

Literature Report

Remote Migratory Cross-Electrophile Coupling and Olefin Hydroarylation Reactions Enabled by in Situ Generation of NiH

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Checker: Xiao-Yong Zhai

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Contents

- ◆ **Introduction**
- ◆ **Ni-catalyzed Reductive Arylation of Remote Olefins**
- ◆ **Ni-catalyzed Reductive Arylation of Remote Alkyl Bromides**
- ◆ **Summary**

CV of Zhu Shaolin

Position: Professor in Nanjing University

- *Nanjing University* (2005 B.S.)
- *Shanghai Institute of Organic Chemistry (SIOC)* (2010 Ph.D., with Prof. Ma, D.-W)
- *Princeton University* (2010-2013 Post-doctoral Fellow, with Prof. MacMillan, D. W. C)
- *Massachusetts Institute of Technology (MIT)* (2013-2015 Post-doctoral Fellow. with Prof. Buchwald, S. L)
- *Nanjing University* (Prof. 2015-now)

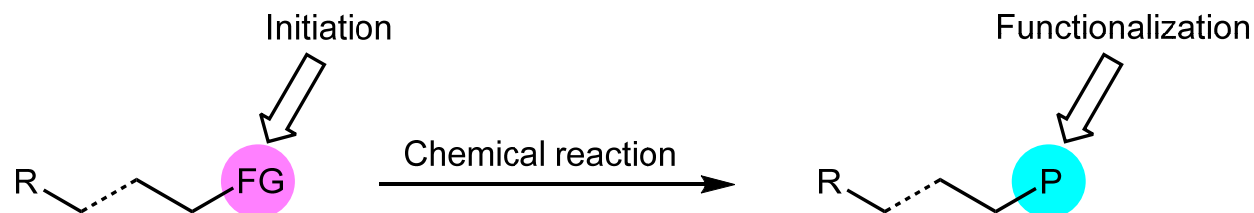


Research

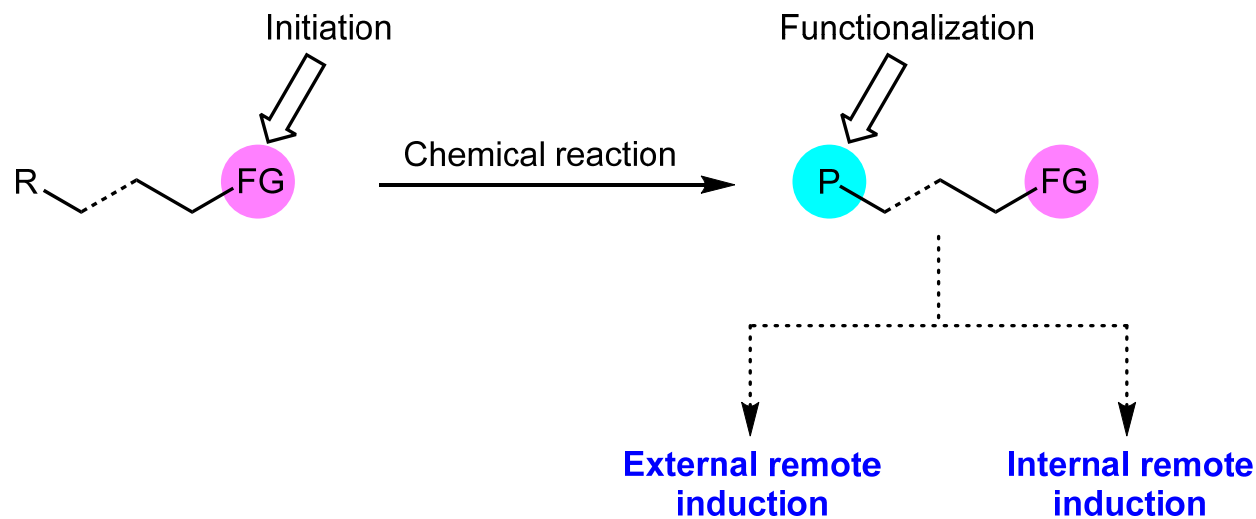
- ✓ Asymmetric catalysis
- ✓ Organic synthesis
- ✓ Pharmaceutical chemistry

Selective functionalization of organic molecule

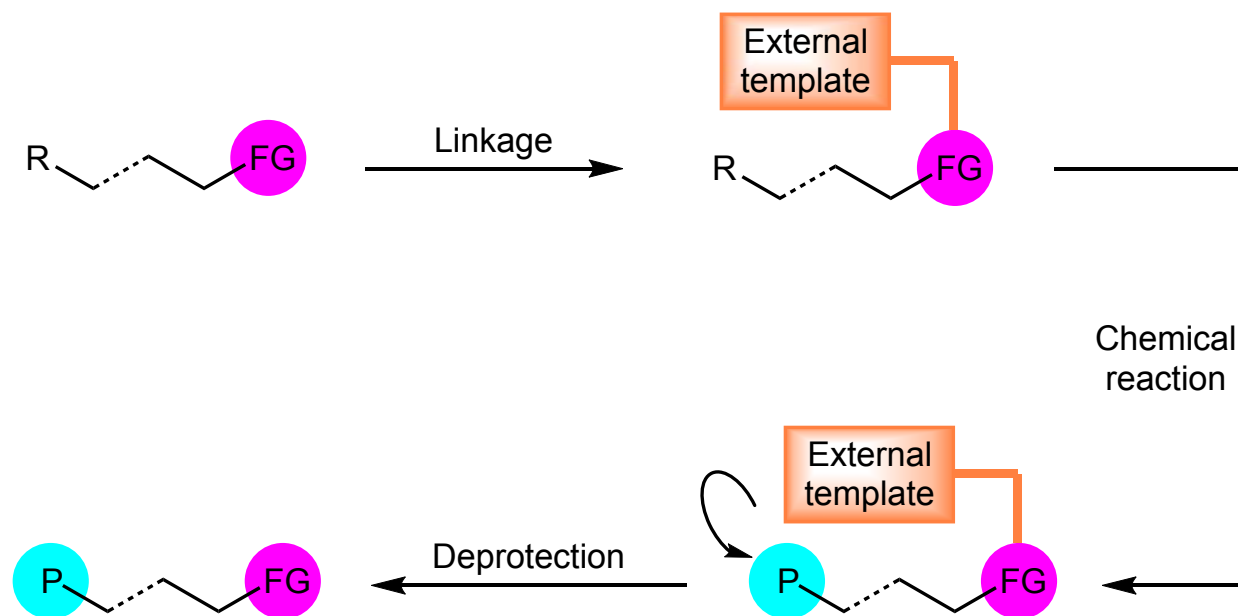
a Functionalization at the most reactive centre



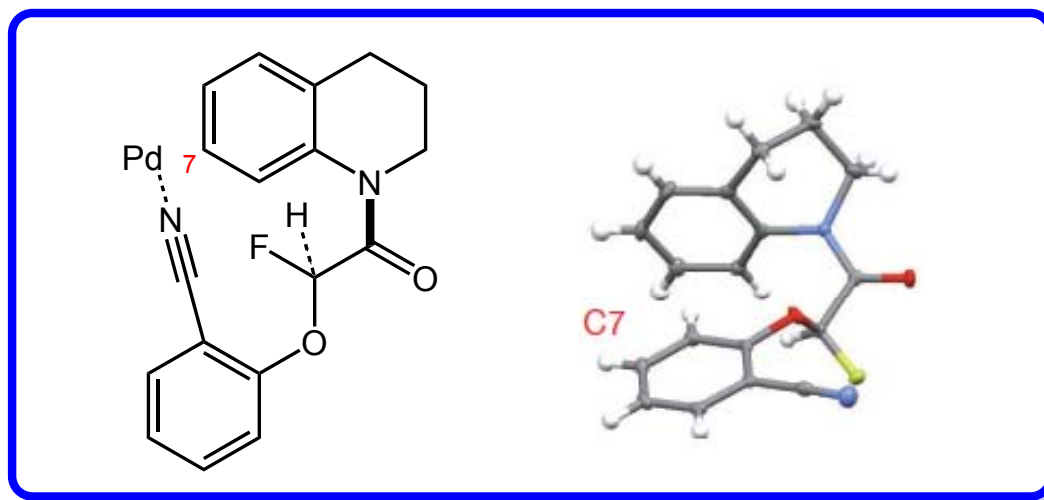
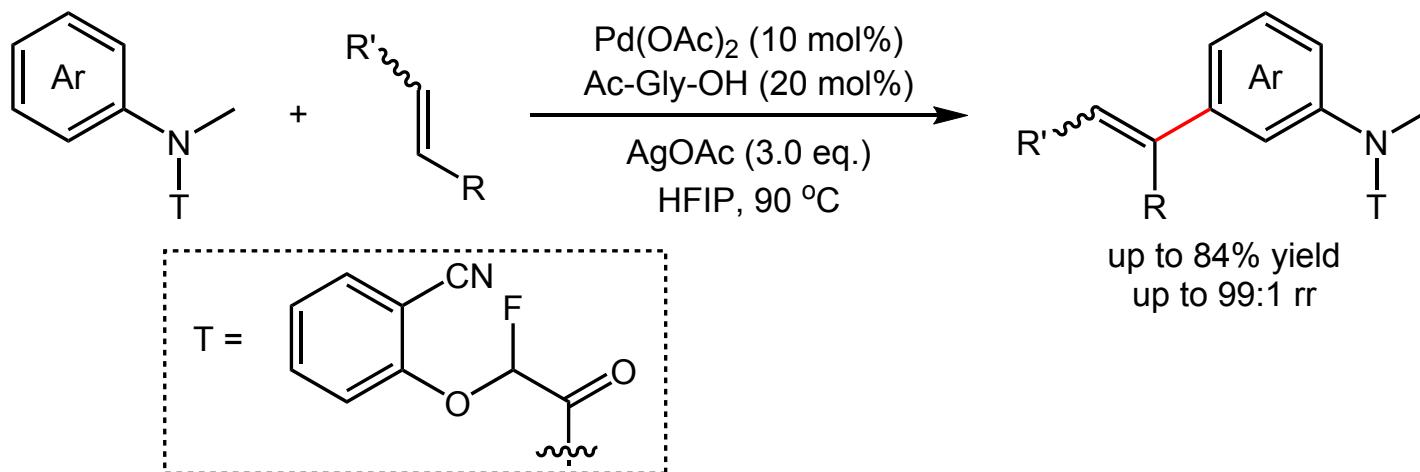
b Remote functionalization (functionalization at a position distal to FG)



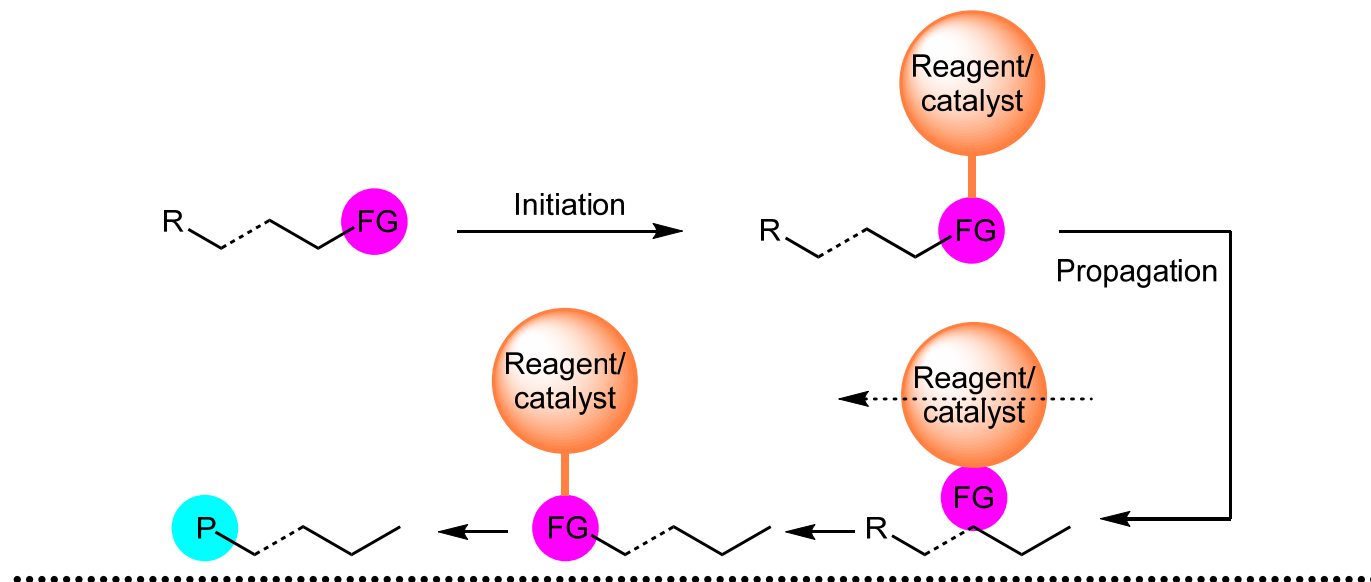
External remote induction



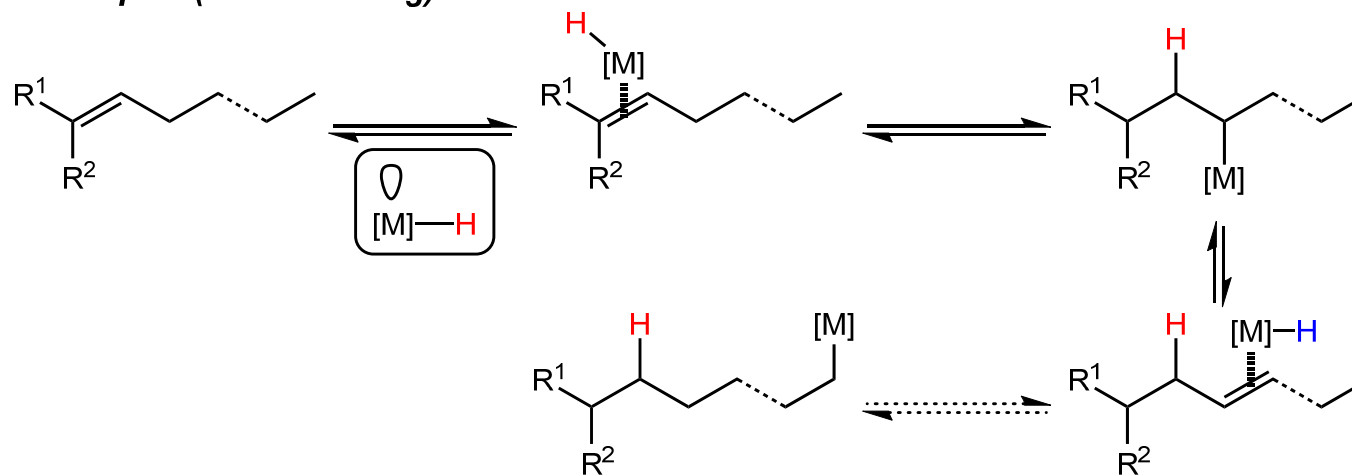
External remote induction



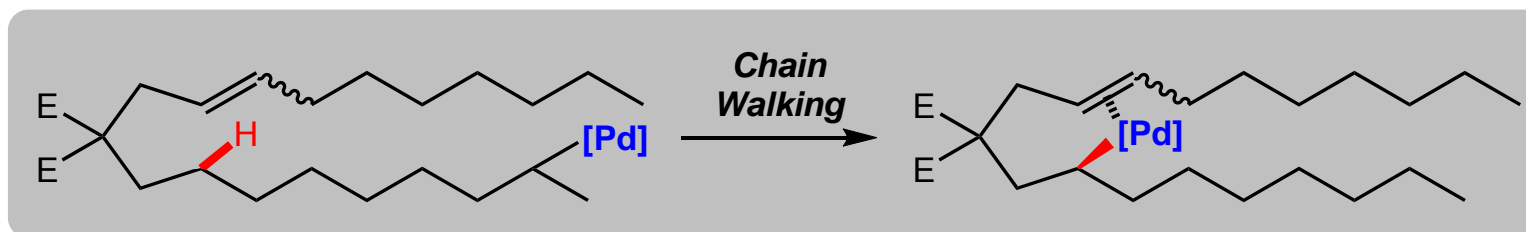
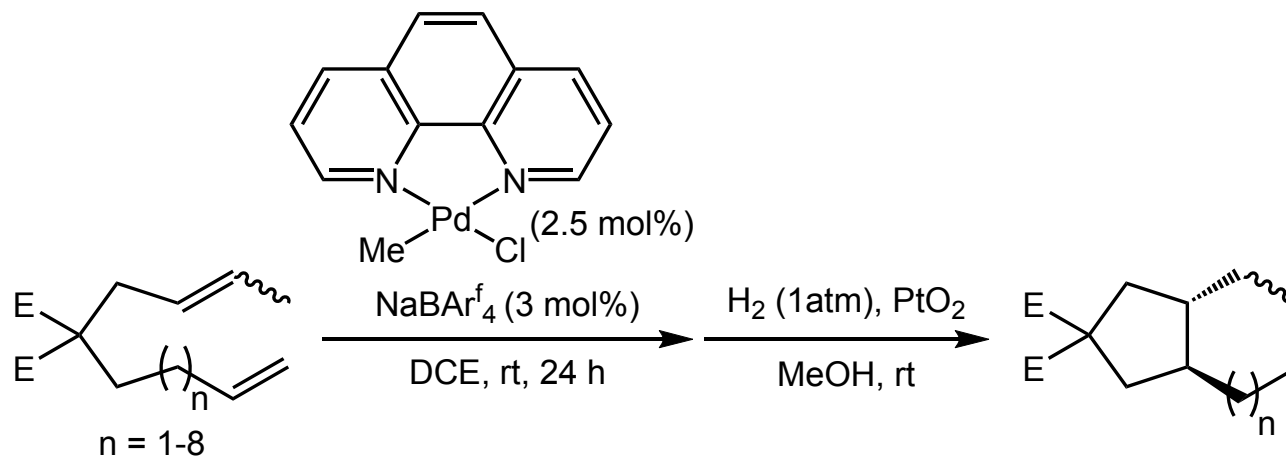
Internal remote induction



This report (chain walking):

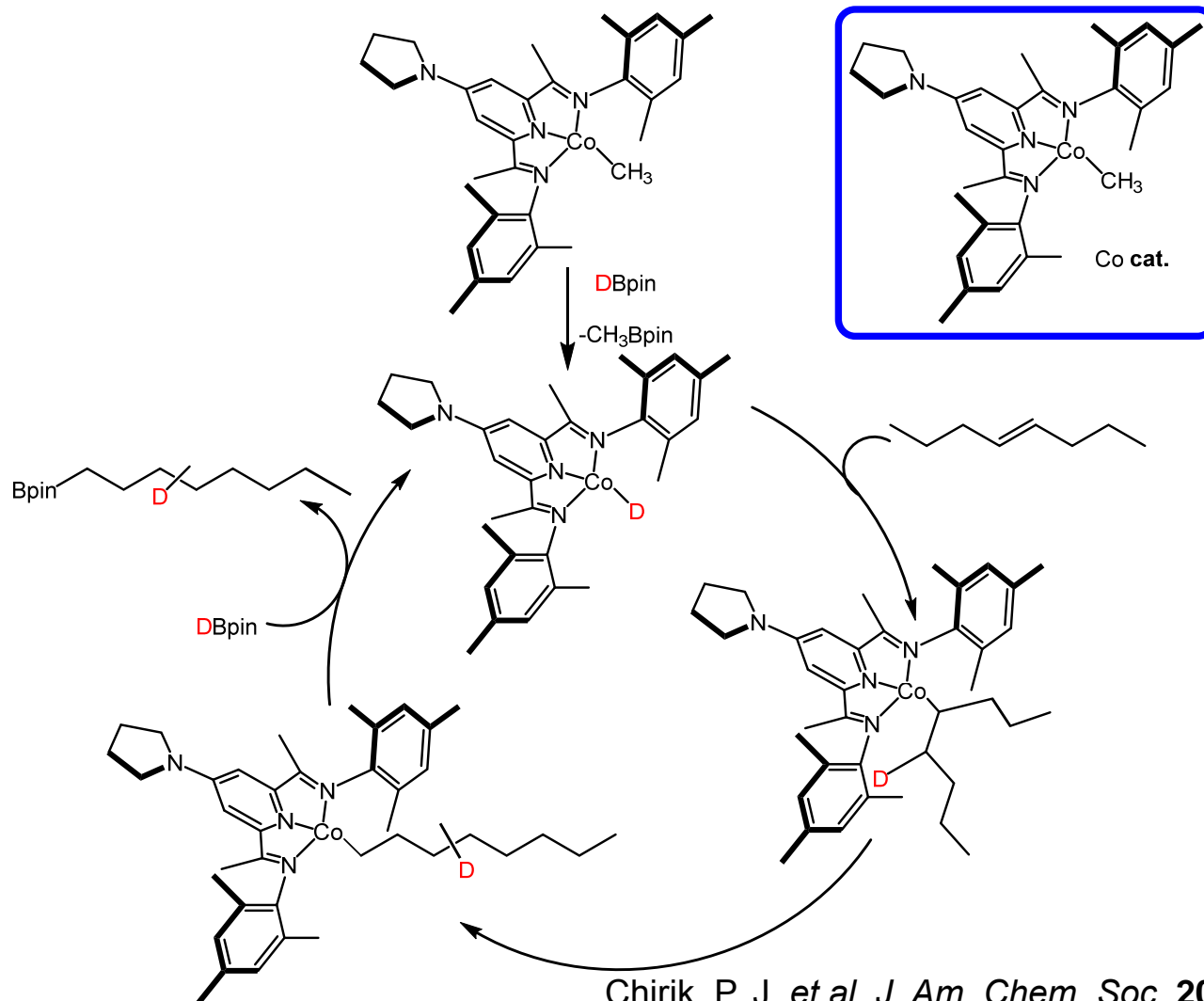
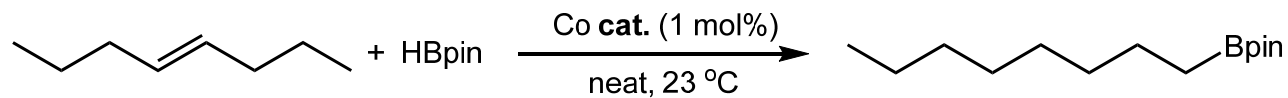


Pd-catalyzed remote functionalization

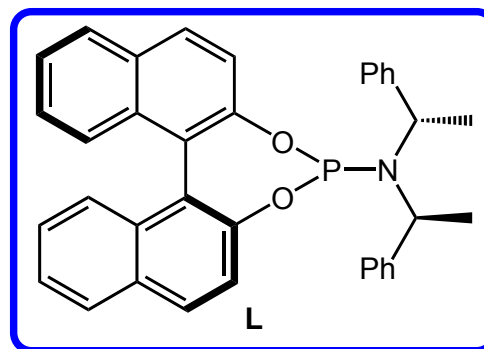
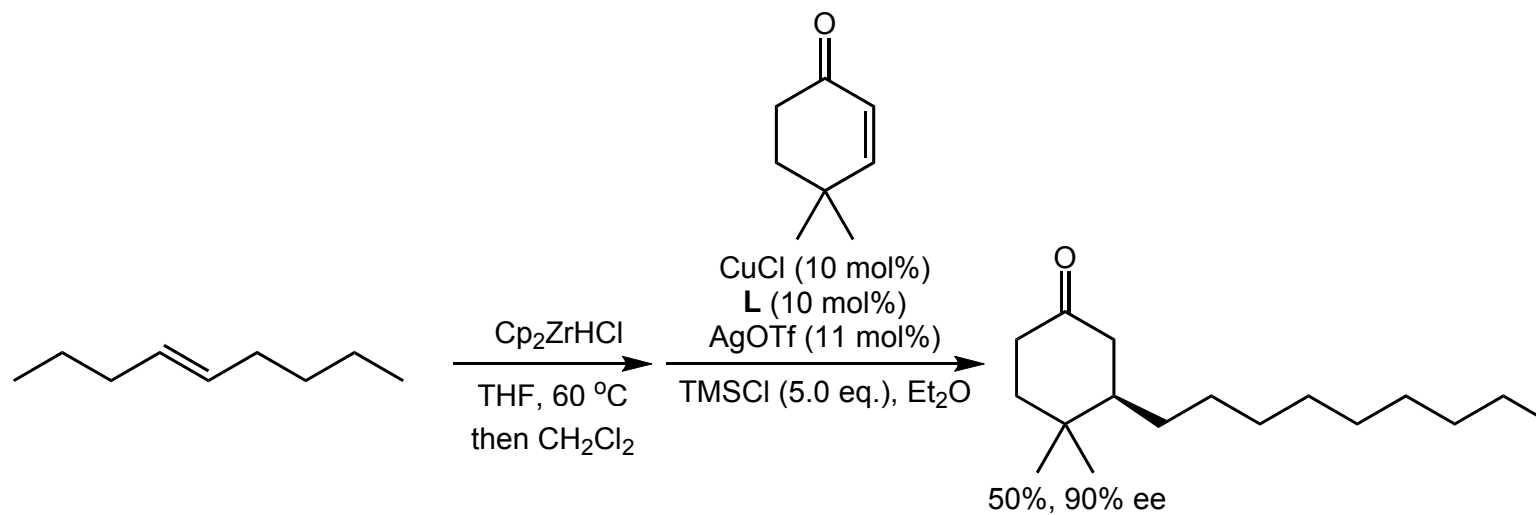


Kochi, T. *et al.* *J. Am. Chem. Soc.* **2015**, *137*, 16163.

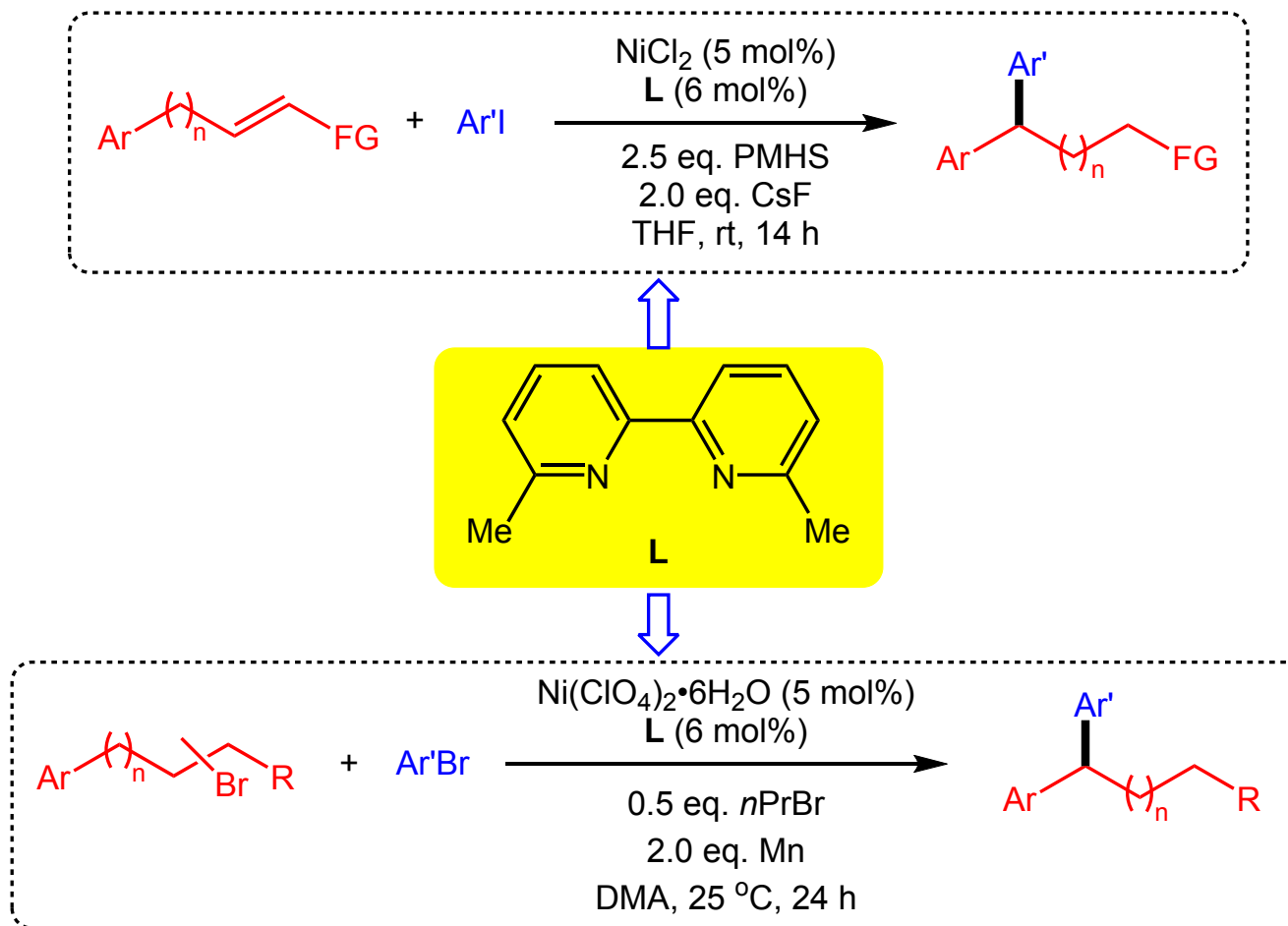
Co-catalyzed remote functionalization



Zr-catalyzed remote functionalization

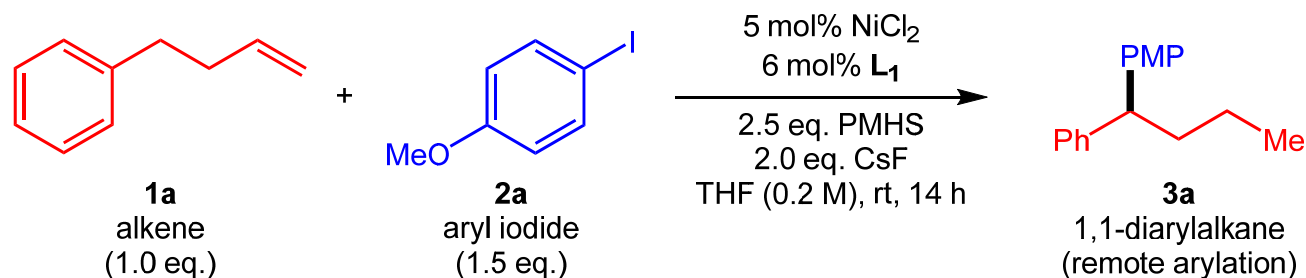


Ni-catalyzed remote functionalization

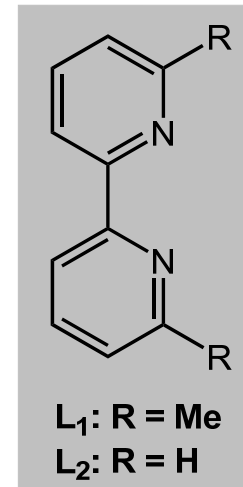


Zhu, S. *et al.* *J. Am. Chem. Soc.* **2017**, *139*, 1061;
Zhu, S. *et al.* *J. Am. Chem. Soc.* **2017**, *139*, 13929.

Variation of Reaction Parameters

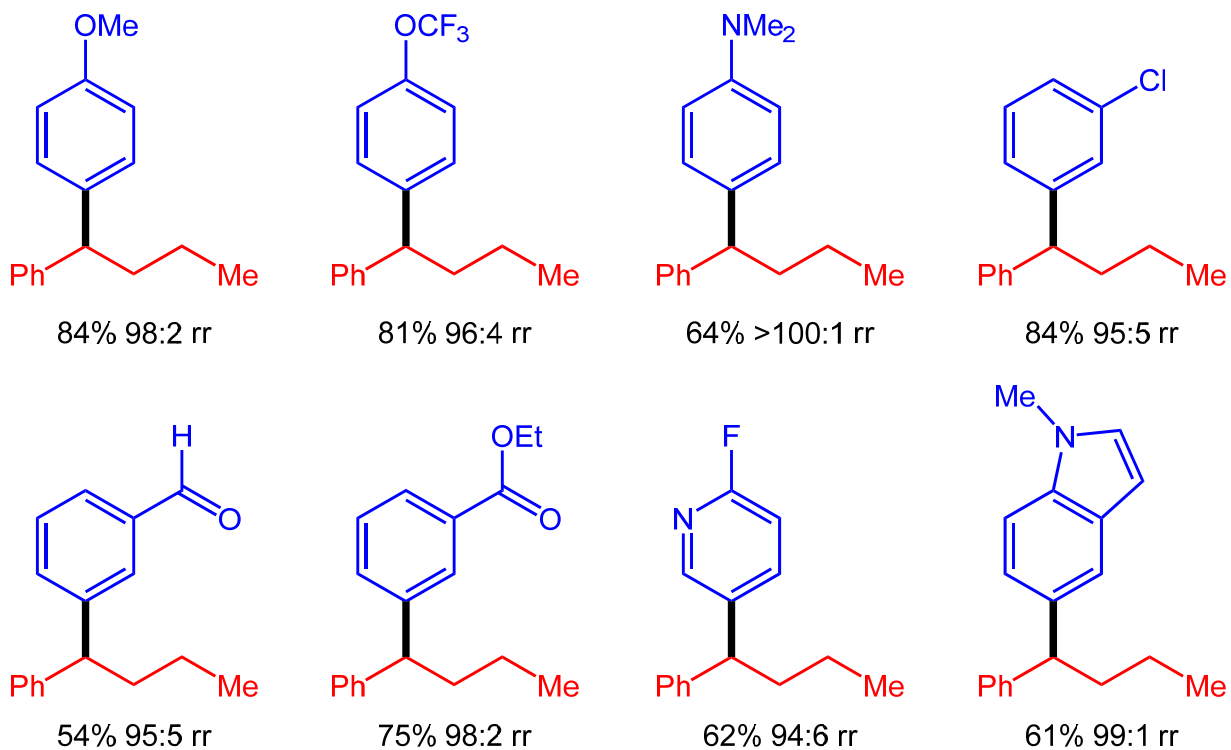
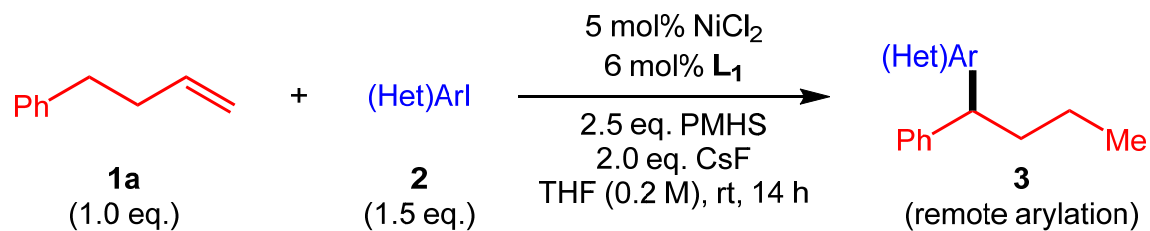


entry	deviation from standard conditions	yield (%) ^a	rr ^b
1	none	91	98:2
2	NiBr ₂ instead of NiCl ₂	76	96:4
3	L ₂ instead of L ₁	0	--
4	DMMS instead of PMHS	75	97:3
5	(EtO) ₃ SiH instead of PMHS	91	97:3
6	KF instead of CsF	6	>100:1
7	40 °C	71	97:3
8	4-Bromoanisole instead of 2a	24	>100:1
9	2.0 eq. of 2a	94	97:3

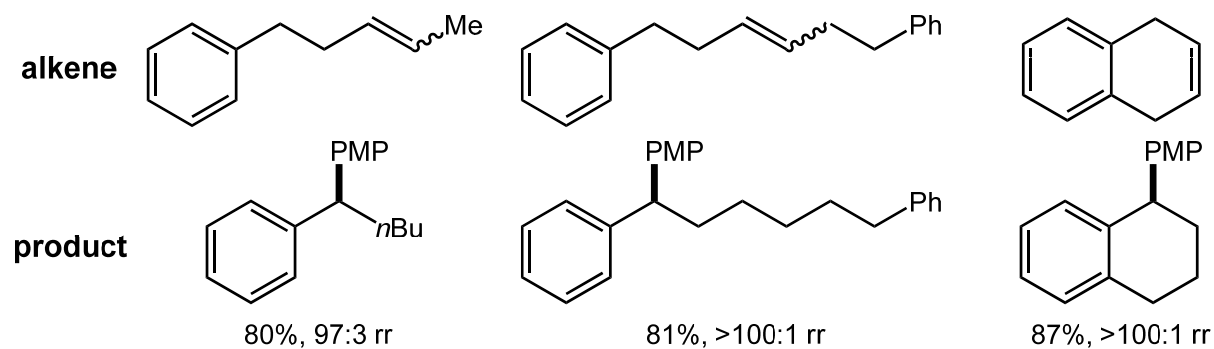
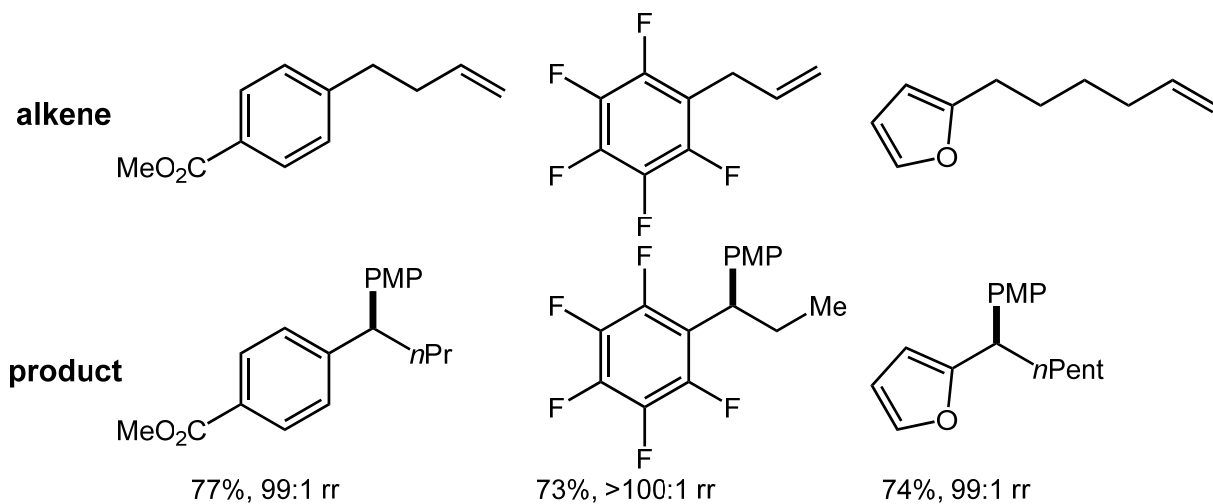
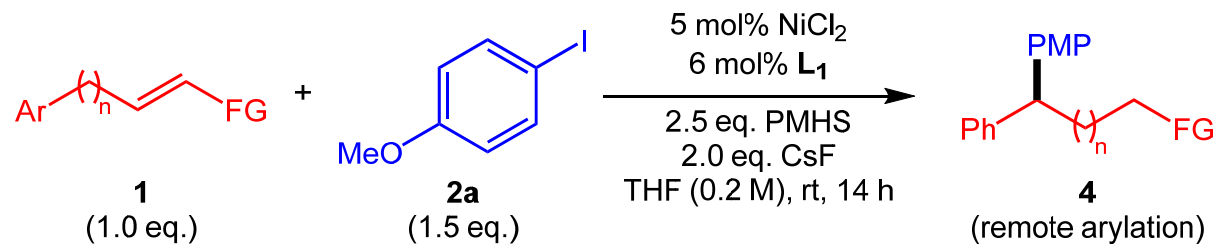


^a Yields determined by GC using dodecane as the internal. ^b rr is regioisomeric ratio, represents the ratio of the major (1,1-diaryllkane) product to the sum of all other isomers as determined by GC analysis.

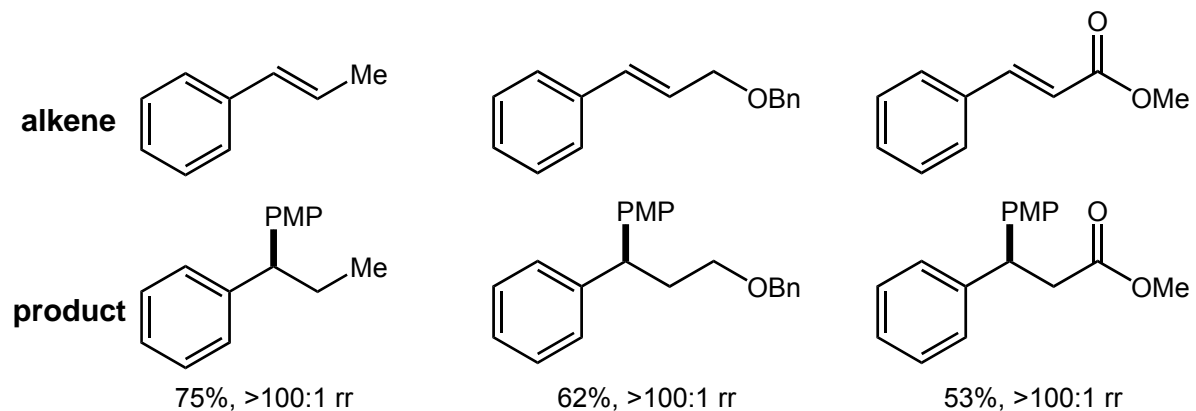
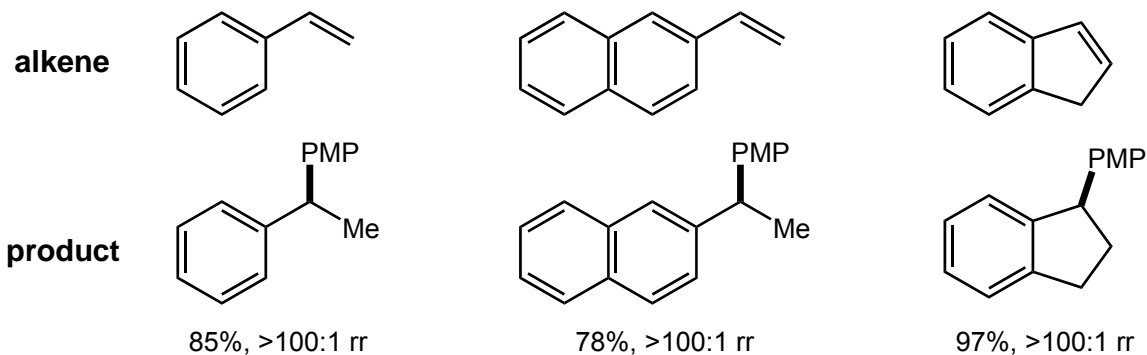
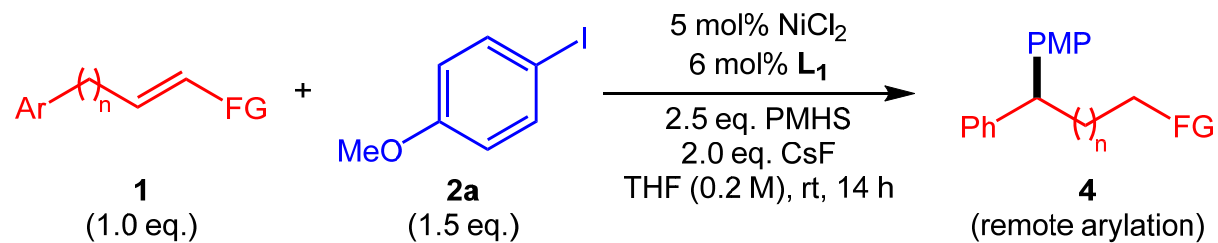
Scope of Aryl Iodide Coupling Partner



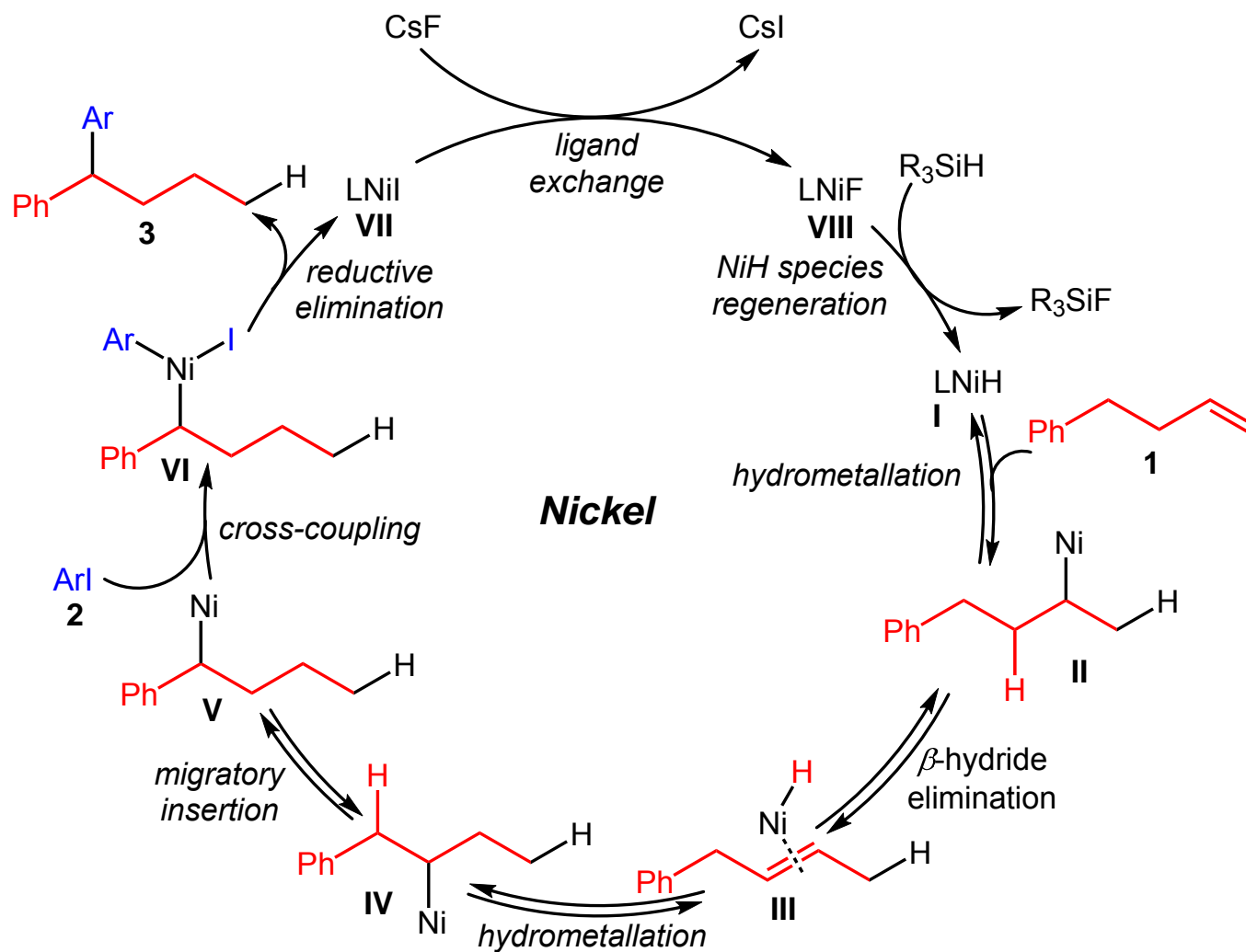
Scope of Alkene Coupling Partner



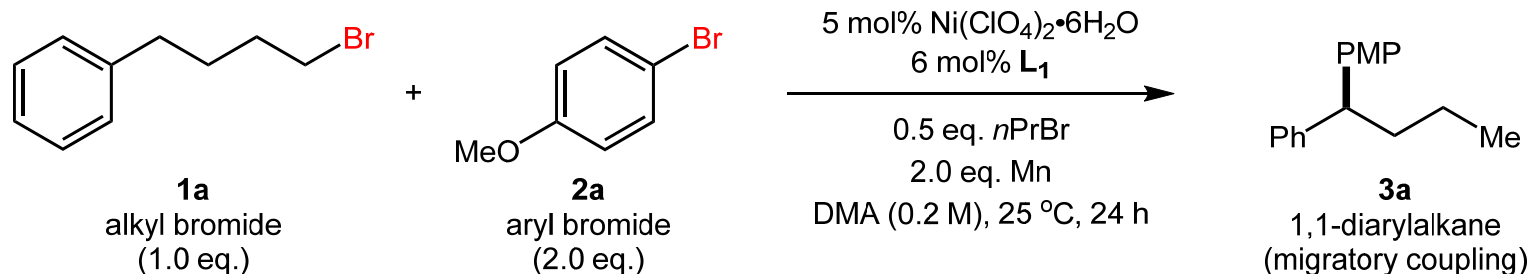
Scope of Alkene Coupling Partner



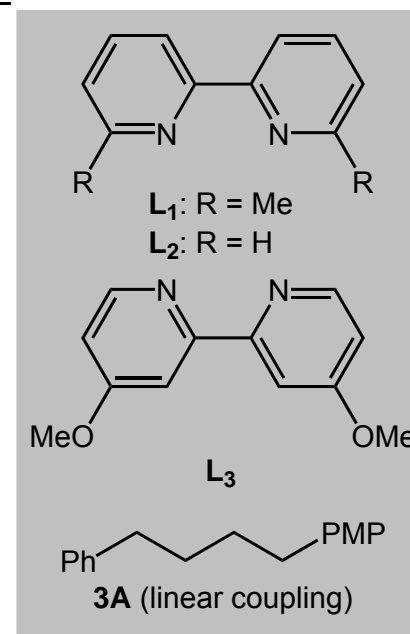
Proposed pathway



Variation of Reaction Parameters



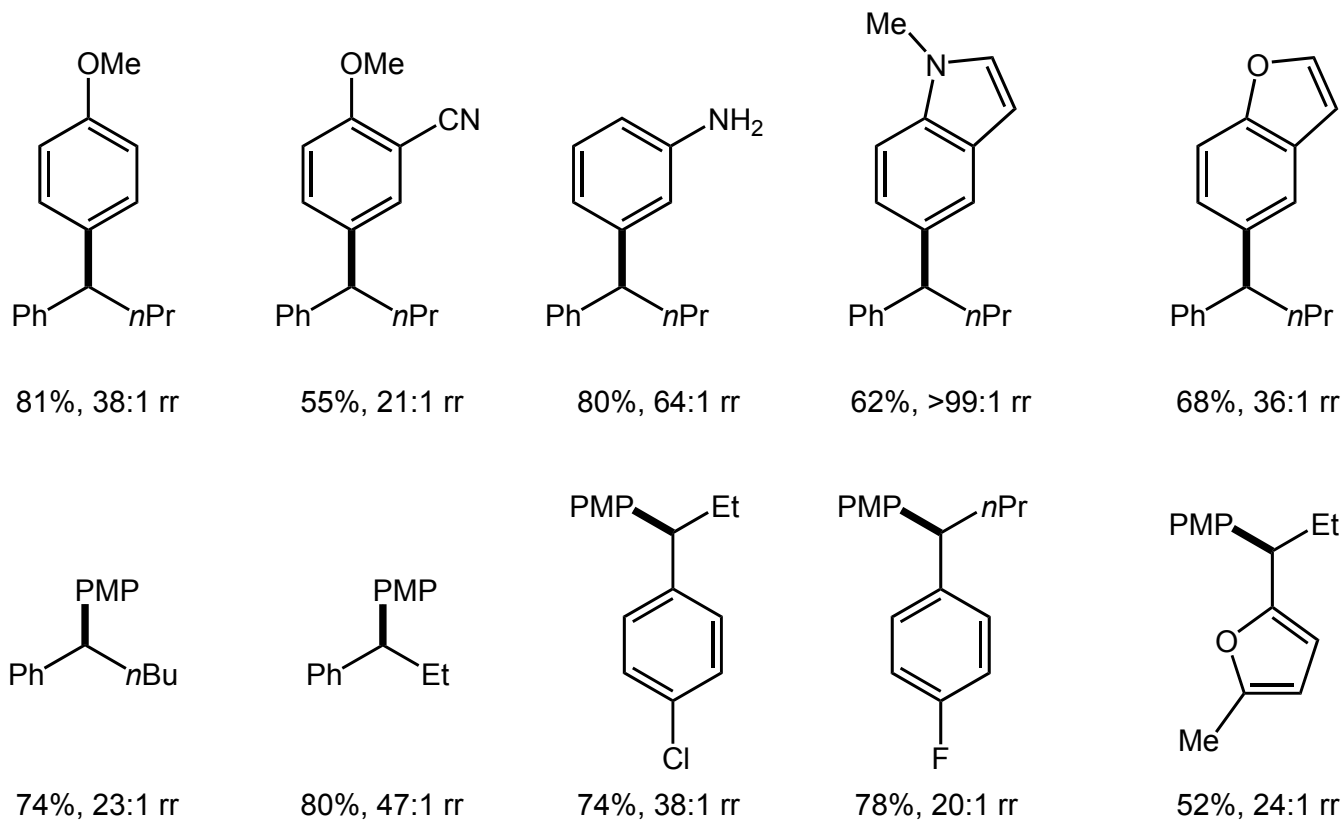
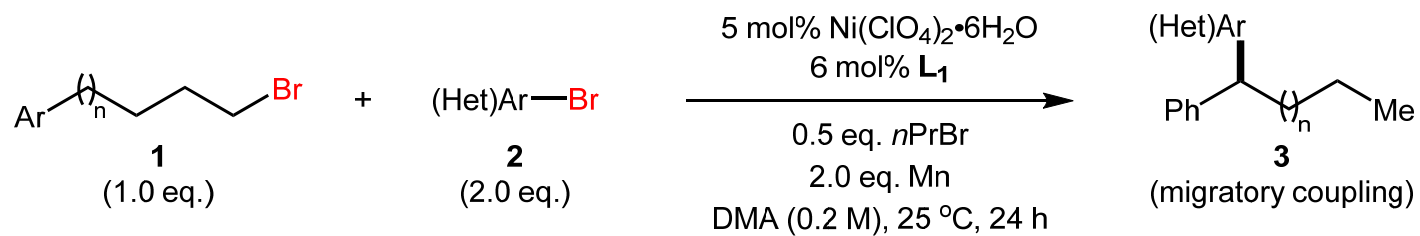
entry	deviation from standard conditions	yield (%) ^a	rr ^b
1	none	88	38:1
2	no <i>n</i> PrBr	67	23:1
3	Zn instead of Mn	11	6:1
4	THF instead of DMA	55	33:1
5	DMF instead of DMA	74	34:1
6	40 °C	71	27:1
7	1.5 eq. of 2a	74	33:1
8	4-Iodoanisole instead of 2a	20	1:1
9	L ₂ instead of L ₁	0	--
10	L ₃ instead of L ₁	0	--



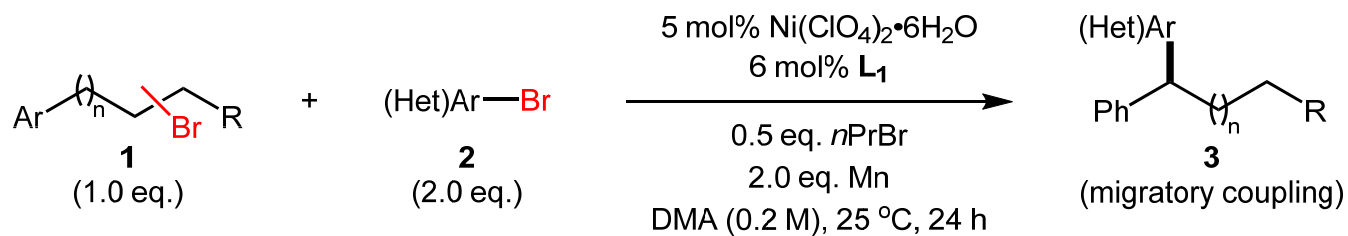
^a Yields determined by GC using dodecane as the internal standard. ^b rr is regioisomeric ratio, represents the ratio of the major (1,1-diarylalkane) product to the sum of all other isomers as determined by GC analysis.

Zhu, S. *et al. J. Am. Chem. Soc.* **2017**, *139*, 13929.

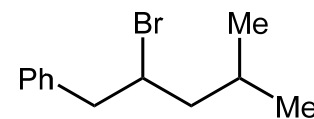
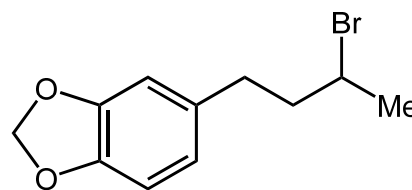
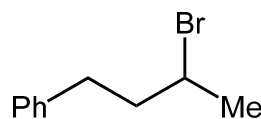
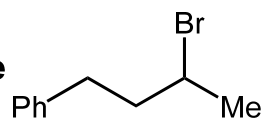
Substrate scope



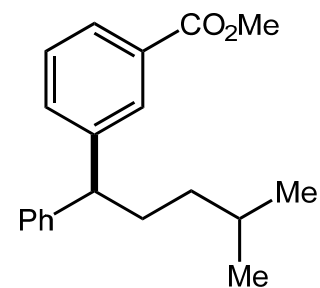
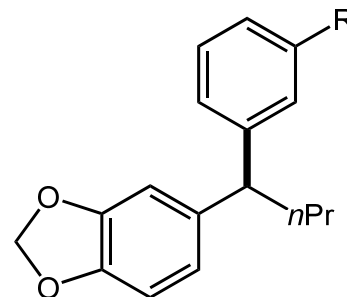
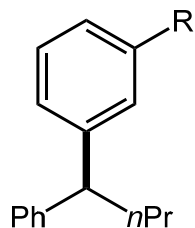
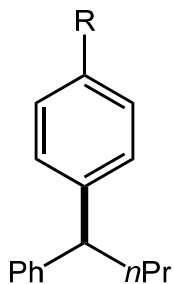
Substrate scope



2° Bromide



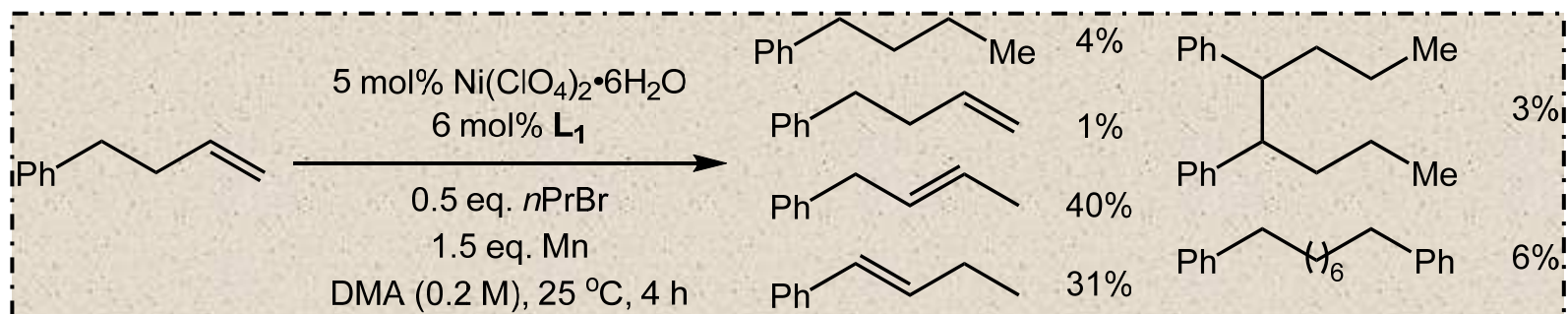
product



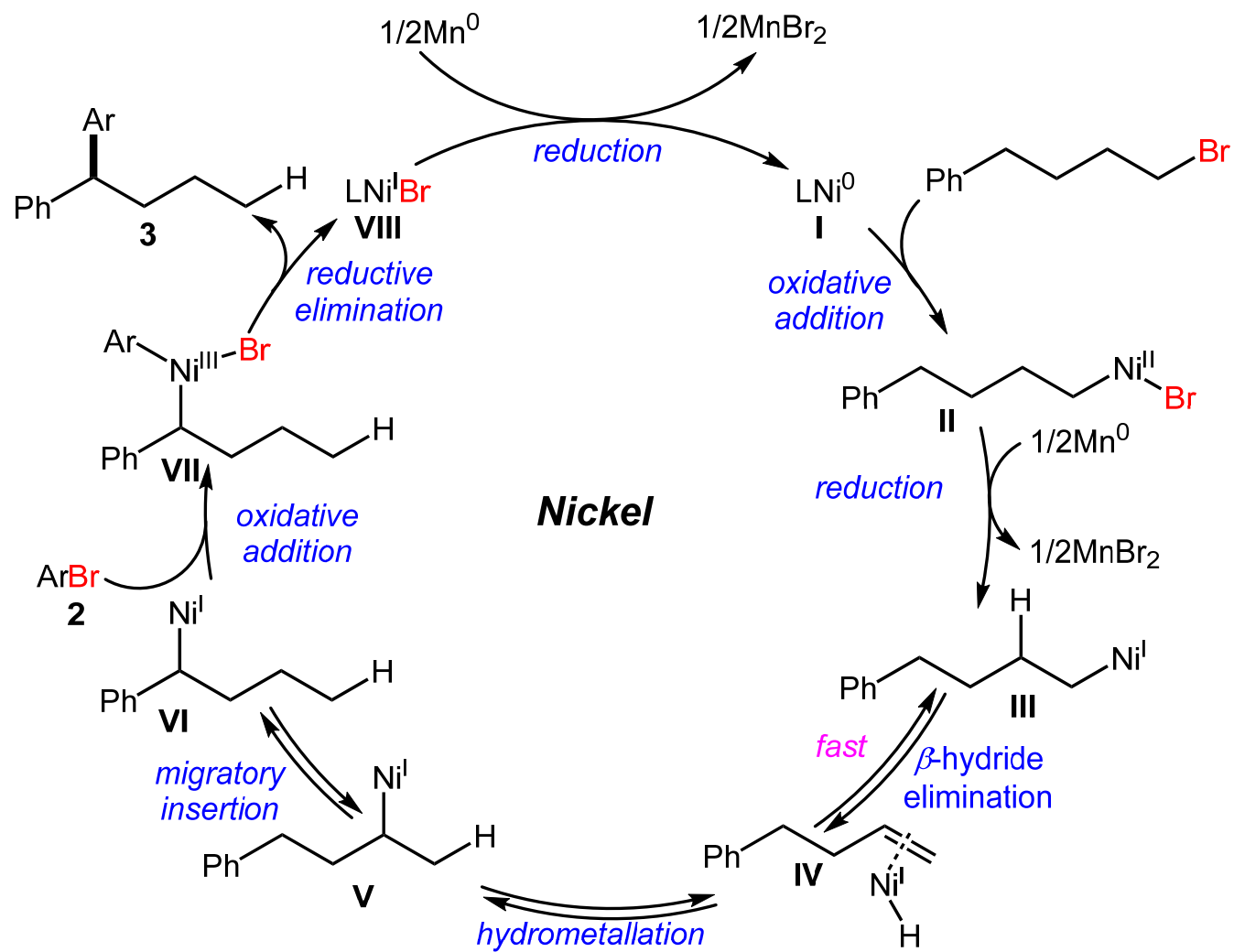
R = OCF₃, 76%, 36:1 rr R = Ac, 74%, 13:1 rr R = F, 74%, 66:1 rr
 R = CO₂Me, 73%, 26:1 rr R = CO₂Me, 85%, 34:1 rr R = CO₂Me, 78%, 54:1 rr

65%, >99:1 rr

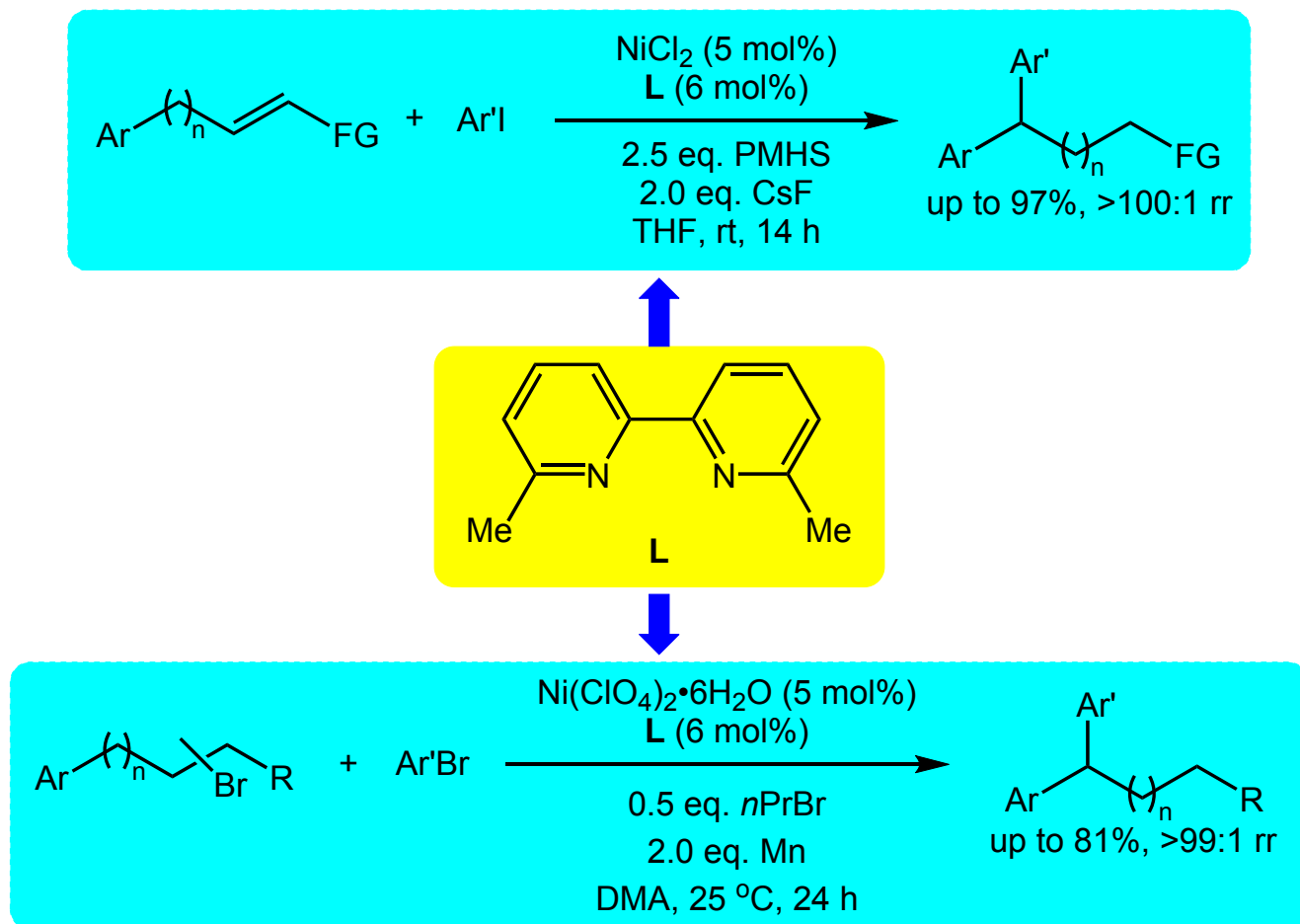
Olefin isomerization without aryl bromides



Proposed pathway



Summary



Zhu, S. *et al.* *J. Am. Chem. Soc.* **2017**, *139*, 1061;
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The first paragraph

Cross-coupling chemistry is a powerful technology for the construction of carbon–carbon bonds. In classical cross-coupling reactions, C–C bond formation occurs at the site of reactive functional groups preinstalled on two coupling partners. Complementary techniques that allow the new C–C bond formation at remote, unfunctionalized sites would enable new strategies for complex molecule synthesis to be employed and allow access to structures that would otherwise be difficult to prepare. An iterative migratory insertion/ β -hydrogen elimination process mediated by metal hydride intermediates represents a profitable approach for the activation of remote unfunctionalized sites.

The first paragraph

The combined application of cross-coupling and metal-hydride chemistry in remote C–H functionalization, however, is reported in only a few contexts. **As an important class of compounds, alkyl halides are reactive, yet bench-stable and readily available starting materials for synthesis.** Nevertheless, their use in transition metal-catalyzed coupling reactions, is often limited by isomerization brought about by β -hydrogen elimination and reinsertion. **We felt that this facile and often undesired side reaction could, in fact, be used advantageously in a regioselective, migratory and reductive cross-coupling of alkyl and aryl halides.**

The last paragraph

In conclusion, we have developed a mild and highly robust nickel-catalyzed migratory remote cross-electrophile coupling reaction via the formation of NiH in situ from alkyl halides. Excellent regio- and chemoselectivity were observed, in terms of both alkyl bromides and alkenes precursors. This versatile protocol provides a versatile and synthetically valuable addition to the current processes for reductive cross-coupling. Mechanistic studies are consistent with a mechanism in which a nickel(I) hydride species effects the rapid isomerization of olefin isomers, with the ultimate regiochemical outcome likely determined by the subsequent oxidative addition of the aryl halide. Developing an asymmetric version of the current transformation is under investigation in our laboratory, and progress in this area will be reported in due course.