Metal-Catalyzed Cross-Coupling of Two sp^3-Carbons: Challenges and Solutions

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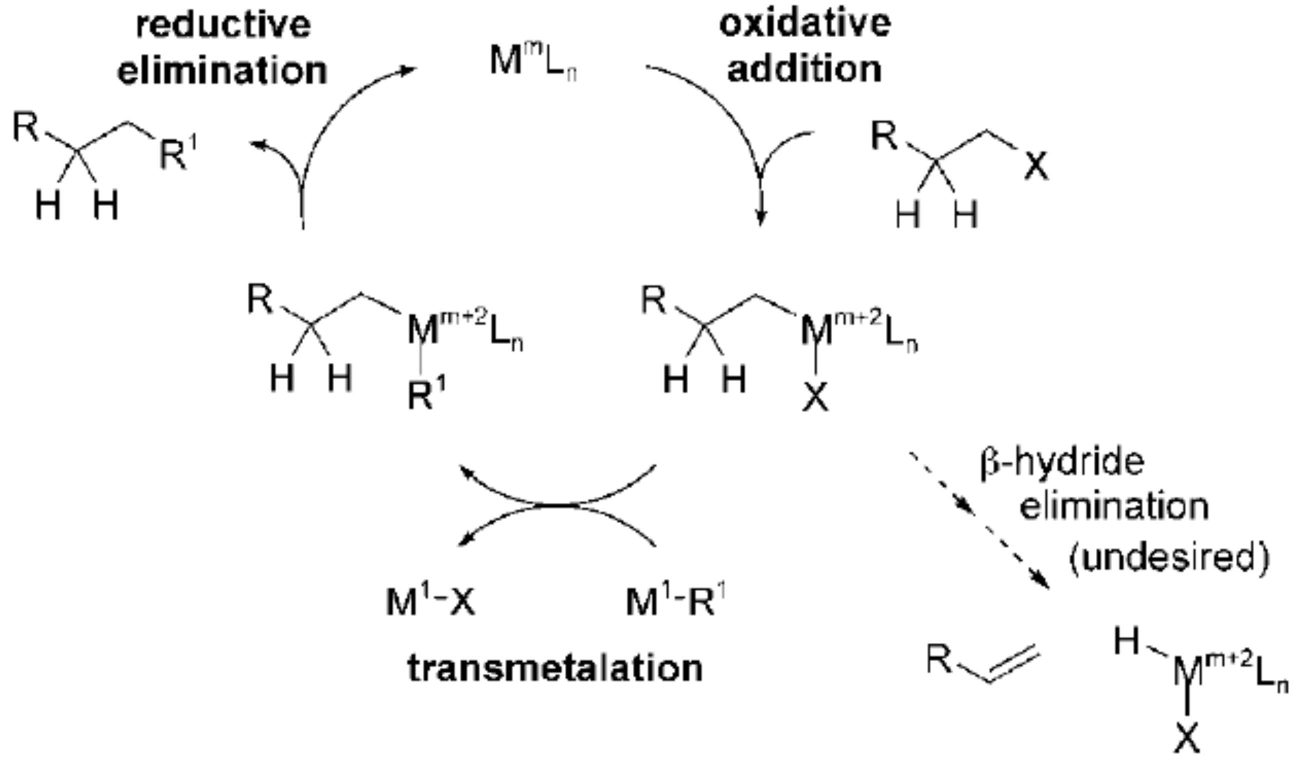
January 17, 2007

General Metal-Catalyzed Cross-Coupling Mechanism



Problems of Unactivated Alkyl Electrophiles: Pd

- Unactivated alkyl halides (even CH_3I) react slowly with Pd^0 complexes.

  Note: The reaction of CH_3I and phosphane-Ni^0 complex is about 10^7 times faster and follows complex pathway in which radical species may be involved.

- β-H-Elimination competes with the usually slower transmetallation.

  Note: β-H-Elimination requires vacant coordination sight and and the feasibility of arranging M-C-C-H atoms in the same plane.

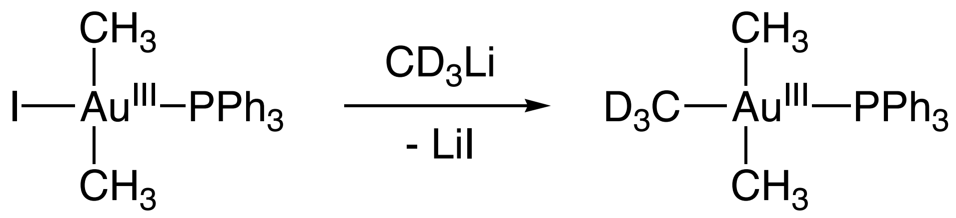
- Reductive elimination from σ-alkyl-π-allyl–Pd^{II} and di-π-allyl–Pd^{II} is usually slow.

  Note: In many cases elimination can be accelerated by the addition of π-acceptors, stabilizing the low-valent state of the metal.

Formation of Alkylmetal Complexes

- Substitution ("metathesis"):

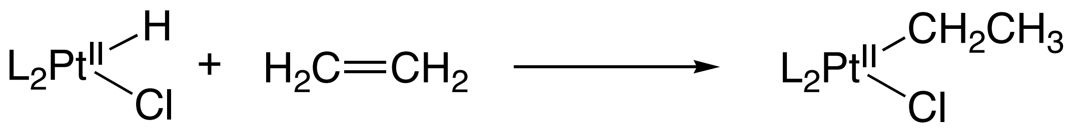
ox. state change = 0



$$I{-}Au^{III}(CH_3)_2{-}PPh_3 \xrightarrow[\text{- LiI}]{CD_3Li} D_3C{-}Au^{III}(CH_3)_2{-}PPh_3$$

- Olefin insertion into metal-ligand bond:

ox. state change = 0



$$L_2Pt^{II}(H)(Cl) + H_2C{=}CH_2 \longrightarrow L_2Pt^{II}(CH_2CH_3)(Cl)$$

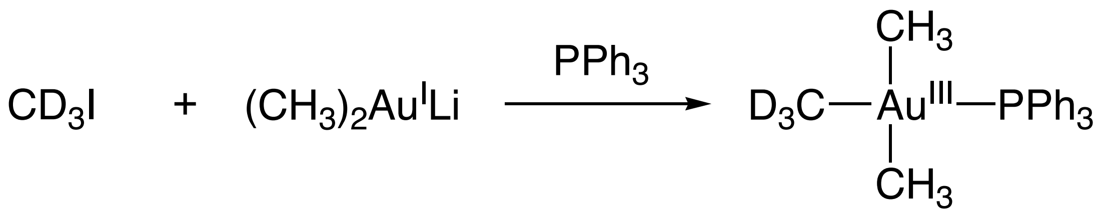
- Radical oxidative addition:

ox. state change = +1

$$CH_3^{\bullet} + Cr^{II}en^{2+} \longrightarrow H_3C{-}Cr^{III}en^{2+}$$

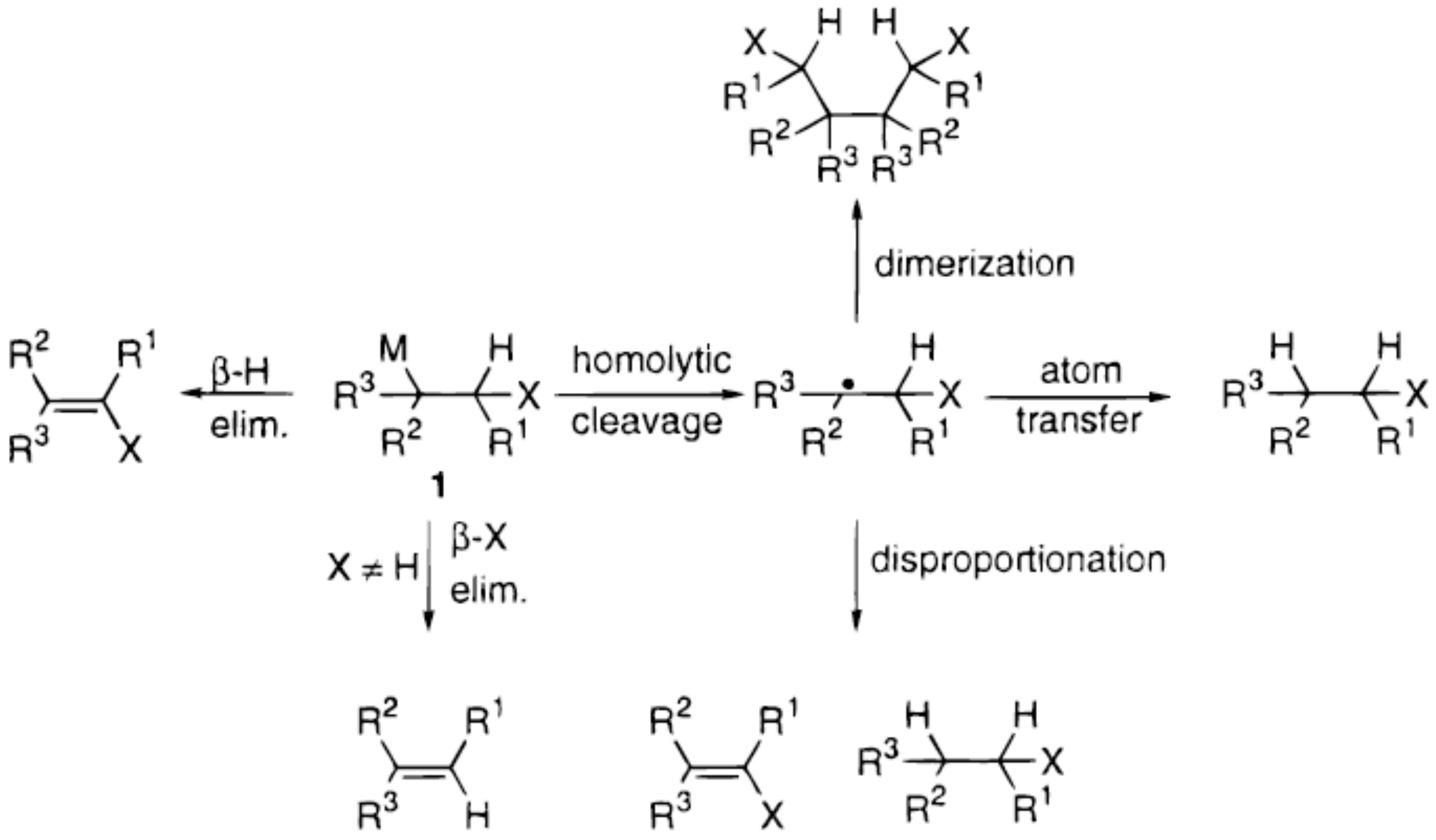
- Carbocation (or its precursor) oxidative addition:

ox. state change = +2



$$CD_3I + (CH_3)_2Au^{I}Li \xrightarrow{PPh_3} D_3C{-}Au^{III}(CH_3)_2{-}PPh_3$$

Decomposition of Alkylmetal Complexes



T.-Y. Luh *et. al.*, *Chem. Rev.* **2000**, *100*, 3187 - 3204

Outline: Reactions

1. Early examples
2. Copper-catalyzed reactions
3. Nickel-catalyzed reactions
4. Palladium-catalyzed reactions
5. Other catalysts

Early Examples Including Copper: Cuprates and Kochi Coupling

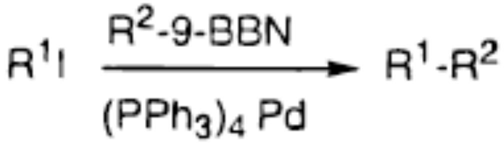
$$R_2CuLi \quad + \quad R'\text{—}LG \longrightarrow R\text{—}R'$$

R, R' - mostly 1°; LG = X

$$R\text{—}MgX \quad + \quad R'\text{—}LG \xrightarrow[\sim 10\%]{Li_2CuCl_4} R\text{—}R'$$

R, R' - mostly 1°; LG = RCOO, X, OTs, etc.

Suzuki Coupling: Some Alkyliodides

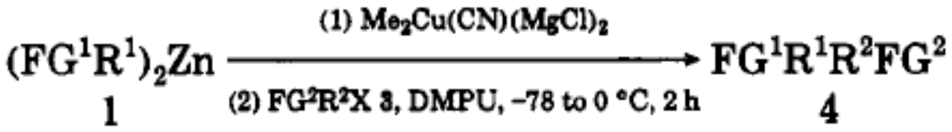


$$R^1I \xrightarrow[(PPh_3)_4\,Pd]{R^2\text{-9-BBN}} R^1\text{-}R^2$$

R^1	R^2	% yield
Me	$MeO_2C(CH_2)_{10}$	71
C_6H_{13}	C_8H_{17}	64^b
t-Bu	$MeO_2C(CH_2)_{10}$	45
C_6H_{13}	$BnOCH_2CH_2CHMe$	58^b
	$MeO_2C(CH_2)_{10}$	54^b
$NC(CH_2)_3$	$Me_2C{=}CH(CH_2)_2CHMe(CH_2)_3$-	61
$C_{10}H_{21}$	$Me(CH_2)_3CH{=}CH$	64^b
	Ph	55^b

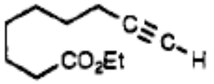
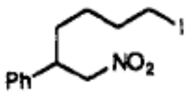
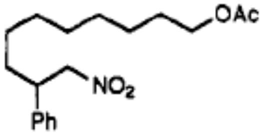
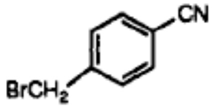
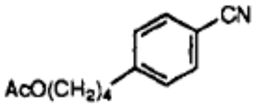
Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691 - 694

Coupling Stoichiometric in Copper



$$\underset{\mathbf{1}}{(FG^1R^1)_2Zn} \xrightarrow[\text{(2) } FG^2R^2X \ \mathbf{3}\text{, DMPU, –78 to 0 °C, 2 h}]{\text{(1) } Me_2Cu(CN)(MgCl)_2} \underset{\mathbf{4}}{FG^1R^1R^2FG^2}$$

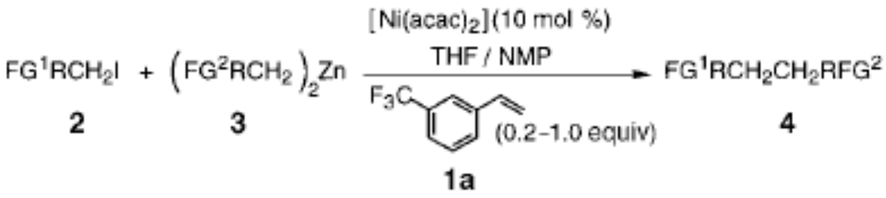
Table I. Cross-Coupling Products 4a–j Prepared from the Reaction of the Zinc–Copper Reagents 2 and the Iodides or Benzylic Bromides 3

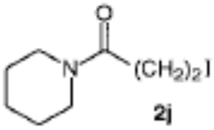
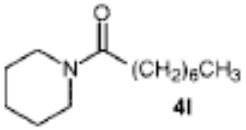
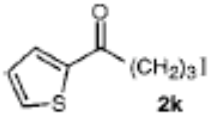
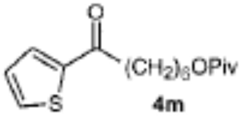
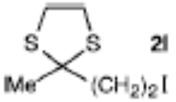
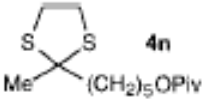
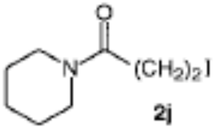
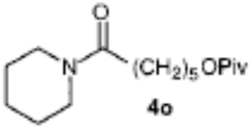
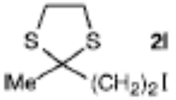
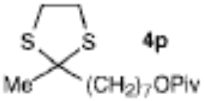
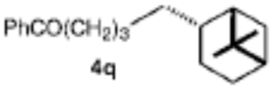
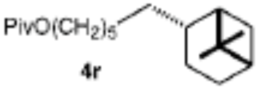
entry	$(FGR)_2Cu(CN)(MgX)_2$ 2 (FGR)	alkyl halide 3	product of type 4		yield (%)[a]
1	$AcO(CH_2)_5$	OctI	$AcO(CH_2)_{12}CH_3$	**4a**	80 (77)[b]
2	$AcO(CH_2)_5$	$EtO_2C(CH_2)_3I$	$AcO(CH_2)_8CO_2Et$	**4b**	74 (65)[b]
3	$AcO(CH_2)_5$	$NC(CH_2)_3I$	$AcO(CH_2)_8CN$	**4c**	81
4	$EtO_2C(CH_2)_3$	OctI	$EtO_2C(CH_2)_{10}CH_3$	**4d**	72
5	$EtO_2C(CH_2)_3$	$I(CH_2)_3C{\equiv}CH$		**4e**	71
6	$AcO(CH_2)_4$			**4f**	83
7	$AcO(CH_2)_4$	$PhCH_2N(Tf)(CH_2)_3I$	$PhCH_2N(Tf)(CH_2)_7OAc$	**4g**	87
8	$PhCH_2N(Tf)(CH_2)_3$	$NC(CH_2)_3I$	$PhCH_2N(Tf)(CH_2)_6CN$	**4h**	77
9	$NC(CH_2)_6$	$PhCH_2Br$	$NC(CH_2)_7Ph$	**4i**	93
10	$AcO(CH_2)_3$			**4j**	88

[a] Isolated yields of analytically pure products. [b] Yield obtained using the copper reagent $(FGR)_2Cu(CN)Li_2{\cdot}Me_2Zn$.

Tucker, C.E.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 4781 - 4782

Nickel-Catalyzed Coupling of Zinc Derivatives

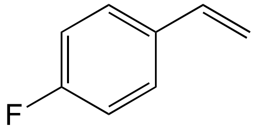


Entry	Iodalkane 2	R_2Zn 3, R =	4	Yield [%][a]	Co-cat. (equiv)
1	$PhS(CH_2)_3I$ **2g**	**3a**, Pent	$PhS(CH_2)_7CH_3$ **4g**	71	**1a** (0.5)
2	$PivO(CH_2)_5I$ **2h**[b]	**3a**	$PivO(CH_2)_9CH_3$ **4h**	78	**1a** (0.3)
3	$PhCO(CH_2)_3I$ **2c**	**3b**, $PivO(CH_2)_3$	$PhCO(CH_2)_6OPiv$ **4i**	76	**1a** (0.2)
4	$BuCO(CH_2)_3I$ **2d**	**3b**	$BuCO(CH_2)_6OPiv$ **4j**	68	**1c** (0.5)
5	$BnO_2C(CH_2)_2I$ **2i**[c]	**3a**	$BnO_2C(CH_2)_6CH_3$ **4k**	76	**1a** (1.0)
6	 **2j**	**3a**	 **4l**	70	**1c** (1.0)
7	 **2k**	**3b**	 **4m**	70	**1c** (0.5)
8	 **2l**	**3b**	 **4n**	70	**1a** (0.5)
9	 **2j**	**3b**	 **4o**	68	**1a** (1.0)
10	 **2l**	**3c**, $PivO(CH_2)_5$	 **4p**	67	**1a** (0.3)
11	$PhCO(CH_2)_3I$ **2c**	**3d**, 	 **4q**	66	**1c** (1.0)
12	$PivO(CH_2)_5I$ **2h**	**3d**	 **4r**	74	**1a** (1.0)

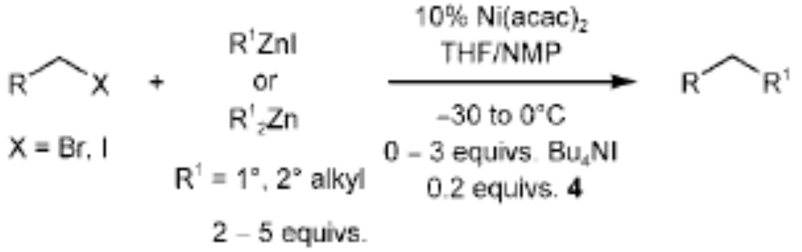
[a] Yields of the isolated, analytically pure products. [b] Piv = pivaloyl. [c] Bn = benzyl.

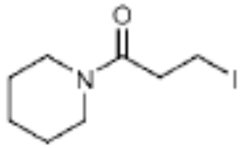
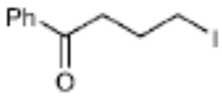
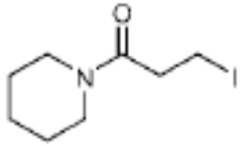
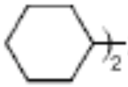
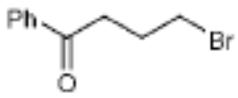
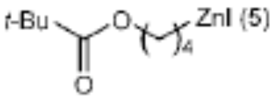
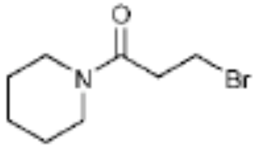
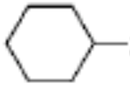
P. Knochel *et. al., ACIEE* **1998**, 2387

Nickel-Catalyzed Coupling: 2° Organozinc Derivatives



4



Entry	Alkyl Halide	Organozinc Reagent (equivs.)	Conditions (time; temp; Bu_4NI)	Yield [%]
1		*n*-pentylZnI (3)	30 h; 0 °C; 3 equivs.	62
2		*n*-pentylZnI (5)	30 h; 0 °C; 3 equivs.	71
3		*i*-Pr_2Zn (2)	3 h; –30 °C; 0 equivs.	63
4		 Zn (4)	16 h; –15 °C; 0 equivs.	73
5		 (5)	20 h; –5 °C; 3 equivs.	73
6		 ZnI (3)	16 h; –5 °C; 3 equivs.	63

Jensen, A.E.; Knochel, P. *J. Org. Chem*. **2002**, *67*, 79 - 85

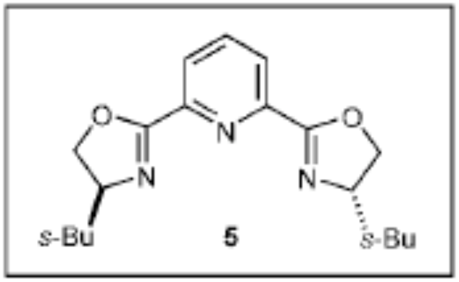
Nickel-Catalyzed Coupling: 2° Halides

$$R_{alkyl}-X \quad + \quad R^1_{alkyl}-ZnY \xrightarrow[\text{DMA, rt, 20 h}]{\substack{\text{4\% Ni(cod)}_2 \\ \text{8\% } s\text{-Bu-Py-box } (\mathbf{5})}} R_{alkyl}-R^1_{alkyl}$$

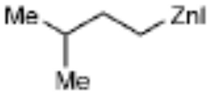
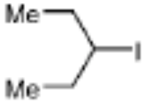
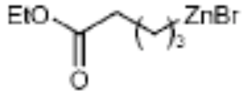
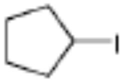
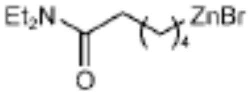
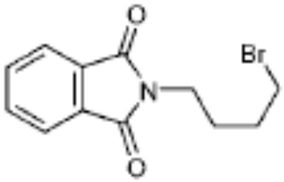
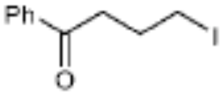
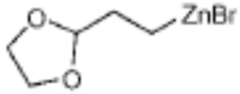
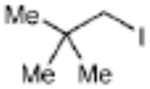
R_{alkyl} = 1°, 2°
X = Br, I

1.6 equivs.

62 – 88%

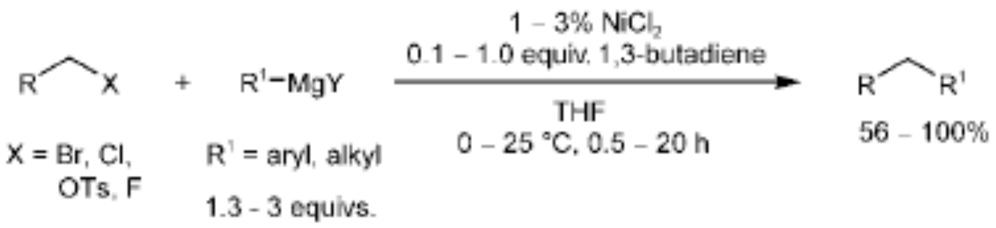


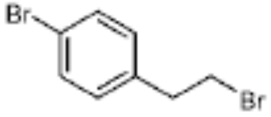
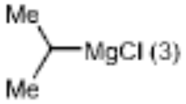
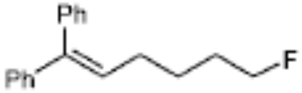
5

Entry	Alkyl Halide	Alkylzinc Halide	Yield [%]
1			66
2			62
3			78
4			65
5			74
6			73

Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* **2003**, *125*, 14726

Nickel-Catalyzed Coupling: Grignard Reagents, Revised

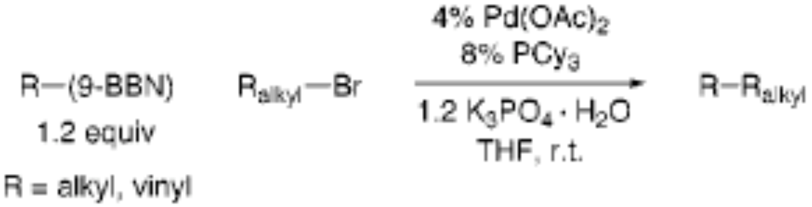


Entry	Alkyl Electrophile	Grignard Reagent (equivs.)	Conditions (% NiCl$_2$; % diene)	Yield [%][a]
1		*n*-BuMgCl (1.3)	1; 10	100
2		EtMgBr (1.3)	3; 30	87
3		PhMgBr (1.3)	3; 100	56
4	*n*-octyl-Br		3; 30	72
5	*n*-octyl-Cl	*n*-BuMgCl (2)	3; 50	96
6		*n*-PrMgBr[b]	3; 100	72

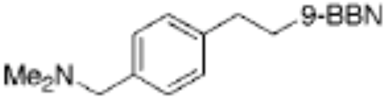
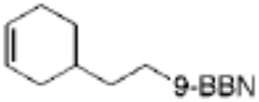
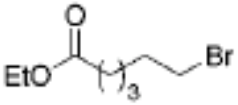
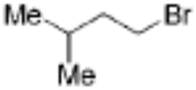
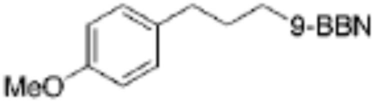
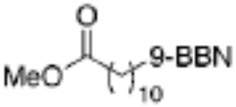
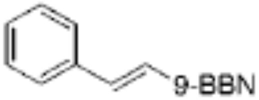
[a] Yield determined by GC.
[b] Amount of Grignard reagent not reported.

N. Kambe *et. al.*, *JACS* **2002**, *124*, 4222; *JACS* **2003**, *125*, 5646

Suzuki Coupling: Alkyl Bromides

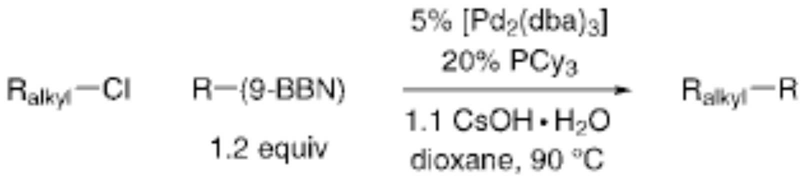


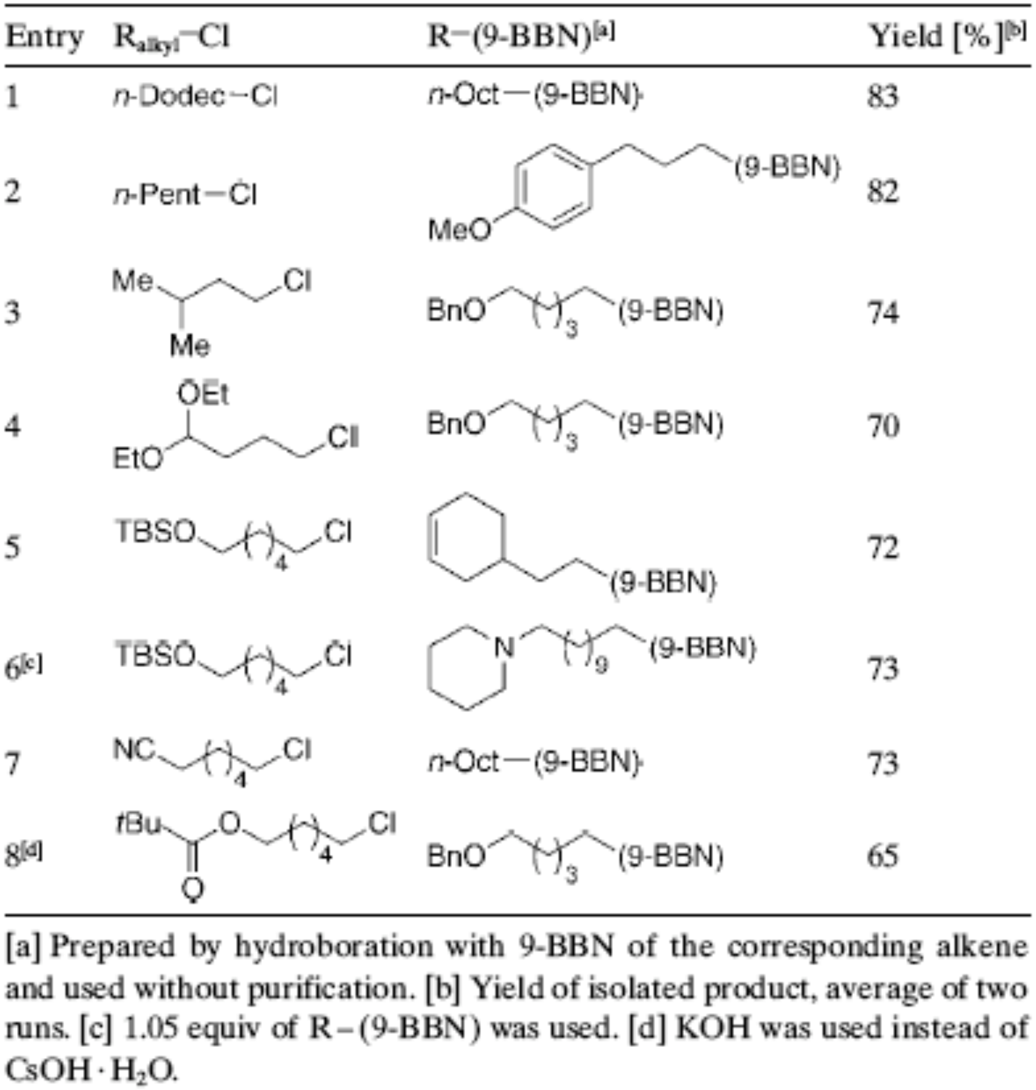
Netherton, M.R.; Dai, C.; Neuschutz, K.; Fu, G.C. *J. Am. Chem. Soc.* **2001**, *123*, 10099

entry	R—(9-BBN)[a]	R$_{alkyl}$—Br	yield (%)[b]
1	*n*-Hex—(9-BBN)	*n*-Dodec—Br	93
2		*n*-Dodec—Br	78[c]
3		*n*-Dodec—Br	85
4			58
5			72
6		*n*-Hex—Br	80
7			81
8			81
9		*n*-Dodec—Br	66

[a] Prepared by hydroboration with 9-BBN of the corresponding alkene/alkyne and used without purification. [b] Isolated yield, average of two runs. [c] 1.05 equiv of R-(9-BBN) was used.

Suzuki Coupling: Alkyl Chlorides



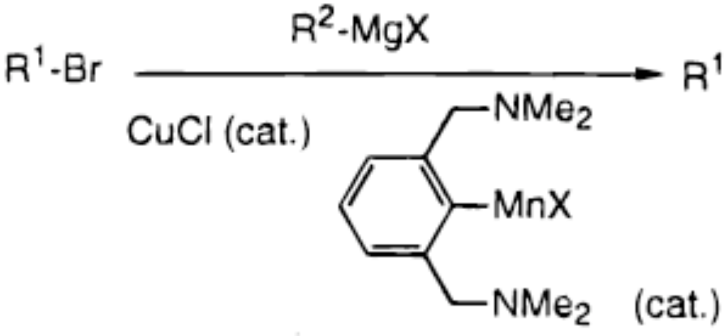


Entry	R_{alkyl}–Cl	R–(9-BBN)[a]	Yield [%][b]
1	*n*-Dodec–Cl	*n*-Oct–(9-BBN)	83
2	*n*-Pent–Cl	MeO, (9-BBN)	82
3	Me, Cl, Me	BnO, $(\,)_3$, (9-BBN)	74
4	OEt, EtO, Cl	BnO, $(\,)_3$, (9-BBN)	70
5	TBSO, $(\,)_4$, Cl	(9-BBN)	72
6[c]	TBSO, $(\,)_4$, Cl	N, $(\,)_9$, (9-BBN)	73
7	NC, $(\,)_4$, Cl	*n*-Oct–(9-BBN)	73
8[d]	*t*Bu, O, $(\,)_4$, Cl, O	BnO, $(\,)_3$, (9-BBN)	65

[a] Prepared by hydroboration with 9-BBN of the corresponding alkene and used without purification. [b] Yield of isolated product, average of two runs. [c] 1.05 equiv of R–(9-BBN) was used. [d] KOH was used instead of $CsOH \cdot H_2O$.

Kirchhoff, J.H.; Dai, C.; Fu, G.C.
Angew. Chem. Int. Ed. Engl.
2002, *41*, No. 11, 1945

Manganese-Catalyzed Coupling



8 X = Cl_2Li or Bu

R^1	R^2	% yield
C_8H_{17}	Bu	83
	i-Pr	75
	t-Bu	84
	s-Bu	92
BuCHMe	Et	94
	Bu	91
$EtO_2C(CH_2)_2$	Bu	89
$CH_2{=}CH(CH_2)_2$	$C_{14}H_{29}$	91
$Me_3SiC{\equiv}C(CH_2)_2$	$C_{14}H_{29}$	89

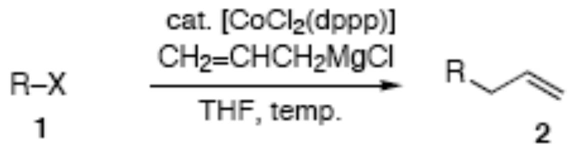
Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, J. T. B. H.; Cahiez,G.; van Koten, G. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 547-548.
Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, J. T. B. H.; Gossage, R. A.; Cahiez, G.; van Koten, G. *J. Organomet. Chem*. **1998**, *558*, 61-69.

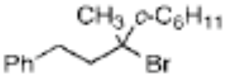
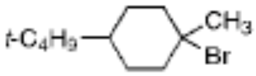
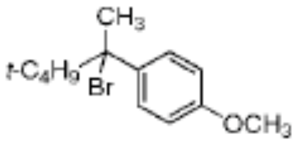
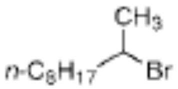
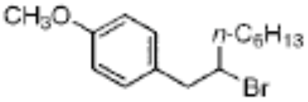
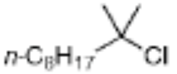
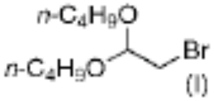
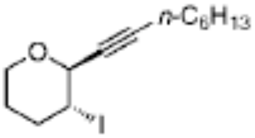
Cobalt-Phosphine-Catalyzed

Cross-coupling

Reaction

Tsuji, T.; Yorimitsu, H.; Oshima, K.
Angew. Chem., Int. Ed.
2002, *41*, 4137-4139



1		Temperature [°C]	Yield of 2 [%]
	**1b**	−20	83
	**1c**[a]	0	76[b]
	**1d**	−20	73[c]
	**1e**	0	57
	**1f**	−20	84
	**1g**	0	30
	1g-I	−40	82
	**1a-Cl**	20	31
	**1h**	0	49
	1h-I	−40	82
	**1i-I**	−40	76[d]

[a] *trans*/*cis* = 87/13. [b] *trans*/*cis* = 82/18. [c] DPPE was used. [d] *trans*/*cis* = 86/14.

Conclusion:

Impossible…

Conclusion:

Impossible…

… Is Nothing!

That’s it, pretty much.