Literature Report

Functionalization of C(sp^3)–H Bonds Using a Transient Directing Group

Reporter: Mu-Wang Chen
Checker: Yue Ji
Date: 2016-04-05

Yu, J.-Q. *et al.*
Science **2016**, *351*, 252-256.

Scripps Research Institute

Contents

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

Shanghai Institute of Organic Chemistry - Shanghai, China
Coursework for M.S. degree
September 1987 - July 1988

East China Normal University - Shanghai, China
B.S. in Chemistry
Top 5% of national examination for admission to SIOC
Supervisors: L. X. Dai and B. Q. Wu
September 1982 - July 1987

Introduction

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

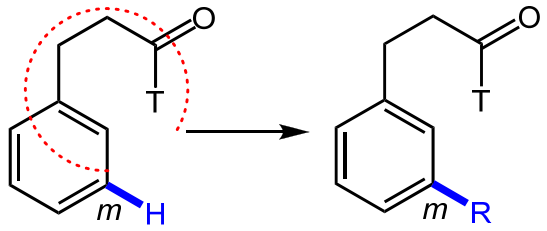
University of Cambridge - Cambridge, UK

Royal Society Research Fellow, 2003 - 2004

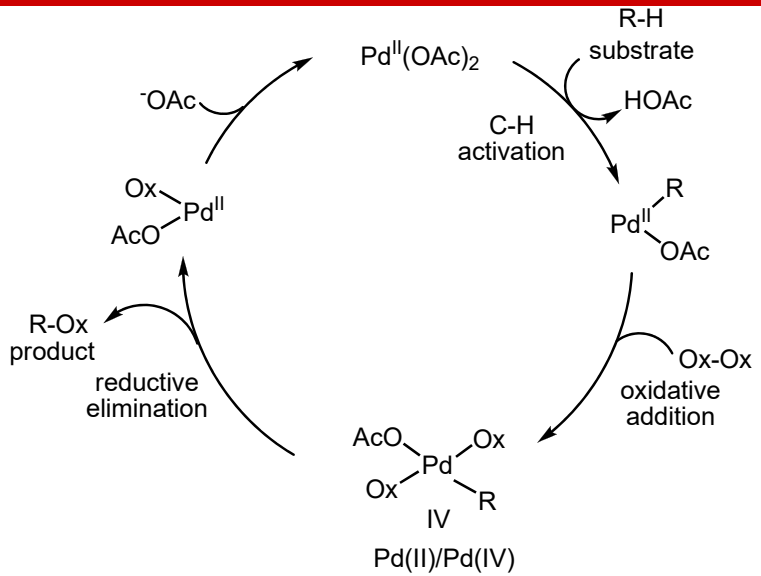
Research Focus:

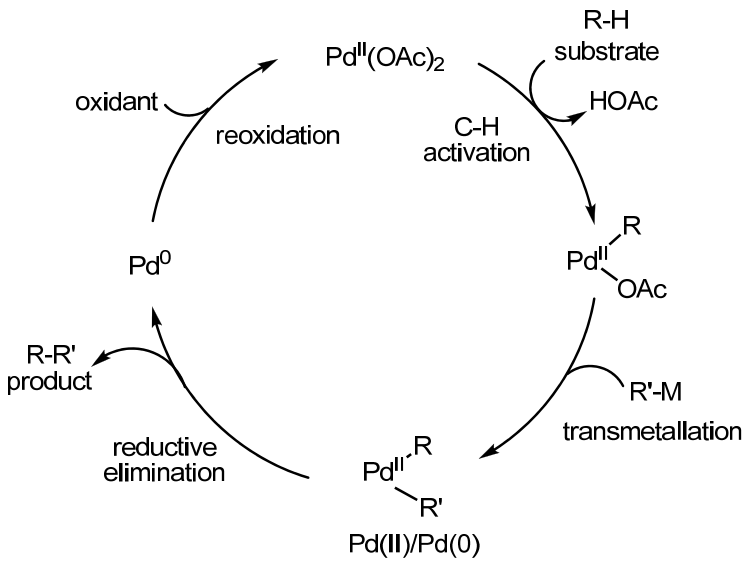
Discovering new reactions for synthesis through C-H activation

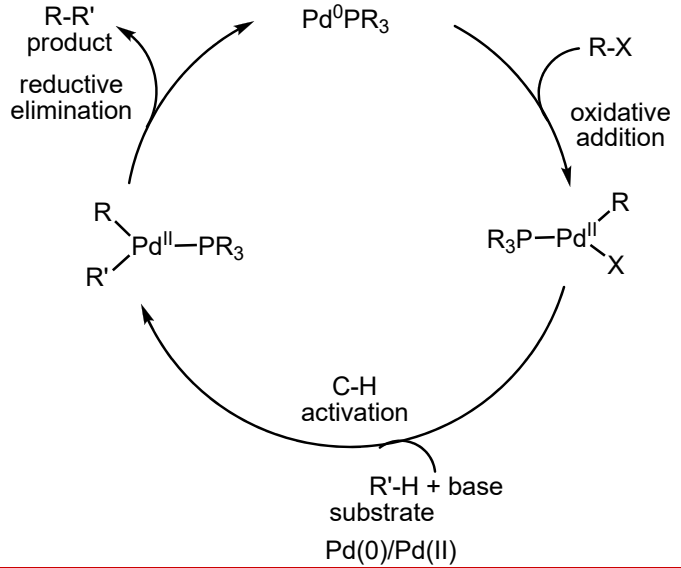
1. Ligand-controlled C(sp^3)-H C-H activation;
2. C-H bonds C-H activation directed by a U-shaped template.



Introduction

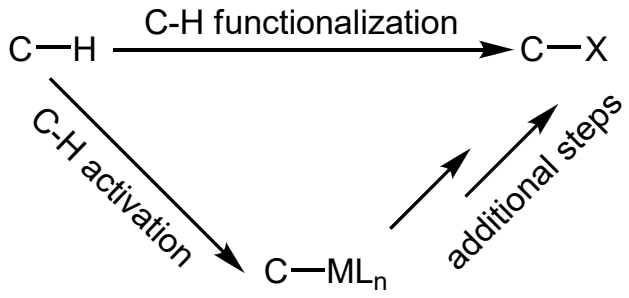






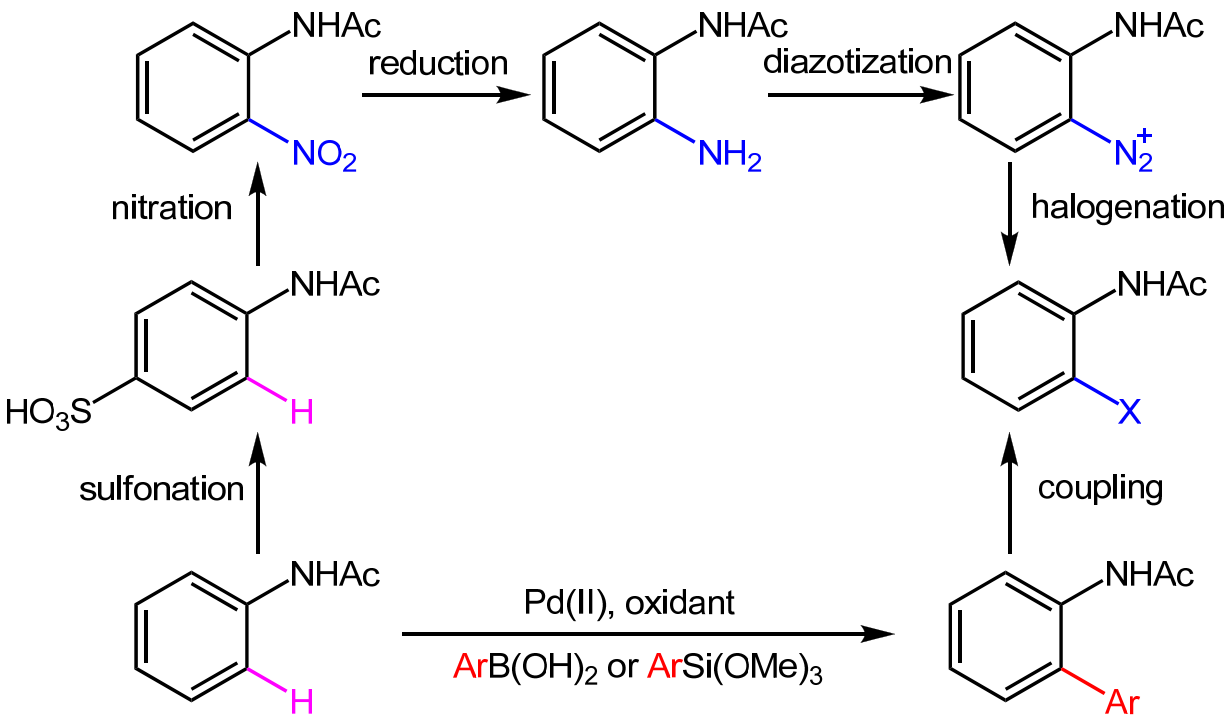
Introduction

Carbon–hydrogen bond functionalization (**C–H functionalization**) is a type of reaction in which a carbon-hydrogen bond is cleaved and replaced with a carbon-X bond (where X is usually carbon, oxygen or nitrogen). The term usually implies that a transition metal is involved in the C-H cleavage process. Reactions classified by the term typically involve the hydrocarbon first to react with a metal catalyst to create an organometallic complex in which the hydrocarbon is coordinated to the inner-sphere of a metal, either *via* an intermediate "alkane or arene complex" or as a transition state leading to a "M−C" intermediate.



General scheme for C-H functionalization

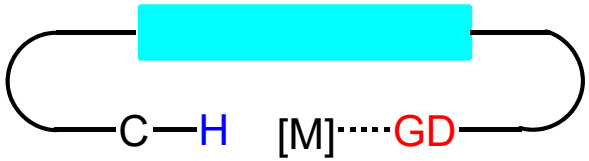
Introduction



Introduction

Two Strategies for Directed C-H Activation

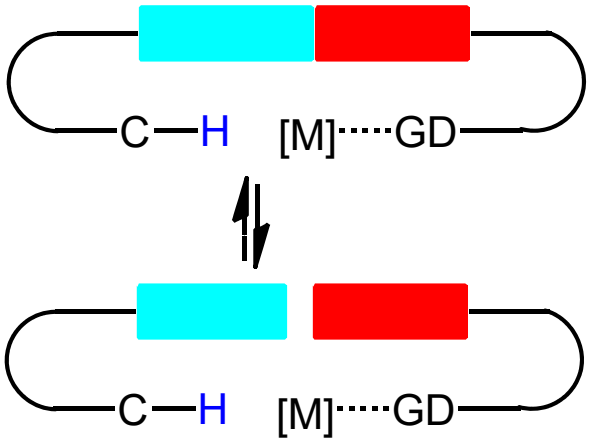
pre-installed directing groups



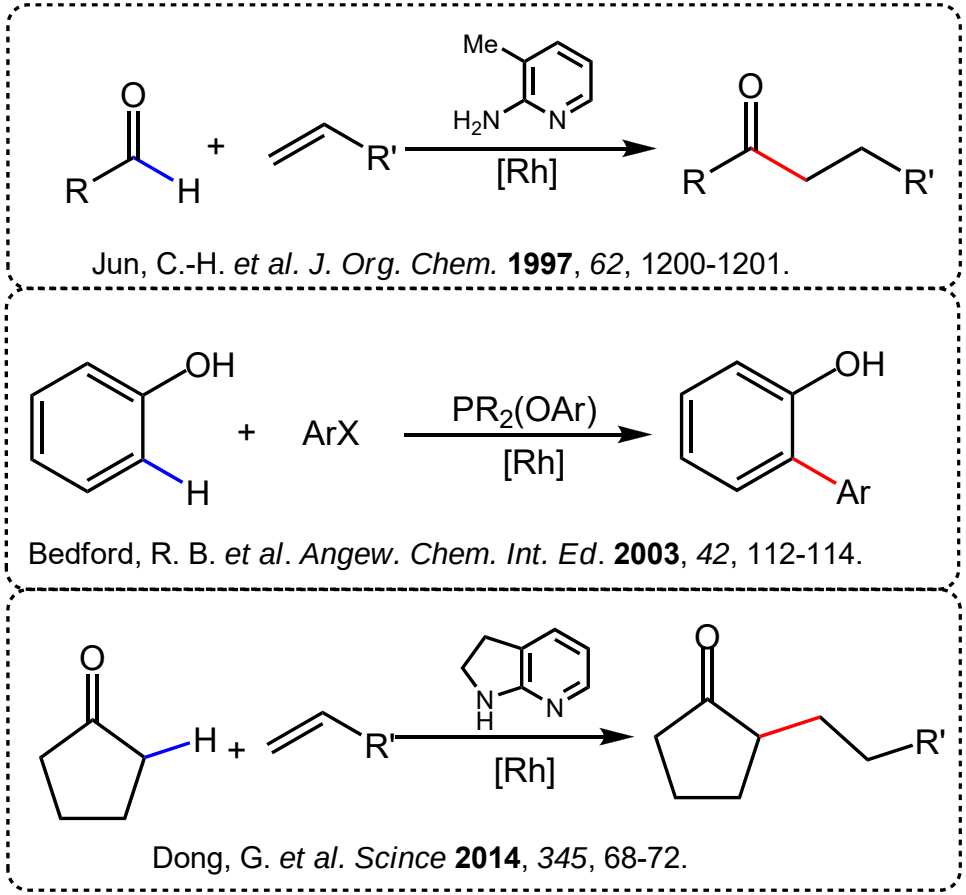
DG: directing group

Disadvantange: requires installation and removal of the directing group

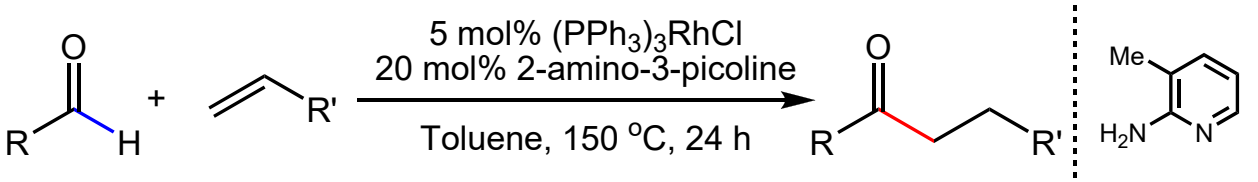
transient directing groups

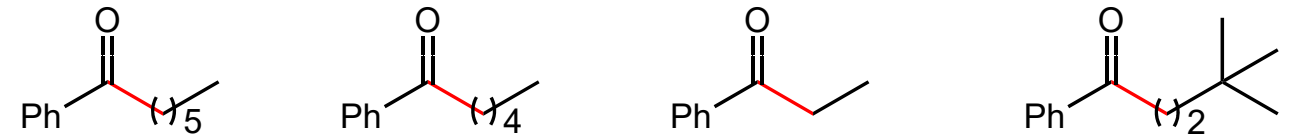


Pioneering Examples of Reversibly Linked Directing Groups



Chelation-Assisted Intermolecular Hydroacylation: Direct Synthesis of Ketone from Aldehyde and 1-Alkene

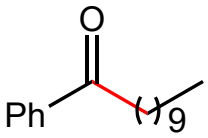


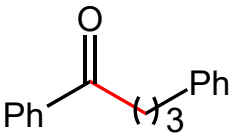

72% yield

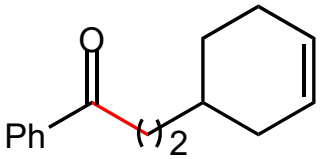
75% yield

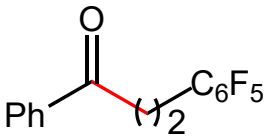
92% yield

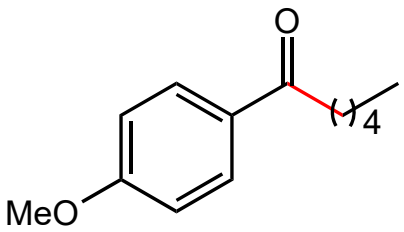
68% yield

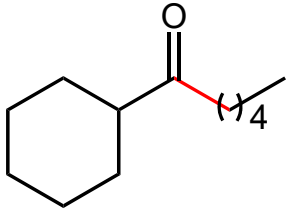

74% yield

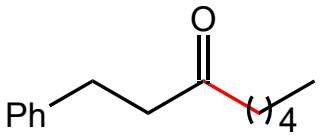

83% yield


67% yield


90% yield

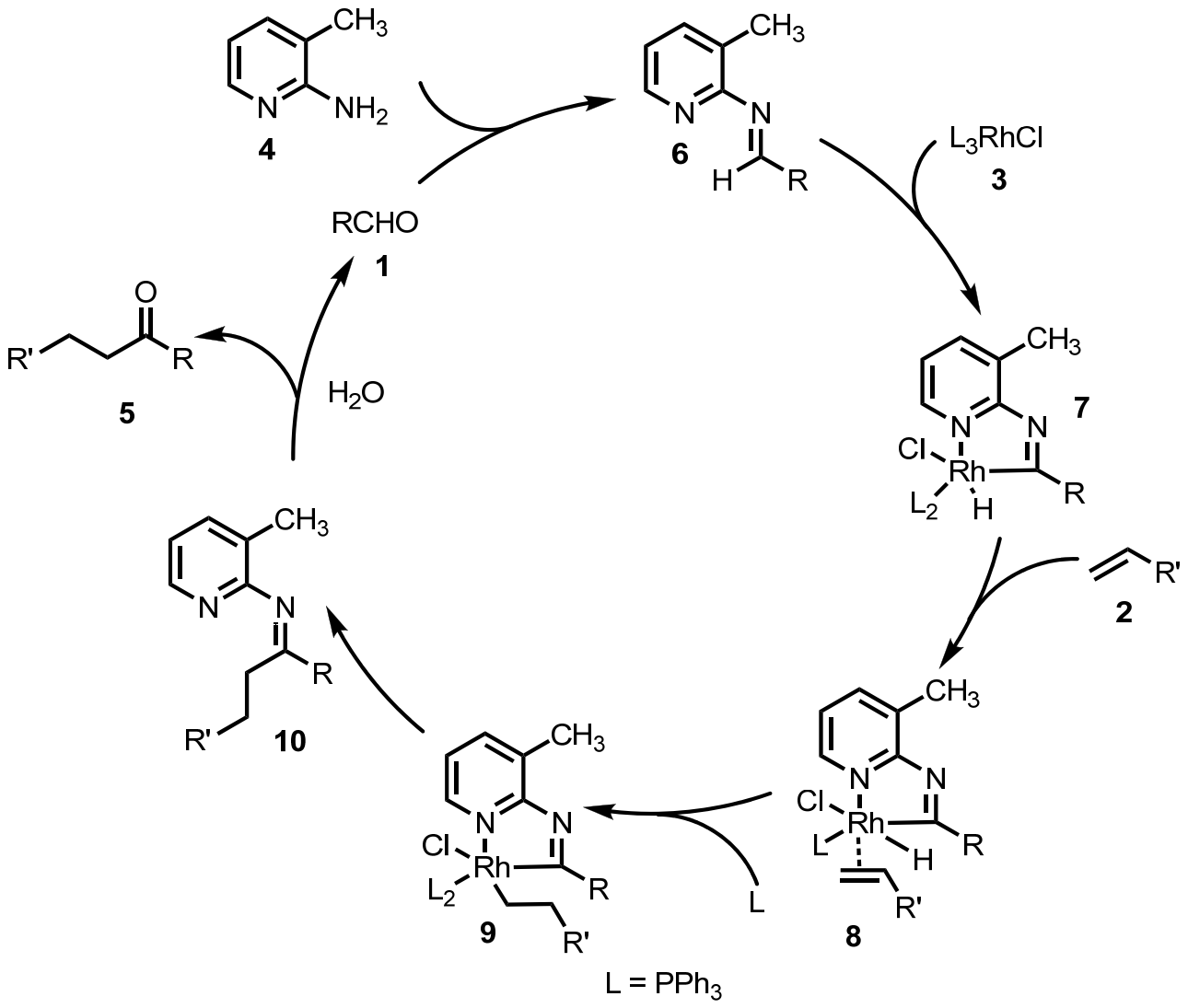

66% yield


67% yield

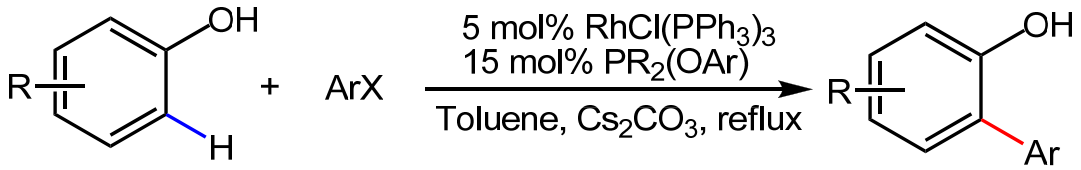

67% yield

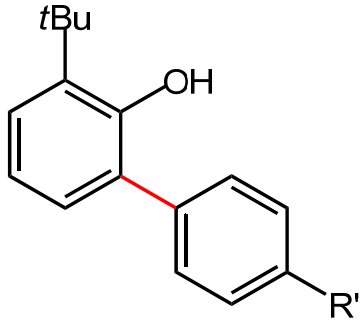
Jun, C.-H. *et al*. *J. Org. Chem*. **1997**, *62*, 1200-1201.

Proposed Catalytic Cycle for Ligand-Assisted Hydroacylation

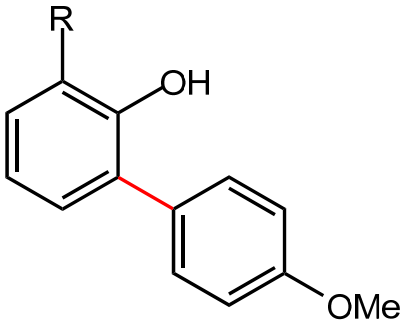


The Catalytic Intermolecular Orthoarylation of Phenols





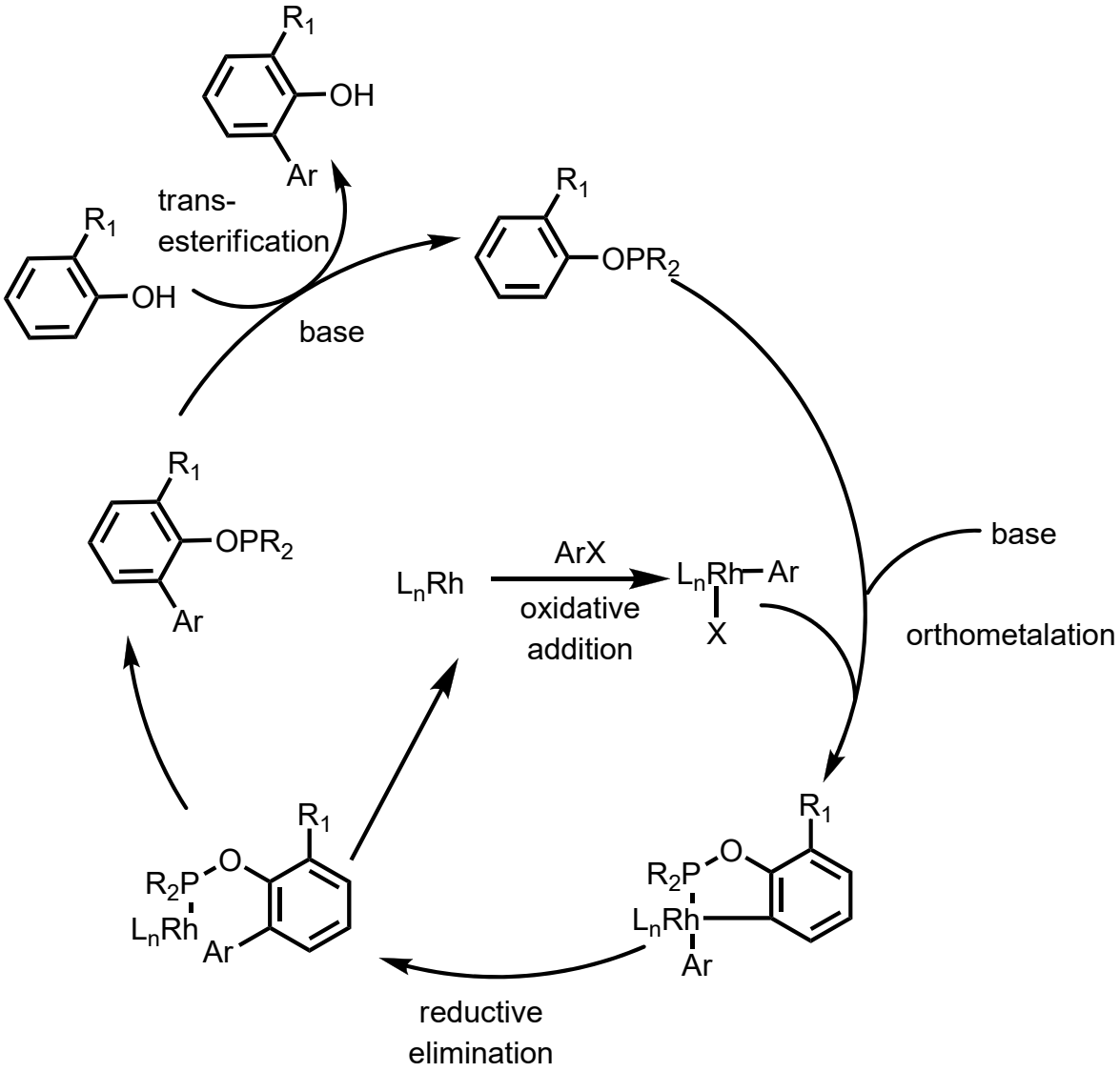
R' = $COCH_3$ 96% yield;
R' = OMe 79% yield;
R' = H 84% yield;
R' = Me 35% yield;
R' = 2,5-Me_2 100% yield;



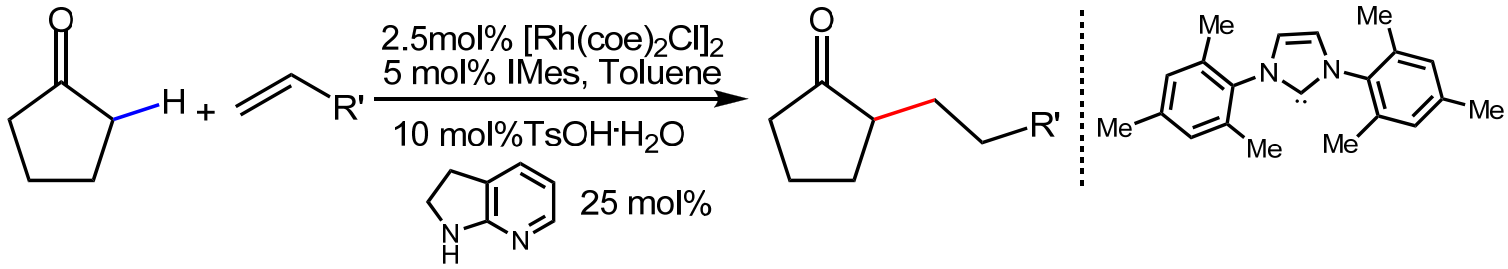
R = *i*Pr 68% yield;
R = Et 53% yield;
R = Me 52% yield;

Bedford, R. B. *et al*. *Angew. Chem. Int. Ed*. **2003**, *42*, 112-114.

Plausible Reaction Mechanism



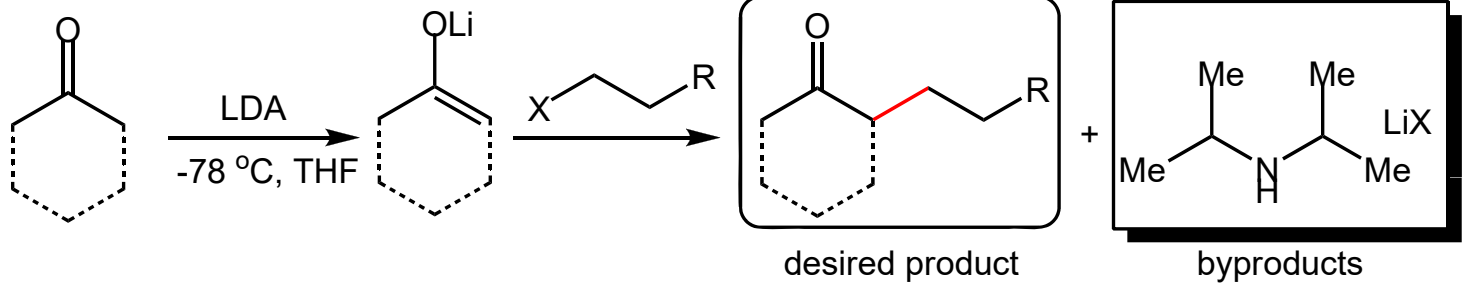
Regioselective Ketone α-Alkylation with Simple Olefins *via* Dual Activation



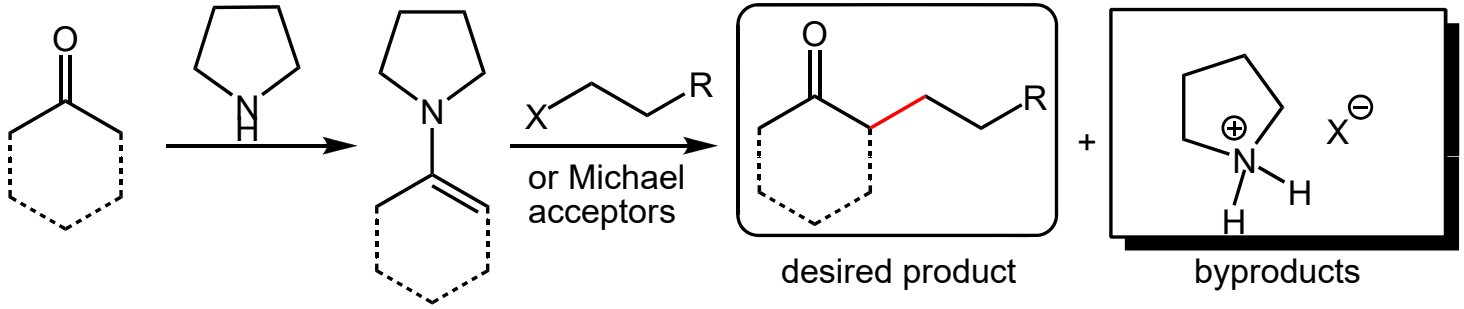
Dong, G. *et al. Scince* **2014**, *345*, 68-72.

Different Approaches to Ketone Alkylation

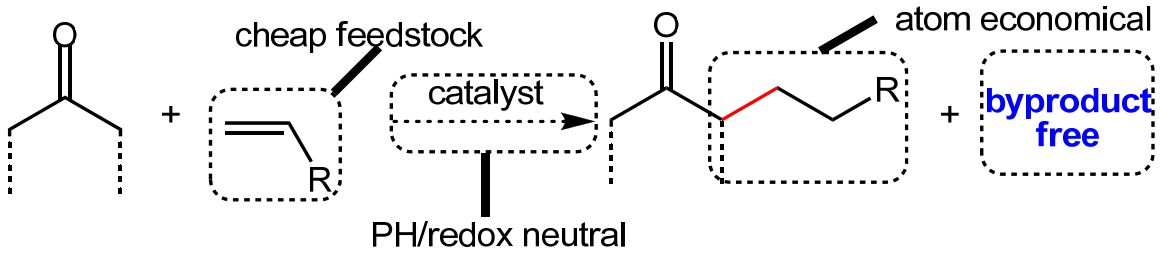
A *Enolate Alkylation*



B *Stork Enamine Reaction*



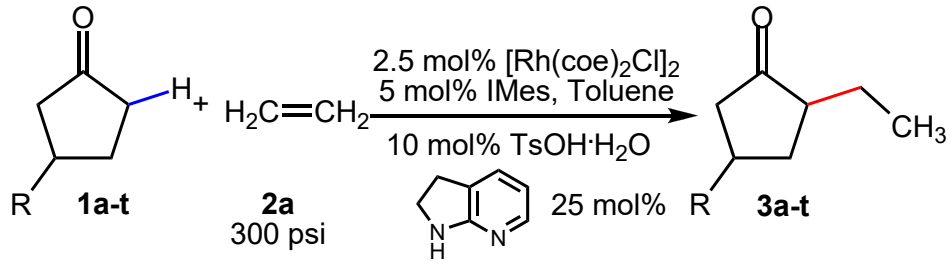
C *Simple Olefins as Alkylating Agents*

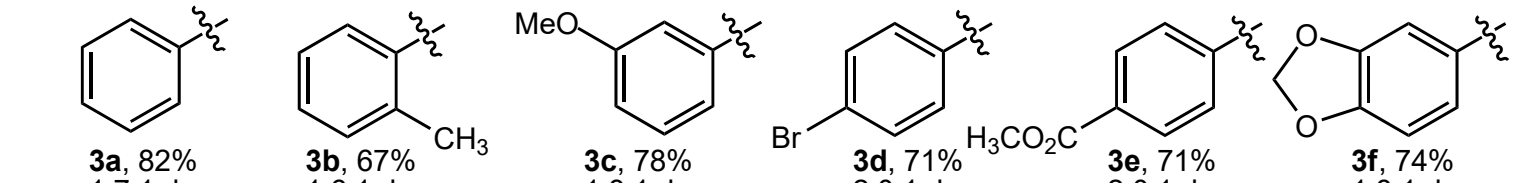


D Cost of Alkylating Agents

	$H_2C{=}CH_2$	ICH_2CH_3	$BrCH_2CH_3$
estimated cost:	$ 0.028/mol	$ 43.7/mol	$ 6.0/mol
molecular weight:	28	156	109

Regioselective Ketone α-Alkylation with Simple Olefins





3a, 82%
1.7:1 dr

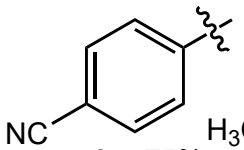
3b, 67%
1.6:1 dr

3c, 78%
1.8:1 dr

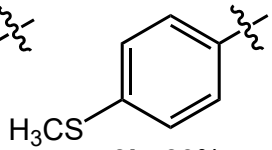
3d, 71%
2.0:1 dr

3e, 71%
2.0:1 dr

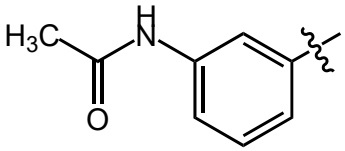
3f, 74%
1.8:1 dr



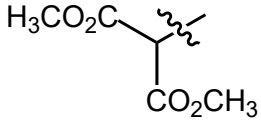
3g, 75%
1.8:1 dr



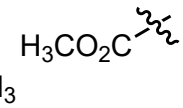
3h, 60%
1.8:1 dr



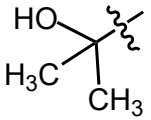
3i, 84%
1.9:1 dr



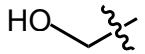
3j, 87%
1.6:1 dr



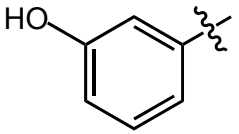
3k, 96%
1.3:1 dr



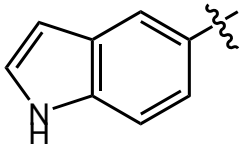
3l, 88%
2.1:1 dr



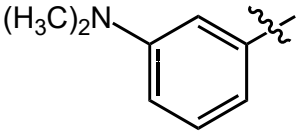
3m, 60%
1.6:1 dr



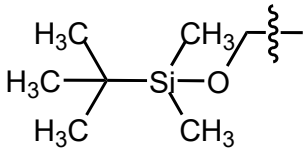
3n, 65%
1.8:1 dr



3o, 52%
2:1 dr



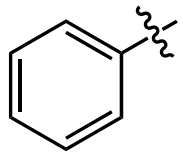
3p, 62%
1.3:1 dr



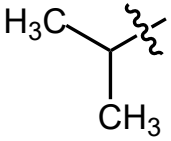
3q, 62%
1:1 dr

Regioselective Ketone α-Alkylation with Simple Olefins

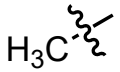
Scalability



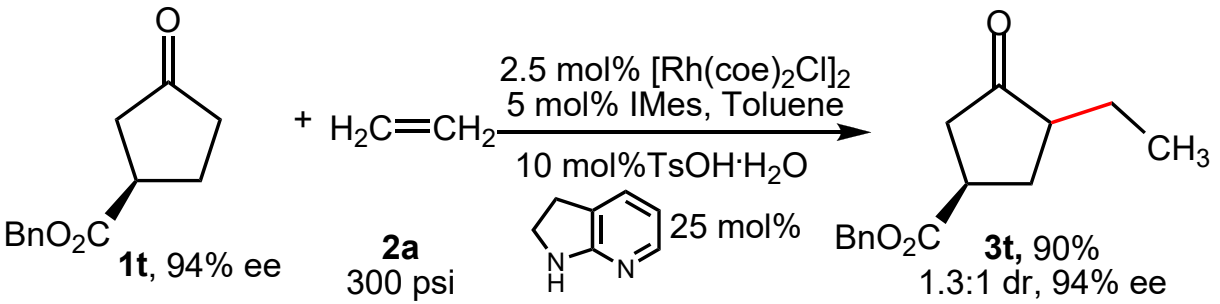
3a, 96%
1.7:1 dr
2 mmol scale



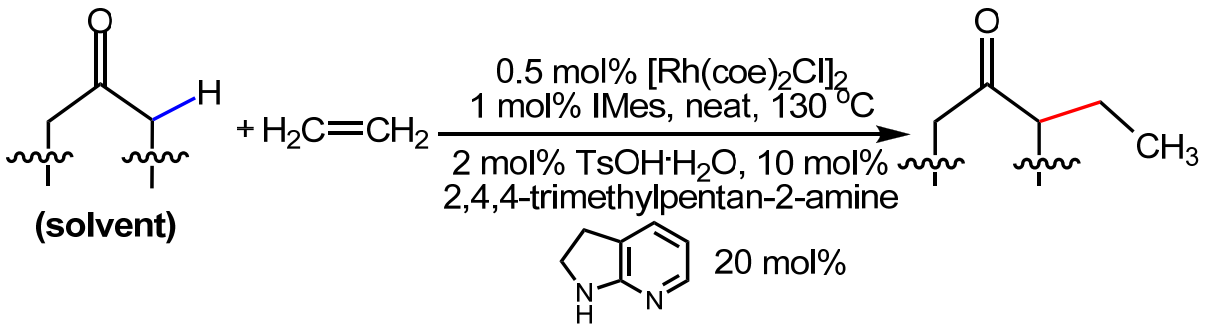
3r, 78%
2.9:1 dr
2 mmol scale

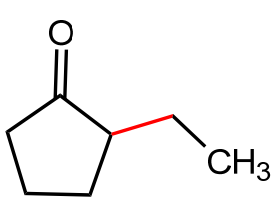


3s, 75%
1.7:1 dr
10 mmol scale

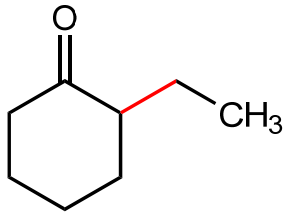


Regioselective Ketone α-Alkylation with Simple Olefins

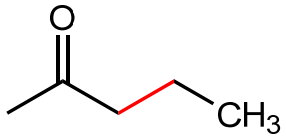




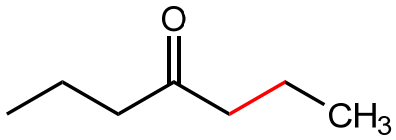
3u, TON 110



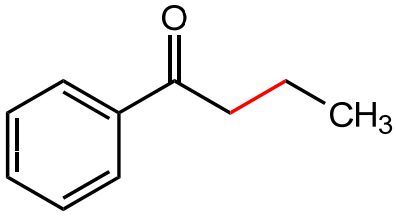
3v, TON 15



3w, TON 16

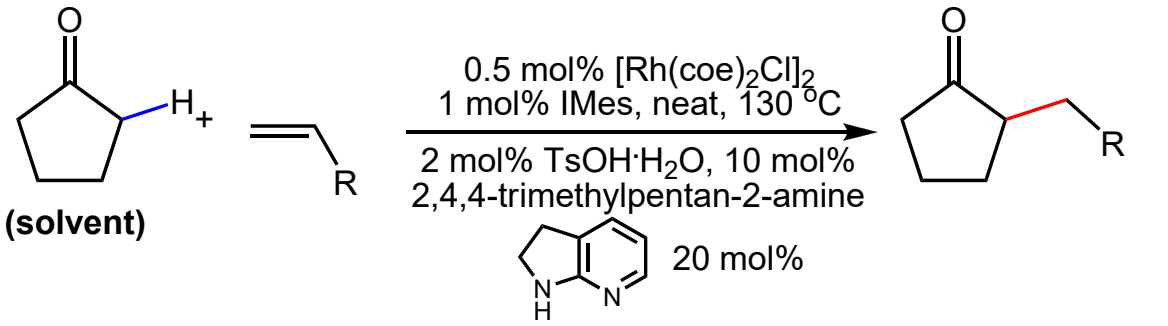


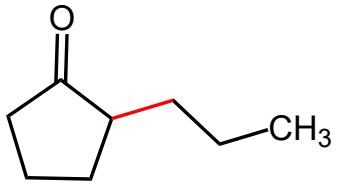
3x, TON 20



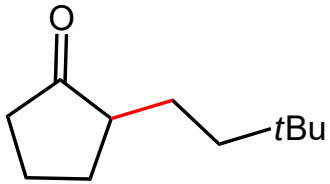
3y, TON 37

Regioselective Ketone α-alkylation with Simple Olefins

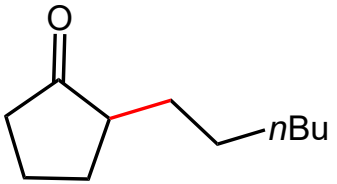




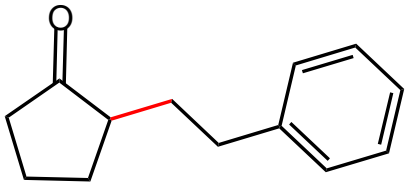
3z, TON 18



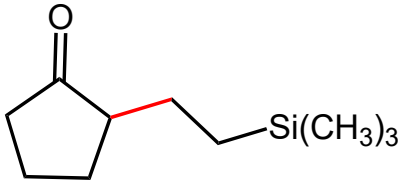
3aa, TON 28



3ab, TON 7

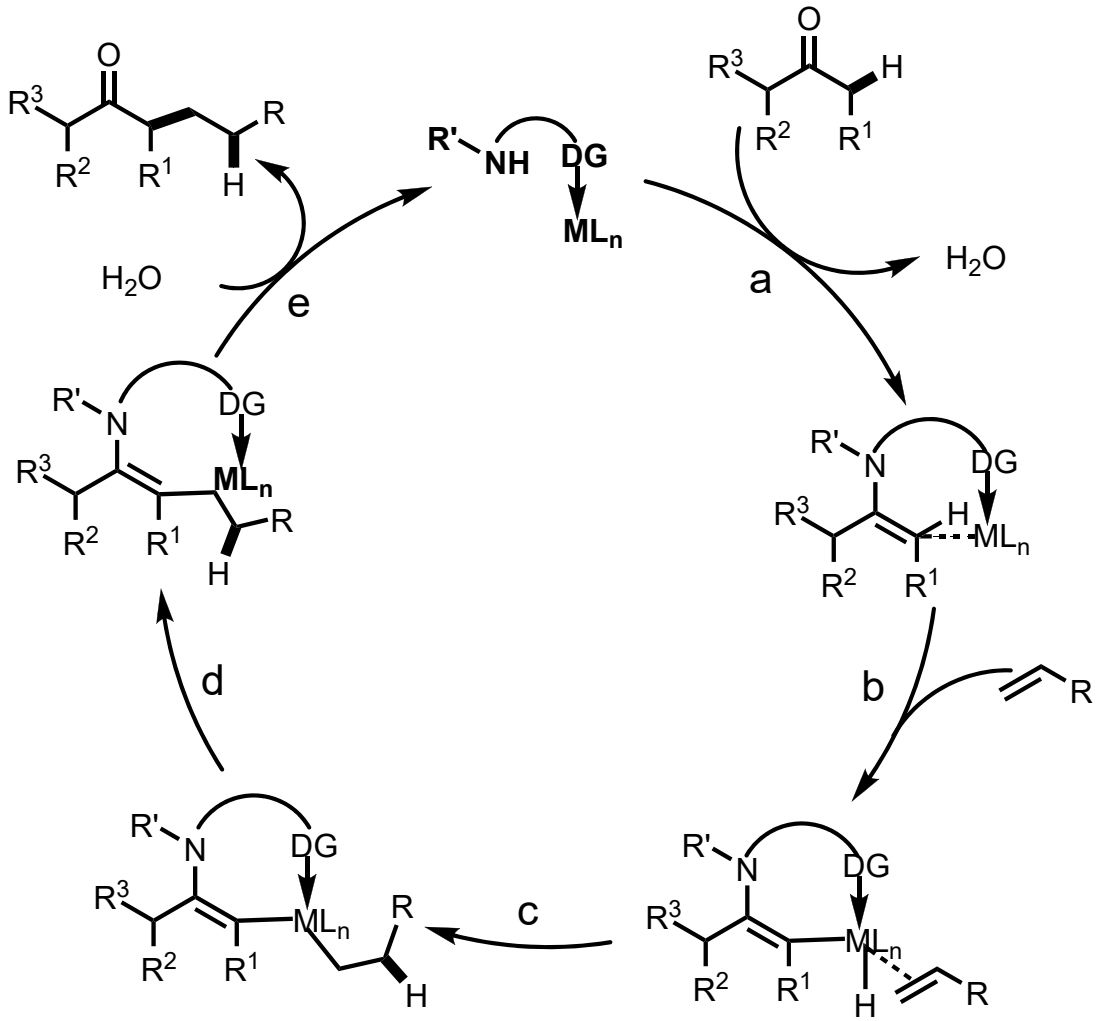


3ac, TON 14.5

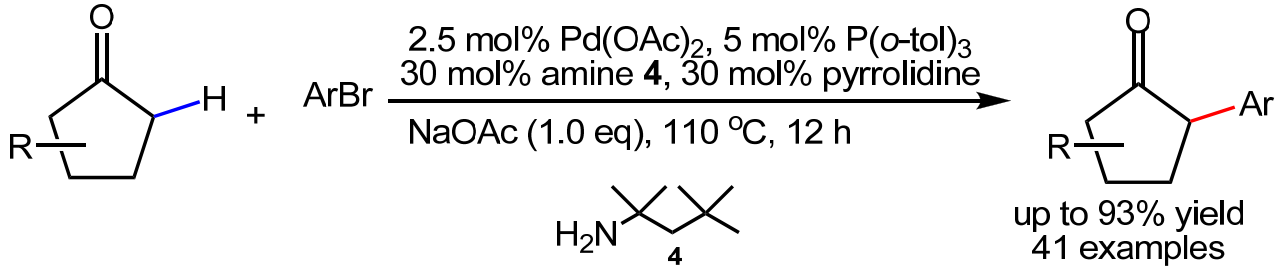


3ad, TON 22

Design of a Bifunctional Catalyst and Proposed Catalytic Cycle



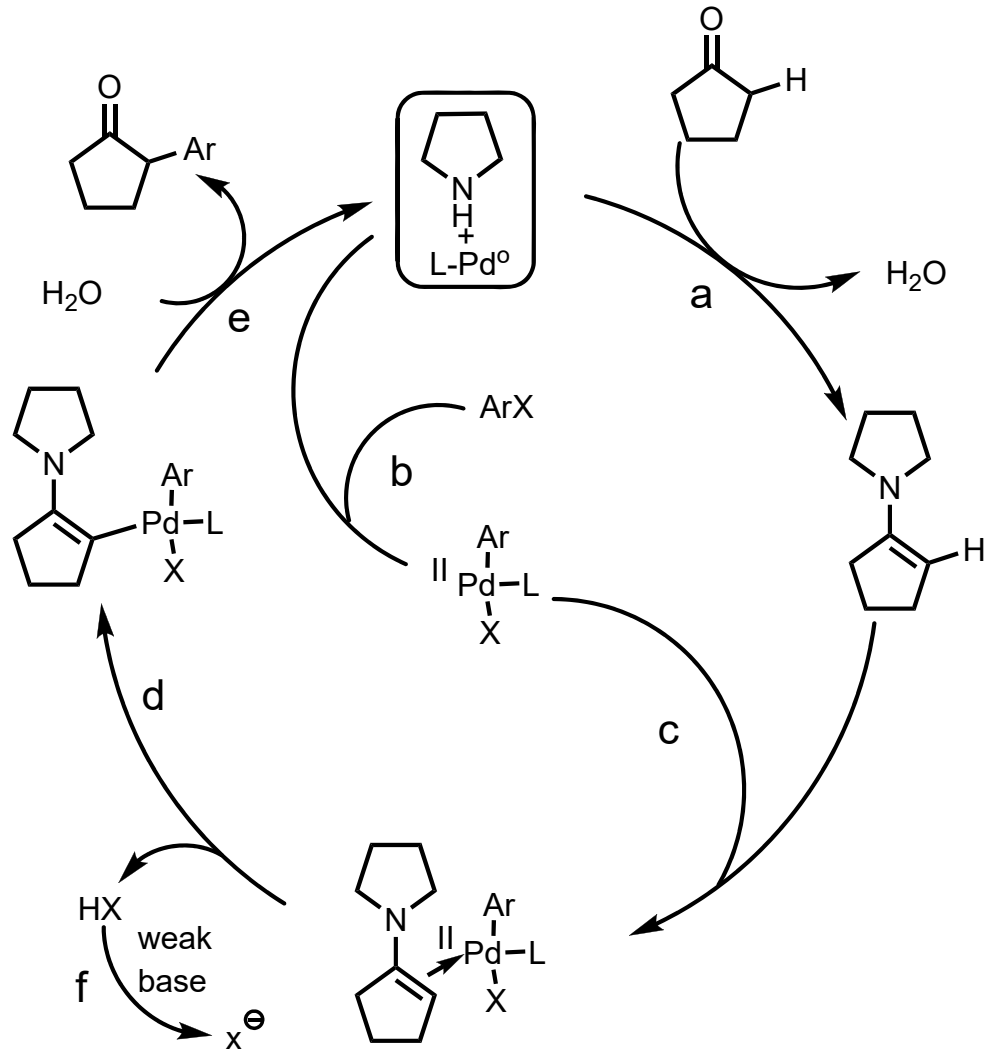
Practical Direct α-Arylation of Cyclopentanones by Palladium/Enamine Cooperative Catalysis



- selective for monoarylation
- strong base/acid free
- broad FG tolerance -[Si], -[B], -OH, -COOH

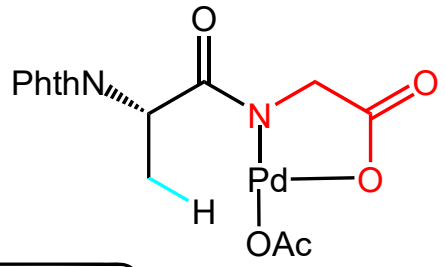
Dong, G. *et al. Angew. Chem. Int. Ed*. **2016**, *55*, 2559–2563.

Proposed Strategy

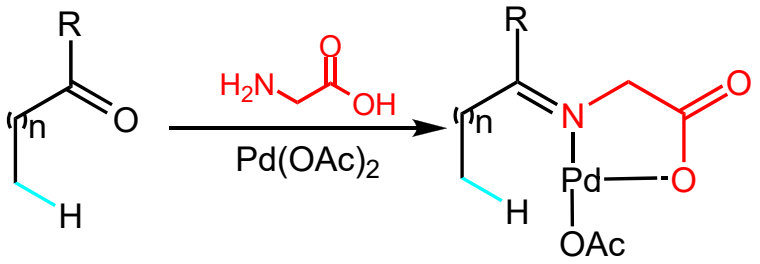


C(sp^3)-H Arylation Using Acid as Transient Directing Group

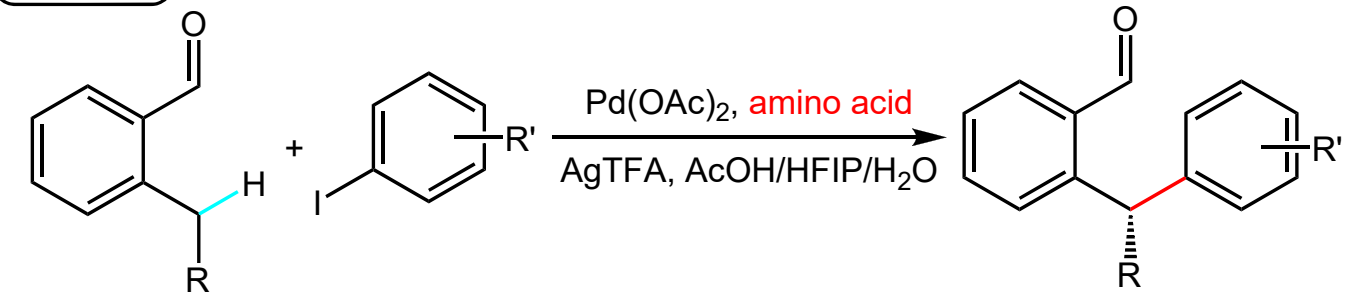
C(sp^3)-H Activation of Peptides

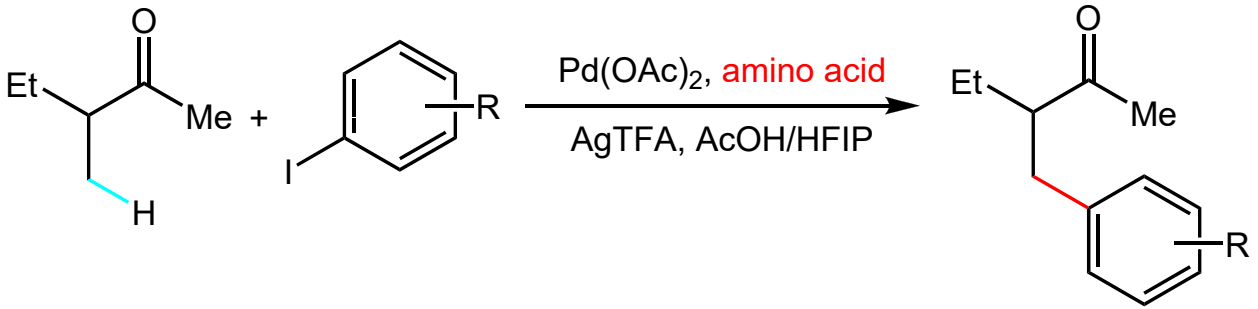


Design of Transient Amino Acid Directing Group



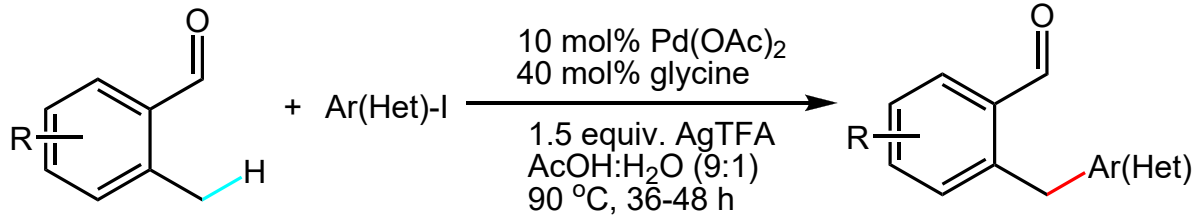
This Work



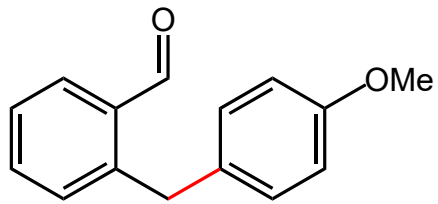


Yu, J.-Q. *et al. Science* **2016**, *351*, 252-256.

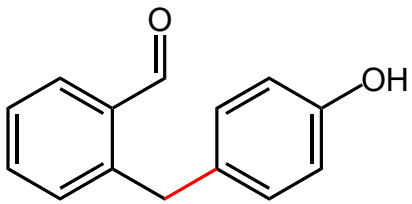
Palladium-Catalyzed Benzylic C(sp^3)-H Arylation of Aldehydes



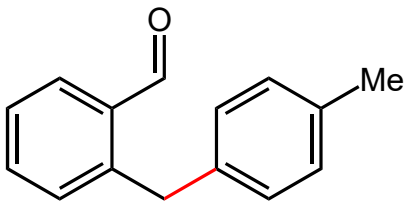
1a-1i (1.2 equiv.) 1.0 equiv. **2a-2ad**



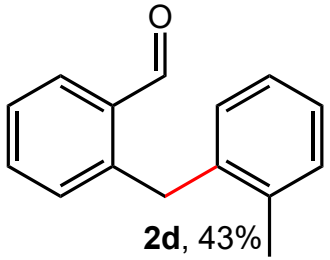
2a, 72%



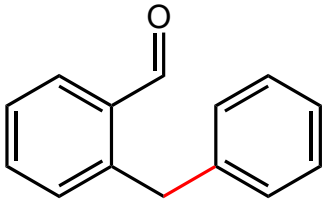
2b, 82%



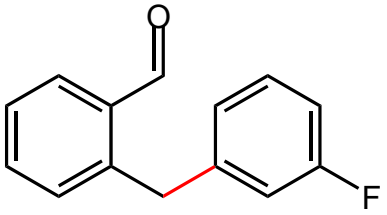
2c, 74%



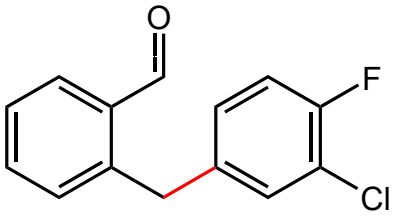
2d, 43%



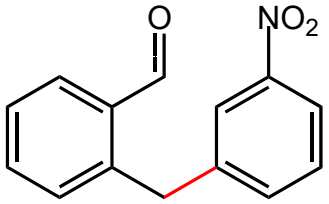
2e, 70%



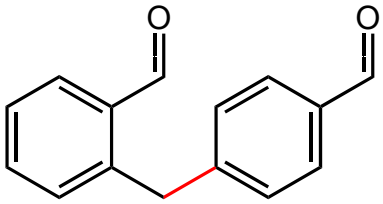
2f, 81%



2g, 79%

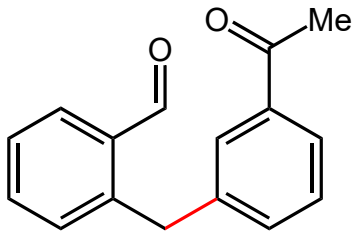


2h, 70%

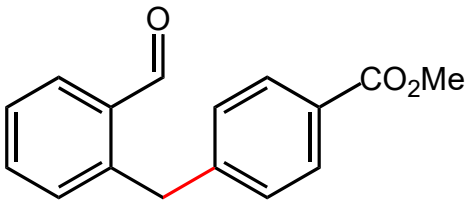


2i, 81%

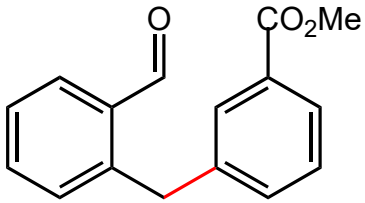
Palladium-Catalyzed Benzylic C(sp^3)-H Arylation of Aldehydes



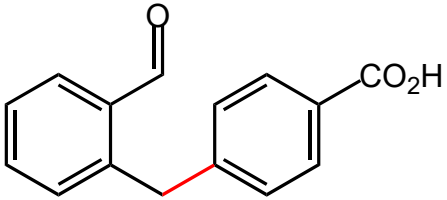
2j, 76%



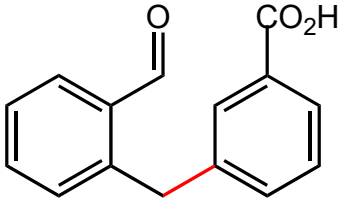
2k, 74%



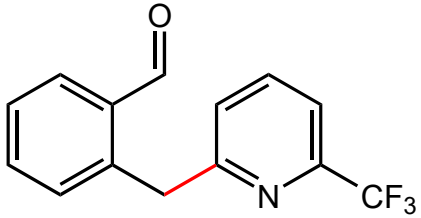
2l, 78%



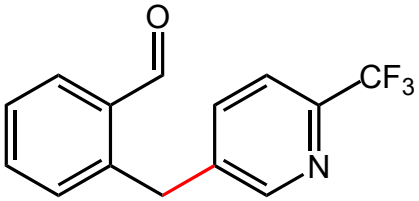
2m, 73%



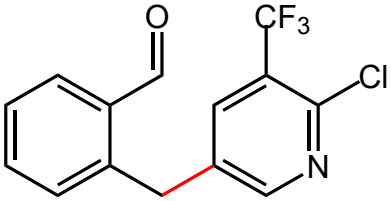
2n, 74%



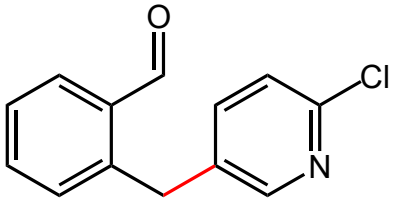
2o, 71%



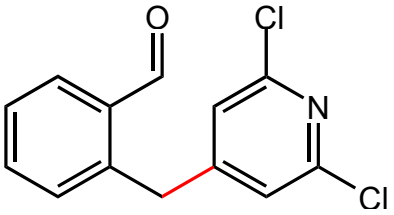
2p, 68%



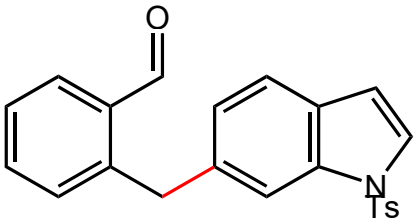
2q, 52%



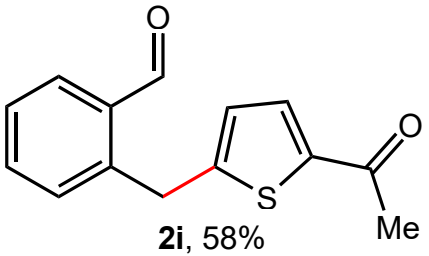
2r, 57%



2s, 47%

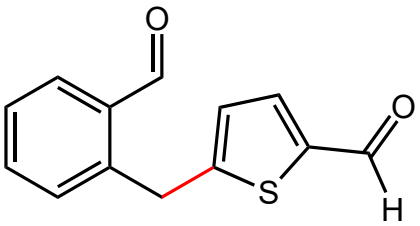


2t, 72%

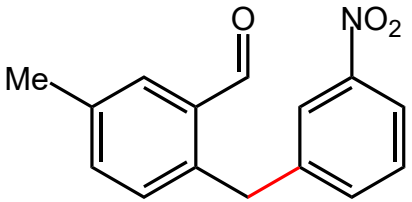


2i, 58%

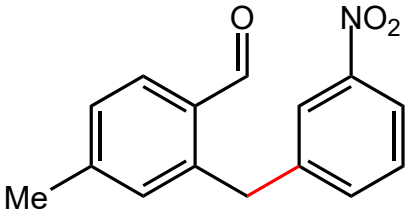
Palladium-Catalyzed Benzylic C(sp^3)-H Arylation of Aldehydes



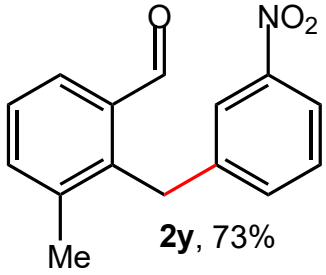
2v, 54%



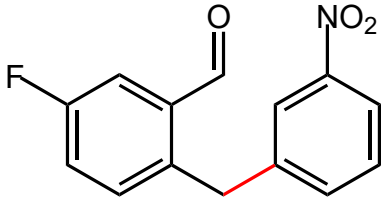
2w, 77%



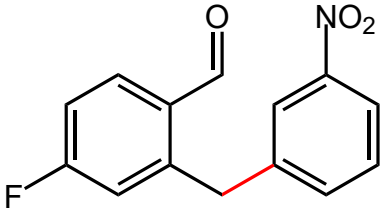
2x, 84%



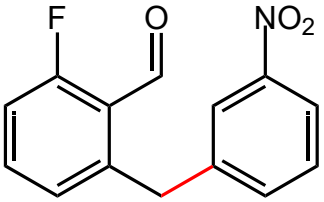
2y, 73%



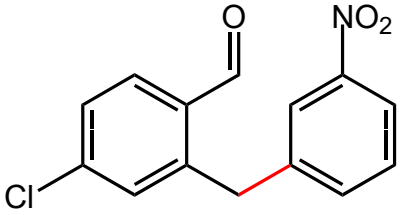
2z, 64%



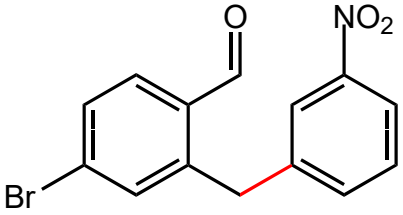
2aa, 76%



2ab, 81%

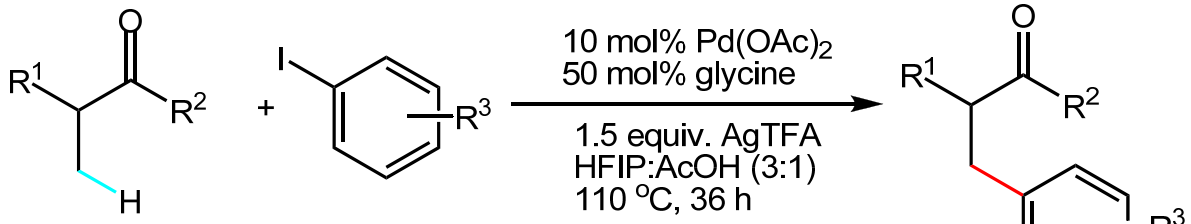


2ac, 60%

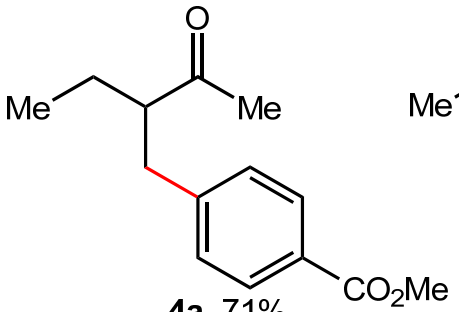


2ad, 68%

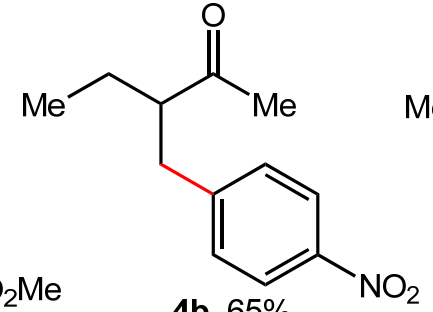
Palladium-Catalyzed Benzylic C(sp^3)-H Arylation Ketones



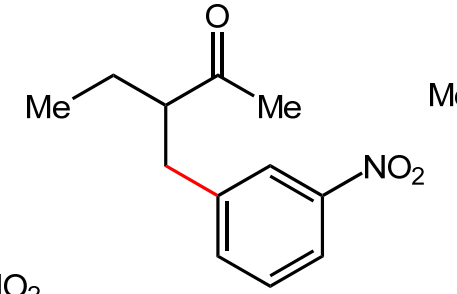
3a-3n (1.0 equiv.) 2.0 equiv. **4a-4r**



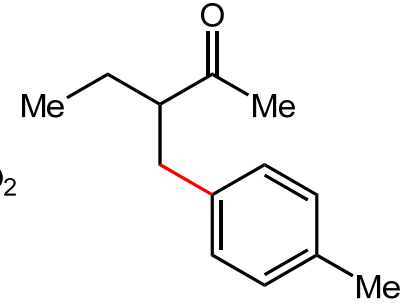
4a, 71%



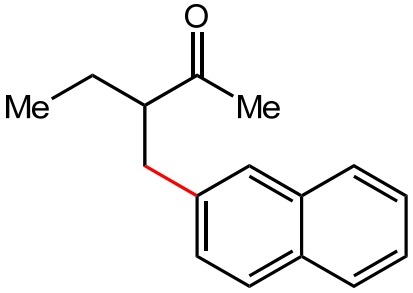
4b, 65%



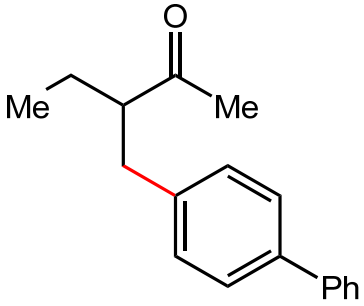
4c, 62%



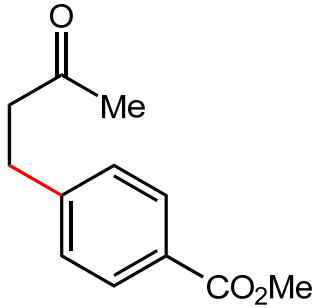
4d, 60%



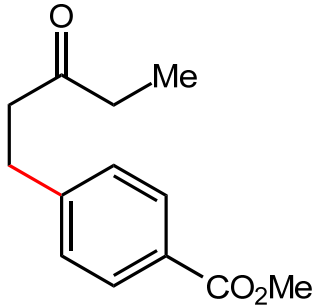
4e, 53%



4f, 47%

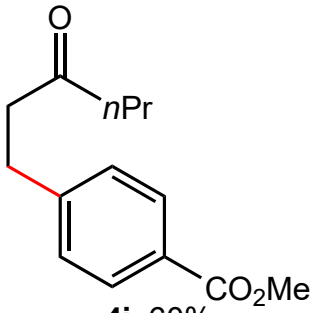


4g, 47%

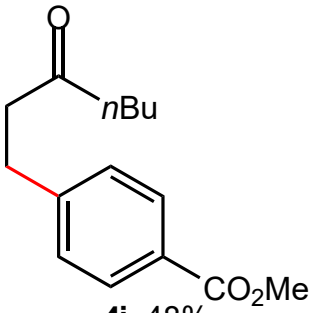


4h, 59%:26% (mono:di)

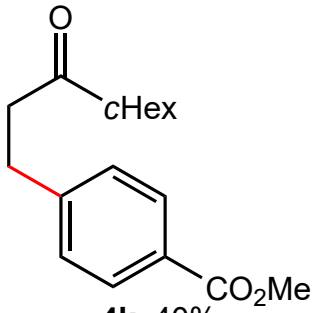
Palladium-Catalyzed Benzylic C(sp^3)-H Arylation Ketones



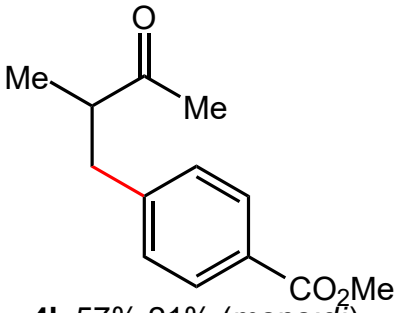
4i, 60%



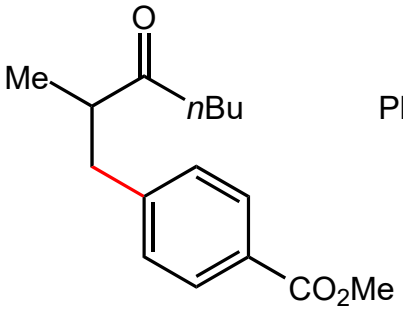
4j, 48%



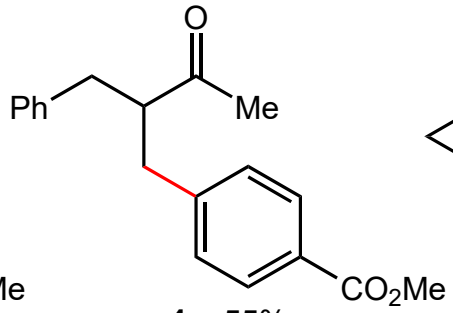
4k, 40%



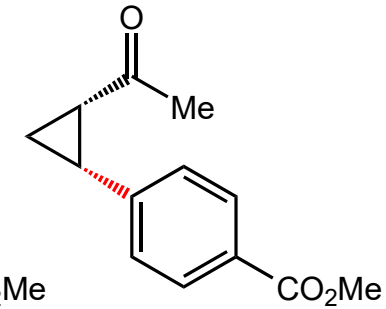
4l, 57%:21% (*mono:di*)



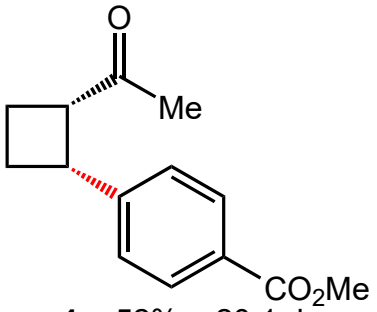
4m, 38%:15% (*mono:di*)



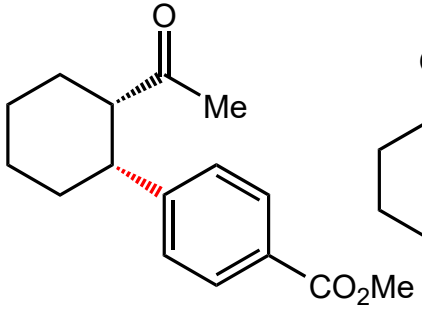
4n, 55%



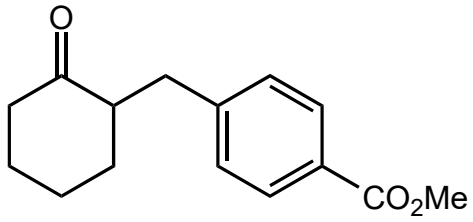
4o, 39%, 20:1 dr



4p, 52%, >20:1 dr

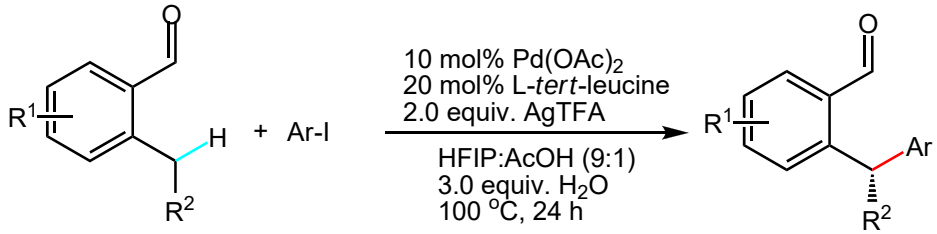


4q, 54%, >20:1 dr

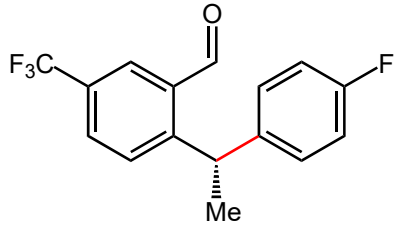


4r, 60%

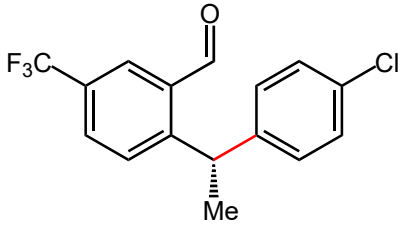
Palladium-Catalyzed Enantioselective Benzylic C(sp^3)-H Arylation Aldehydes



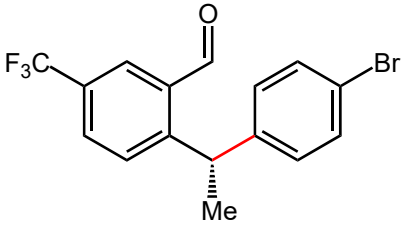
5a-5h (1.0 equiv.) 3.0 equiv. **6a-6p**



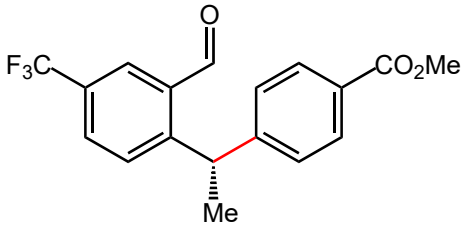
6a, 80%, 96% ee



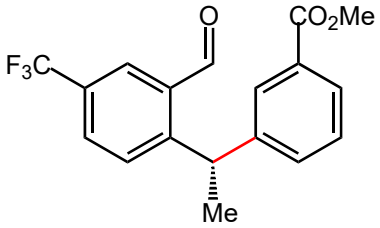
6b, 72%, 94% ee



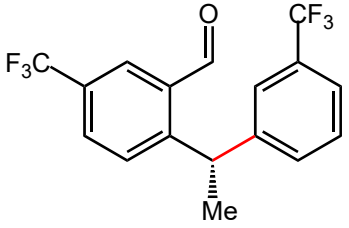
6c, 77%, 96% ee



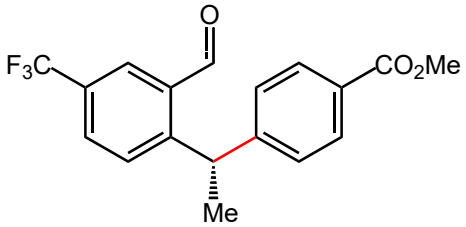
6d, 73%, 96% ee



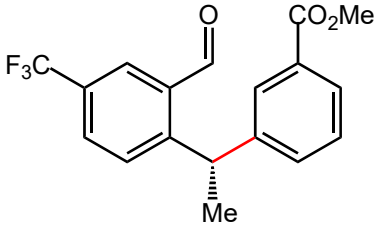
6e, 88%, 96% ee



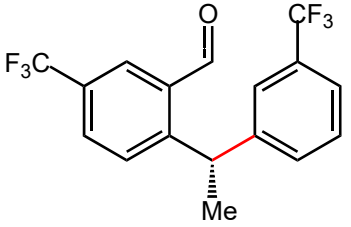
6f, 77%, 96% ee



6g, 63%, 96% ee

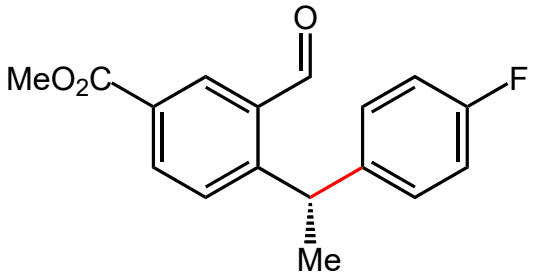


6h, 62%, 96% ee

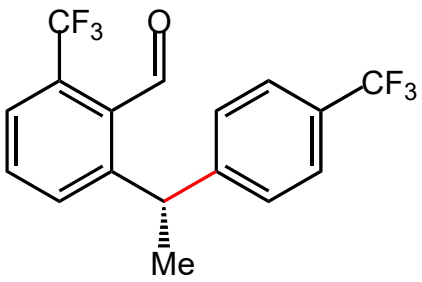


6i, 63%, 90% ee

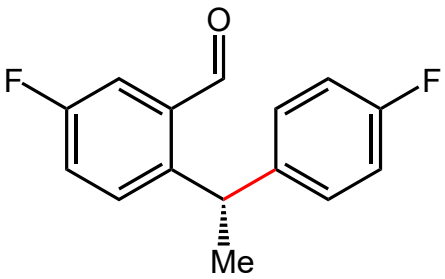
Palladium-Catalyzed Enantioselective Benzylic C(sp^3)-H Arylation Aldehydes



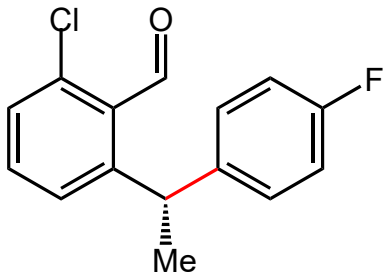
6j, 71%, 92% ee



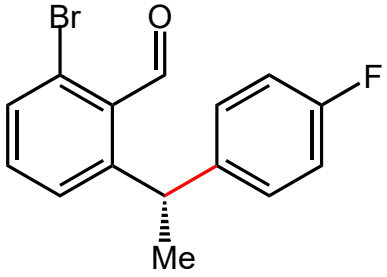
6k, 69%, 94% ee



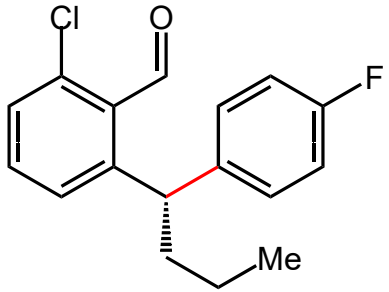
6l, 64%, 92% ee



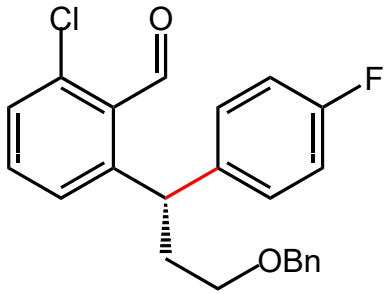
6m, 67%, 94% ee



6n, 60%, 94% ee



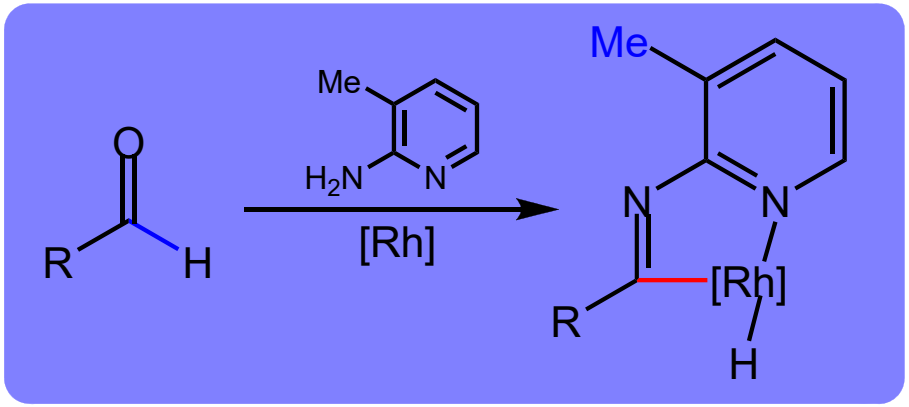
6o, 68%, 94% ee



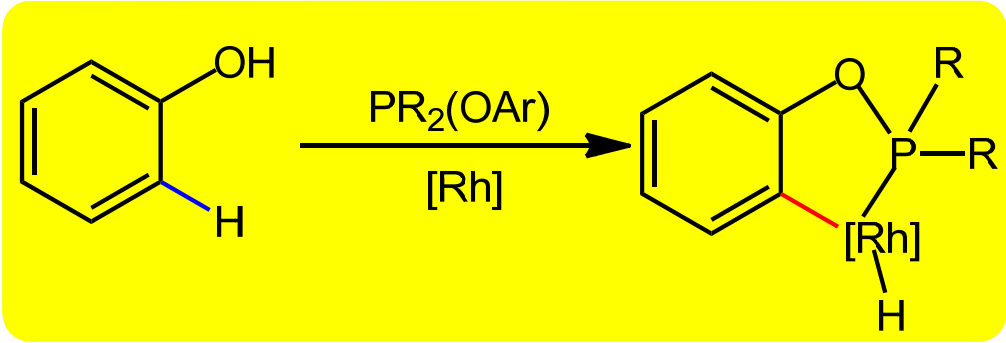
6p, 54%, 96% ee

Summary

Jun's work

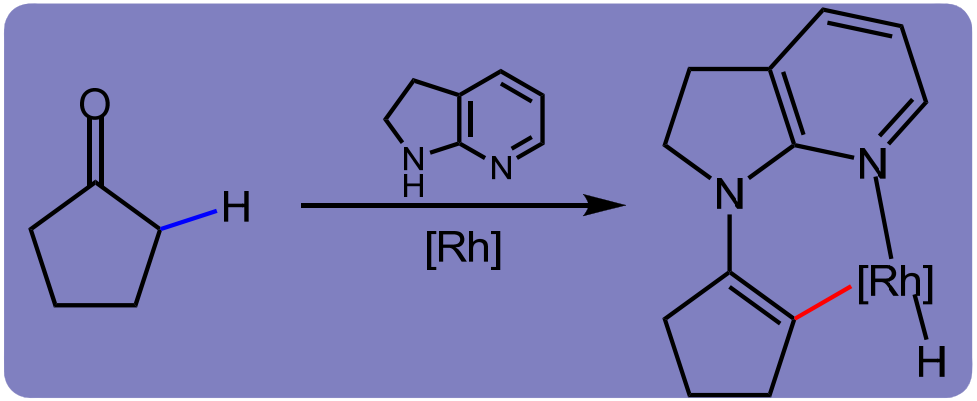


Bedford's work

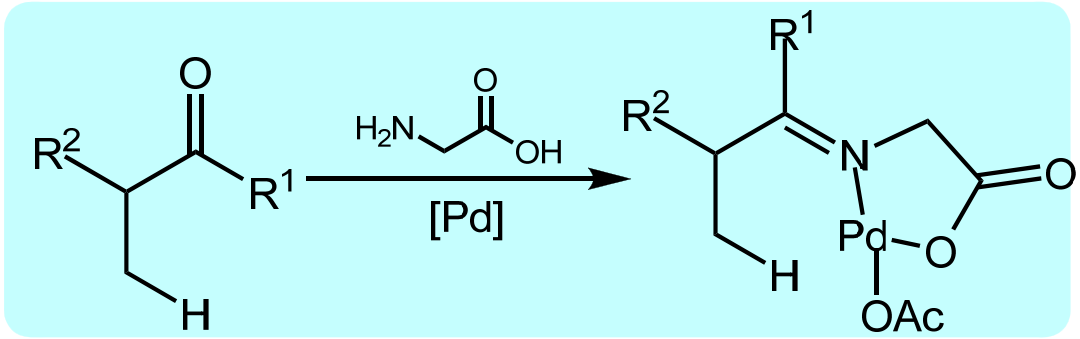


Summary

Dong's work



Yu's work



Precoordination of a metal with functional groups in substrates has been extensively exploited to control selectivity and promote reactivity in metal-catalyzed or –mediated reactions. The same approach has been successfully implemented in directed C–H activation reactions. However, the covalent installation and removal of directing groups is a major drawback for synthetic applications. First, an additional two steps must be added to the synthetic sequence. Second, the conditions for installation or removal of the directing groups are sometimes incompatible with other functional groups present in advanced synthetic intermediates. It is therefore highly desirable to devise a functionally tolerant reagent that can be reversibly linked to the substrate and can serve as a directing group. Upon C–H activation and subsequent functionalization, this reagent would dissociate from the product and transiently link to another substrate molecule so that only a catalytic quantity of the directing group would be needed. This approach has been successfully implemented in Rh(I)-catalyzed C(sp^2)–H activation reactions in a number of pioneering examples. Jun *et al.* reported the use of 2-amino pyridine as a transient directing group for Rh-catalyzed activation of aldehydic C–H bonds.

Recently, using a related strategy, Mo and Dong reported a Rh-catalyzed α-alkylation of ketones *via* a vinyl C–H activation step, featuring an enamine intermediate with a pyridine moiety as the transient directing group. Bedford *et al*. developed a Rh-catalyzed ortho-arylation through reversible *in situ* transesterification of catalytic amounts of phosphinite ligands with the phenol substrate.