

Cross-Electrophile Coupling

Education and professional experience:

2000 B.S., Columbia University, New York (Prof. Thomas Katz)
 2005 Ph. D. University of California, Berkeley, California (Prof. Jonathan Ellman)
 2005-2008 Postdoctoral fellow, University of California, Berkeley, California (Prof. John Hartwig)
 2008-present Associate professor of chemistry, University of Rochester, New York



Honors and awards:

2000-2003 UC-Berkeley Outstanding Graduate Student Instructor Award
 2005-2008 NIH Ruth L. Kirschstein National Research Service Award
 2012 Sigma-Aldrich Distinguished Lecturer, University of Colorado
 2013 Thieme Chemistry Journal Award
 2013 Alfred P. Sloan Research Fellow
 2013 Kavli Fellow
 2014 Novartis Early Career Award

Research interest:

Development of conceptually new catalytic methods for organic synthesis using first-row transition-metals (Mn, Fe, Co, Ni, Cu)

Recent development:
 Nickel catalysed cross-electrophile coupling

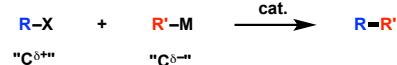
170203_LS_Daiki_Kamakura

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<http://www2.chem.rochester.edu/~djwgrp/index.php>

Introduction for Cross-Electrophile Coupling

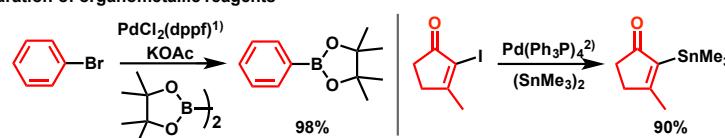
Conventional cross coupling



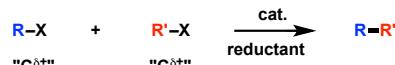
X = halogen or pseudohalogen
 M = MgX, ZnX, B(OR"), SnR", SiR"

cat. = Pd, Ni, ...

Preparation of organometallic reagents



More straightforward method: Direct cross coupling of two electrophiles



1) Ishiyama, T., Murata, M., Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508
 2) Shipe, W. D., Sorensen, E. *J. Org. Lett.* **2002**, *4*, 2063.

Difficulty of Cross Coupling

Wurtz coupling



R = alkyl

Ullmann Coupling

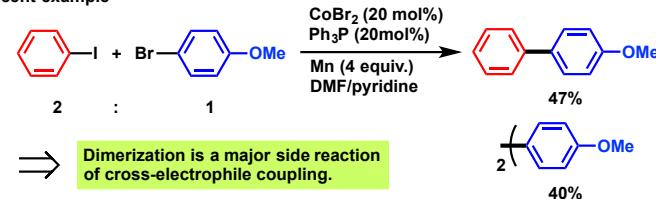


R = aryl

Approach toward cross coupling



Recent example¹⁾

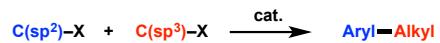


⇒ Dimerization is a major side reaction of cross-electrophile coupling.

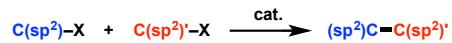
1) Amatore, M., Gosmini, G. *Angew. Chem. int. Ed.* **2008**, *47*, 2089

Contents

1. Cross-electrophile coupling of C(sp²) halides with C (sp³) halides

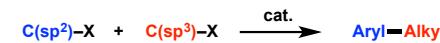


2. Cross-electrophile coupling of C(sp²) halides with C(sp²) halides

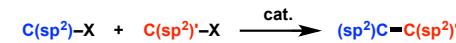


Contents

1. Cross-electrophile coupling of C(sp²) halides with C (sp³) halides



2. Cross-electrophile coupling of C(sp²) halides



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Cross Coupling of Aryl Halide with Alkyl Halide

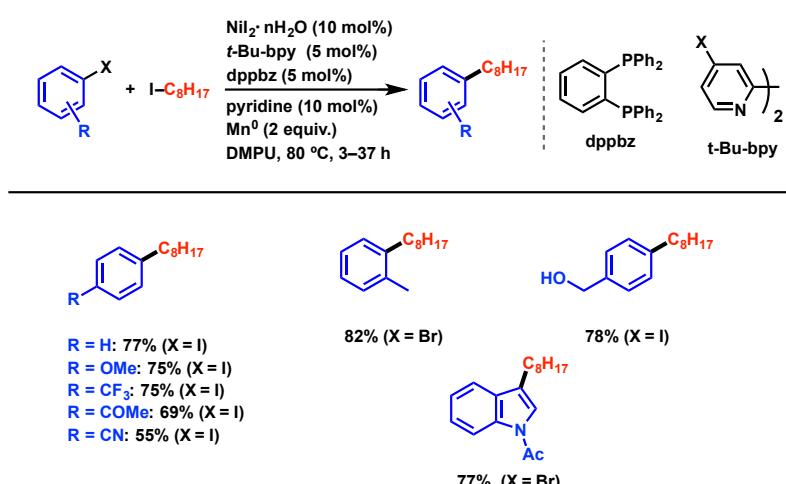
entry	ligand	solvent	Temp. (°C)	GC area%			
				Ph-C ₈ H ₁₇	dimer	reduced compounds	
1	dppe	DMF	60	16	7	77	
2	dppbz	DMF	60	27	16	58	
3	bpy	DMF	60	52	20	28	X = H: bpy
4	t-Bu-bpy	DMF	60	60	21	20	X = t-Bu: t-Bu-bpy
5	t-Bu-bpy + dppbz	DMPU	80	82 (77) ^a	4	9	

^a Isolated yield in parenthesis.

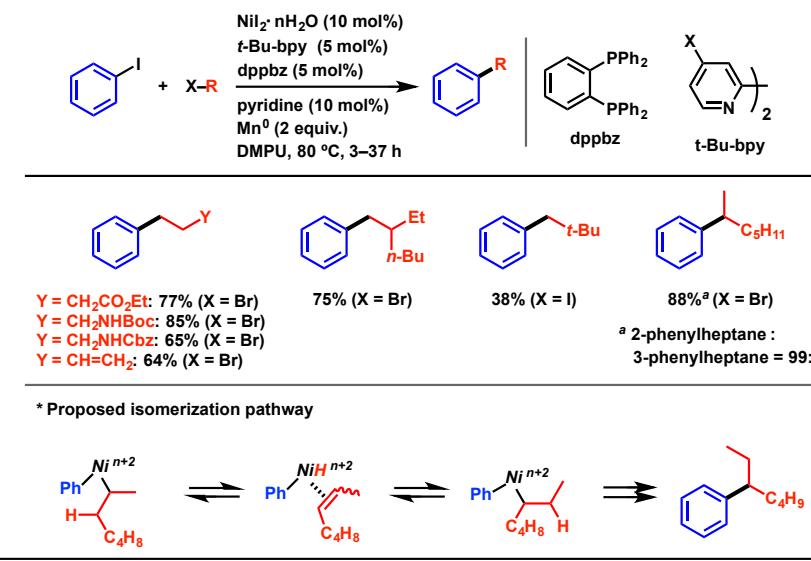
Everson, D. A. Shrestha, R. Weix, D. J. *J. Am. Chem. Soc.* **2010**, 132, 920

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Substrate Scope of Aryl Halides



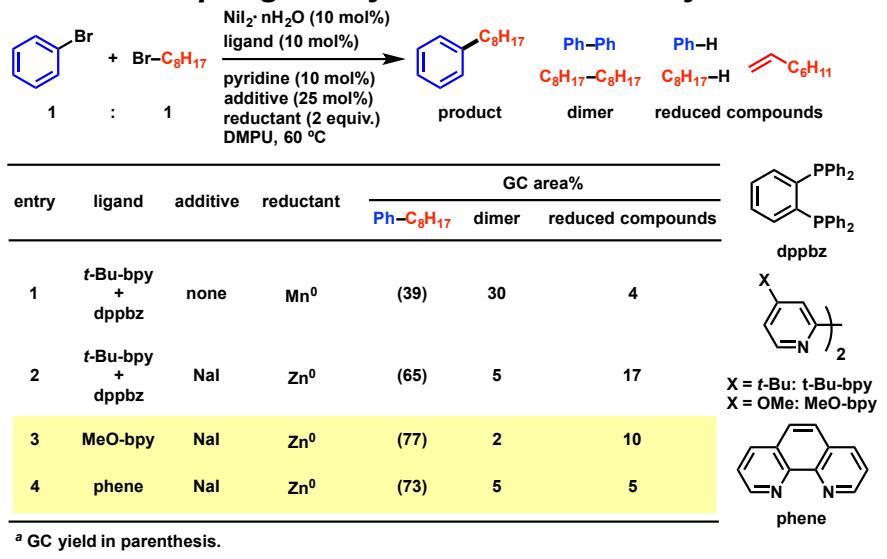
Substrate Scope of Alkyl Halides



Everson, D. A. Shrestha, R. Weix, D. J. *J. Am. Chem. Soc.* 2010, 132, 920

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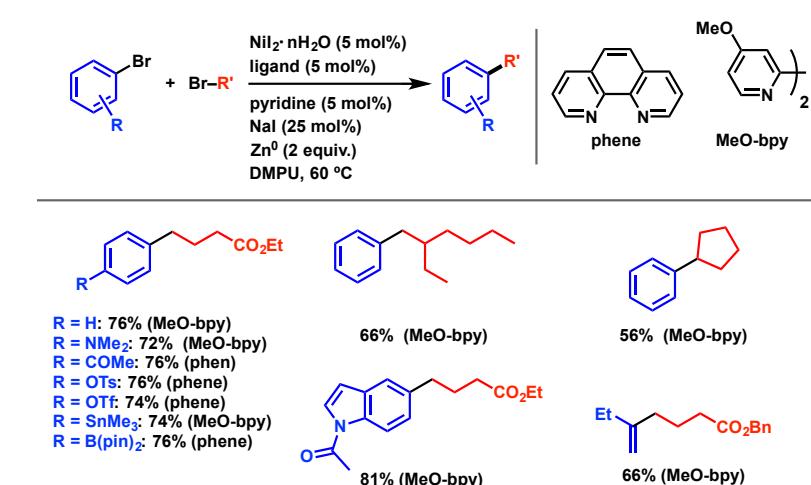
Cross Coupling of Aryl Bromide with Alkyl Bromide



Everson, D. A., Jones, B. A., Weix, D. J. *J. Am. Chem. Soc.* 2012, 134, 6146.

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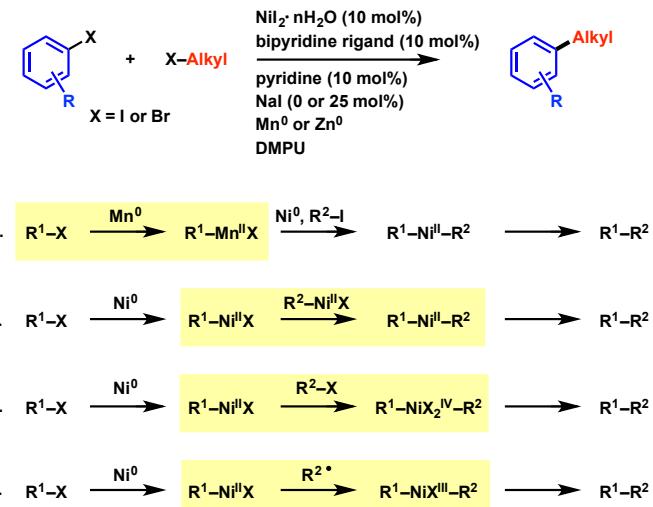
Substrate Scope



Everson, D. A., Jones, B. A., Weix, D. J. *J. Am. Chem. Soc.* 2012, 134, 6146.

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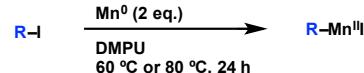
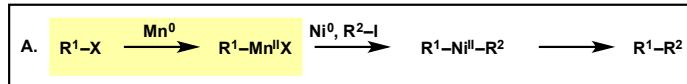
Potential Mechanisms for Cross Coupling



Biswas, S. Weix, D. J. *J. Am. Chem. Soc.* 2013, 135, 16192.

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Control Experiment: Direct Insertion of Mn⁰



Substrate	Temp (°C)	Consumption of R-I (%) ^a
Ph-I	60	0
Ph-I	80	0
C ₈ H ₁₇ -I	60	0
C ₈ H ₁₇ -I	80	19

^a Determined by GC. Based on unreacted iodide (dodecane was used as an internal standard).

* Catalytic cross coupling of Ph-I and C₈H₁₇-I is complete in 3 hours

⇒ In this coupling reaction, organomanganese species (R-Mn^{III}) was not formed.

Everson, D. A. Shrestha, R. Weix, D. J. J. Am. Chem. Soc. 2010, 132, 920

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Effects of the amount of Ni catalyst

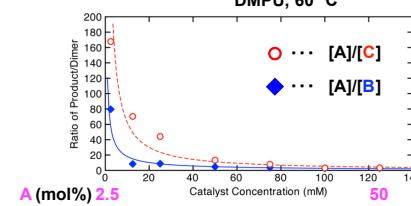
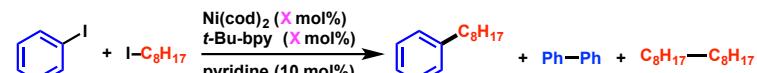
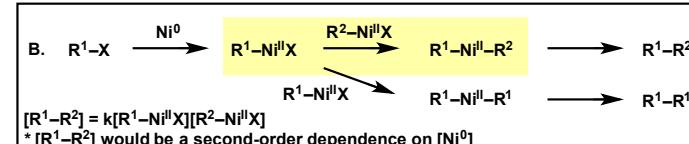


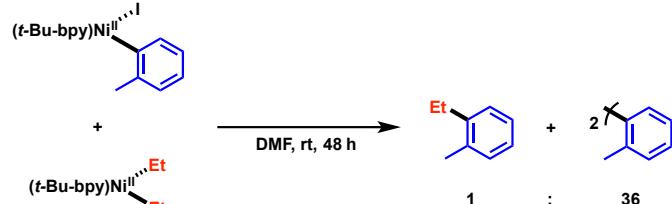
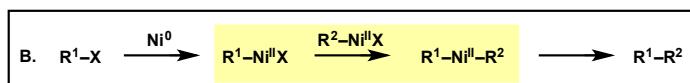
Figure 1. Change of the molar ratio of [A]/[B] (red) and [A]/[C] (blue) with catalyst concentration
 $\text{O } f(x) = 121.05x^{-0.824} (\text{R}^2 = 0.94)$ $\text{◆ } f(x) = 723.81x^{-1.063} (\text{R}^2 = 0.92)$

Product and dimers would arise from different mechanisms
 $(\text{R}^1\text{-R}^2)$ would be a first-order dependence on $[\text{Ni}^0]$.

Biswas, S. Weix, D. J. J. Am. Chem. Soc. 2013, 135, 16192.

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Reaction of Arylnickel with Alkylnickel

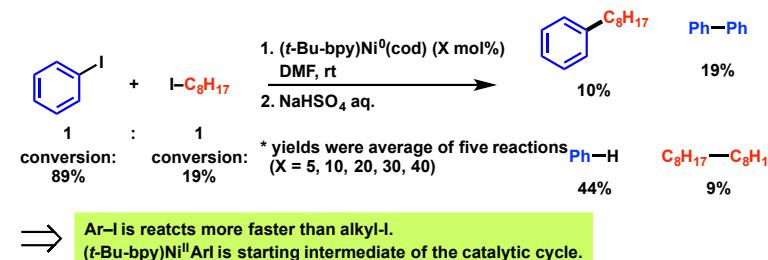
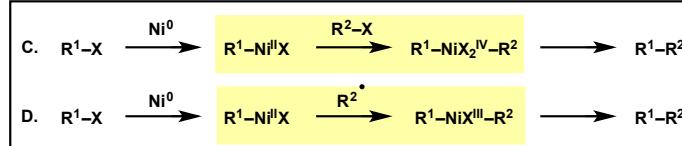


⇒ Transmetalation between $\text{R}^1\text{-Ni}^{\text{II}}\text{X}$ and $\text{R}^2\text{-Ni}^{\text{II}}\text{X}$ is a wrong pathway.

Biswas, S. Weix, D. J. J. Am. Chem. Soc. 2013, 135, 16192.

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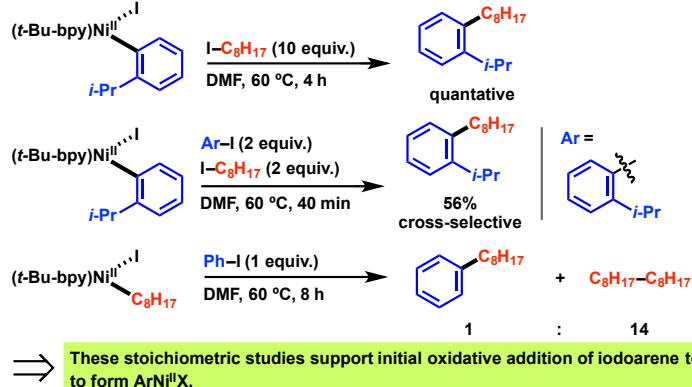
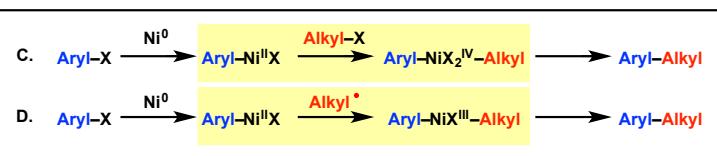
Selectivity in Oxidative Addition



Biswas, S. Weix, D. J. J. Am. Chem. Soc. 2013, 135, 16192.

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Reaction of Organonickels with Halides



Biswas, S. Weix, D. J. J. Am. Chem. Soc. 2013, 135, 16192.

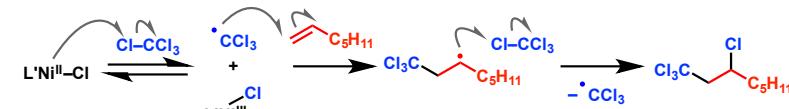
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Using Ni^{II} catalyst as a radical initiator

Nickel catalyzed Kharasch reaction



proposed mechanism

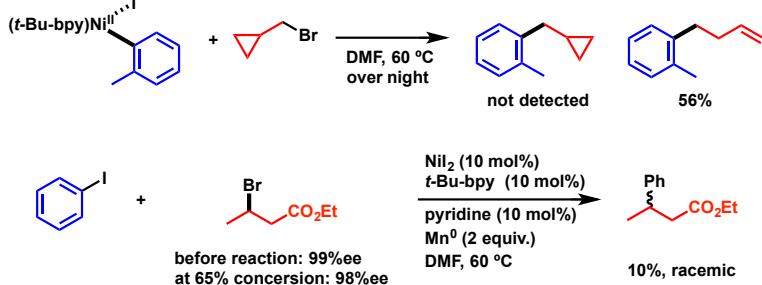


van de Kuil, L. A.; Grove, D. M., Gossage, R. A., Zwikker, G. J. W., Jenneskens, L. W., Drenth, W., van Koten, G. *Organometallics*, 1997, 16, 4985.

Alkyl halides would be reduced by $\text{R}^2\text{-Ni}^{\text{II}}\text{X}$ to form alkyl radical.

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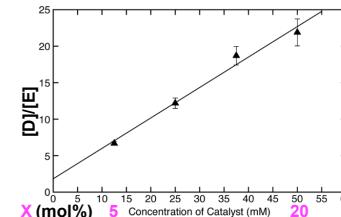
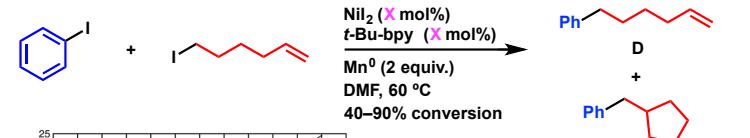
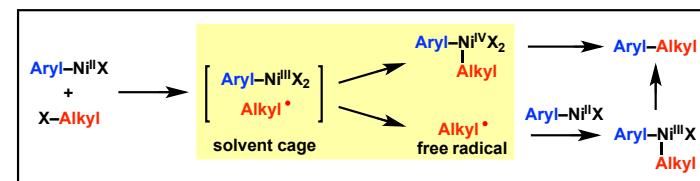
Presence of the Alkyl Radica Intermediate (1)



Biswas, S. Weix, D. J. J. Am. Chem. Soc. 2013, 135, 16192.

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Presence of the Alkyl Radica Intermediate (2)

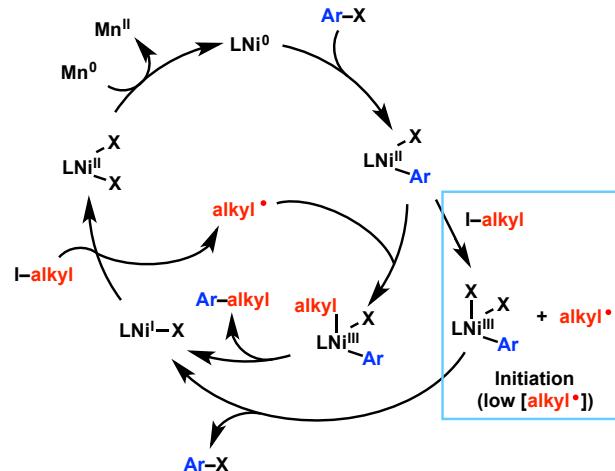


Alkyl radical would be involved in catalytic cycle.

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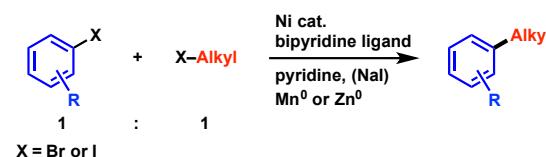
Mechanism for Cross-Electrophile Coupling



Biswas, S., Weix, D. J. *J. Am. Chem. Soc.* 2013, 135, 16192.

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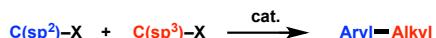
Short Summary



Selective oxidative addition of haloarene over haloalkane
Selective formation of an alkyl radical over aryl radical

Contents

1. Cross-electrophile coupling of $\text{C(sp}^2\text{)}\text{-halides}$ with $\text{C(sp}^3\text{)}\text{-halides}$



2. Cross-electrophile coupling of $\text{C(sp}^2\text{)}\text{-halides}$

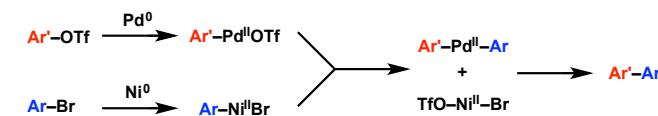


Working Hypothesis

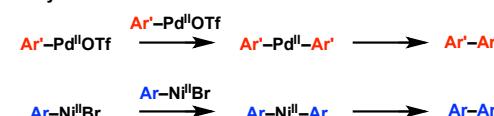
relative reactivity of Ni and Pd catalysis



Working Hypothesis



Difficulty



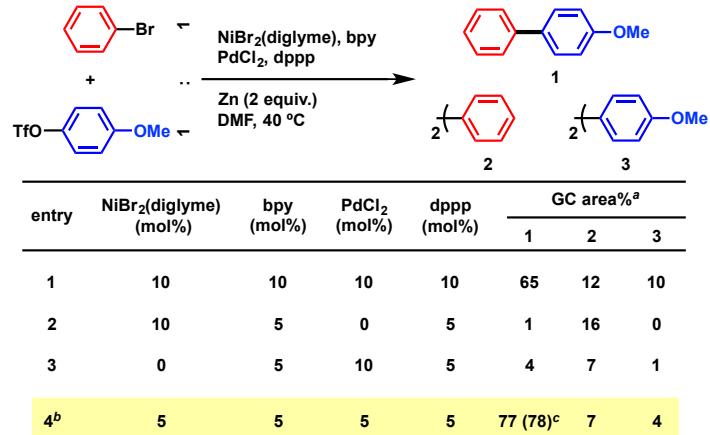
electron negativity
Pd: 2.2 Ni: 1.9

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Ackerman, L. K., Lovell, M. M., Weix, D. J. *Nature*. 2015, 524, 454.

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Cross-Electrophile Coupling of C(sp²) halides



^a Determined by GC. Based on coupling adduct, biaryl, reduced compounds (ArH) and SM.

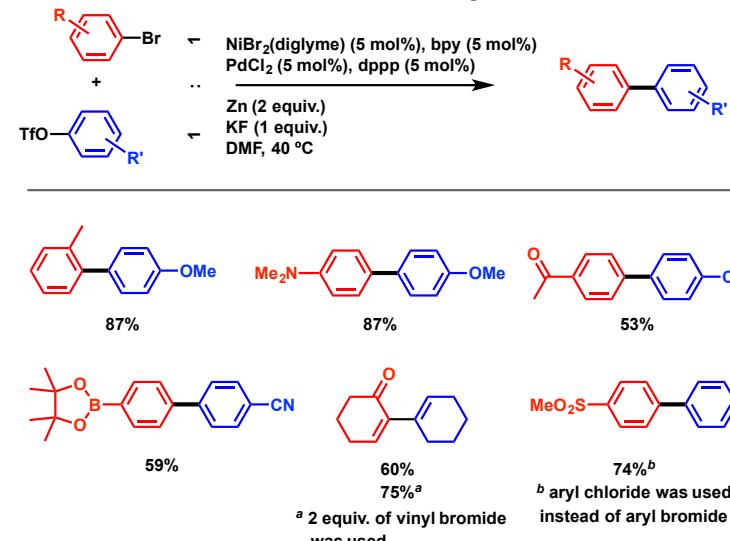
^b KF (1 equiv.) was used as an additive

^c Isolated yield in parenthesis.

Ackerman, L. K., Lovell, M. M., Weix, D. J. *Nature*. 2015, 524, 454.

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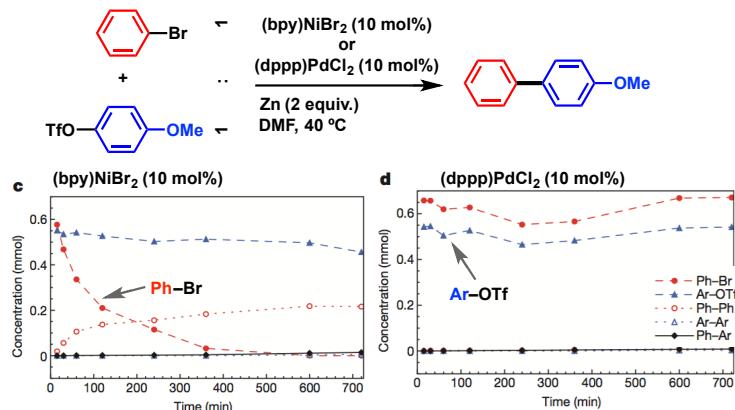
Substrate Scope



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Reactivity of Ni⁰ and Pd⁰ catalyst



*(bpy)Ni⁰ was reacted with aryl bromide selectively. (bpy)Ni^{II}PhBr was unstable under this condition (biphenyl was gradually formed).

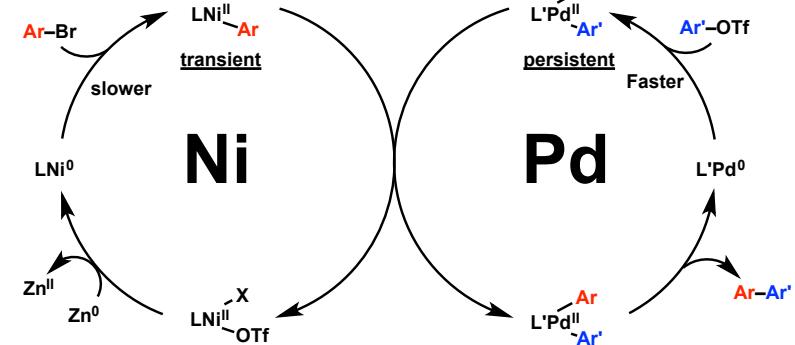
*On the other hand, (dppp)Pd⁰ was reacted with aryltriflate to give relatively stable (dppp)PdArOTf.

*(dppp)Pd⁰ was reacted faster than (bpy)Ni⁰.

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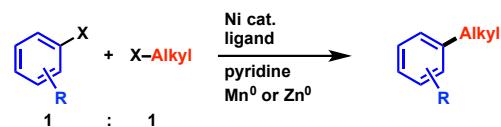
Proposed Catalytic Cycle



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Summary



* Selective oxidative addition to aryl halides
* Selective formation of alkyl radical

Everson, D. A. Shrestha, R. Weix, D. J. J. Am. Chem. Soc. 2010, 132, 920.
Biswas, S. Weix, D. J. J. Am. Chem. Soc. 2013, 135, 16192.



* Selective oxidative addition to aryl bromide
* Faster oxidative addition of palladium to aryl triflate

Ackerman, L. K., Lovell, M. M., Weix, D. J. Nature. 2015, 524, 454.