

Literature Report

Ligand-Controlled C(sp³)-H Arylation and Olefination in Synthesis of Unnatural Chiral α -Amino Acids

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Date: 2014-10-14

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Scripps Research Institute

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Summary

Introduction

Education:

Harvard University - Cambridge, MA, USA

Postdoctoral Fellow, supervisor: E. J. Corey
February 2001 - May 2002

University of Cambridge - Cambridge, UK

Junior Research Fellow (JRF) of St. John's College
October 1999 - October 2003

University of Cambridge - Cambridge, UK

Ph.D. in Chemistry with Jonathan Spencer
October 1994 - September 1999

Guangzhou Institute of Chemistry - Guangzhou, China

M.Sc. in Chemistry with S. D. Xiao
September 1988 - July 1990

Shanghai Institute of Organic Chemistry - Shanghai, China

Coursework for M.Sc. degree
September 1987 - July 1988

East China Normal University - Shanghai, China

B.Sc. in Chemistry
Top 5% of national examination for admission to SIOC
Supervisors: L. X. Dai and B. Q. Wu
September 1982 - July 1987

Academic Positions:

Scripps Research Institute - La Jolla, CA, USA

Frank and Bertha Hupp Professor of Chemistry, 2012

Professor of Chemistry, 2010 – 2012

Associate Professor of Chemistry, 2007 - 2010

Brandeis University - Waltham, MA, USA

Assistant Professor of Chemistry, 2004 - 2007

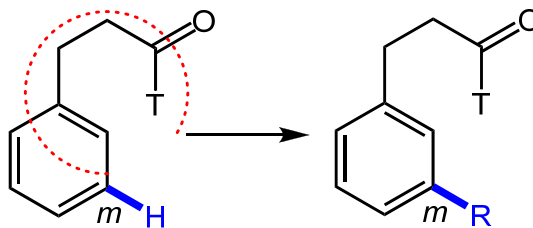
University of Cambridge - Cambridge, UK

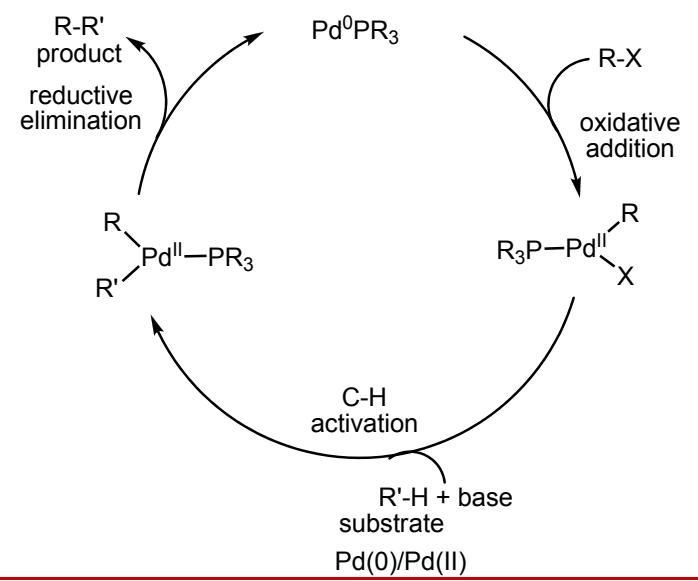
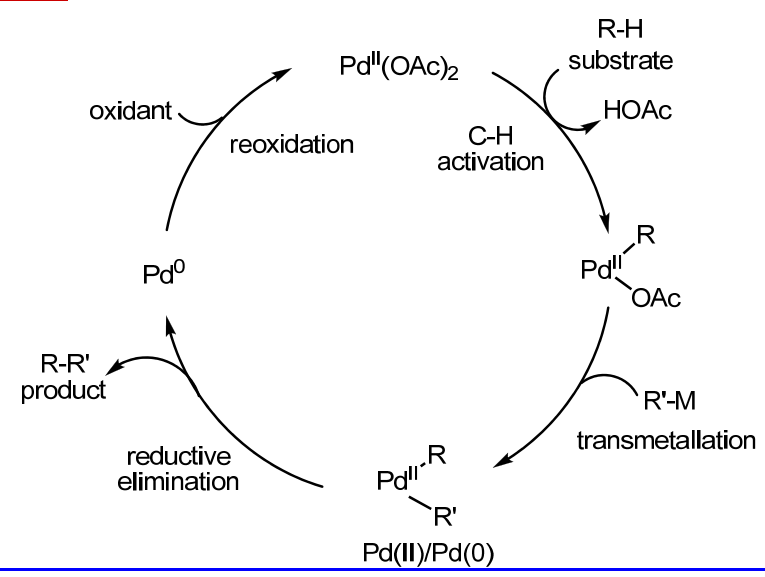
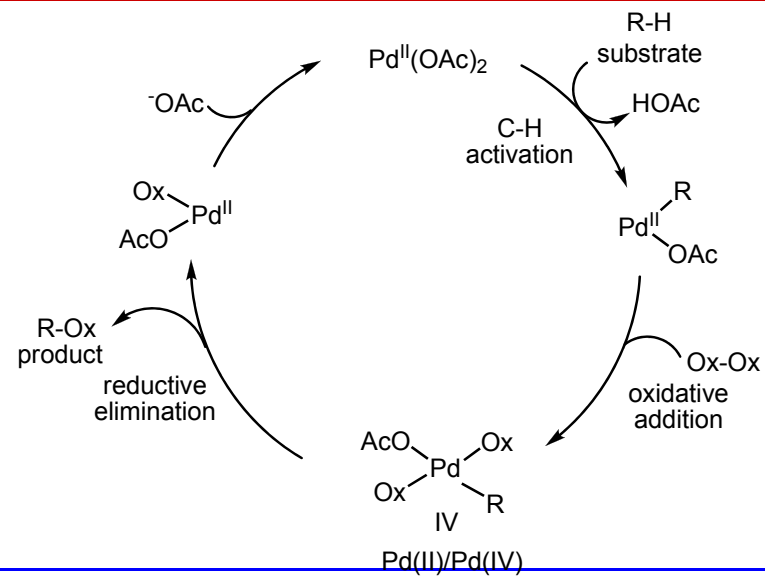
Royal Society Research Fellow, 2003 - 2004

Research Focus:

Discovering new reactions for synthesis through **C-H** activation

1. **Ligand-Controlled C(sp³)-H;**
2. **C-H Bonds Directed by a U-Shaped Template.**



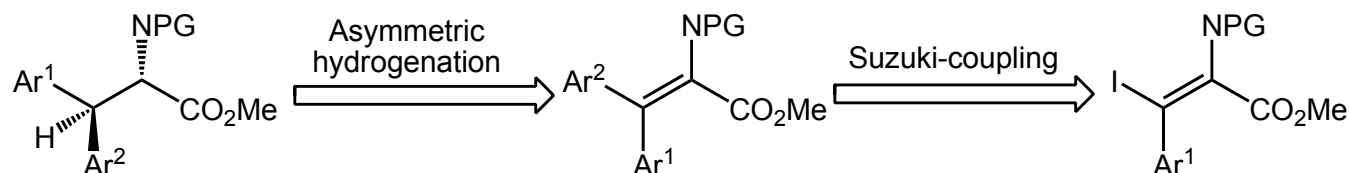


Ligand-Controlled C(sp³)-H Arylation and Olefination in Synthesis of Unnatural Chiral α -Amino Acids

Method for synthesizing chiral β -Ar- β -Ar'- α -amino acids

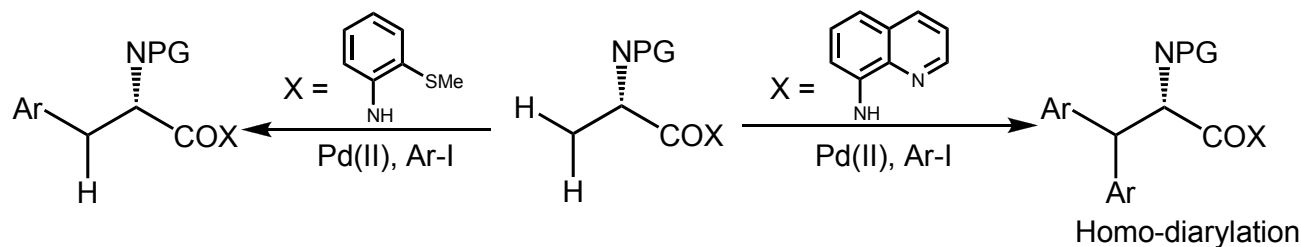
A

Asymmetric hydrogenation



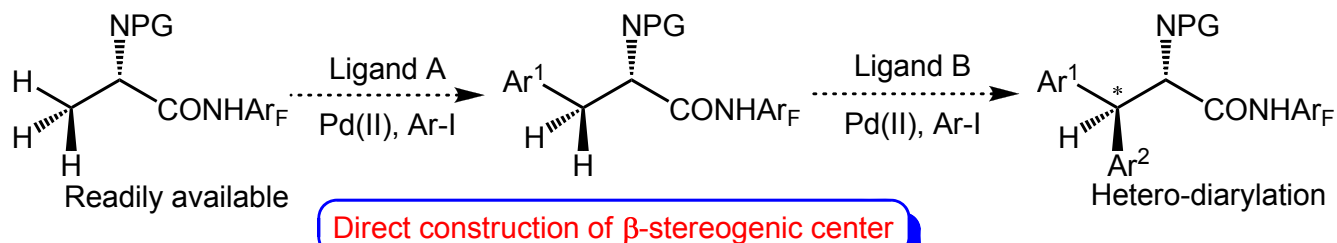
B

Auxiliary-controlled C(sp³)-H arylation

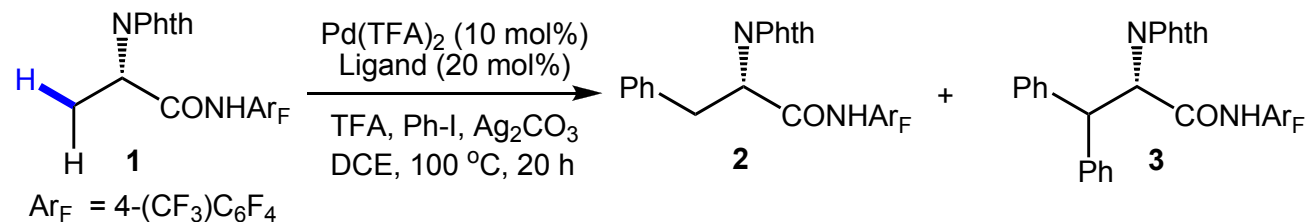


C

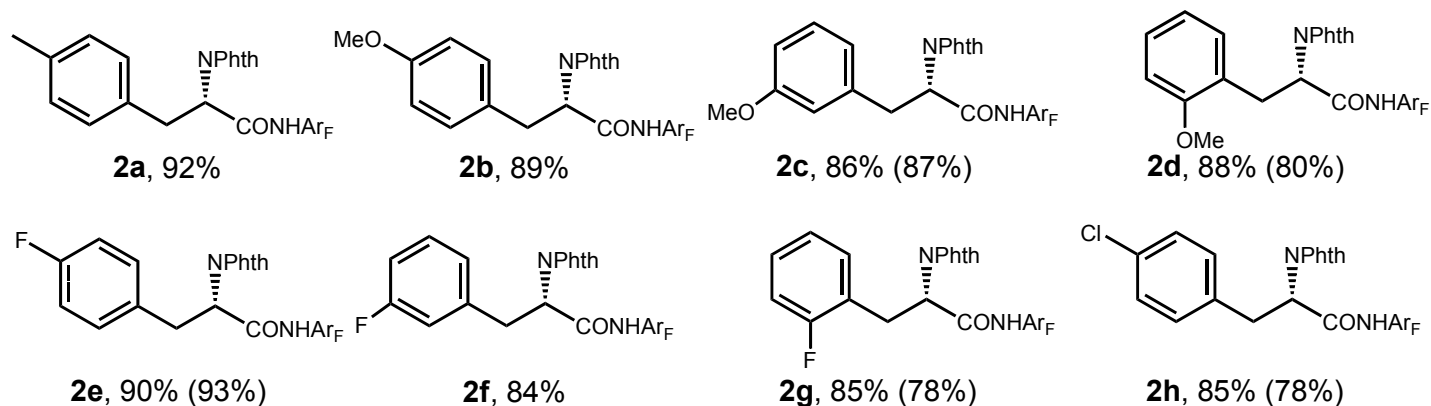
Ligand-controlled C(sp³)-H arylation

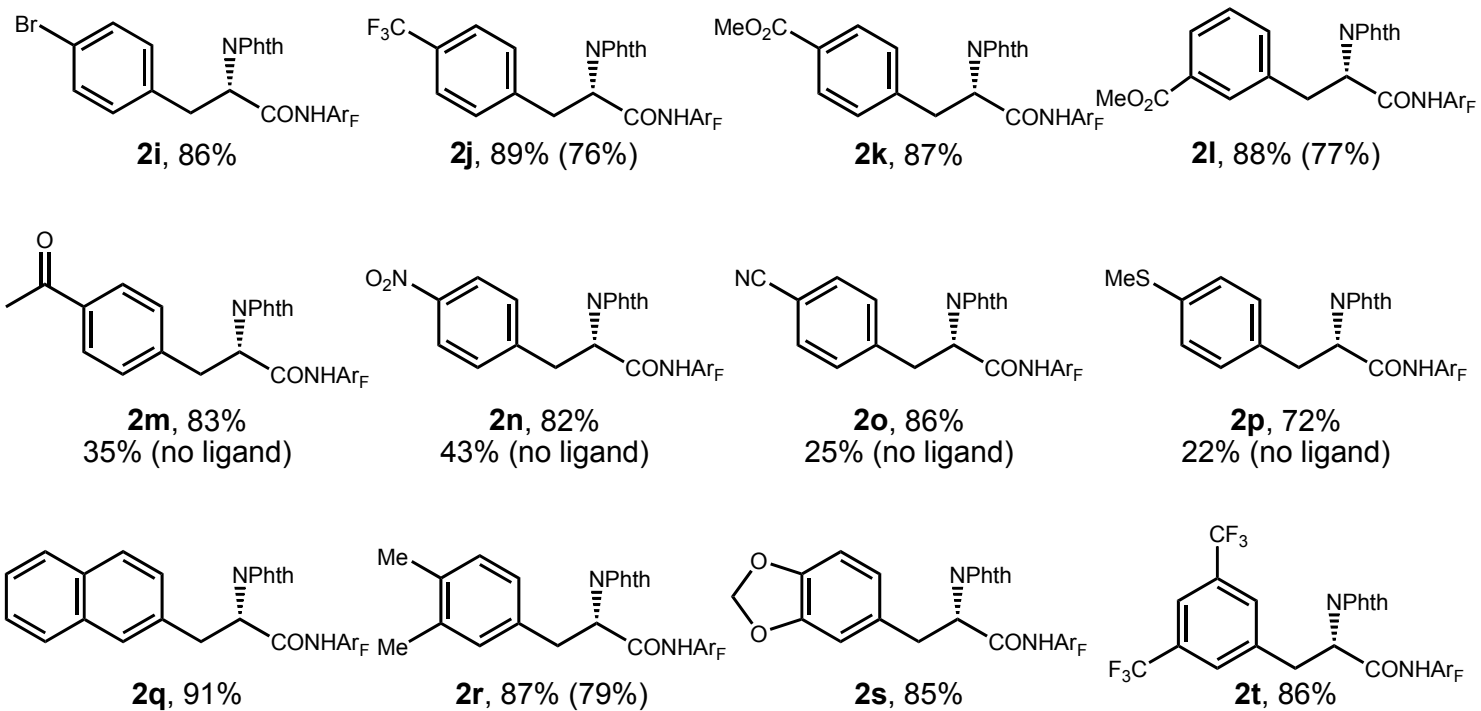


Palladium-Catalyzed Arylation of Primary C(sp³)-H Bonds

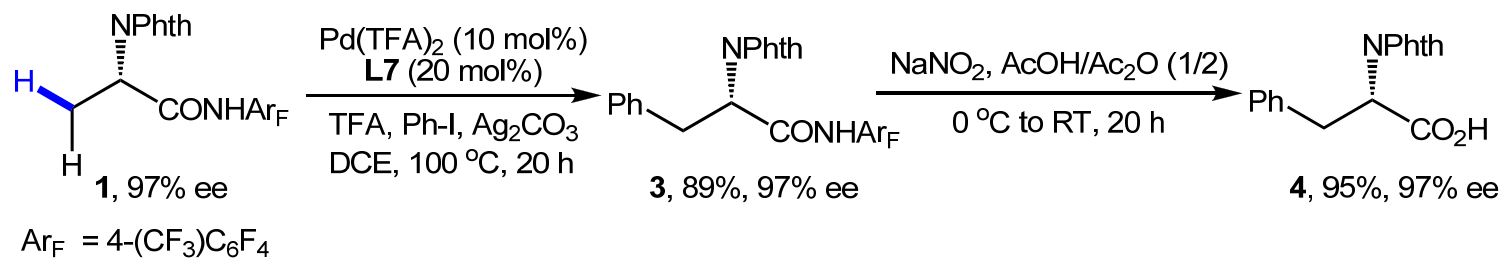


	-	L1	L2	L3	L4	L5	L6	L7
2:	47%	29%	52%	65%	87%	88%	91%	94%
3:	1%	0%	0%	2%	13%	12%	9%	2%

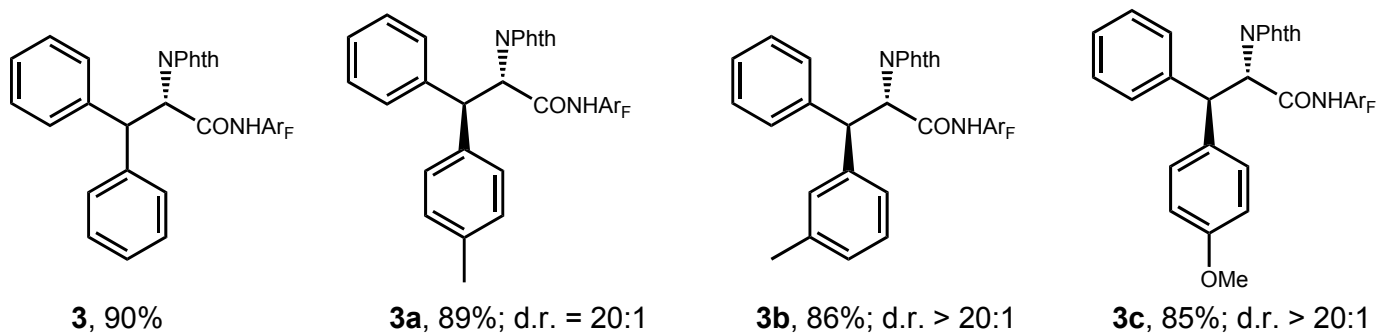
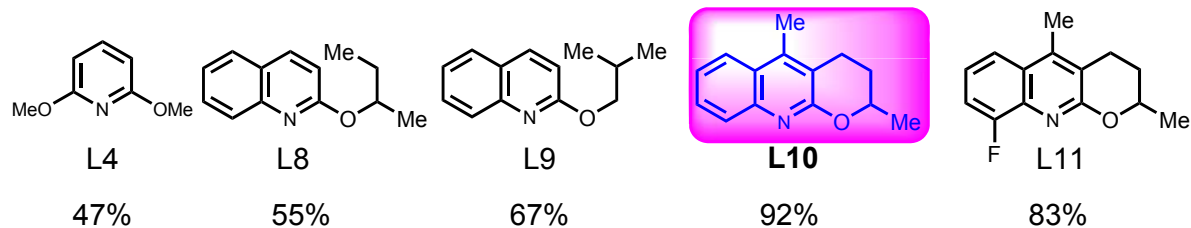
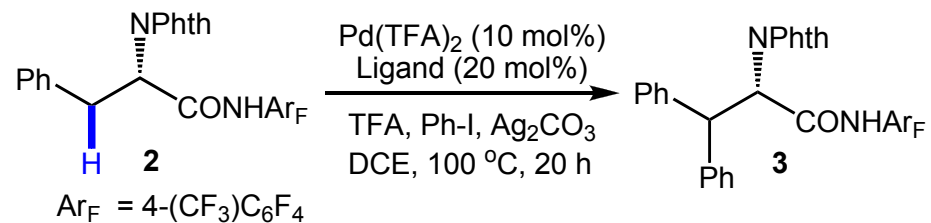


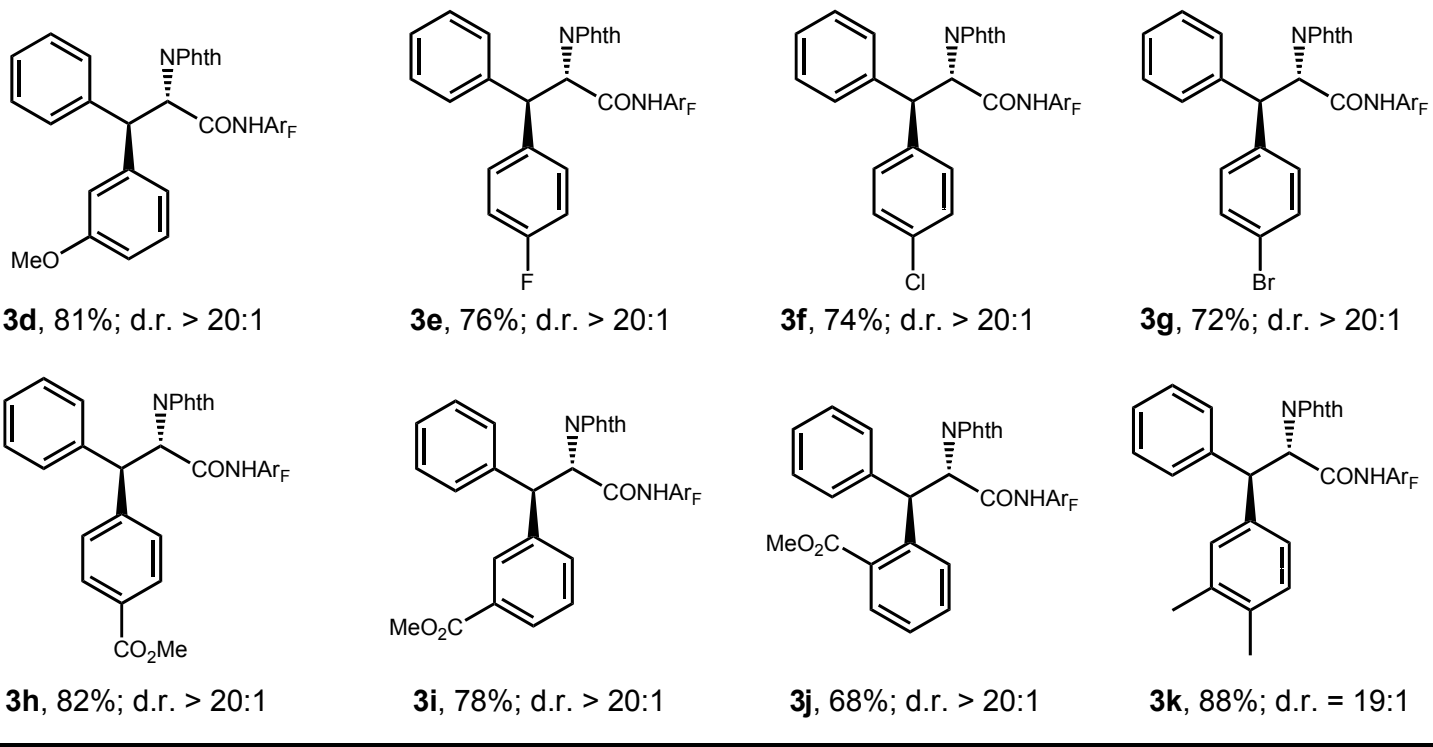


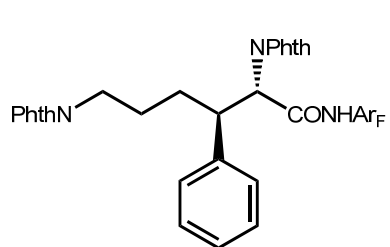
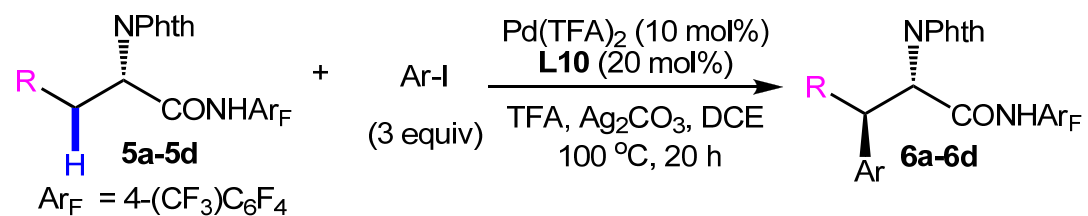
Removal of Amide Auxiliary



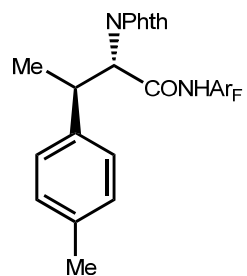
Palladium-Catalyzed Arylation of Secondary C(sp³)-H Bonds



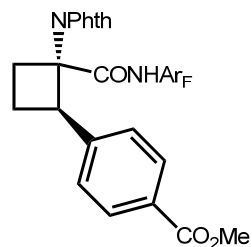




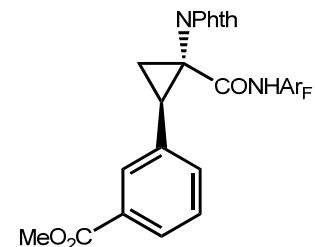
6a, 66%; d.r. > 20:1



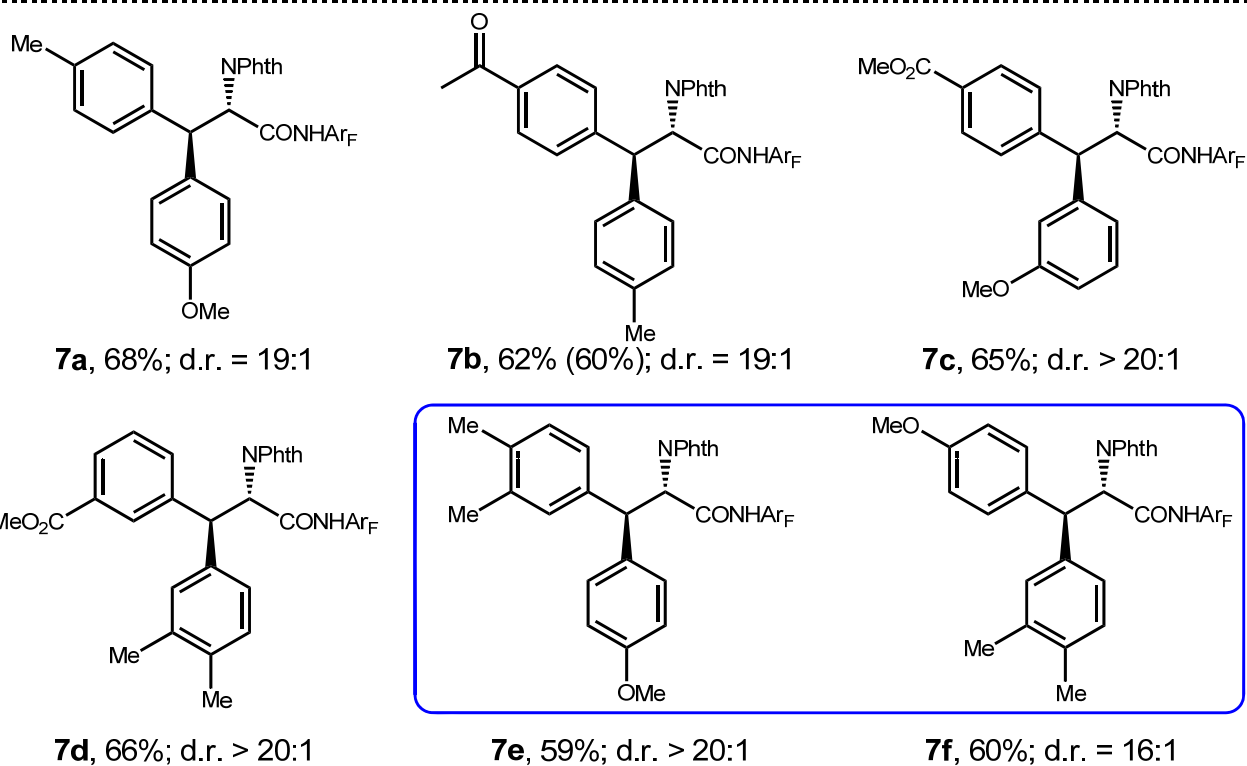
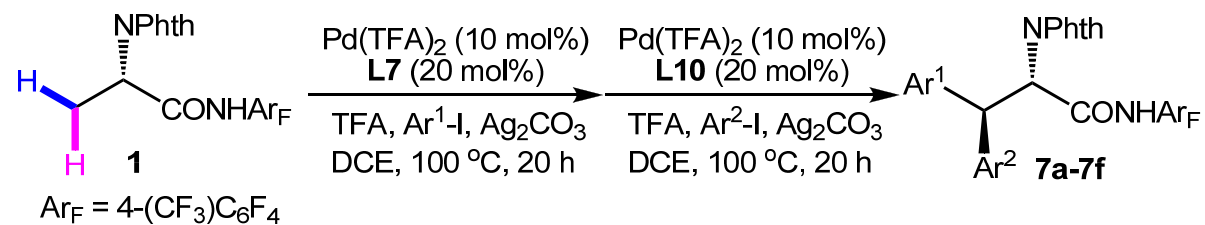
6b, 88%; d.r. = 15:1



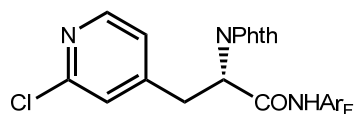
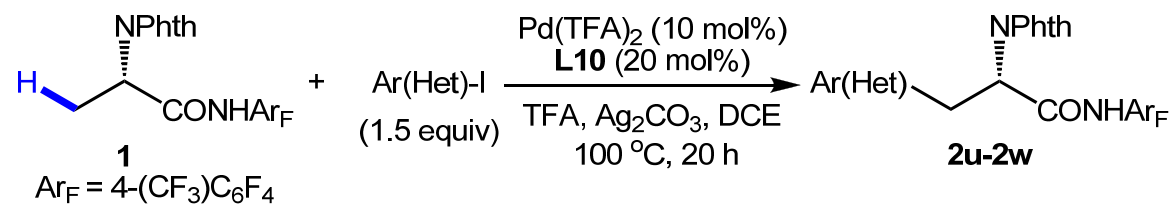
6c, 90%; mono:di = 2:1
single diastereomers



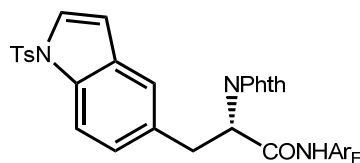
6d, 70%; mono:di > 20:1
single diastereomers



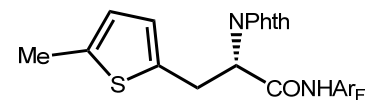
Further Applications of Pd Catalysis with L10



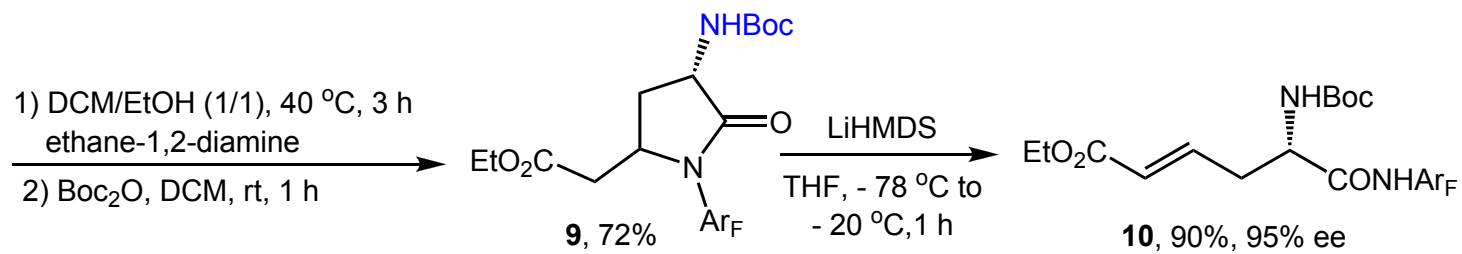
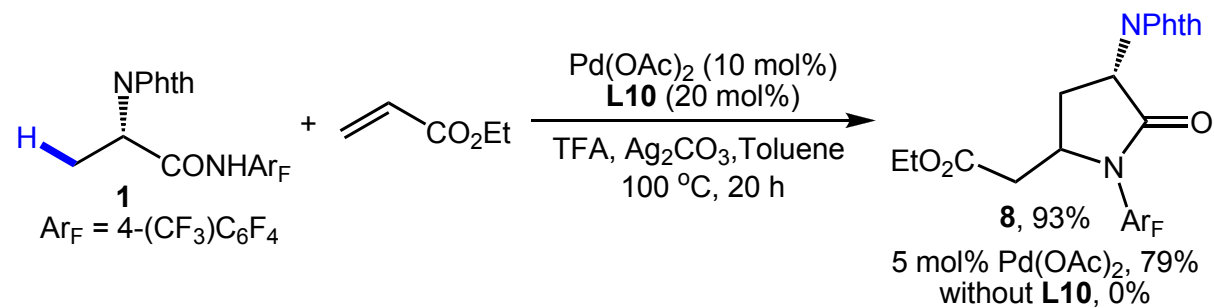
2u, 55%



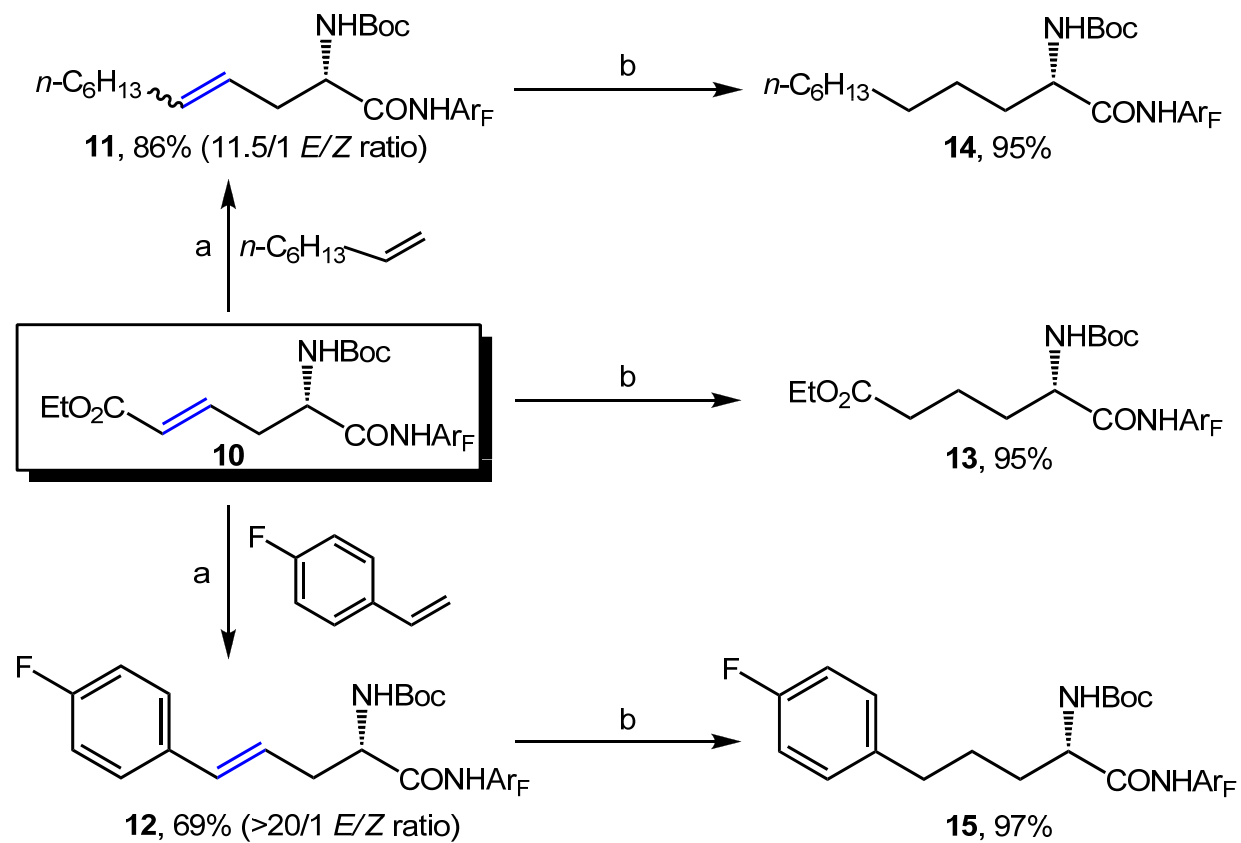
2v, 65%



2w, 72%

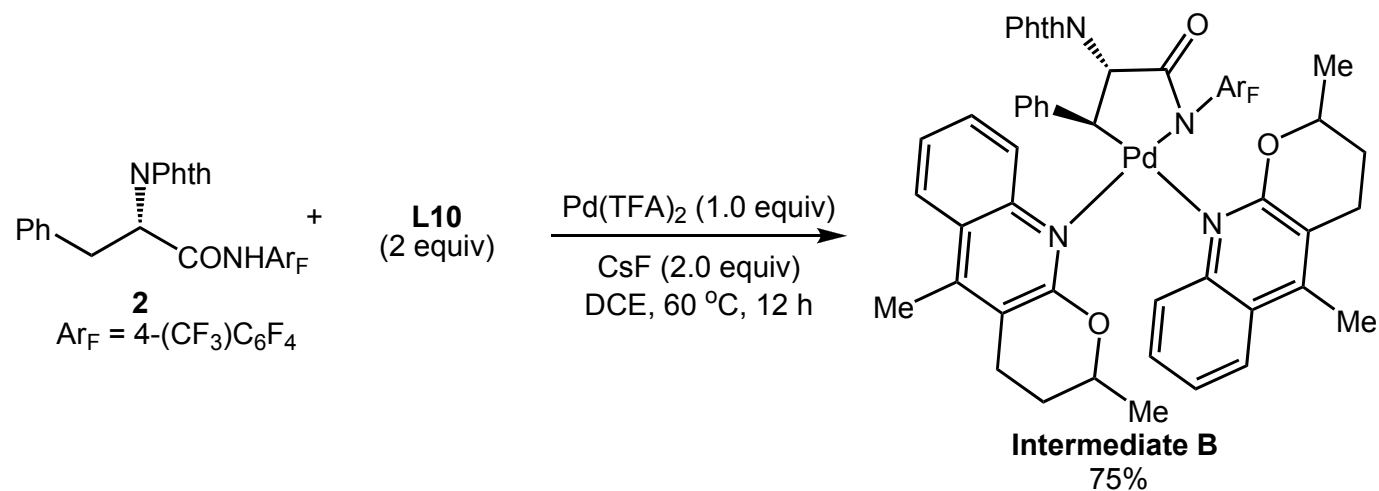
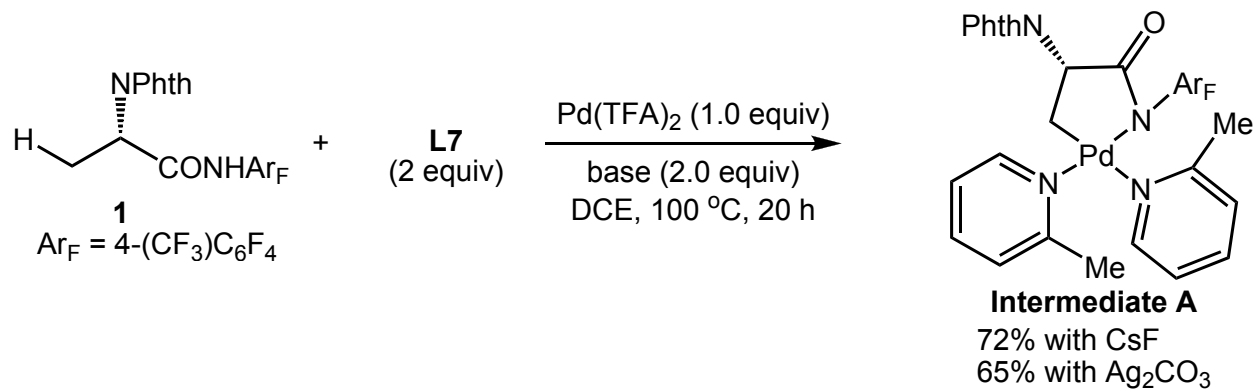


Unnatural α -Amino Acid Elaboration

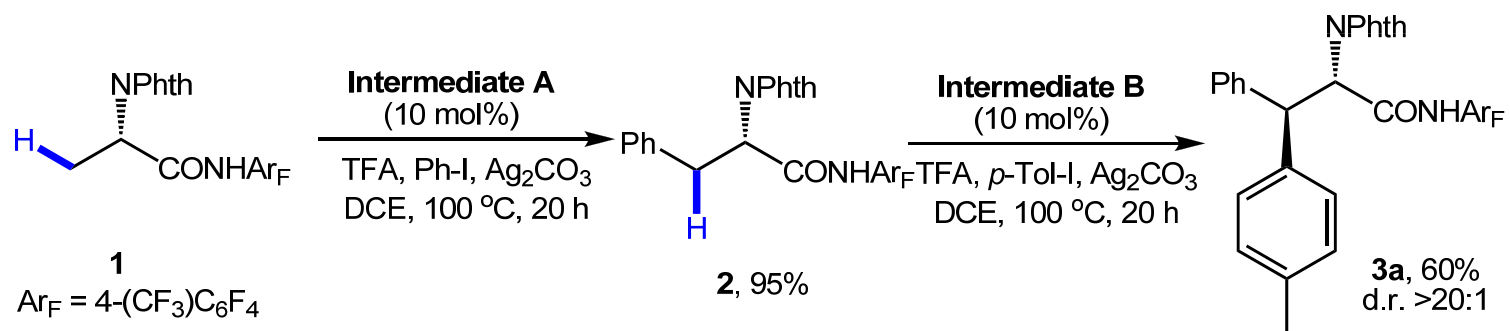


- a) 5 mol% Grubbs Catalyst 2nd Generation, DCM, 50 °C, 16-19 h;
b) Pd/C, H₂, rt, EtOAc, 40 min-24 h.

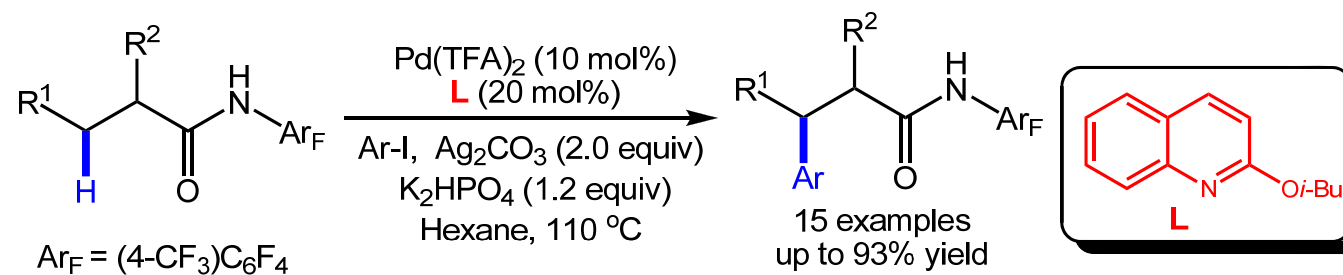
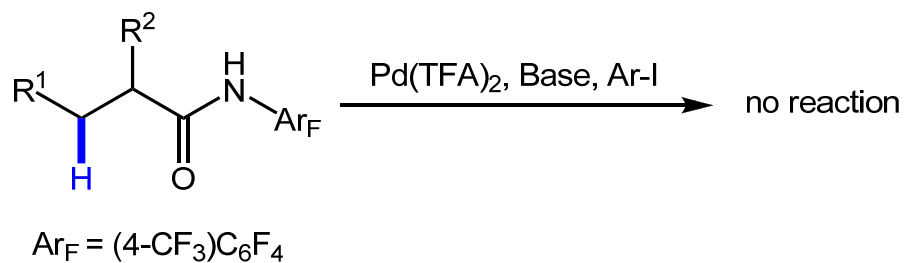
Synthesis and Crystallography of Primary and Secondary C(sp³)-H Activation Intermediates



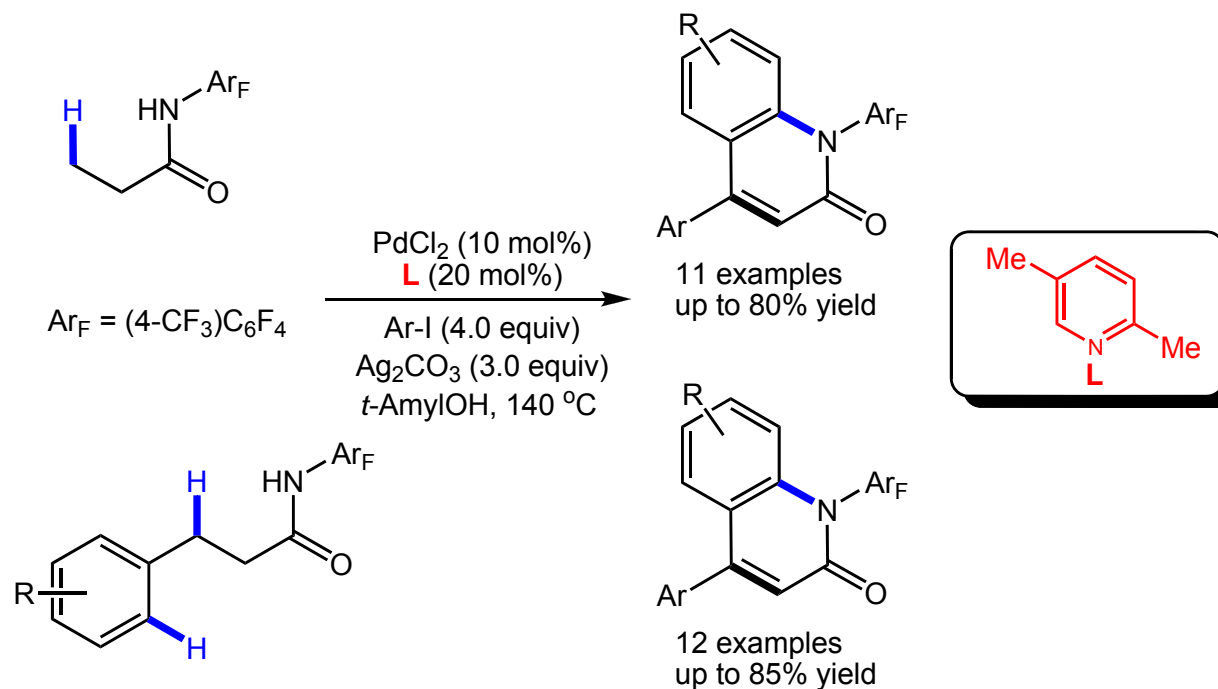
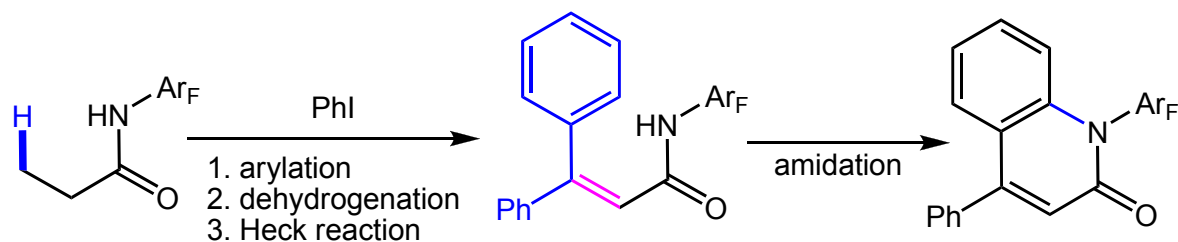
Catalytic Reaction of Intermediates in C(sp³)-H Arylation Reactions



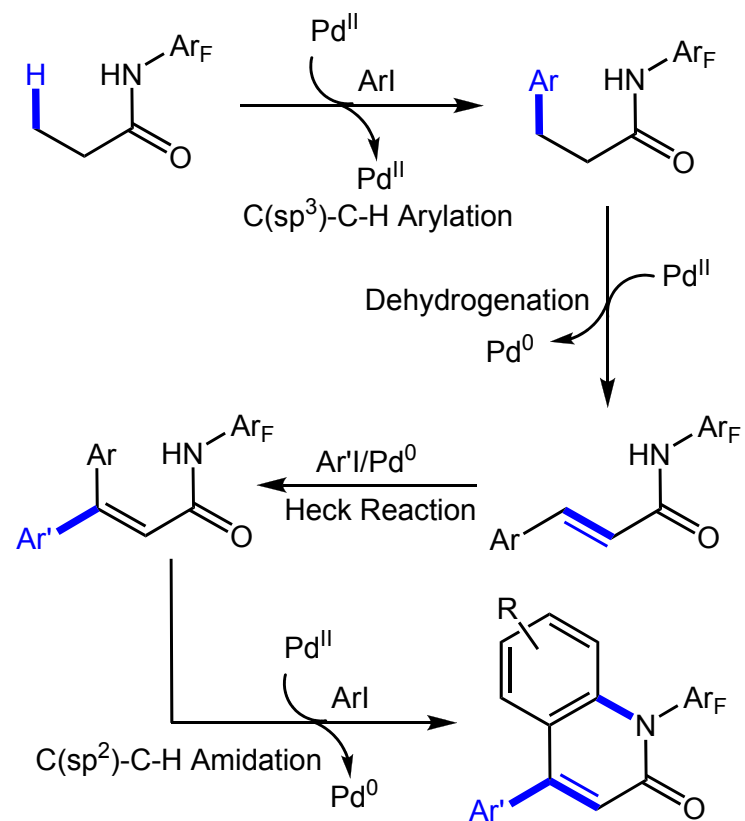
Ligand-Enabled Methylene C(sp³)-H Bond Activation with a Pd^{II} Catalyst



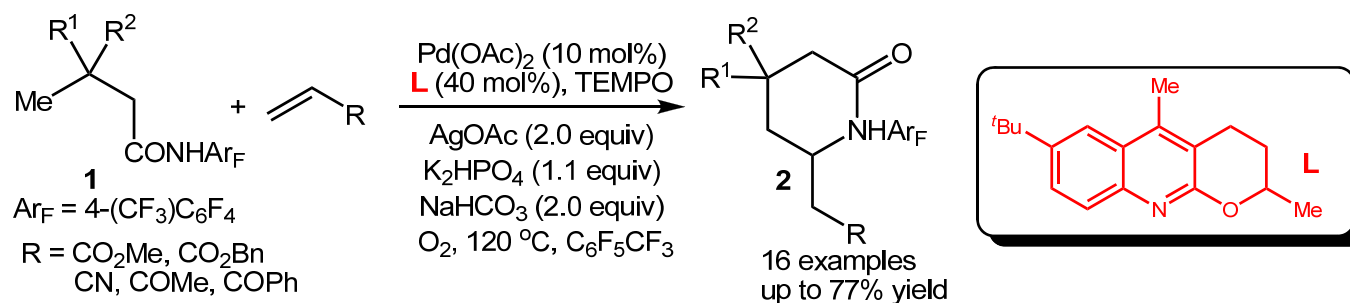
Ligand-Enabled Triple C-H Activation Reactions: One-Pot Synthesis of Diverse 4-Aryl -2-quinolinones from Propionamides



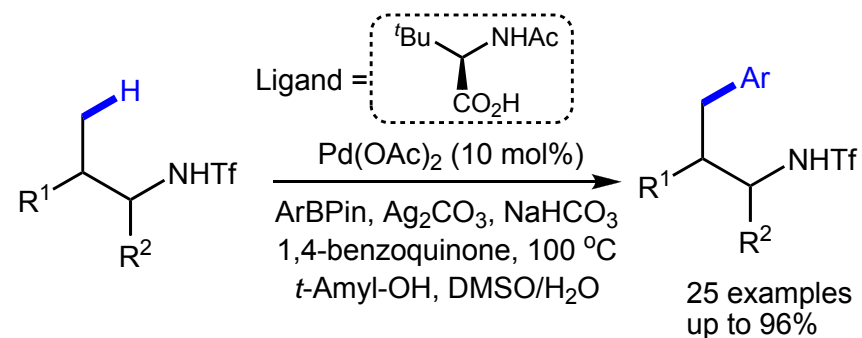
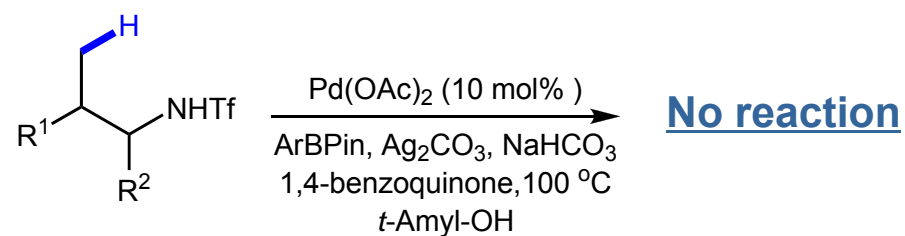
Proposed Catalytic Pathway



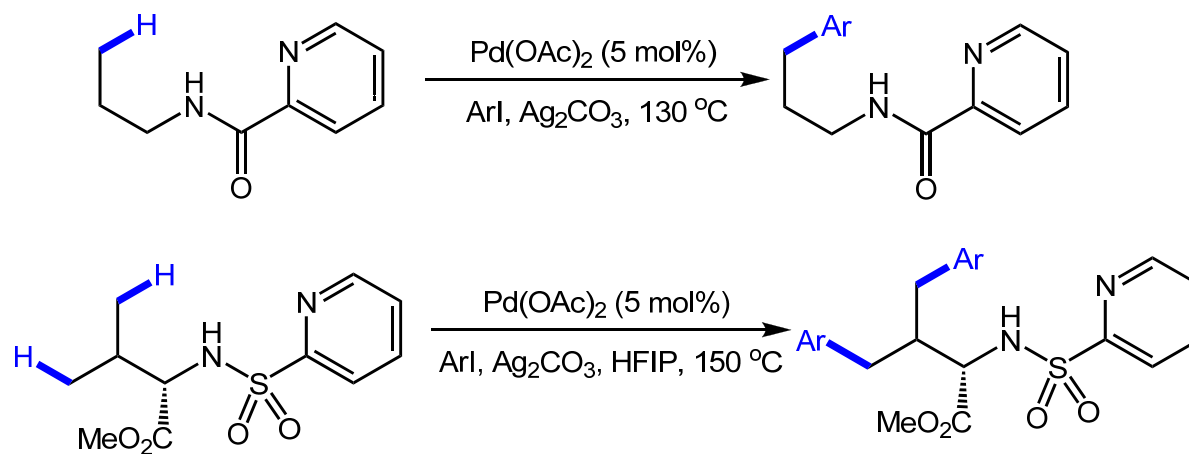
Ligand-Enabled γ -C-H Olefination and Carbonylation: Construction of β -Quaternary Carbon Centers



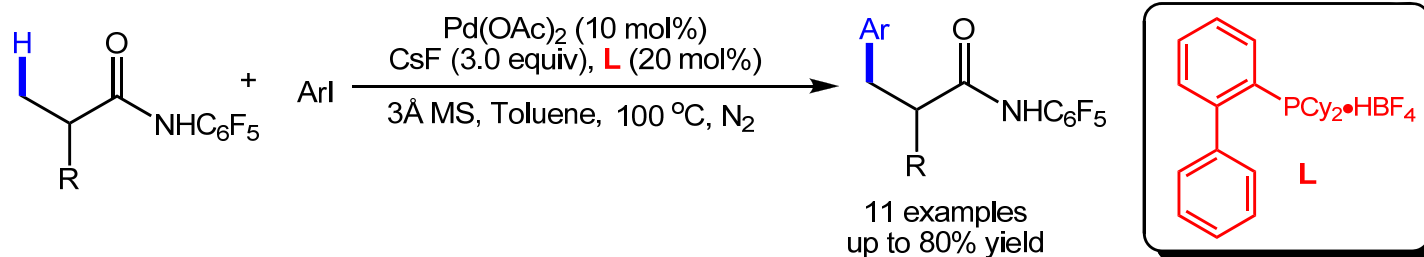
Ligand-Enabled Cross-Coupling of C(sp³)-H bonds with Arylboron Reagents *via* Pd(II)/Pd(0) Catalysis



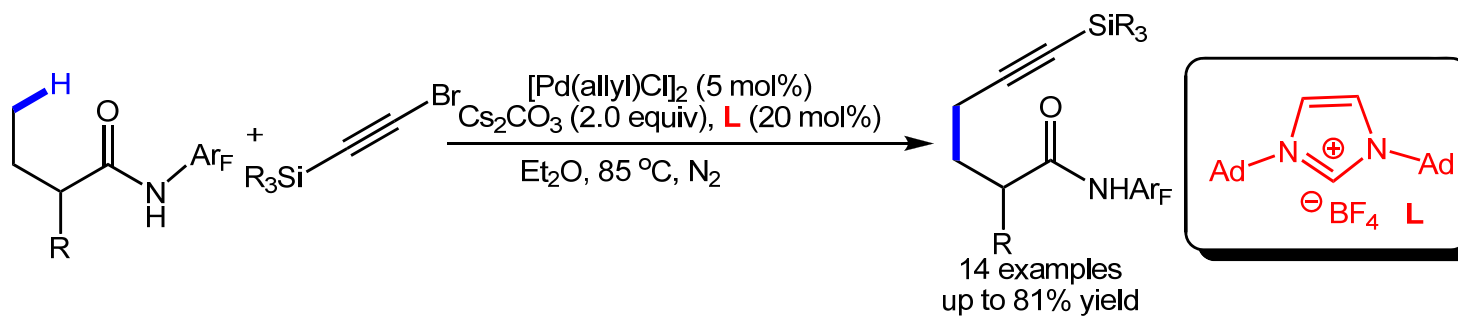
C-H Activation of Aliphatic Amines Directed by Strong δ Chelation



Palladium(0)-Catalyzed Intermolecular Arylation/Alkynylation of C(sp³)-H Bonds

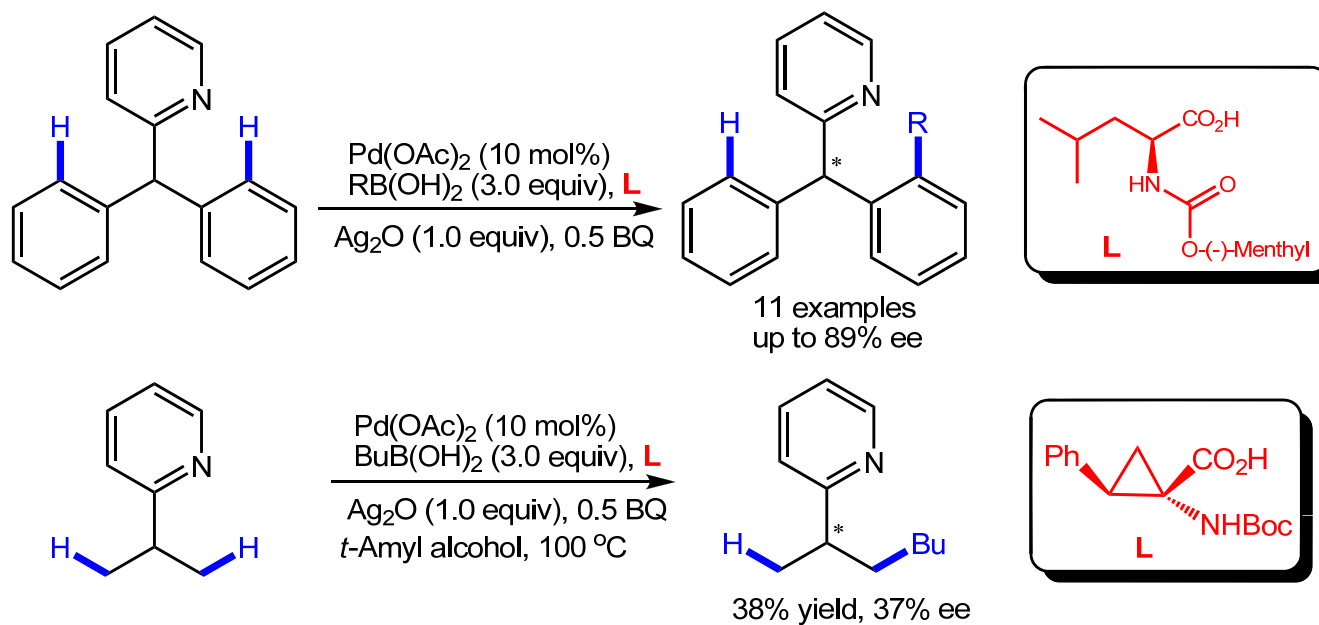


Yu, J.-Q. *et al.* *J. Am. Chem. Soc.* **2009**, *131*, 9886–9887.

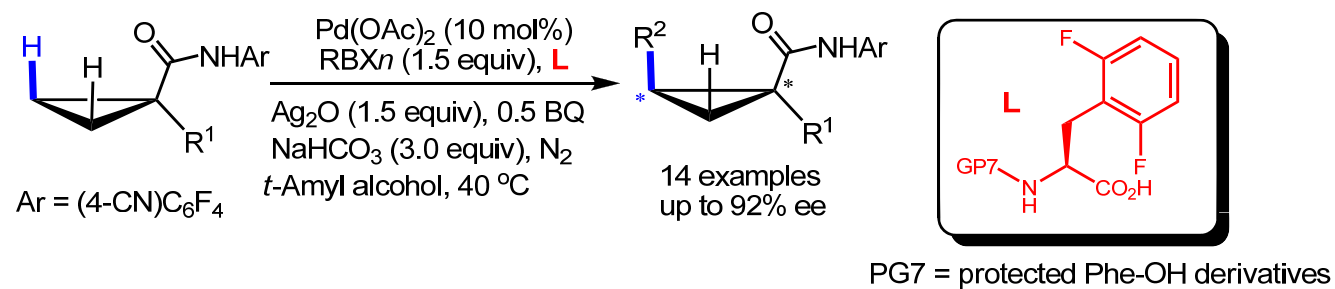


Yu, J.-Q. *et al.* *J. Am. Chem. Soc.* **2013**, *135*, 3387–3390.

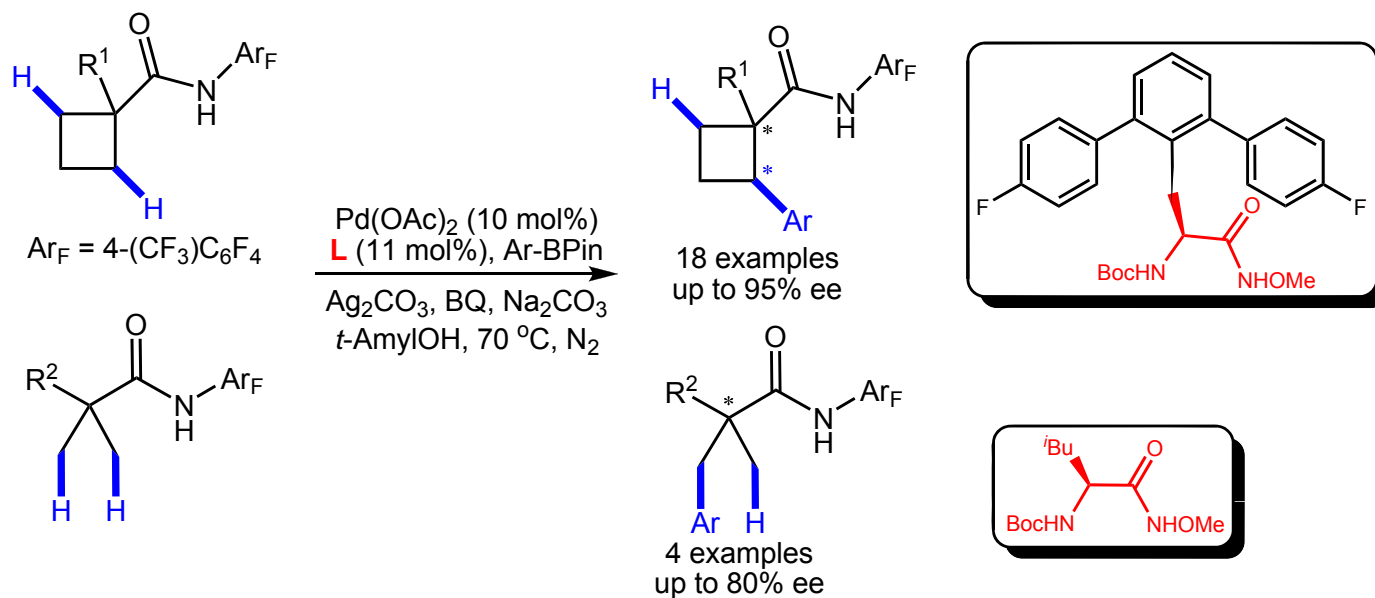
Pd^{II}-Catalyzed Enantioselective Activation of C(sp²)-H and C(sp³)-H Bonds Using Monoprotected Amino Acids as Chiral Ligands



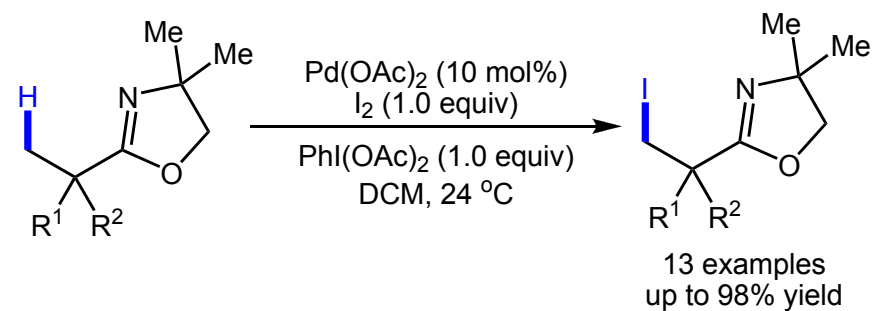
Pd^{II}-Catalyzed Enantioselective C-H Activation of Cyclopropanes



Palladium^{II}-Catalyzed Enantioselective C(sp³)-H Activation Using a Chiral Hydroxamic Acid Ligand



Pd-Catalyzed Asymmetric Iodination of Unactivated C-H Bonds under Mild Conditions

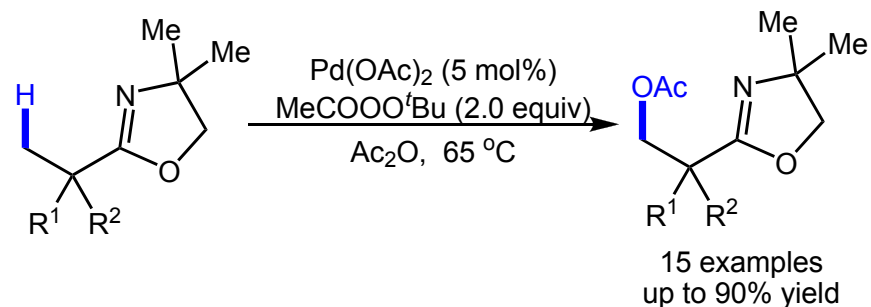


Catalyst recycling experiments

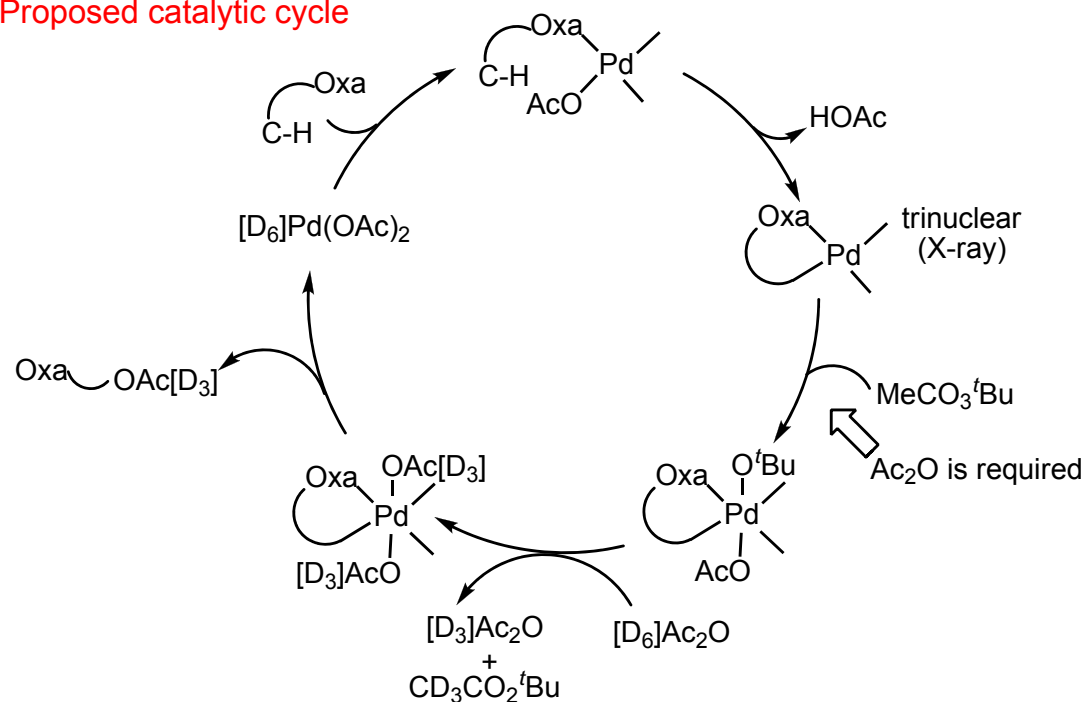
Run	1	2	3	4	5
Yield (%)	98	97	93	88	84

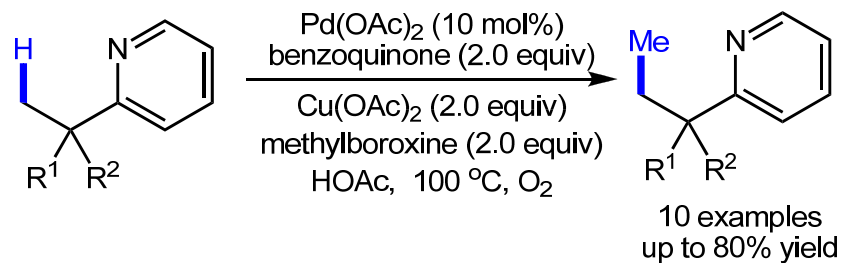
Yu, J.-Q. *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 2112-2115.

Pd-Catalyzed Stereoselective Oxidation of Methyl Groups by Inexpensive Oxidants under Mild Conditions

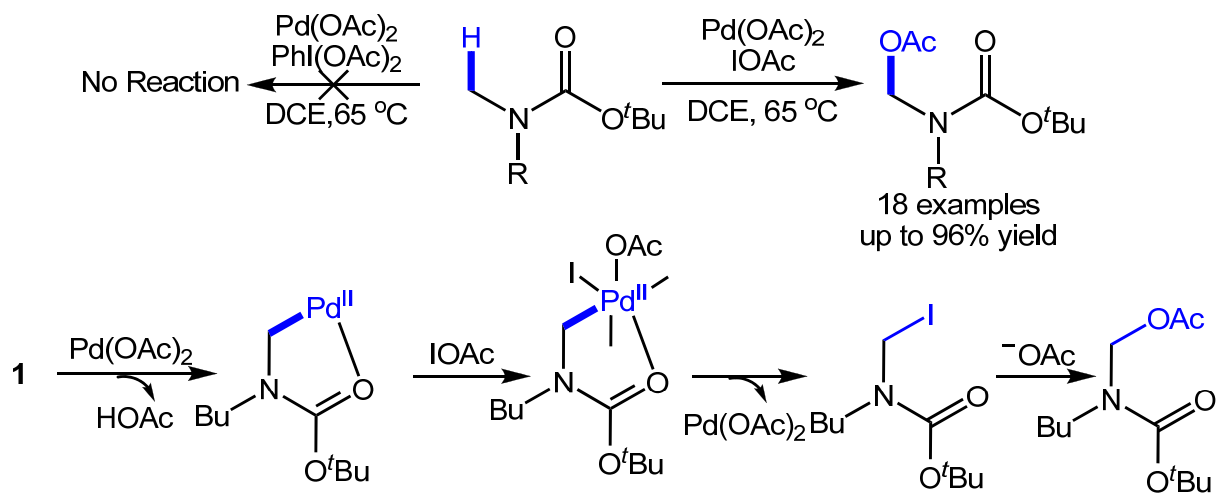


Proposed catalytic cycle

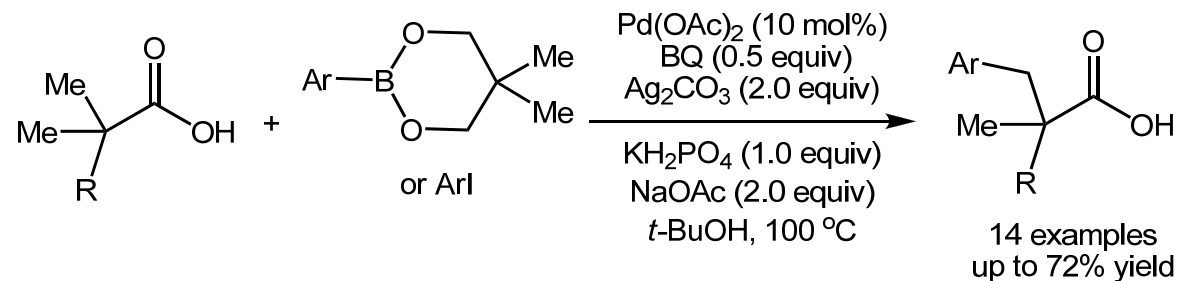




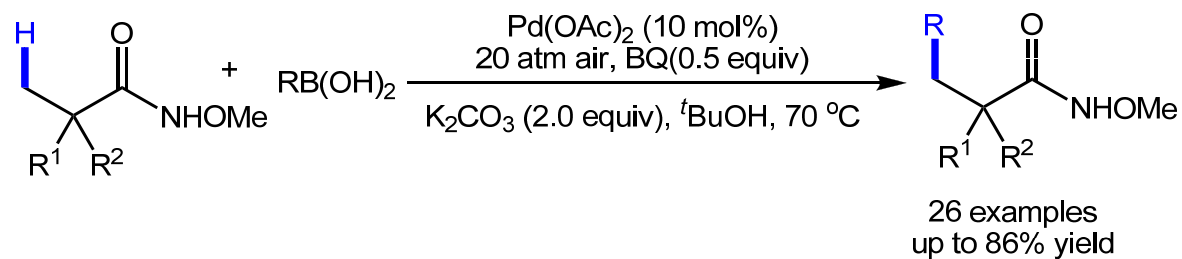
Yu, J.-Q. *et al. J. Am. Chem. Soc.* **2006**, 128, 12634-12635.



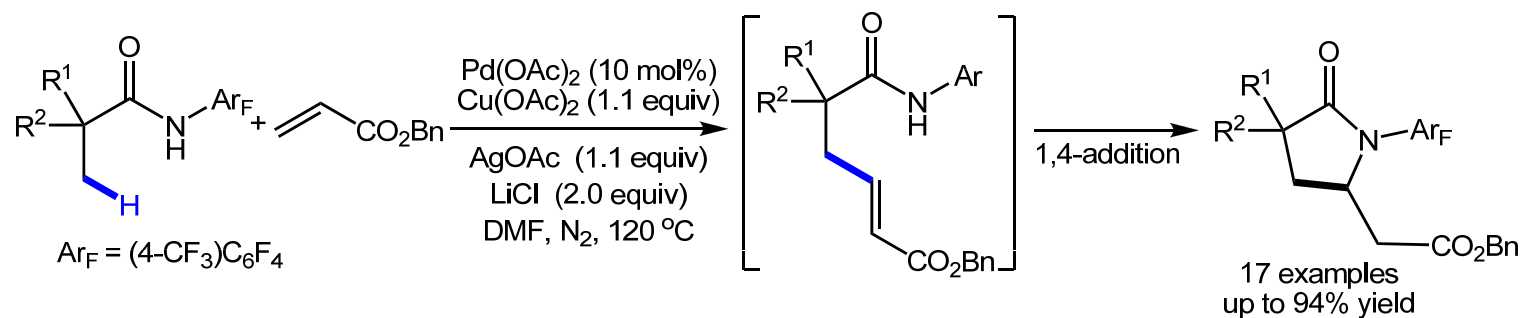
Yu, J.-Q. *et al. Org. Lett.* **2006**, 8, 3387-3390.



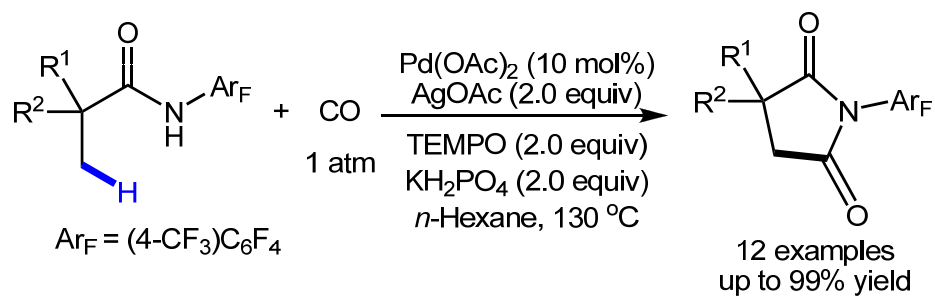
Yu, J.-Q. *et al. J. Am. Chem. Soc.* **2007**, *129*, 3510-3511.



Yu, J.-Q. *et al. J. Am. Chem. Soc.* **2008**, *130*, 7190-7191.



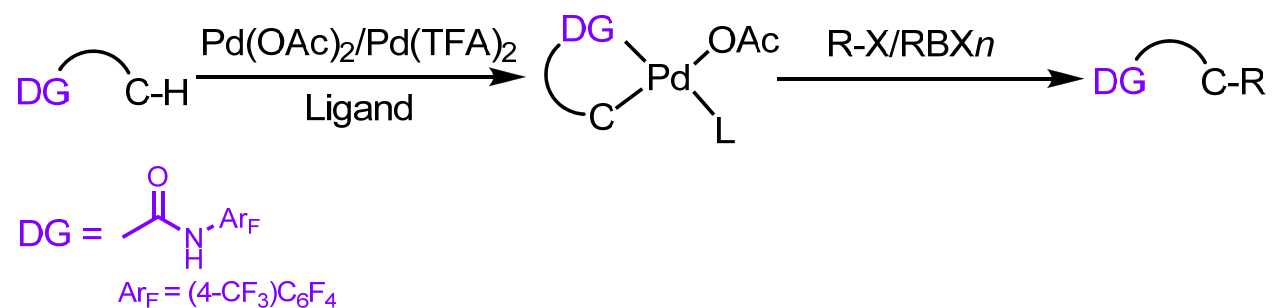
Yu, J.-Q. *et al. J. Am. Chem. Soc.* **2010**, *132*, 3680-3681.



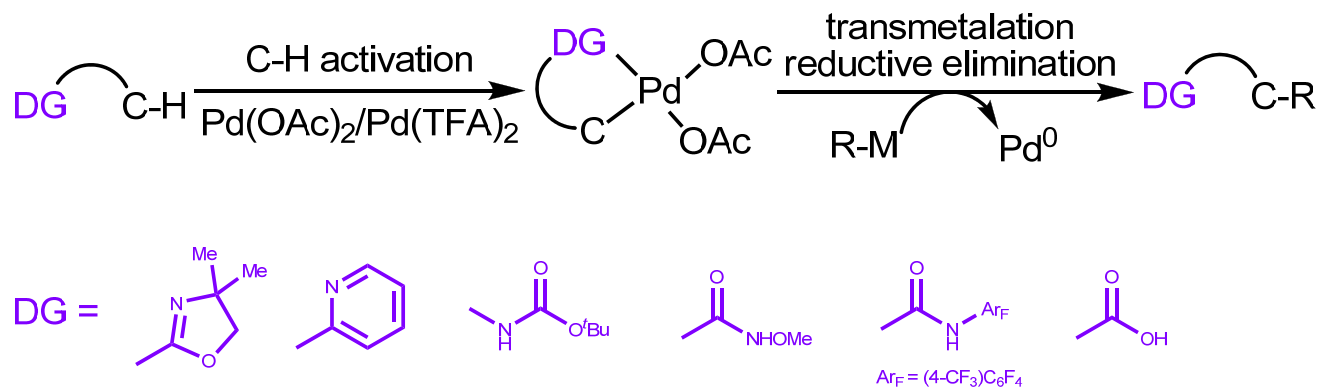
Yu, J.-Q. *et al. J. Am. Chem. Soc.* **2010**, *132*, 17378-17380.

Summary

Ligand-Controlled C(sp³)-H



Auxiliary-Controlled C(sp³)-H



Over the past decade, substantial progress has been achieved in the palladium catalyzed activation of the inert β -C(sp³)-H bonds of aliphatic carboxylic acid derivatives using chiral oxazolines, the 8-aminoquinoline auxiliary, and a variety of weakly coordinating amide directing groups. In particular, the synthesis of unnatural amino acids *via* the direct β functionalization of α -amino acids has been an area of extensive research since a seminal report by Reddy et al. We envisioned that a sequential diarylation of alanine with two different aryl iodides could potentially provide an efficient route for the preparation of β -Ar- β -Ar'- α -amino acids containing a β -chiral center. Although the more strongly coordinating 8-aminoquinoline auxiliary developed by Zaitsev et al. is a powerful directing group for the β -arylation of alanine, this auxiliary provides predominantly β,β -homo-diarylated products, which prevents the sequential installation of two different aryl groups. It is possible to use a specifically designed 2-methylthioaniline auxiliary to achieve monoarylation of alanine in moderate yield and then use a different auxiliary to perform the secondary C(sp³)-H arylation with a distinct aryl iodide. However, this hypothetical route has not yet been used

for preparing β -Ar- β -Ar'- α -amino acids because the removal and installation of the second auxiliary would add three synthetic steps to the sequence. In addition, the basic reaction conditions used in the first arylation step partially racemize the amino acid to 90% enantiomeric excess.

Herein, we report the discovery that a pyridine-based ligand promotes monoarylation of primary β -C(sp³)-H bonds exclusively and that a second, quinoline-based ligand enables introduction of a distinct aryl group *via* subsequent secondary β -C(sp³)-H activation in one pot. The reactions proceed with excellent levels of diastereoselectivity with respect to the starting configuration at the α carbon. As such, both configurations at the new β -stereogenic center can be constructed by simply choosing the order of aryl group installation. We further demonstrate that the use of the quinoline-based ligand enables the C(sp³)-H olefination of an alanine derived substrate to afford olefin-substituted chiral α -amino acids.
