Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

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2. General mechanisms/Challenges
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ii) Radical mechanism
iii) Oxidative addition of Pd to alkyl halides

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1. Pd catalysis
i) Suzuki-Miyaura coupling
ii) Negishi coupling
iii) Kumada coupling
2. Ni catalysis
i) Negishi coupling
ii) Suzuki-Miyaura coupling
iii) Kumada coupling
iv) Reductive coupling
3. Fe catalysis
i) Kumada coupling
ii) Suzuki-Miyaura coupling

III. Applications in Total Synthesis
i) (+)-spirolaxine methyl ether
ii) sorangiolides A and B
iii) α-cembra-2,7,11-triene-4,6-diol
vi) carolactone

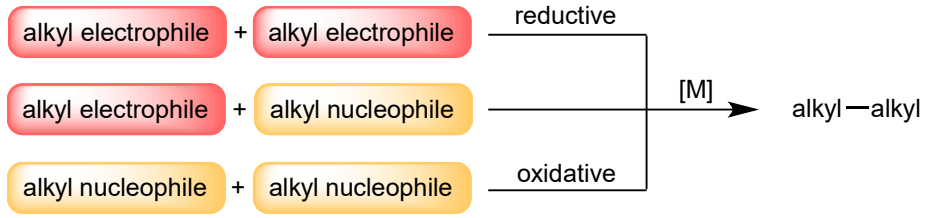
VI. Conclusion

Key references (reviews):
Chem. Rev., **2011**, *111*, 1417.
ACIE, **2005**, *44*, 674.
ACIE, **2009**, *48*, 2656.
Adv. Synth. Catal. **2004**, *346*, 1525.
Chem. Soc. Rev. **2011**, *40*, 4937.

Materials not covered:
- Cross-couplings that do not involve classical electrophile (alkyl halides,/pseudohalides) and nucleophiles (organometallic reagents)
- Catalysis with other metals (ex. Co, Cu)
- Reactions involve C-H activations

I. Introduction

1. General scheme of transition metal-catalyzed $C(sp^3)$-$C(sp^3)$ cross-coupling reactions



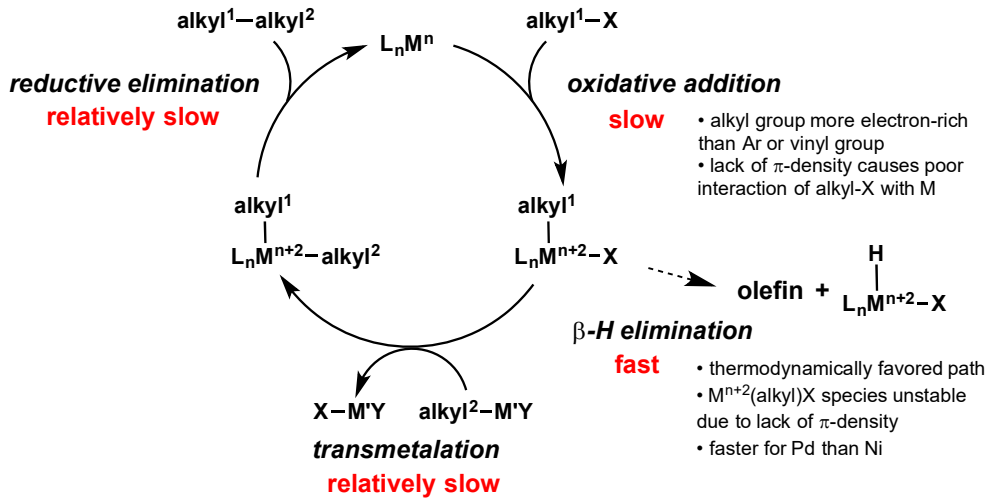
– Why $C(sp^3)$-$C(sp^3)$ coupling reactions with transition metals?
• higher functional group tolerance and selectivity is achieved compared to traditional S_N2-type reactions with alkyl-X and organometallic reagents

– Common transition metal catalysts employed: Pd, Ni, Fe

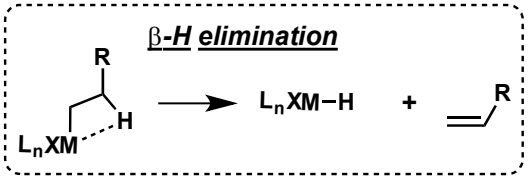
– alkyl electrophiles: R-X (X = halides, OTf, OTs, $OPO(OR)_2$, etc.)
alkyl nucleophiles: R-MX (M = B, Zn, Mg, Sn, Si, In)

2. General mechanisms/Challenges

i) Polar mechanism (two electron process)



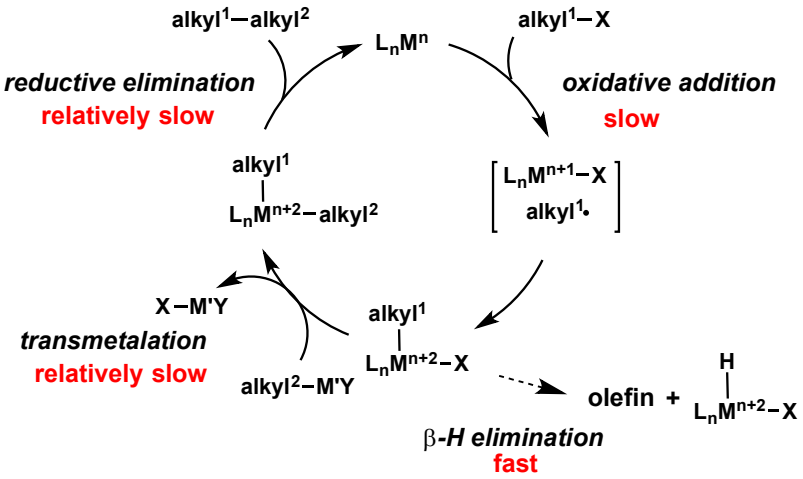
ACIE, **1999**, *38*, 3108.



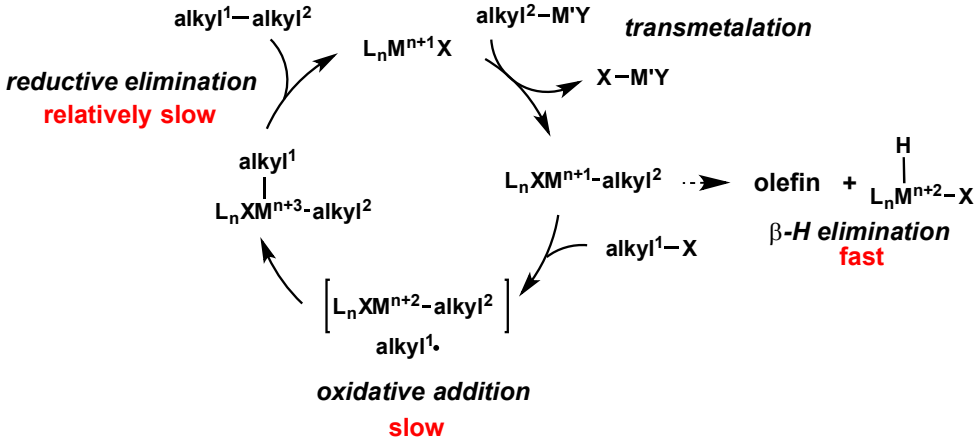
Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

ii) Radical mechanism

Type 1: Oxidative addition, then transmetalation



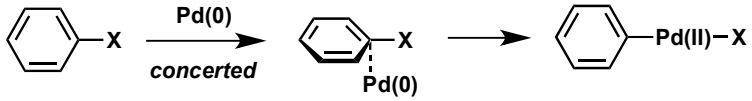
Type 2: Transmetalation, then oxidative addition

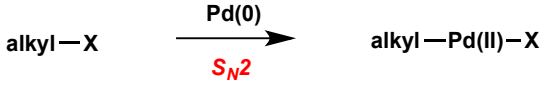


– Most of Ni and Fe catalysis is thought to proceed via radical mechanism, but exact mechanism is yet to be elucidated
(References for Ni: *Chem Sci*, **2011**, *2*,1867; *Chin. J. Catal*, **2015**, *36*, 3; etc.)

iii) Oxidative addition of Pd to alkyl halides

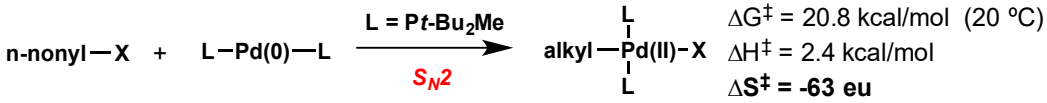
Fu, *ACIE*, **2003**, *42*, 5749.





Evidence for S_N2-type pathway for alkyl halides

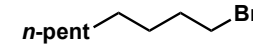
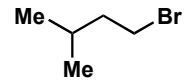
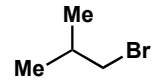
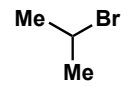
– Large negative $\Delta G^{\ddagger}$ consistent with associative S_N2-type pathway



– Increase in the polarity of solvent leads to decrease in activation energy

– Relative ability of alkyl electrophiles to undergo oxidative addition with P*t*-Bu_2Me increases as the C-X bond strength decreases
– Dependence of the reaction rate on steric demand of the alkyl group

X	$t_1/_2$
I	2.2 h at -60 °C
Br	2.3 h at 0 °C
Cl	2.0 d at 60 °C
F	<2% after 43 h at 60 °C
OTs	10.4 h at 40 °C

RBr	k_{rel}	$\Delta G^{\ddagger}$ (kcal/mol)
	1.0	19.5
	0.19	20.3
	0.054	21.0
	<0.0001	>24.0

How to overcome these challenges in $C(sp^3)$-$C(sp^3)$ couplings?

- choice of transition metal (Pd, Ni, Fe)
- ligand control
- rate acceleration by additives

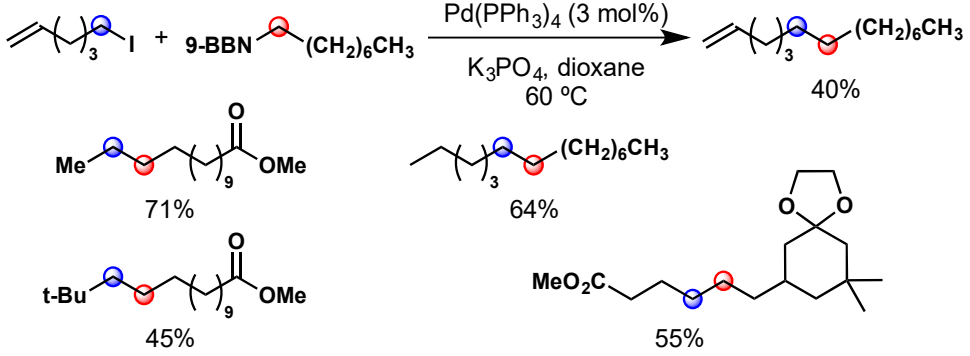
Transition Metal-Catalyzed C(sp^3)-C(sp^3) Cross-Coupling Reactions

II. Examples of transition metal-catalyzed C(sp^3)-C(sp^3) cross-coupling reactions

1. Pd catalysis

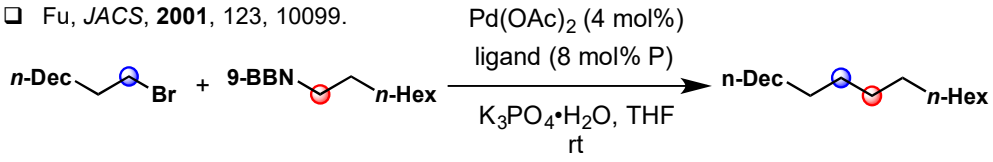
i) Suzuki-Miyaura coupling

❑ Suzuki, *Chem. Lett.* **1992**, 691.



– PPh_3 was the most effective ligand. Bidentate phosphine ligands like dppf gave β–H eliminated product
– Only 9-BBN derivatives gave high yields. Other boron nucleophiles, Mg, Zn, Al, Sn, Zr, and Hg based nucleophiles gave poor yields

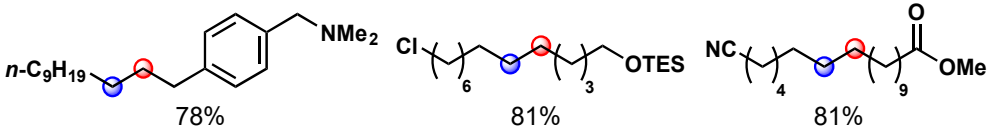
❑ Fu, *JACS*, **2001**, 123, 10099.



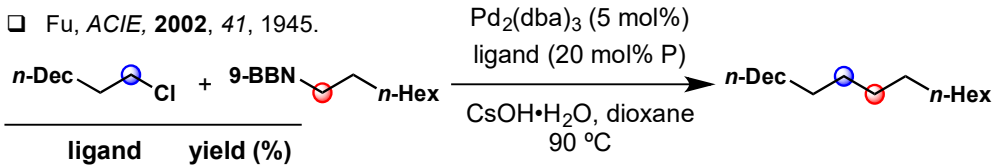
ligand	cone angle (°)[b]	yield (%)[a] n-Dec–n-Hex	yield (%)[a] n-Dec–
PCy_3	170	85	<2
P^tBu_3	182	<2	21
P^iPr_3	160	68	6
P^nBu_3	132	9	27
PPh_3	145	<2	<2
dppf	125	<2	12
dcpe	142	<2	21

a) reaction time: 16 h. b) cf. *Chem. Rev.* **1977**, *77*, 313.

– First report using alkyl bromides that possess β–hydrogen (alkyl chlorides are intact)
– Steric and electronic nature of phosphine ligand was key for efficient cross-coupling

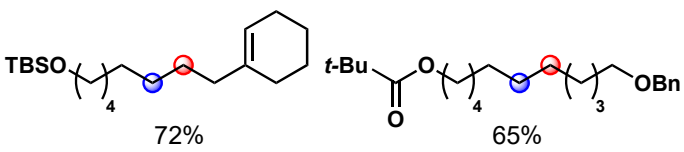


❑ Fu, *ACIE*, **2002**, *41*, 1945.

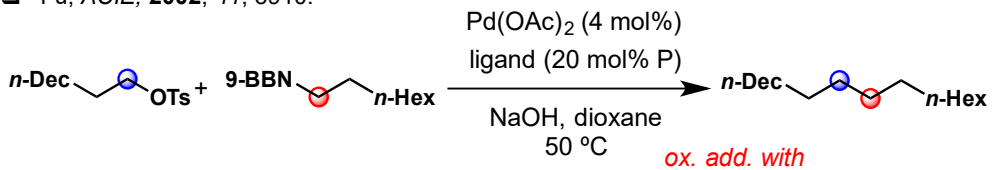


ligand	yield (%)
PCy_3	77
P^tBu_3	<2
P^iPr_3	53
P^nBu_3	5
PPh_3	<2
dppf	<2
dcpe[a]	<2
Mes–N(:)–N–Mes	8

a) dcpe = 1,2-bis(dicyclohexyl-phophino)ethane.

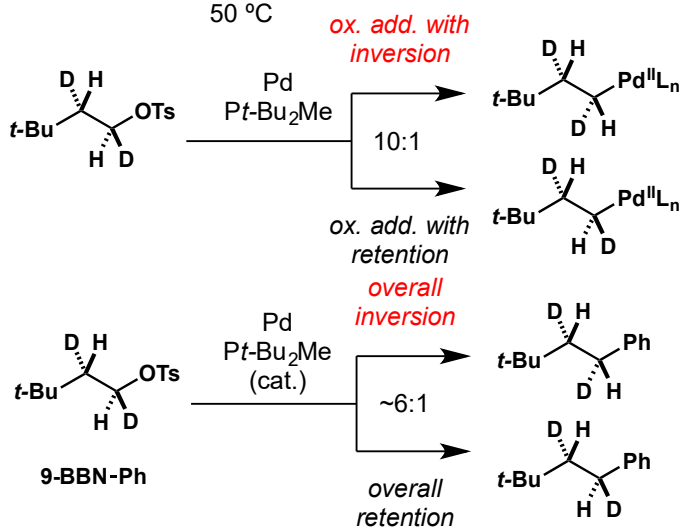


❑ Fu, *ACIE*, **2002**, *41*, 3910.



ligand	yield (%)
PCy_3	45
$PCy_2{}^iPr$	44
PCy_2Et	70
PCy_2Me	48
$P^tBu_2{}^iPr$	<2
P^tBu_2Et	<2
P^tBu_2Me	78
$[HP^tBu_2Me]BF_4$[a]	82

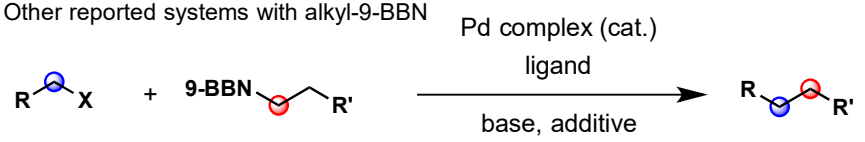
a) Bench-stable salt



– P*t*-Bu_2Me gave the best result; corresponding phosphine salt $[HPt\text{-}Bu_2Me]BF_4$ also gave similar yield
– Mechanistic investigation suggested that oxidative addition proceeds with stereoinversion, and reductive elimination with stereoretention

Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

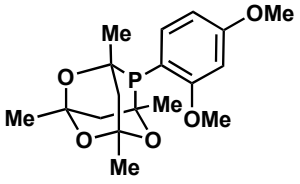
❑ Other reported systems with alkyl-9-BBN



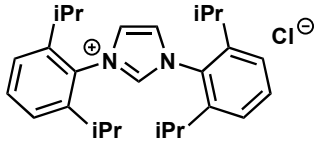
Capretta
JOC, **2004**, *69*, 7635.
X = Br, Cl, OTs

Hitchcock
TL, **2004**, *45*, 3511.
X = Br

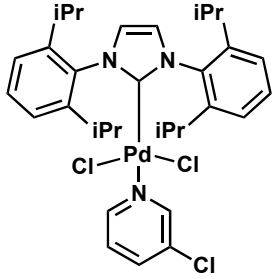
Organ
Chem. Commun, **2008**, 735.
X = Br



$Pd(OAc)_2$
$K_3PO_4 \cdot H_2O$

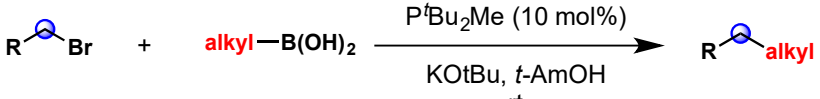


$Pd(dba)_2$
KOtBu
AgOTf (cat.)

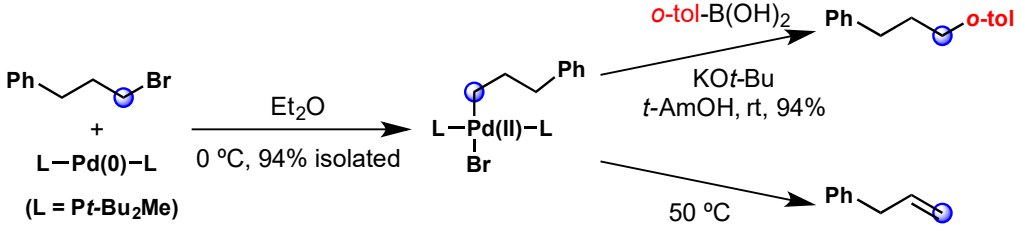


$K_3PO_4 \cdot H_2O$

❑ Fu, *JACS,* **2002**, *124*, 13662.

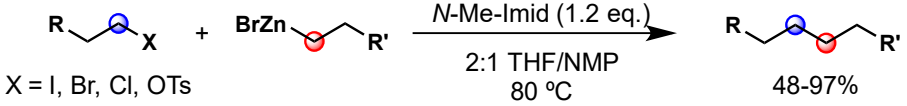


– Investigations with stoichiometric Pd intermediate revealed that the coupling proceeds at lower temperature with P^tBu_2Me, preventing competing β–H elimination



ii) Negishi coupling

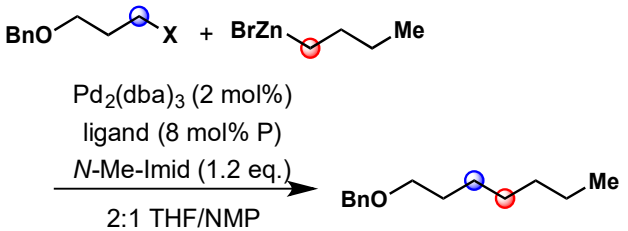
❑ Fu, *JACS,* **2003**, *125*, 12527.

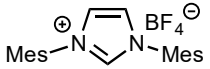


X = I, Br, Cl, OTs

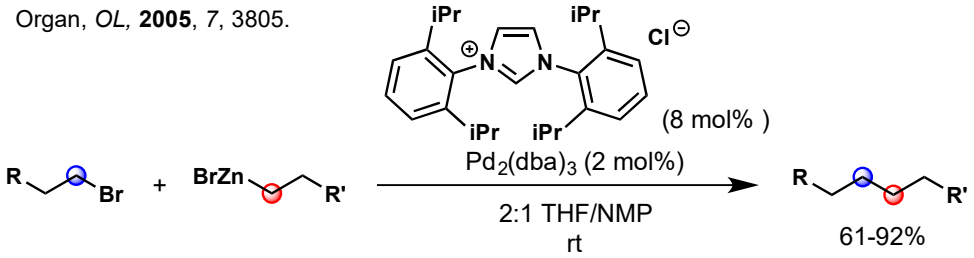
48-97%

– This system was applicable to variety of electrophiles (X = I, Br, Cl, and OTs) unlike Suzuki coupling reactions reported by Fu
– Choice of ligand greatly affect the yield



ligand	yield (%)
$PCyp_3$[a]	70
PCy_3	65
P^tBu_3	3
P^iPr_3	59
P^tBu_2Me	55
P^nBu_3	9
	4

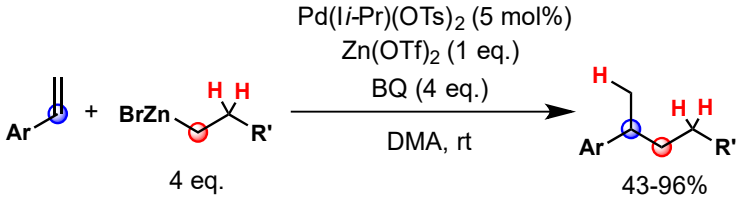
❑ Organ, *OL,* **2005**, *7*, 3805.



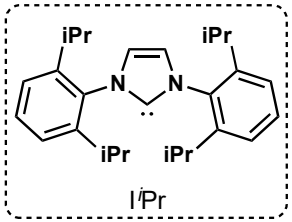
61-92%

– Bulky NHC ligand effectively promoted the coupling reaction in mild conditions (rt)

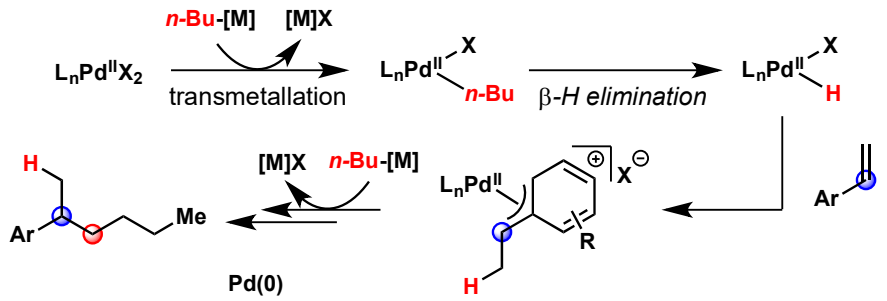
❑ Sigman, *JACS,* **2009**, *131*, 18042.



43-96%



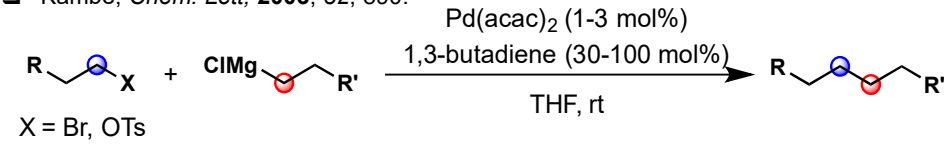
– Oxidative Negishi coupling (or hydroalkylation of olefin) was achieved using bulky NHC ligand
– Deuterium labeling study with n-C_4D_9ZnBr showed that the hydride source comes from n-C_4D_9ZnBr

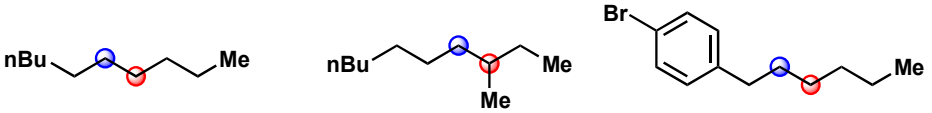


Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

iii) Kumada coupling

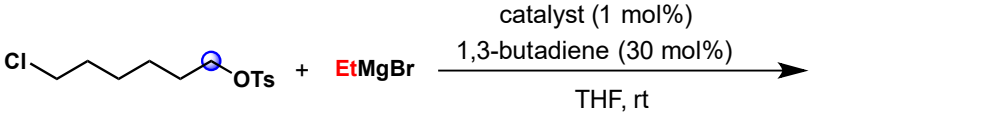
❑ Kambe, *Chem. Lett,* **2003**, *32*, 890.

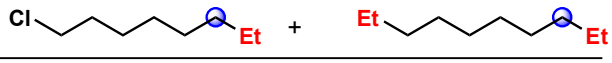




93% 71% 71%

– First alkyl-alkyl Kumada coupling reaction using Pd complex
– Dienes as ligand are essential for this reaction to proceed (detailed mechanism see Ni Kumada coupling section)
– Comparison with Ni catalyst revealed that Pd catalyst is more selective



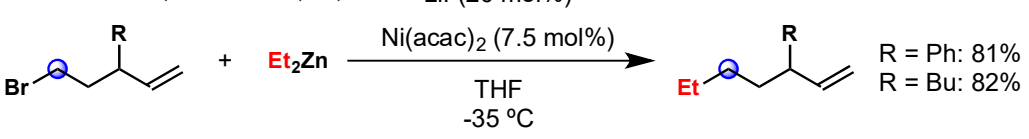


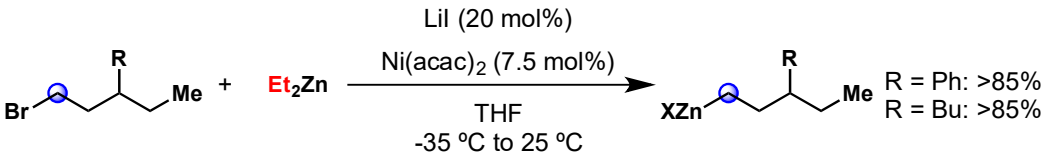
$Pd(acac)_2$	86%	0%
$NiCl_2$	87%	13%

2. Ni catalysis

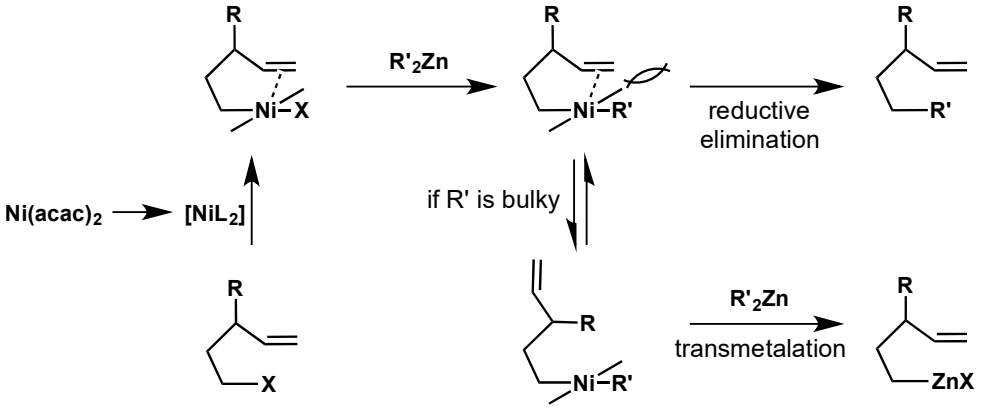
i) Negishi coupling

❑ Knochel, *ACIE*. **1995**, *34,* 2723.





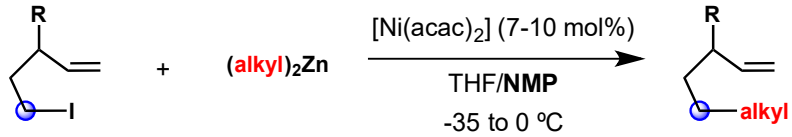
– Cross-coupling is only achieved in the presence of unsaturated group on the substrate (substrate-controlled cross-coupling)
– Ni(0)/Ni(II) mechanism with two electron process was proposed
– **Coordination of double bond is thought to promote reductive elimination by pulling electron density away from metal center**

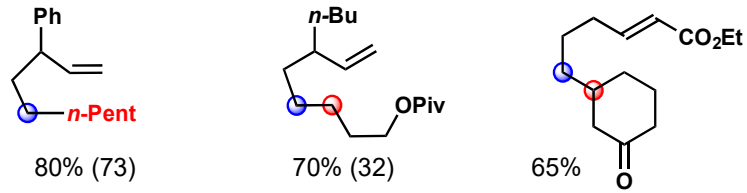


– Position of the unsaturated group had great impact on reaction rate

faster slower

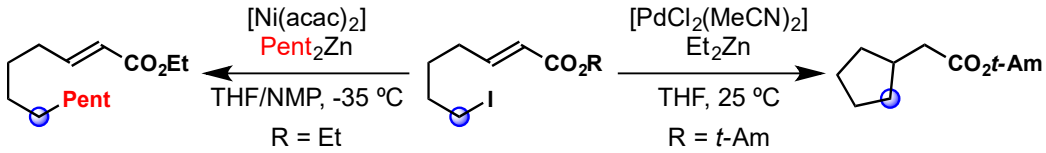
– Addition of NMP (N-methylpyrrolidinone) as co-solvent improved yield for many substrates (yield for reaction only in THF in paranthesis)





80% (73) 70% (32) 65%

– Different chemoselectivity was obtained between Ni and Pd catalysts

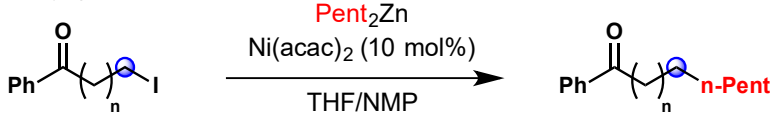


Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

❑ Knochel, *ACIE*, **1998**, *37*, 2387; *JOC*, **1999**, *64, 3544.*

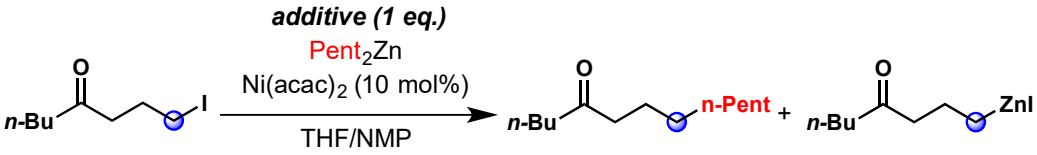
– Both **internal** and **external** aromatic carbonyl groups were found to promote cross-coupling between alkyl iodides and dialkyl zinc reagent
– External aromatic carbonyl group was especially important for less reactive substrates to facilitate desired cross-coupling and inhibit undesired iodide-zinc exchange

Internal carbonyl group



n=1: 65%
n=2: 71%

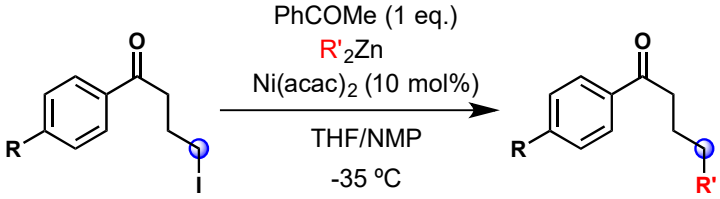
External carbonyl group



without **PhCOMe**: 20%
with **PhCOMe**: 71%

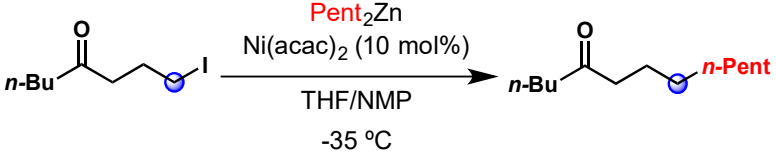
57%
<5%

– Alkyl iodides bearing electron-poor aromatic ketones gave higher yields

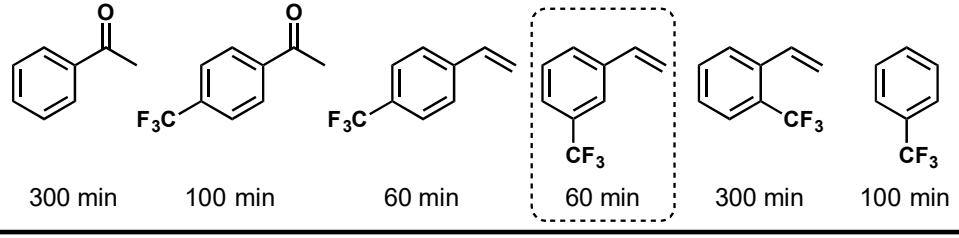


R = H, R' = Pent: 88%
R = OMe, R' = Bu: 71%
R = CF_3, R' = Pent: 92%

– Further screening of π–acid additive revealed that *m*-CF_3-styrene gave best yield and fastest reaction rate

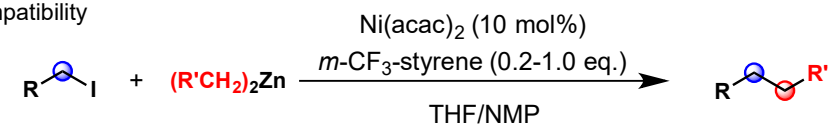


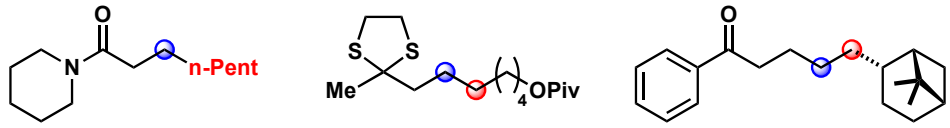
time requred for full conversion:



300 min | 100 min | 60 min | 60 min | 300 min | 100 min

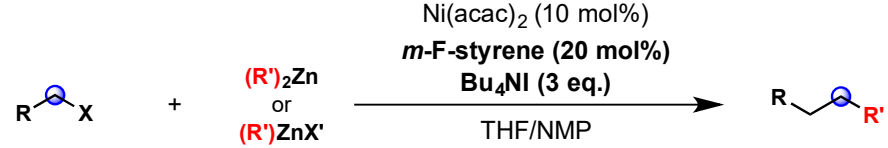
– With *m*-CF_3-styrene as promoter, broad substrate scope with high functional group compatibility





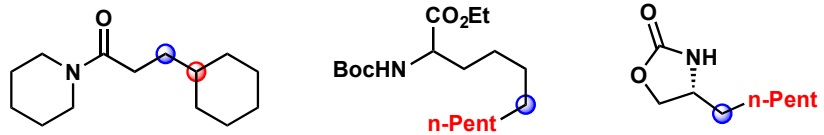
70% | 67% | 66%

❑ Knochel, *OL*, **1999**, *1*, 1323; *JOC*. **2002,** *67, 79.*



X = I, **Br**

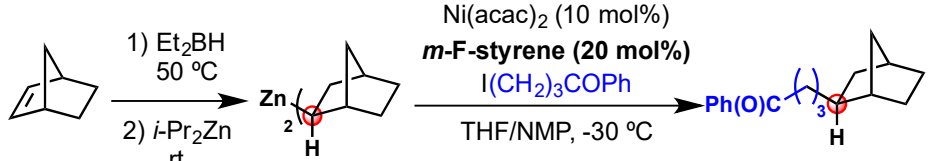
R' = primary, **secondary** alkyl



63% | 56% | 60%

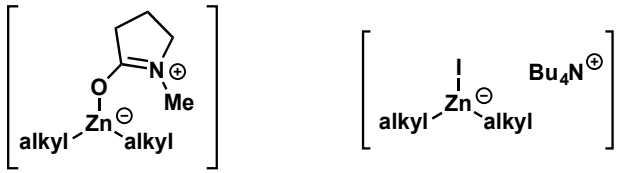
– *m*-F-styrene as co-catalyst and Bu_4NI as additive enabled cross-coupling of alkyl bromides and less reactive primary as well as secondary zinc reagents
– Broad substrate scope include tolerance of free amines

– Transmetalation proceeds stereospecifically



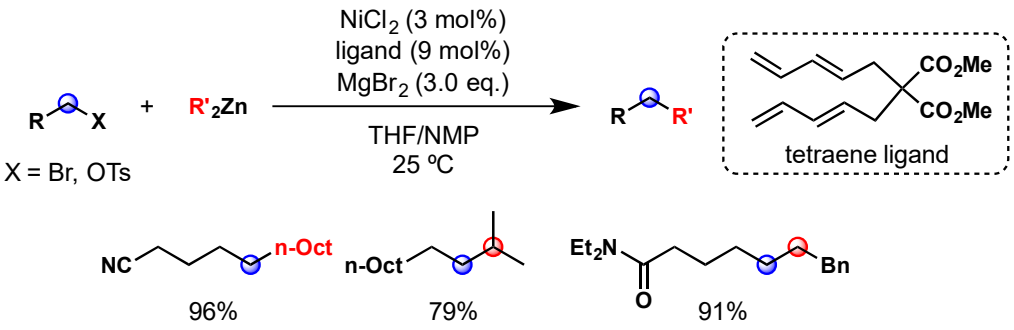
61%
endo:exo >95:5
stereoretentive

– Possible roles of Bu_4NI and NMP: activate organozinc nucleophile?



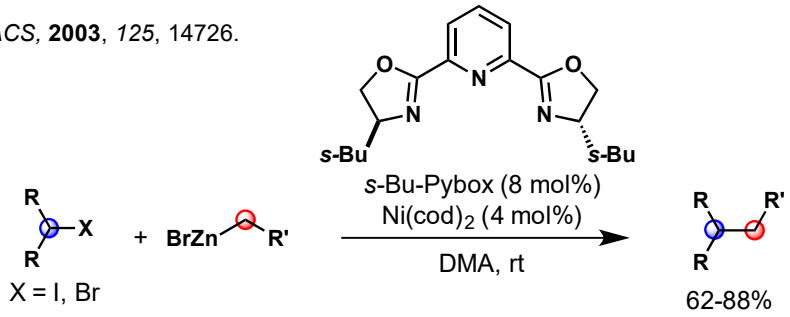
Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

❑ Kambe, *ACIE,* **2004**, *43*, 6180.

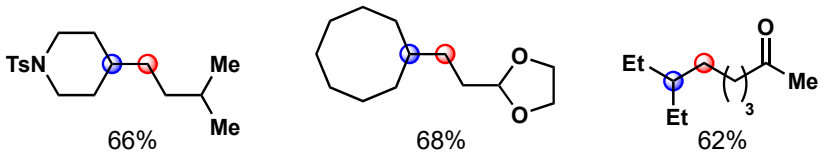


– Alkyl bromides and tosylates were effectively cross-coupled using $NiCl_2$ and tetraene ligand.
– Detailed mechanism see Ni Kumada coupling section.

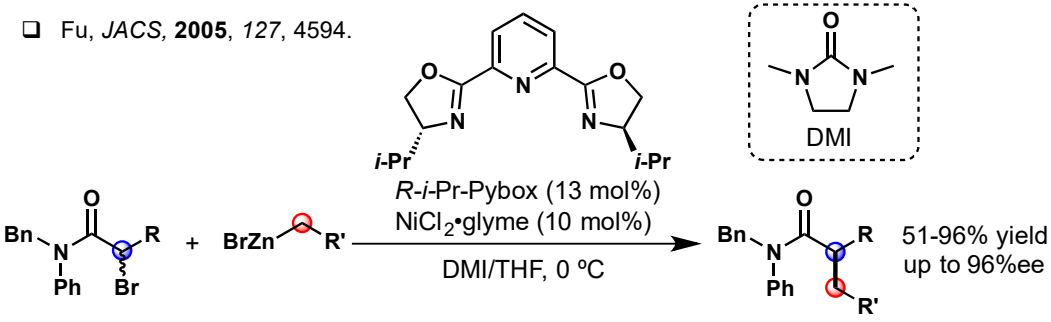
❑ Fu, *JACS,* **2003**, *125*, 14726.



– First example with secondary alkyl halides

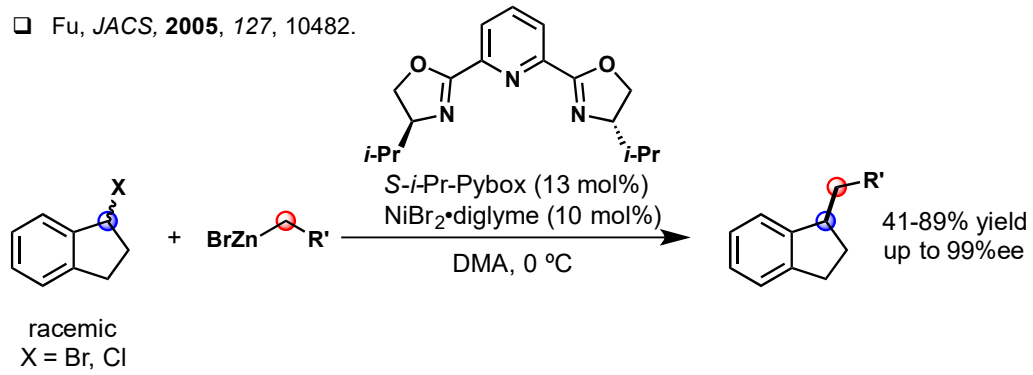


❑ Fu, *JACS,* **2005**, *127*, 4594.



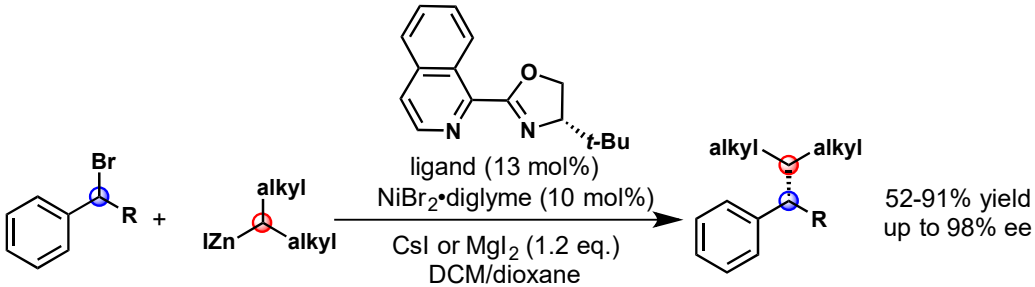
– First catalytic enantioselective cross-coupling of secondary alkyl electrophiles (α-bromo amides)
– Stereoconvergent process using racemic starting material
– Recovered starting material being racemic implied that this process is not via kinetic resolution

❑ Fu, *JACS,* **2005**, *127*, 10482.

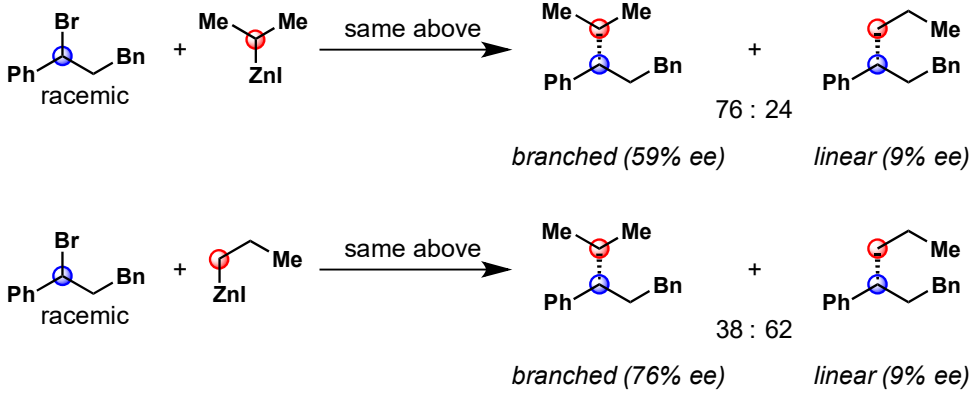


– Both racemic benzyl bromide and chlorides successfully coupled with primary alkylzinc bromides with high enantioselectivity

❑ Fu, *JACS,* **2012**, *135*, 10946.

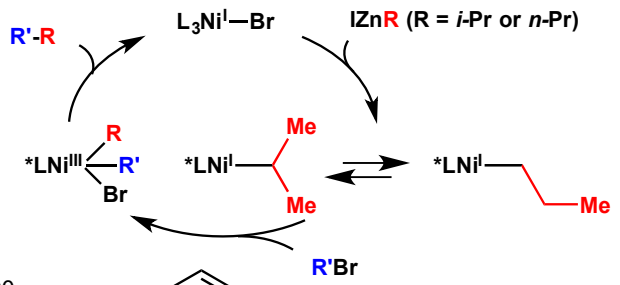


– Secondary alkylzinc iodides were applicable
– With acyclic alkyl iodides, both branched and linear products were obtained. Possible mechanism suggested includes initial transmetalation of alkyl group followed by isomerization

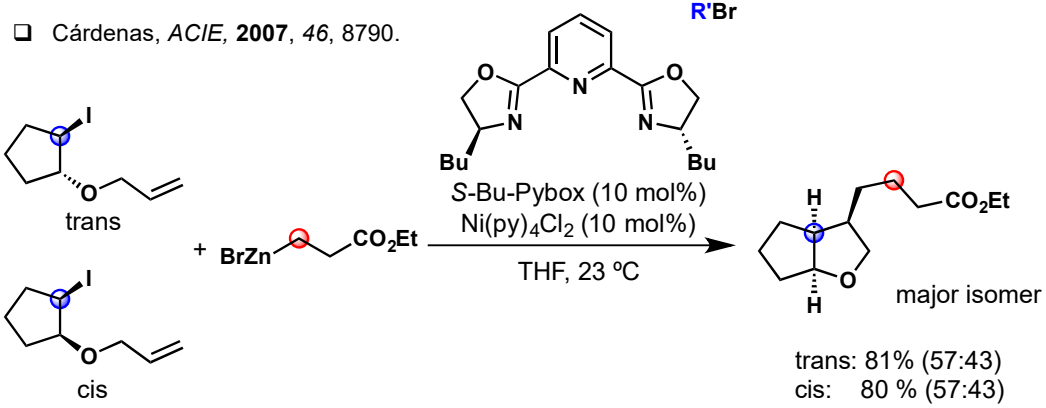


Transition Metal-Catalyzed C(sp^3)-C(sp^3) Cross-Coupling Reactions

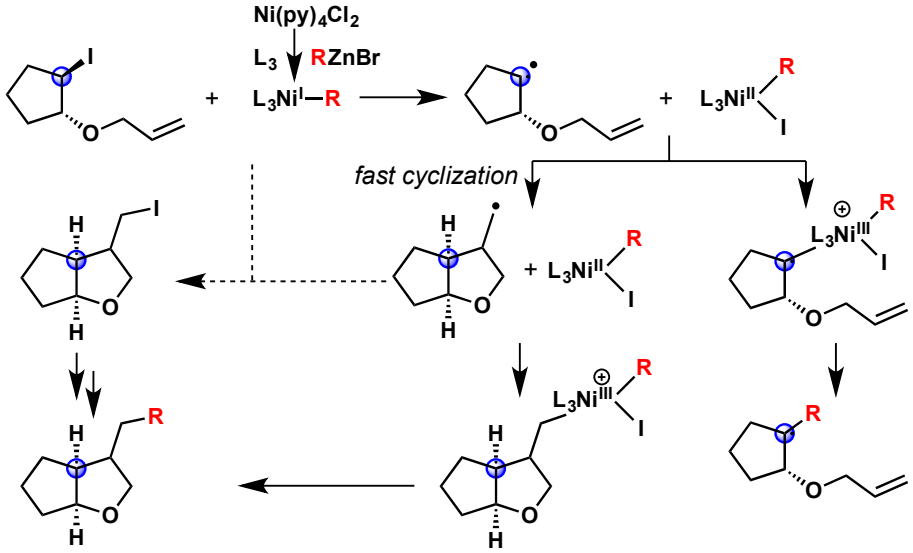
Proposed mechanism



❑ Cárdenas, *ACIE,* **2007**, *46*, 8790.

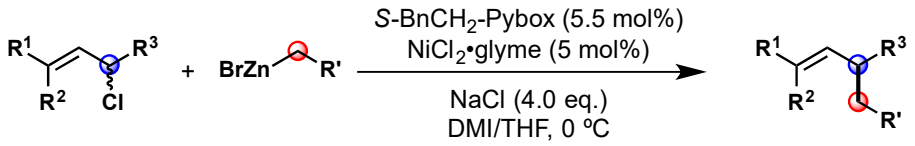


– Mechanism proposed include transmetalation of organozinc reagent to Ni(I) as a initial step, followed by cyclization, then reductive elimination

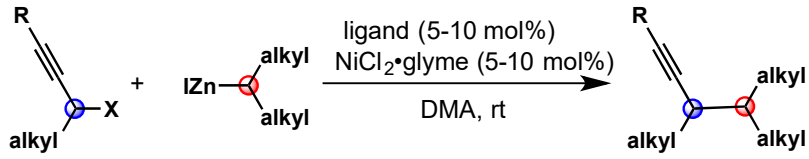


❑ Fu, *JACS,* **2008**, *130*, 2756.

– Racemic secondary allylic chlorides successfully coupled to alkylzinc bromides with high enantioselectivity



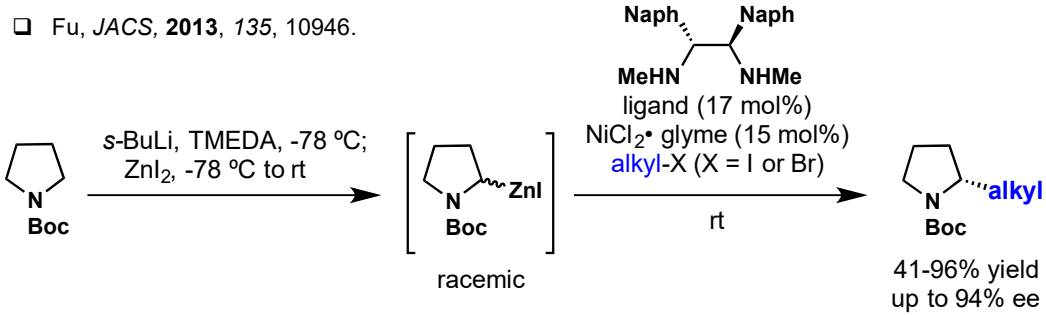
❑ Fu, *ACIE,* **2008**, *47*, 9334.



X = Br, Cl
R = TIPS, tBu

– Cross-coupling between secondary nucleophiles with secondary propargylic electrophiles were achieved with tri-nitrogen ligands

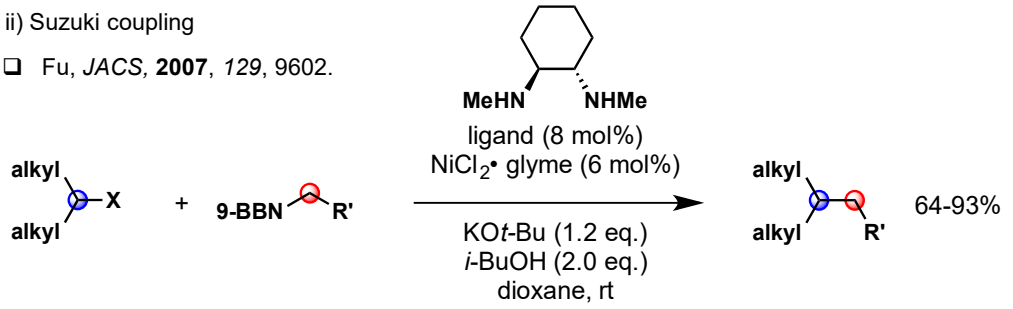
❑ Fu, *JACS,* **2013**, *135*, 10946.



– Unlike other examples, where racemic electrophiles were subjected to stereoconvergent coupling, racemic organozinc nucleophile was generated *in-situ* to furnish stereoconvergent coupling with alkyl electrophiles

ii) Suzuki coupling

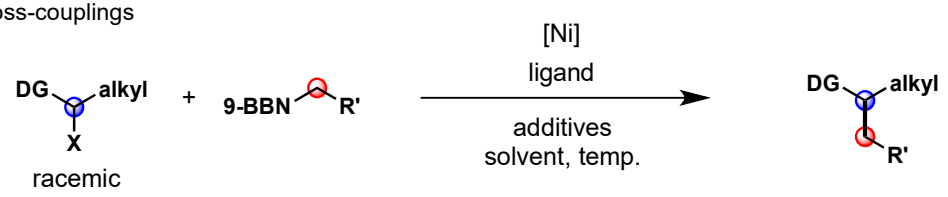
❑ Fu, *JACS,* **2007**, *129*, 9602.

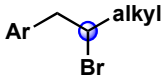
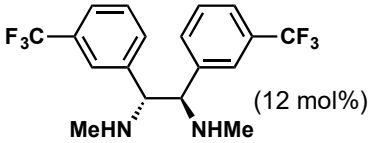
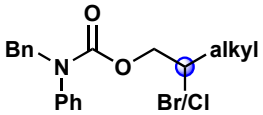
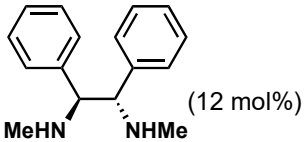
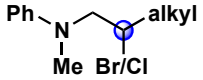
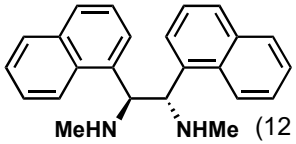
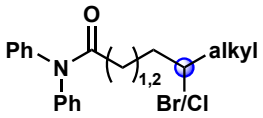
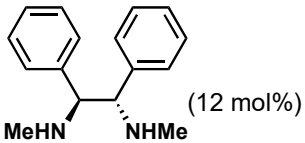
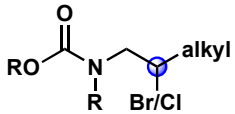
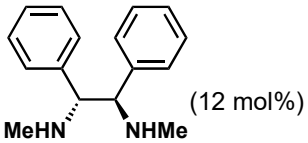
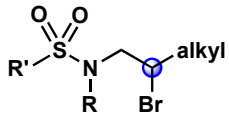
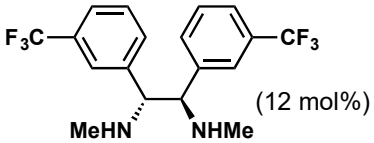
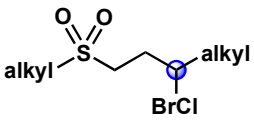
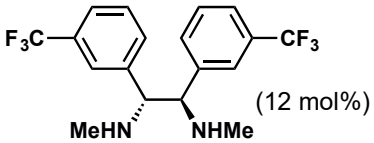


– First report on Suzuki coupling with unactivated secondary halides
– Both KO*t*-Bu and *i*-BuOH were essential for reactivity. ^{11}B NMR spectroscopy revealed the formation of tetravalent -ate complex with alkoxides

Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

- Directed asymmetric/stereoconvergent cross-couplings



substrate	conditions	ligand	yield (%)/ee (%)	reference
	$Ni(COD)_2$ (10 mol%) KO*t*-Bu (1.2 eq.) *i*-BuOH (2.0 eq.) *i*-Pr_2O, 5 ºC to rt	 (12 mol%)	62-86% yield up to 94% ee	Fu, *JACS*, **2008**, *130*, 6694.
	$NiBr_2$•diglyme (10 mol%) KO*t*-Bu (1.4 eq.) *n*-hexanol (1.8 eq.) *i*-Pr_2O, rt	 (12 mol%)	62-82% yield up to 98% ee	Fu, *JACS*, **2010**, *132*, 11908.
	$NiBr_2$•diglyme (10 mol%) KO*t*-Bu (1.2 eq.) *n*-hexanol (2.0 eq.) *i*-Pr_2O, rt	 (12 mol%)	52-86% yield up to 96% ee	Fu, *JACS*, **2011**, *133*, 8154.
	$NiBr_2$•diglyme (10 mol%) KO*t*-Bu (1.4 eq.) *n*-hexanol (1.8 eq.) Et_2O/Hexane, rt	 (12 mol%)	51-83% yield up to 91% ee	Fu, *JACS*, **2011**, *133*, 15362.
	$NiBr_2$•diglyme (10 mol%) KO*t*-Bu (1.4 eq.) *n*-hexanol (1.8 eq.) *i*-Pr_2O, rt	 (12 mol%)	56-83% yield up to 91% ee	Fu, *JACS*, **2012**, *134*, 5794.
	$NiBr_2$•diglyme (10 mol%) KO*t*-Bu (1.4 eq.) *i*-BuOH (1.8 eq.) *i*-Pr_2O, rt	 (12 mol%)	54-68% yield up to 90% ee	
	$NiBr_2$•diglyme (10 mol%) KO*t*-Bu (1.4 eq.) *i*-BuOH (1.8 eq.) *i*-Pr_2O, rt	 (12 mol%)	79-84% yield up to 90% ee	

Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

– With amine-directed substrates, the rate law was determined to be:

catalyst	1st order
organoborane	1st order
electrophile	zero order

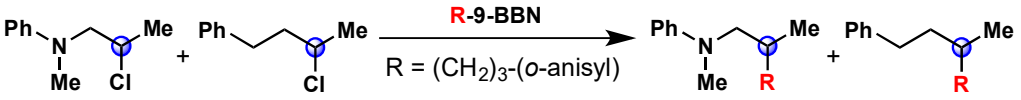
– With above rate law, transmetalation is thought to be the turnover-limiting step

– Position of heteroatom or π-density from the directing group is crucial for enantioselectivity, but not for the reactivity of alkyl halides. This also supports the oxidative addition *not* to be the turnover-limiting step.

Reaction with *n*-Hex-9-BBN:

86% ee | 88% ee | <5% ee | 41% ee

Rate comparison with/without DG

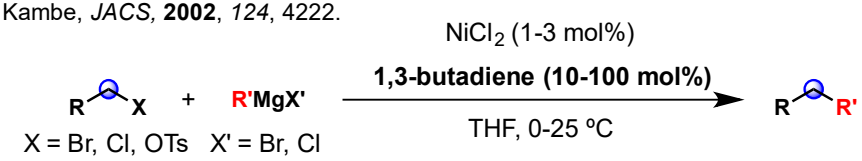


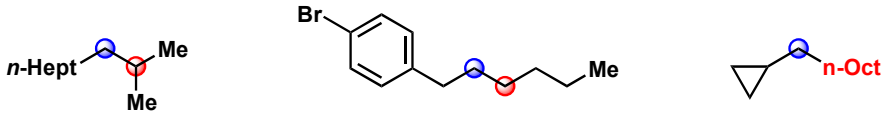
1:1

initial rates of formation: k(**A**)/k(**B**) ~2

iii) Kumada coupling

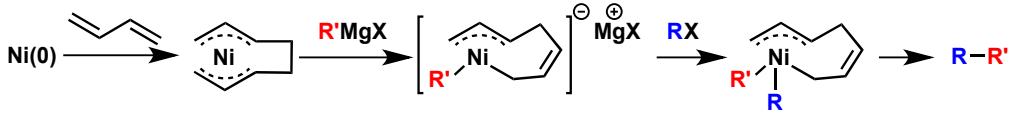
❑ Kambe, *JACS*, **2002**, *124*, 4222.



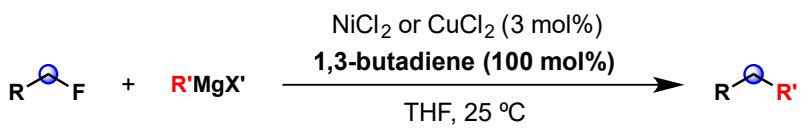


X = Br, 72% | X = Br, 100% | X = Br; 87%

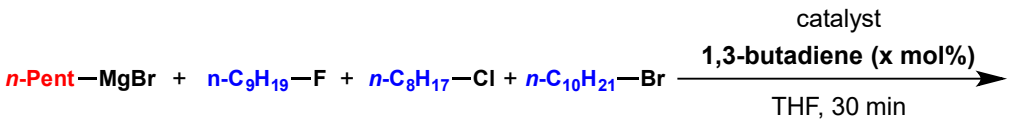
– Addition of dienes as ligand was crucial for catalytic activity
– Proposed mechanism involves the formation of bis-π-allyl Ni complex, which reacts with Grignard reagents
– Unreacted cyclopropane as a substrate ruled out radical mechanism



❑ Kambe, *JACS*, **2003**, *125*, 5646.

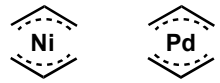


– Alkyl fluorides were employed in Negishi coupling for the first time using Ni or Cu catalysts.
– Competition study revealed that the reactivity order of alkyl halides in this system is:
Br > F > Cl



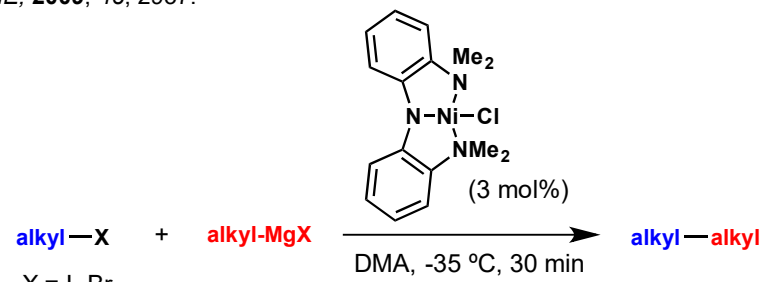
	n-C9H19—n-Pent	n-C8H17—n-Pent	n-C10H21—n-Pent
NiCl2 (100)	8%	0%	39%
CuCl2 (10)	16%	0%	40%

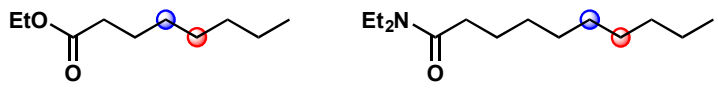
❑ Kambe, *Chem. Commun.*, **2007**, 825.



– Efficient coupling of alkyl halides (X = F, Cl, Br, OTs) with alkyl Grignard reagents using bis-π-allyl complex supported the formation of bis-π-allyl intermediate in former reports

❑ Hu, *ACIE*, **2009**, *48*, 2937.



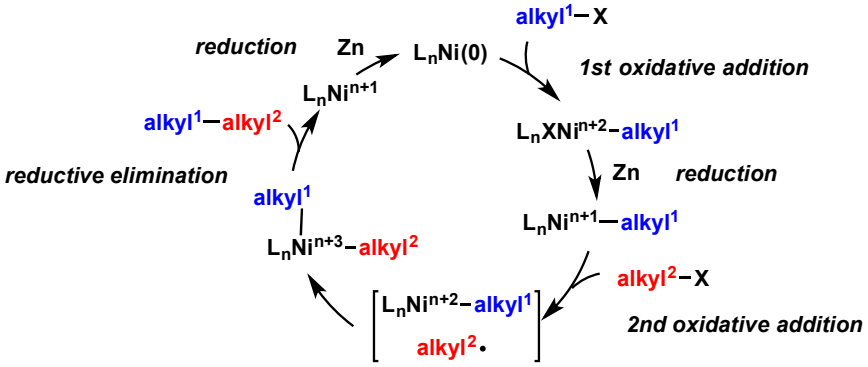


85% | 78%

Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

iii) Reductive coupling

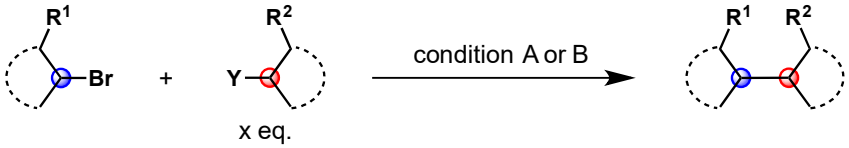
General mechanism



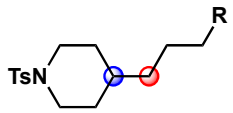
Org. Chem. Front, **2015**, *2*, 1411.

– Proposed mechanism involved two oxidative addition steps and two reduction steps

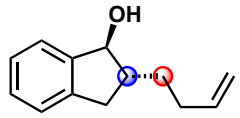
❑ Gong, *OL,* **2011**, *13*, 2138.



condition A (x = 3)	ligand	condition b (x = 1.5)
$Ni(COD)_2$ (10 mol%) ligand **1** (8 mol%) Zn (300 mol%) DMA, 25 ºC	Y = Br: 4-Cl-PyBox Y = I: *S-s*-Bu-PyBox	NiI_2 (10 mol%) ligand **2** (8 mol%) B_2pin_2, LiOMe NMP, 40 ºC



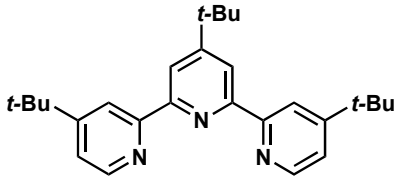
R = CH_3, Y = Br: 67% (condition 1)
R = Ph, Y = Br: 79% (condition 2)



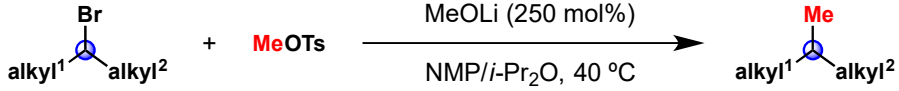
Y = Br: 65%, dr = 4:1 (condition 1)

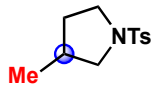
– Both Zn and B_2pin_2 were effective reductant
– High selectivity towards cross-coupling is achieved by having one of the electrophile excess

❑ Gong, *OL,* **2014**, *16*, 5620.

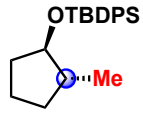


ligand (10 mol%)
$NiCl_2$diglyme (10 mol%)
B_2pin_2 (200 mol%)
MeOLi (250 mol%)

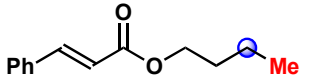




54%



69%

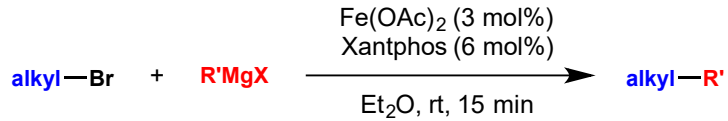


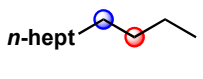
59%

3. Fe catalysis

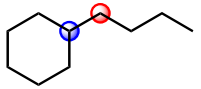
i) Kumada coupling

❑ Chai, *Adv. Synth. Catal.,* **2007**, *349*, 1015.



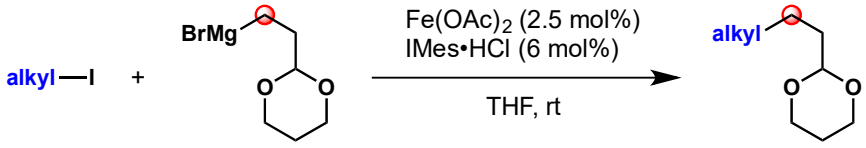


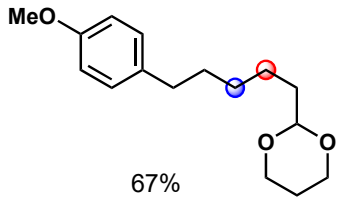
64%



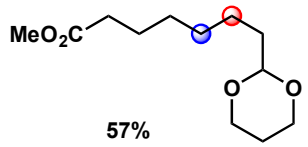
34%

❑ Cárdenas, *Chem. Sci.,* **2013**, *4*, 1098.





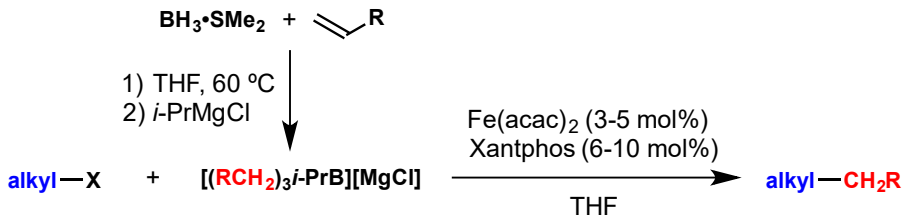
67%



57%

Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

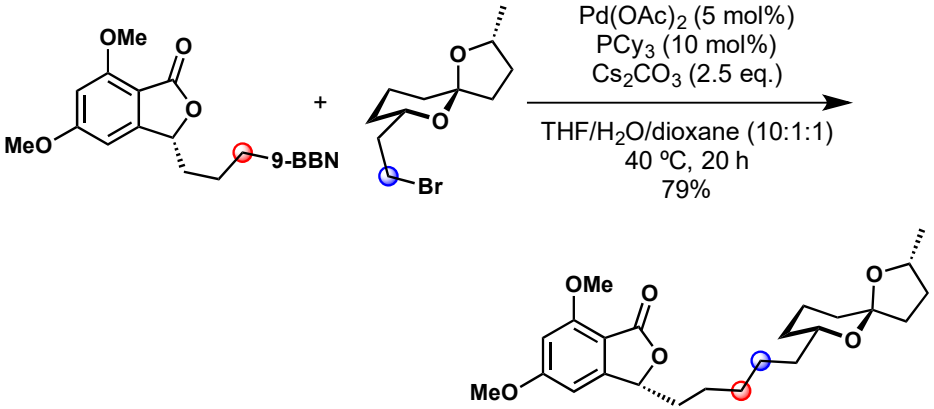
❑ Nakamura, *ACIE,* **2012**, *51*, 8834.



82% 56%

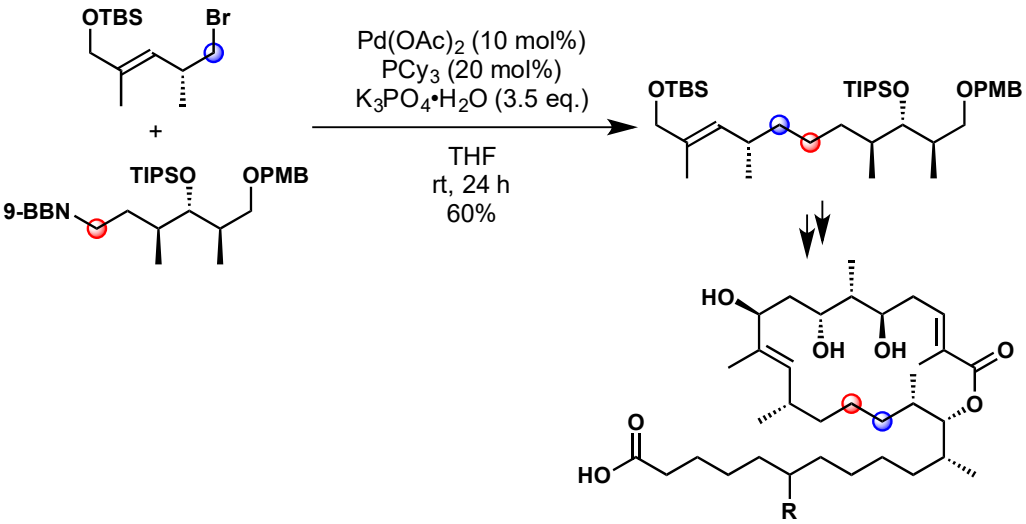
III. Application to Total Synthesis *Nat. Pro. Rep.,* **2014**, *31*, 441.

❑ Phillips, *OL,* **2007**, *9*, 2717.



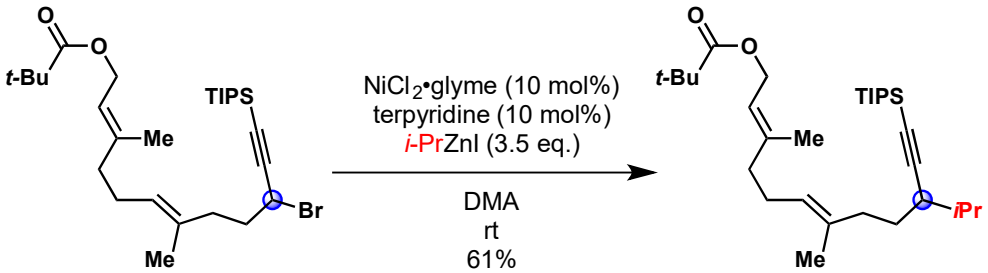
(+)-spirolaxine methyl ether

❑ Phillips, *OL,* **2008**, *10*, 4955.

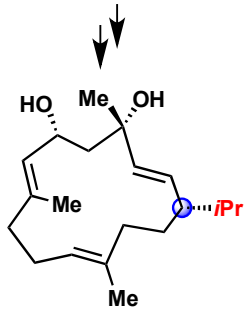


R = H: sorangiolide A
R = OH: sorangiolide B

❑ Fu, *ACIE,* **2008**, *47*, 9334.



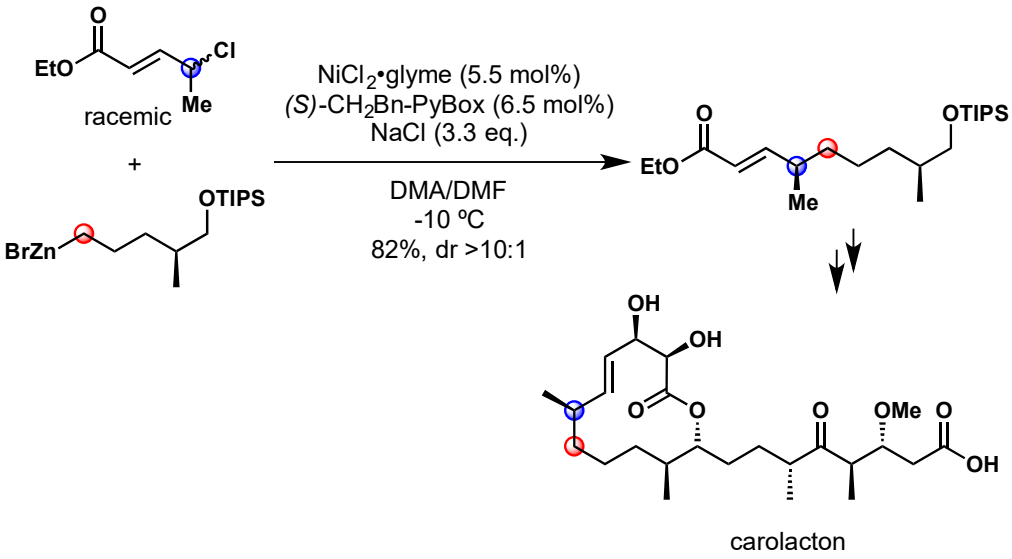
racemic racemic



α-cembra-2,7-11-triene-4,6-diol

Transition Metal-Catalyzed $C(sp^3)$-$C(sp^3)$ Cross-Coupling Reactions

- Krischning, *ACIE,* **2012**, *51*, 1063.



Vi. Conclusion

– Since the first development of $C(sp^3)$-$C(sp^3)$ Suzuki cross-coupling by Suzuki, various types of cross-coupling reactions using alkyl electrophiles and nucleophiles have been achieved, and applied to complex molecule syntheses

– Unactivated alkyl groups such as secondary alkyl groups can be employed in many cases

– Enantioselective coupling reactions through stereoconvergent processes are enabled by Ni catalysis using racemic starting materials

– Further developments needed:

1) broader scope of electrophiles and nucleophiles (ex: tertiary alkyl groups)
2) higher functional group tolerance
3) enantioselective variants
4) understanding of reaction mechanisms for Ni and Fe catalysis