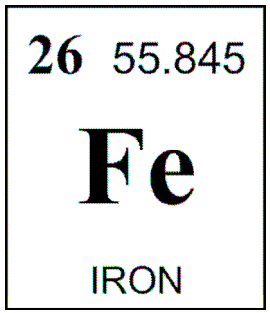
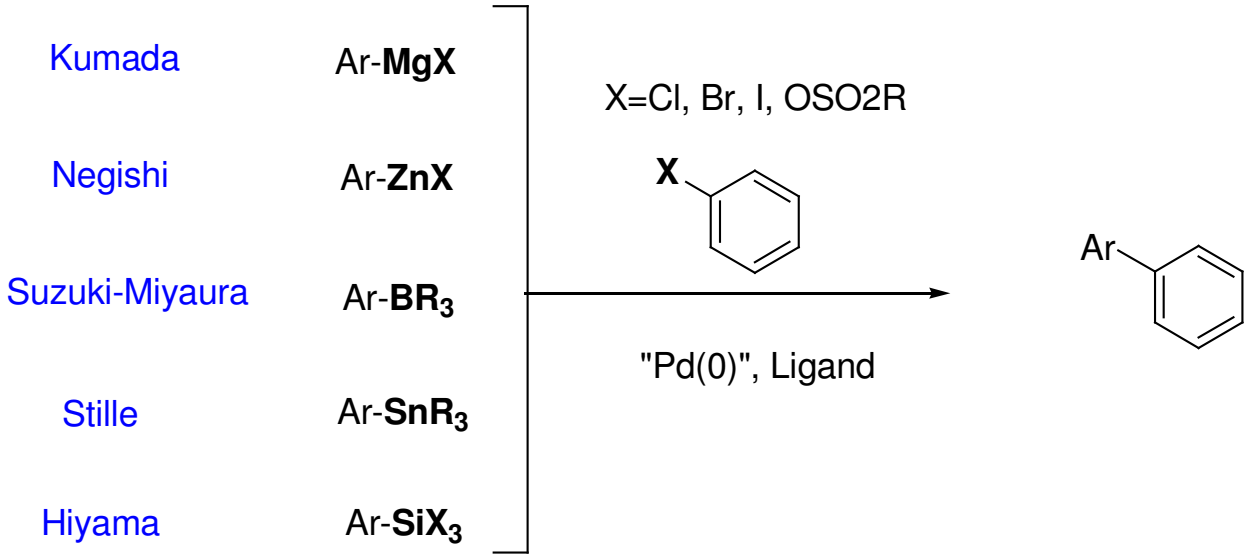
Iron –Catalyzed Direct Arylation through Directed C-H Bond Activation



Jakob Norinder, Arimasa Matsumoto, Naohiko Yoshikai, and Eichi Nakamura

J. Am. Chem. Soc. **2008**, *130*, 5858-5859

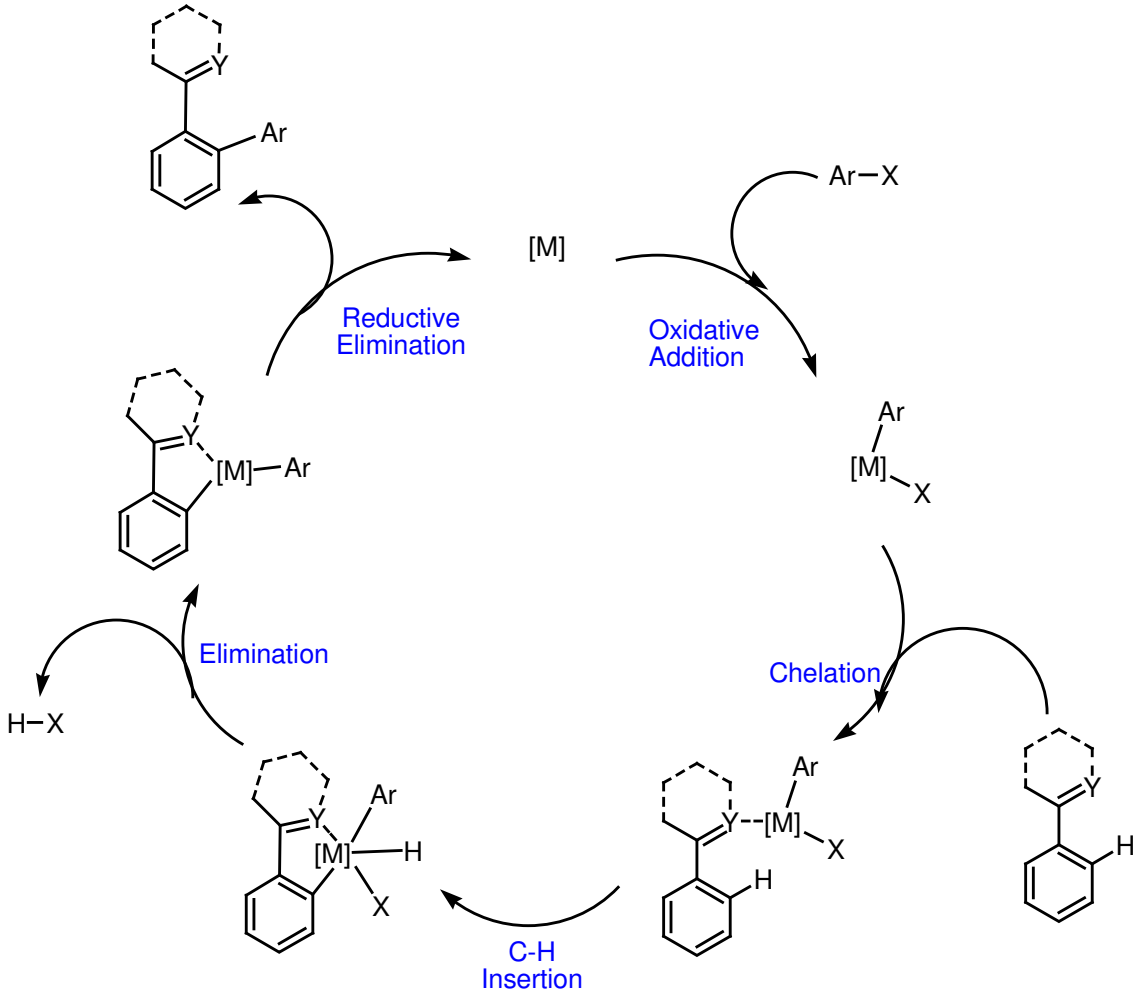
Classical Palladium-Catalyzed Coupling



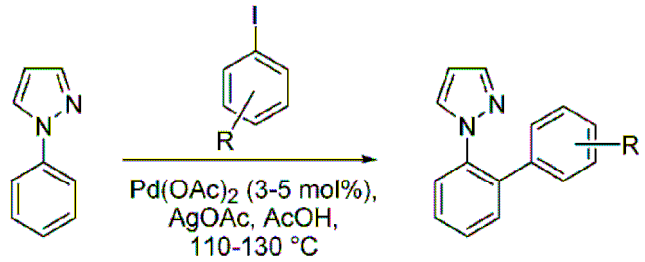
-Needs the Simultaneous Activation of the Substrate and the Reagent

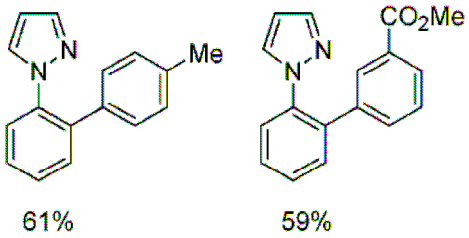
-Question of cost and atom economy

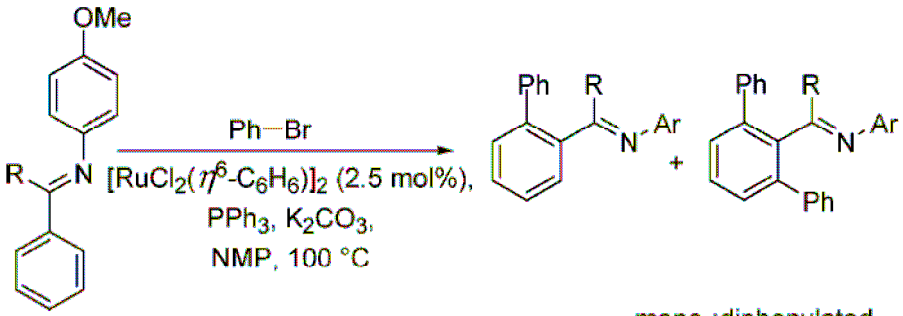
Metal Catalyzed C-H Insertion: General Principle



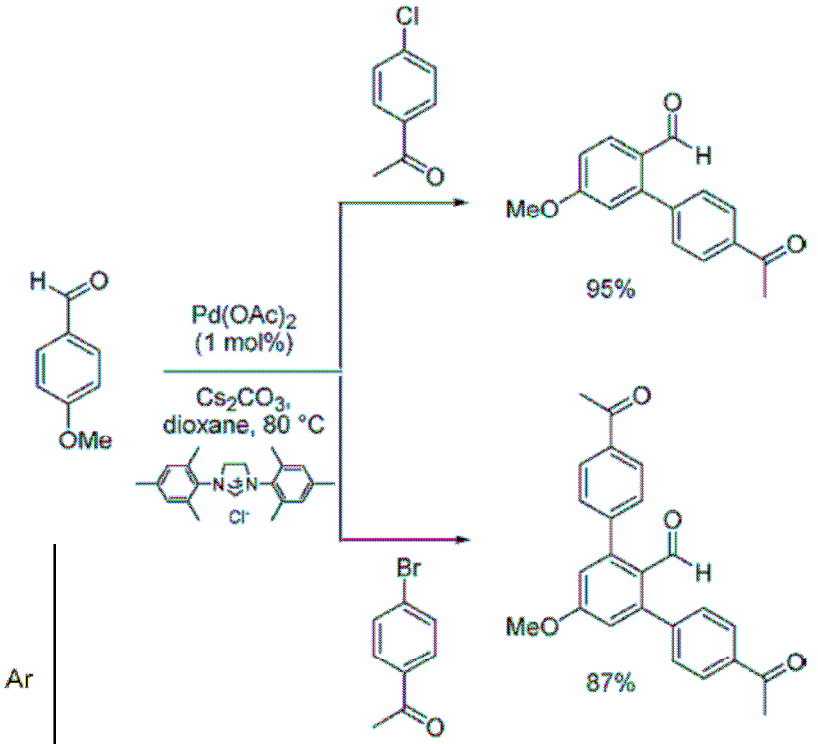
Metal-Catalyzed C-H Insertion: Applications







			mono-:diphenylated
R =	Me	90%	81:19
	Et	91%	78:22
	H	92%	0:100



Lautens, M. et al., *Chem. Rev.* **2007,** *107*, 174-238

Iron in Organic Chemistry

	44 101.07 Ru RUTHENIUM	45 102.91 Rh RHODIUM	46 106.42 Pd PALLADIUM
Crust abondance:	9.9×10^{-8} %	7.0×10^{-8} %	6.3×10^{-7}%
Price (aldrich):	$RuCl_3$ 11 $/g	$RhCl_3$ 132 $/g	$PdCl_2$ 30 $/g

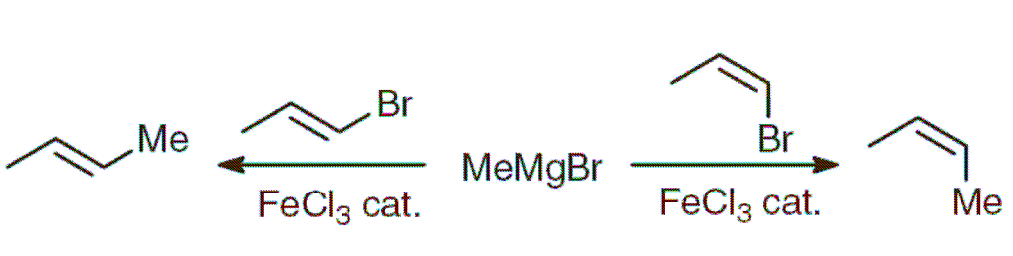
26 55.845 Fe IRON

-Crust abondance: **6.3%**

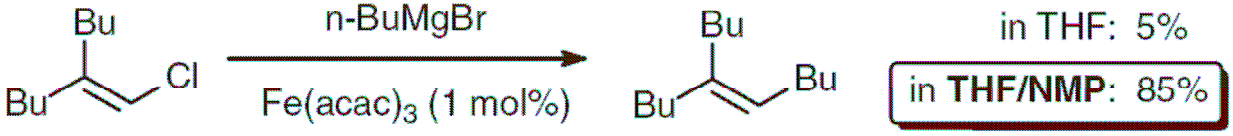
-Price (aldrich): $FeCl_3$ **0.08 $/g**

-No toxicity

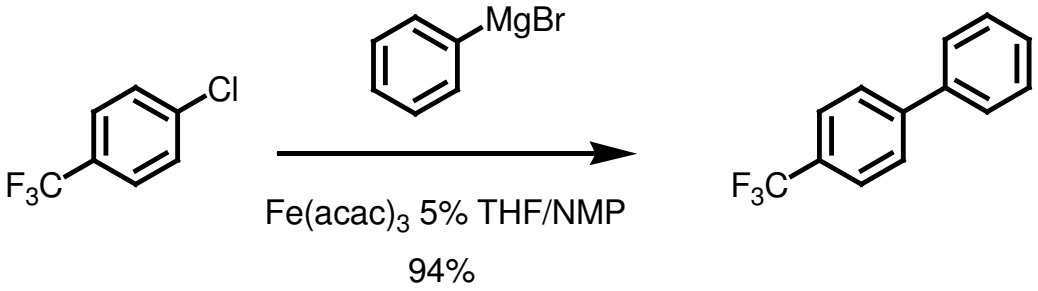
Iron-Catalyzed Cross-Coupling: Applications



Kochi et al. *J. Am. Chem. Soc.* **1971**, *93*, 1487.

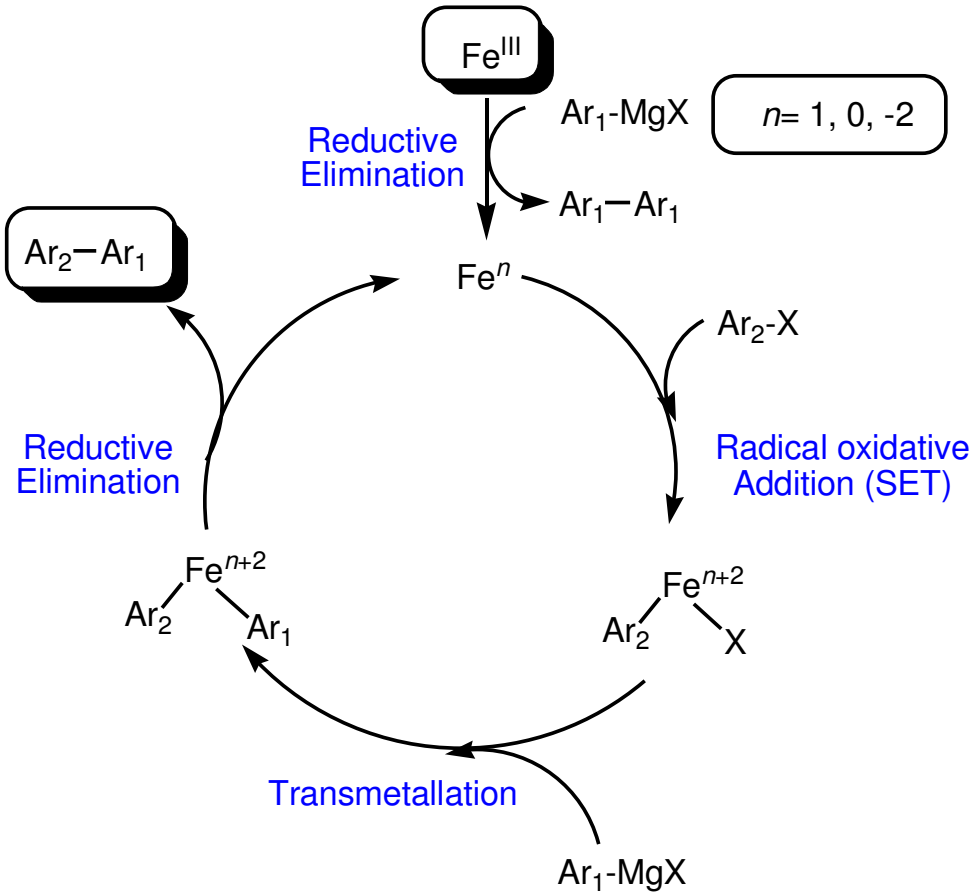


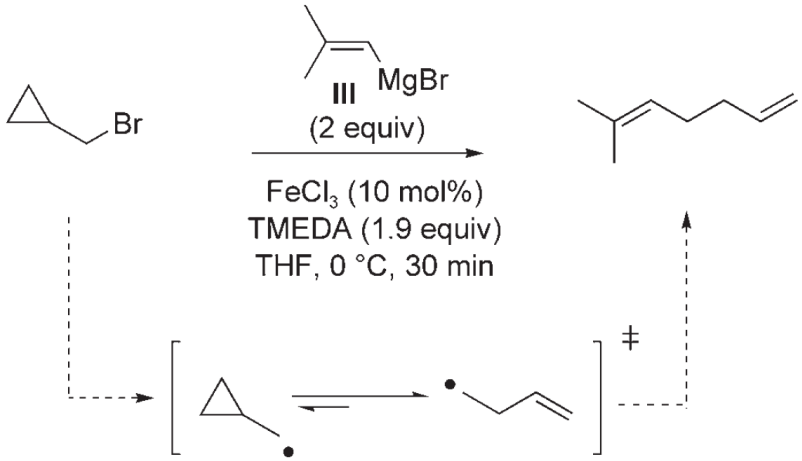
Cahiez et al. *Synthesis,* **1998**, 1199.



Fürstner et al. *J. Am. Chem. Soc.* **2002**, *124*, 13856.

Iron-Catalyzed Cross-Coupling: Postulated Mechanism

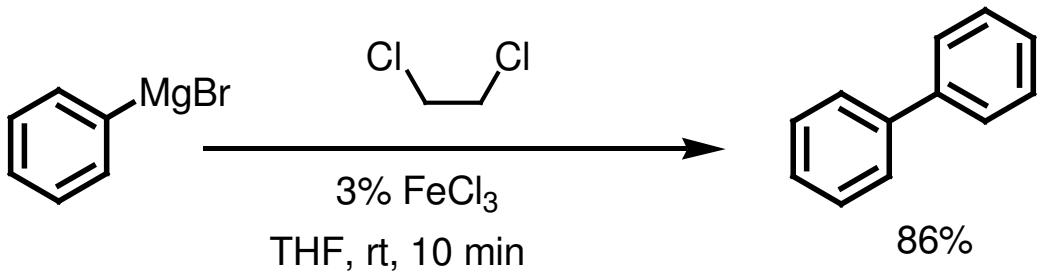


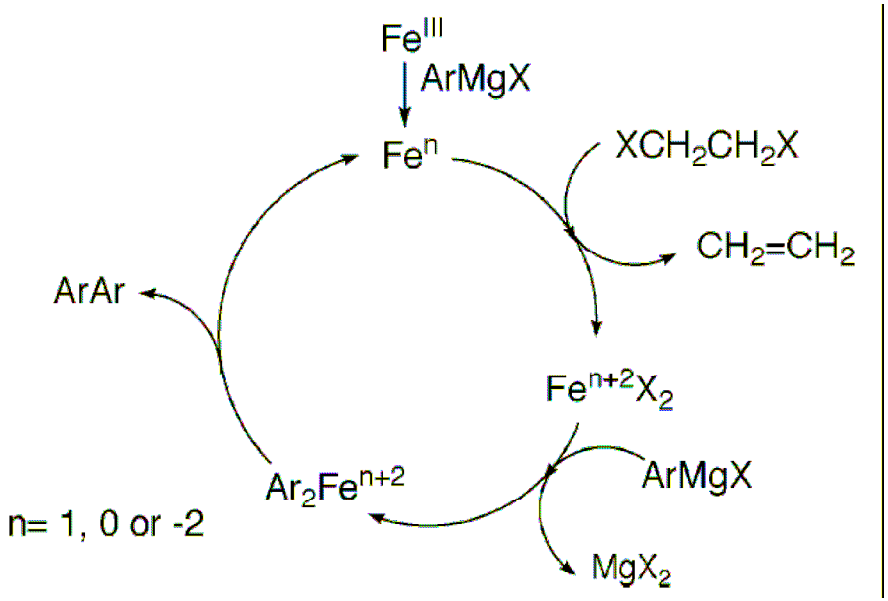


A proof of the radical oxidative pathway

Cossy al. *Angew. Chem. Int. Ed.* **2007**, *46*, 6521.

Iron Catalyzed Homocoupling of Grignard Reagents





Cahiez et al. *Organic Letters,* **2005**, 1943.

Summary

-The Palladium catalyzed cross coupling reaction is the most widely used organometallic transformation, but suffers from a low atom economy.

-Improvements in the directed C-H insertion via Pd, Ru, Rh chemistry allow atom economical transformations.

-However, These metals are rare and expensive and some industrial applications are limited due to the cost of the catalysts.

-Iron, because of its very low price and low toxicity is a very promising alternative to palladium cross-coupling.

-What about the C-H insertion iron-catalyzed cross coupling?

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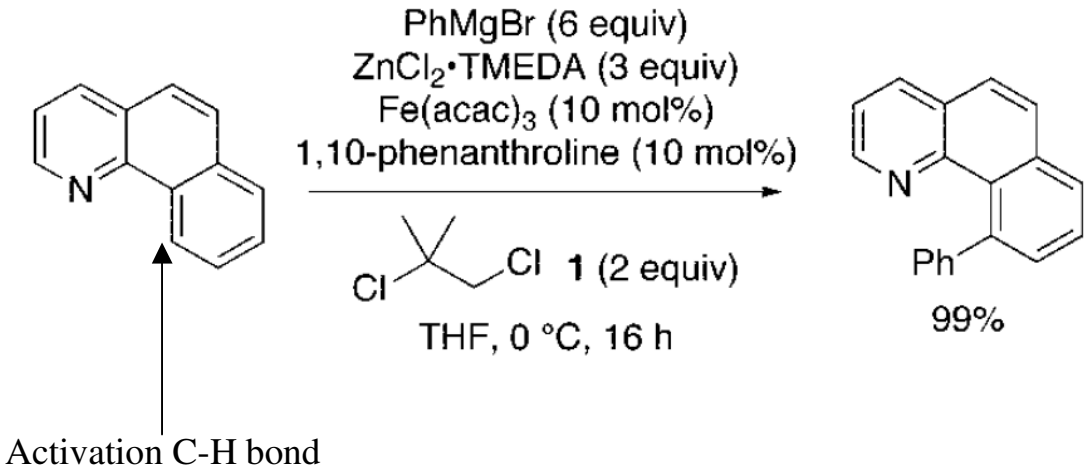
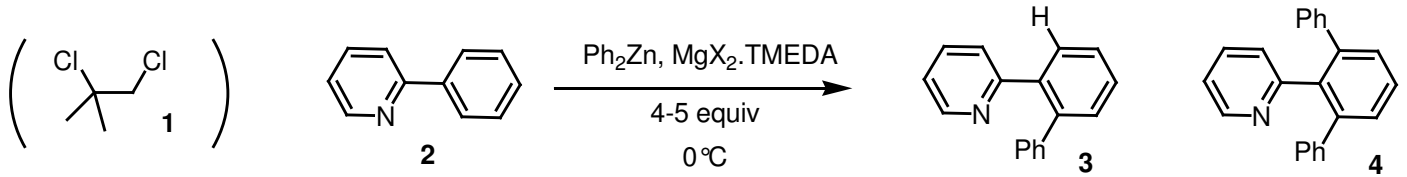


Screening of the Conditions



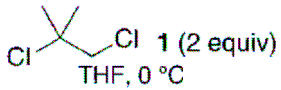
entry	catalyst (mol %)	additive (equiv)	time (h)	yield/%[b] 3	4	
1	$FeCl_3$ (15)	none	36	0	0	
2	$FeCl_3$/bpy (15)	none	36	15	0	
3	$FeCl_3$/bpy (15)	$Cl(CH_2)_2Cl$ (3)	72	53	2	
4	$FeCl_3$/bpy (15)	**1** (3)	24	82	9	
5	$FeCl_3$/bpy (10)	**1** (2)	9	53	2	
→ 6	$FeCl_3$/phen (10)	**1** (2)	9	79	16	
7	$FeCl_3$/neocuproine (10)	**1** (2)	24	0	0	
8	$FeCl_3$/terpy (10)	**1** (2)	24	0	0	
→ 9	$FeCl_2$/phen (10)	**1** (2)	9	81	16	
→ 10	$Fe(acac)_3$/phen (10)	**1** (2)	9	83	13	
11[c]	$FeCl_3$/bpy (15)	**1** (3)	24	15	<1	(No TMEDA)

- PhMgBr or ZnClPh gave almost no coupling product

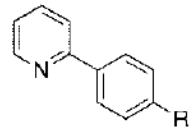
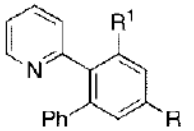
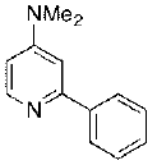
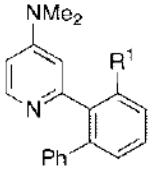
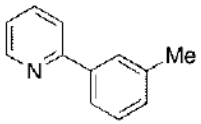
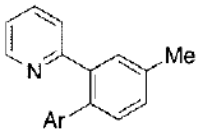
- The oxidation state and the counter anion of the iron show no significant effect

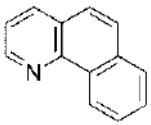
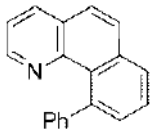
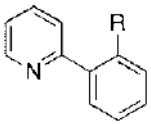
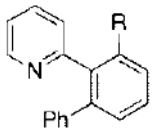
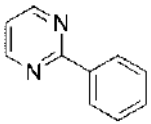
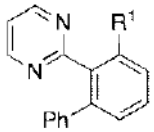
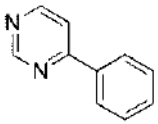
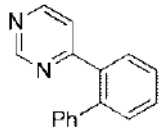
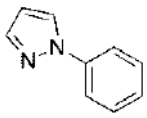
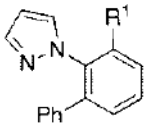
Screening of The Substrates and Reagents

$ZnCl_2$•TMEDA (3 equiv)
$Fe(acac)_3$ (10 mol%)
1,10-phenanthroline (10 mol%)

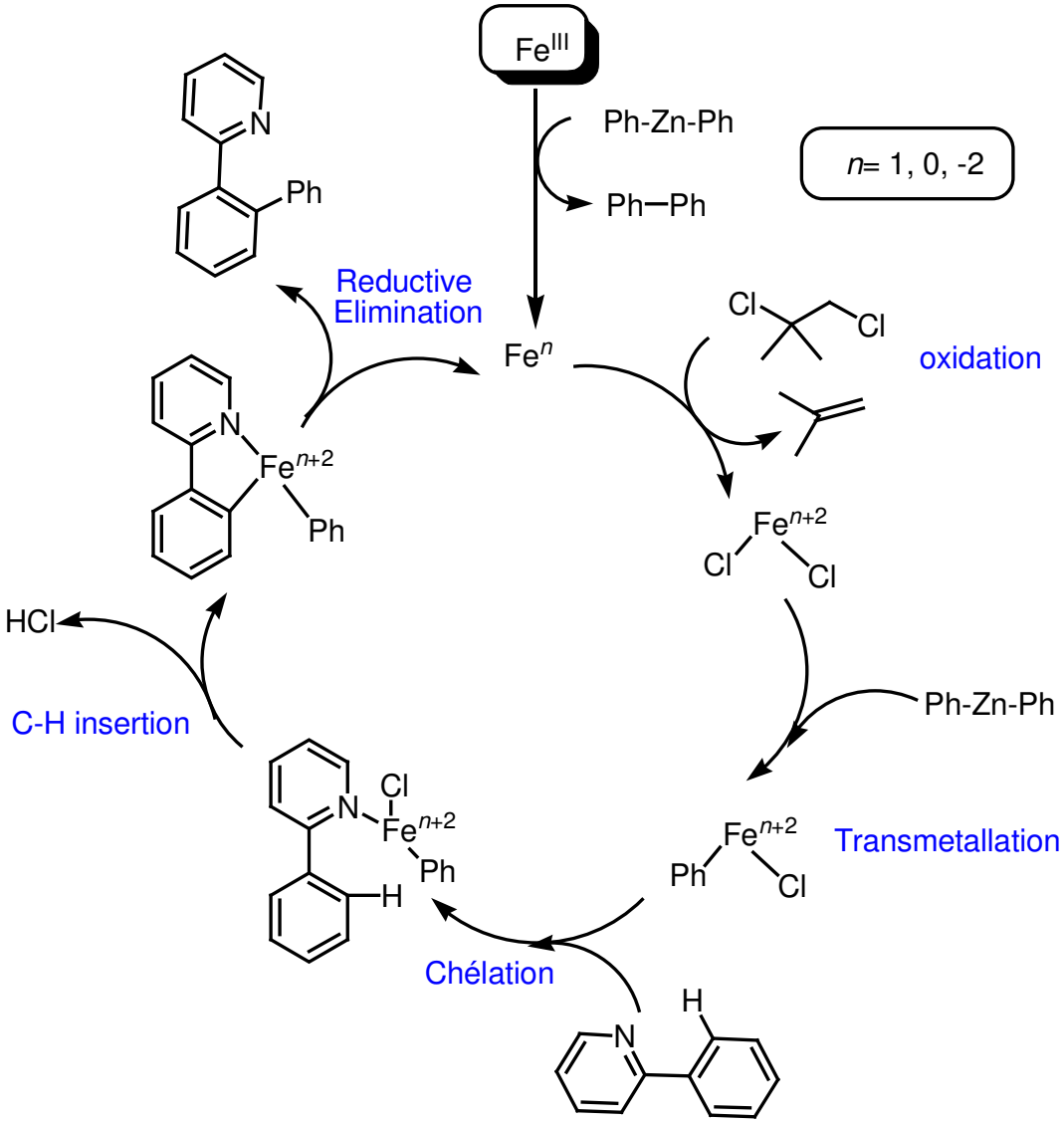


1 (2 equiv)
THF, 0 °C

entry	substrate	Ar	product(s)	time (h)	yield (%)[b] mono + di
1	 **2**	Ph	 **3** (R^1 = H) **4** (R^1 = Ph)	15	82 + 12 (R = H)
2				6	65 + 21 (R = OMe)
3				48	80 + 20 (R = F)
4				48	77 + 13 (R = CO_2Et)
5		Ph	 R^1 = H (mono), R^1 = Ph (di)	24	66 + 17
6		Ph		16	89
7		4-FC_6H_4		36	78
8		3-FC_6H_4		36	82
9		4-$tBuC_6H_4$		36	82
10		4-$MeOC_6H_4$		36	76
11		2-MeC_6H_4		36	0

entry	substrate	Ar	product(s)	time (h)	yield (%)[b] mono + di
12		Ph		16	99 (98)[c]
13		Ph		48	60 (R = Ph)
14				48	17 (R = Me)
15		Ph	 R^1 = H (mono), R^1 = Ph (di)	48	81 + 9
16[d]		Ph		48	18
17[d]		Ph	 R^1 = H (mono), R^1 = Ph (di)	48	59 + 10

Postulated Mechanism



Conclusion

- One of the rare exemple of an Iron catalyzed C-H activation

- The reaction takes place at 0°C when all other metal catalyzed C-H activation reactions require a temperature above 80°C.

- The limitation of the reaction is the utilization of aromatic Grignard reagents: alkyl grignard do not work.

-The Iron used in catalytic, is less expensive than Zn ot Mg, used in stochiometric…