

Cross-Electrophile Coupling

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20150919

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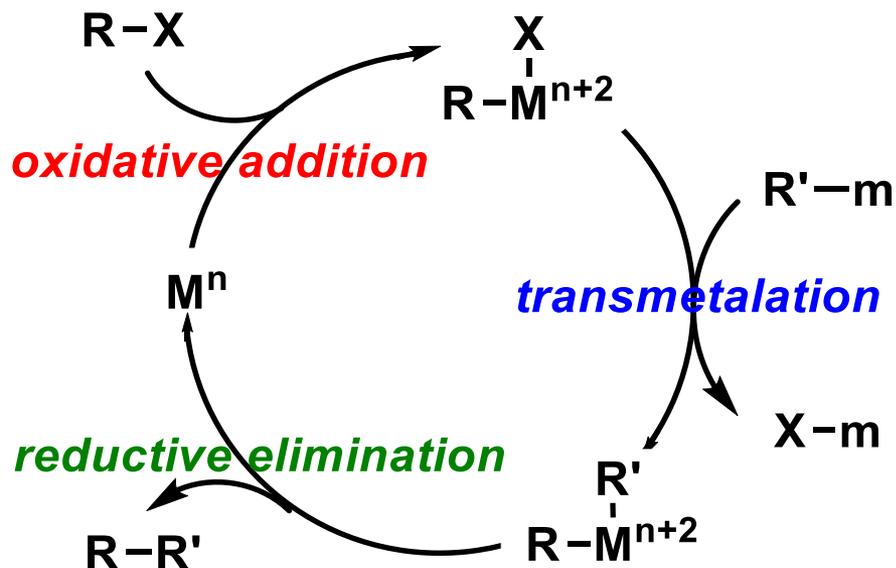
1. *Introduction*

2. *Cross-Electrophile Coupling*

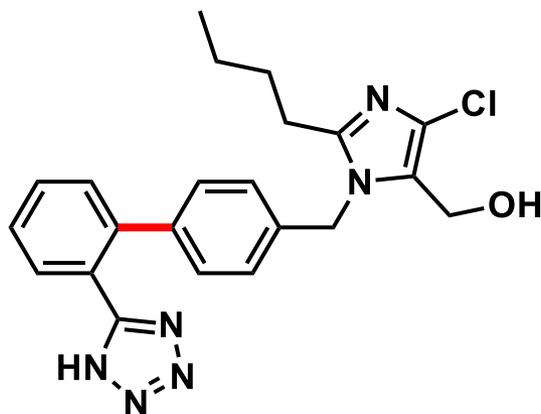
3. *Cross-Electrophile Coupling ~ co-catalyst system*

1. Introduction

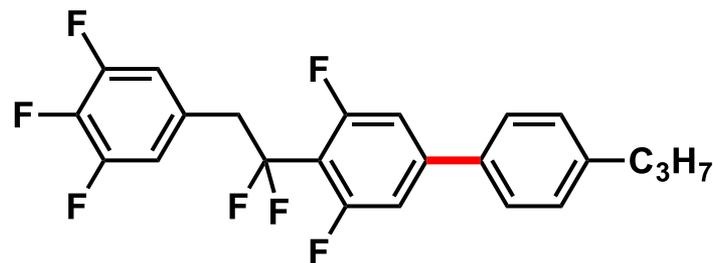
Cross-Coupling



The advent of transition-metal catalyzed strategies for forming new C-C bonds has revolutionized the field of organic chemistry.

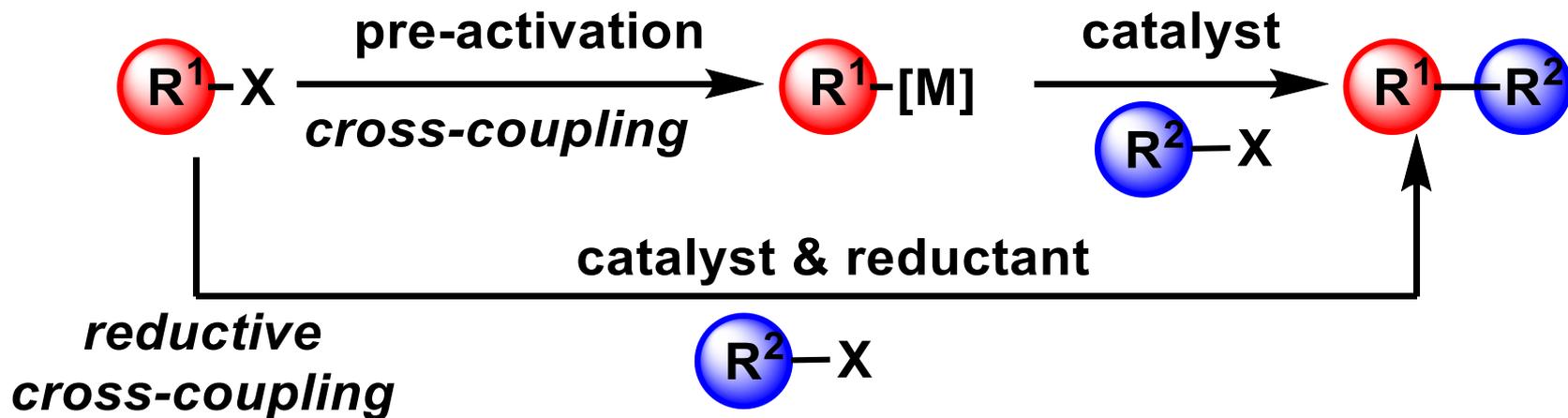


Losartane



Liquid cristal display

Cross-Coupling vs Reductive Cross-Coupling



commercially available (2011)

R-B 5000

R-I 80000

R-Br 700000

demerit of organometallic reagent

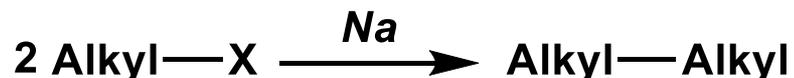
⇒ Special care to exclude oxygen moisture.

⇒ Inherent reactivity (RMgX, RZnX)

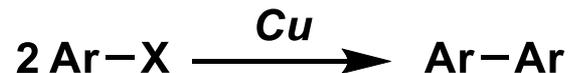
⇒ Basic reagent require to facilitate transmetalation.

Reductive dimerization of electrophiles were known (Wurtz, Ullman), but **general methods have lagged far behind cross-couplings.**

Wurtz coupling



Ullman coupling

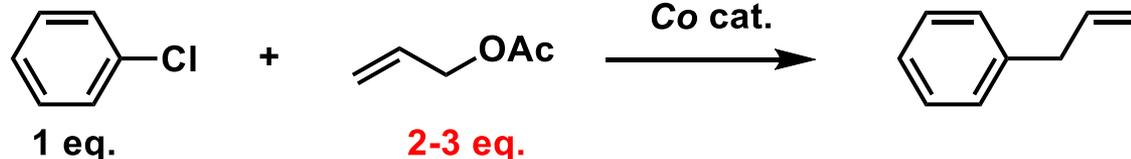


Cross Selectivity-Major Approach-

until now...

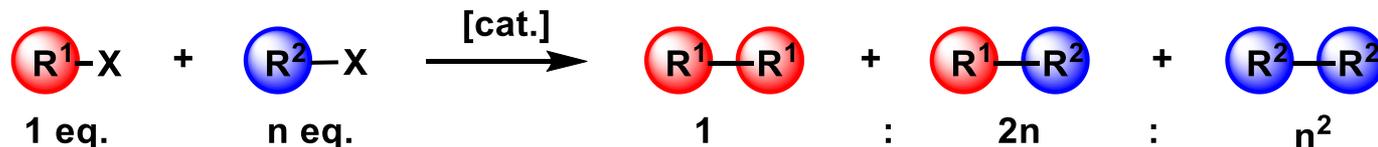
cross selectivity

- 1) a substantial excess of one organic halide
- 2) slow addition of one reactant
- 3) both of 1) and 2)



(C. Gosmini et al. *J. Org. Chem.* 2003, 68, 1142.)

Effects of increasing the equivalents of one substrate on maximum statistical yield and waste.



n = 1 50% maximum statistical yield, 1 : 1 product : dimers

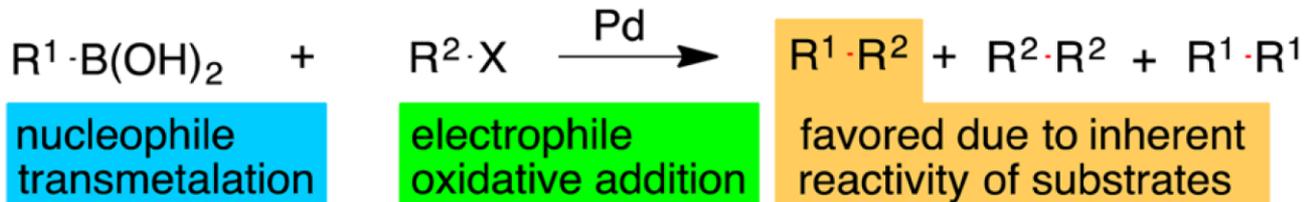
n = 2 80% maximum statistical yield, 1 : 1.25 product : dimers

n = 3 86% maximum statistical yield, 1 : 1.67 product : dimers

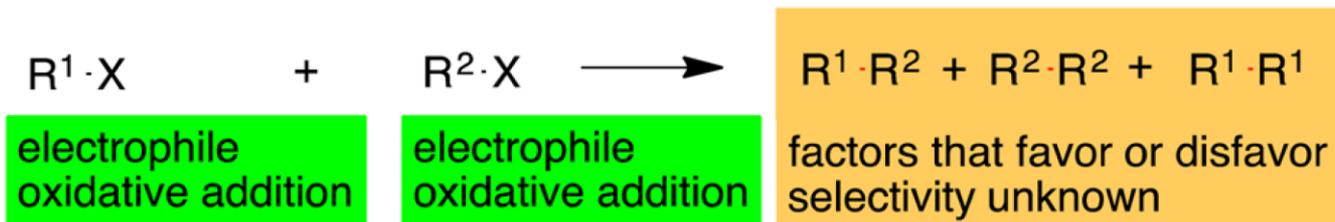


Less wasteful approach is the development of *catalysts* able to differentiate the two electrophilic reagents.

Cross-Coupling of Nucleophiles with Electrophiles



Cross-Electrophile Coupling – *This Work*



Dr. Daniel J. Weix

BA : Columbia University (Thomas Katz)

PhD : UC Berkeley (Jonathan Ellman)

Postdoctoral fellow : Yale University and the University of Illinois (John Hartwig)

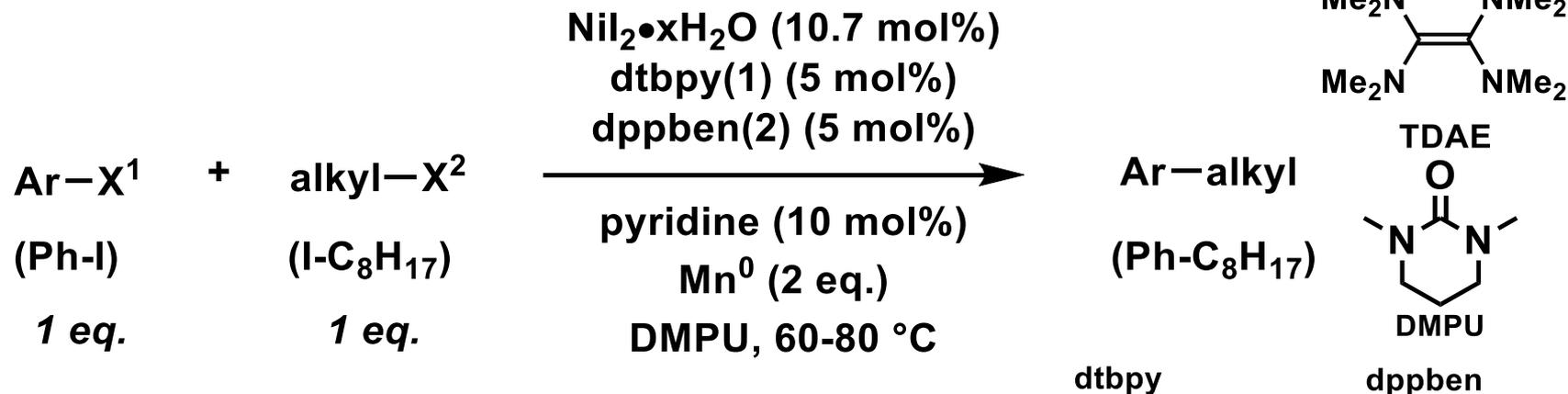
Independent career : the University of Rochester as associate professor (2014)

Research : Cross-electrophile coupling reactions Ni and Co

2. Cross-Electrophile Coupling

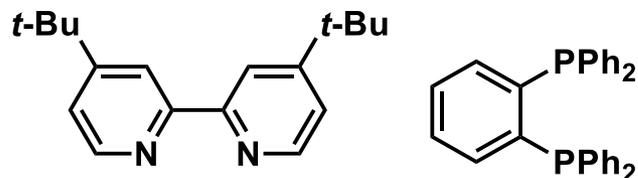
Initial Discovery of The Coupling of Aryl-I with Alkyl-I

Dual-ligand Ni catalyst system



Entry	Deviation from Standard Conditions	Yield (%) ^b
1	none	88
2	10 mol % 1 in place of a mixture of 1 and 2	83
3	10 mol % 2 in place of a mixture of 1 and 2	19
4	5 mol % 1 in place of a mixture of 1 and 2	81
5	no ligands added	6
6	no Mn ⁰ added	<1
7	pyridine omitted	67
8	Br-C ₈ H ₁₇ in place of I-C ₈ H ₁₇	85
9	Br-Ph in place of I-Ph	77
10	Br-C ₈ H ₁₇ and Br-Ph in place of I-C ₈ H ₁₇ and I-Ph	65
11	TDAE in place of Mn ⁰ , 2.5 equiv of I-C ₈ H ₁₇	57

^a Organohalides (0.5 mmol each), 0.054 mmol of NiI₂·xH₂O, 0.025 mmol of **1**, 0.025 mmol of **2**, 0.05 mmol of pyridine, 1 mmol of Mn⁰ powder, and 2 mL of DMPU were heated for up to 24 h. ^b Corrected GC yield.



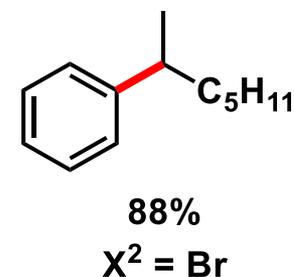
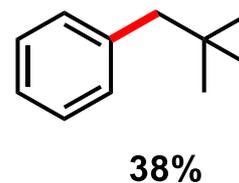
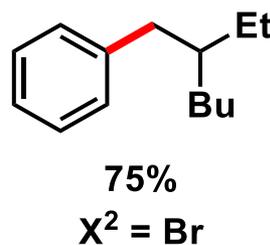
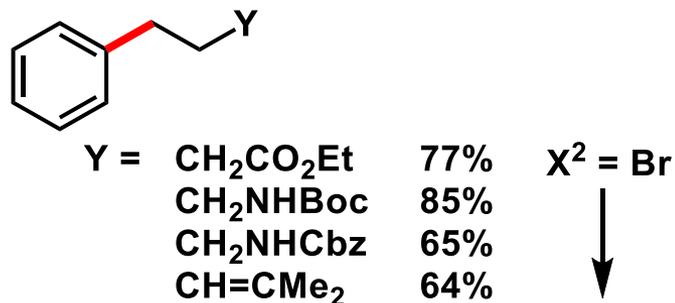
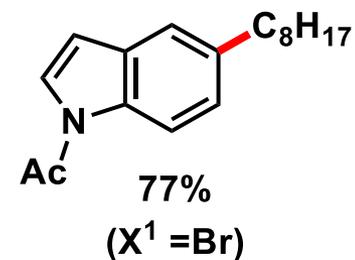
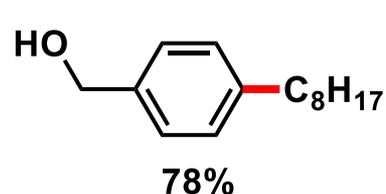
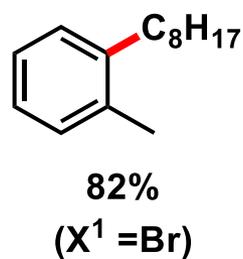
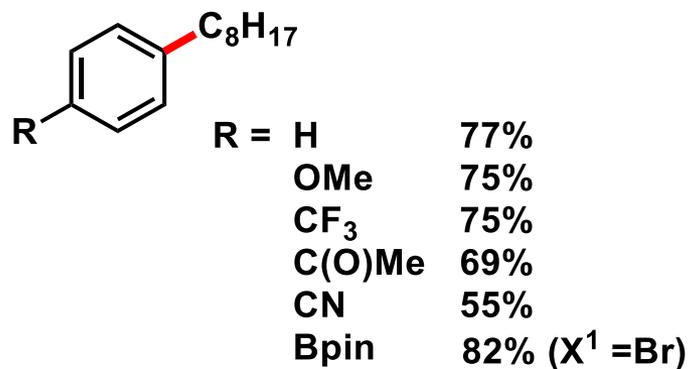
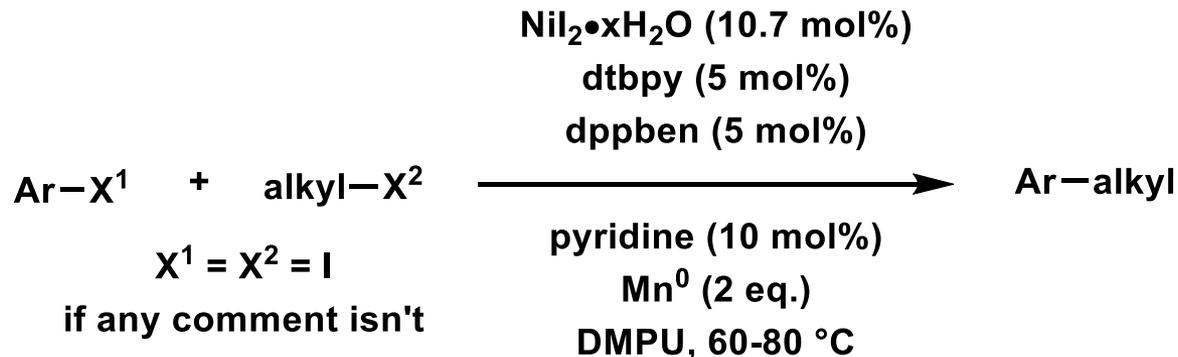
Byproducts...

**Biaryl, β-Hydride Elimination,
Bialkyl, Reduce Arene**

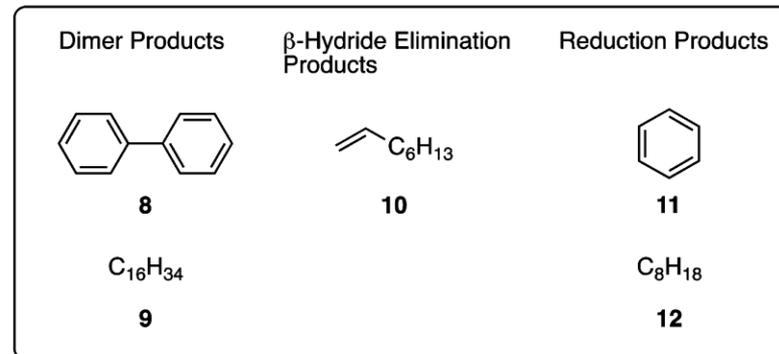
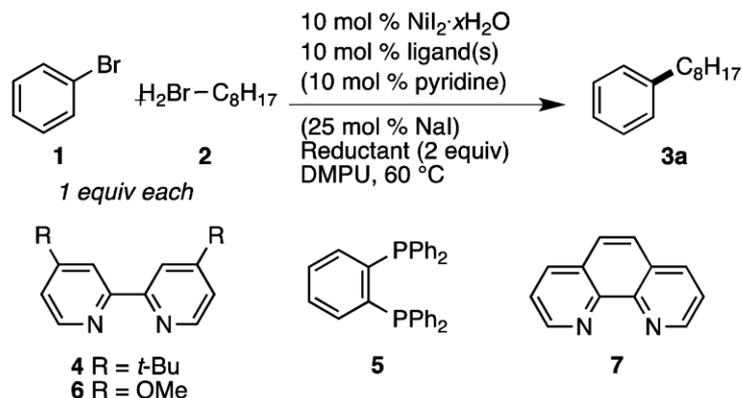
**Dual-ligand system
With Pyridine, fewer products
from β-Hydride elimination**

**Using TDAE as reductant, 57%
(6 turnover number)**

Substrate Scope



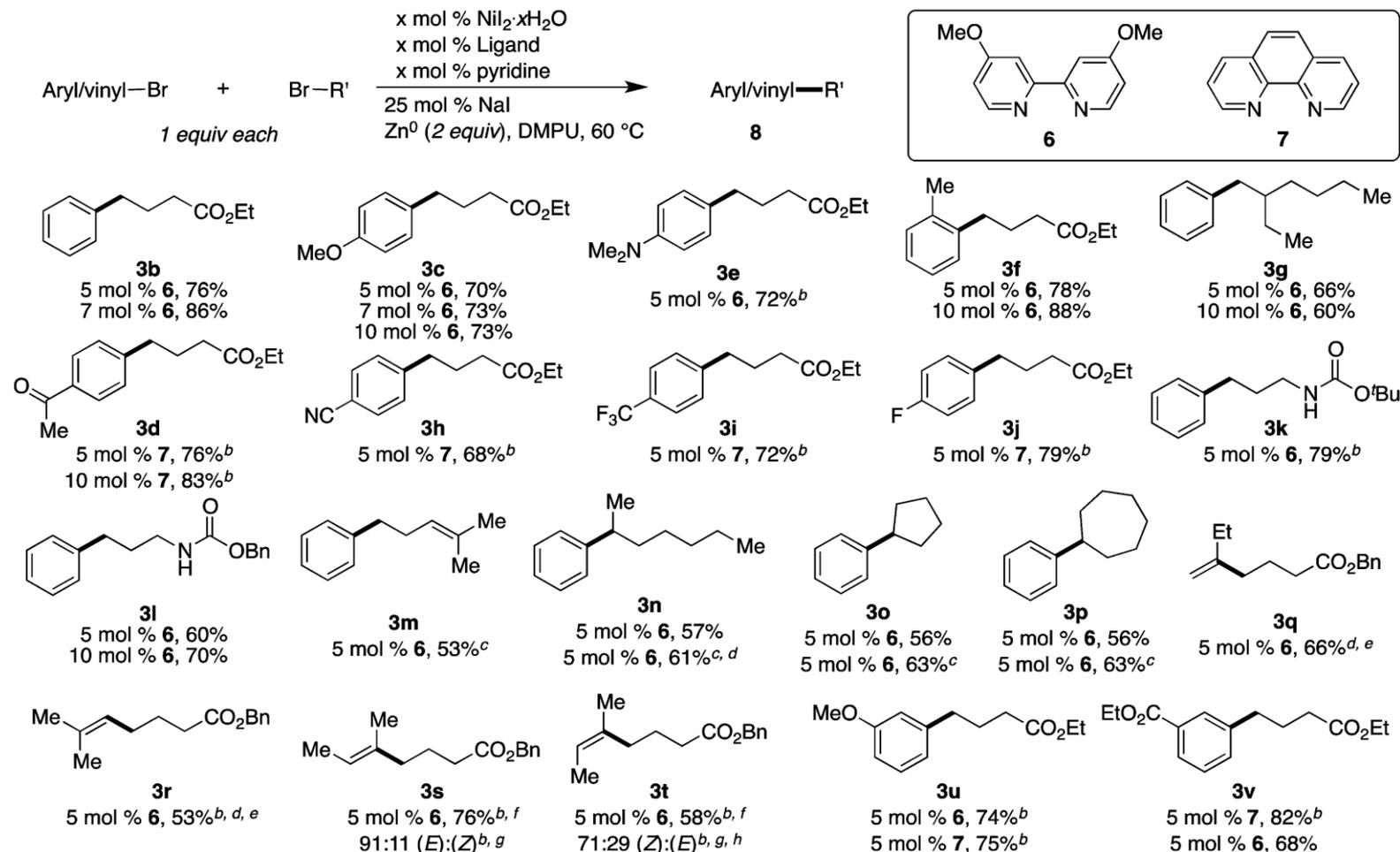
Coupling of Alkyl-Br with Ar-Br or Ar-Cl



entry	ligand	additives	reductant	yield 3a (%) ^b	8 (A%) ^c	9 (A%) ^c	10 (A%) ^c	11 (A%) ^c	12 (A%) ^c
1	4 + 5 ^{d,e}	py	Mn	39	17	13	1	3	0
2	4 + 5	py, NaI	Mn	50	7	11	2	5	3
3	4 + 5	py, NaI	Zn	65	3	2	1	8	8
4	4 ^f	py, NaI	Zn	67	8	3	3	6	5
5	4	py, NaI	Zn	75	2	4	2	10	3
6	6	py, NaI	Zn	77	1	1	1	6	3
7	6	py, NaI	Mn	39	25	15	4	3	4
8	7	py, NaI	Zn	73	2	3	1	3	1
9		py, NaI	Zn	11	0.5	0	0	2	2
10	6 ^g	py, NaI	Zn	NR	0	0	0	0	0
11	6 ^h	py, NaI	Zn	53	7	6	4	8	3
12	6 ⁱ	py, NaI	Zn	49	10	6	6	11	6
13	6	py	Zn	66	2	3	2	6	5
14	6	NaI	Zn	75	3	5	2	3	2
15	6 ^j	py, NaI	Zn	76	2	5	4	5	4
16	6	py, NaI		NR	0	0	0	0	0

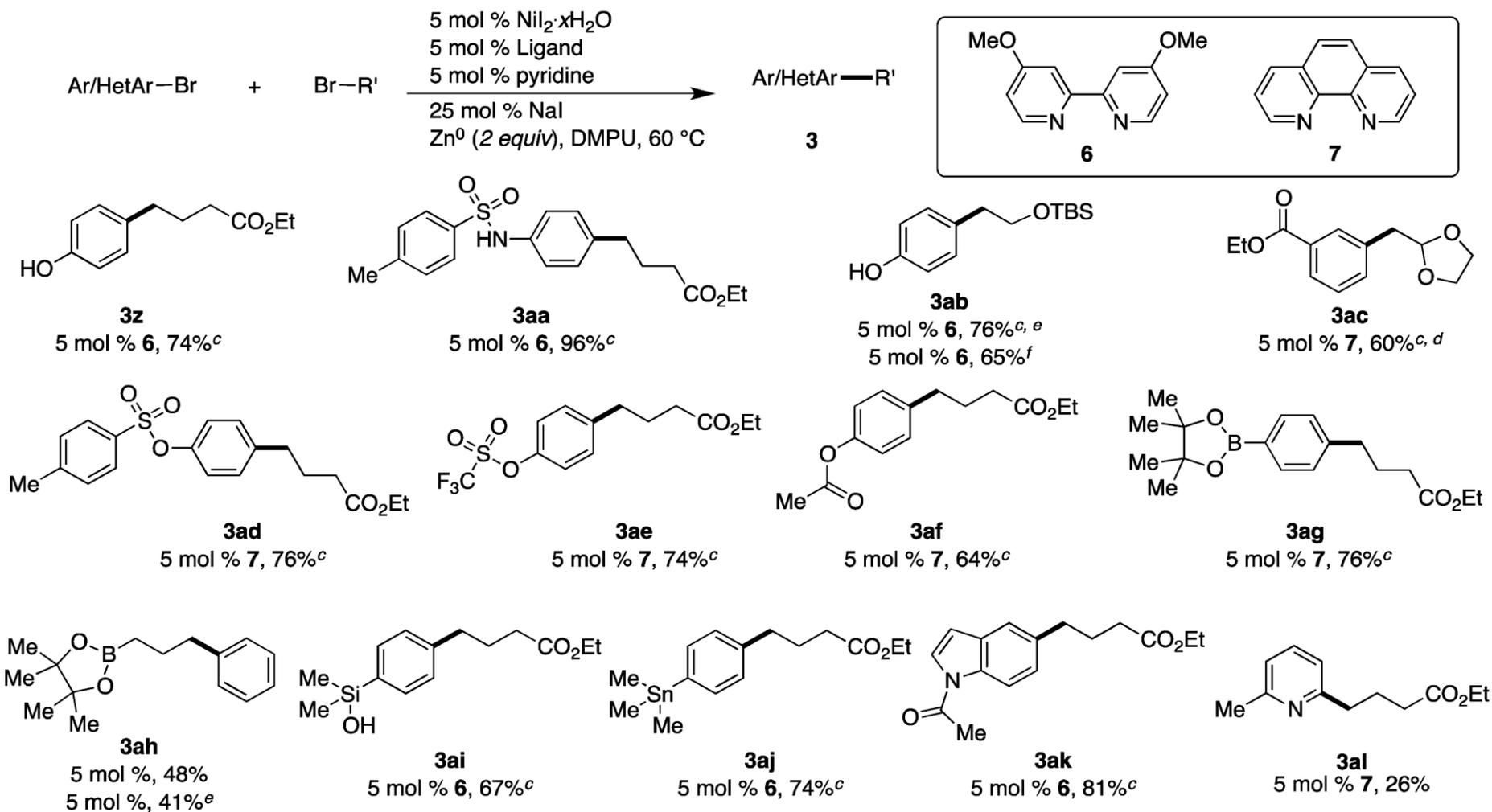
^aReactions were assembled on the benchtop on 0.5 mmol scale in 2 mL of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU). The reaction mixtures were heated for 3.5–36 h, and reaction progress was monitored by GC analysis. See Supporting Information for full details. ^bYield of 3a was determined by GC analysis vs an internal standard and is corrected. ^cThe amounts of these products are area % (A%) data. ^dReaction conducted with 5 mol % 4 and 5 mol % 5. ^eReaction run on 1 mmol scale; yield reported is the isolated yield. ^fReaction run with 5 mol % 4/NiI₂·xH₂O/pyridine. ^gReaction run with no nickel. ^hReaction run at 70 °C. ⁱReaction run at 80 °C. ^jTMSCl and 1,2-dibromoethane (4 μ L each) were added sequentially as the last two reagents to the reaction vial.

Substrate Scope of Aryl and Alkyl Bromides



^aReaction conditions: organic halides (0.75 mmol each), NiI₂·xH₂O (0.054–0.078 mmol), ligand (0.05–0.075 mmol), pyridine (0.05–0.075 mmol), sodium iodide (0.19 mmol), zinc dust (>10 μm, 1.5 mmol), and DMPU (3 mL) were assembled on the bench in a 1 dram vial and heated for 5–41 h under air. Yields are of isolated and purified product. ^bAverage of two runs. ^cUsed 1.25 equiv of alkyl bromide (0.94 mmol). ^dThe 2-bromoheptane contained 11% 3-bromoheptane (NMR). Product **3n** was isolated as an 83:17 ratio of **3n**:heptan-3-ylbenzene (NMR). ^eIsolated as an inseparable mixture with benzyl butyrate; yields determined by NMR analysis of this mixture. ^fIsolated as an inseparable mixture of (E) and (Z) isomers. ^gIsomer ratio determined by NMR analysis. ^hStarting material (2-bromo-2-butene) was an 88:12 ratio of (Z) and (E) isomers.

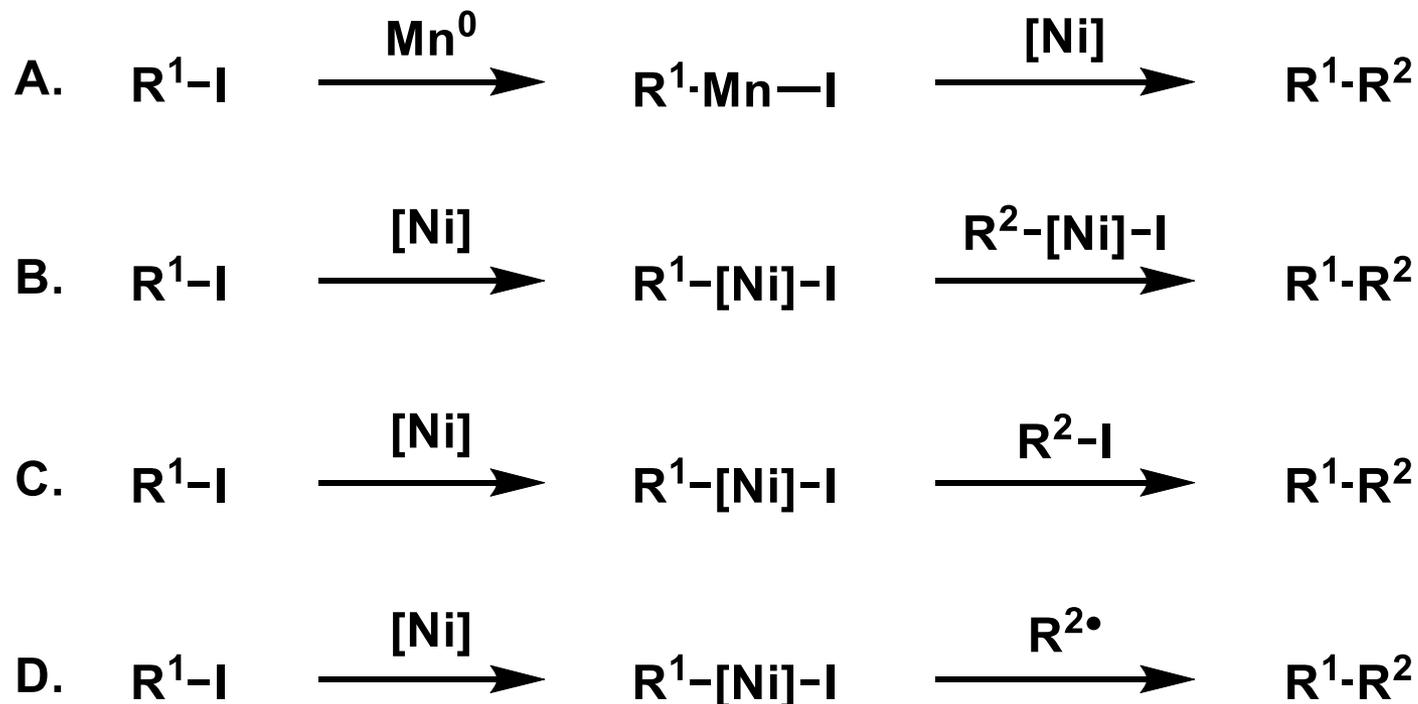
Chemoselectivity and Functional Group Compatibility



^aReaction conditions: organic bromides (0.75 mmol each), NiI₂·xH₂O (0.054 mmol), ligand (0.05 mmol), pyridine (0.05 mmol), sodium iodide (0.19 mmol), zinc dust (>10 μm, 1.5 mmol), and DMPU (3 mL) were assembled on the bench in a 1 dram vial and heated for 3.5–23 h under air.

^bYields are of isolated and purified product. ^cAverage of two runs. ^dRun at 80 °C and with 1 equiv of sodium iodide. ^eRun with 1.25 equiv of alkyl bromide (0.94 mmol). ^fZinc was activated in situ with TMS-Cl and 1,2-dibromoethane (6 μL each).

Potential Mechanisms for Cross-Electrophile Coupling



A) *in situ* formation of an organometallic reagent
followed by cross-coupling

B) transmetalation between two organonickel species

C) sequential oxidative additions at a single nickel center

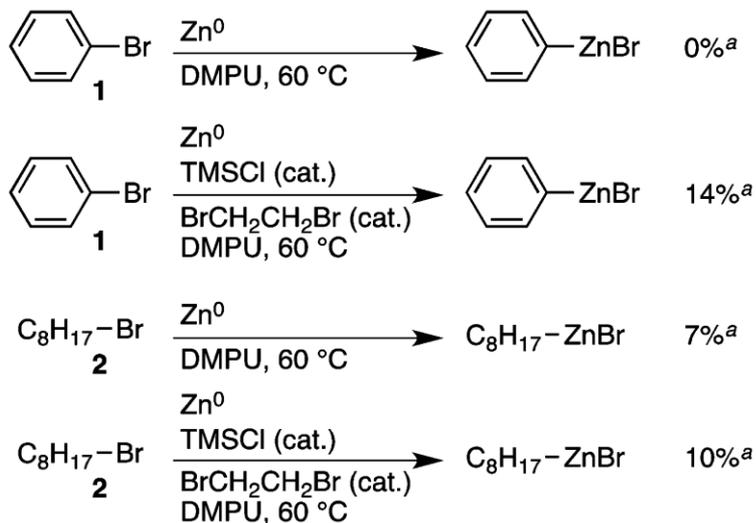
D) radical chain reaction

Mechanism A



A) *in situ* formation of an organometallic reagent followed by cross-coupling

Scheme 6. Direct Insertion of Zinc and Activated Zinc



^aGC yield at 24 h based on unreacted 1 or 2, corrected vs dodecane internal standard.

1) Tolerance of functional groups

2) Direct insertion slower than reductive coupling. (left scheme)

3) Zn to TDAE nonmetallic reducing agent. (6 turnover number)

From above, **A** ⇒ ×

Mechanism B



B)transmetalation between two organonickel species

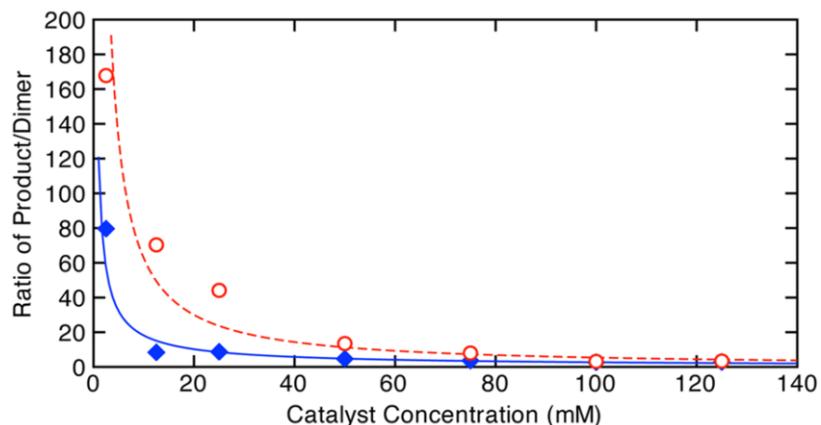
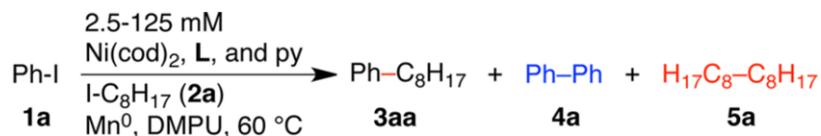


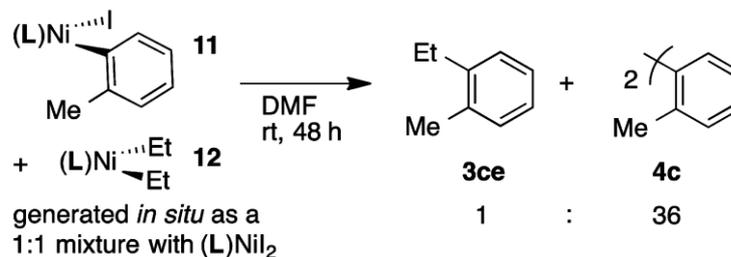
Figure 3. Change of the molar ratio of 3aa/5a (red circles) and 3aa/4a (blue triangles) with catalyst concentration, suggesting product and dimers arise from different mechanisms. Exponential fits: solid blue line, $f(x) = 121.05x^{-0.824}$, $R^2 = 0.94$; dashed red line, $f(x) = 723.81x^{-1.063}$, $R^2 = 0.92$.

B)second-order dependence on Ni concentration

(K. Osakada *et al. Coord. Chem. Rev.* 2000, 198, 379.)

If cross-coupled product was obtained by a similar transmetalation mechanism, $[\text{cross}]/[\text{dimer}] = 1$ (independence on $[\text{Ni}]$).

\Rightarrow cross selectivity at low temperature (above figure)

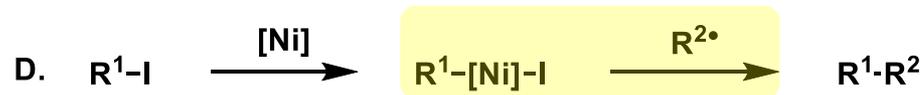
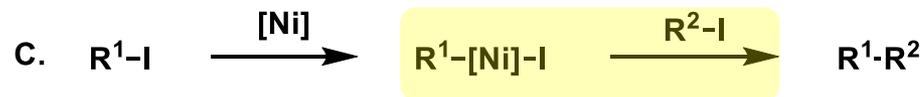


stoichiometric experiment \Rightarrow dimer was obtained mainly.

\Rightarrow B \times

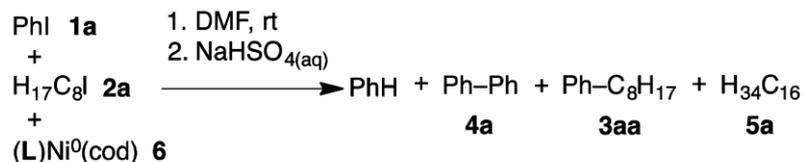
Mechanism C & D~ begin with Ar-Ni-I or Alkyl-Ni-I? ~

Potential mechanisms for cross-electrophile coupling



C) sequential oxidative additions at a single nickel center
D) radical chain reaction

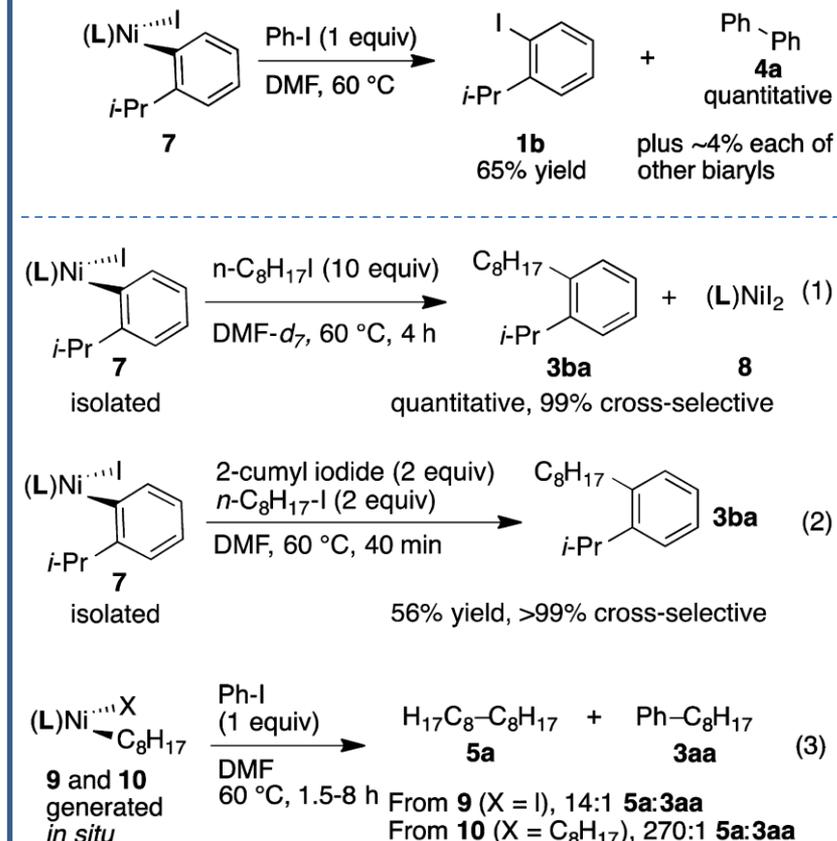
Table 2. Selectivity in Oxidative Addition to $(L)Ni^0(cod)^a$



substrate	total conv (%) ^b	yield (%) ^c			
		alkyl-H or Ph-H	4a	3aa	5a
Ph-I	89	49	21	13	NA
$H_{17}C_8-I$	19	0	NA	51	45

^aA 1:1 mixture of **1a**:**2a** was added to a DMF solution of **6**. Samples were analyzed by GC. Reported values are an average of data using between 2 and 40 equiv each of **1a** and **2a** to **6**. See Supporting Information for full experimental details. ^bConversion with respect to amount of **6**. ^cYield with respect to amount of **6**. NA = not applicable.

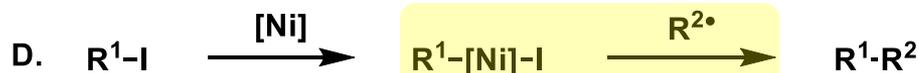
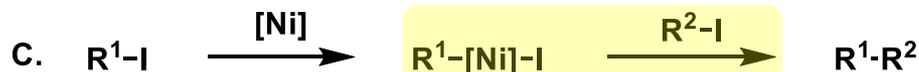
Scheme 2. Apparent Reversibility of Oxidative Addition



These stoichiometric studies
⇒ initial oxidative addition of Ar-I to Ni(0)

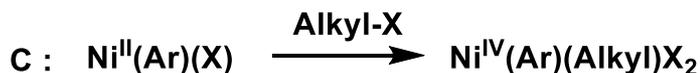
Radical intermediate & Which one is more reasonable C or D?

Potential mechanisms for cross-electrophile coupling



C) sequential oxidative additions at a single nickel center

D) radical chain reaction



1) Oxidative addition may or may not involve an alkyl radical intermediate.

2) The radical would be generated and consumed at **the same nickel center**.



1) must involve a radical intermediate

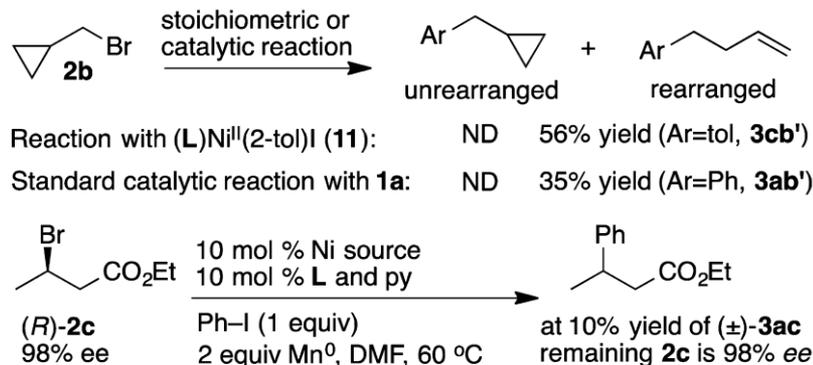
2) The radical is generated and consumed at **different nickel centers**.

from the right Figure, U/R depends on [Ni].

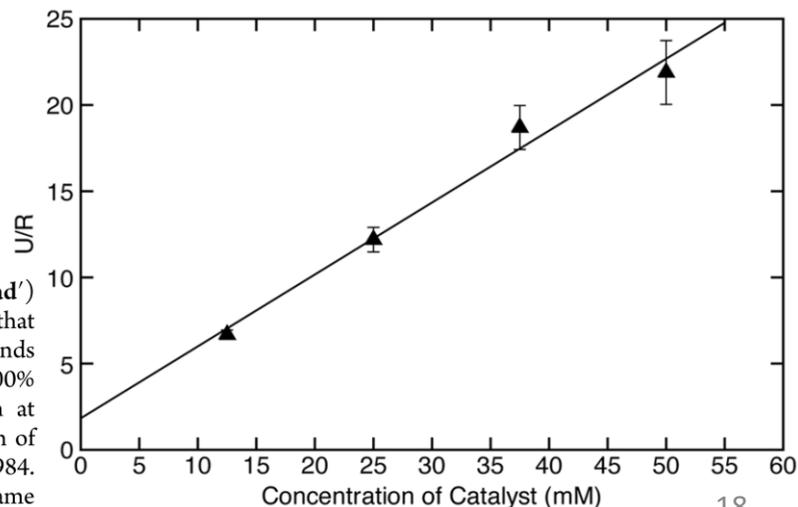
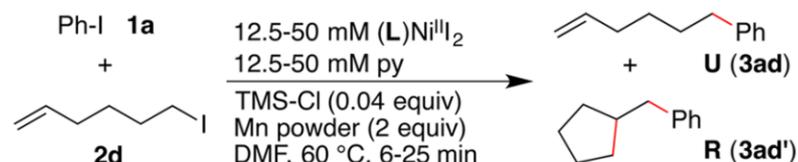
⇒ **D is reasonable**.

Figure 4. Ratio of U (3ad, includes olefin isomers) to R (3ad') formed in reactions at different catalyst concentrations, showing that the degree of rearrangement, a measure of the radical lifetime, depends upon nickel concentration. The data shown are for 50–100% conversion to avoid fluctuations in active catalyst concentration at the beginning of the reaction. Error bars are the standard deviation of the data used for the plot. Linear fit: $f(x) = 0.417x + 1.83$; $R^2 = 0.984$. The same experiment run with unactivated Mn gave the same conclusion, but the reactions had longer induction periods (Figure S2).

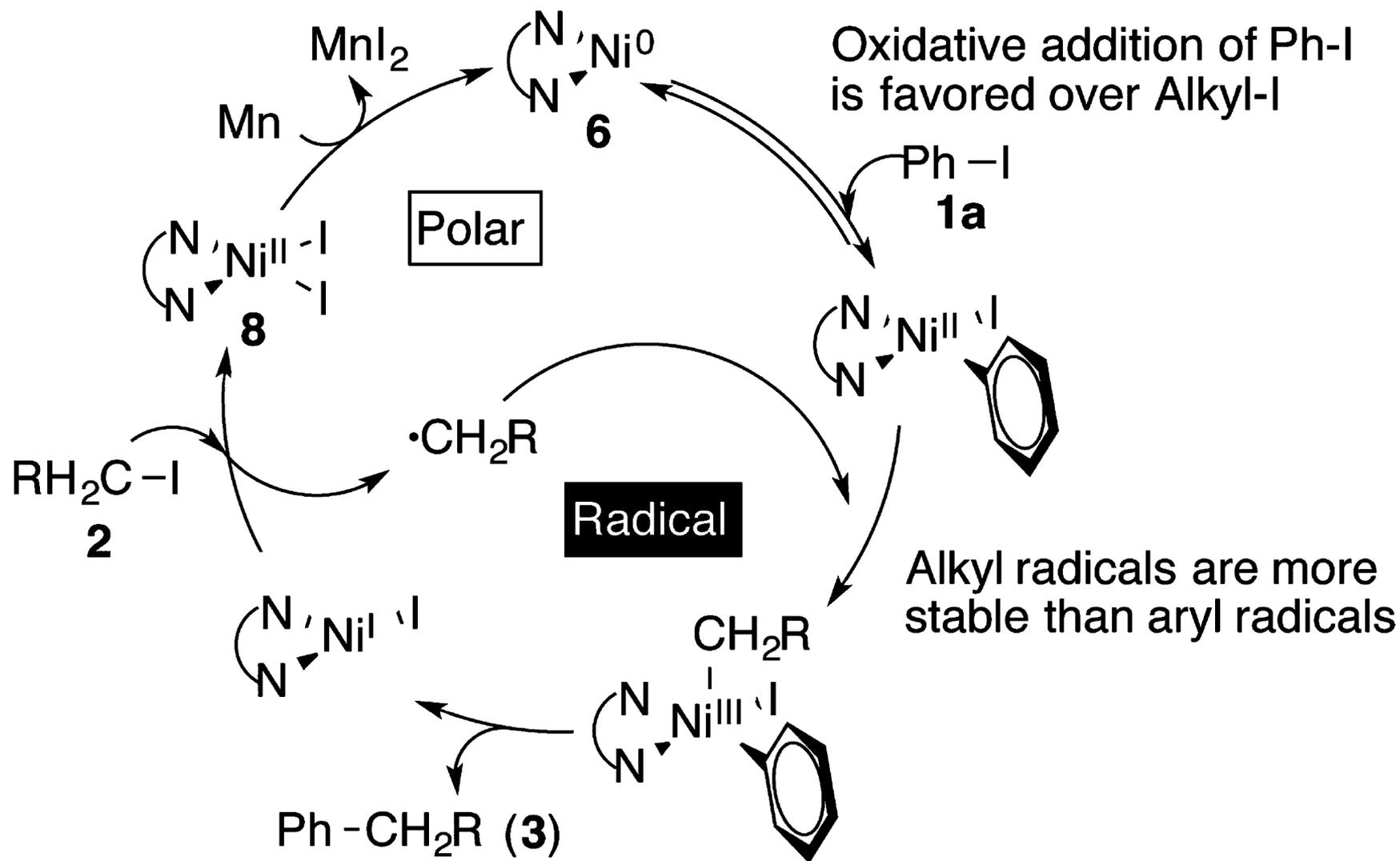
Scheme 3. Radical Clock Experiments^a



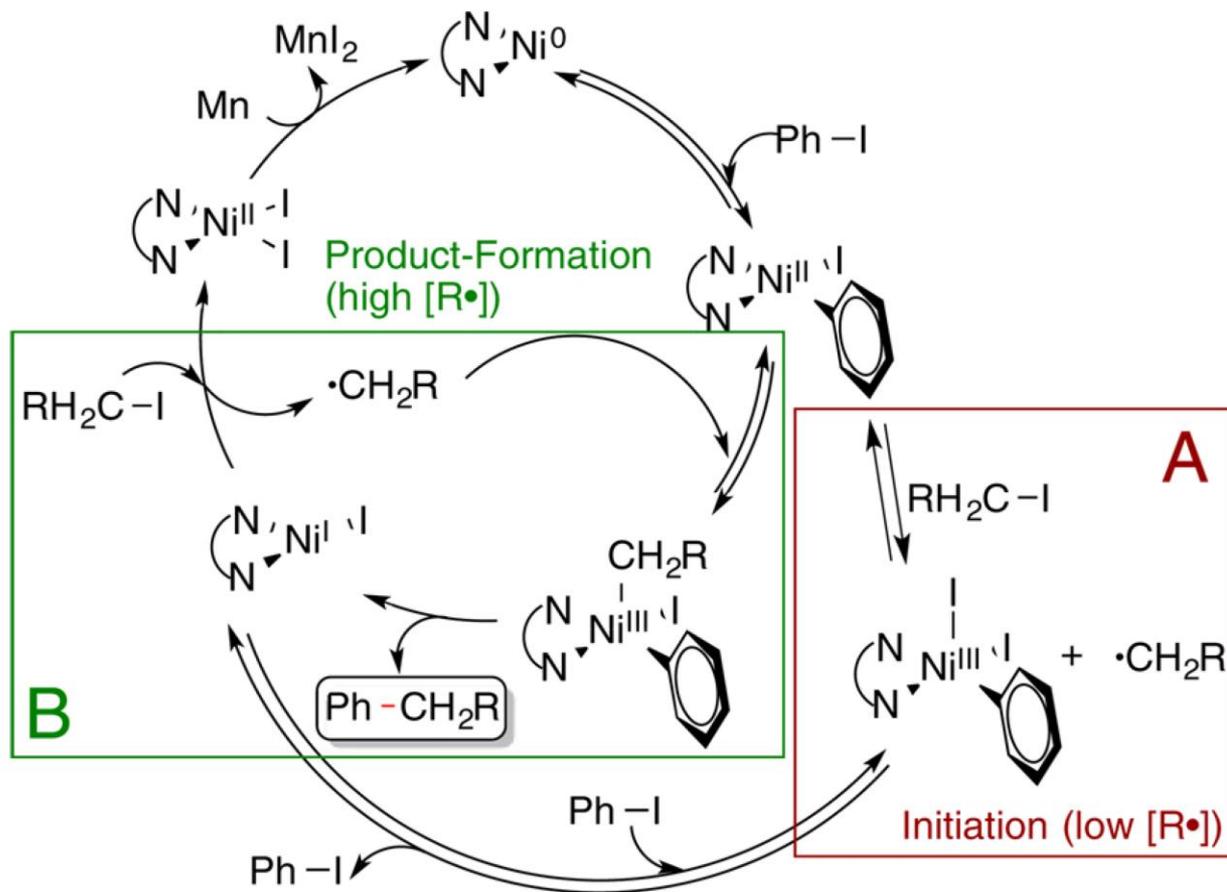
^aND = none detected. Catalytic reaction as in Table 1, entry 1.



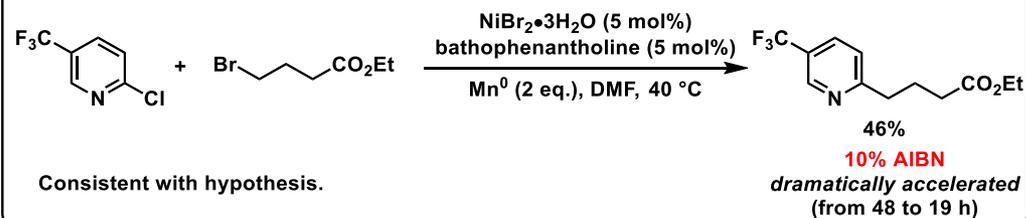
Proposed Mechanism



Hypothesis for Self-Initiation

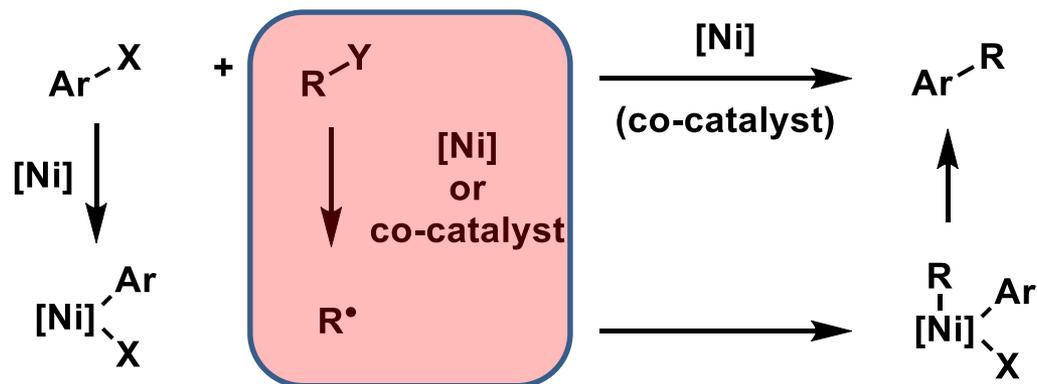


cf) Weix, *Synlett*, 2014, 25, 233.



3. Co-Catalyst System

Co-Catalyst System



	Mechanism	R-Y	Co-catalyst	R•	Group
1	SET halogen abstraction	Alkyl-X	$\xrightarrow{[Ni^I]}$	Alkyl•	Weix, Ni ^I /Ni ^{III} , 2013
2	photoredox SET oxidation	Ar-N ₂ ⁺	$\xrightarrow[h\nu, +e^-]{Ru(bpy)_3Cl_2}$	Ar•	Sanford, Pd/Ru, 2011
3	photoredox SET reduction	Bn-BF ₃ K Ar-NMe ₂ Alkyl-CO ₂ ⁻	$\xrightarrow[h\nu, -e^-]{Ir(F-bpy)_2(bpy)PF_6}$	Bn• ArN(Me)CH ₂ • Alkyl•	Molander, Ni/Ir, 2014 Doyle and Macmillan, Ni/Ir, 2014
4	SET reductive ring opening		$\xrightarrow{Cp_2Ti^{III}Cl}$		Weix, Ni/Ti, 2014
5	SN ₂ followed by homolysis	Bn-OMs	$\xrightarrow{Co^I(Pc)}$	Bn•	Weix, Ni/Co, 2015

Nickel-Catalyzed Regiodivergent Opening of Epoxides with Aryl Halides: Co-Catalysis Controls Regioselectivity

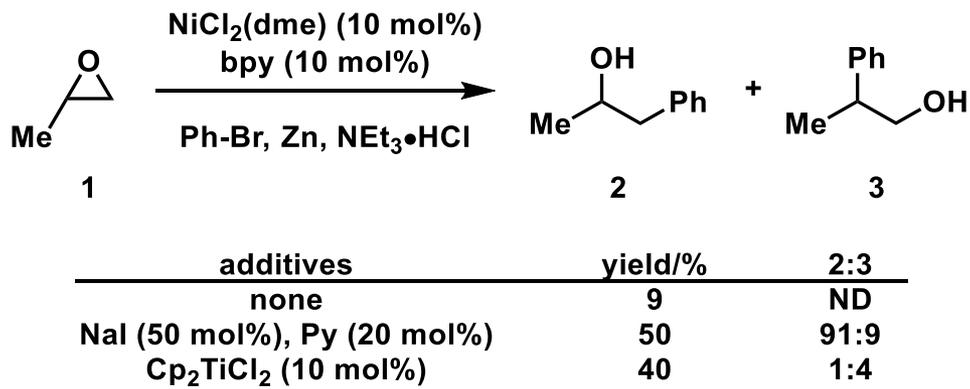
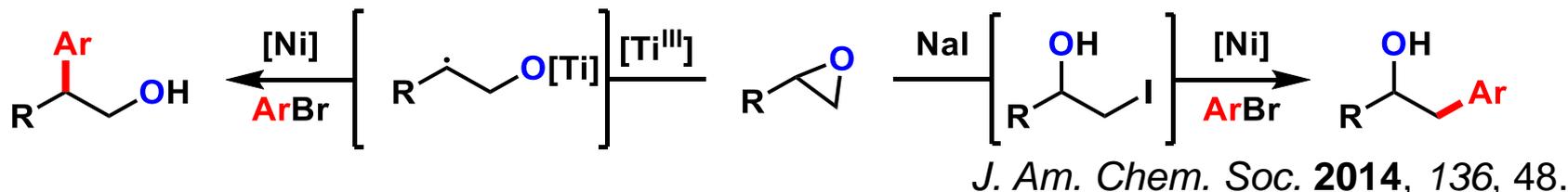


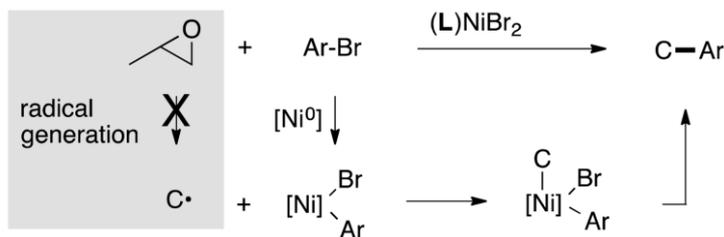
Table 2. Nickel/Iodide Co-catalyzed Epoxide Ring-Opening with Aryl Halides^a



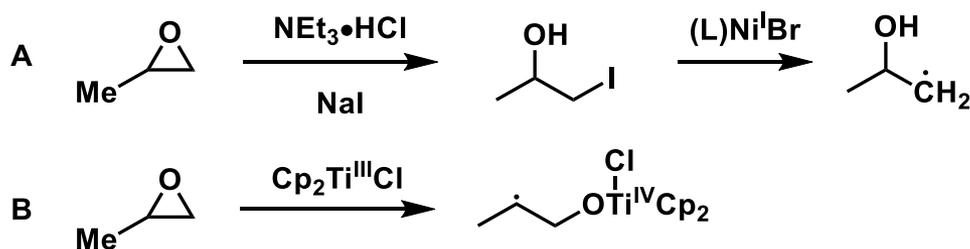
entry	deviation from above	yield (%) ^b	2:3
1	none	81	>95:5
2	no TEA·HCl	32	89:11
3	15 mol % NaI	67	>95:5
4	25 mol % Bu ₄ NI in place of NaI	79	95:5
5	12.5 mol % ZnI ₂ in place of NaI	46	88:12
6	12.5 mol % MnI ₂ in place of NaI	61	95:5
7	no NaI, 12 h	68	>95:5
8	no NaI, 24 h	75	>95:5
9	25 mol % NaBr in place of NaI	52	>95:5
12	NiI ₂ in place of NiI ₂ ·xH ₂ O	86	>95:5
13	2 equiv of Mn in place of Zn	59	95:5
14 ^c	2 equiv of TDAE in place of Zn	48 ^d	>95:5
15	heated to 60 °C for 12 h	50	93:7
16	I-Ph in place of Br-Ph	51	91:9

^aReactions were run with 1 equiv of Et₃N·HCl and 2 equiv of zinc dust; 0.1 equiv nickel catalyst, ligand; 0.2 equiv pyridine, 0.25 equiv sodium iodide, and 1.34 equiv of **1a** in 3 mL DMPU. ^bUncorrected GC yield of **2aa**. ^cTDAE = tetrakis(dimethylamino)ethylene. ^dBromo-benzene (52%) remained, but no biaryl or benzene was formed.

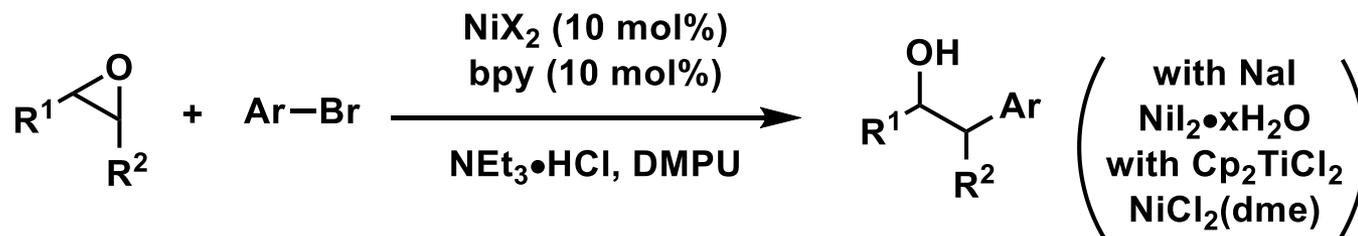
Problematic Point



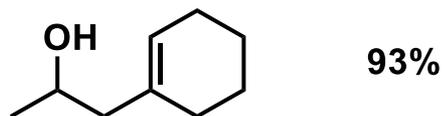
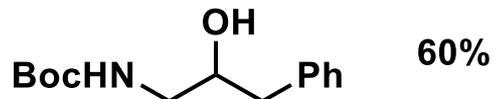
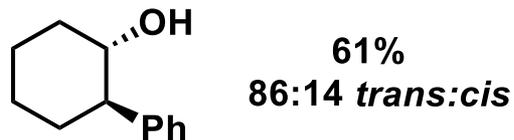
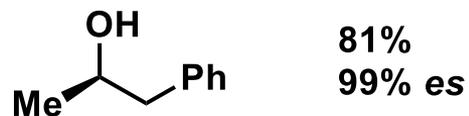
Solutions



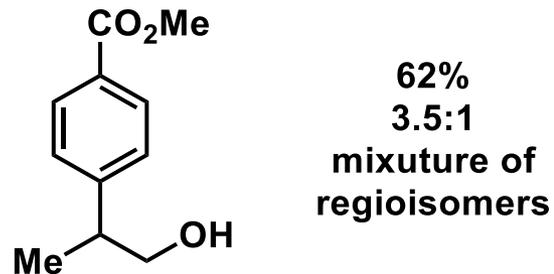
Substrate Scope



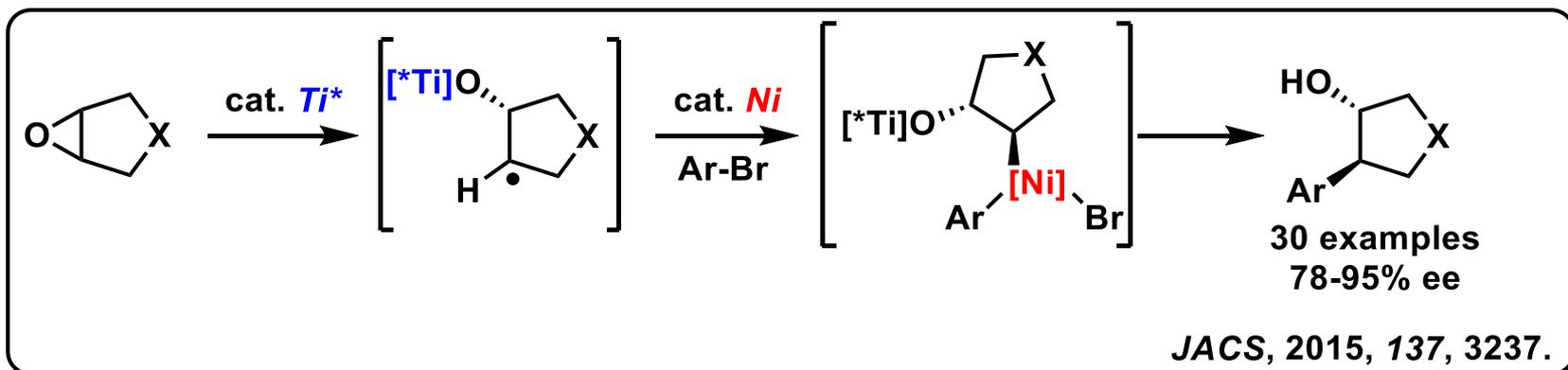
with NaI, Py, and Zn^0



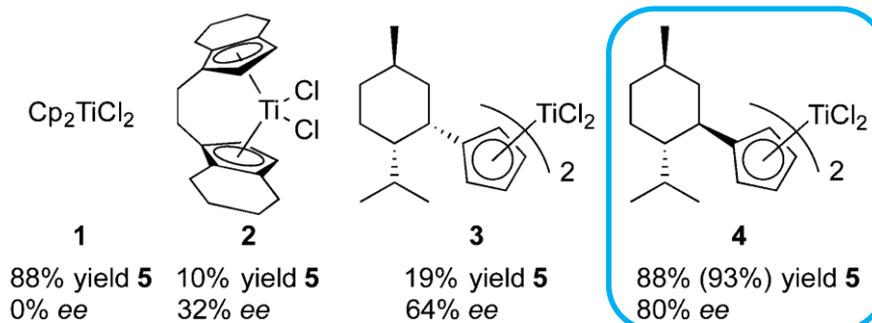
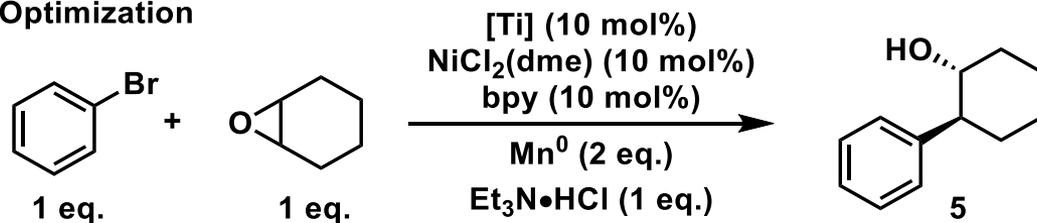
with Cp_2TiCl_2 and Mn^0



Enantioselective Arylation of *meso*-Epoxides

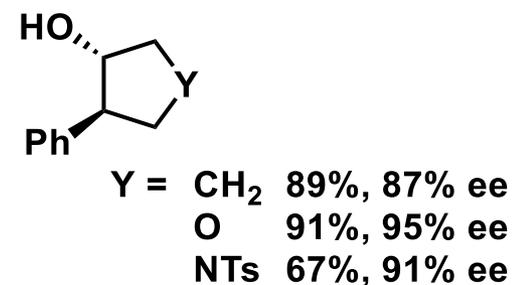
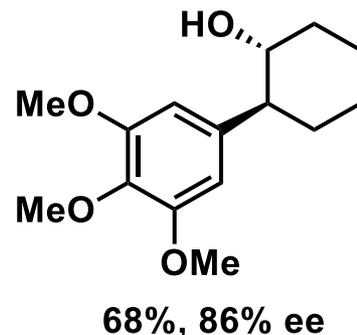
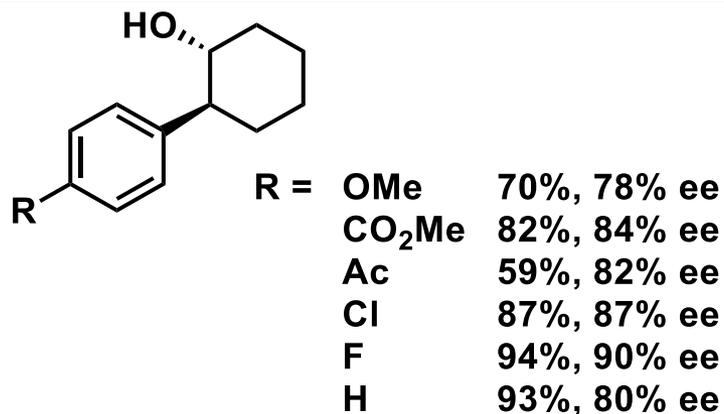
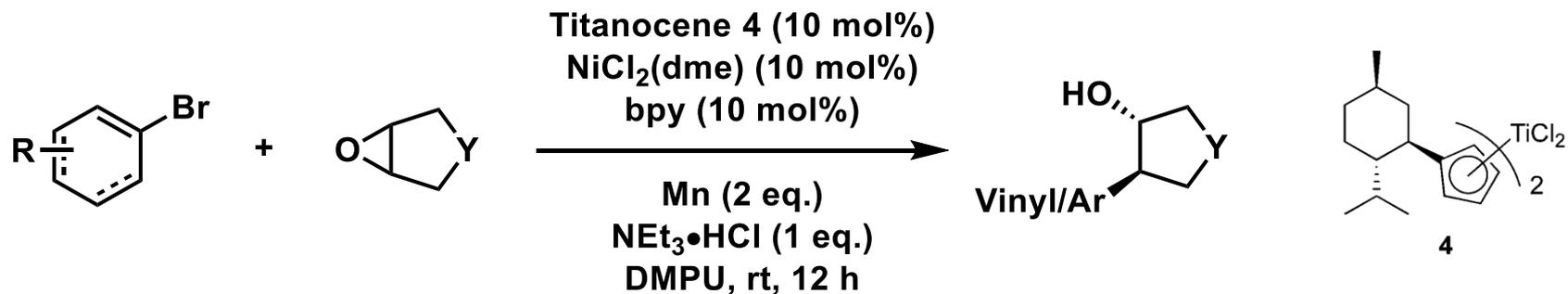


Optimization

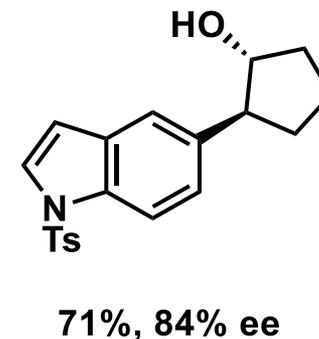
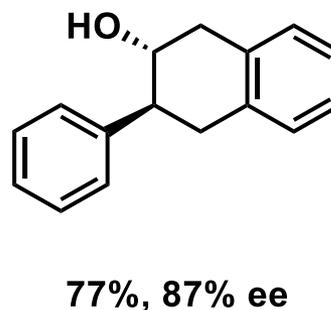
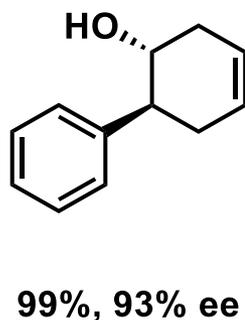
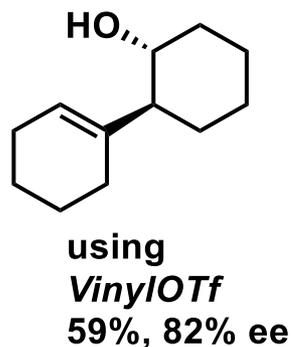


^aReactions were run with 1.0:2.0:0.1:0.1:0.1 Et₃N·HCl/Mn⁰/titanocene/NiCl₂(dme)/bipyridine in DMPU with stirring for 12 h at rt. Assay yields (GC area %) are shown, with an isolated yield in parentheses. Enantiomeric excesses were determined by chiral-phase GC or SFC analysis.

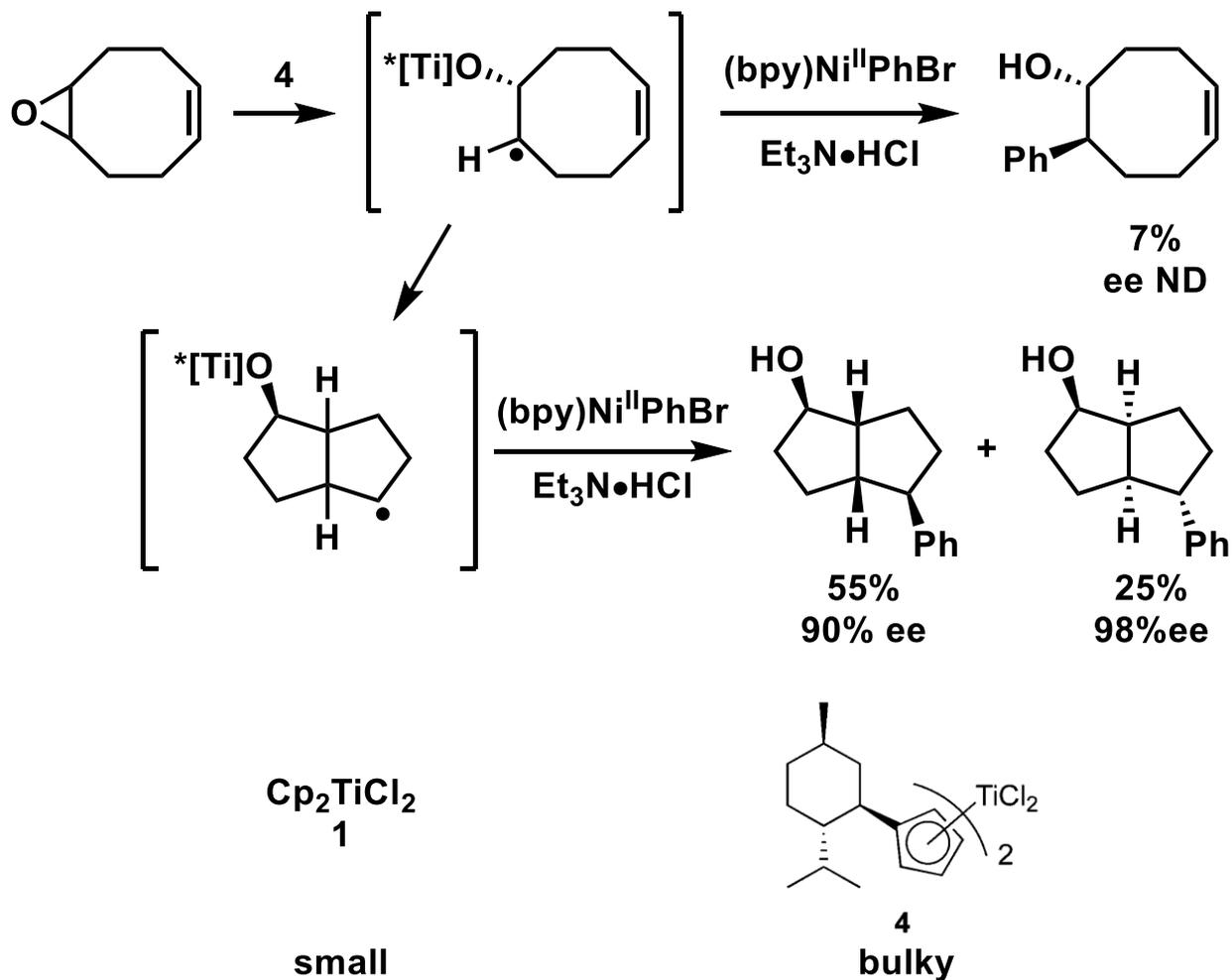
Substrate Scope



ortho-substituted... didn't work well.



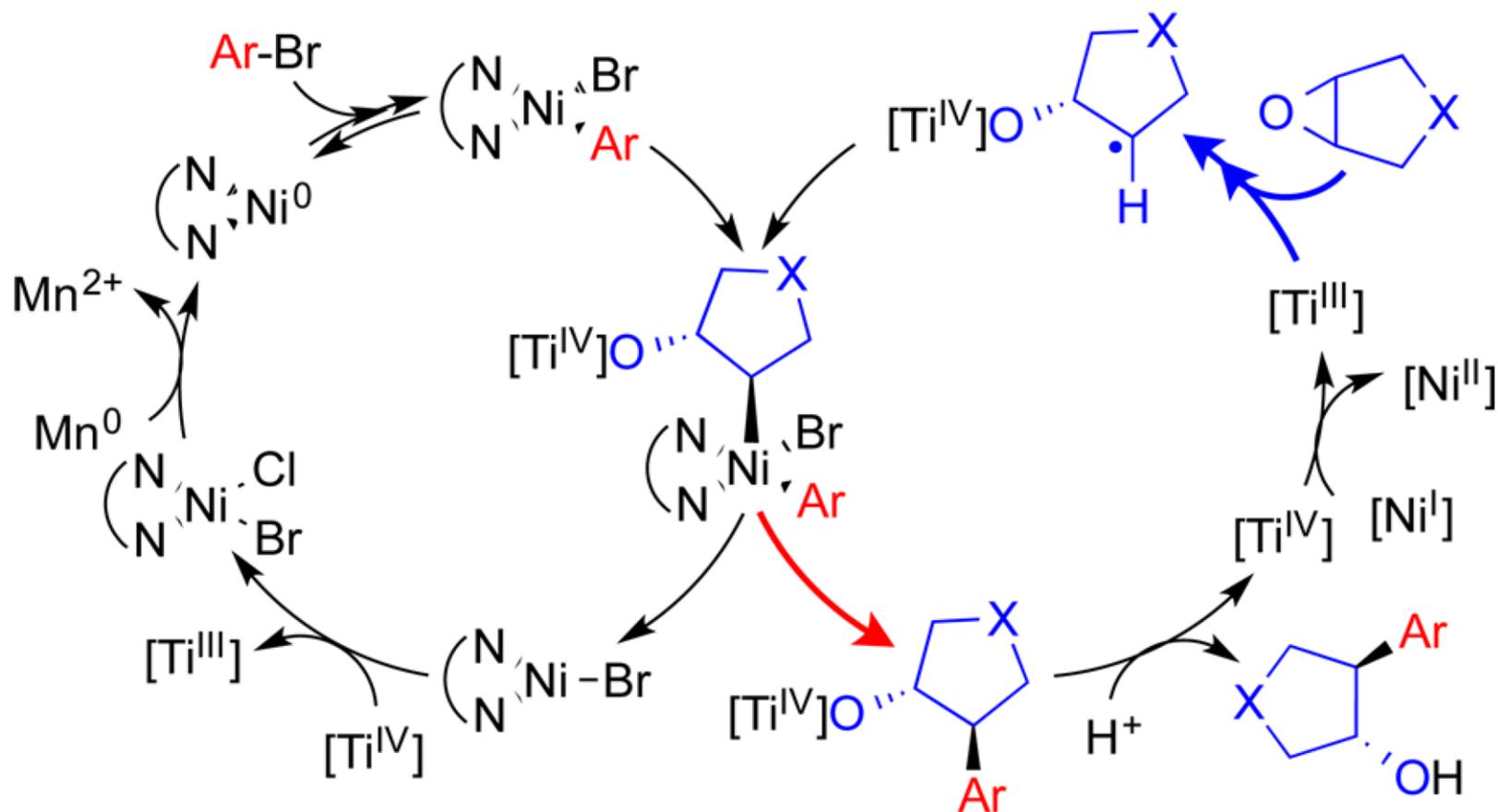
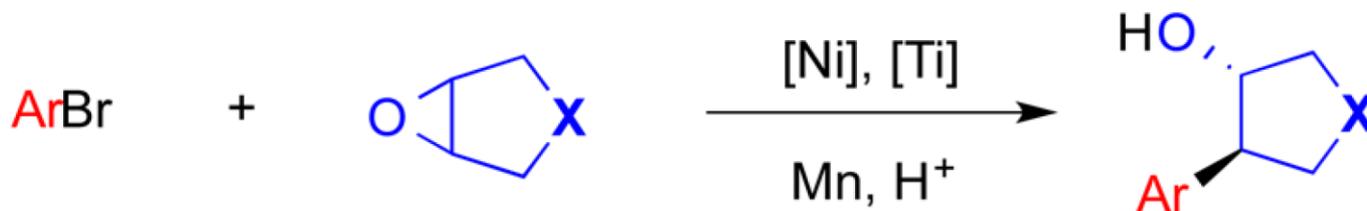
Formation of [3, 3, 0]Bicycoocatanol Products



With the smaller titanocene dichloride 1, *only rearranged product* was formed.

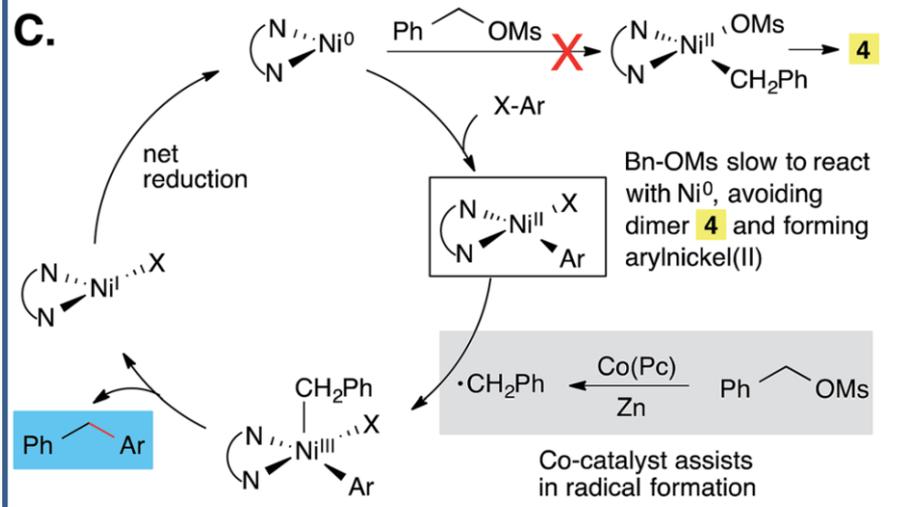
⇒ The coupling of the β -titanoxy radical with an arylnickel intermediate is slowed by steric interactions.

Proposed Catalytic Cycle

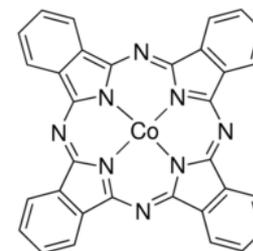


Solution & Optimization

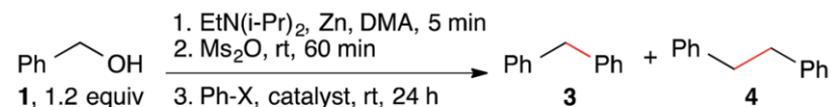
Mechanism based solution



Ar-I was also employed as coupling partners. Added NaI depressed the yield only slightly. (13, 9) \Rightarrow PhI competes with in situ formed BnI more effectively than PhBr for oxidative addition to nickel.



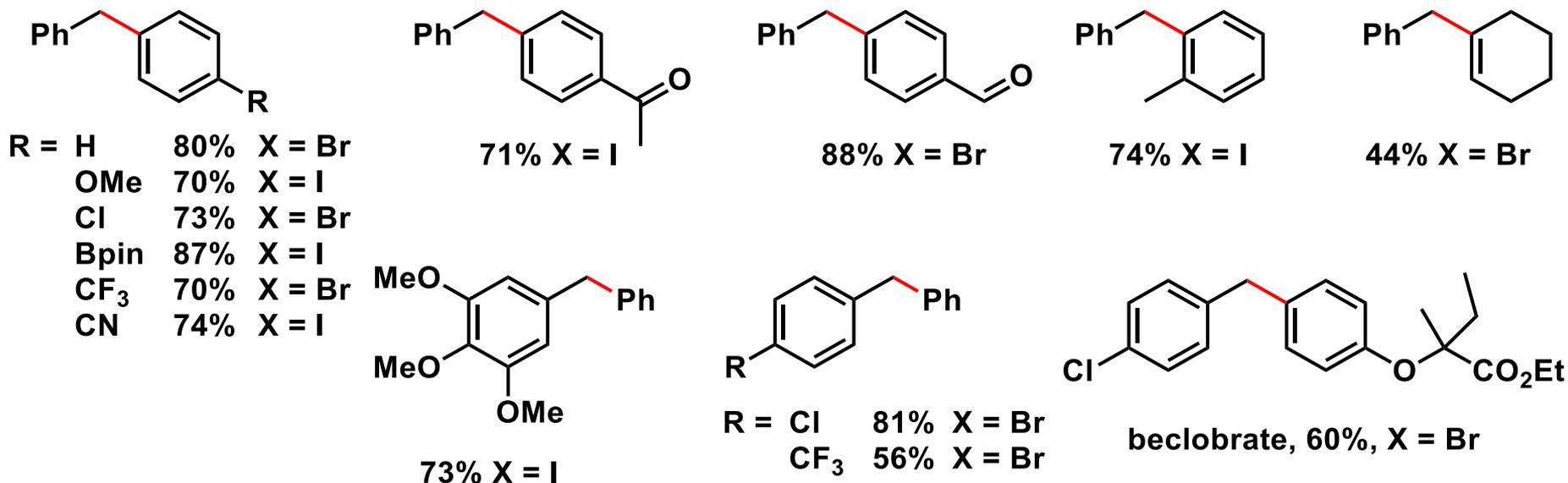
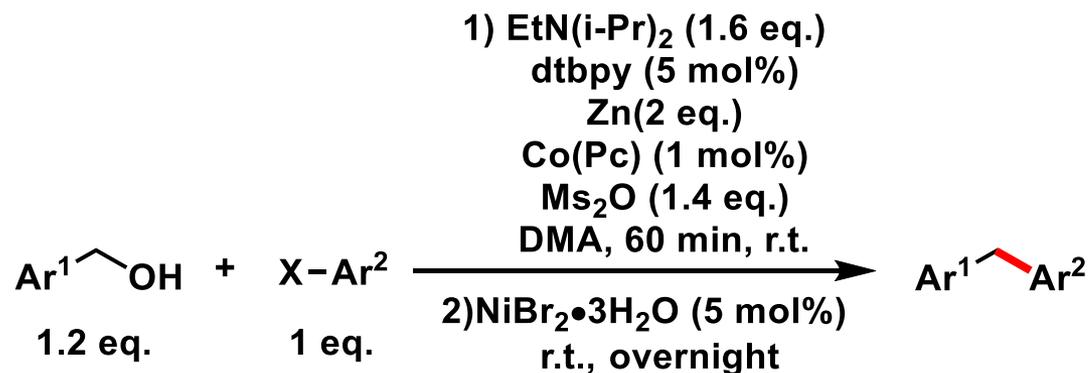
Κορσι(II) βιμψιολανθιμ (Co(Pc))



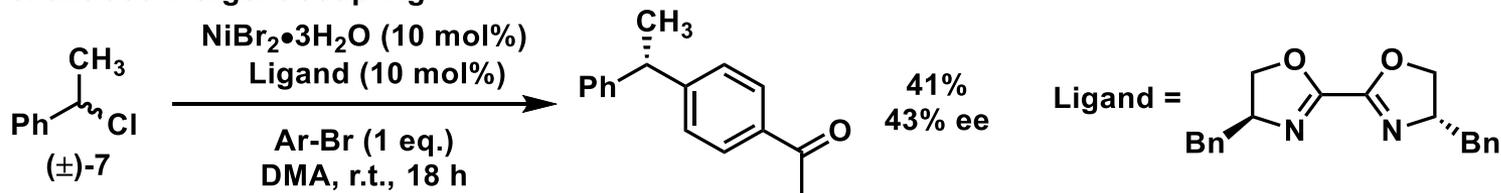
Entry	X	Catalyst ^b	Yield 3 ^c (A%)	3 : 4
1	Br	[Ni] only	3	1 : 1
2	Br	Co(Pc) only	0	ND : 3
3	Br	[Ni], Co(Pc)	73	1 : ND
4	Br	[Ni], CoCl ₂	4	4 : 1
5	Br	[Ni], NaI (25 mol%)	25	1 : 1
6	Br	[Ni], Co(Pc), Mn instead of Zn	64	4 : 1
7	Br	NiBr ₂ ·3H ₂ O, Co(Pc)	1	1 : 6
8	Br	No [Ni] and no Co(Pc)	0	0 : 1
9 ^{d,e}	I	[Ni] only	71	7 : 1
10 ^e	I	Co(Pc) only	0	ND : 1
11 ^{d,e}	I	[Ni], Co(Pc)	83	17 : 1
12	I	[Ni], Co(Pc)	83	83 : 1
13	I	[Ni], NaI (25 mol%)	64	8 : 1
14	I	[Ni], Co(Pc), Mn instead of Zn	42	1.4 : 1

^a Reactions run at 0.25 M in DMA. BnOMs was formed *in situ* from BnOH, Ms₂O (1.44 equiv.), and EtN(i-Pr)₂ (1.6 equiv.). See ESI. ^b [Ni] = 7 mol% NiBr₂·3H₂O and 5 mol% dtbbpy.¹⁹ Co(Pc) = 1 mol% cobalt phthalocyanine. ^c Yields and ratios reported as GC area%. ^d Reaction run at 60 °C. ^e Reaction complete within 1 h.

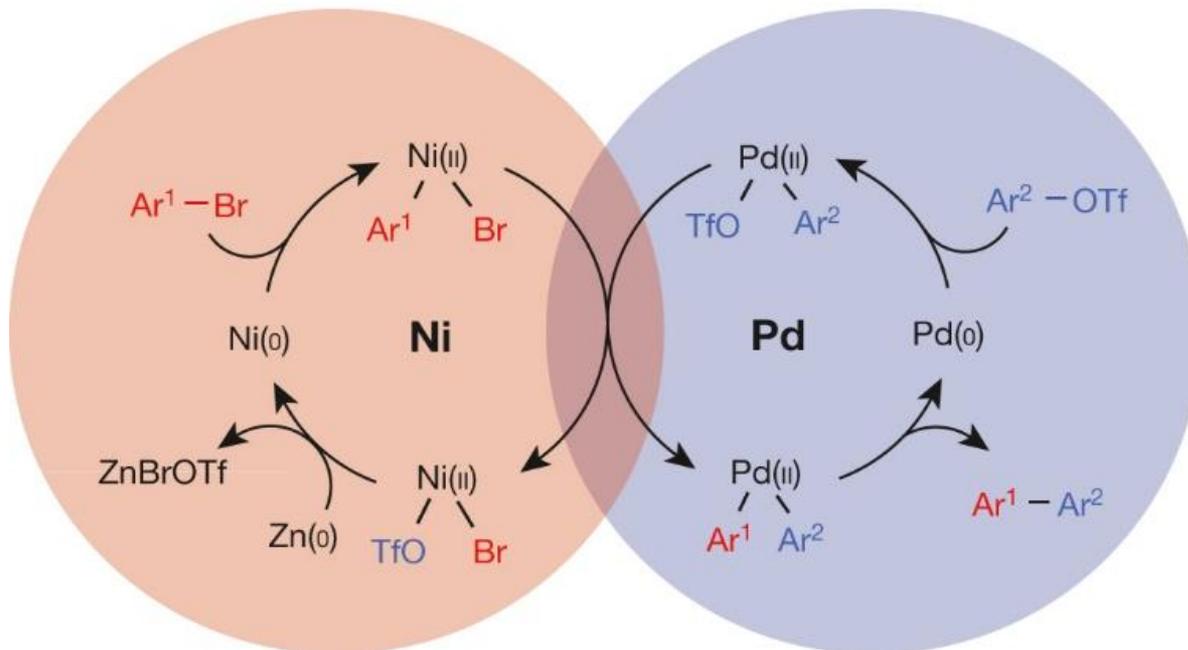
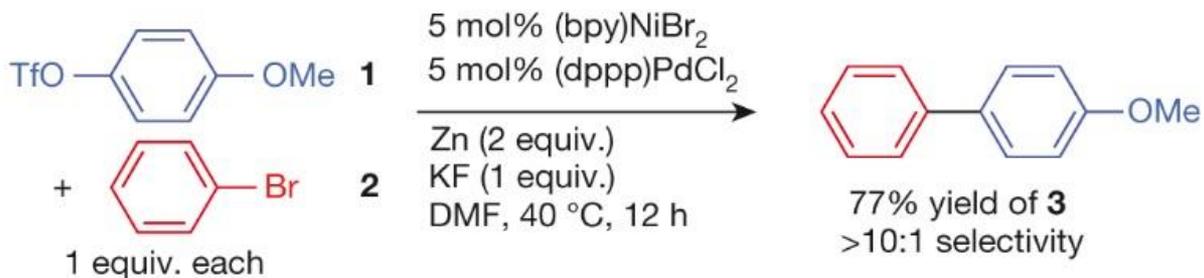
Optimization & Substrate Scope



Preliminary enantioconvergent coupling

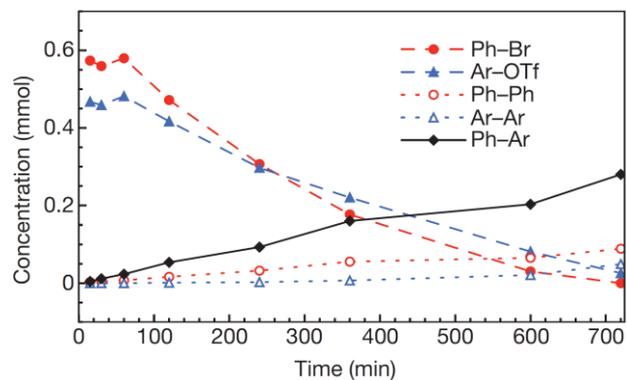
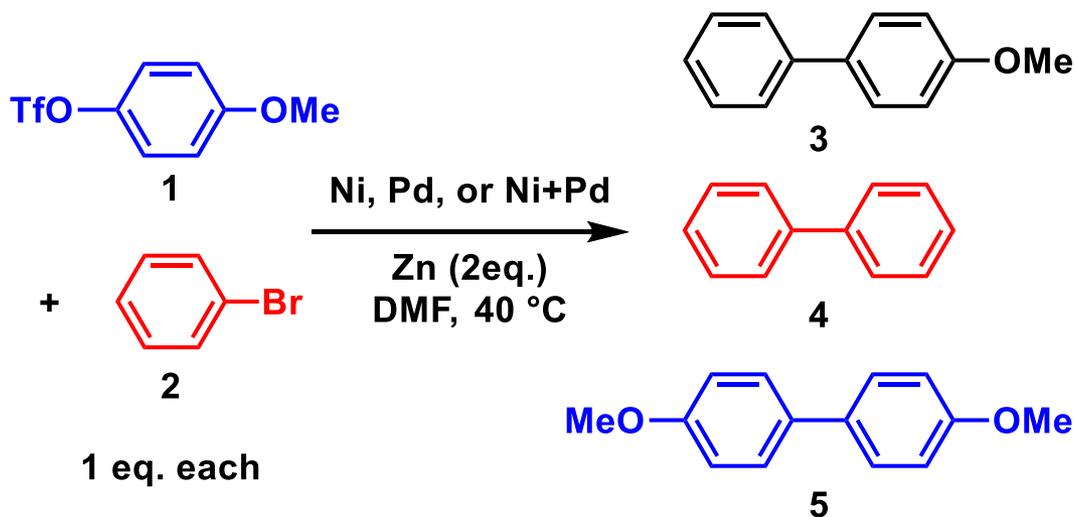


Multimetallic Catalysed Cross-coupling of Aryl Bromides with Aryl Triflates

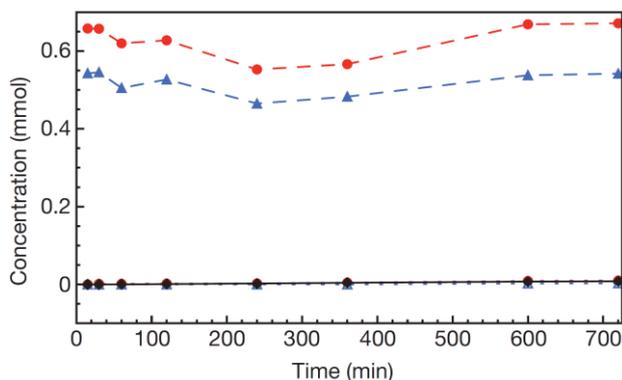


Nature, 2015, 524, 454–457.

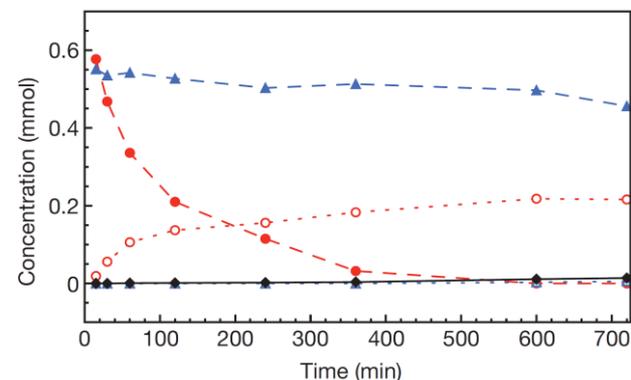
Selectivities of Nickel and Palladium



a) (dppp)PdCl₂ and (bpy)NiBr₂ (10 mol%)

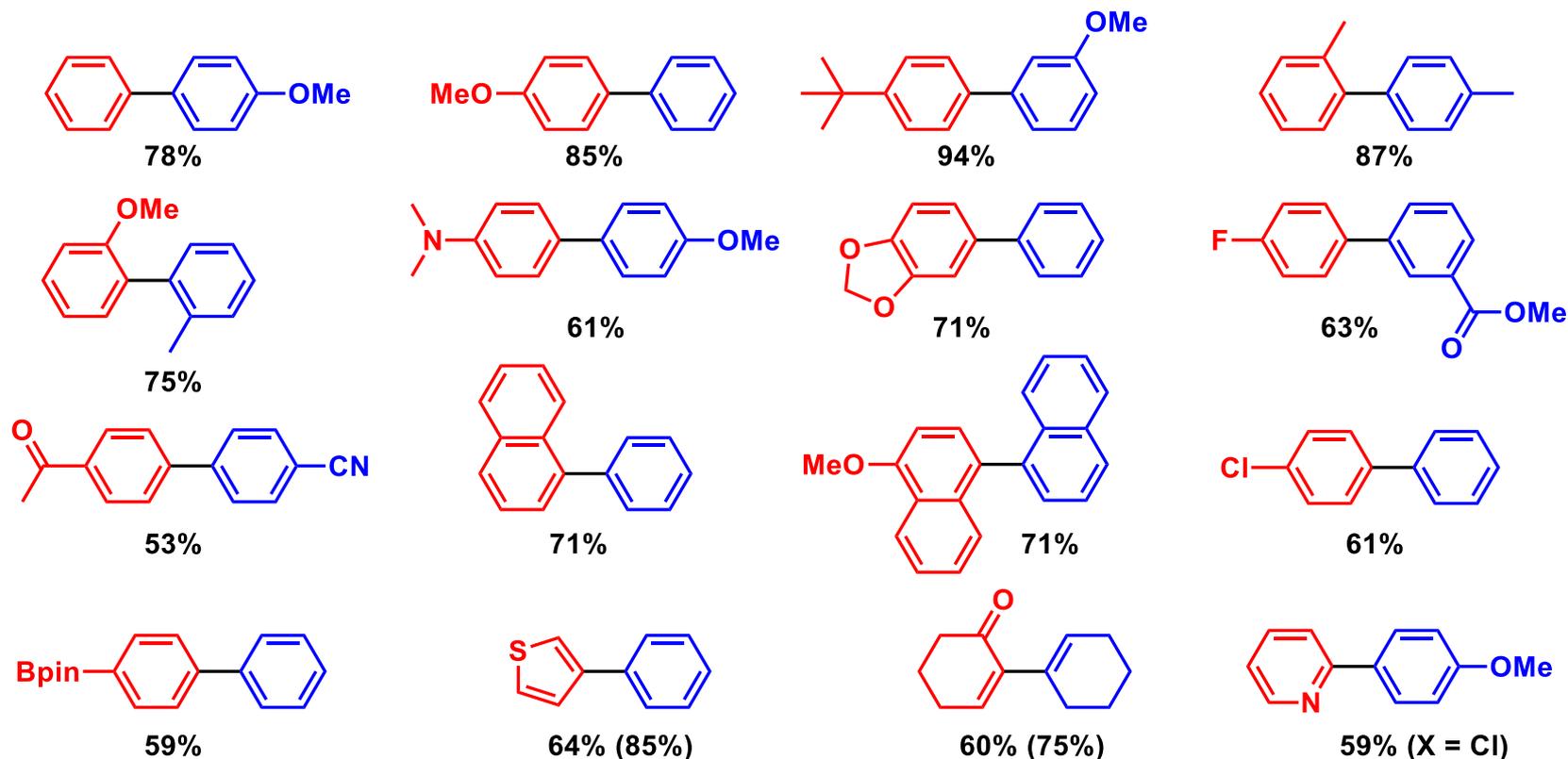
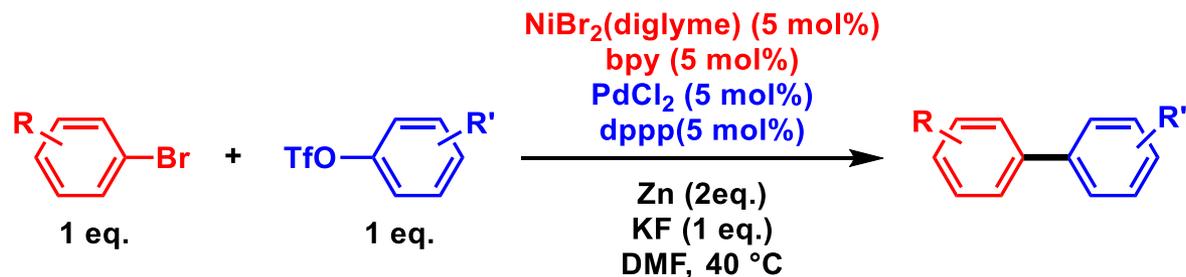


b) (bpy)NiBr₂ (10 mol%)



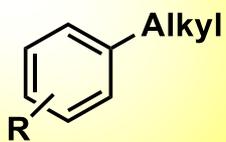
c) (dppp)PdCl₂ (10 mol%)

Conditions for the Multimetal-Catalyzed Cross-Ulmann Reaction

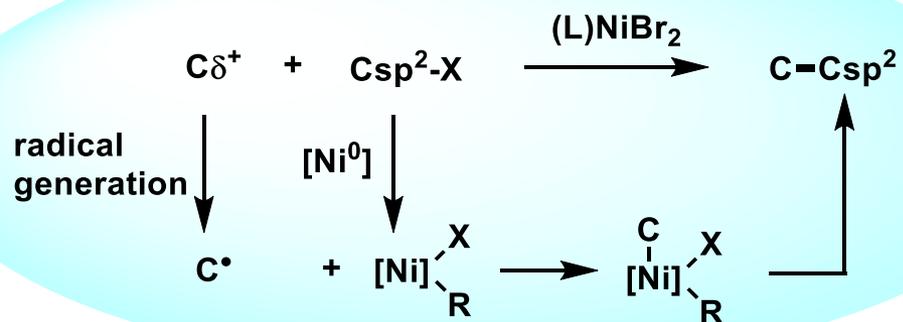


Summary

Discovery



Mechanism



Design

