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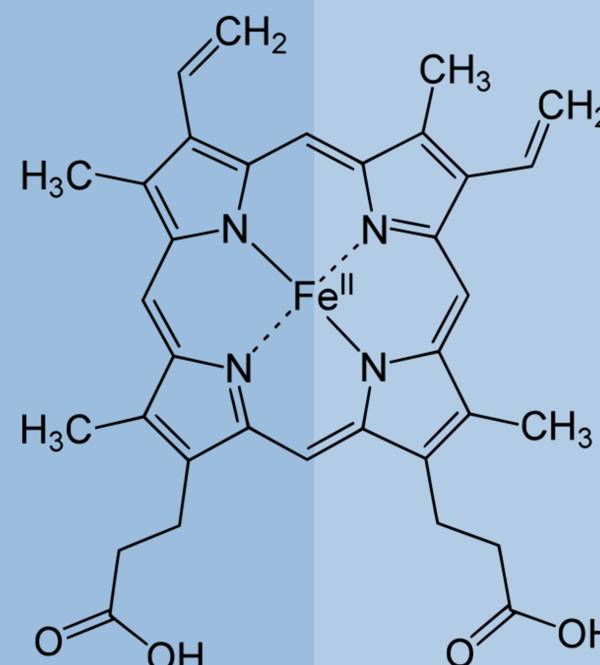
BERN

Iron Catalysis in Organic Synthesis
Multitasking Champion



Current literature
Andrey Kuzovlev
02.03.2017

Introduction

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- Readily available, cheap, relatively nontoxic, 1.300 ppm residual iron is acceptable in drug substances. It is < 10 ppm for other metals.
- Located in center of the d-block, just above Ru, iron is hence "early" and "late" transition metal in the same time.
- Iron spans formal oxidation states ranging from – II to + VI.
- Lewis acidity varies from fairly modest to very high.
- Iron cations binds well to many N- or O-based ligands, N-heterocyclic carbenes.
- Iron-dependent enzymes are vital for all forms of life.

Alois Furstner *ACS Cent. Sci.* **2016**, *2*, 778 – 789.

Catalytic abilities

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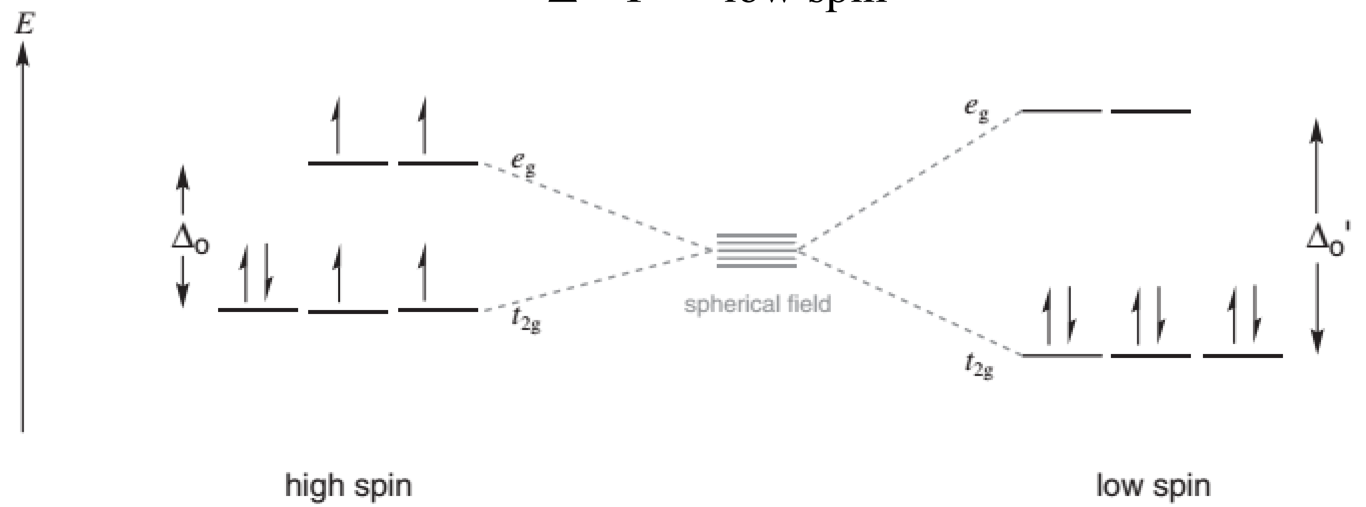
- Heterogenic iron catalysis:
  - Heber-Bosch process (Fe_3O_4)
  - Fischer-Tropsch process (Fe)
  - Conversion of methane to ethylene, aromatics and hydrogen
- Homogeneous catalysis:
  - Reduction of imines and aldehydes
  - Oxidation with peroxides
  - Coupling reactions
  - Cycloaddition
  - Aldol reaction
  - Radical reactions
  - O-H bond insertion
  - Hydrofluorination
  - Hydromethylation

Weak and strong ligands (d^6). Fe^{2+}

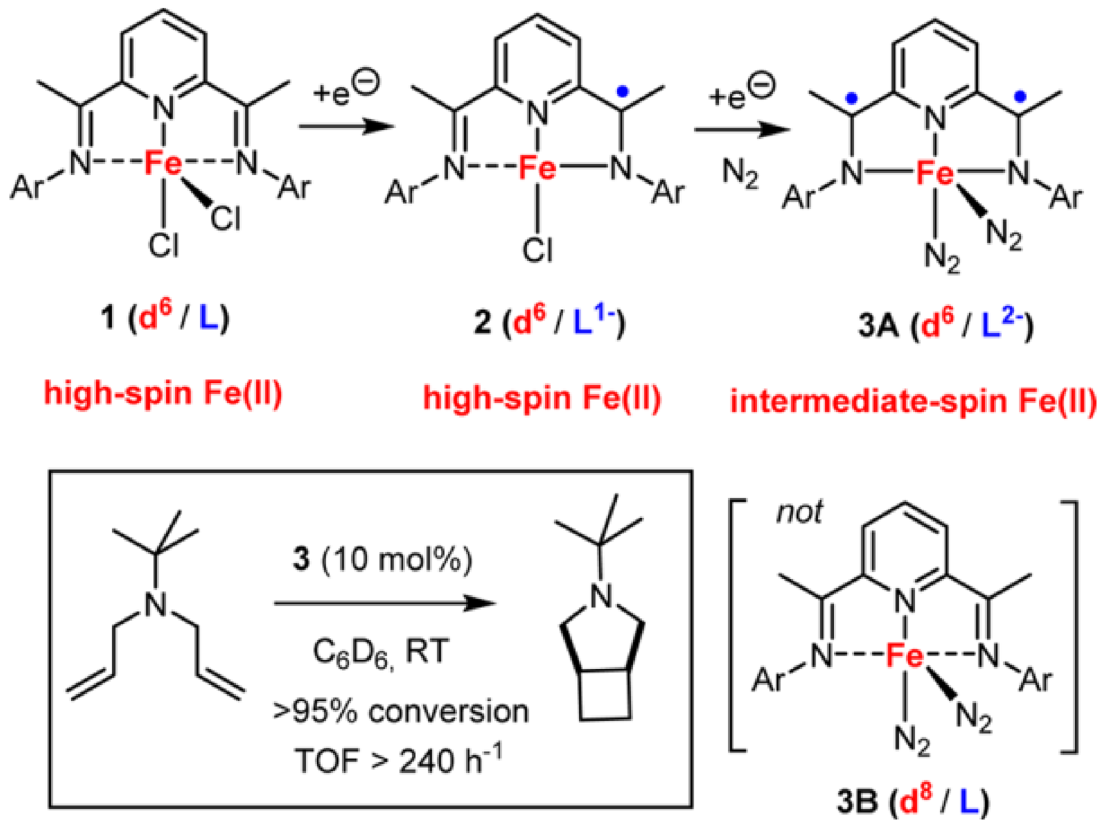
$\Delta < P \rightarrow$ high spin
$\Delta > P \rightarrow$ low spin



$I^- < Br^- < S^{2-} < SCN^- < Cl^- < NO_3^- < N_3^- < F^- < OH^- < C_2O_4^{2-} < H_2O < NCS^- < CH_3CN <$ py $< NH_3 <$ en $<$ 2,2'-bipyridine $<$ phen $< NO_2^- < PPh_3 < CN^- <$ CO

Geoffrey A. Lawrance *Introduction to Coordination Chemistry;* John Wiley and Sons Ltd: Chichester, 2010.

Metal/Ligand Cooperativity. “Non-innocent” Ligands



[a]Ar = 2,6-di(isopropyl)phenyl.

Alois Furstner *ACS Cent. Sci.* **2016**, *2*, 778 – 789.

Intermolecular [2+2] cycloaddition

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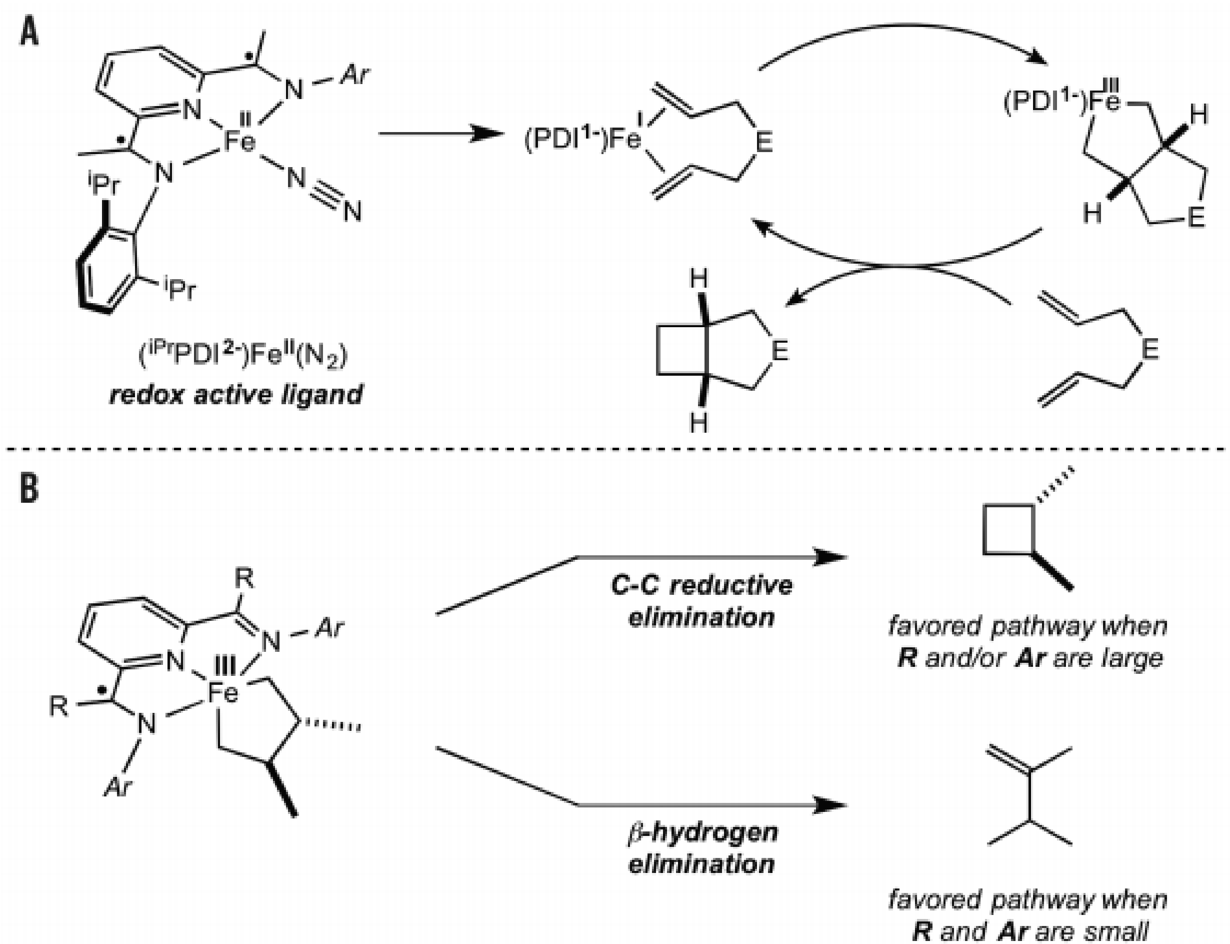
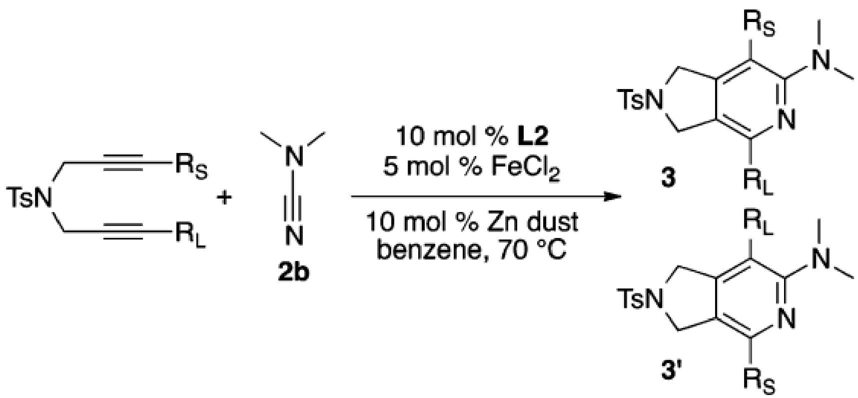
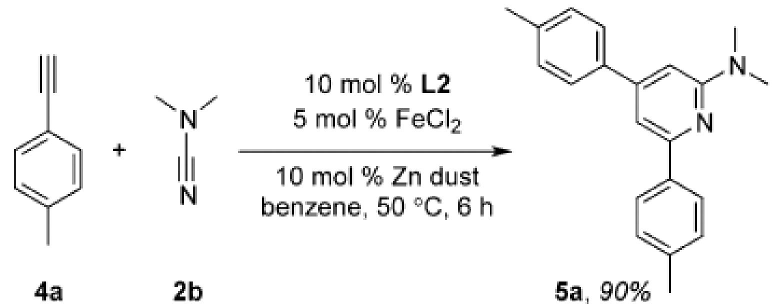


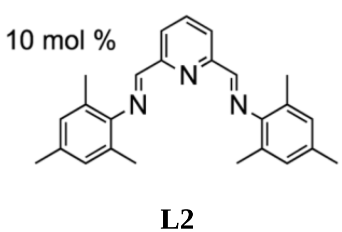
J. M. Hoyt, V. A. Schmidt, A. M. Tondreau, P. J. Chirik *Science* **2015**, *349*, 960 – 963.

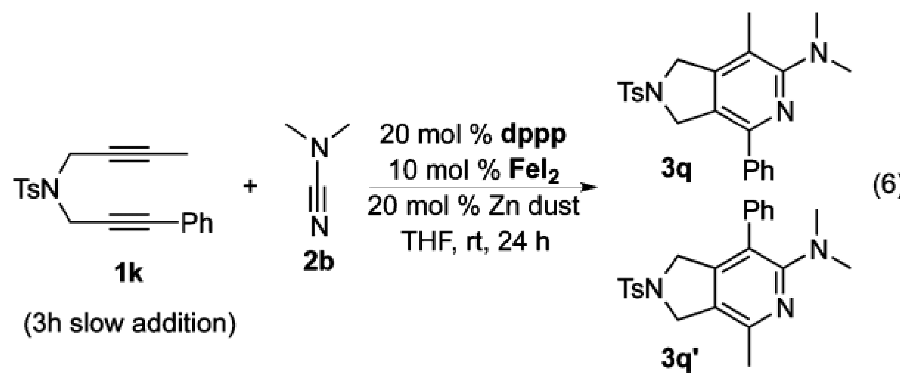
Iron-catalyzed Formation of 2-Aminopyridines



entry	substrate	product	yield[a] (3:3′)[b]
1	**1i**, R_S = H, R_L = Me	**3o**	72 (85:15)
2	**1j**, R_S = Me, R_L = ^{t}Bu	**3p**	80 (86:14)
3	**1k**, R_S = Me, R_L = Ph	**3q**	67 (88:12)







63%, 10:90 (**3q**:**3q'**)

T. K. Lane, B. R. D’Souza, J. Louie *J. Org. Chem.* **2012**, *77*, 7555 – 7563.

Iron-catalyzed Formation of 2-Aminopyridines

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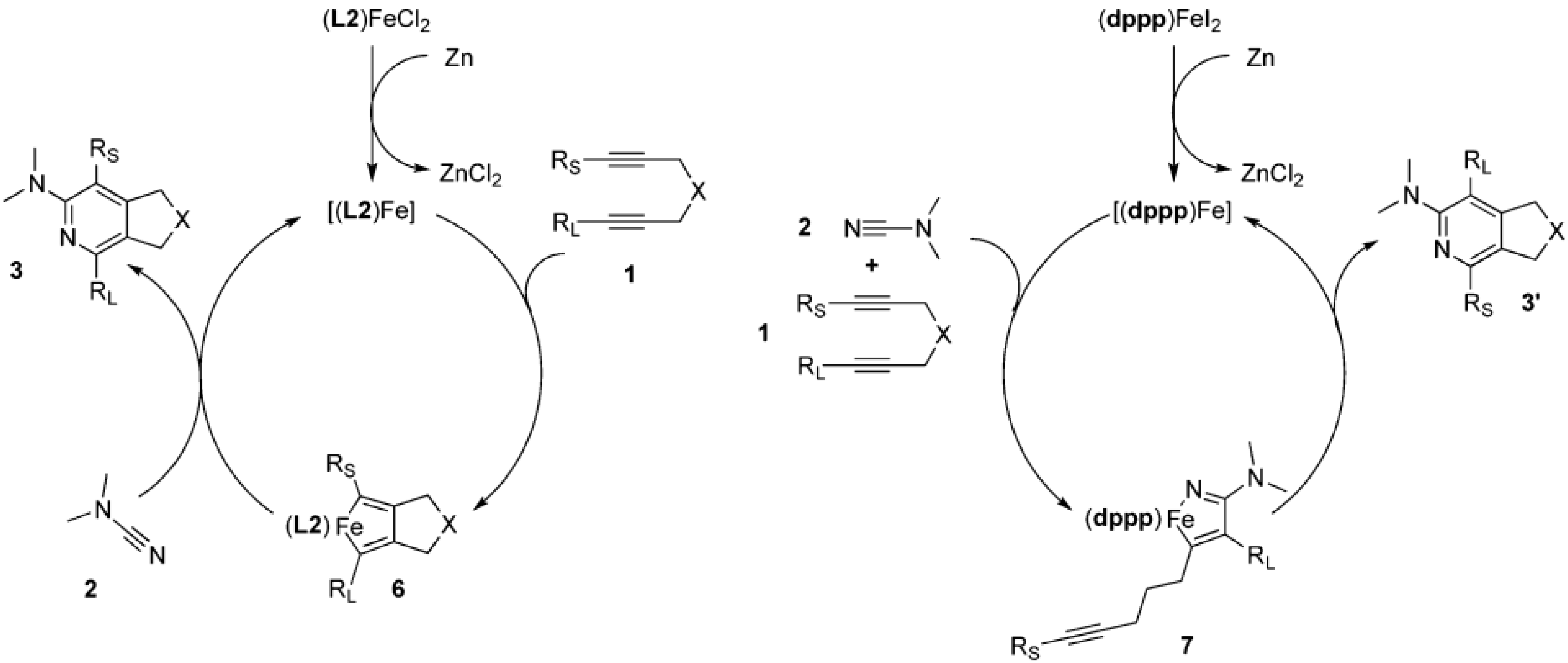
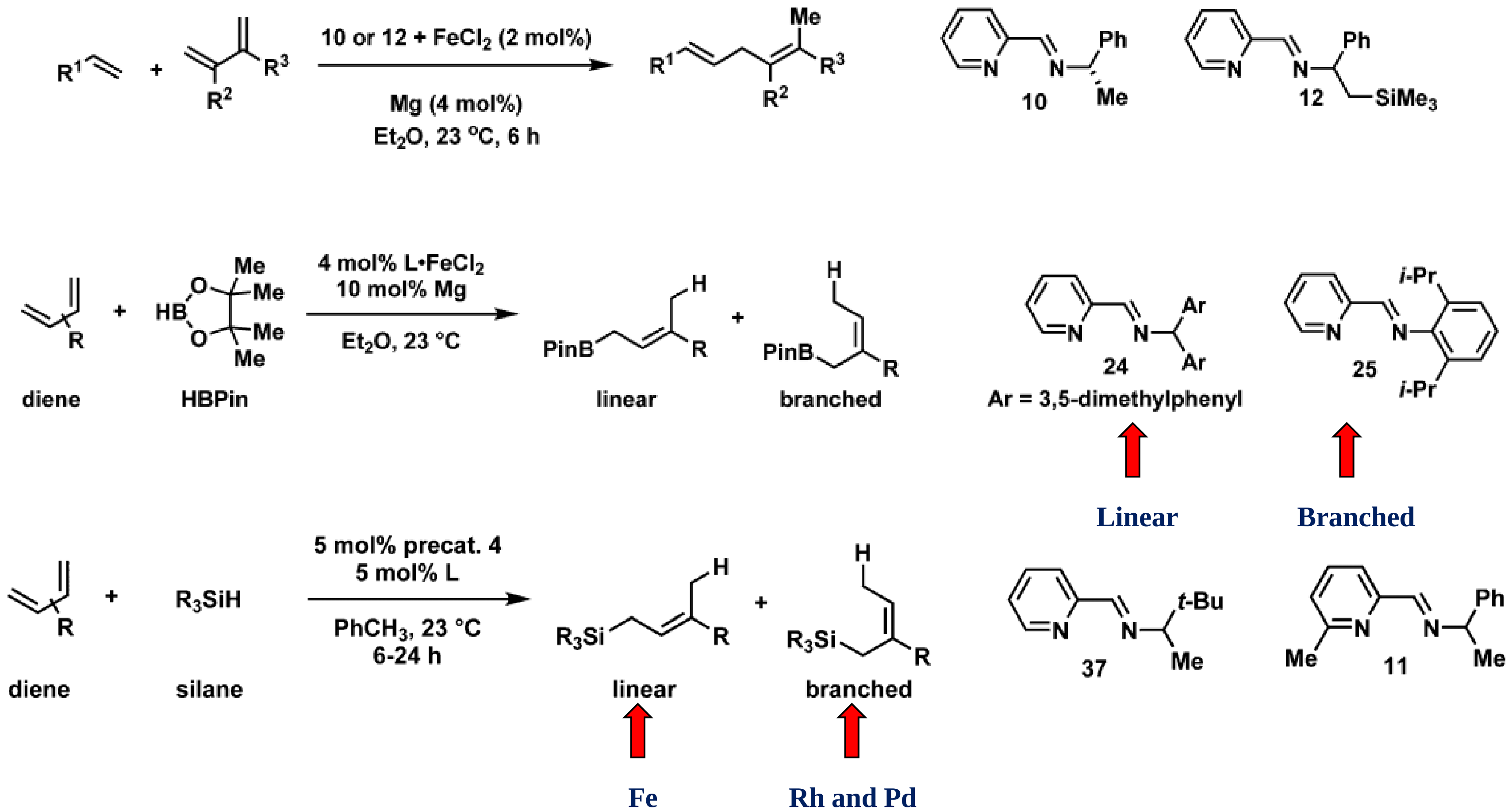


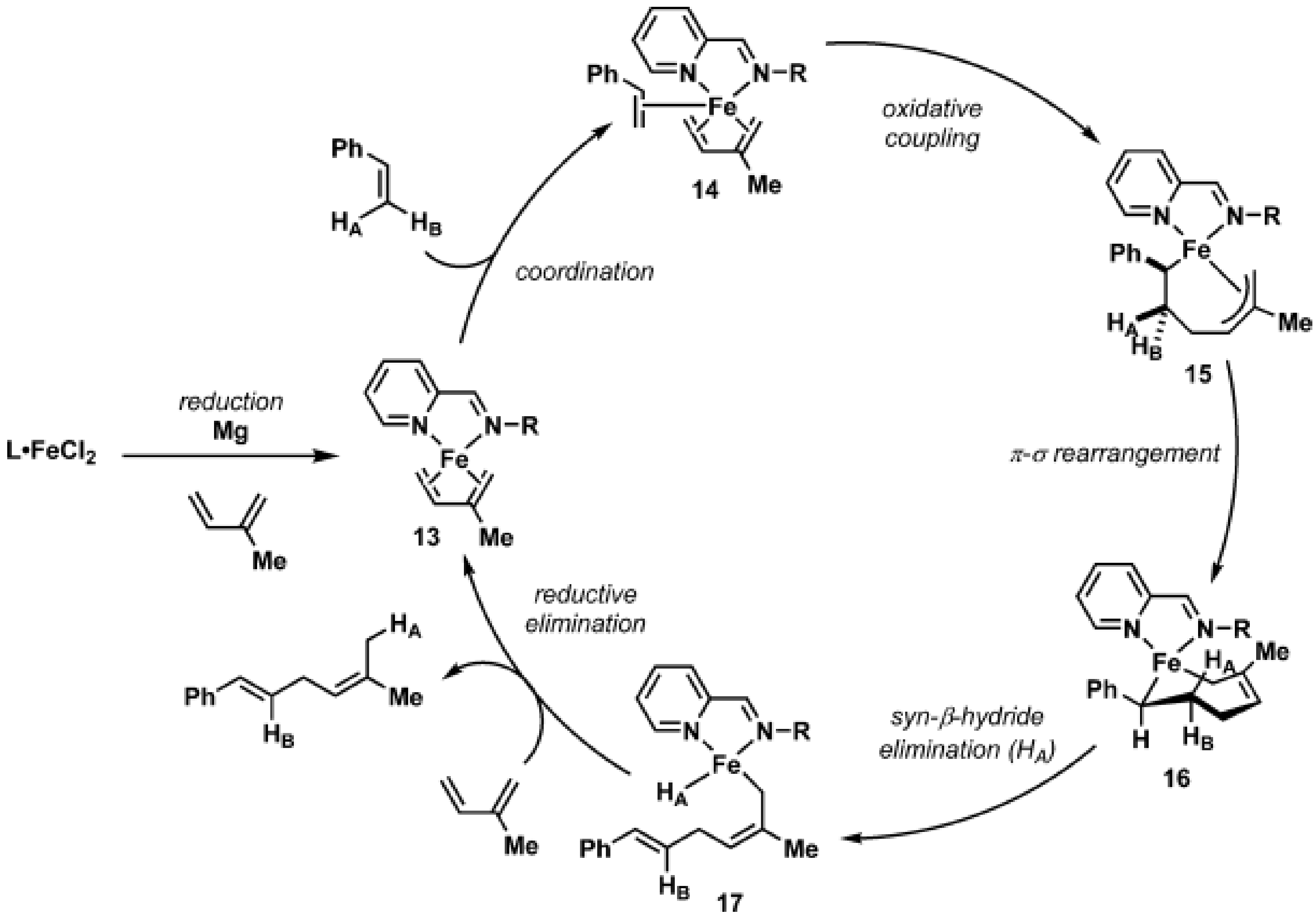
T. K. Lane, B. R. D’Souza, J. Louie *J. Org. Chem.* **2012**, *77*, 7555 – 7563.

Iron-catalyzed 1,4-Functionalization of 1,3-Dienes



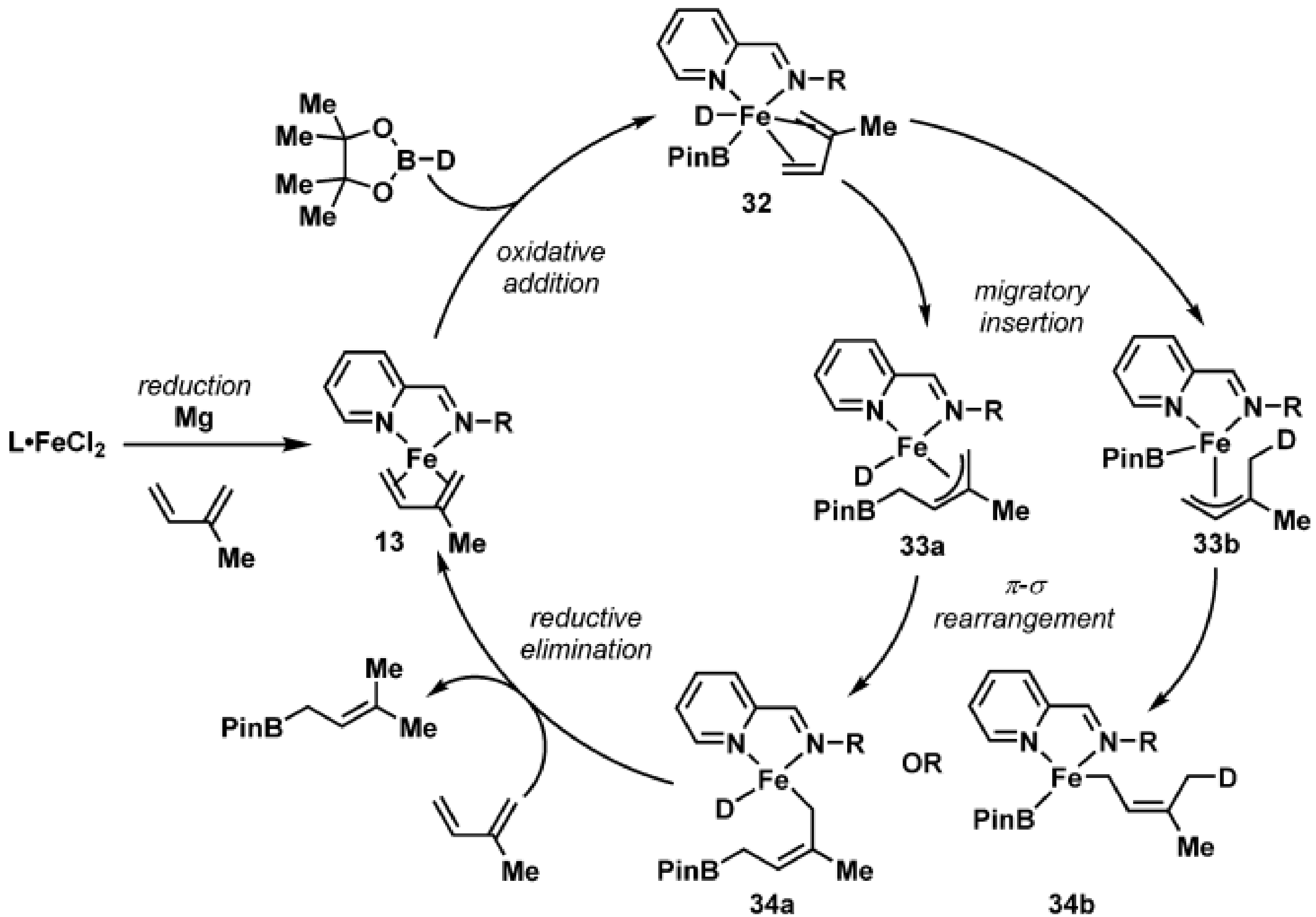
E. McNeill, T. Ritter *Acc. Chem. Res.* **2015**, *48*, 2330 – 2343.

Iron-catalyzed 1,4-Hydrovinylation of 1,3-Dienes



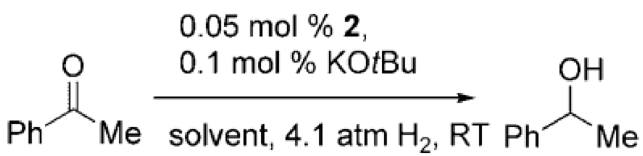
E. McNeill, T. Ritter *Acc. Chem. Res.* **2015**, *48*, 2330 – 2343.

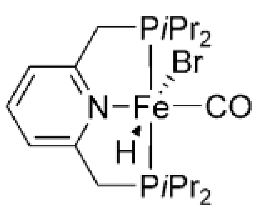
Iron-catalyzed 1,4-Hydroboration of 1,3-Dienes



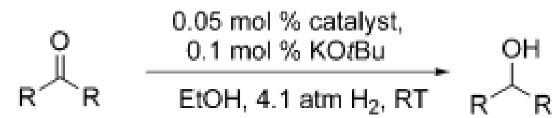
E. McNeill, T. Ritter *Acc. Chem. Res.* **2015**, *48*, 2330 – 2343.

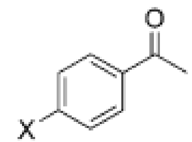
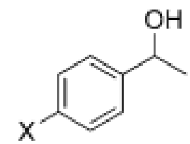
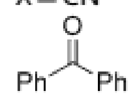
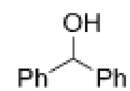
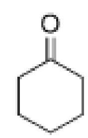
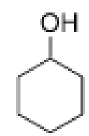
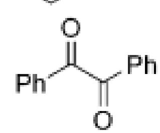
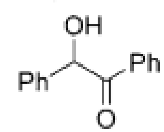
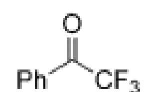
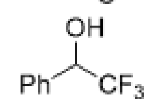
Carbonyl reduction. Pincer complexes





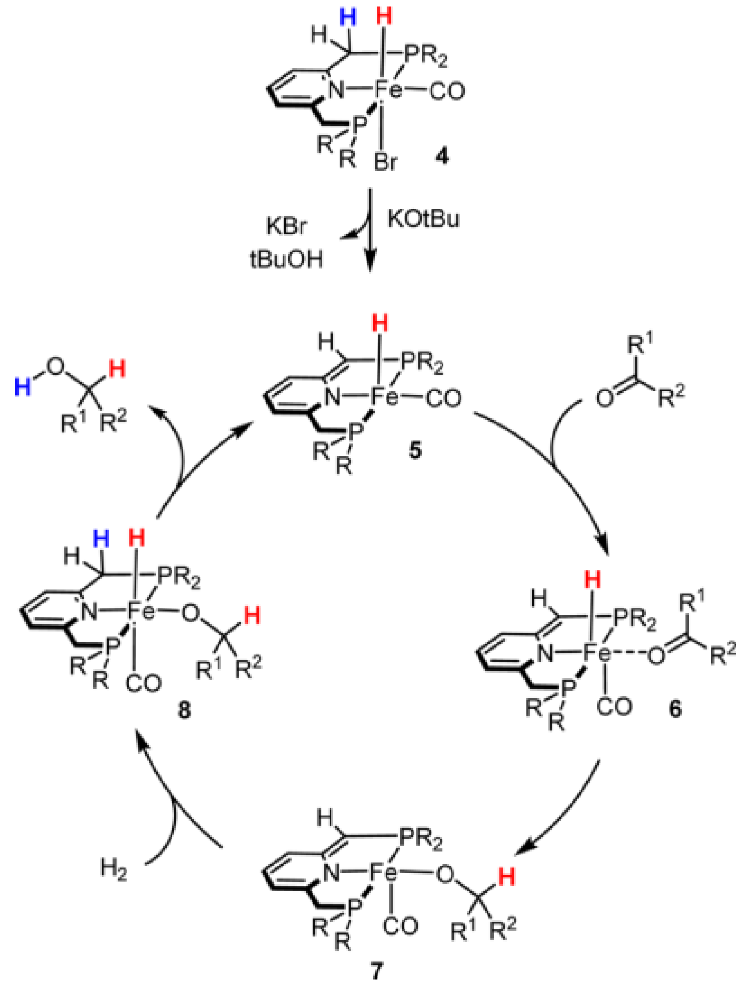
2 86%



Entry	Substrate	Product	*t* [h]	Yield [%][b]	TON
					
1	X=H		21.5	94 (94)	1880
2	X=Cl		18	86 (89)	1720
3	X=Br		22	78 (78)	1560
4	X=Me		22	72 (73)	1440
5	X=NH_2		24	0 (0)	0
6	X=CN		24	0 (0)	0
7			24	70 (74)	1400
8			24	64 (67)	1280
9			20	67	1340
10			15	54 (54)	1080

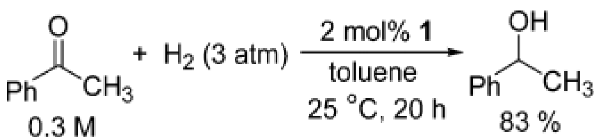
R. Langer, G. Leitus, Y. Ben-David, D. Milstein *Angew. Chem. Int. Ed.* **2011**, *50*, 2120 – 2124.

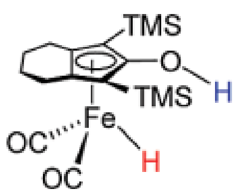
Carbonyl reduction. Pincer complexes



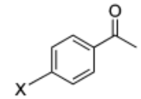
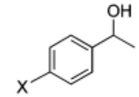
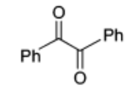
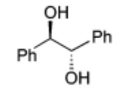
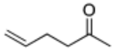
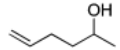
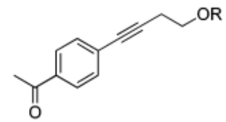
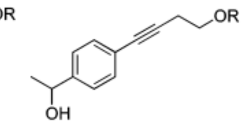
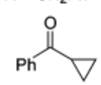
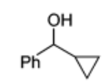
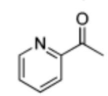
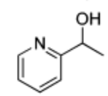
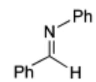
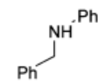
Alois Furstner *ACS Cent. Sci.* **2016**, *2*, 778 – 789.

Carbonyl Reduction. Knolker’s Catalyst



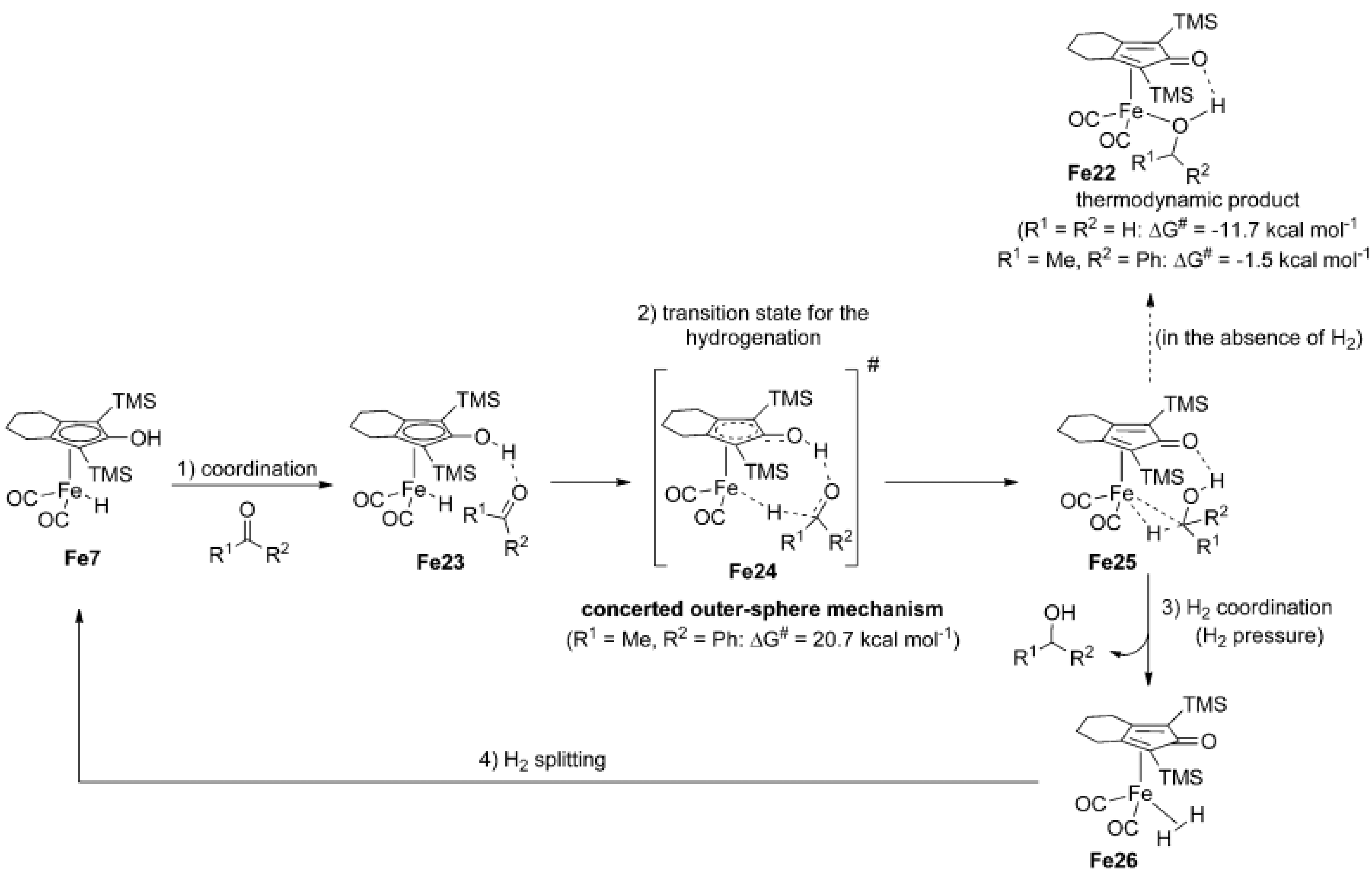


1

entry	substrate	product	time	yield [d]
1	PhCHO	$PhCH_2OH$	1 h	90% (100%)
2	$PhCH_2CH_2COCH_3$	$PhCH_2CH_2CH(OH)CH_3$	24 h	88% (98%)
				
3	X = H		20 h	83% (99%)
4	X = Br		24 h	91% (99%)
5	X = I		20 h	84% (99%)
6	X = NO_2		6 h	89% (99%)
7	X = CN		19 h	(< 1%)
8	PhCOPh	PhCH(OH)Ph	72 h	55% (69%)
9	$PhCOCF_3$	$PhCH(OH)CF_3$	10 min	91% (100%)
10			2 h	86% (100%) (*meso*/*dl* = 25)
11 [b]			36 h	87% (100%)
				
12	R = H		24 h	57% (71%)
13	R = CH_2Ph		20 h	84% (87%)
14			68 h	46% (50%)
15			8 h	87% (100%)
16 [c]			40 h	50% (54%)

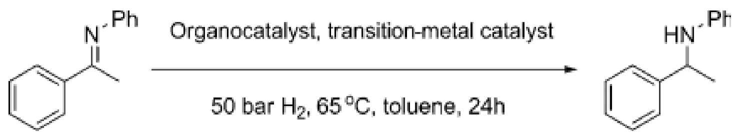
C. P. Casey, H. Guan *J. Am. Chem. Soc.* **2007**, *129*, 5816 – 5817.

Carbonyl Reduction. Knolker's Catalyst



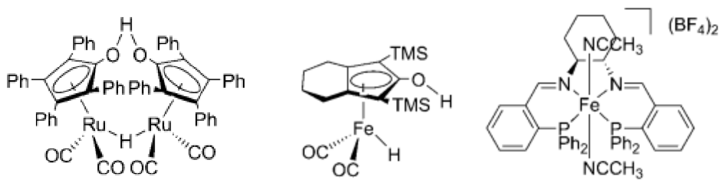
A. Quintard, J. Rodriguez *Ang. Chem. Int. Ed.* **2014**, *53*, 4044 – 4055.

Enantioselective Hydrogenation of Imines

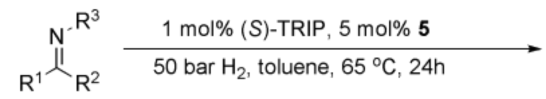


2a → **3a**

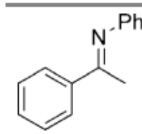
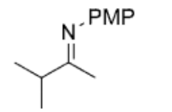
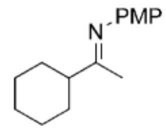
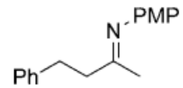
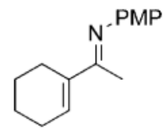
Brønsted catalyst (mol%)	Transition-metal catalyst (mol%)	Conv.[b] [%]	Yield[b] [%]	ee[c] [%]
1e (5)	–	80	0	–
1e (1)	**4** (0.5)	>99	71	8
1e (1)	$[(Ph_3P)_3RhCl]$ (1)	>99	45	0
1e (1)	$[Rh(CO)H(PPh_3)_3]$ (1)	97	3	0
1e (1)	$[\{IrCl(C_8H_{12})\}_2]$ (0.5)	>99	62	0
1e (1)	Rh/C (1)	>99	16	0
1e (1)	Pd/C (1)	>99	35	0
1e (1)	$[Fe_3(CO)_{12}]$ (1.67)	>99	93	0
1e (1)	$[(C_8H_8)Fe(CO)_3]$ (5)	>99	0	–
1e (1)	**6** (5)	85	0	–
1e (1)	**5** (5)	>99	81	94
1e (1)	$FeCl_3$ (5)	98	0	–
1e (1)	$Fe(OAc)_2$ (5)	98	0	–



Shvo complex **4** Knölker's complex **5** (*S*,*S*)-Morris' complex **6**



2 → **3**

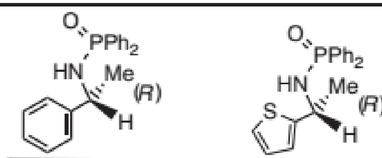
Imine		Yield[b] [%]	ee[c] (*S*) [%]
	**2a**	**3a**: 82 (80)	94
	**2q**	**3q**: 99 (91)	83
	**2r**	**3r**: 99 (93)	81
	**2s**	**3s**: 99 (94)	67
	**2t**	**3r**: 89 (69)	70

S. Zhou, S. Fleischer, K. Junge, M. Beller *Angew. Chem. Int. Ed.* **2011**, *50*, 5120 – 5124.

Amine(imine)diphosphine Iron Catalysts

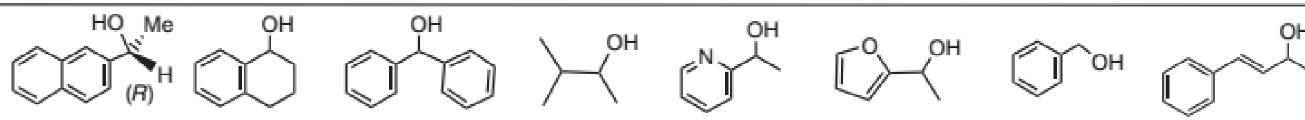
Comparison of catalysts

Amine products using **2a**



	2a	2b	2b*	2c	2a	2c†	2a	2a
Time to equil.:	180 s	180 s	1000 s	180 s	180 s	10 s	20 s	180 s
Yield:	82%	83%	83%	82%	99%	100%	100%	100%
TON at equil.:	5000	5100	5100	5000	6060	2000	100	100
TOF at 50% conv.:	119 s^{-1}	152 s^{-1}	12 s^{-1}	70 s^{-1}	147 s^{-1}	200 s^{-1}	10 s^{-1}	5 s^{-1}
ee at 10 s:	88%	86%	86%	92%	91%	98%	>99%	>99%
ee at equil.:	78%	70%	80%	90%	90%	98%	>99%	>99%

Alcohol products using **2a**

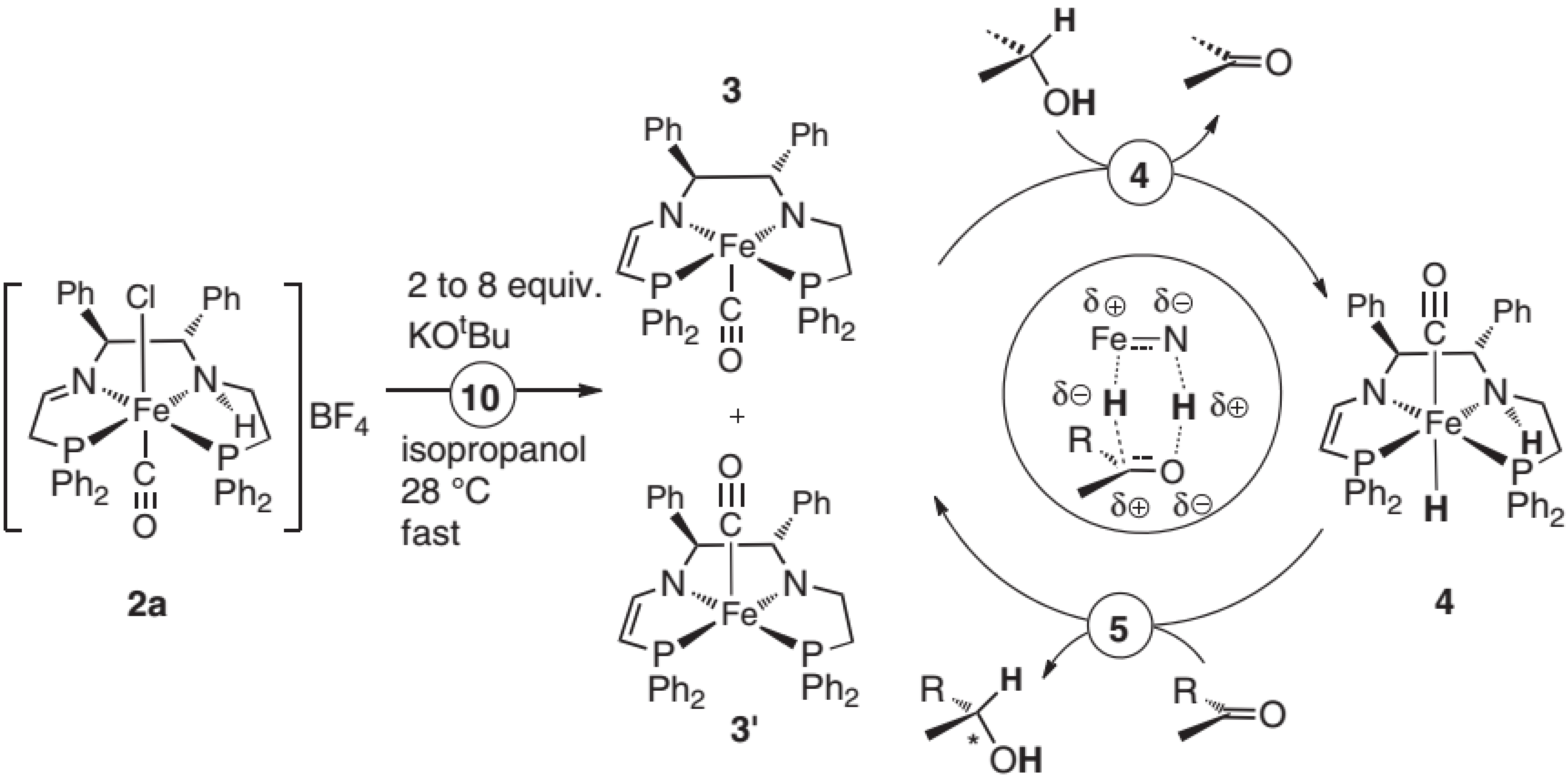


Time to equil.:	180 s	1 h	10 min	1 h	6 min	6 min	25 s	4 min
Yield:	84%	73%	88%	67%	98%	84%	99%	55%
TON at equil.:	5140	4470	5400	4100	6000	5140	6060	3370
TOF at 50% conv.:	158 s^{-1}	4 s^{-1}	38 s^{-1}	3 s^{-1}	100 s^{-1}	61 s^{-1}	242 s^{-1}	14 s^{-1}
ee at 10 s:	92%	34%	-	57%	25%	51%	-	40%
ee at equil.:	83%	33%	-	54%	24%	31%	-	40%

*[Cat, **2b**] = 6.73 × 10^{-5} M, [KO^{t}Bu] = 1.35 × 10^{-4} M, [substrate] = 0.412 M, [^{i}PrOH] = 12.4 M, 28°C. †Ketone: Cat ratio = 2000:1 to prevent poisoning by the acidic alcohol product.

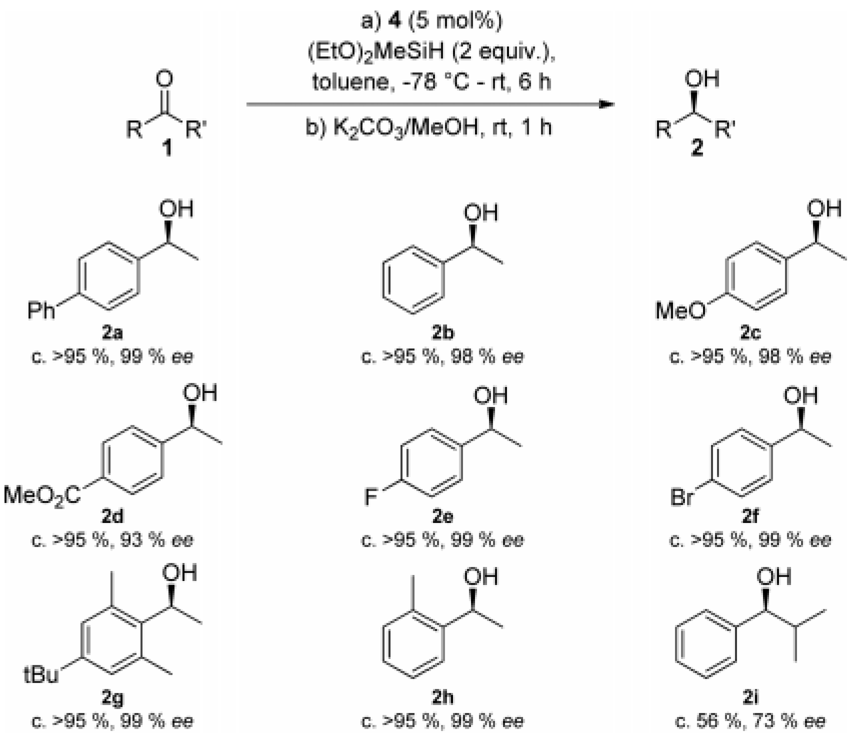
W. Zuo, A. J. Lough, Y. F. Li, R. H. Morris *Science* **2013**, *342*, 1080 – 1083.

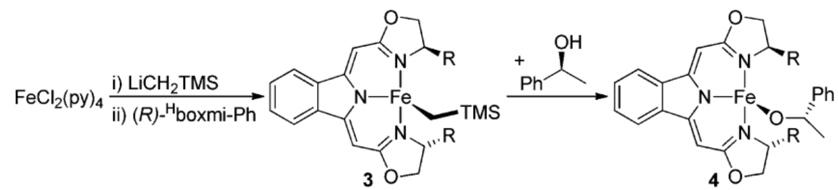
Amine(imine)diphosphine Iron Catalysts

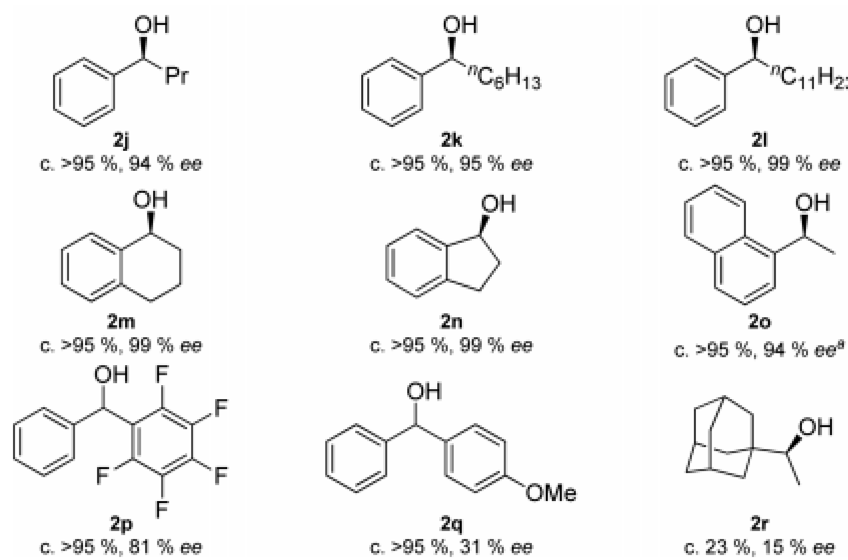


W. Zuo, A. J. Lough, Y. F. Li, R. H. Morris *Science* **2013**, *342*, 1080 – 1083.

Nobel Metal Reactivity and Selectivity
Hydrosilylation of Ketones

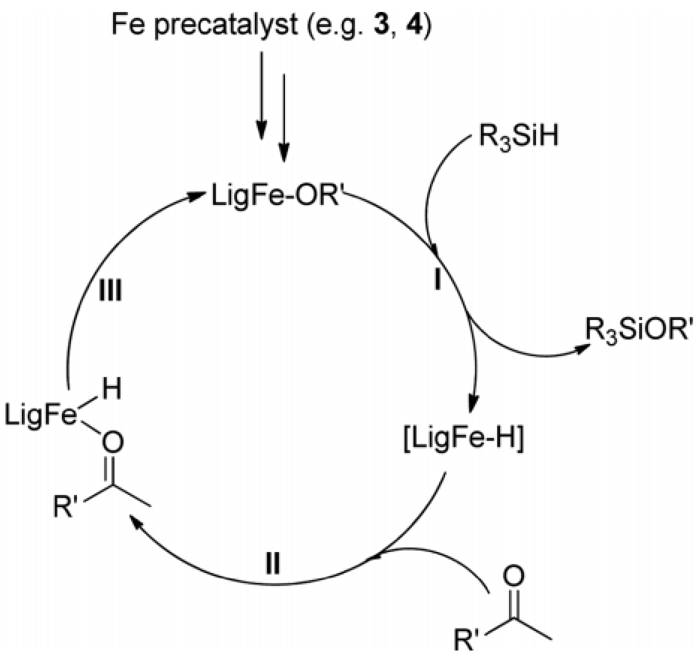


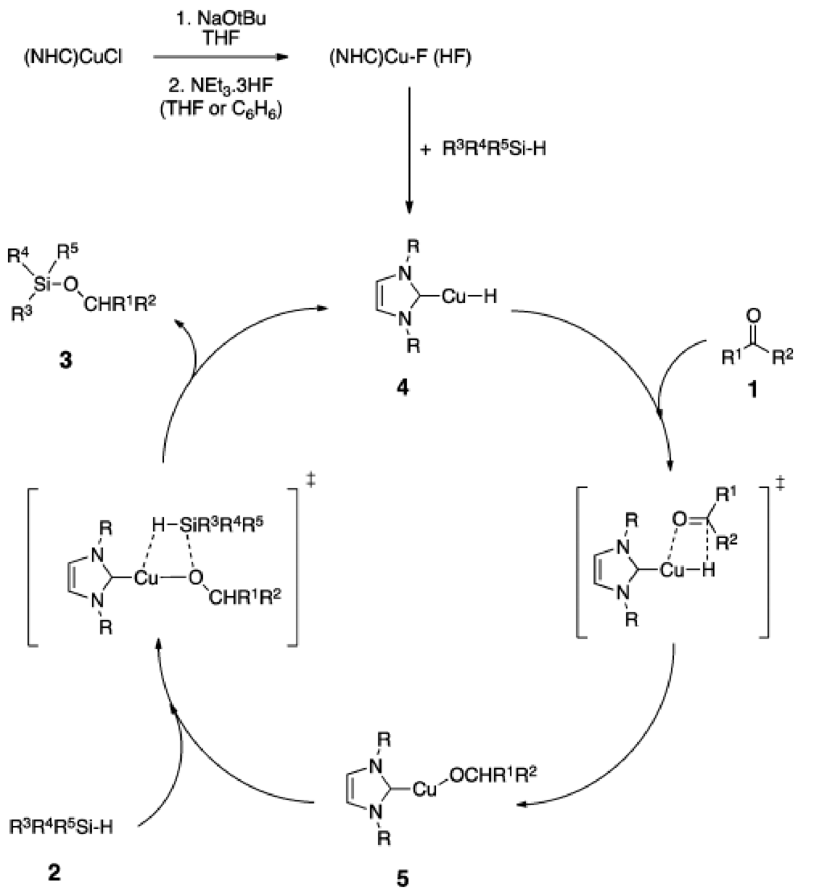




T. Bleith, H. Wadepohl, L. H. Gade *J. Am. Chem. Soc.* **2015**, *137*, 2456 – 2459.

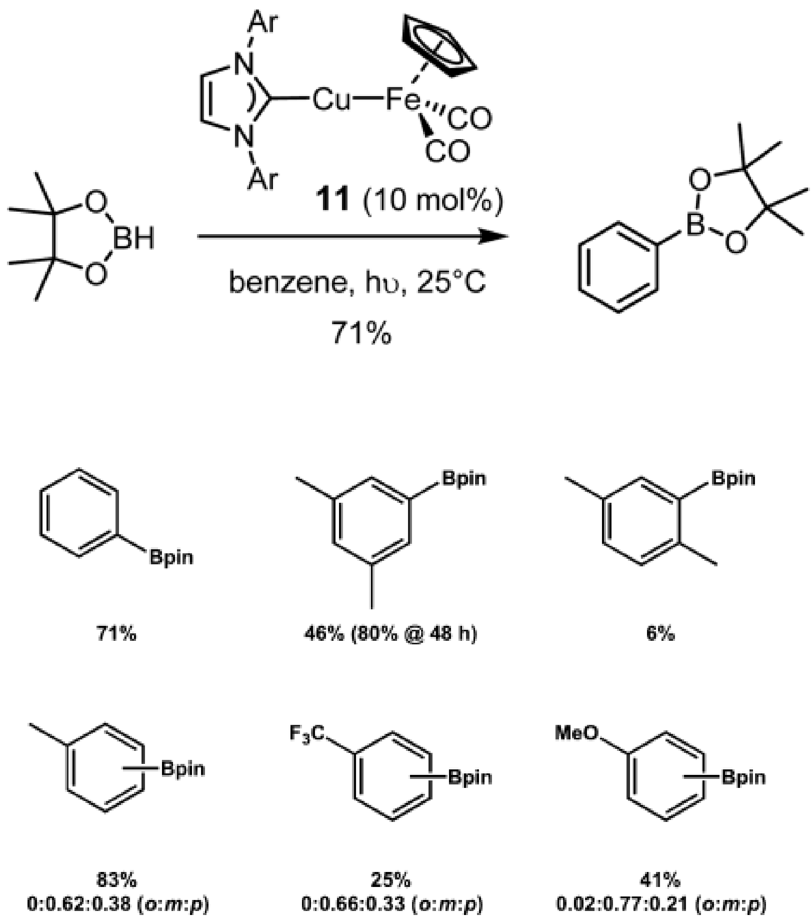
Nobel Metal Reactivity and Selectivity
Hydrosilylation of Ketones

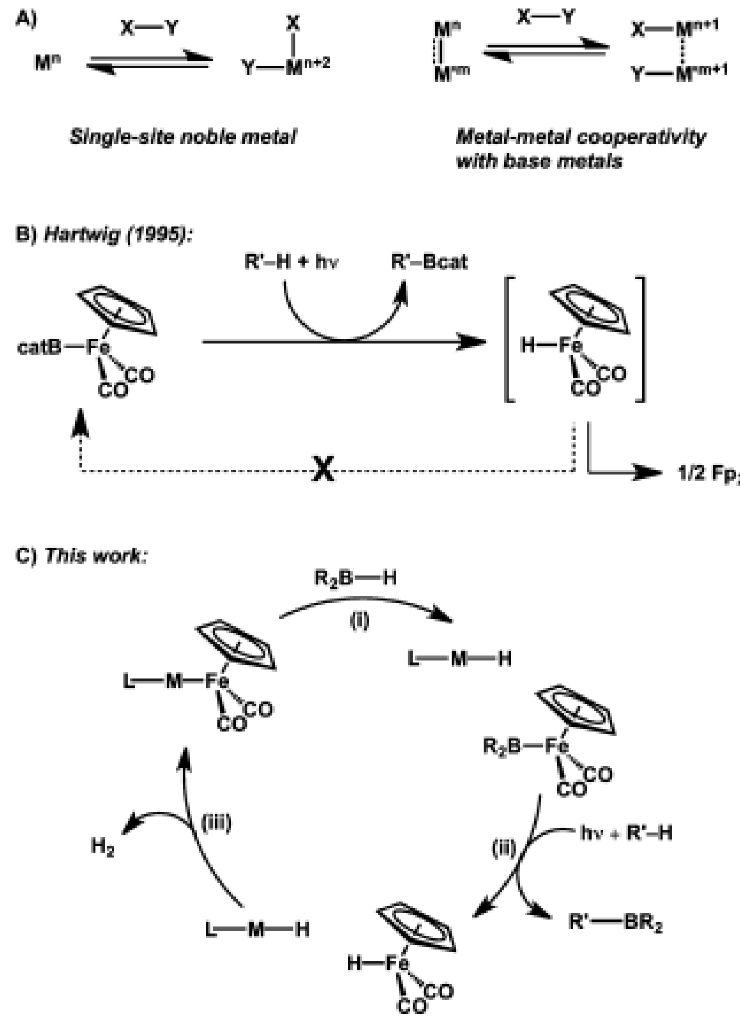




T. Bleith, H. Wadepohl, L. H. Gade *J. Am. Chem. Soc.* **2015**, *137*, 2456 – 2459.
T. Vergote et al. *Organometallics* **2014**, *33*, 1953 – 1963.

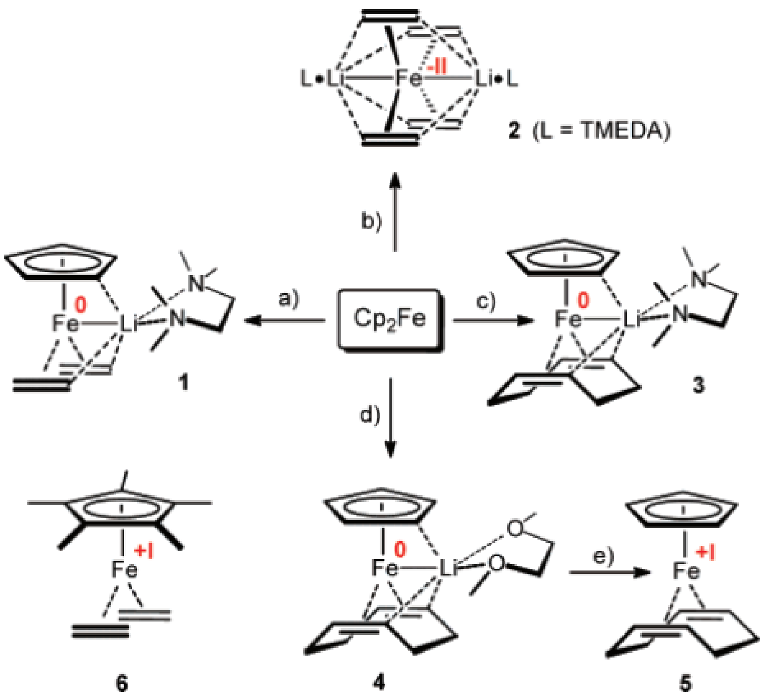
Metal/Metal Cooperativity

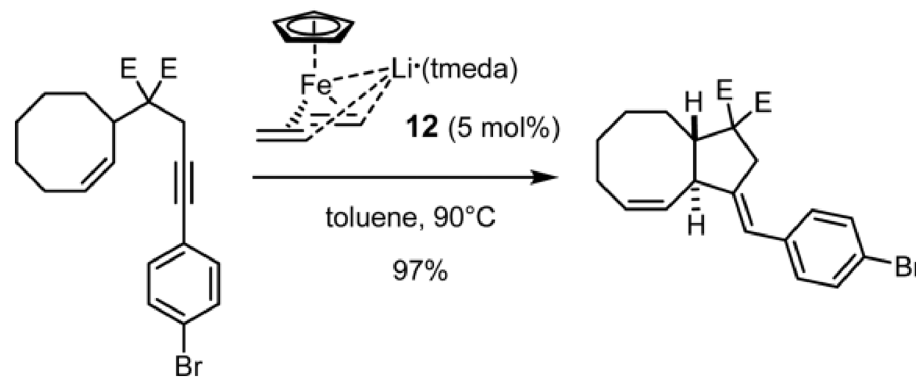




T. J. Mazzacano, N. P. Mankad *J. Am. Chem. Soc.* **2013**, *135*, 17258 – 17261.

Metal/Metal Cooperativity





Alois Furstner *ACS Cent. Sci.* **2016**, *2*, 778 – 789.
Alois Furstner et al. *J. Am. Chem. Soc.* **2008**, *130*, 1992 – 2004.

Asymetric Aqueous Mukaiyama Aldol Addition

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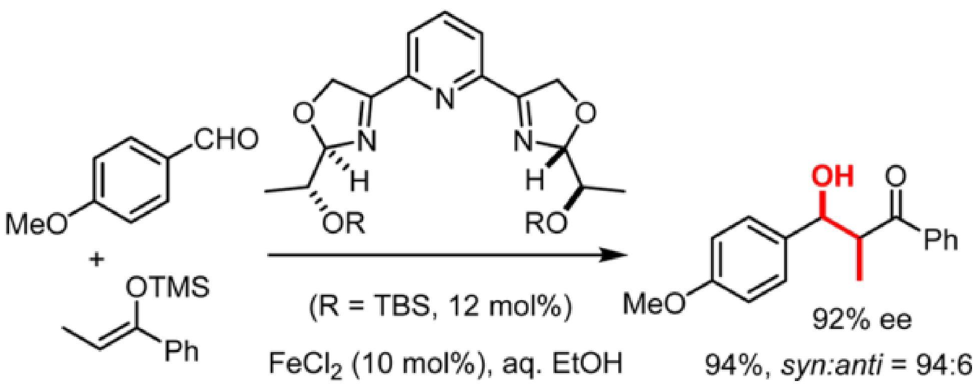
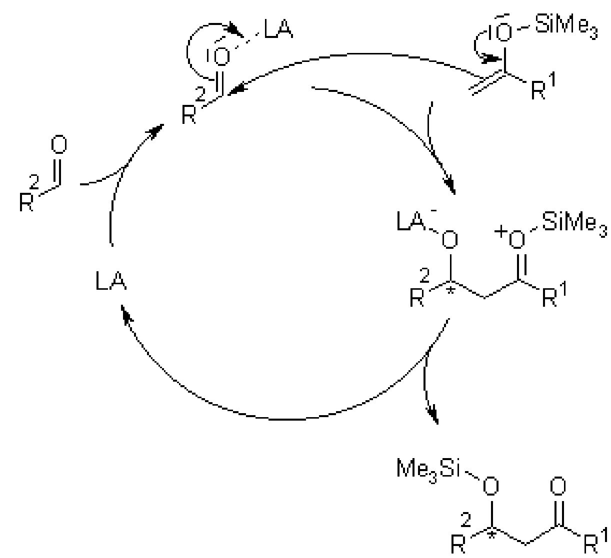
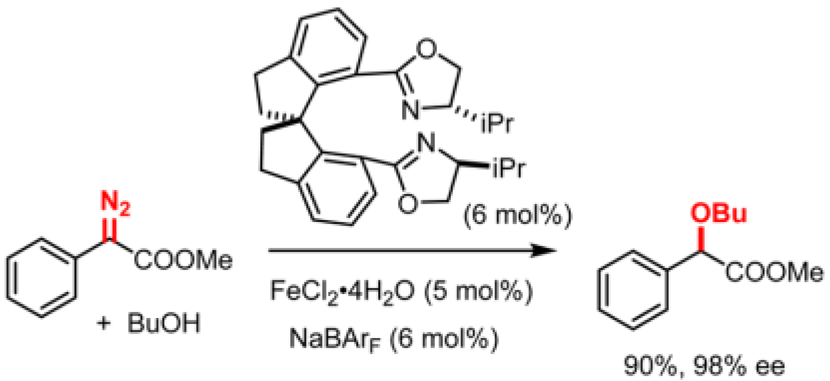
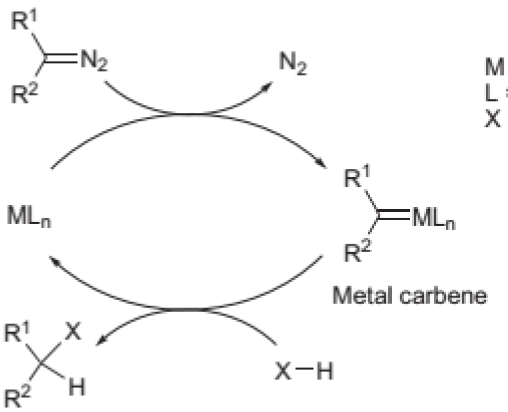




J. Jankowska, J. Paradowska, B. Rakiel, J. Mlinarski *J. Org. Chem.* **2007**, *72*, 2228-2231.

O-H bond insertion

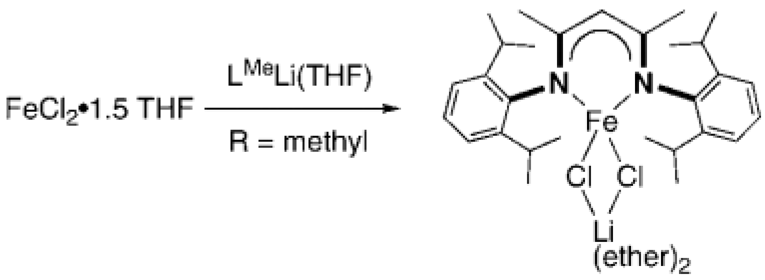


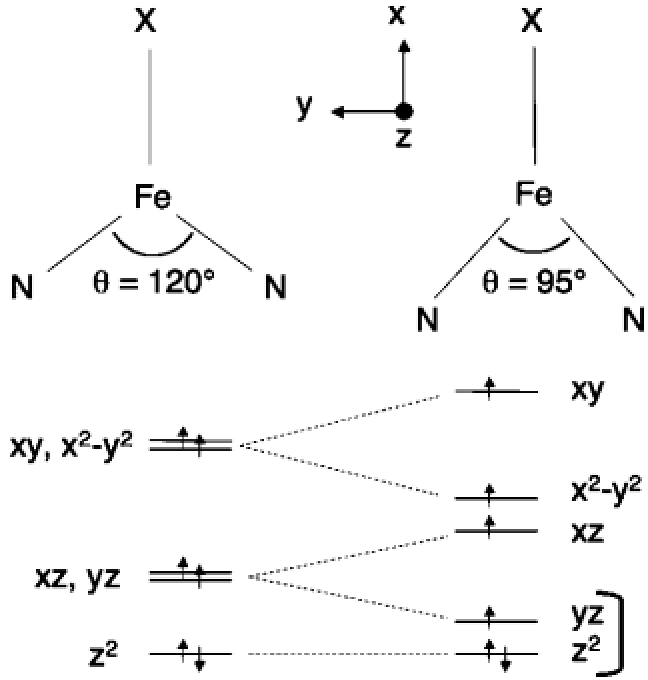


M = Transition metal
L = Ligand
X = C, Si, O, N, S, etc.

Zhu, S.-F.; Cai, Y.; Mao, H.-X.; Xie, J.-H.; Zhou, Q.-L. *Nat. Chem.* **2010**, *2*, 546-551.

Three-Coordinate Iron Complexes





P. L. Holland *Acc. Chem. Res.* **2008**, *41*, 905-914.

C-H Functionalization

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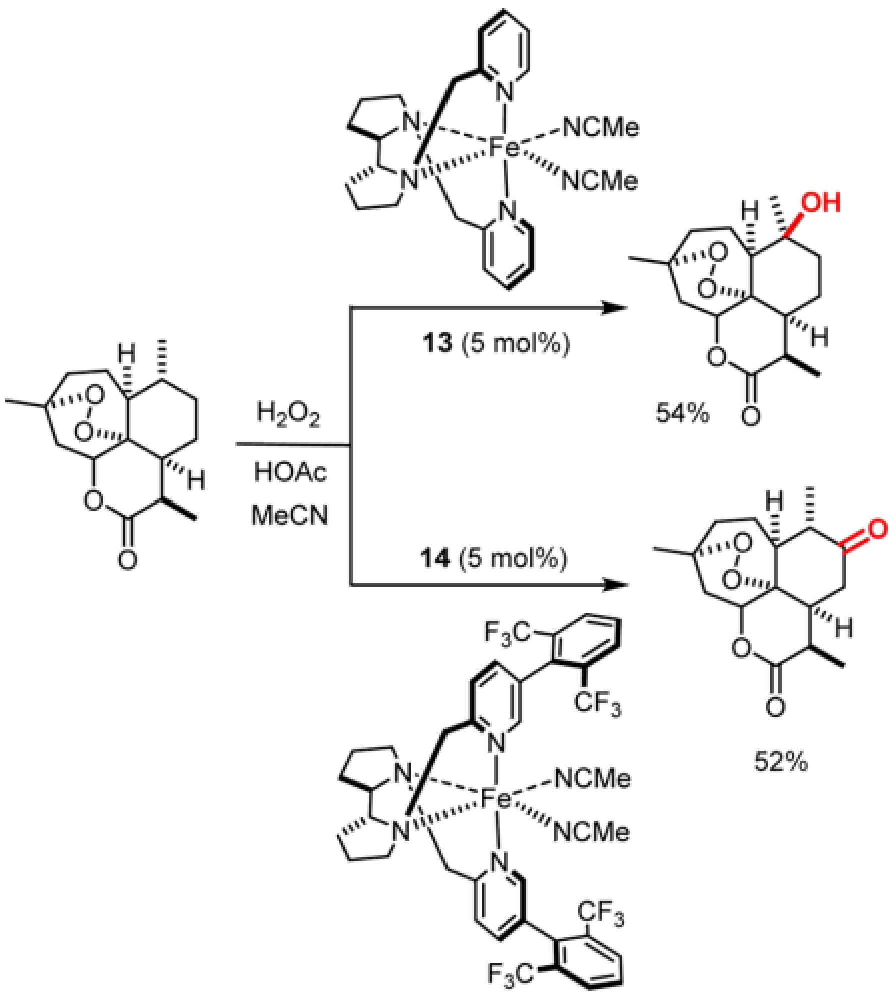
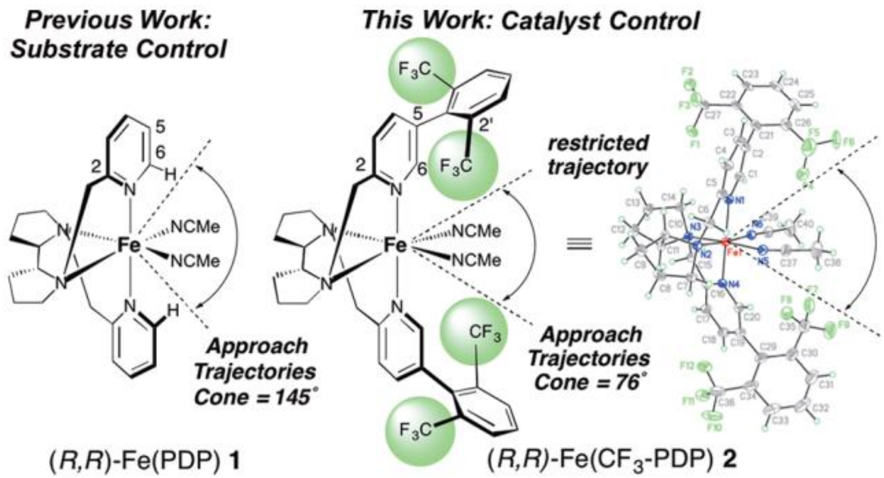




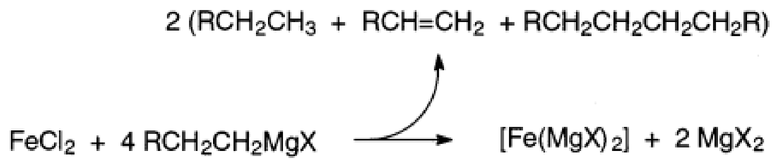
Paul E. Gormisky and M. Christina White *J. Am. Chem. Soc.* **2013**, *135*, 14052 – 14055.

Cross-Coupling reactions

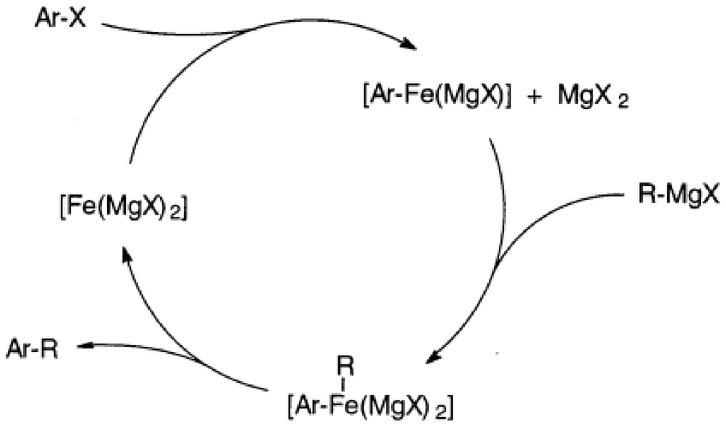
$$\text{Ar-X} + \text{R-MgX} \xrightarrow[\text{5 - 10 min, rt}]{\text{Fe(acac)}_3,\ \text{THF / NMP}} \text{Ar-X}$$

X = Cl, OTf, OTs

Scheme 1

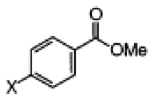
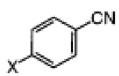
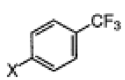
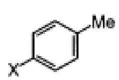
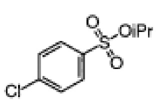
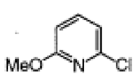
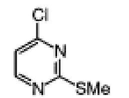
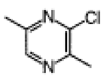
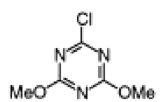
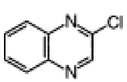
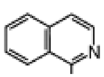
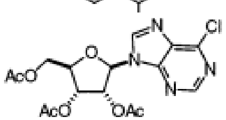


Scheme 2



A. Furstner, A. Leitner, M. Mendez, H. Krause *J. Am. Chem. Soc.* **2002**, *124*, 13856 – 13863.

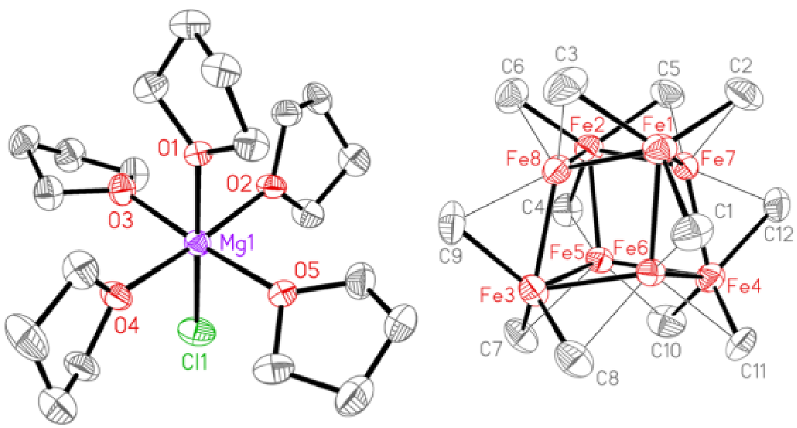
Cross-Coupling reactions

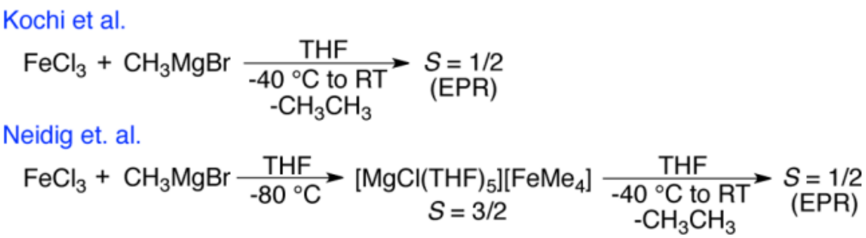
Entry	Ar–X	R–MgBr	Ar–R (Yield)
1		n-C_6H_{13}MgBr	91% (X = Cl)
2			87% (X = OTf)
3			83% (X = OTs)
4			91%
5			88%
6			85%
7			91% (X = Cl)
8		n-$C_{14}H_{29}$MgBr	80% (X = OTf)
9			74% (X = OTs)
10			94% (X = Cl)
11		n-$C_{14}H_{29}$MgBr	72% (X = OTf)
12			75% (X = OTs)
13		n-$C_{14}H_{29}$MgBr	0% (X = Cl)
14			81% (X = OTf)
15		n-C_6H_{13}MgBr	85%
25		n-$C_{14}H_{29}$MgBr	95%
26			56%
27		n-$C_{14}H_{29}$MgBr	93%
28		n-$C_{14}H_{29}$MgBr	41%
29		n-$C_{14}H_{29}$MgBr	68%
30		n-$C_{14}H_{29}$MgBr	89%
31		n-$C_{14}H_{29}$MgBr	94%
32		n-$C_{14}H_{29}$MgBr	84%
33		n-$C_{14}H_{29}$MgBr	95%
34		n-$C_{14}H_{29}$MgBr	95%
42		n-$C_{14}H_{29}$MgBr	72%

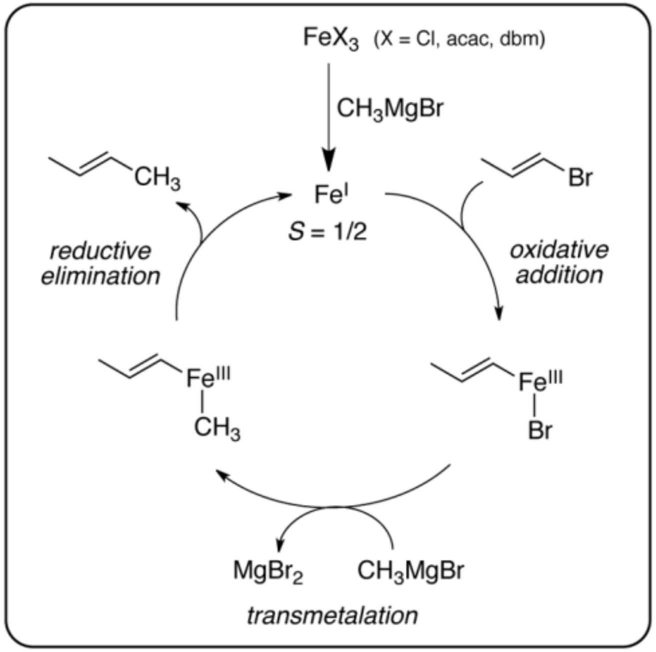
A. Furstner, A. Leitner, M. Mendez, H. Krause *J. Am. Chem. Soc.* **2002**, *124*, 13856 – 13863.

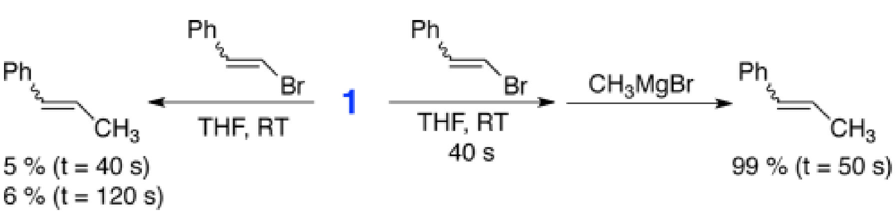
Cross-Coupling reactions

$[MgCl(THF)_5][Fe_8Me_{12}]$



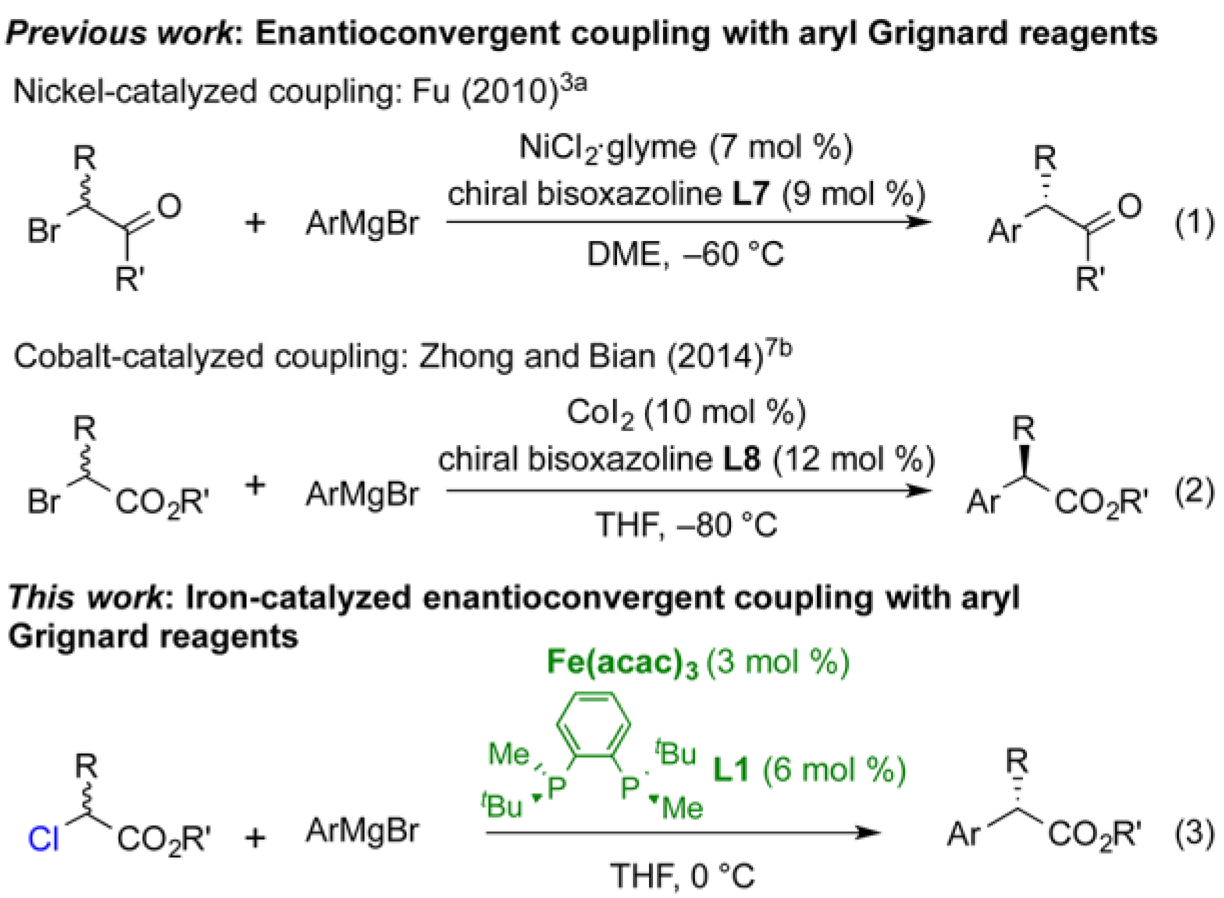






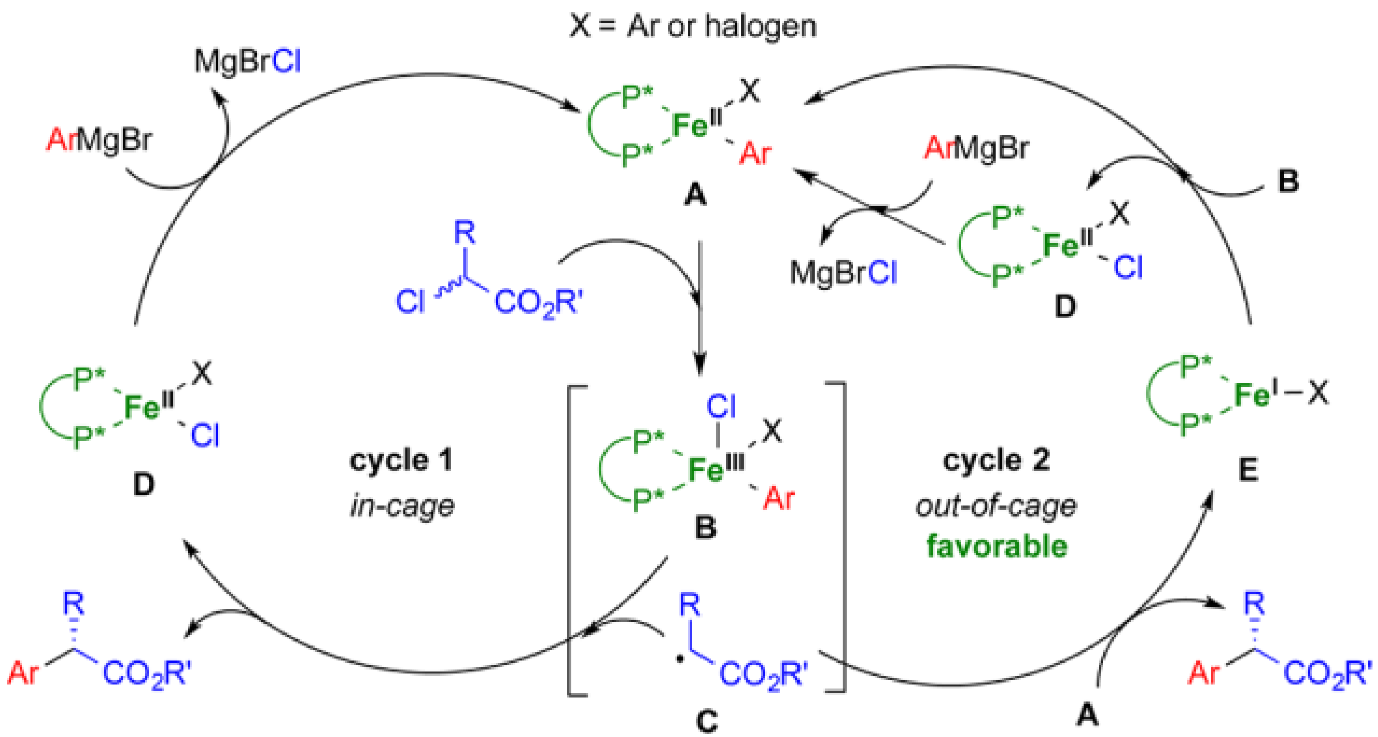
S. B. Munoz III, S.L. Daifuku, W. W. Brennesel, M. L. Neidig *J. Am. Chem. Soc.* **2016**, *138*, 7492 – 7495.

Iron-Catalyzed Enantioselective Cross-Coupling



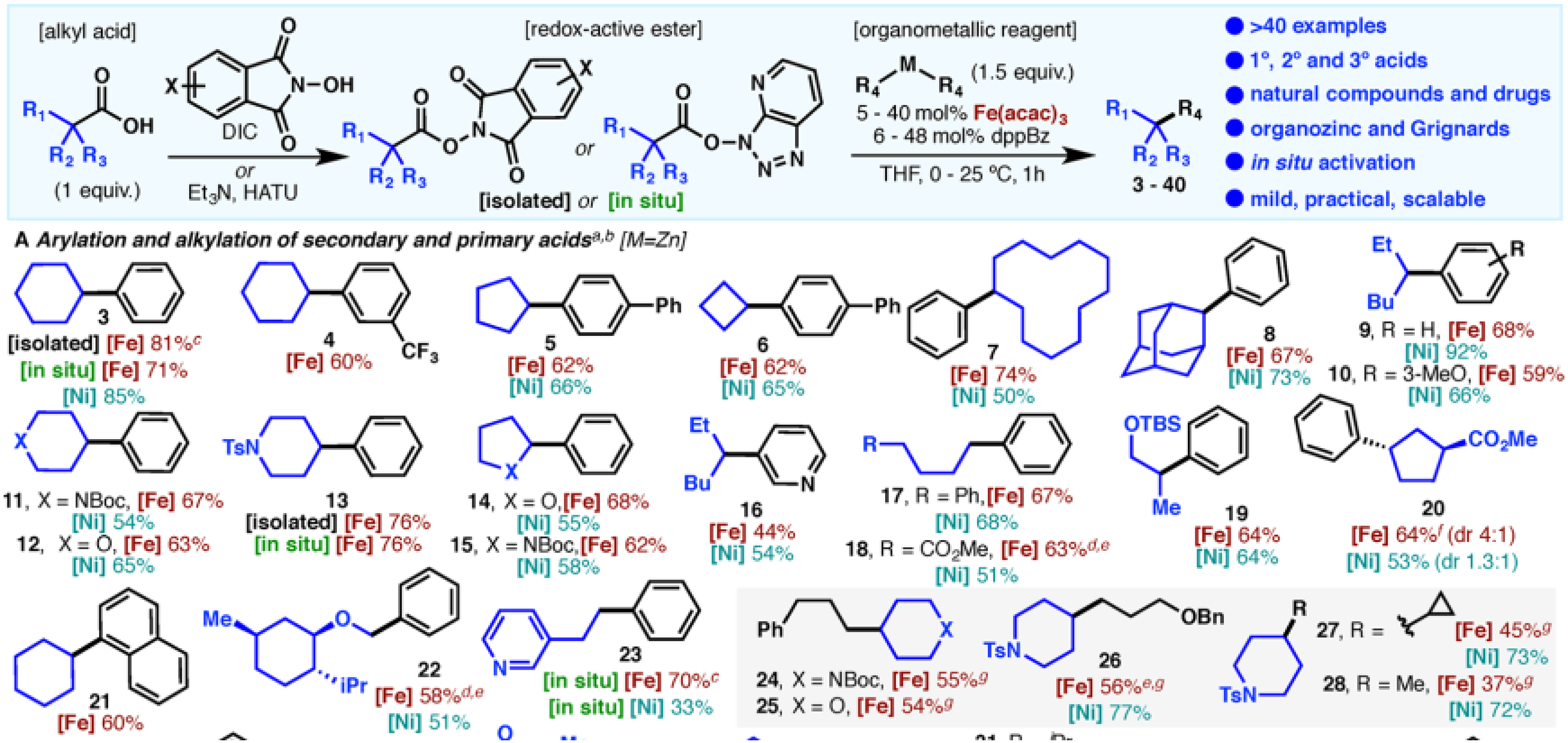
M. Jin, L. Adak, M. Nakamura *J. Am. Chem. Soc.* **2015**, *137*, 7128 – 7134.

Iron-Catalyzed Enantioselective Cross-Coupling



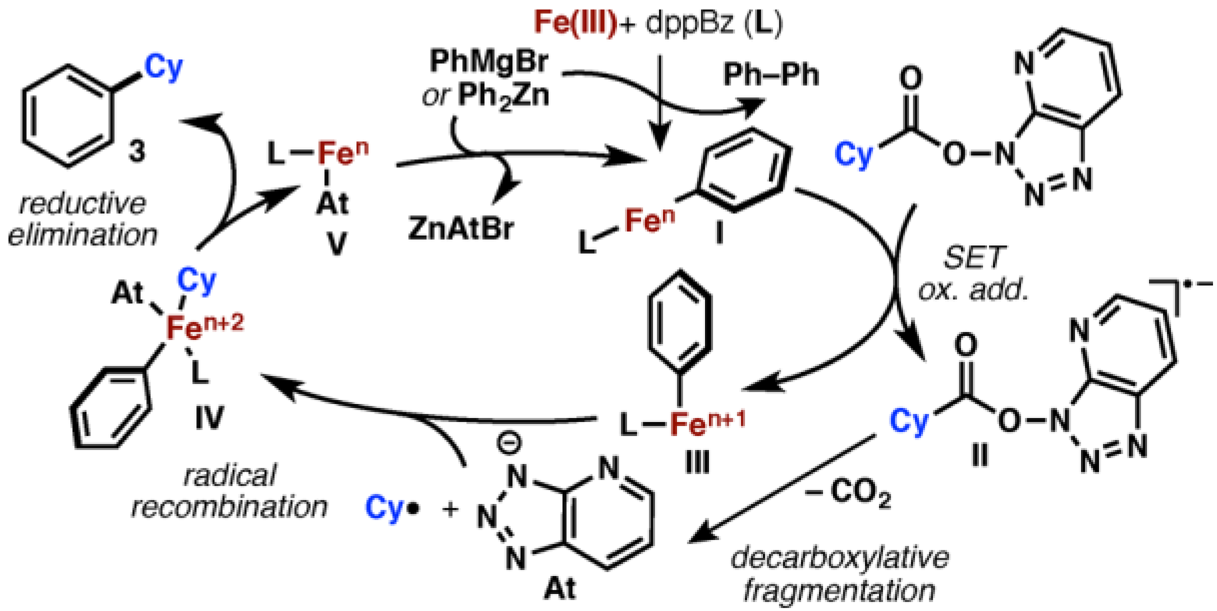
M. Jin, L. Adak, M. Nakamura *J. Am. Chem. Soc.* **2015**, *137*, 7128 – 7134.

Redox-Active Esters in Fe-catalyzed C-C Coupling



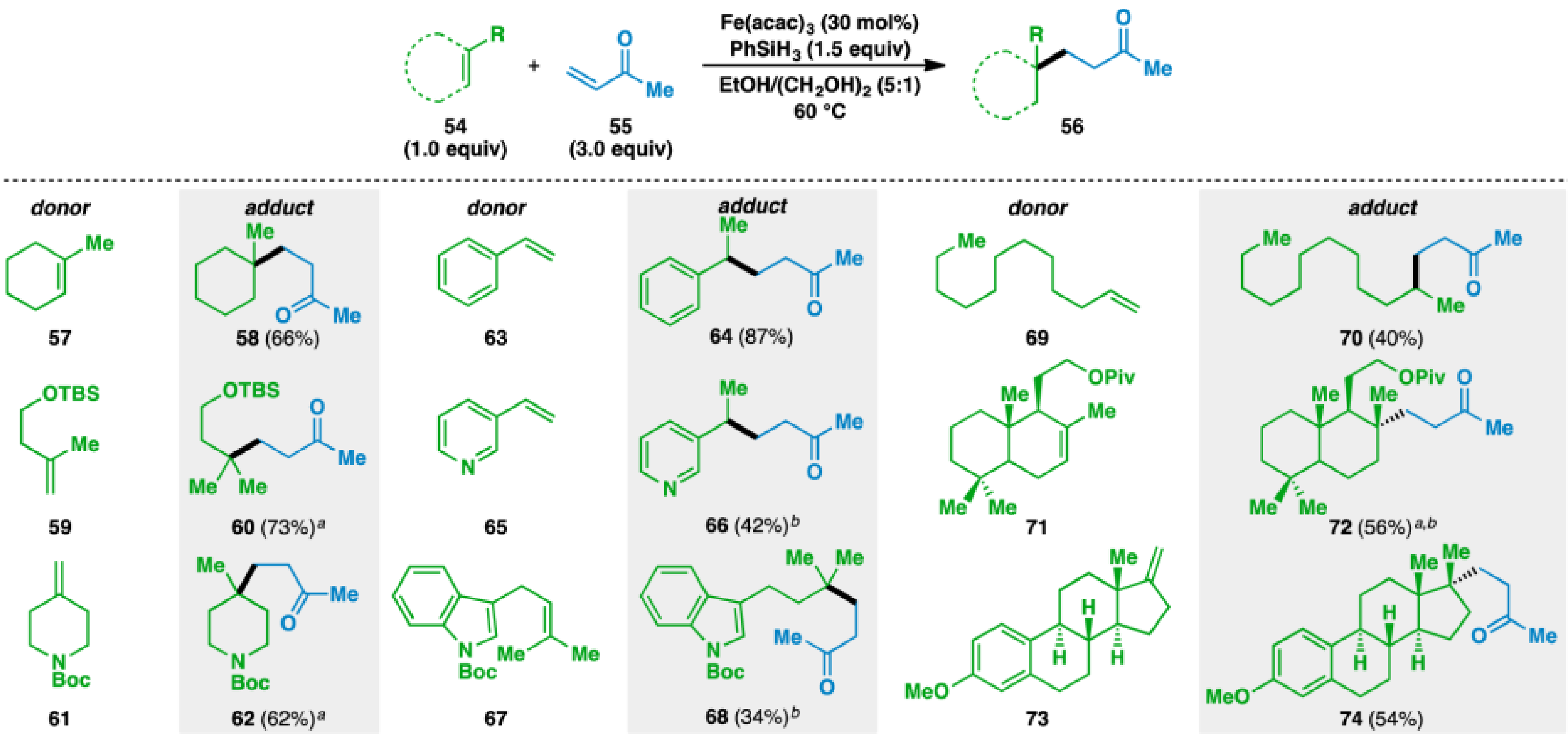
Phil S. Baran and co-workers *J. Am. Chem. Soc.* **2016**, *138*, 11132 – 11135.

Redox-Active Esters in Fe-catalyzed C-C Coupling



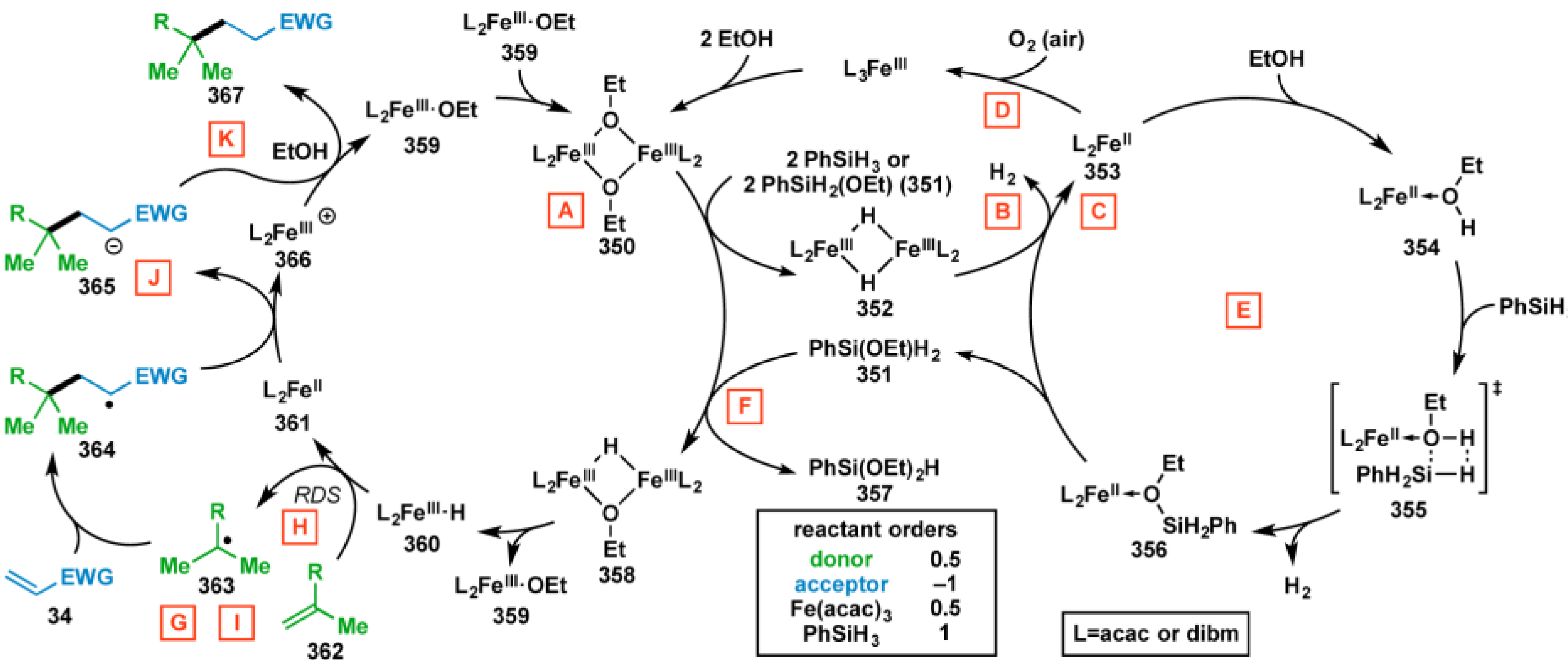
Phil S. Baran and co-workers *J. Am. Chem. Soc.* **2016**, *138*, 11132 – 11135.

C-C Bond Construction from Olefins via Radicals



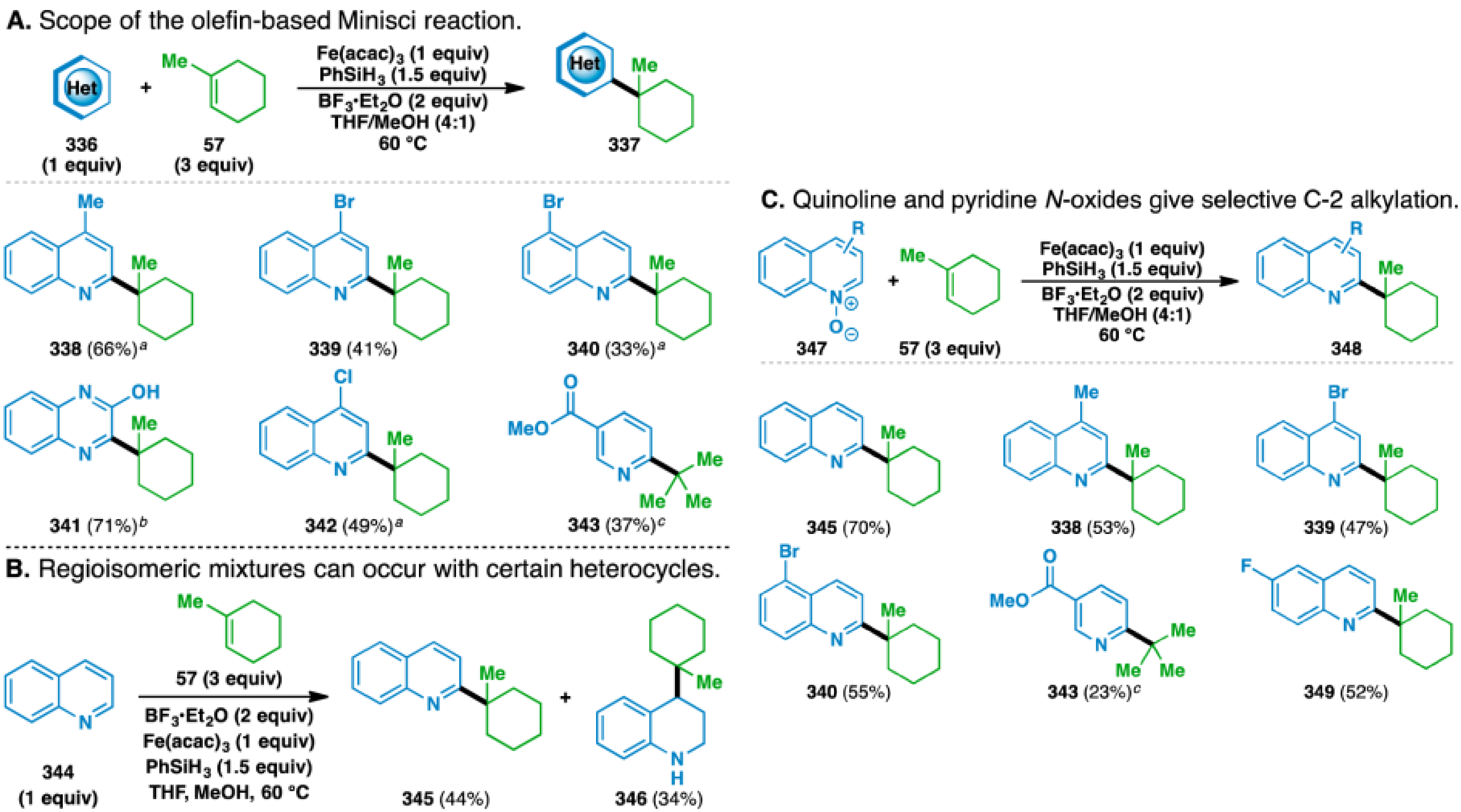
Phil S. Baran and co-workers *J. Am. Chem. Soc.* **2017**, **DOI:** 10.1021/jacs.6b13155.

C-C Bond Construction from Olefins via Radicals



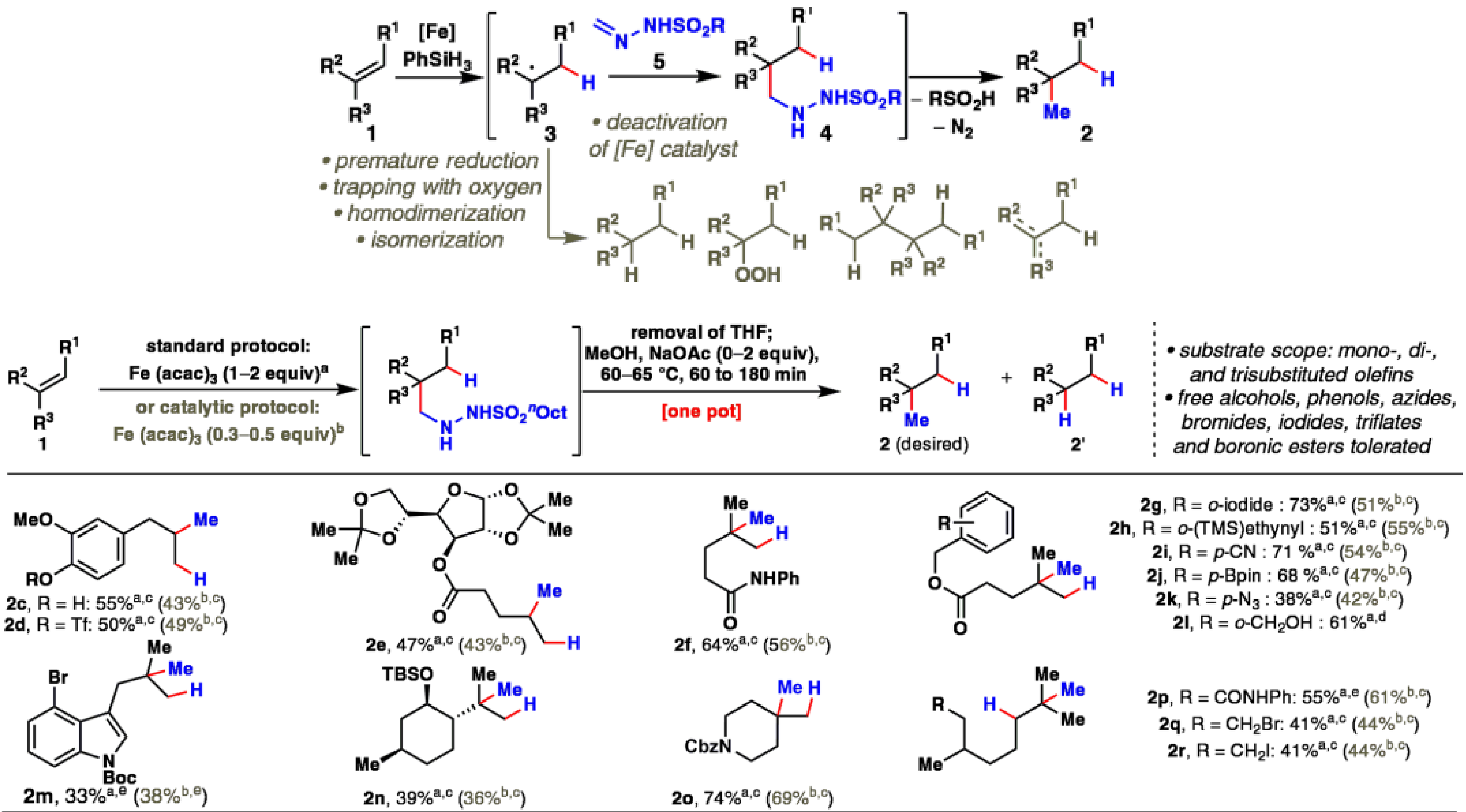
Phil S. Baran and co-workers *J. Am. Chem. Soc.* **2017**, **DOI:** 10.1021/jacs.6b13155.

Baran's method in Minisci-type reactions (Specially for Sam)



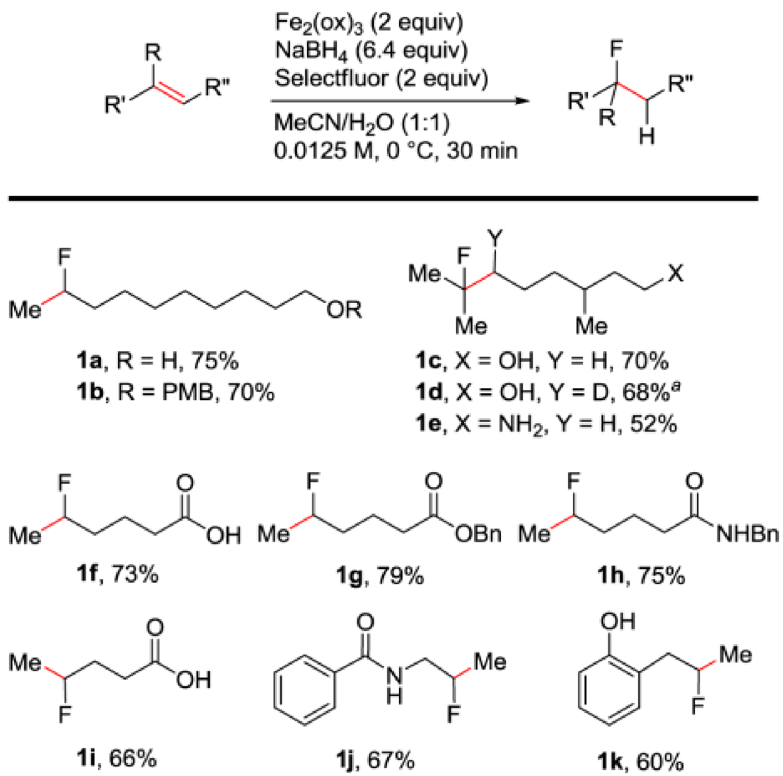
Phil S. Baran and co-workers *J. Am. Chem. Soc.* **2017**, **DOI:** 10.1021/jacs.6b13155.

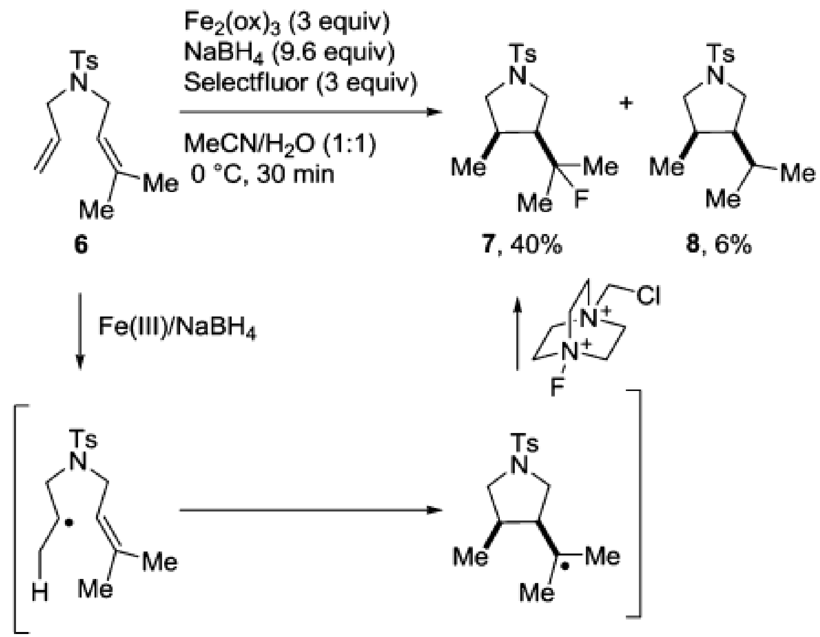
Hydromethylation of Unactivated Olefins (Specially for Camilo)



Phil S. Baran and co-workers *J. Am. Chem. Soc.* **2015**, *137*, 8046-8049.

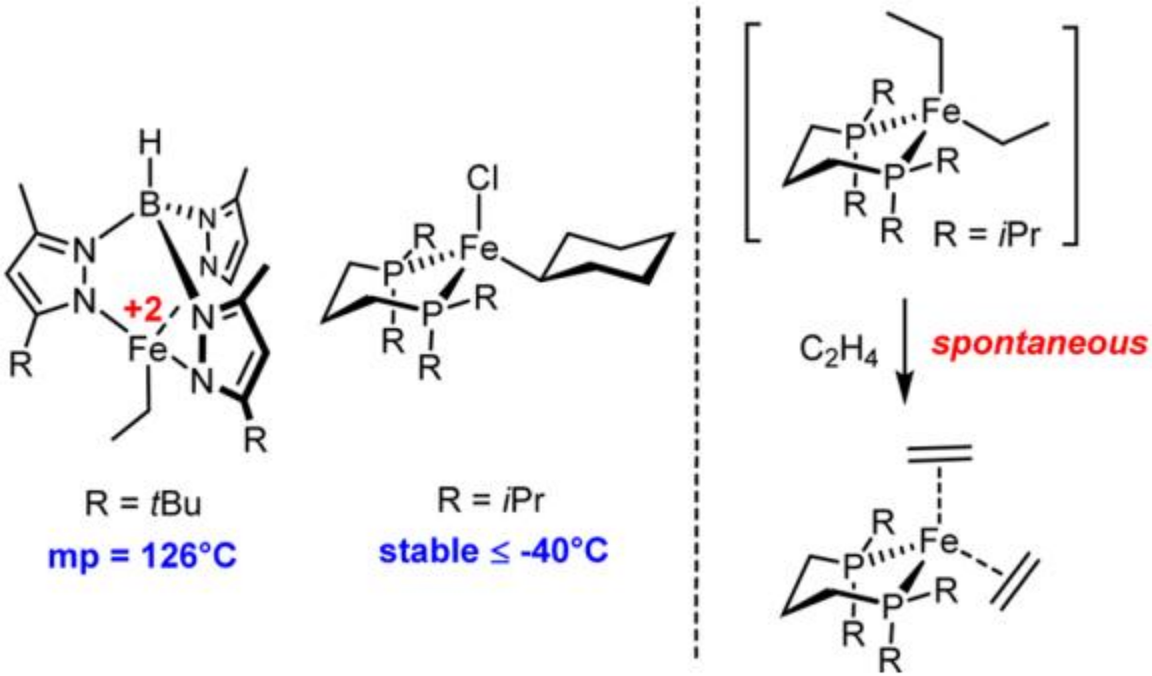
Free Radical Hydrofluorination (Specially for Daniel)





T. J. Barker, D. L. Boger *J. Am. Chem. Soc.* **2012**, *134*, 13588-13591.

Role of Spin State



Alois Furstner *ACS Cent. Sci.* **2016**, *2*, 778 – 789.

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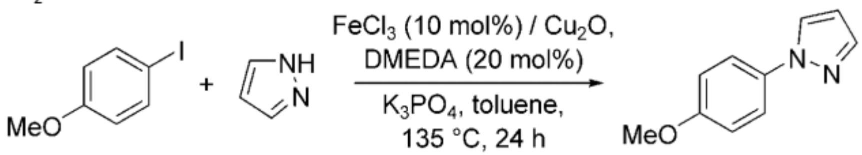
Impurities in Iron Metal as the Actual Catalyst?

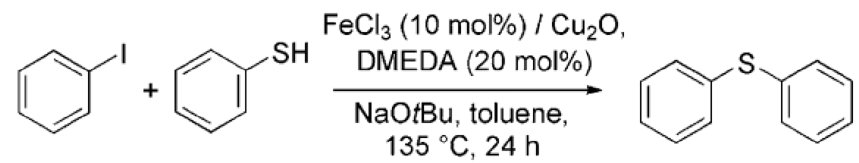
Table 1: N-Arylation of pyrrazole in the presence or absence of $FeCl_3$ and Cu_2O.[a]



$FeCl_3/Cu_2O$	Yield [%] (GC)
> 98 % (Merck)	87 (ref. [3a])
> 98 % (Aldrich)	26
> 99.99 (Aldrich)	9
> 99.99 % + 5 ppm Cu_2O	78
> 99.99 % + 10 ppm Cu_2O	79
no Fe + ligand + 5 ppm Cu_2O	77
no Fe + no ligand + 5 ppm Cu_2O	23

[a] DMEDA = *N,N'*-Dimethylethylenediamine.

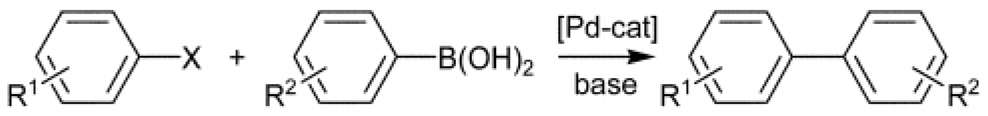
10 ppm of Cu_2O is enough for Sufficient catalysis



$FeCl_3/Cu_2O$	Yield [%] (GC)
> 98 % (Merck)	91 (ref. [3 f])
> 98 % (Aldrich)	4
> 99.99 (Aldrich)	2
> 99.99 % + 10 ppm Cu_2O	42
> 99.99 % + 100 ppm Cu_2O	99
> 99.99 % + 1000 ppm Cu_2O	93

S.L. Buchwald, C. Bolm *Angew. Chem. Int. Ed.* **2009**, *548*, 5586– 5587.

Impurities in Iron Metal as the Actual Catalyst?



Entry	Aryl halide	Catalyst ([Pd]/mol% Pd)	Conversion (%)[a]	TON/10^3 (mol product/ mol Pd)
1	4-Bromoacetophenone	**4a** (10^{-4})	90	900
2	4-Bromoacetophenone	**4a** (10^{-5})	20	2 000
3	4-Bromoanisole	**4a** (10^{-4})	85	850
4	4-Bromoanisole	**4a** (10^{-5})	26	2 600
5	4-Bromoanisole	**4b** (10^{-4})	91	910 000
6	4-Bromoanisole	**4b** (10^{-5})	42	4 200
7	4-Bromoanisole	**4c** (10^{-4})	29	290
8	4-Bromoanisole	**4a** + **3a** (10^{-4})	100	1 000
9	4-Bromoanisole	$Pd(dba)_2$ + 2 **3a** (10^{-4})	36	360
10	4-Bromoanisole	**4a** + **3a** (10^{-5})	87.5	8 750
11	4-Bromoanisole	**4b** + **3b** (10^{-5})	50	5 000
12	4-Bromoacetophenone	**4b** + **3b** (10^{-6})[b]	100	100 000
13	4-Bromoacetophenone	**4b** + **3b** (10^{-7})[b]	47.5	475 000
14	2-Bromotoluene	**4b** + **3b** (10^{-3})	100	100
15	2-Bromo-*m*-xylene	**4b** + **3b** (10^{-3})	48	48
16	4-Chloroanisole	**4b** (1.0)	6	0.006

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Thank you for your attention!