Beyond Palladium – The New Iron Age

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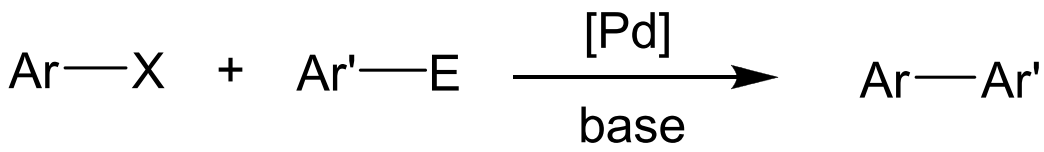
University of Bristol

Palladium catalysed cross-coupling



E = B(OR)$_2$, MgX, SnR$_3$, ZnX, Si(OR)$_3$

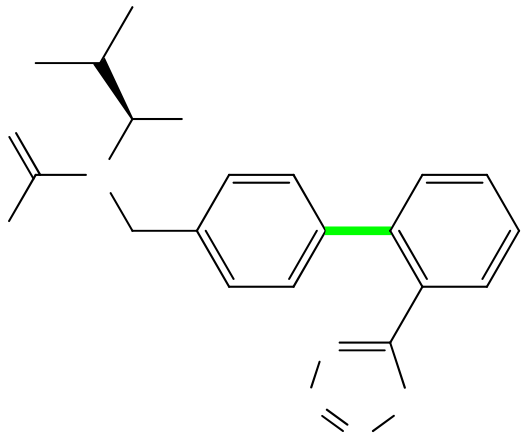
- Powerful method for the synthesis of C-C bonds

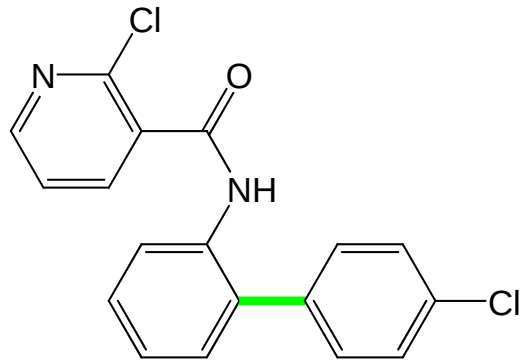
- Well established technology, ***but*** with new advances being made (e.g. use of deactivated aryl chlorides and heteroaromatic substrates)

2

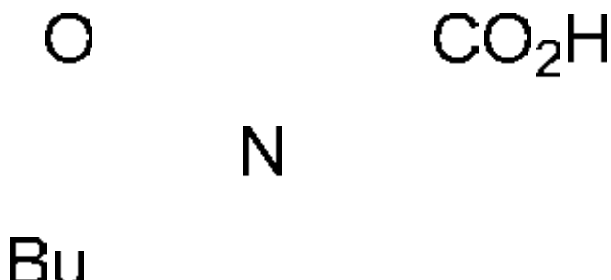
- Used in the commercial synthesis of a range of compounds

Commercial applications of the Suzuki reaction:

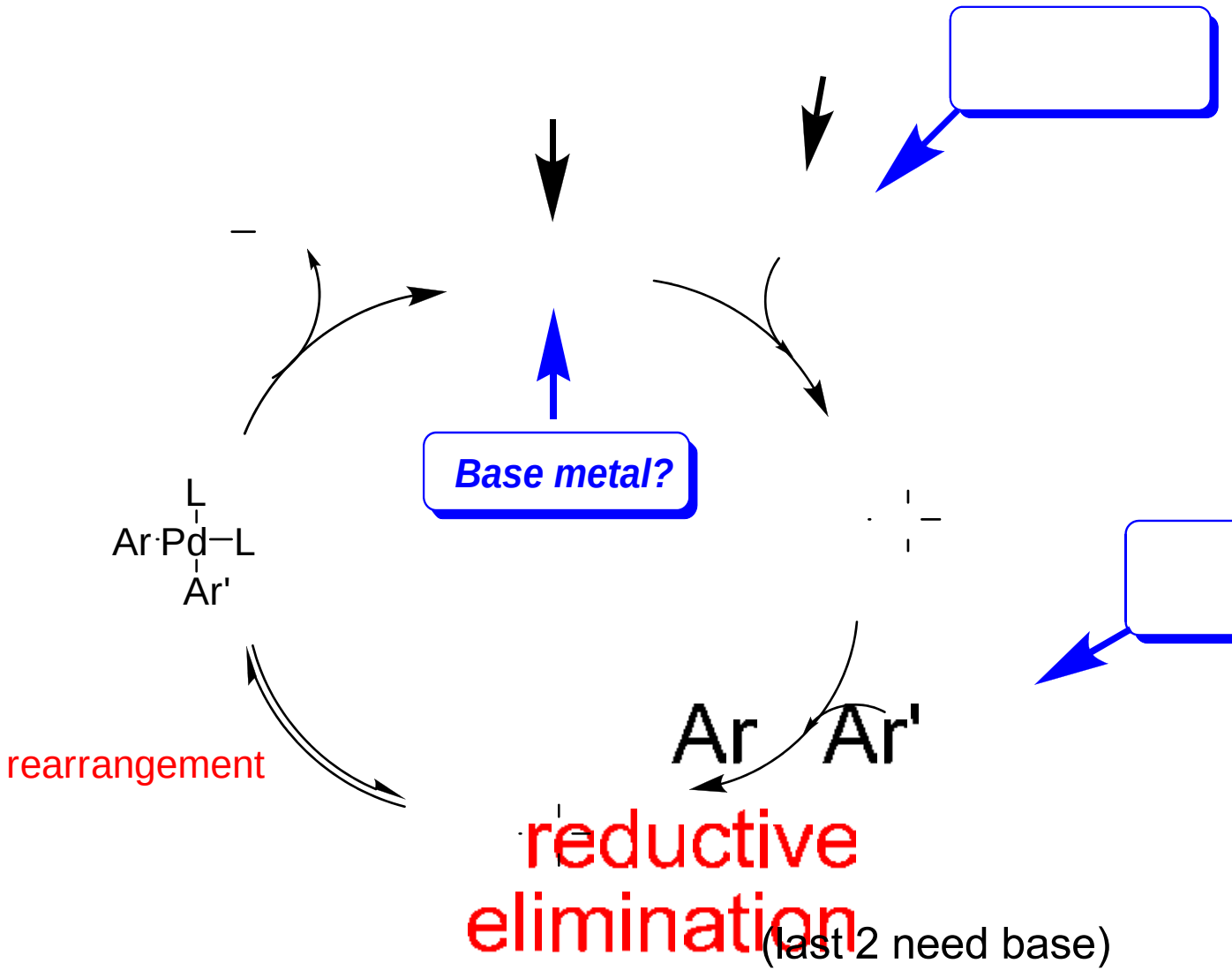




Boscalid
fungicide
(BASF)



Pd Coupling Catalytic Cycle (highly simplified)



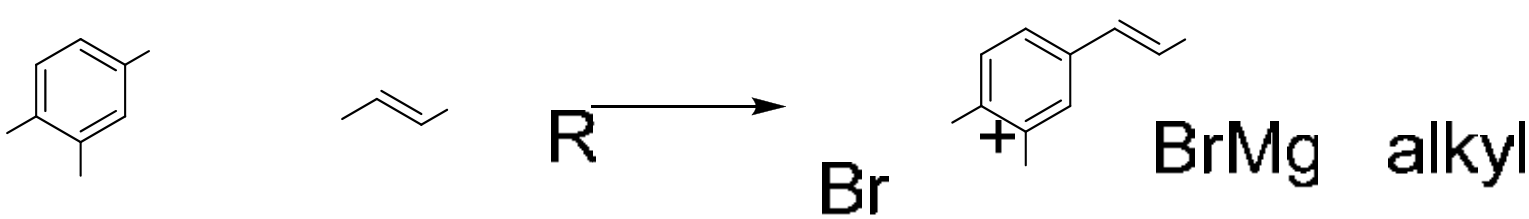
Why bring the iron curtain down on nobility?

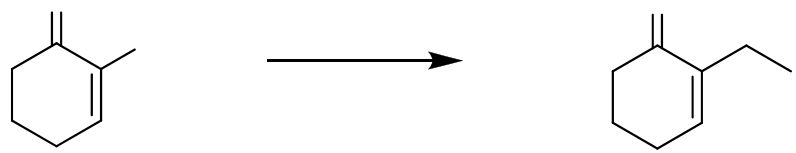
Property	Pd	Fe
Cost	$234 / troy oz	~ 0.3c /troy oz
Toxicity	FDA guidelines < ~5 – 10 ppm on APIs	FDA: can be used to make pills look ‘nicer’ - pearlescence
Selectivity/scope/ limitations	Well established, robust, but with limitations (e.g. alkyl halides)	Being established, new/complementary
Mechanisms and ease of study	Well understood organometallic chemistry – ‘classic’ 2 electron redox cycles	Hard to study directly (paramagnetic) May be more than one manifold - SET

Grignard Cross-Coupling
1. Vinyl halides

- Kochi

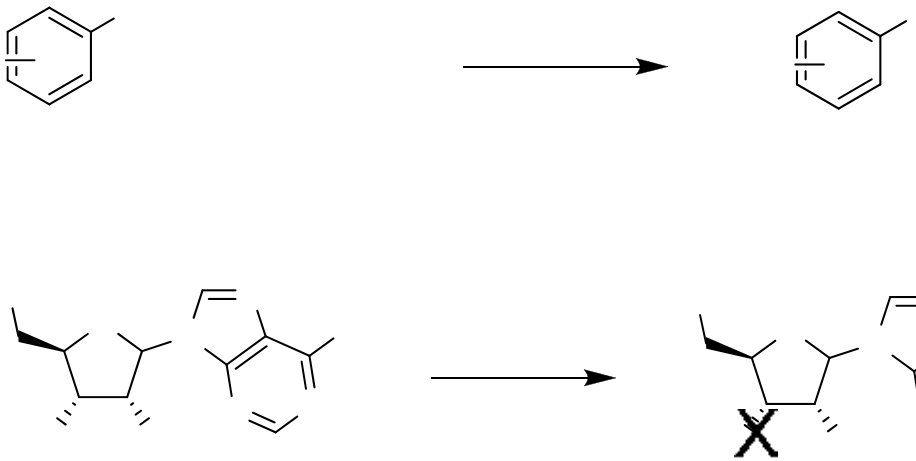
- Cahiez – tolerance of functionality

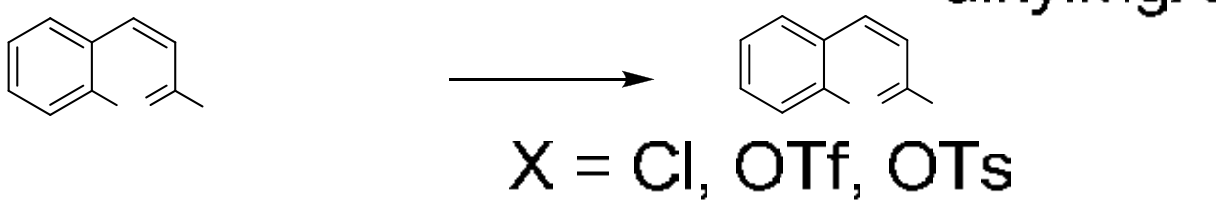


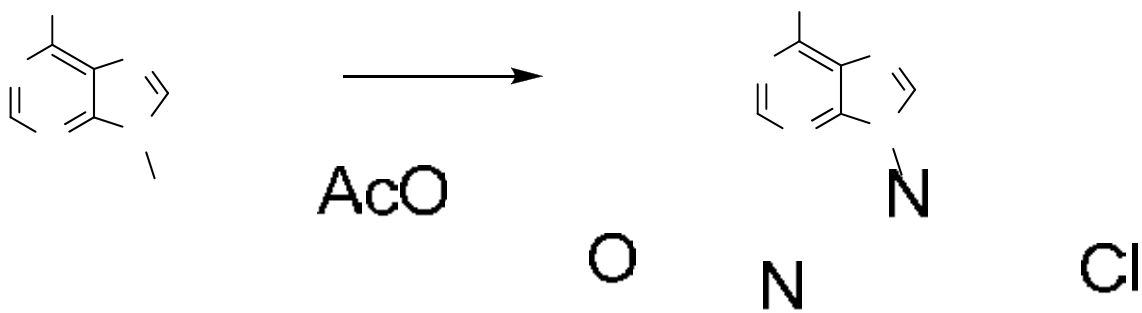


2. Aryl halides

- Fürstner

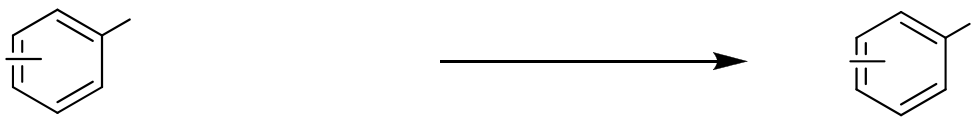


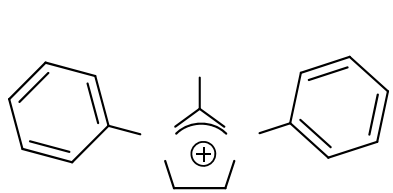




3. Biaryl formation

- Nakamura - Grignard Cross-coupling





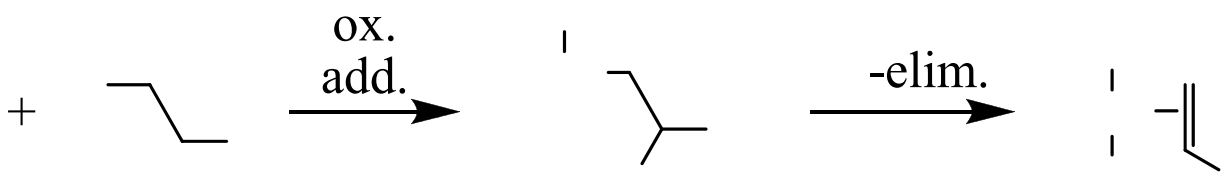
Cl

R + ArMgX

[Fe-F

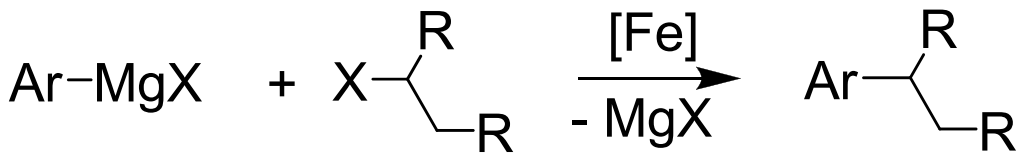
THF, 60

4. Alkyl halides as substrates: Overcoming β-elimination



- Particularly pronounced for secondary alkyls
- Are there catalysts that can prevent this?
- None based on Pd for secondary alkyl halides (so far)

Iron Will



- Nakamura – $FeCl_3$ + (e.g.) TMEDA
- (*J. Am. Chem. Soc.*, 2004, **126**, 3686)

1

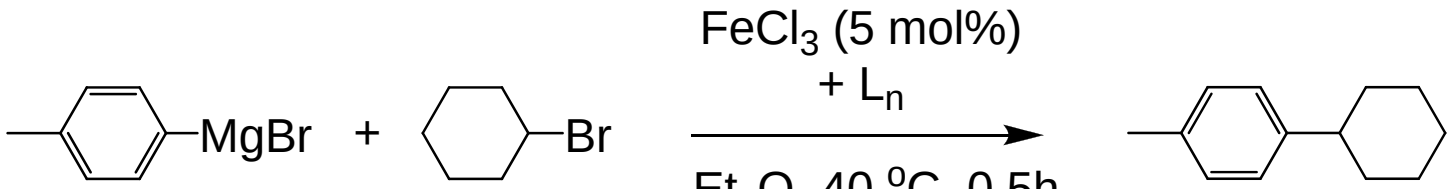
- Hayashi – $[Fe(acac)_3]$
- (*Org. Lett.*, 2004, **6**, 1297)

- Fürstner – $[Li(TMEDA)_2][Fe(ethene)_4]$
- (*Angew. Chem. In. Ed.*, 2004, **43**, 3995)

Simpler Catalyst Systems?

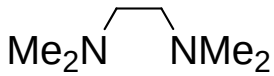
- Nakamura – $FeCl_3$ + amine (e.g. TMEDA)
- Problems
  - Done at low temperature (typically -78 to -20 °C) otherwise reaction goes black
  - Need greater than stoichiometric amounts of amine (w.r.t. substrates)
  - Need to add Grignard/amine mixture slowly (syringe pump)
- Can these issues be resolved?

Screening of amine ligands



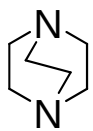
Added rapidly

L_n =



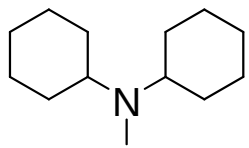
88%

2

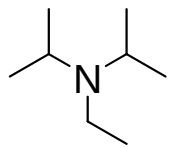


86%

2 NEt_3
97%



82%

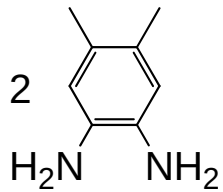


67 %

2 $^{t}Bu{-}NHHN{-}^{t}Bu$

52%

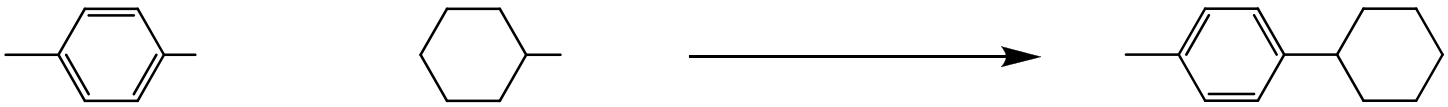
2

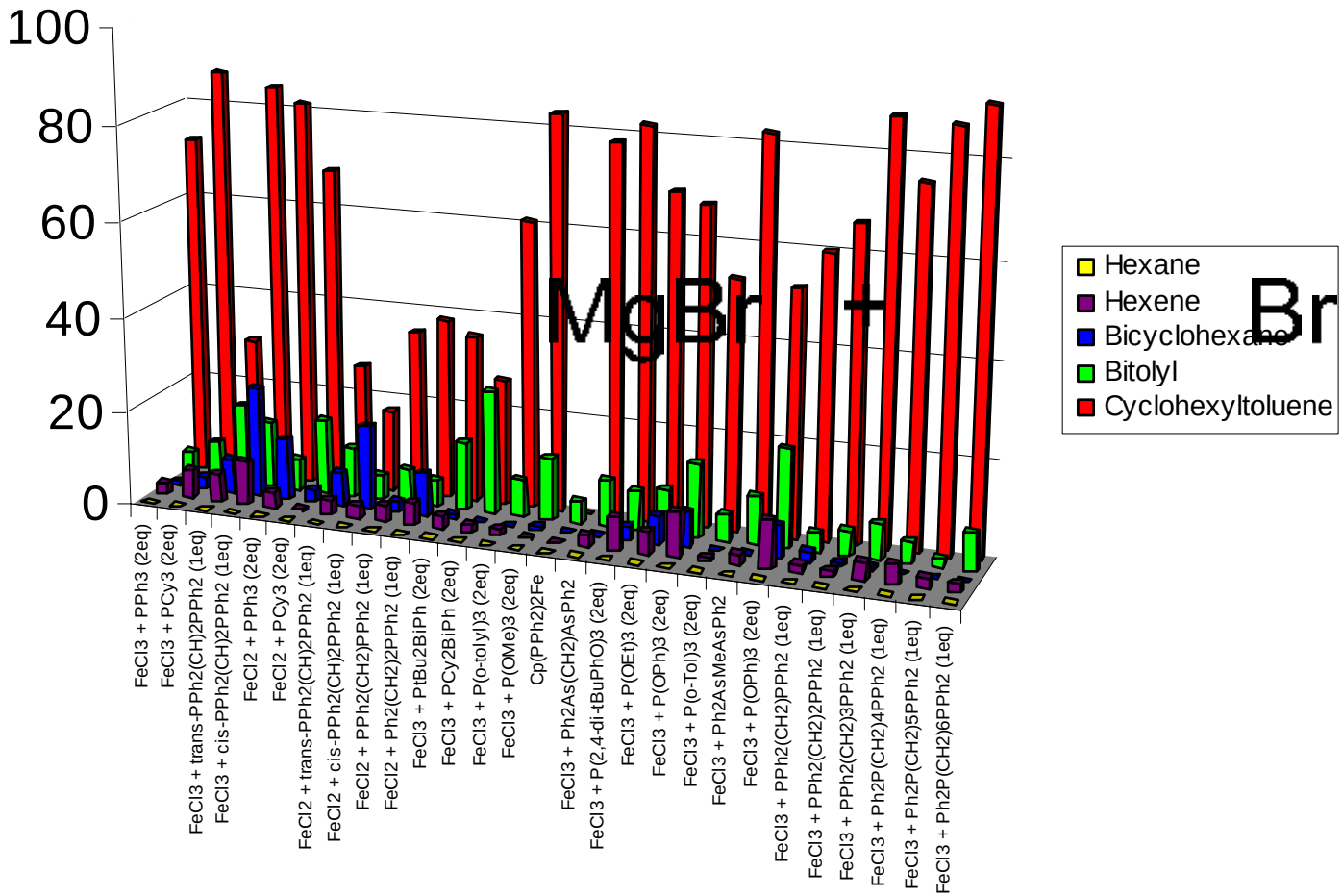


72%

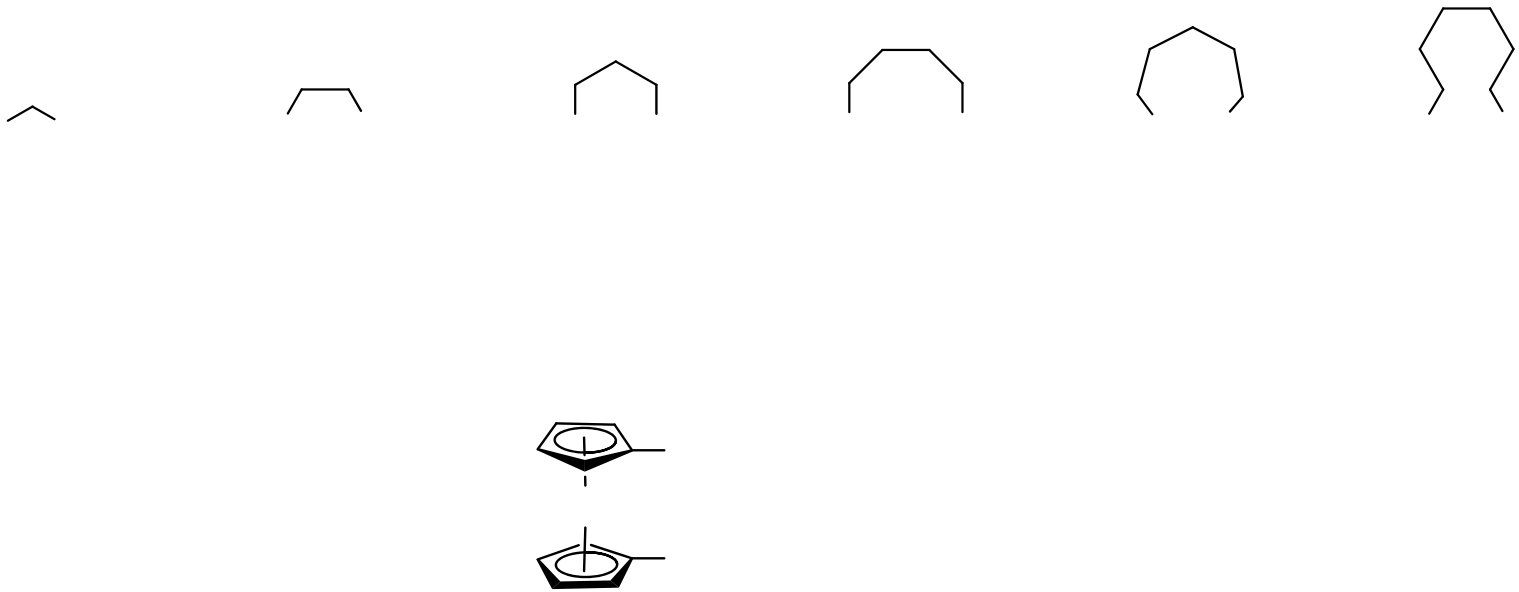
No Ligand
39%

Any Old Iron?



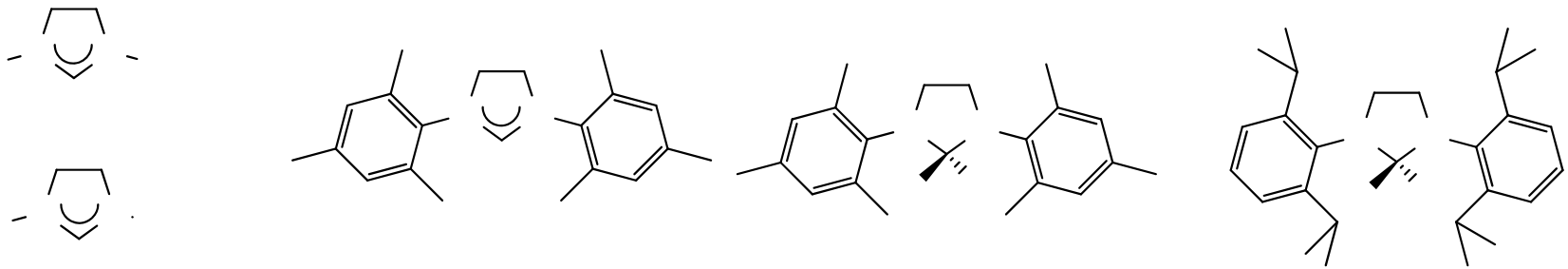

100
80
60
40
20
0
FeCl3 + PPh3 (2eq)
FeCl3 + PCy3 (2eq)
FeCl3 + trans-PPh2(CH)2PPh2 (1eq)
FeCl3 + cis-PPh2(CH)2PPh2 (1eq)
FeCl2 + PPh3 (2eq)
FeCl2 + PCy3 (2eq)
FeCl2 + trans-PPh2(CH)2PPh2 (1eq)
FeCl2 + cis-PPh2(CH)2PPh2 (1eq)
FeCl2 + PPh2(CH2)PPh2 (1eq)
FeCl2 + Ph2(CH2)2PPh2 (1eq)
FeCl3 + PtBu2BiPh (2eq)
FeCl3 + PCy2BiPh (2eq)
FeCl3 + P(o-tolyl)3 (2eq)
FeCl3 + P(OMe)3 (2eq)
Cp(PPh2)2Fe
FeCl3 + Ph2As(CH2)AsPh2
FeCl3 + P(2,4-di-tBuPhO)3 (2eq)
FeCl3 + P(OEt)3 (2eq)
FeCl3 + P(OPh)3 (2eq)
FeCl3 + P(o-Tol)3 (2eq)
FeCl3 + Ph2AsMeAsPh2
FeCl3 + P(OPh)3 (2eq)
FeCl3 + PPh2(CH2)PPh2 (1eq)
FeCl3 + PPh2(CH2)2PPh2 (1eq)
FeCl3 + PPh2(CH2)3PPh2 (1eq)
FeCl3 + Ph2P(CH2)4PPh2 (1eq)
FeCl3 + Ph2P(CH2)5PPh2 (1eq)
FeCl3 + Ph2P(CH2)6PPh2 (1eq)
Hexane
Hexene
Bicyclohexane
Bitolyl
Cyclohexyltoluene

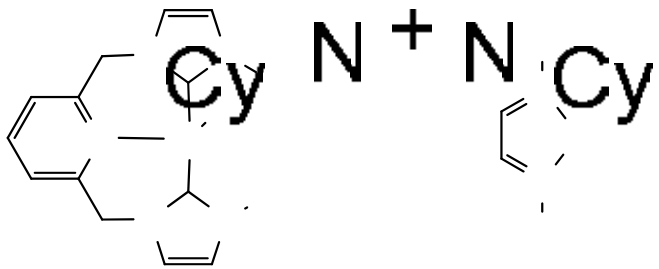
Chelating bis(phosphines) ‘steel’ the show

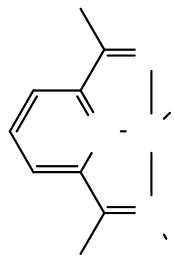


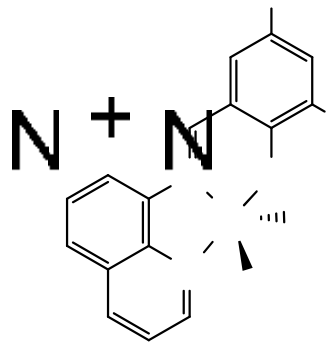
J. Org. Chem.. 2006, **71**, 1104

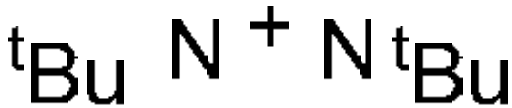
Other Irons in the Fire ?









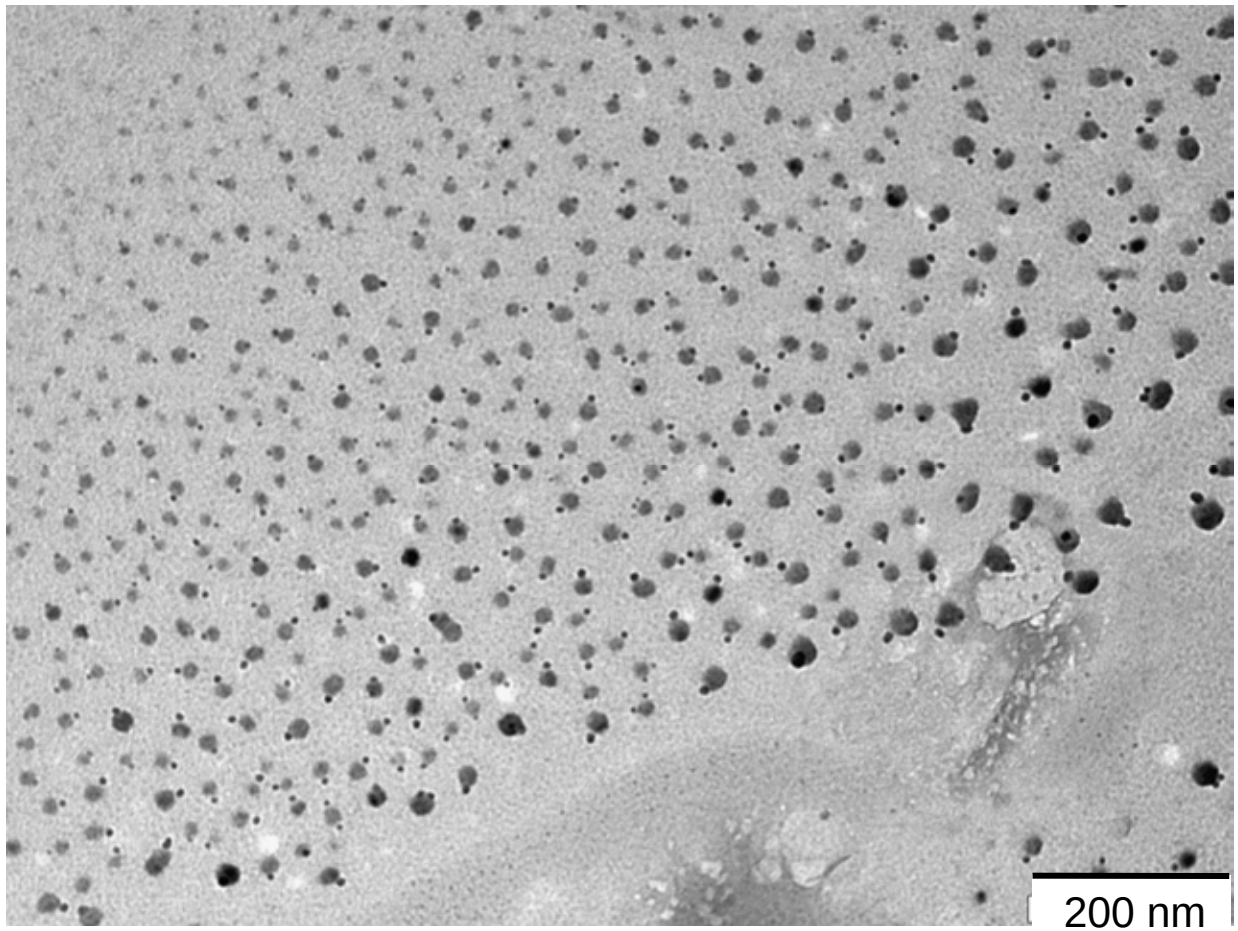


45 – 97% conversions

How different are all the catalysts really?

Active catalyst

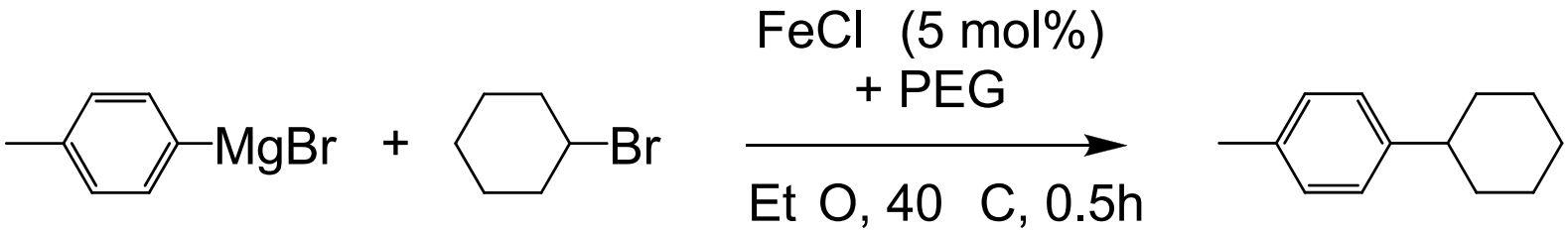
- Very wide range of pre-catalysts
- Significance of long chain on bis-phosphine backbones?
- Appearance
- Nanoparticulate iron?



TEM image of $FeCl_3$/dpph + 5 ArMgBr

$FeCl_3$ – PEG as a catalyst

- Polyethylene glycol stabilises nanoparticles – is Fe-PEG catalytically active?



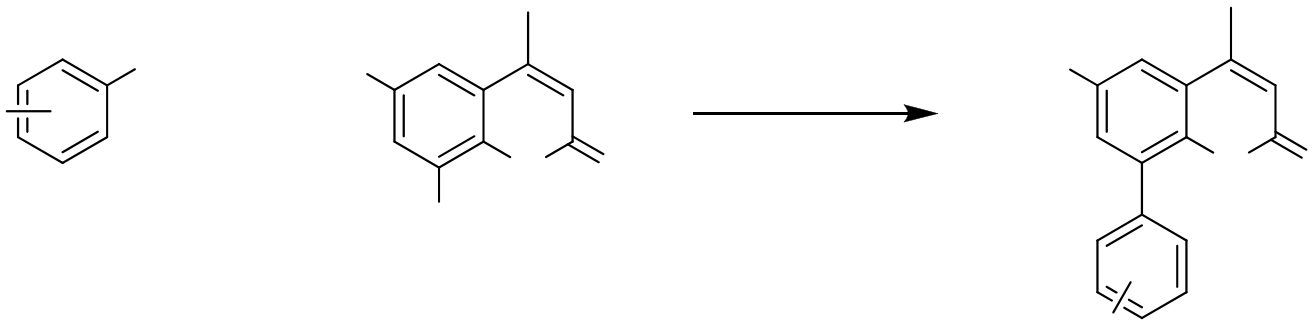
PEG M_w	Fe : monomer	conversion (%)
14,000	1 : 100	0
	1 : 10	0
	1 : 1	**94**
	1 : 0.1	67
35,000	1 : 1	79
200	1 : 1	63

'Bottleable' Nanoparticles

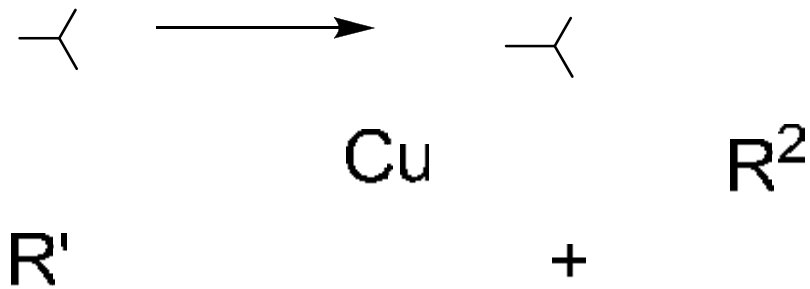
Chem. Commun. 2006, 1398

Softer Nucleophiles – Away from Gignard Reagents

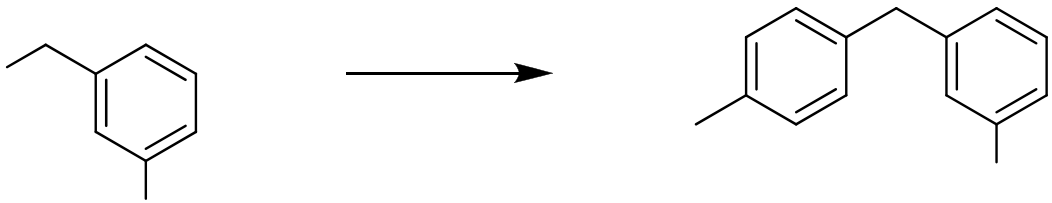
- Knochel – organocuprates and aryl iodides

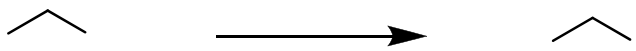


- Negishi coupling - Nakamura



Negishi coupling of benzyl halides and phosphates





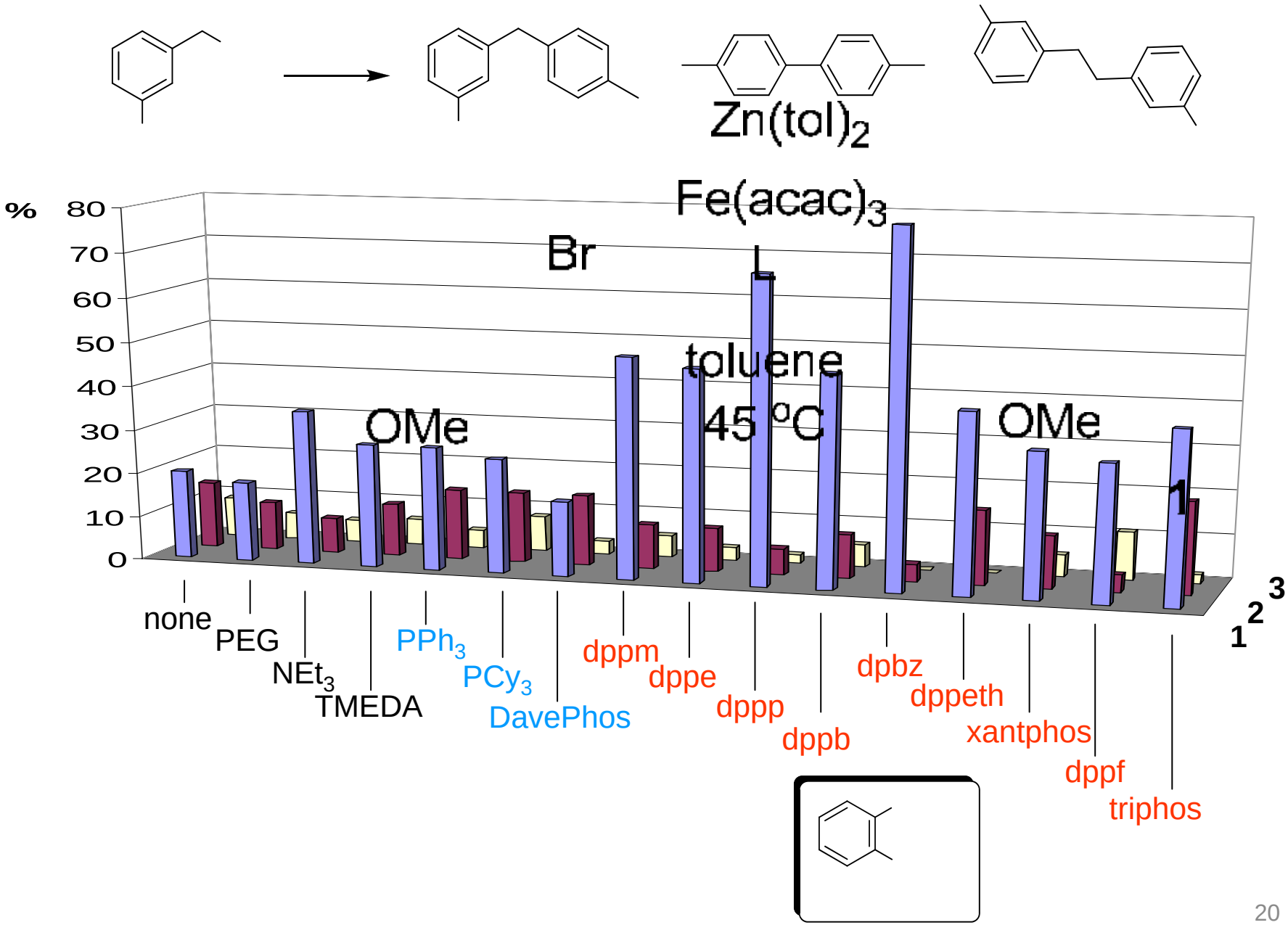
TolMgBr + Br

$FeCl_3$ (
Fe(aca

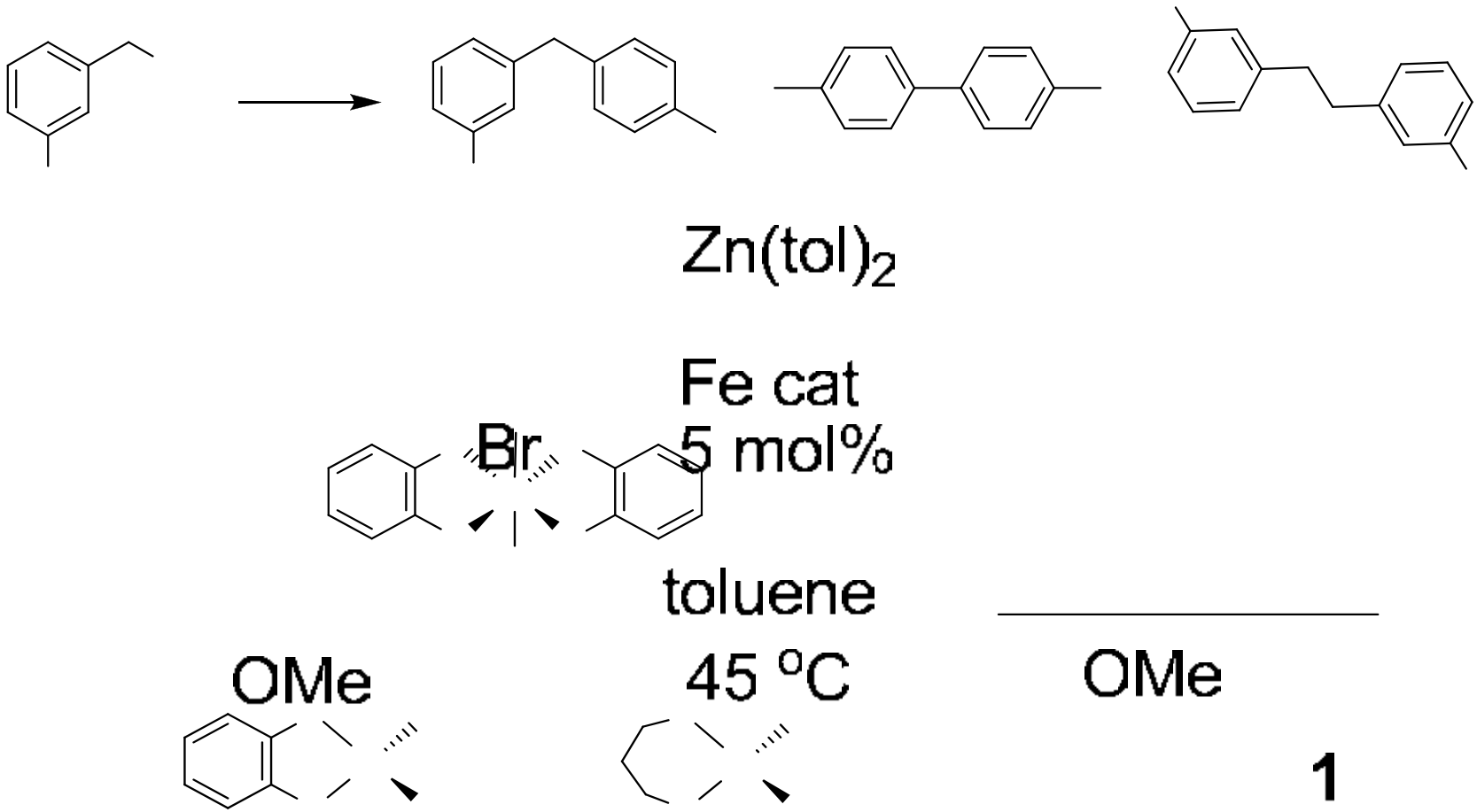
L

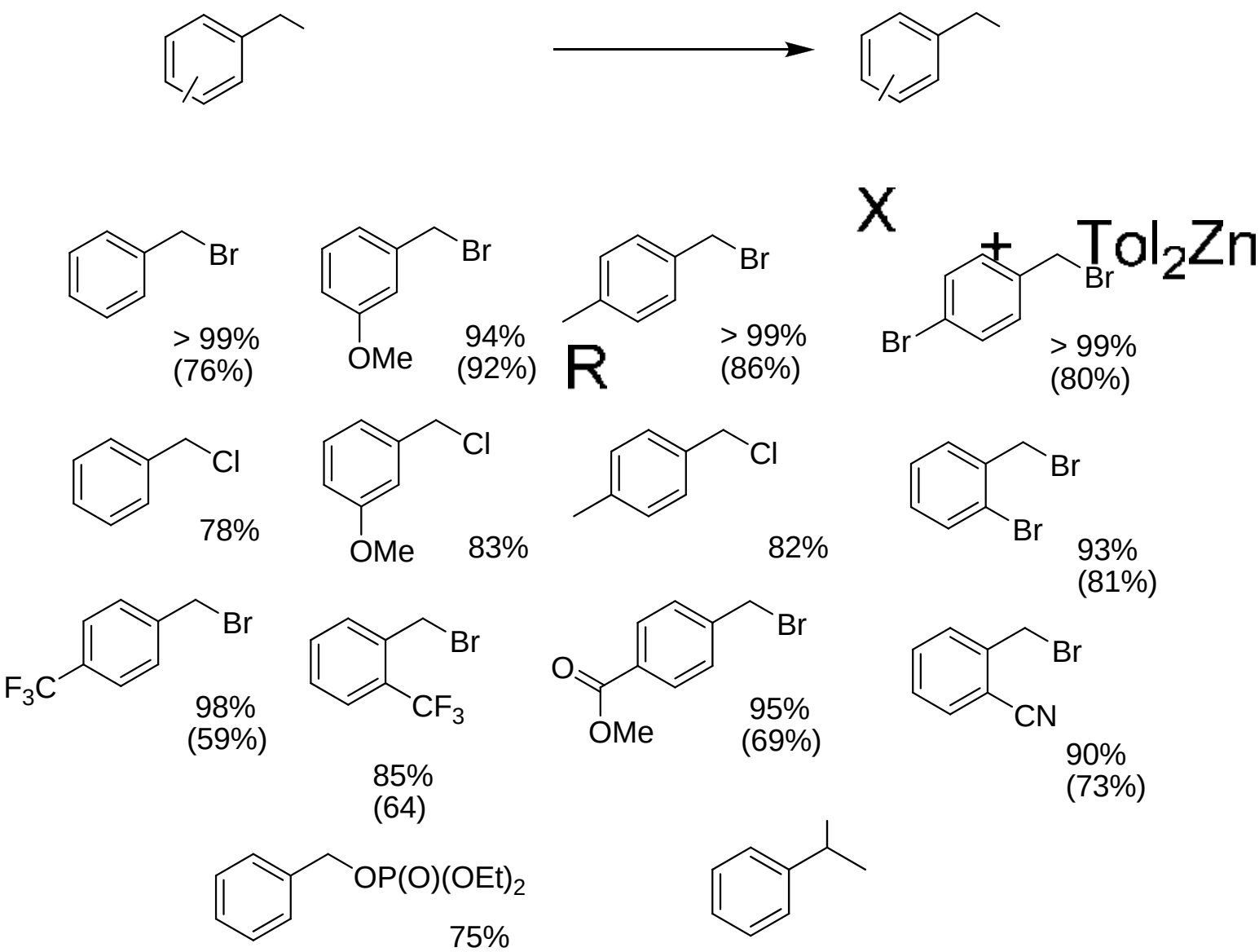
Et_2O (or t

40 °

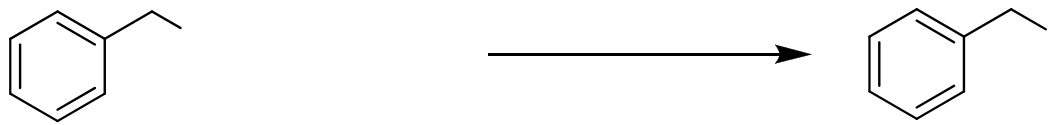

Zn(tol)2
%
80
70
60
50
40
30
20
10
0
Fe(acac)3
Br
L
toluene
45 °C
OMe
OMe
1
2
3
none
PEG
NEt3
TMEDA
PPh3
PCy3
DavePhos
dppm
dppe
dppp
dppb
dpbz
dppeth
xantphos
dppf
triphos

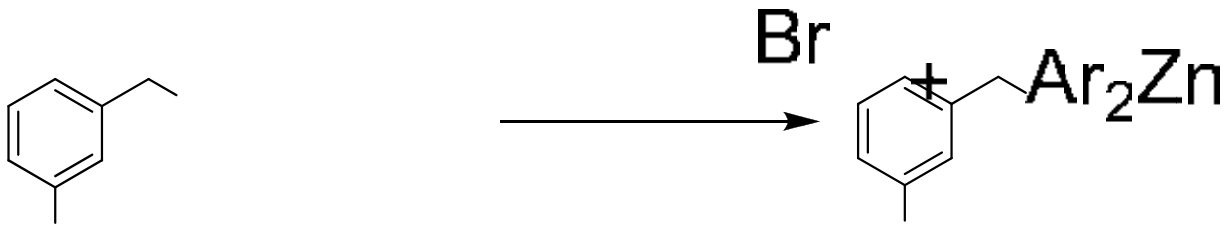
Preformed catalysts





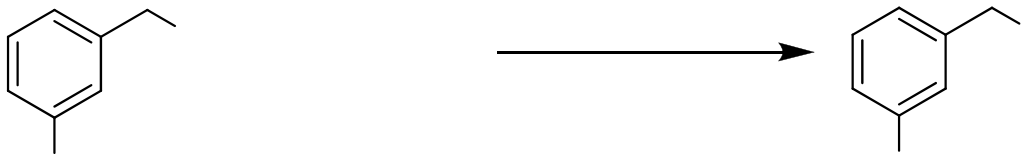
Chem. Commun. 2009, 600





[FeCl

toluene

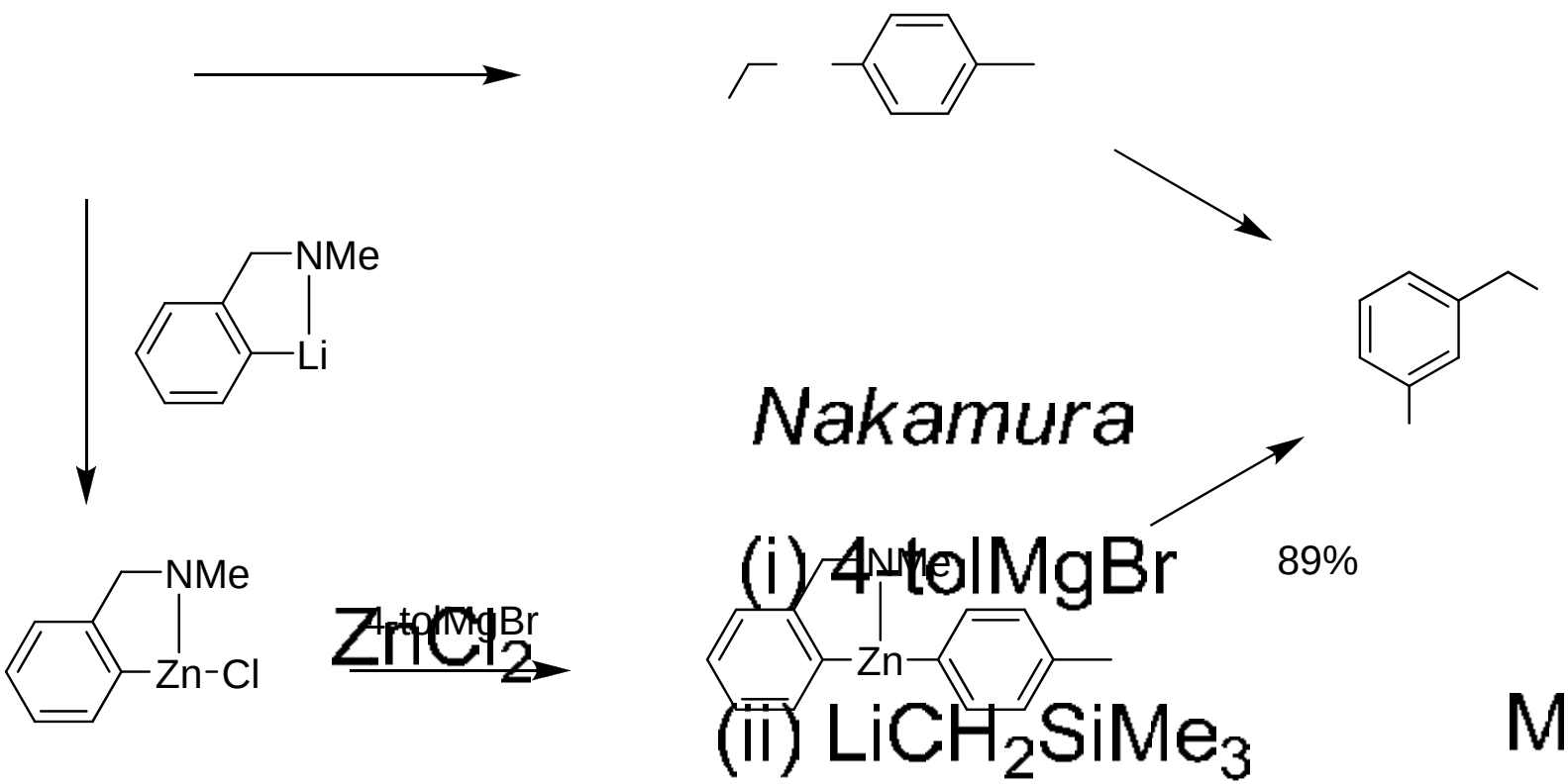


[FeCl

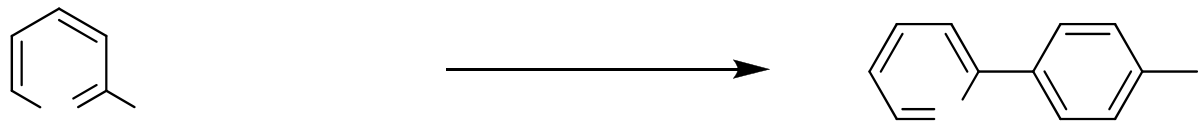
X

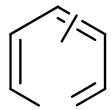
+ ***0.5*** Tol_2Zn

‘Dummy’ ligands



- 2-heteroary halides (unpublished)





[FeCl$_2$(dp

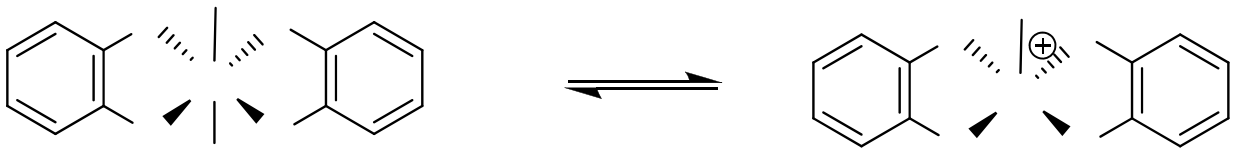
+ tol$_2$Zn

N X

toluene, 100

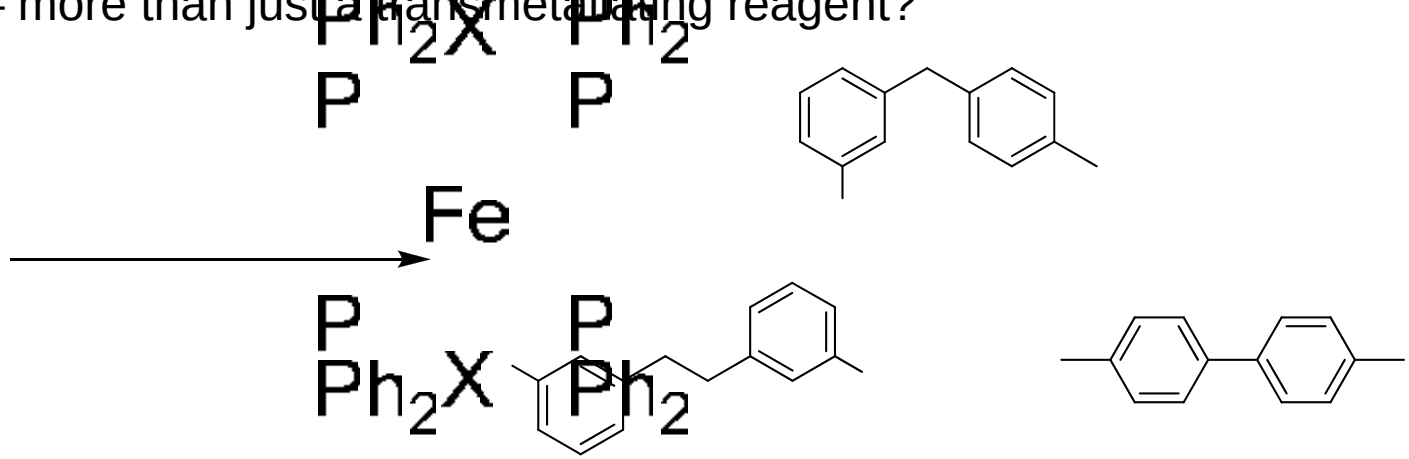
Mechanistic considerations

Cationic catalyst?



High spin complexes? (Fast kinetics)

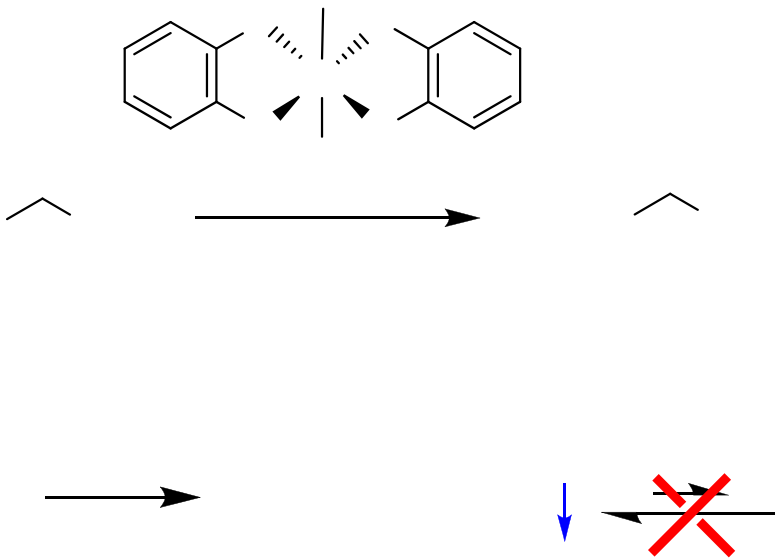
Ar_2Zn – more than just a transmetallating reagent?

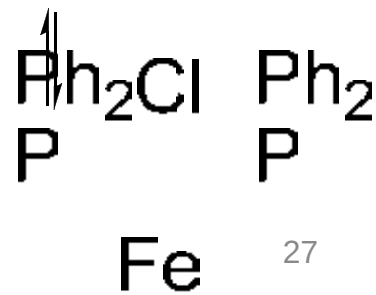


Is Ar_2Zn the transmetallating reagent?

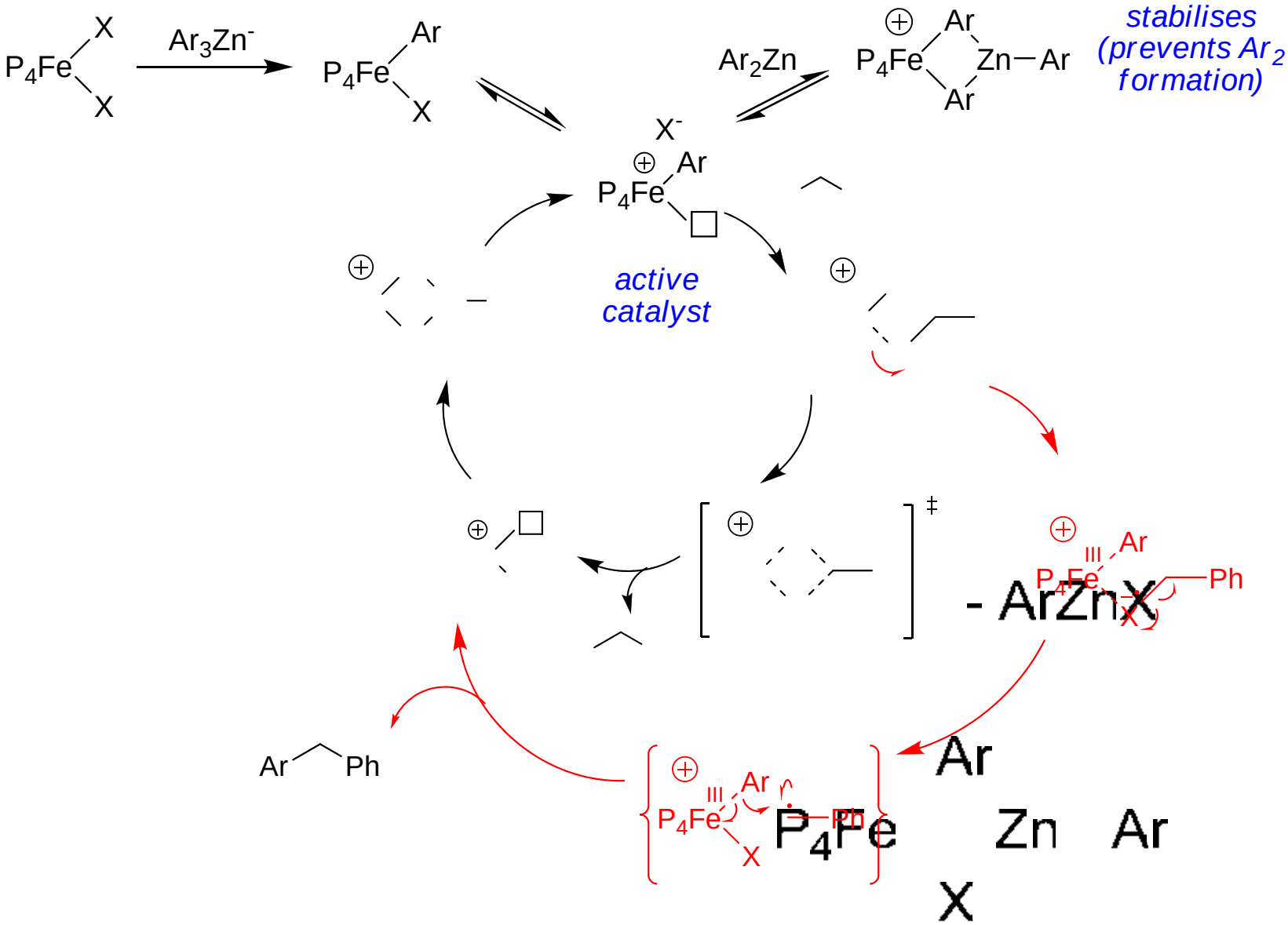
Very low activity (14%) with Ar_2Zn formed from ArLi

Adding $MgBr_2$ (2 equiv.) restores ~ 90% of the activity

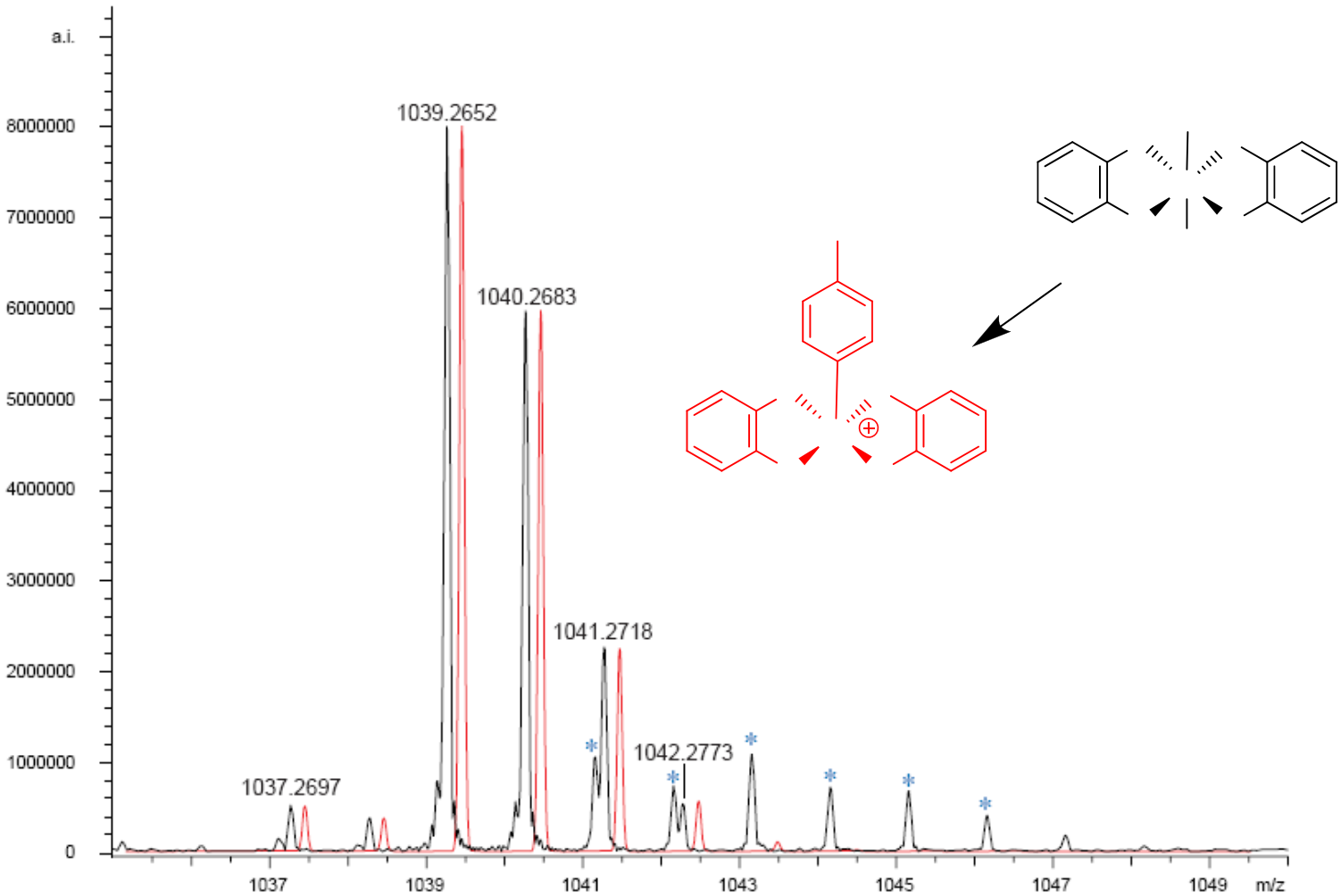




Mechanism – working hypothesis



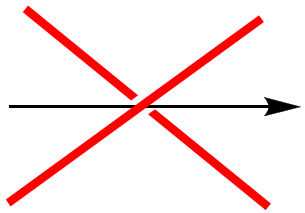
Evidence for active catalyst



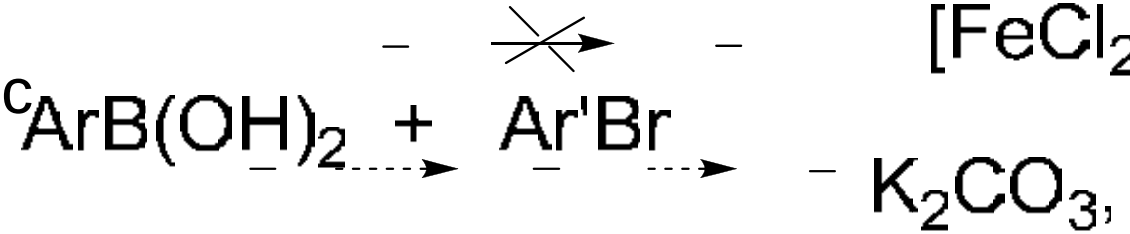
HR-ESI/MS

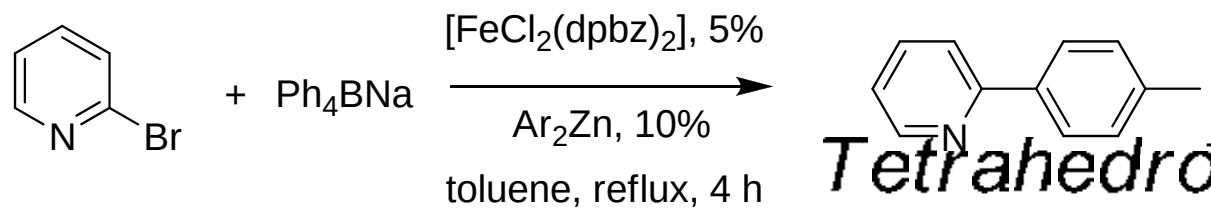
Fe-cat Suzuki achievable?

- Franzen

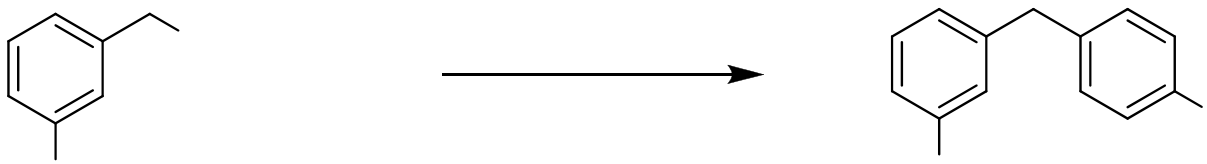


- Using co-catalytic zinc





Tetrahedron Letts. 200



Cast Iron conclusions

- Iron catalysis is undergoing a huge renaissance
- Many reactions that can be catalysed by Pd can also be catalysed by Fe
- Many reactions that can’t be catalysed by Pd can by Fe
- Significant promise for Suzuki coupling and CH activation

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