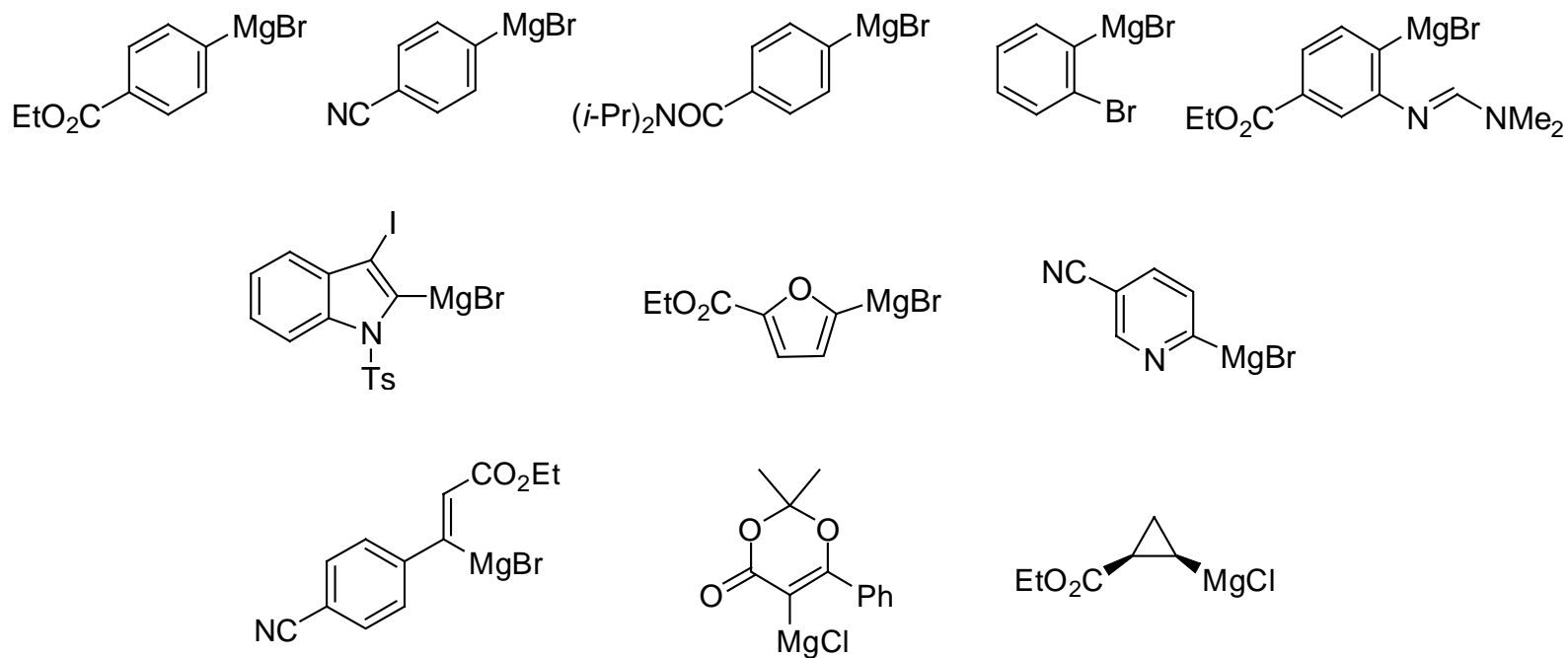
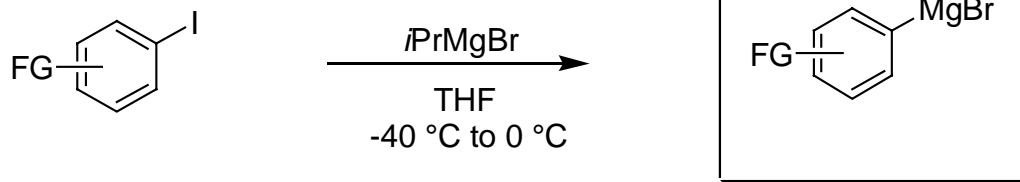


Functionalized Grignard Reagents and Their Applications in New Amination Reactions

Evans Group Seminar

November 9, 2004

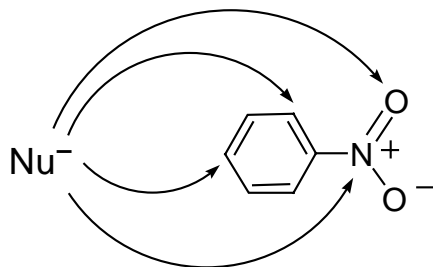
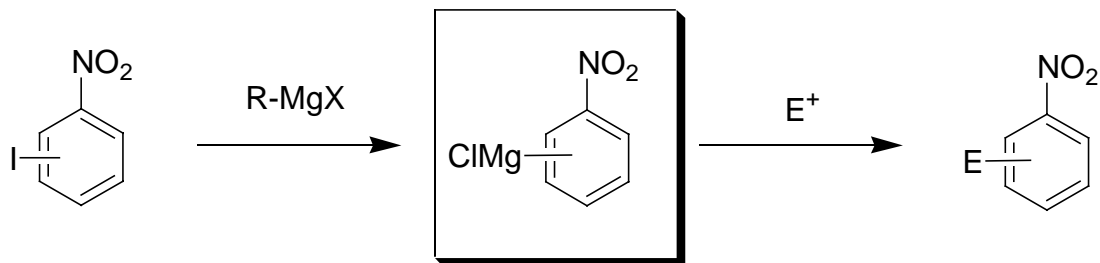
Preparation of Functionalized Organomagnesium Reagents through Halogen-Magnesium Exchange



recent review:

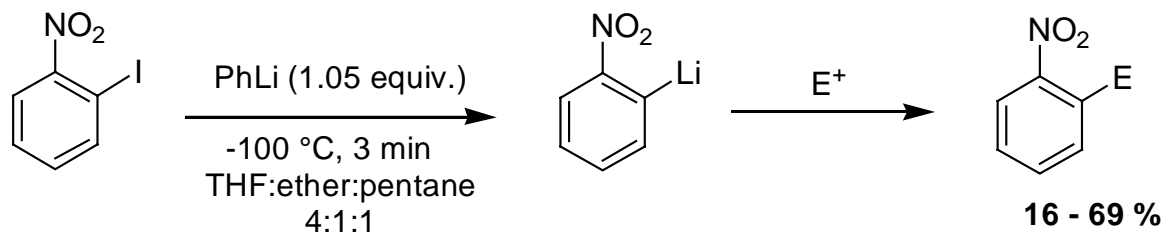
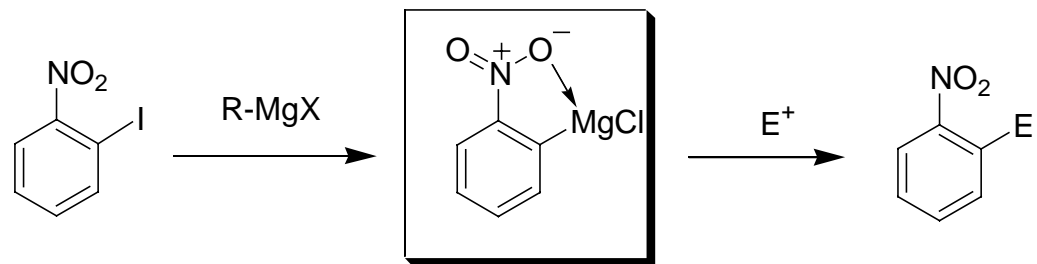
P. Knochel et al. *Angew. Chem. Int. Ed.* **2003**, 42, 4302.

Nitrofunctionalized Grignard Reagents



- 1,2-, 1,4- and 1,6-addition or O-attack possible
- Single-electron transfer (SET) and radical-anion coupling

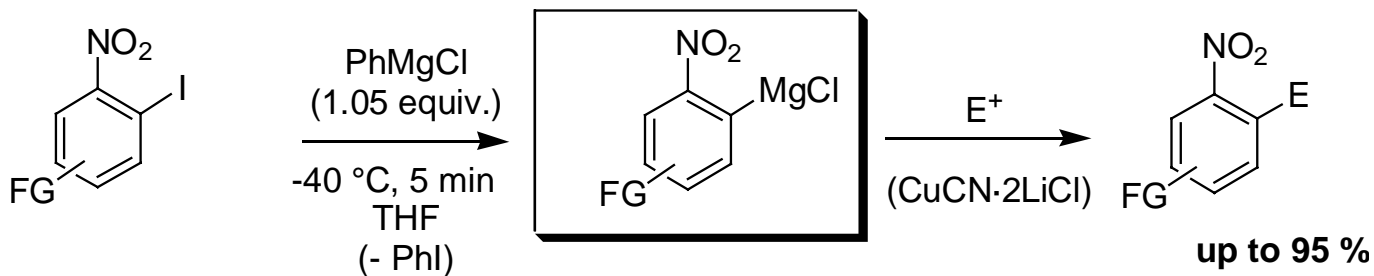
New Amination Reactions using Arylmagnesium Reagents



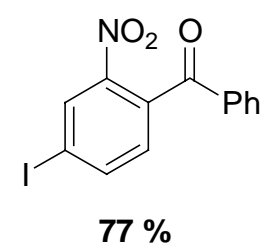
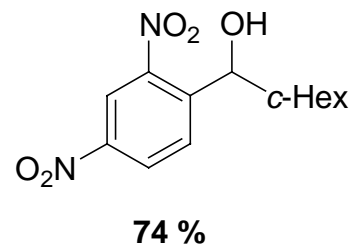
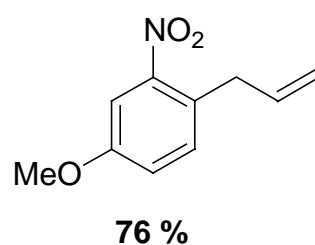
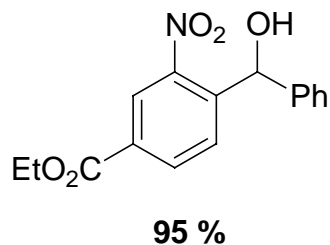
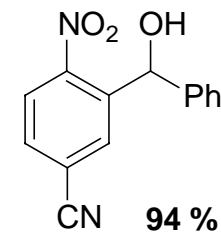
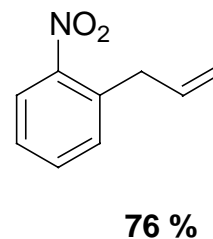
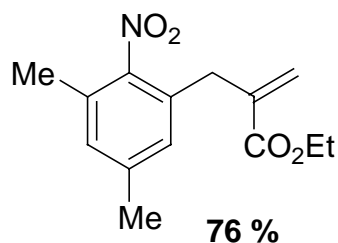
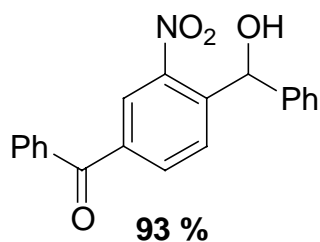
C. E. Tucker, T. N. Majid and P. Knochel, *J. Am. Chem. Soc.*, **1992**, *114*, 3983.

J. F. Cameron and J. M. Fréchet, *J. Am. Chem. Soc.*, **1991**, *113*, 4303.

Nitro-Substituted Arylmagnesium Reagents

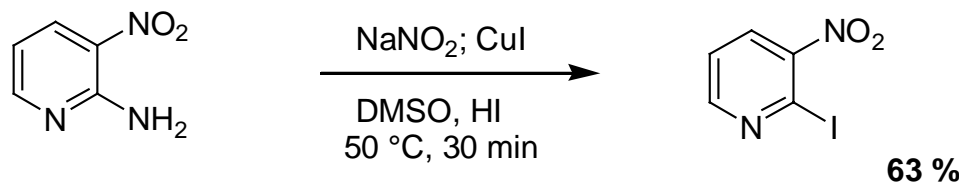
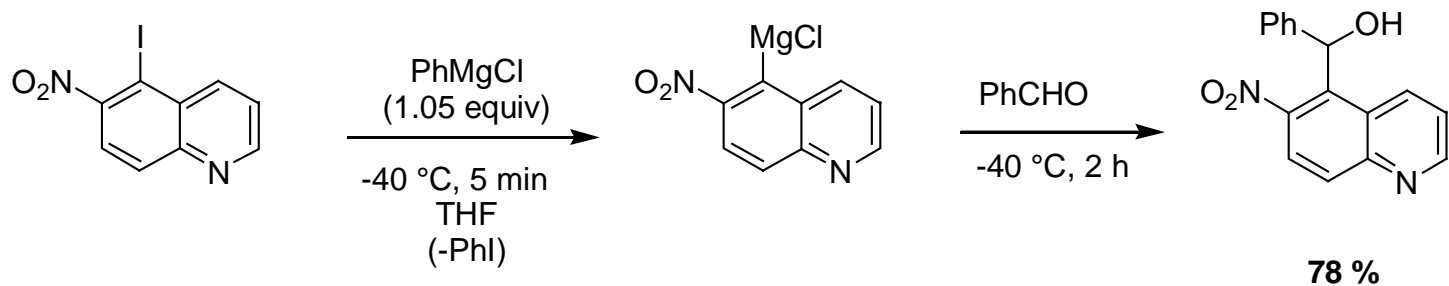
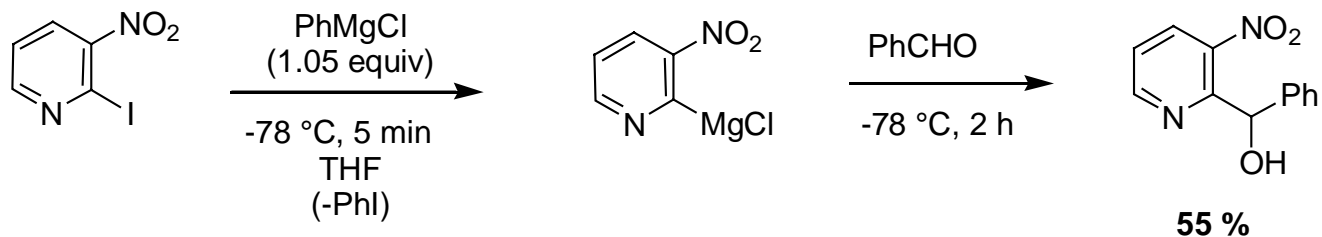


FG: CO₂Et, CN, I, NO₂, OMe, H, Me, C(=O)Ph, CONR₂

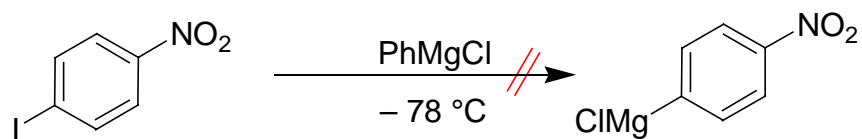
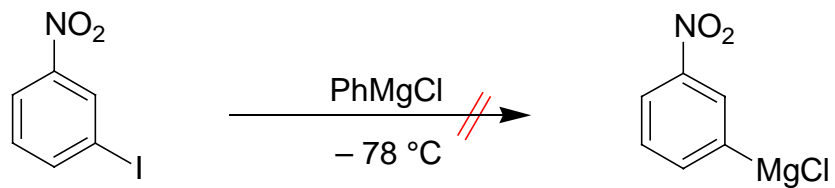


I. Sapountzis, P. Knochel *Angew. Chem.* **2002**, 114, 1680;
Angew. Chem. Int. Ed. **2002**, 41, 1610.

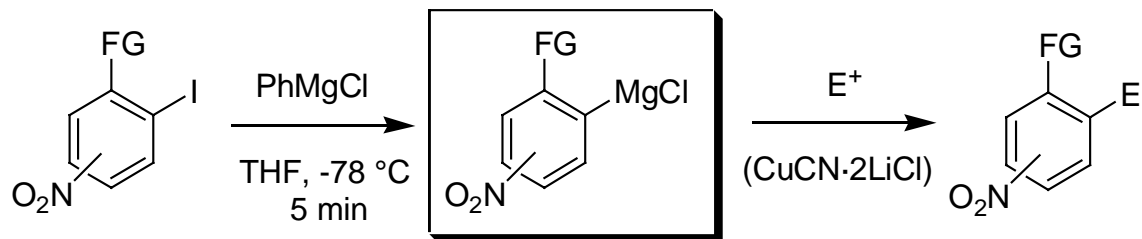
Nitro-Substituted Heteroarylmagnesium Reagents



m- and *p*-Nitro-Substituted Arylmagnesium Reagents

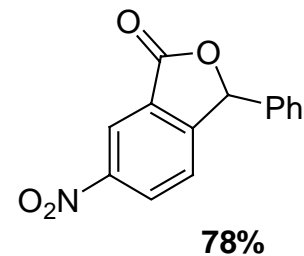
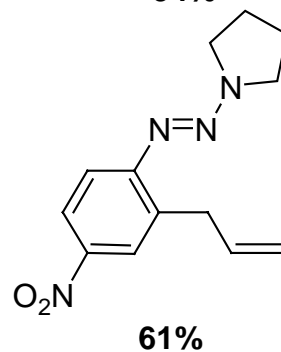
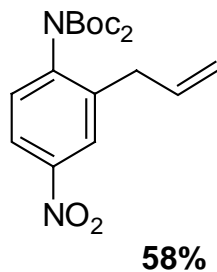
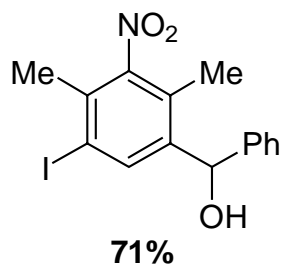
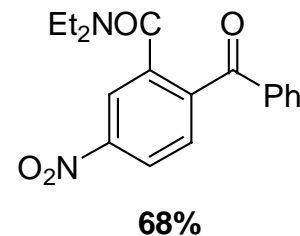
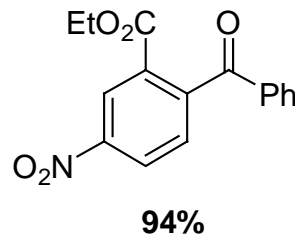
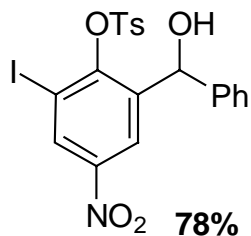
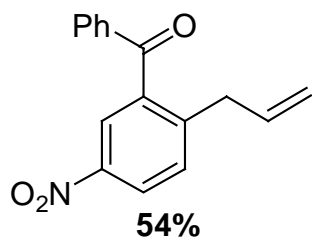


Nitro-Substituted Arylmagnesium Reagents

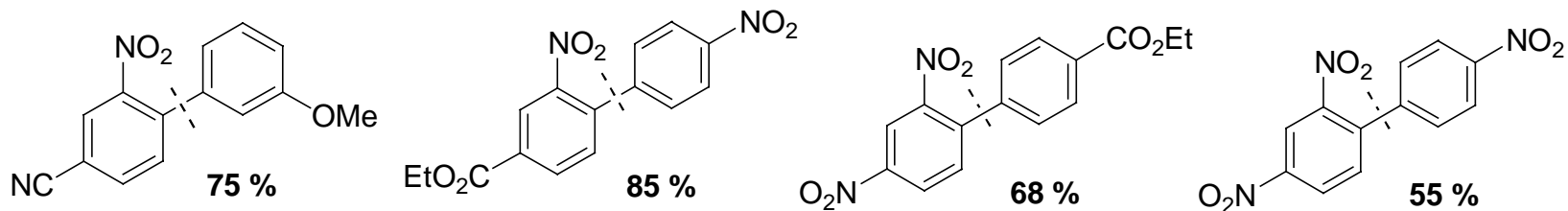
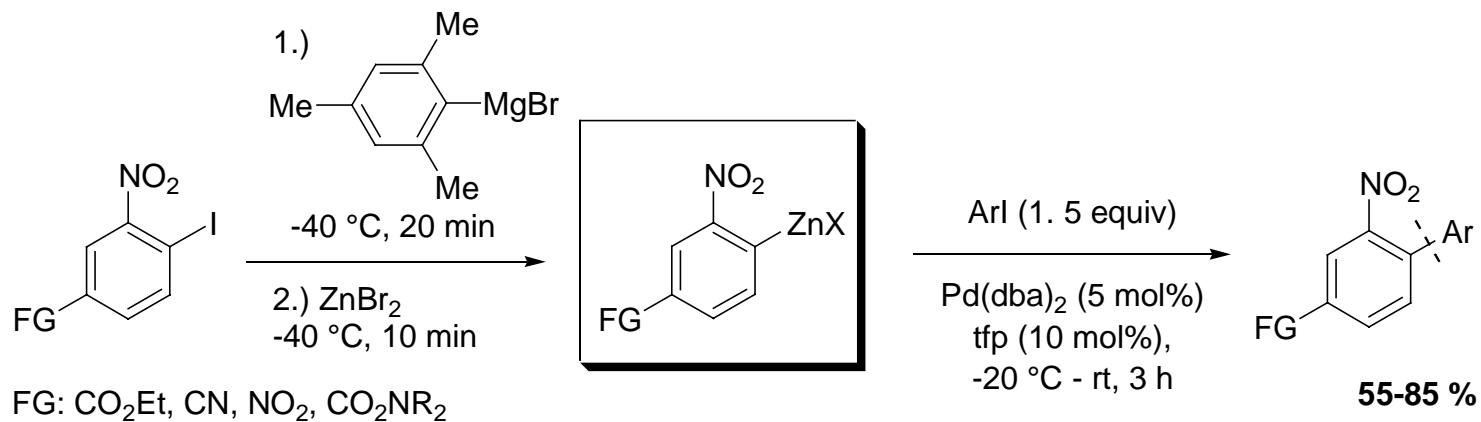
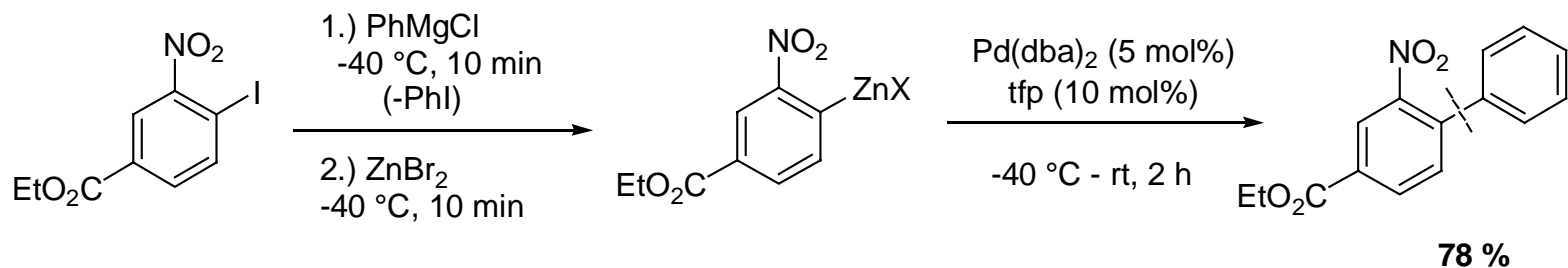


FG = CO_2Et ; CONR_2 ; COPh ;
 $\text{N}=\text{N}-\text{NR}_2$; OTs; Boc_2N

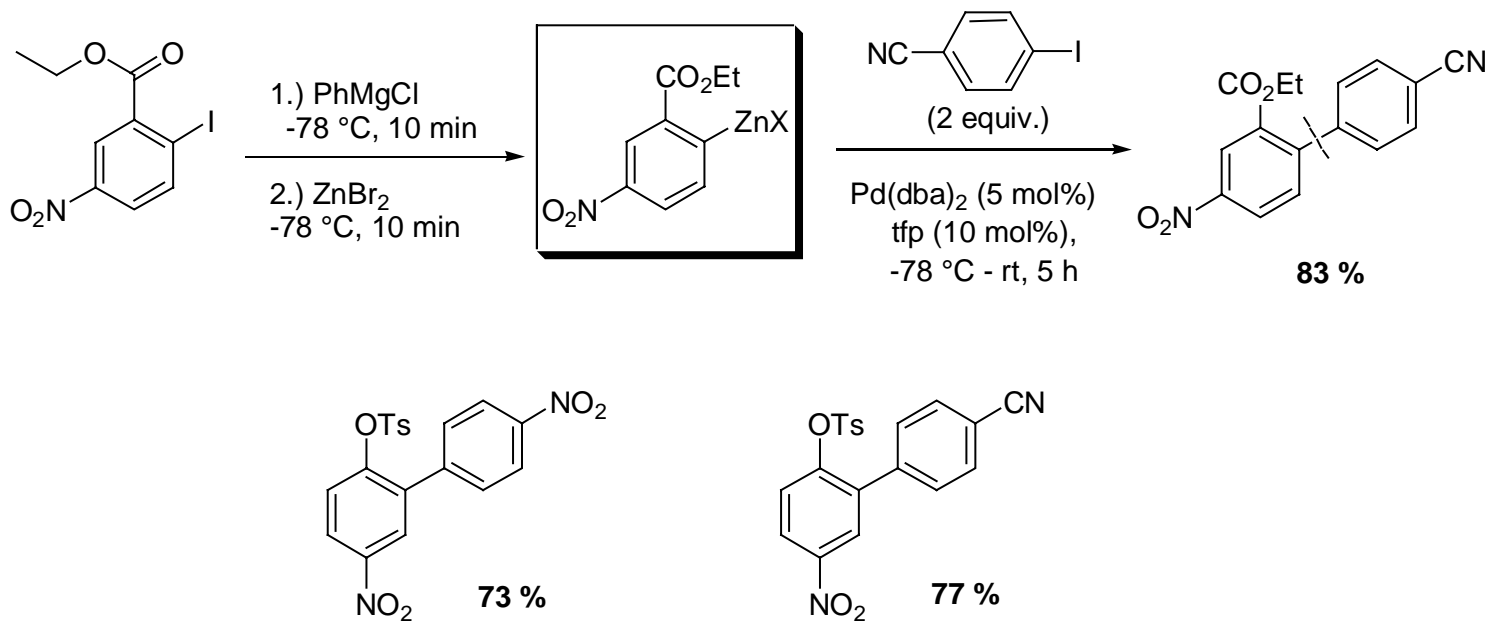
54 - 94 %



Nitro-Substituted Arylmagnesium Reagents in Negishi-cross coupling Reactions

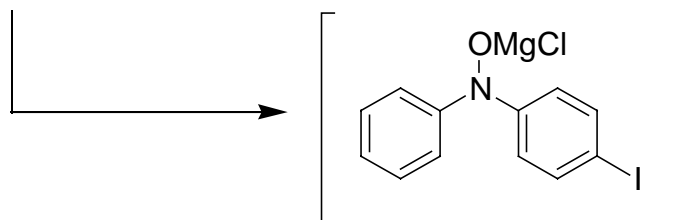
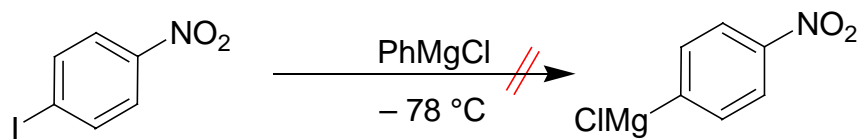
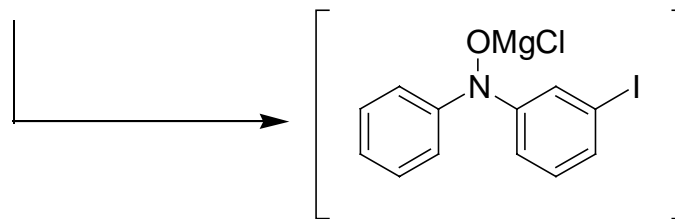
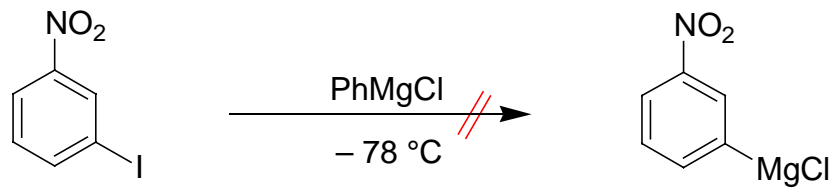


m- and *p*-Nitro-Substituted Arylmagnesium Reagents in Negishi cross-coupling reactions

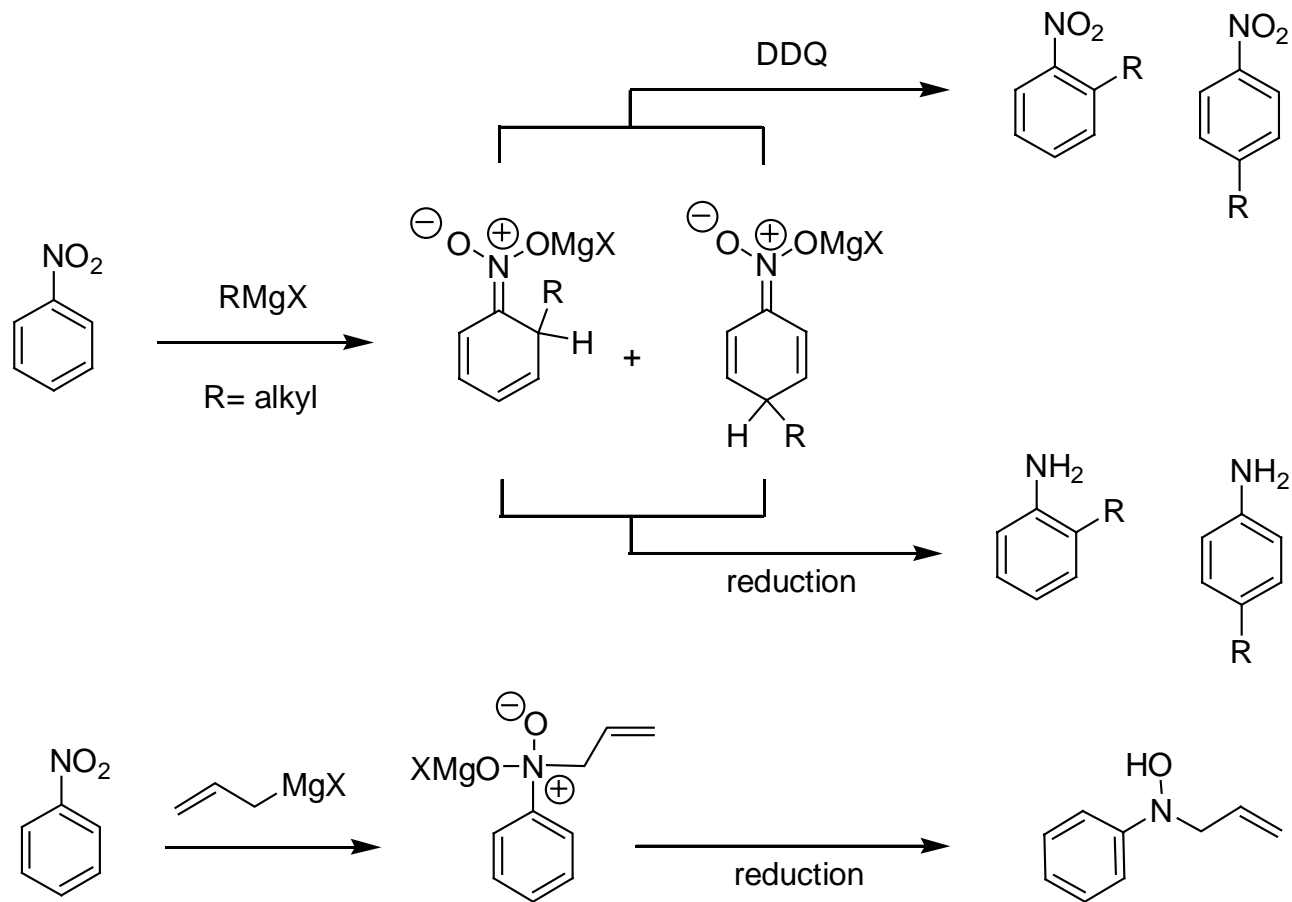


I. Sapountzis, H. Dube, P. Knochel *Adv. Synth. Catal.* **2004**, 346, 709.

A failed reaction?



Early Studies on Reactions between Nitroarenes and Organomagnesium Reagents

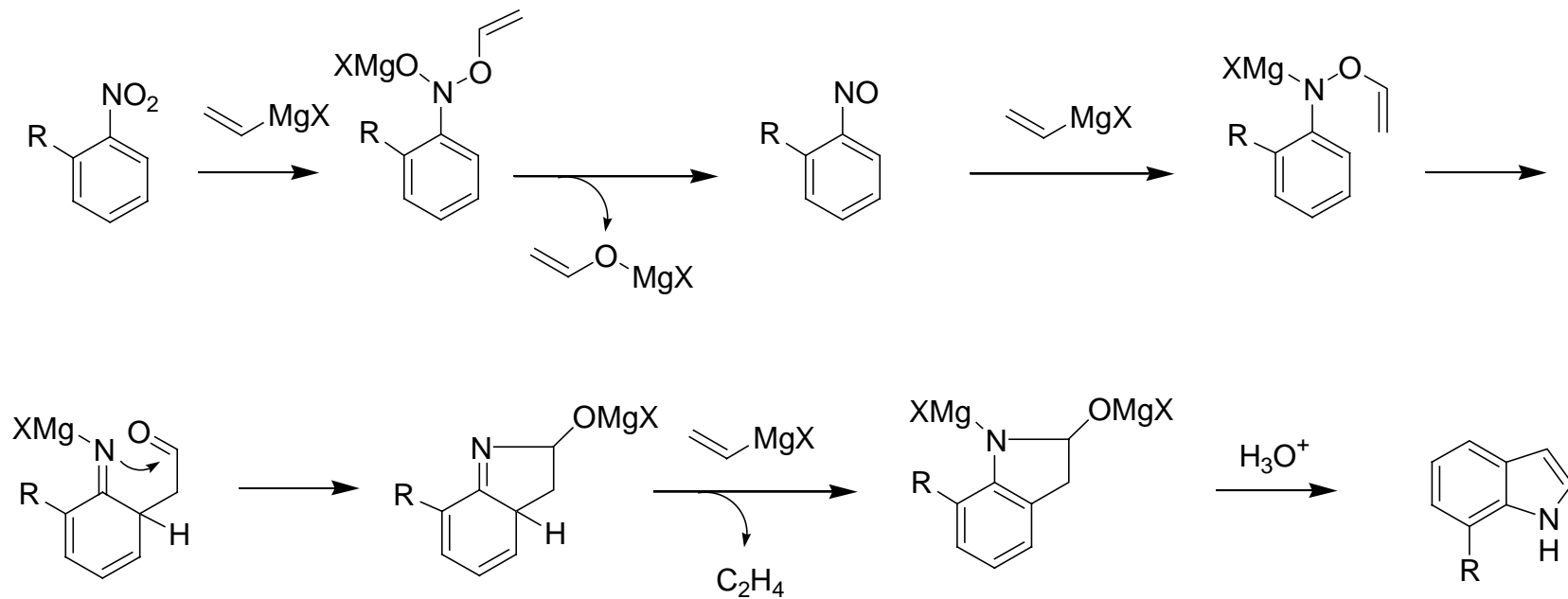


G. Bartoli *Acc. Chem. Res.* **1984**, 17, 109.

Highlight:

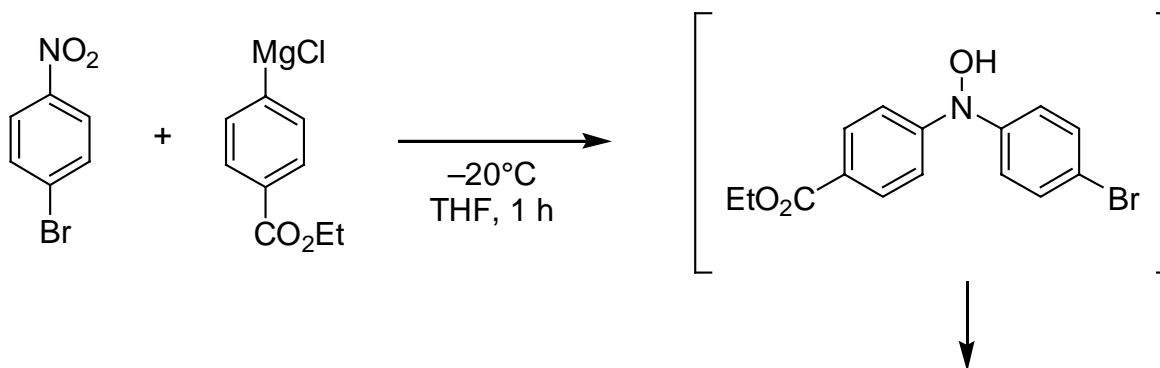
A. Ricci, M. Fochi *Angew. Chem. Int. Ed.* **2003**, 42, 1444

The Bartoli Indole Synthesis



G. Bartoli, G. Palmieri, M. Bosco, R. Dalpozzo *Tetrahedron Lett.* **1989**, 30, 2129.

Reducing the Hydroxylamine – Access to Diarylamines



One-Pot-Procedure desirable

Reduction conditions:

Pd/C-NaBH₄;

Raney Ni;

Fe/AcOH;

BEt₃ in THF;

SnCl₂ in HCl;

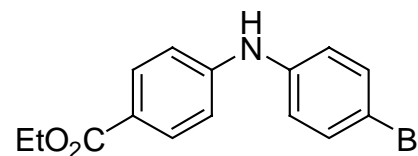
SnCl₂ in EtOH;

Sml₂ in THF;

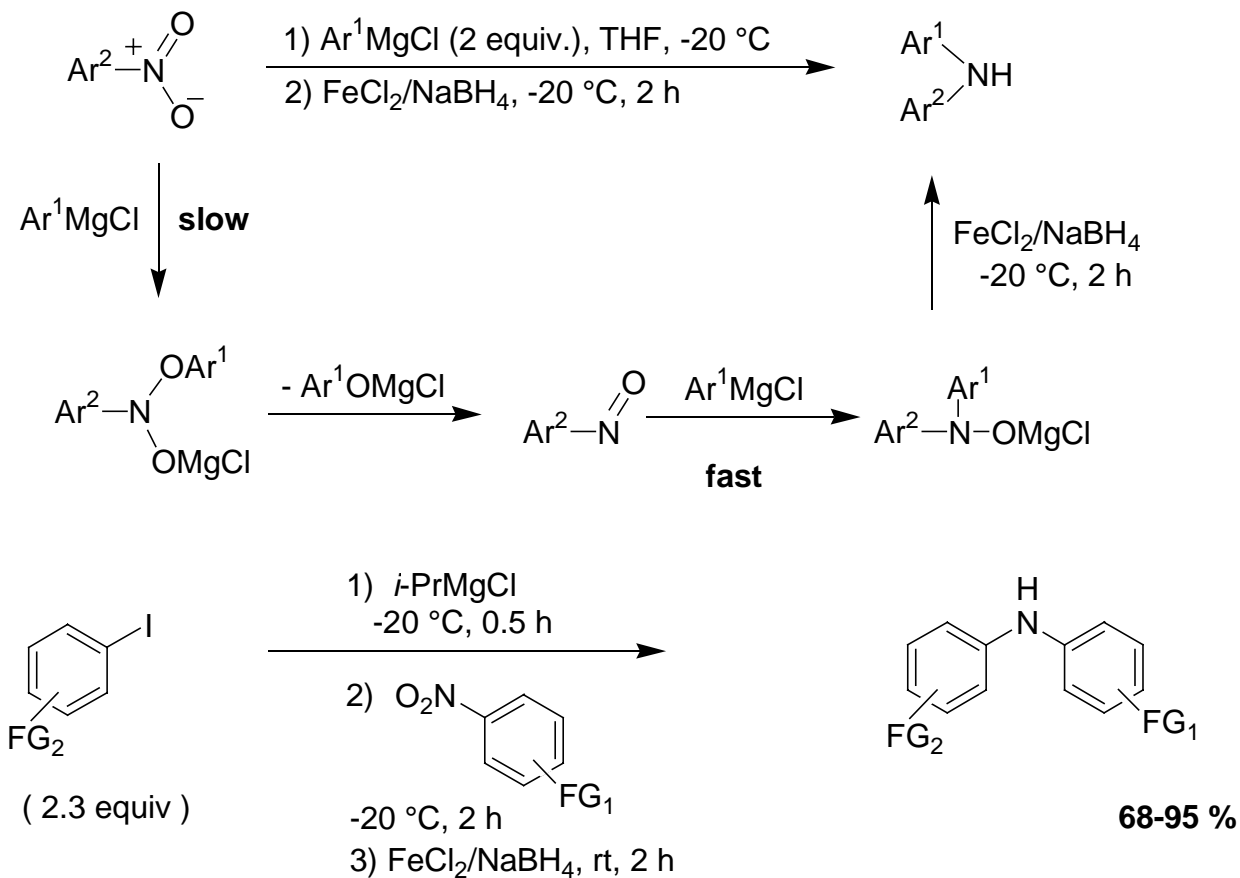
various Lewis acids and

NaBH₄ in different solvents

FeCl₂ in THF + NaBH₄

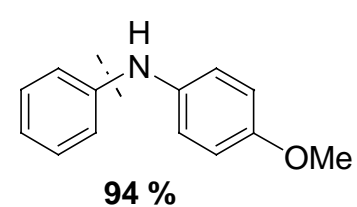
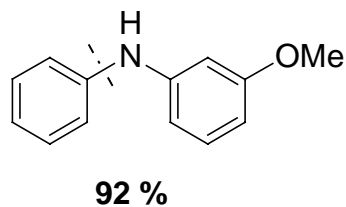
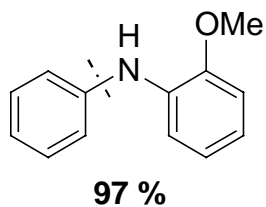
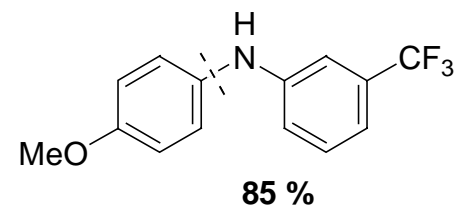
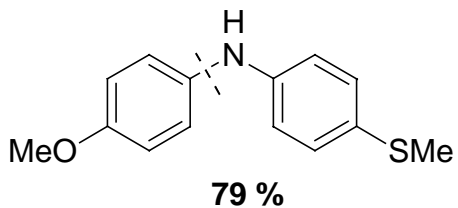
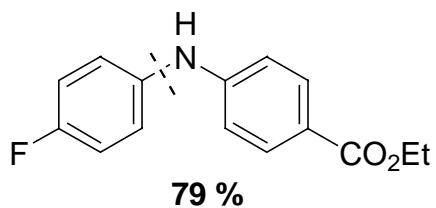
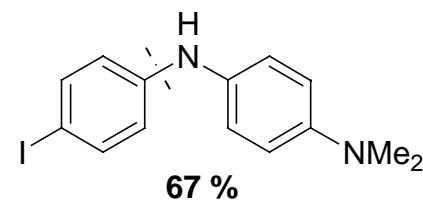
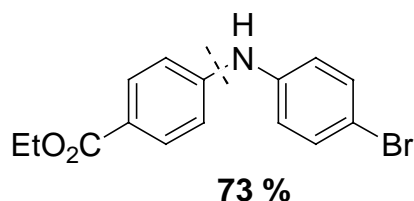
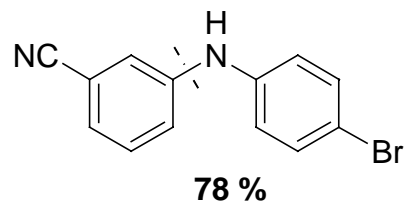
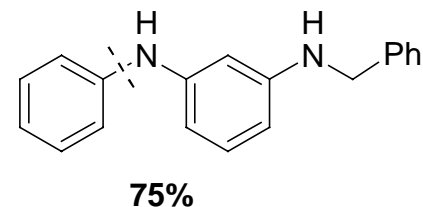
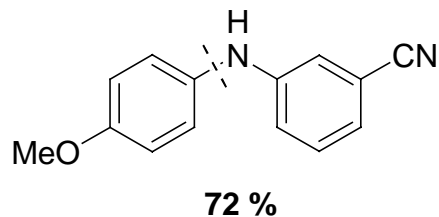
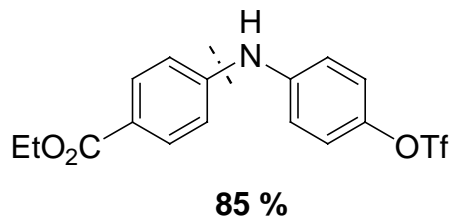


New Amination Reaction using Aryl-Magnesium Reagents and Nitrobenzenes

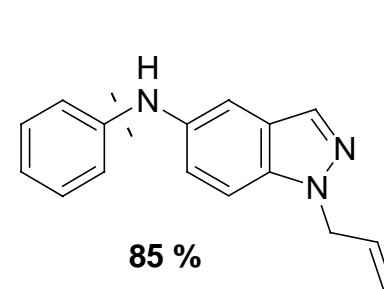
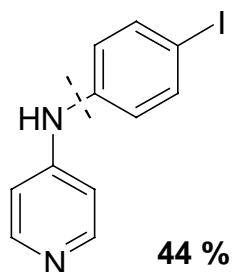
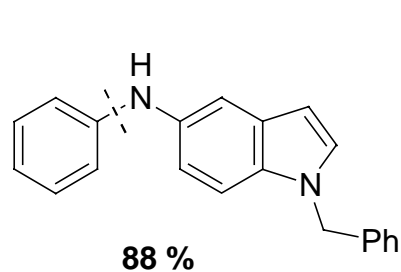
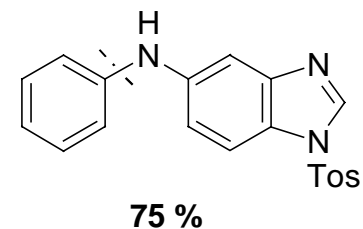
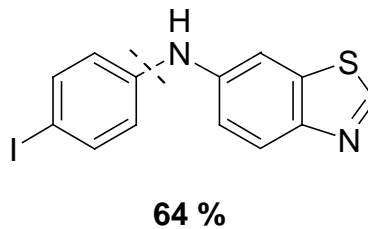
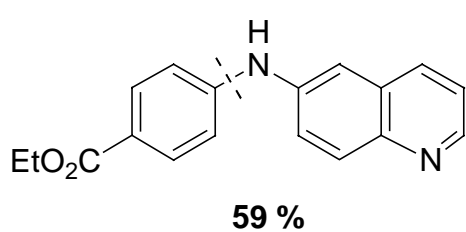
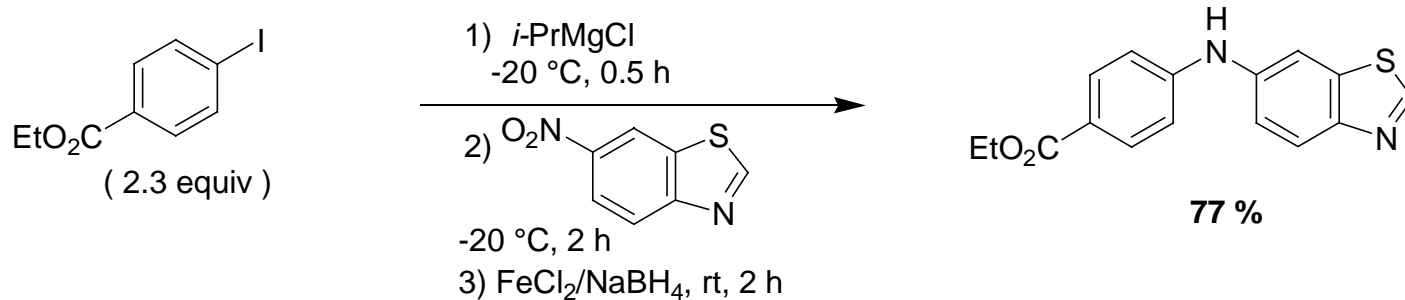


FG: CO₂Et, CN, I, NO₂, OMe, H, F, Br, CF₃, SMe, CONR₂

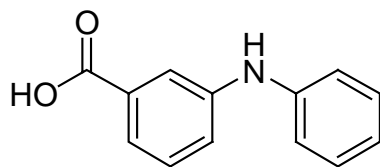
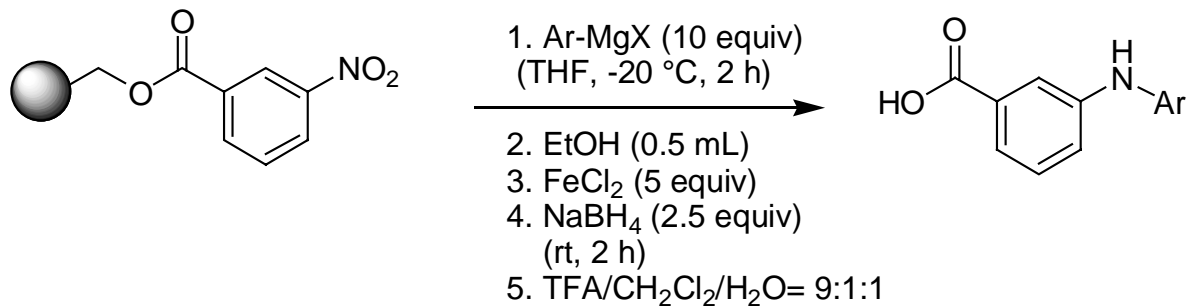
New Amination Reactions using Arylmagnesium Reagents and Nitrobenzenes



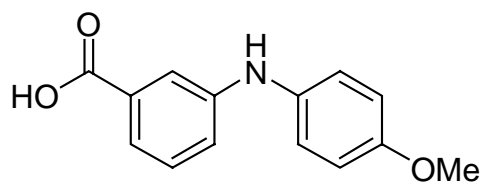
New Amination Reactions of Nitro-Heterocycles using Arylmagnesium Reagents



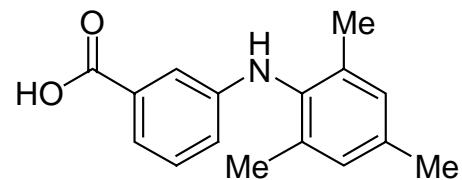
Amination of Solid Phase Supported Nitrobenzenes using Arylmagnesium Reagents



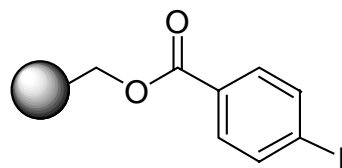
92 % purity
quant.



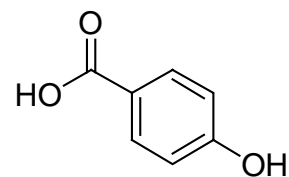
98 % purity
quant.



91 % purity
quant.

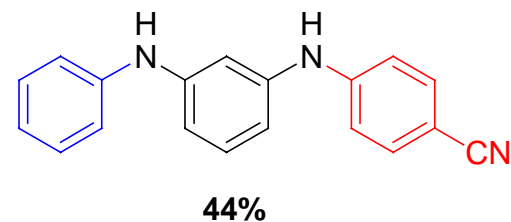
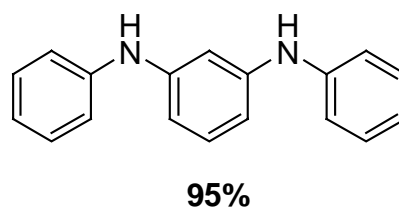
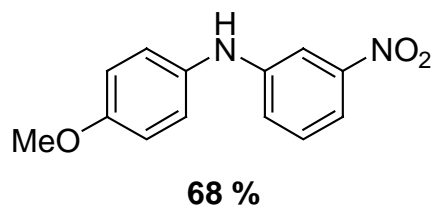
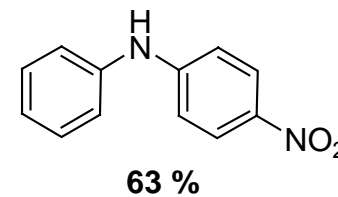
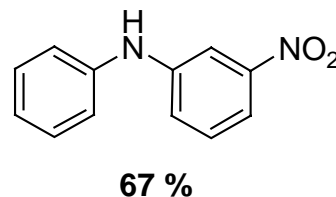
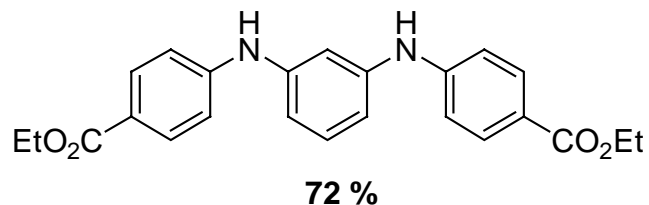
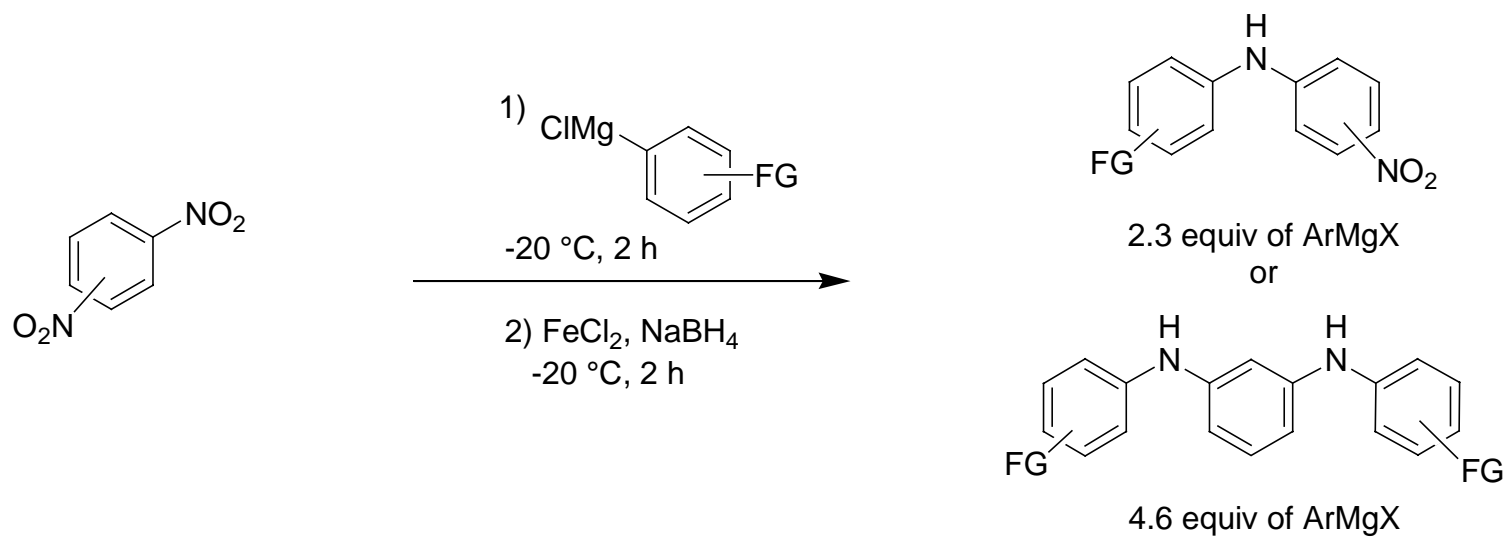


- 1.) *i*PrMgCl (10 Äq.)
THF, -20 °C, 2 h
- 2.) THF, 2x 5 mL
3.) PhNO₂
4.) EtOH (0.5 mL)
5.) FeCl₂ (5 Äq.)
NaBH₄ (2.5 Äq.)
RT, 2 h
6.) TFA/CH₂Cl₂/H₂O= 9:1:1



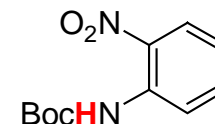
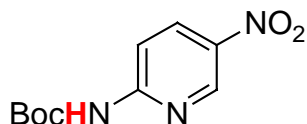
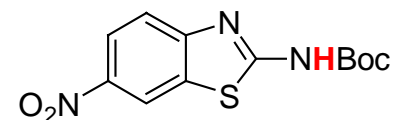
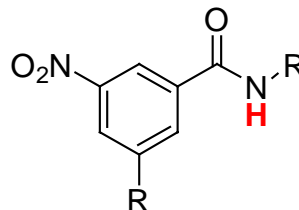
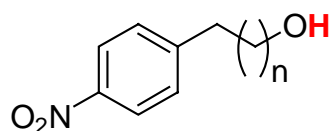
95% purity
quant.

New Amination Reactions using Arylmagnesium Reagents and Nitrobenzenes

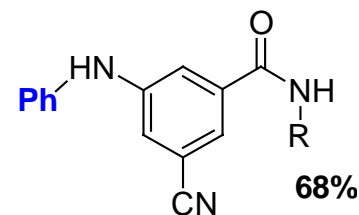
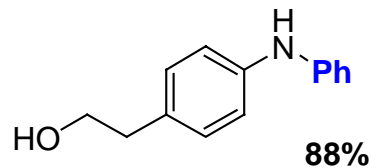
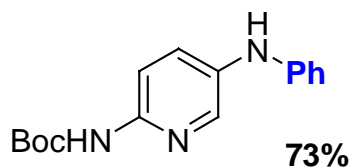


New Amination Reactions using Arylmagnesium Reagents and Amino- or Hydroxy-Substituted Nitrobenzenes

Possible scaffolds that were of interest for Aventis:

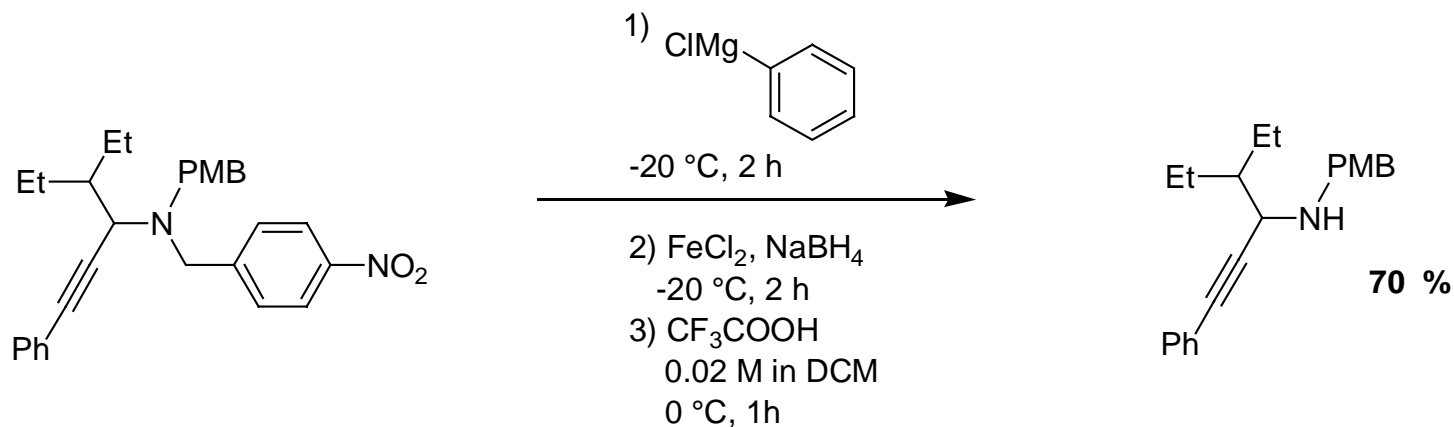
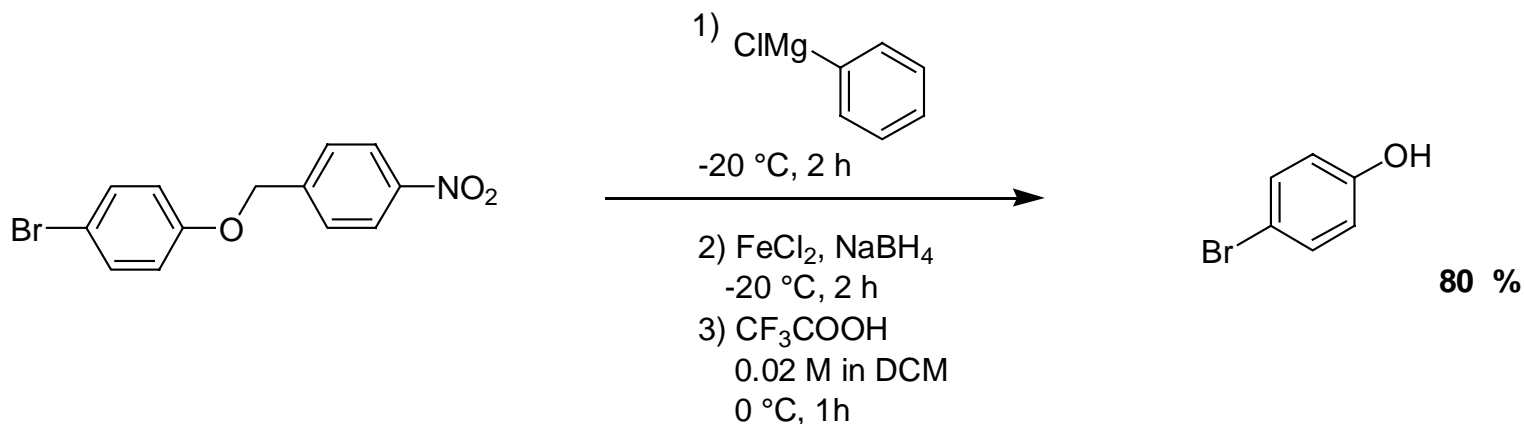


Addition of various aromatic Grignard reagents:



Reduction and Amination saves one step for most of these substrates

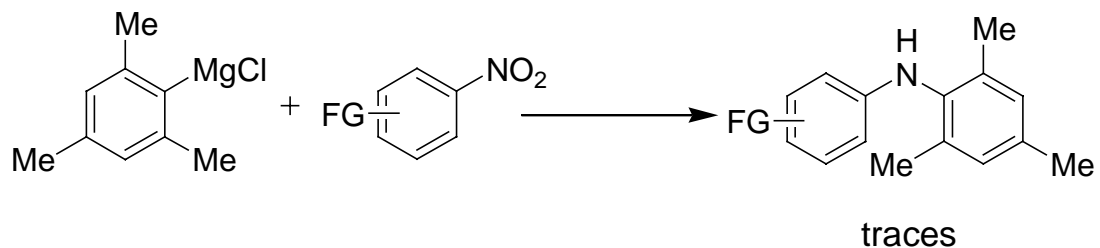
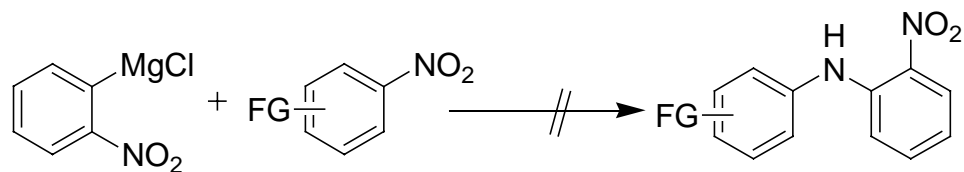
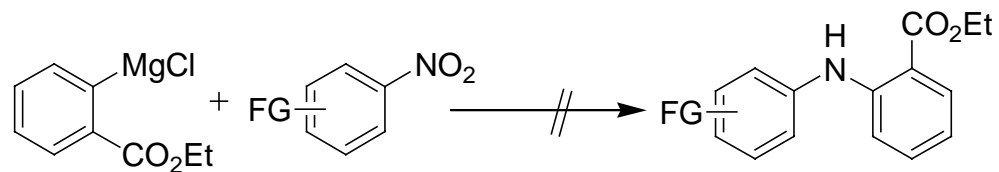
Application in Removal of *p*-Nitrobenzyl Protecting Group



with N. Gommermann

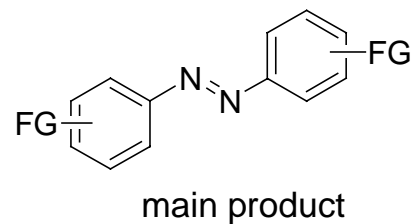
see also: O. J. Plante, S. L. Buchwald and P. H. Seeberger *J. Am. Chem. Soc.* **2000**, *122*, 7148.

Limitations of Amination Reactions using Arylmagnesium Reagents and Nitrobenzenes

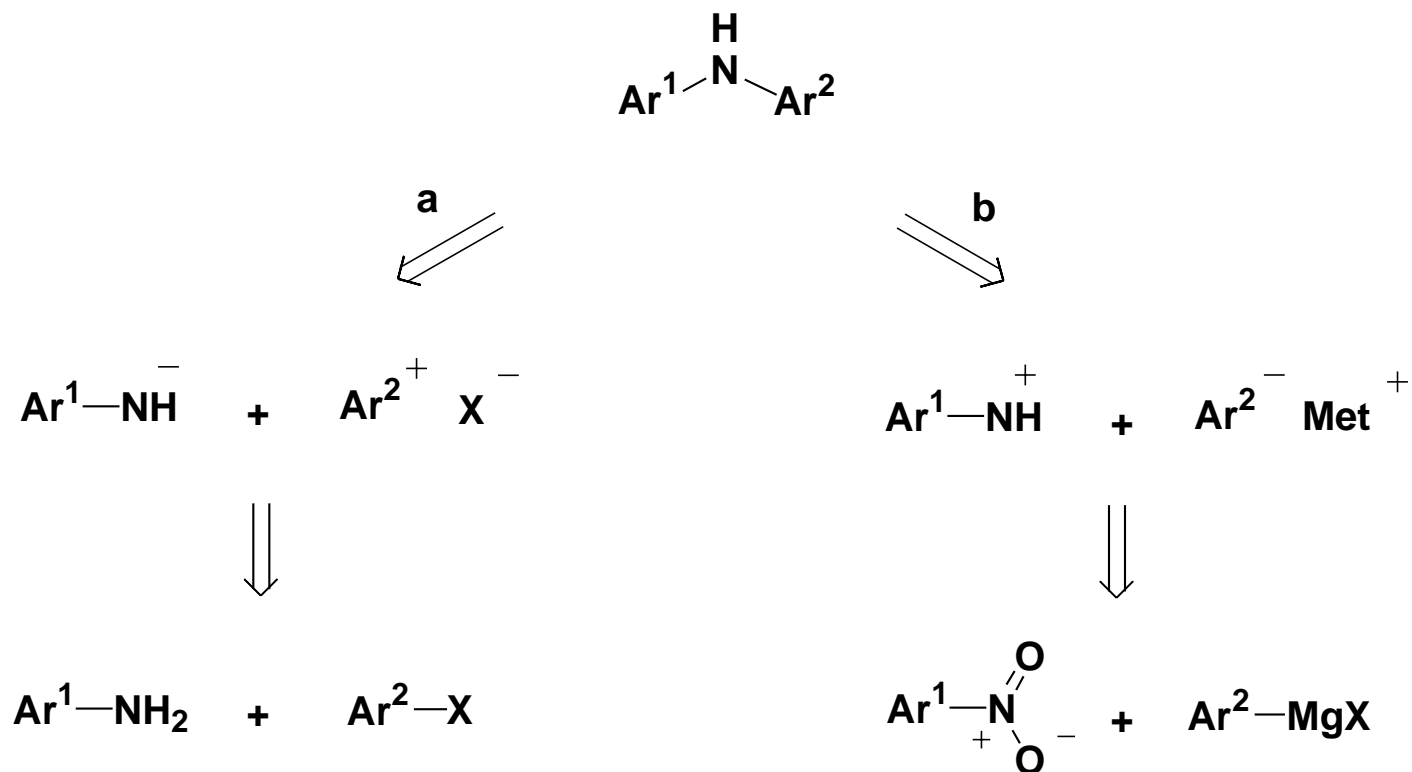


Only Arylmagnesium Reagents

2 equiv. of Grignard needed



New Amination Reactions



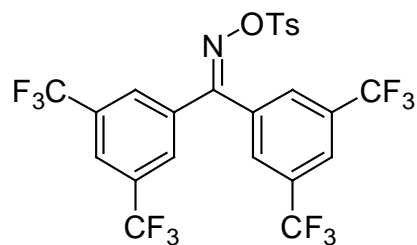
Problems:

leaving group
electron poor aromatics

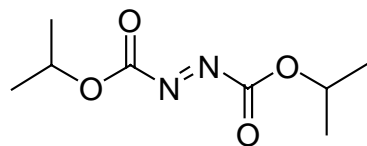
Pd-catalyzed:

Ligand and Base tuning
side reactions

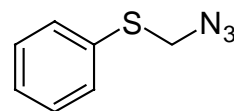
Electrophilic Amination Reactions



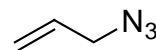
K. Narasaka



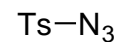
J. P. Genet



B. M. Trost

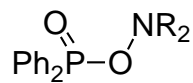


Kabalka

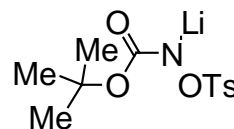


V. Snieckus

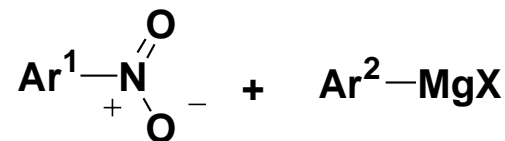
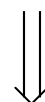
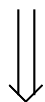
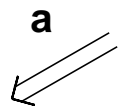
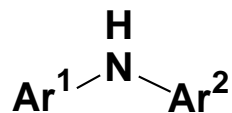
Synthetic equivalents for NH_2^+



G. Boche

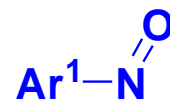


New Amination Reactions



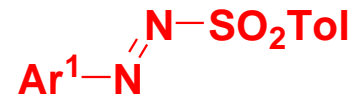
Problems:

leaving group
electron poor aromatics

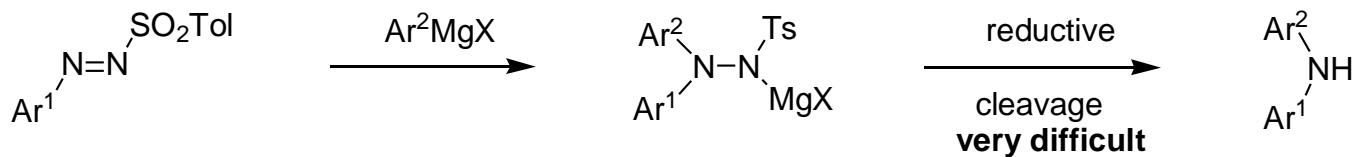


Pd-catalyzed:

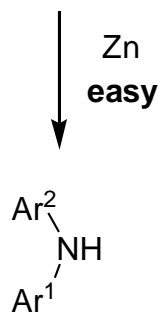
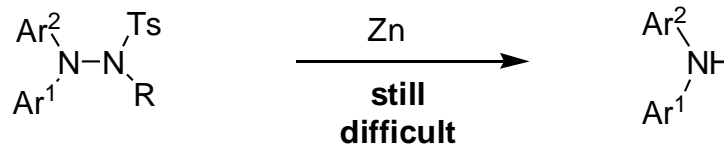
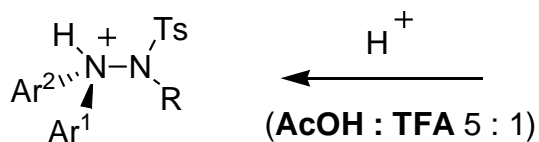
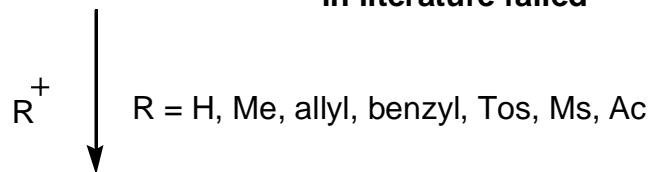
Ligand and Base tuning
side reactions



New Amination Reactions using Arylmagnesium Reagents and Aryl-*p*-Tolylazo Sulfones

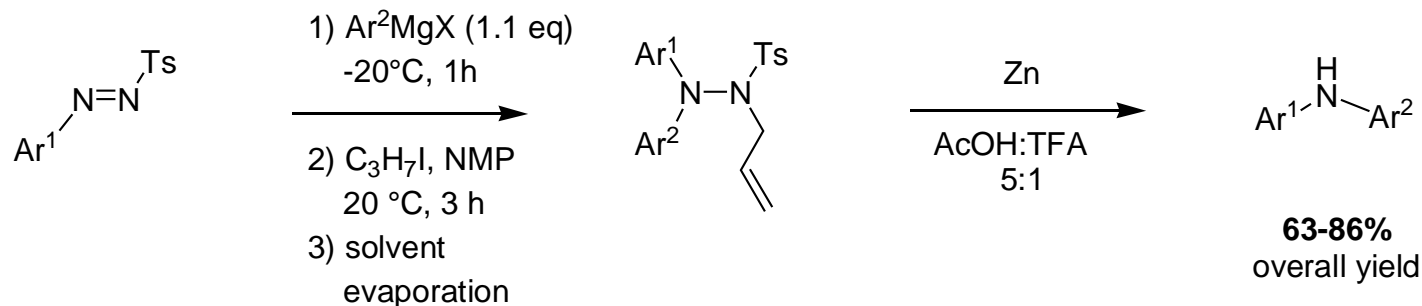
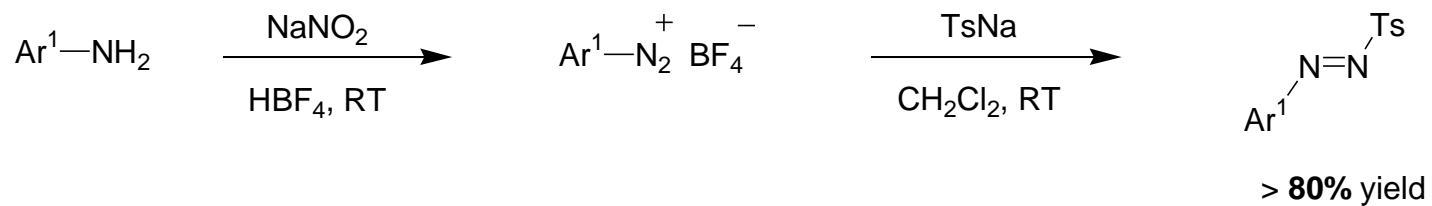


various reduction conditions
everything that is reported
in literature failed



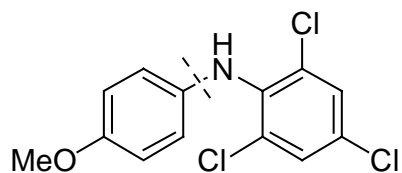
| Acid | Base | Approx. pK _a |
|---|----------------------------------|-------------------------|
| ArSO ₃ H | ArSO ₃ ⁻ | -6.5 |
| Ar₃NH⁺ | Ar ₃ N | -5 |
| F ₃ CCOOH | F ₃ CCOO ⁻ | -1.0 |
| Ar₂NH₂⁺ | Ar ₂ NH | 1 |
| ArNH₃⁺ | ArNH ₂ | 3-5 |
| ArNR₂H⁺ | ArNR ₂ | 3-5 |
| HCOOH | HCOO ⁻ | 3.77 |
| CH ₃ COOH | CH ₃ COO ⁻ | 4.76 |
| NH ₄ ⁺ | NH ₃ | 9.24 |
| R₃NH⁺ | R ₃ N | 10-11 |

New Amination Reactions using Arylmagnesium Reagents and Aryl-*p*-Tolylazo Sulfones

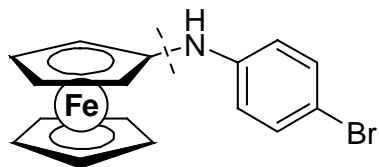


I. Sapountzis, P. Knochel *Angew. Chem. Int. Ed.* **2004**, 43, 897

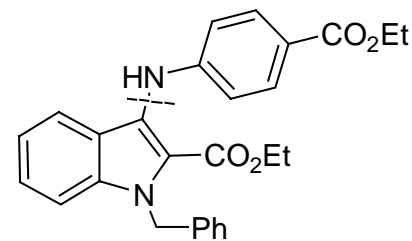
New Amination Reactions using Arylmagnesium Reagents and Aryl-*p*-Tolylazo Sulfones



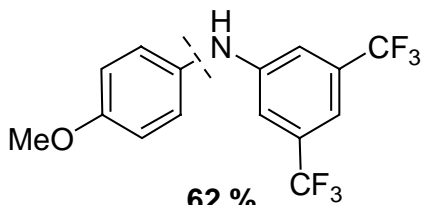
59 %



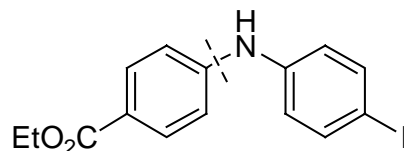
58 %



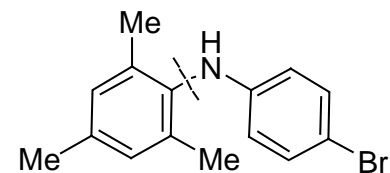
71 %



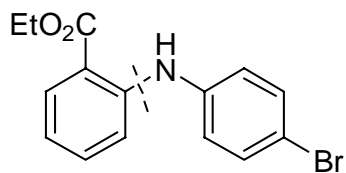
62 %



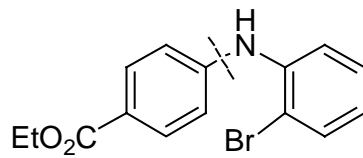
63 %



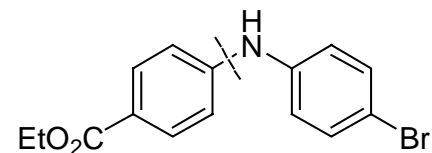
69 %



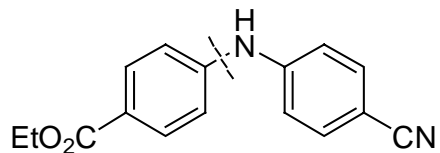
80 %



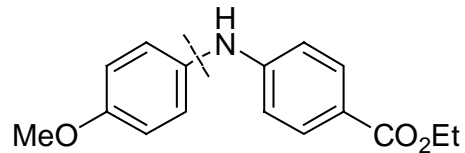
68 %



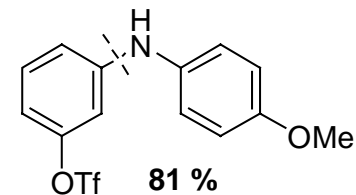
83 %



64 %

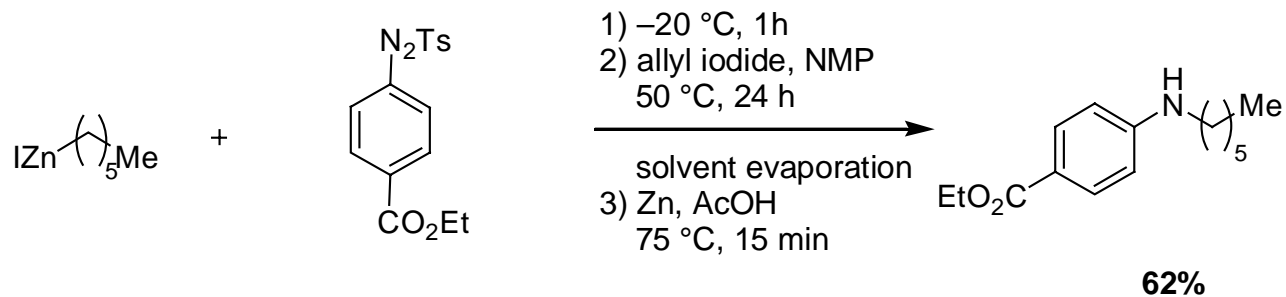
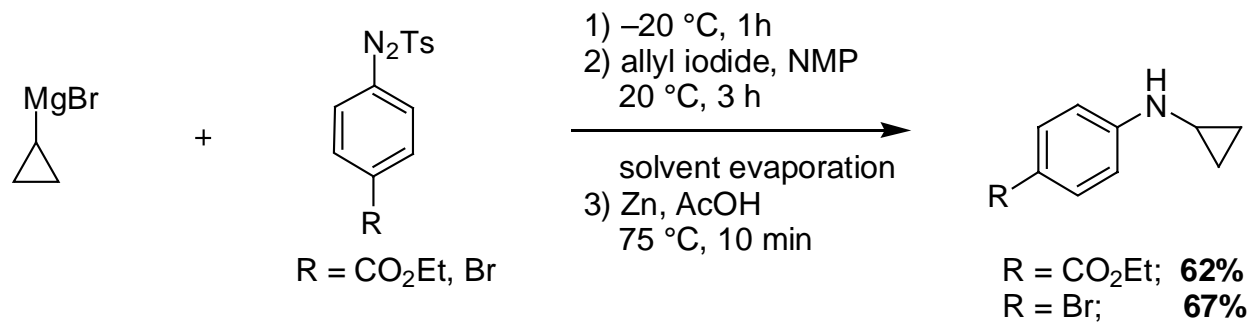


92 %

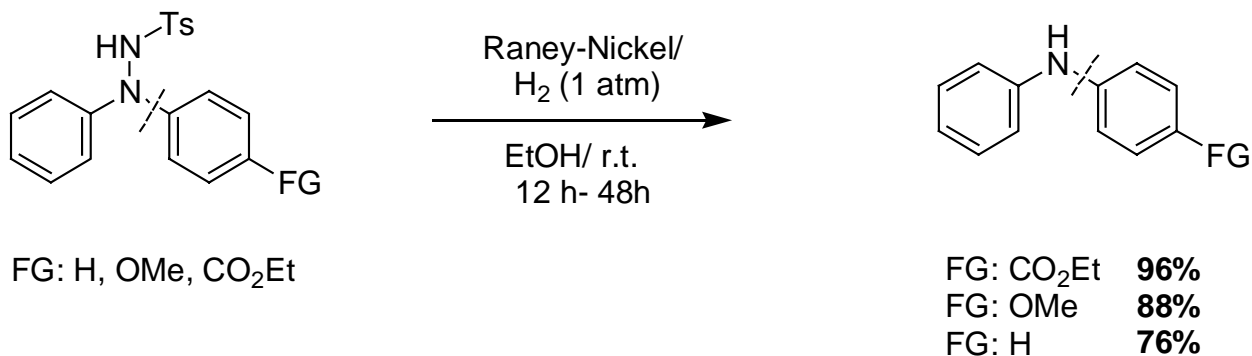
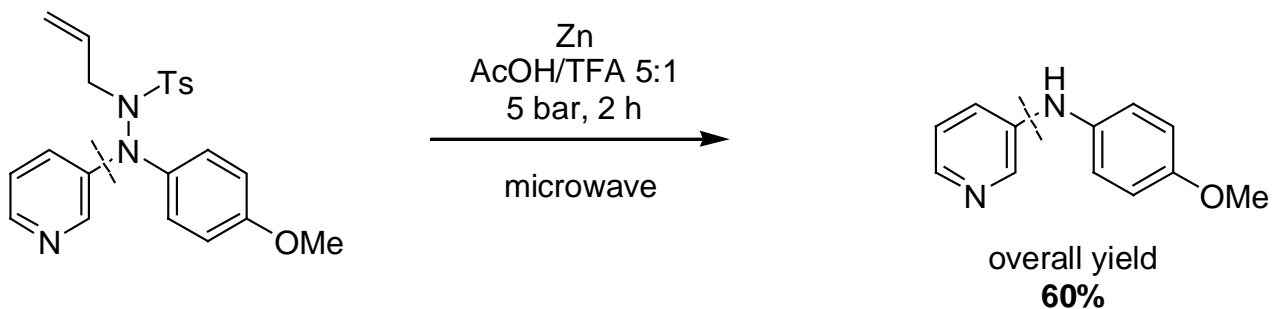
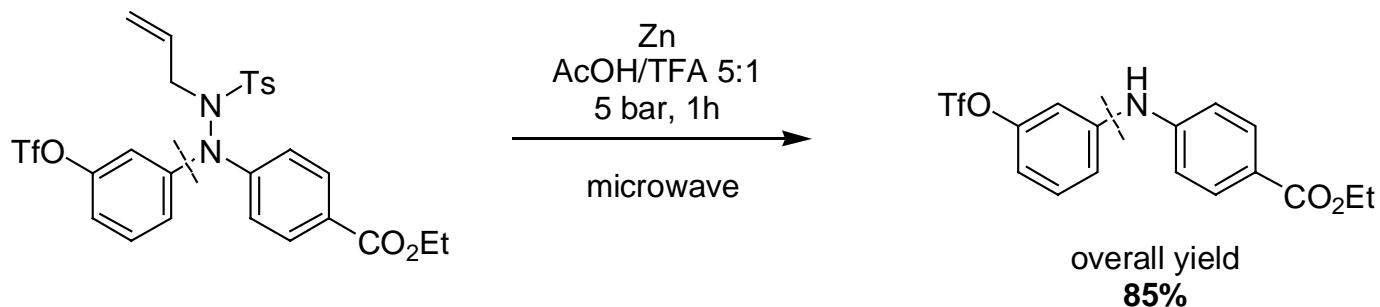


81 %

New Amination Reactions using Arylmagnesium Reagents and Aryl-*p*-Tolylazo Sulfones

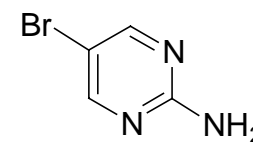
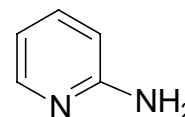
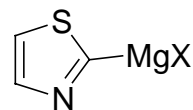
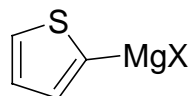
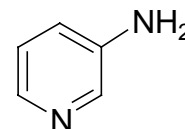
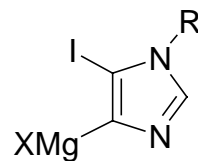
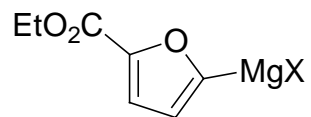


New Amination Reactions using Arylmagnesium Reagents and Aryl-*p*-Tolylazo Sulfones



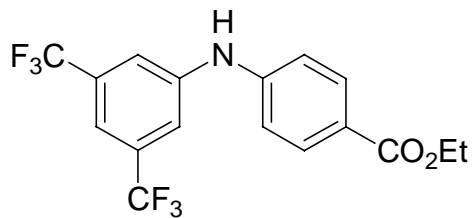
Challenging substrates

some kinds of heterocycles



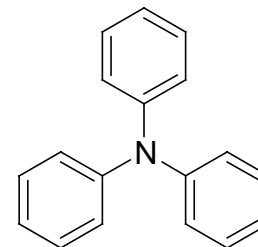
very electron-poor systems

e.g.:

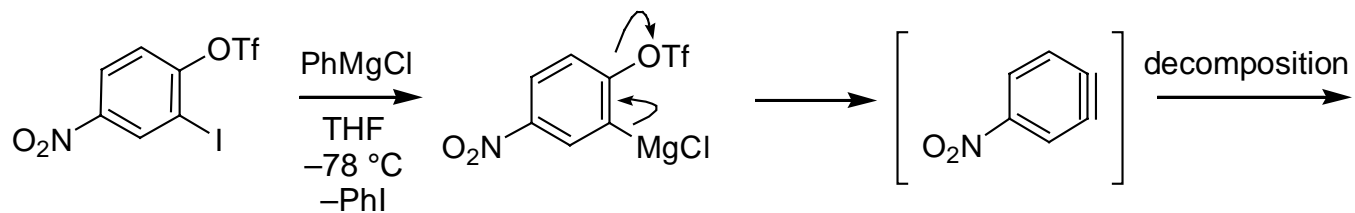
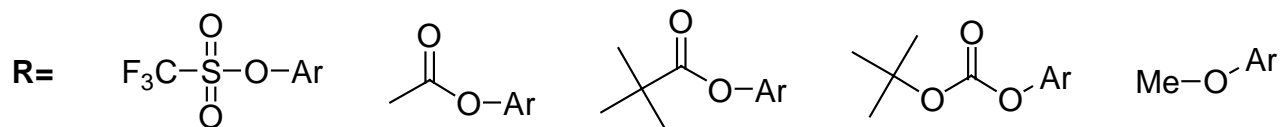
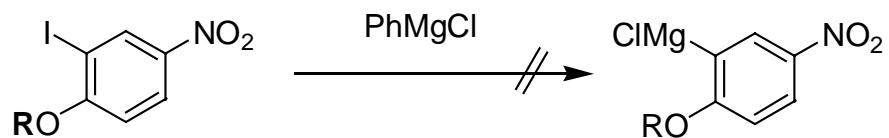


triarylamines are not possible

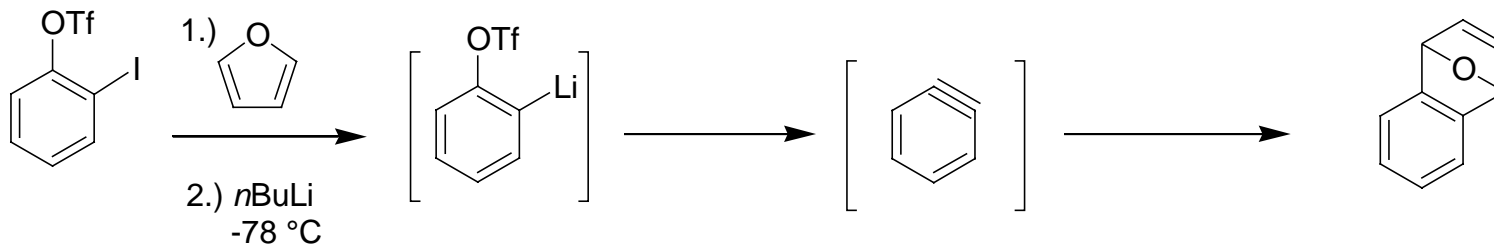
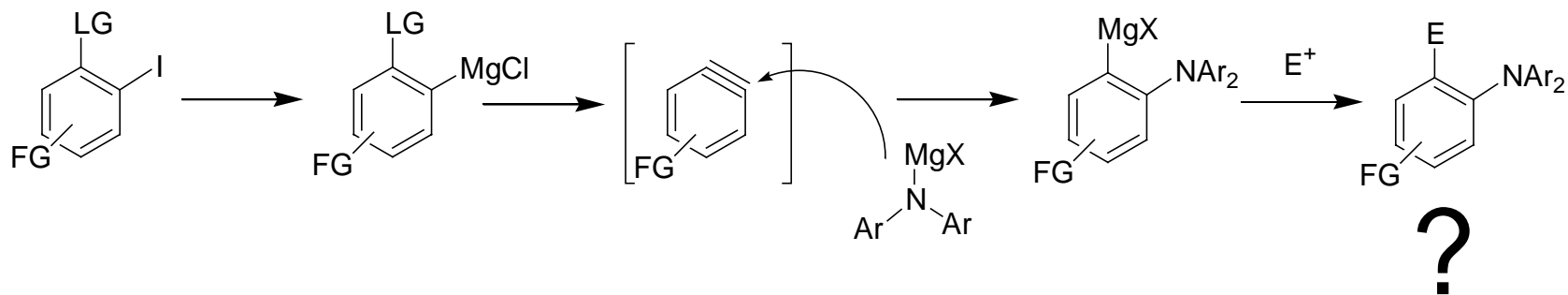
e.g.:



1,2 Dehydrobenzene Formation *via* I/Mg Exchange Reaction

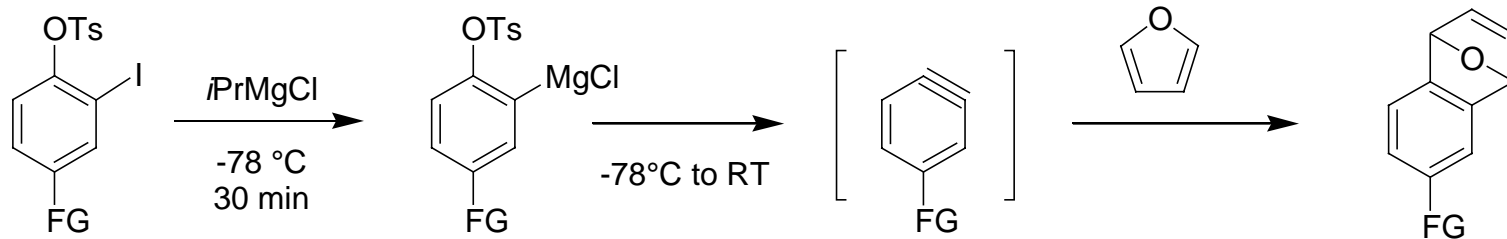
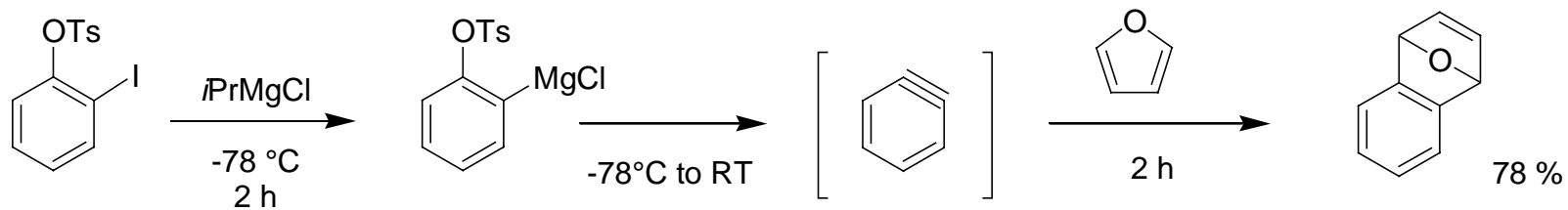
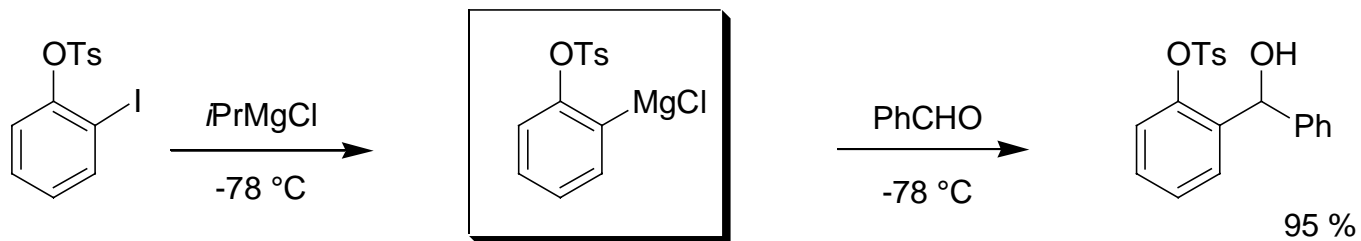


New Amination Using Selective Benzyne Formation *via* I/Mg Exchange Reaction



K. Suzuki *Synlett* **2000**, 520.

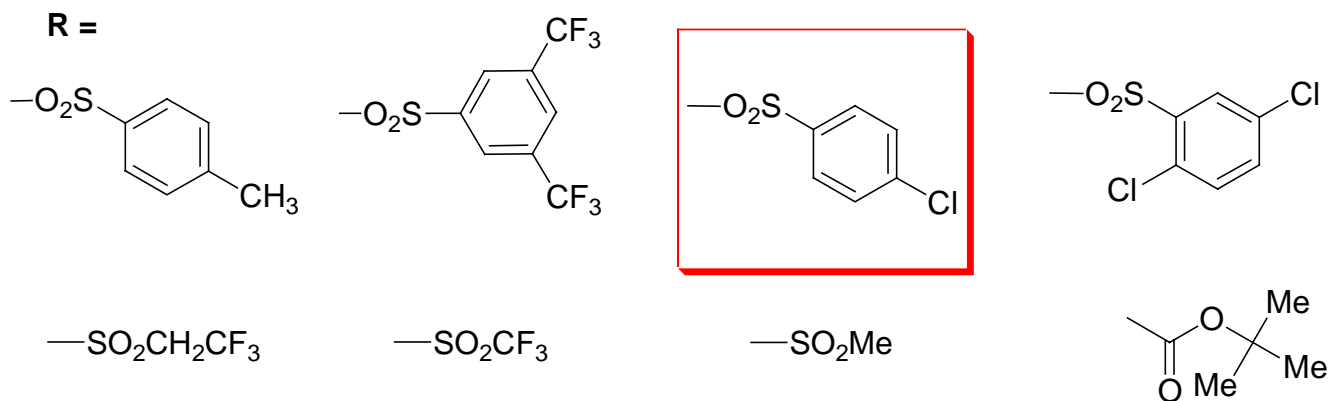
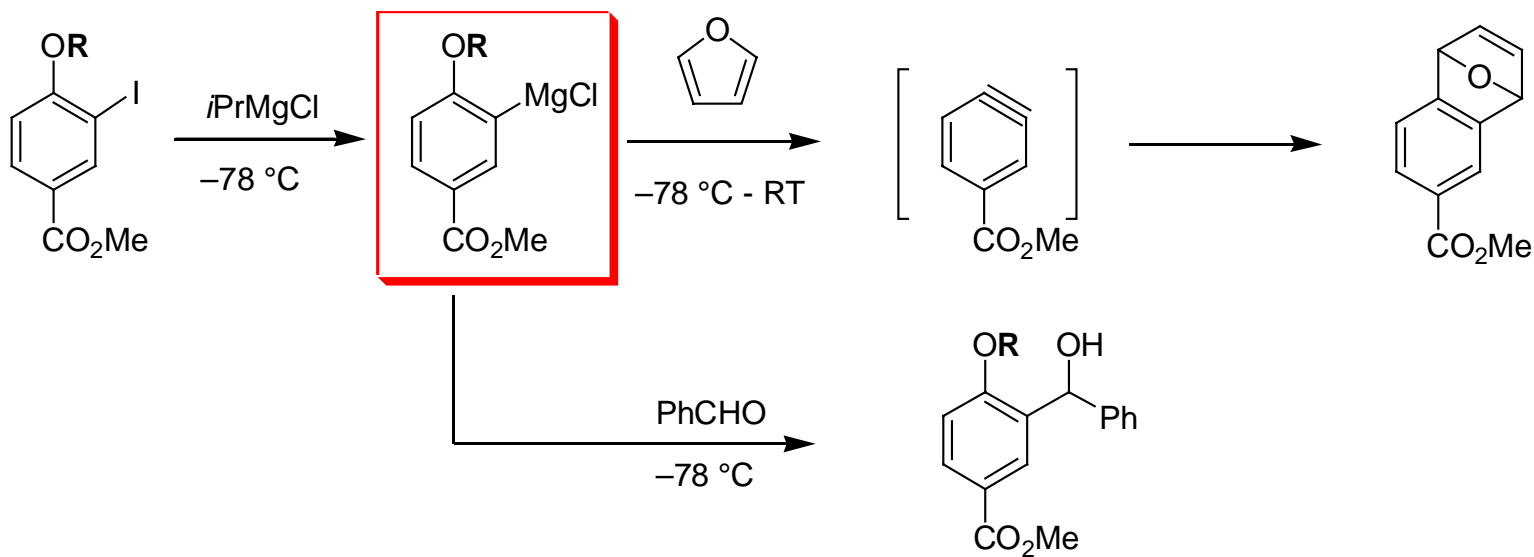
Selective 1,2 Dehydrobenzene Formation via I/Mg Exchange Reaction



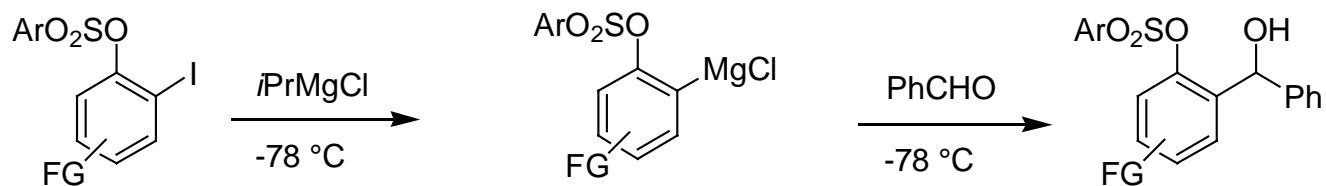
FG: CO_2Me , CN

FG = CO_2Me : 73 %, 15 h
CN: 77 %, 24 h

Selective 1,2 Dehydrobenzene Formation via I/Mg Exchange Reaction

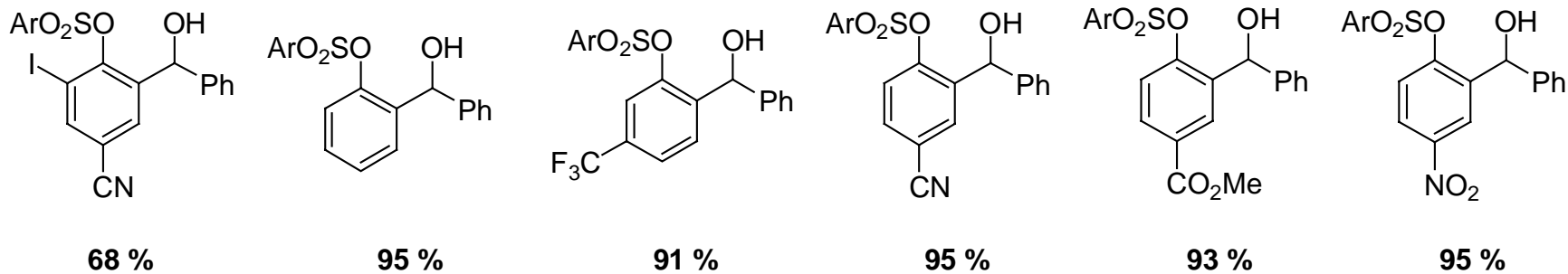


Selective 1,2 Dehydrobenzene Formation via I/Mg Exchange Reaction



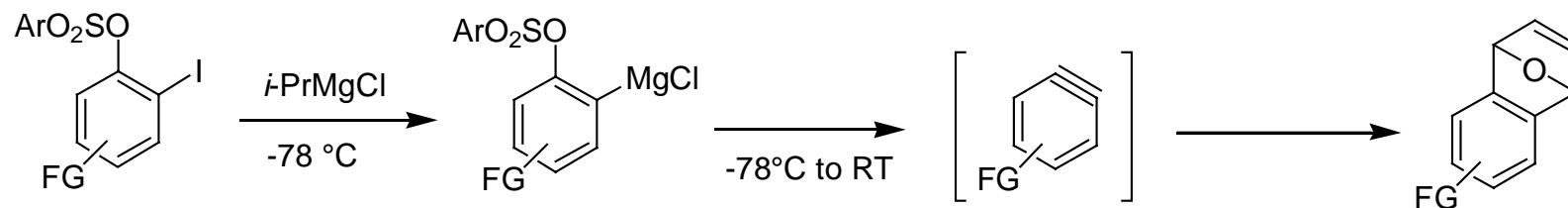
FG = CO₂Me, CN, CF₃, Hal, [NO₂ (PhMgCl)]

Ar= 4-Chlorophenyl



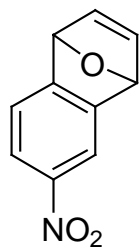
Ar= 4-Chlorophenyl

Selective 1,2 Dehydrobenzene Formation via I/Mg Exchange Reaction

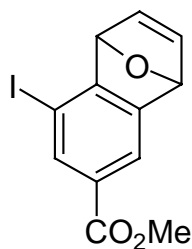


FG = CO₂Me, CN, CF₃, Hal, NO₂

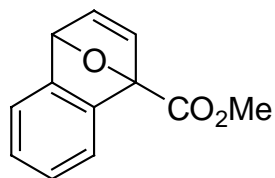
Ar = 4-Chlorophenyl



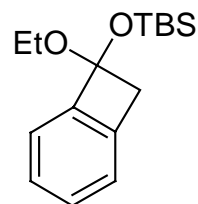
78 %



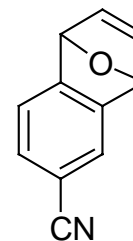
71%



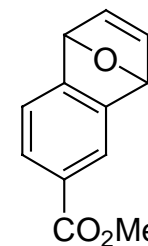
58 %



94 %

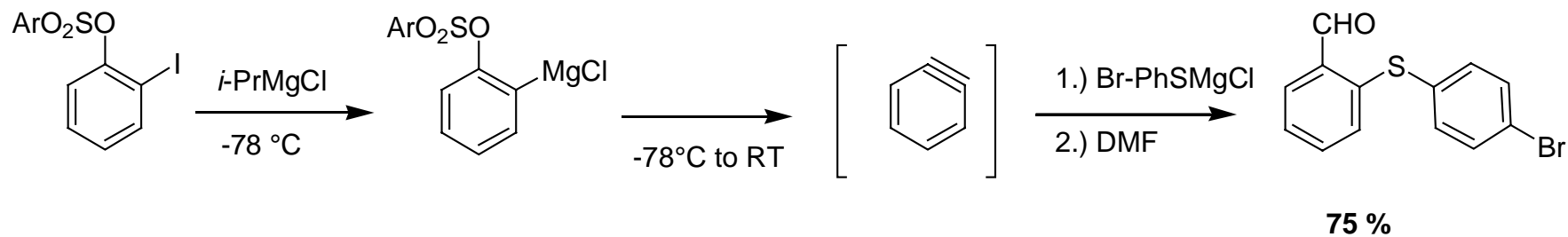
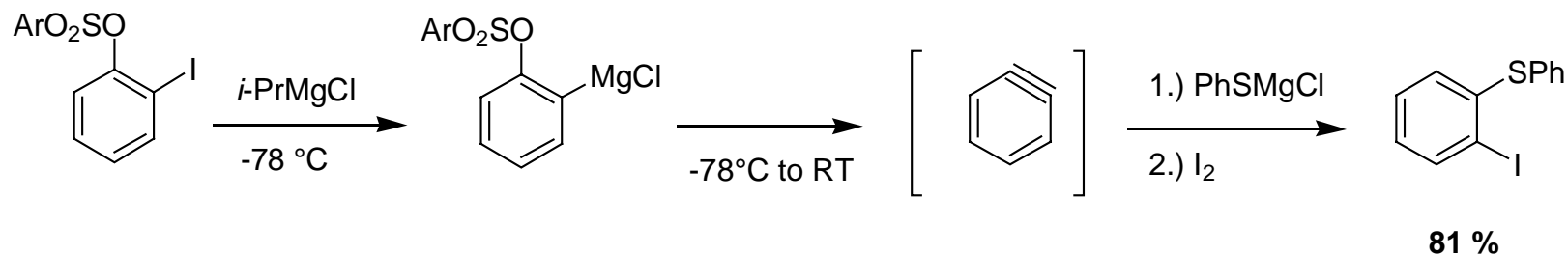
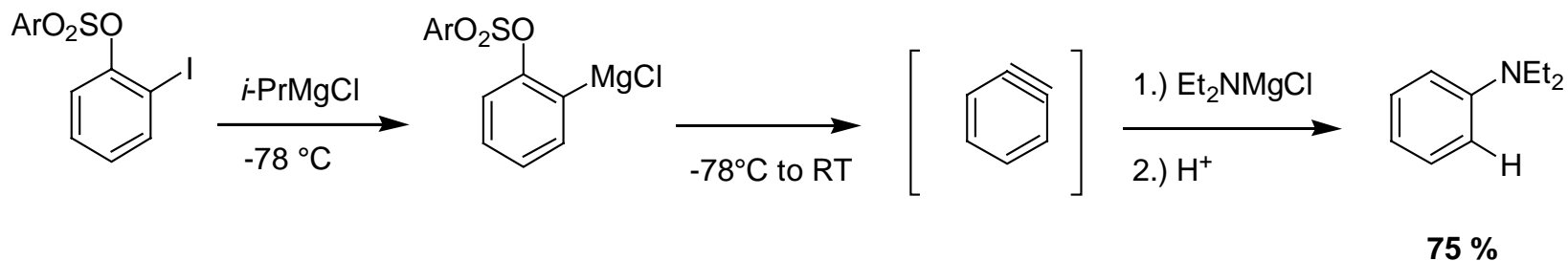


78 %



89 %

New Amination Using Selective 1,2 Dehydrobenzene Formation via I/Mg Exchange Reaction



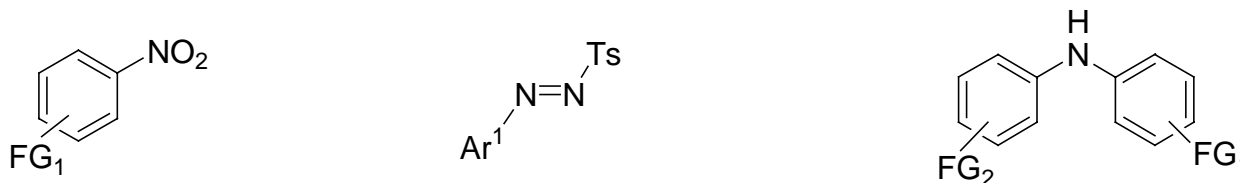
W. Lin

Summary

- **Functionalized Nitrophenylmagnesium Reagents**



- **Electrophilic Aminations using Nitrobenzenes or Arylazosulphones**



- **Preparation of Functionalized Benzynes via I/Mg Exchange**



Acknowledgement



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**Ludwig-Maximilians Universität
Aventis Pharma Germany**

**Krystyna Becker
Henry Dube, Robert Lewis, Markus Tegel, Markus Fischer
and Christina Despotopoulou**