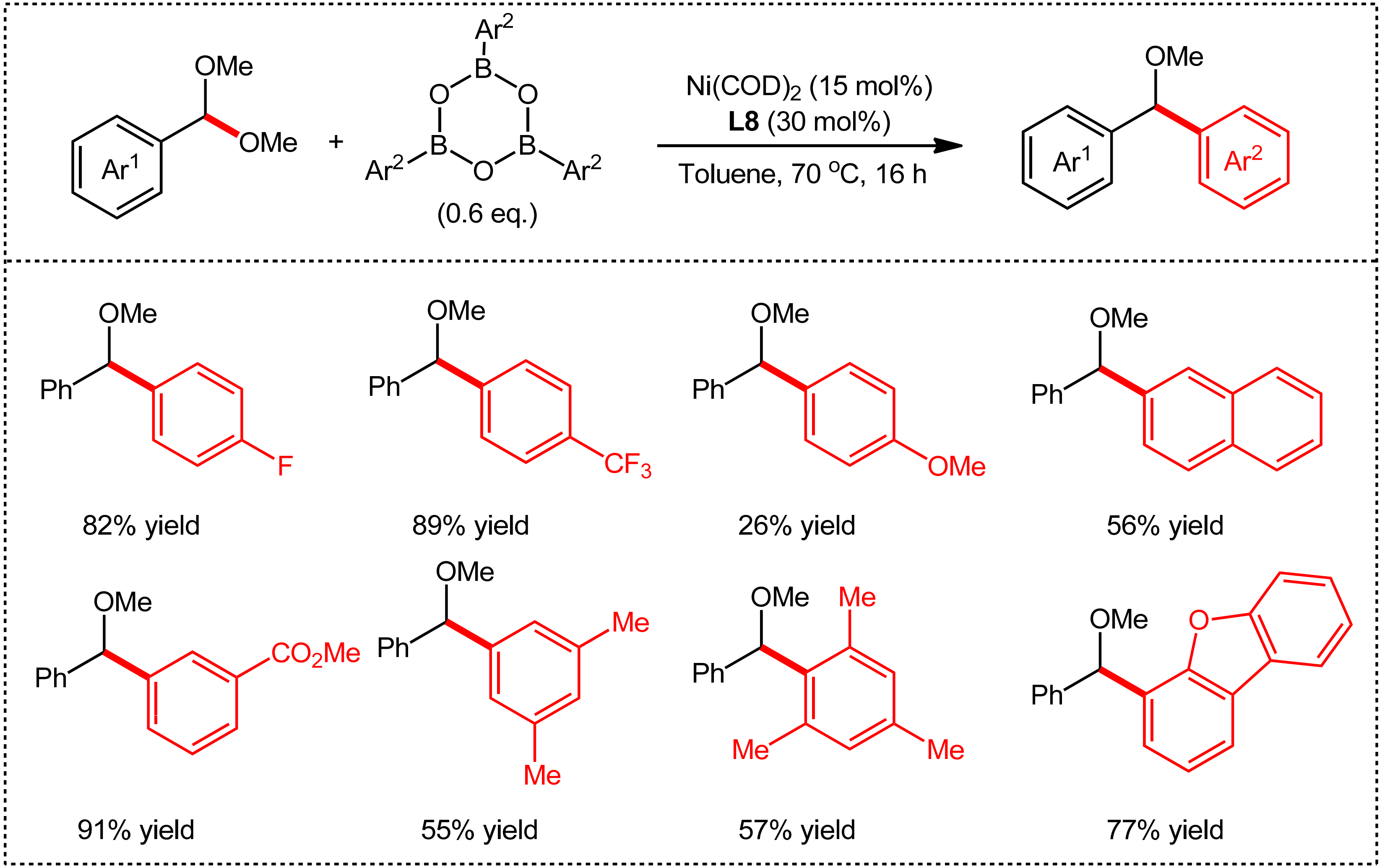
17% yield



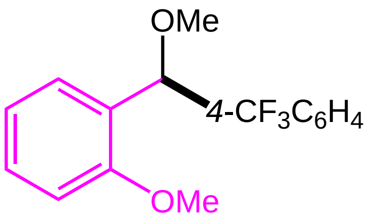
L_8

78% yield

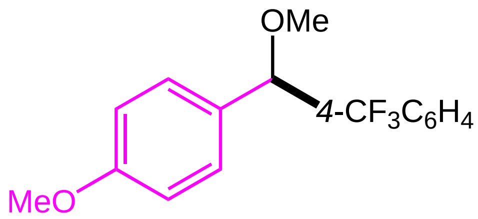
Substrate Scope



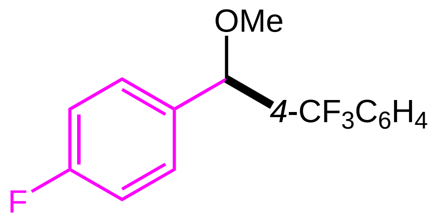
Substrate Scope



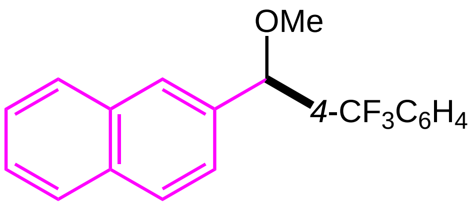
59% yield



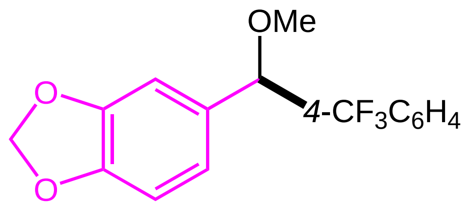
61% yield



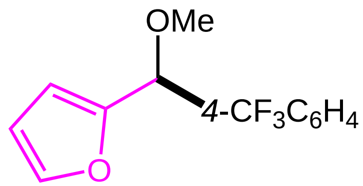
73% yield



86% yield

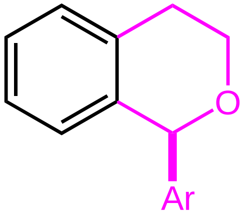


73% yield

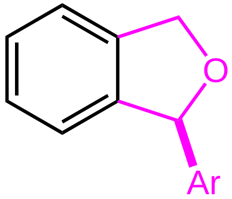


70% yield

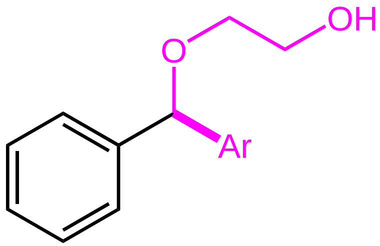
Substrate Scope



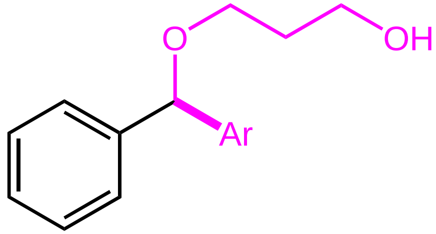
78% yield



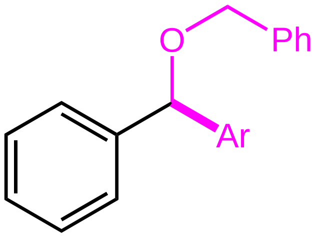
67% yield



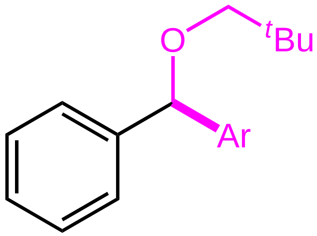
68% yield



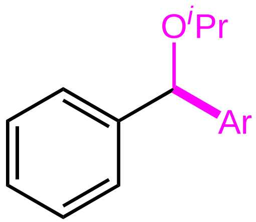
34% yield



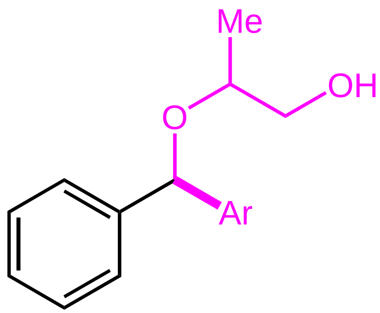
54% yield



85% yield



82% yield

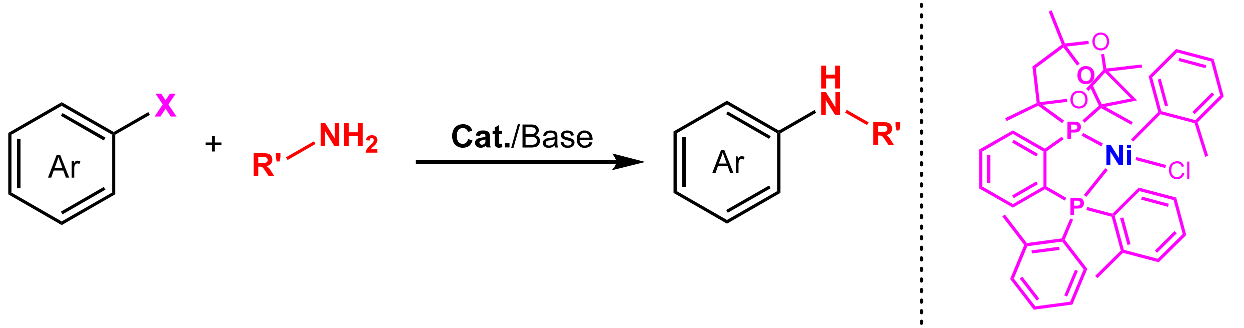


60% yield

Ar = 4-$CF_3C_6H_4$

Summary

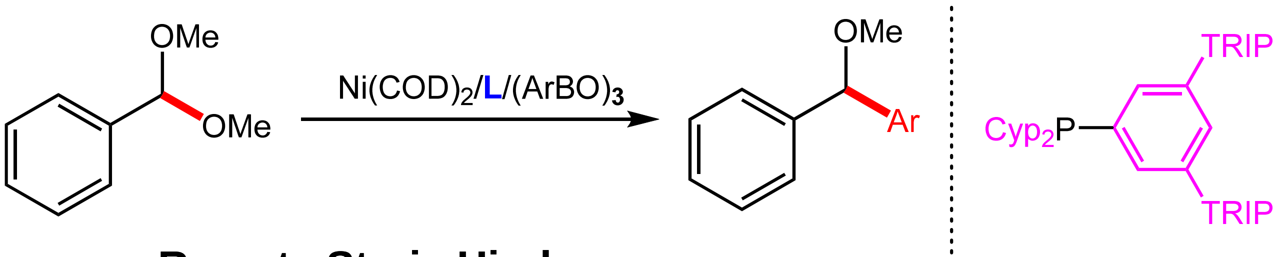
☐ Nickel Catalysed C(sp²)–N Cross-Coupling:



Sterically Demanding and Electron-poor Bisphosphine PAd-DalPhos

Lavoie, C. M.; MacQueen, P. M. *et al*. *Nat. Commun*. **2016**, *7*, 11073

☐ Nickel Catalysed Suzuki Coupling of Benzylic Acetals:



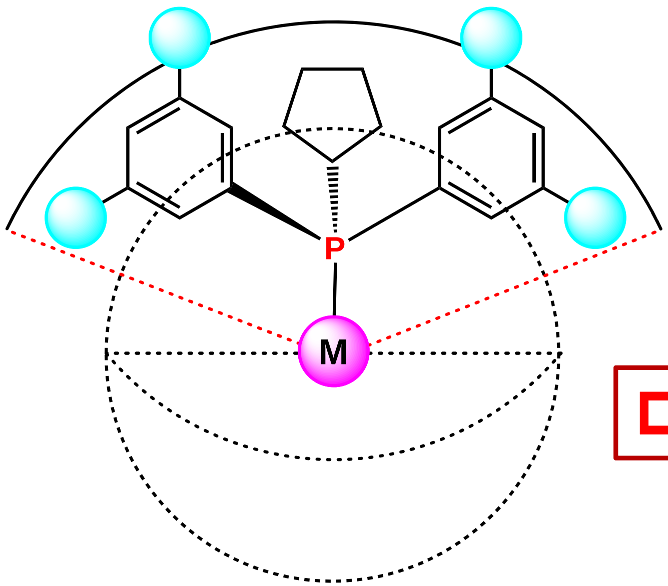
Remote Steric Hindrance

Wu, K.; **Doyle, A. G.** *Nat. Chem.* **2017**, *9,* 779

Perspectives

Ligand Design：

- Rigid Skeleton
- Electronic Effect (Electron-Donating or Withdrawing)
- Steric Effect
- Coordination Ability with Different Metals
- Cone Angle and Dihedral Angle



Remote Steric Hindrance!

The First Paragraph：Introduction

Over the past 50 years, the field of nickel-catalysed cross-coupling has witnessed tremendous activity, but minimal effort has been dedicated to the identification of new ligand. Furthermore, phosphines developed for Pd catalysis have generally proven ineffective for nickel. According to the example set by Pd, the design of new ligands for Ni should facilitate the refinement of existing methods and the identification of new chemical transformations. Herein, we report the development of a new class of phosphines and demonstrate that these ligands facilitate a Ni-catalysed C^{sp3} Suzuki coupling reaction that failed with known ligand architectures for Ni and Pd.

The Last Paragraph：Summary

In conclusion, we have developed a novel class of aryl alkylphosphines that confer high activity upon nickel catalysts for the Suzuki coupling. Parameterization and modelling studies reveal that the effectiveness of these ligands is a function of remote steric hindrance, a structural concept relatively unexplored in ligand design. We reveal a divergence between the cone angle and volume parameters. Whereas $\%V_{bur}$ only describes steric hindrance in the metal's first coordination sphere, cone angle captures it beyond the immediate proximity of the metal. We show that the two can be used in conjunction to develop a quantitative model for predicting ligand reactivity. We believe this new ligand architecture and the concept of **remote steric hindrance** will lead to significant advances in both Ni catalysis and ligand design.

Ackowledgements

Mr. Mu-Wang Chen

Prof. Zhi-Shi Ye

Mrs. Lei Sun

Prof. Lei Shi

Thanks for your attention!