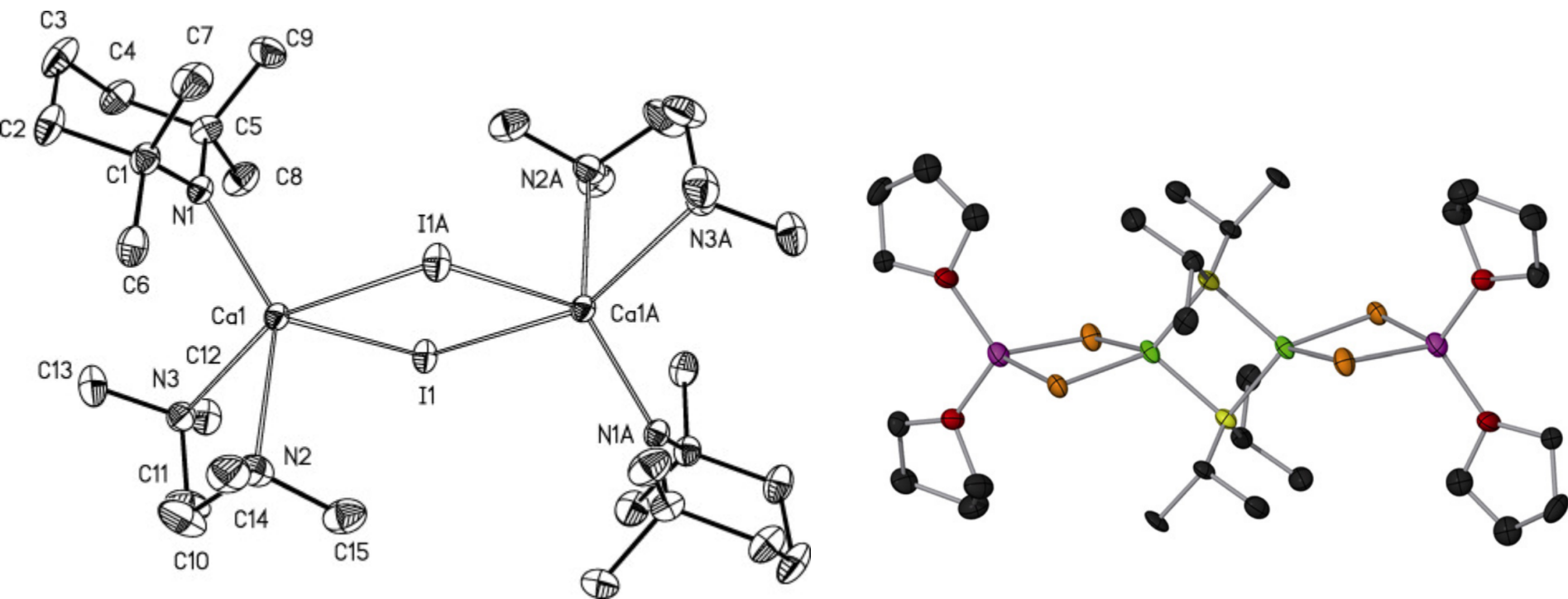


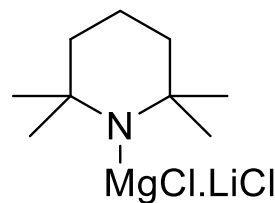
New Reagents for Selective Metalation and Deprotonation

7/04/13 TJD Literature Presentation



Introduction

i-PrMgCl.LiCl
(TurboGrignard)



Knochel-Hauser-Base

Two new reagents developed in the Knochel group which offer a useful alternative to standard Li-based reagents. Both are commercially available and take advantage of the less polar C-Mg bond allowing for greater functional group tolerance and more convenient temperature ranges.

1. Selective Metalation- Why?

i-PrMgCl.LiCl
(TurboGrignard)

- Use of Alkyl-Li is very popular and successful method.
- However moderate functional group tolerance (cyano, nitro, ester, and etc) due to high reactivity of C-Li species.
- Require -78 °C reaction conditions.

- C-Mg bond more covalent like in character thus has better functional group tolerance and has been shown to tolerate cyano, nitro, ester and imine functional groups.
- However poor rate of transmetalation especially with electron-rich aromatics is a limiting factor in their utility.
- Extended periods or increased temperatures increases unproductive side reactions

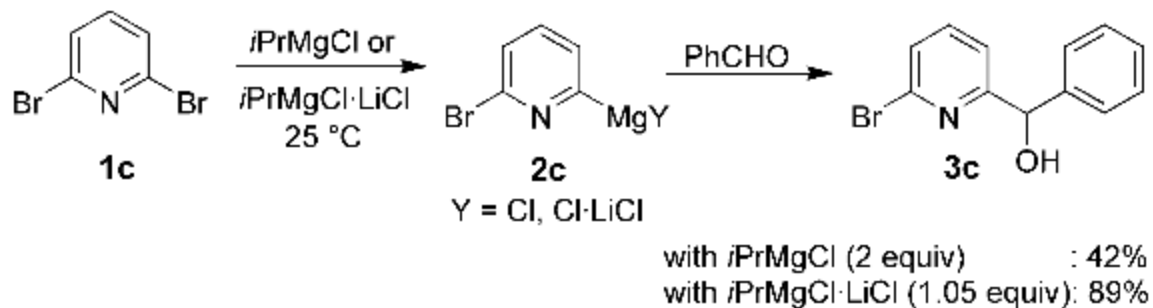
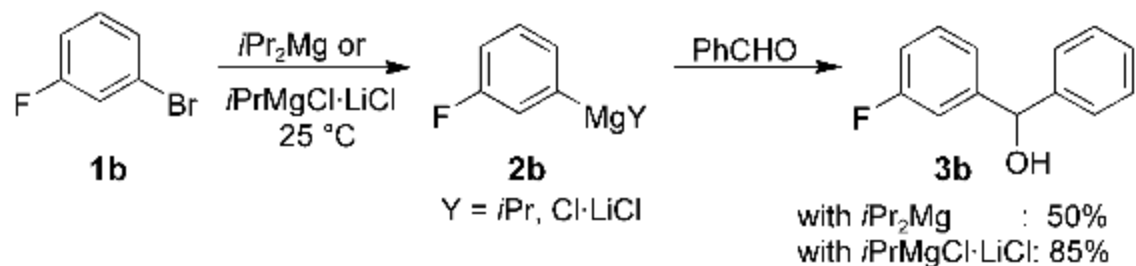
Development of turbo Grignard addresses some of these issues allowing access to range of new sensitive substrates.

Scope

| Entry | Grignard reagent ^[a] | Electrophile | Product | Yield ^[b] | Entry | Grignard reagent ^[a] | Electrophile | Product | Yield ^[b] |
|-------|---------------------------------|---------------|---------|----------------------|-------|---------------------------------|---|---------|----------------------|
| 1 | | PhCHO | | 70 | 8 | | CIPPh ₂ | | 85 ^[d] |
| 2 | | PhCHO | | 81 | 9 | | PhCHO | | 83 |
| 3 | | PhCOCl | | 87 ^[e] | 10 | | PhCHO | | 90 |
| 4 | | PhCOCl | | 88 ^[e] | 11 | | I(CH ₂) ₃ CO ₂ Et | | 81 ^[e] |
| 5 | | allyl bromide | | 93 ^[e] | 12 | | allyl bromide | | 82 ^[e] |
| 6 | | PhCHO | | 90 | 13 | | allyl bromide | | 88 ^[e] |
| 7 | | PhCHO | | 87 | 14 | | PhCHO | | 80 ^[e] |

[a] Y = Cl-LiCl. [b] Yield of isolated analytically pure product. [c] The Grignard reagent was transmetalated with CuCN·2LiCl before reaction with an electrophile. [d] The reaction mixture was worked up oxidatively with aq. H₂O₂. [e] The exchange reaction was conducted in THF/DMPU (1:3).

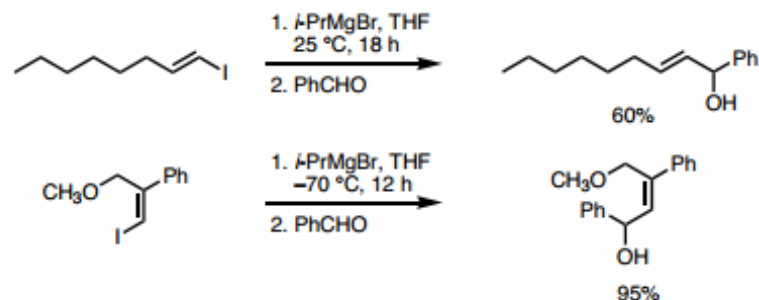
Reactivity compared without LiCl



Reactions are quenched after 3 hrs. Note that reactions are also performed at rt.

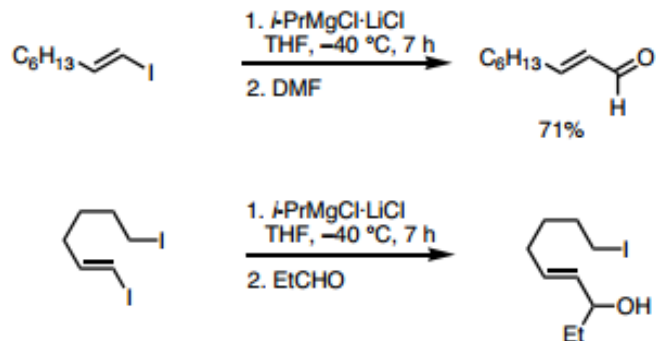
Magnesium/Halogen Exchange with Vinyl Halogens

It is possible to perform Mg/I exchanges stereospecifically using *i*PrMgCl however the reactions require either high temperatures (limiting the presence of sensitive functional groups e.g. esters) or an adjacent directing group (OMe) which limits substrate scope.



M. Rottlander, L. Boymond, G. Cahiez, P. Knochel, *J. Org. Chem.* **1999**, *64*, 1080-1081

However use of *i*PrMgCl.LiCl means reactions can take place at lower temperatures giving better functional group tolerance (including esters and other halogens) .

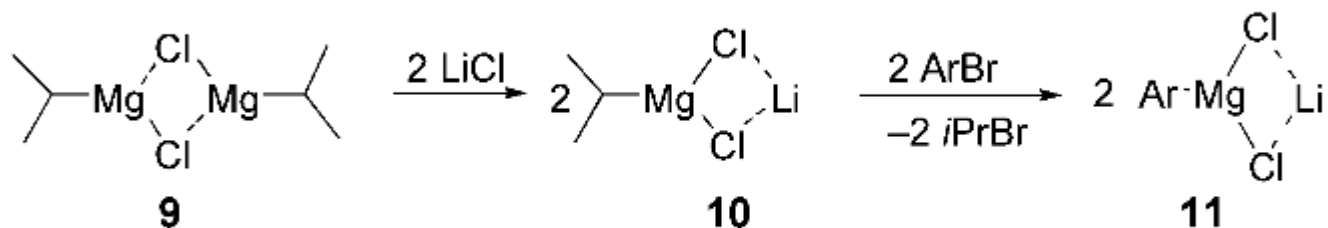


H. Ren, A. Krasovskiy P. Knochel, *Org. Lett.* **2004**, *6*, 4215-4217

How it works

Two proposed effects:

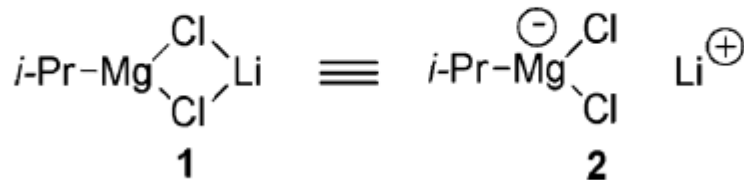
1. LiCl breaks up polymeric aggregates of *i*PrMgCl producing a more reactive complex.



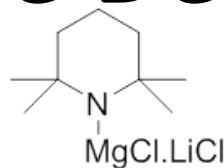
Scheme 4. Catalysis of the Br/Mg exchange reaction with LiCl.

A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, 43, 3333–3336

2. The magnesiate character of the $[\text{iPrMgCl}_2\text{-Li}^+]$, which displays an extra negative charge at the magnesium centre, also enhances the reactivity of the reagent.



2. Selective Deprotonation



Knochel-Hauser-Base

Typically performed using strong bases such as alkyl lithium reagents and lithium amides.

Documented problems include:

- Moderate functional group tolerance (especially above -20 °C)
- Undesirable side reactions due to their high reactivity (e.g. Chichibabin addition).
- Low stability in THF at room temperature requiring *in situ* generation.
- Deprotonation requires low temperatures (-78 °C).

As discussed before C-Mg species have greater functional group tolerance and are stable over a more convenient temperature range. Thus the utilisation of Mg-amides as bases has had some success however the reagents suffer from low solubility and often require large excesses of base which can complicate transmetalation and further reactions with the organometallic species.

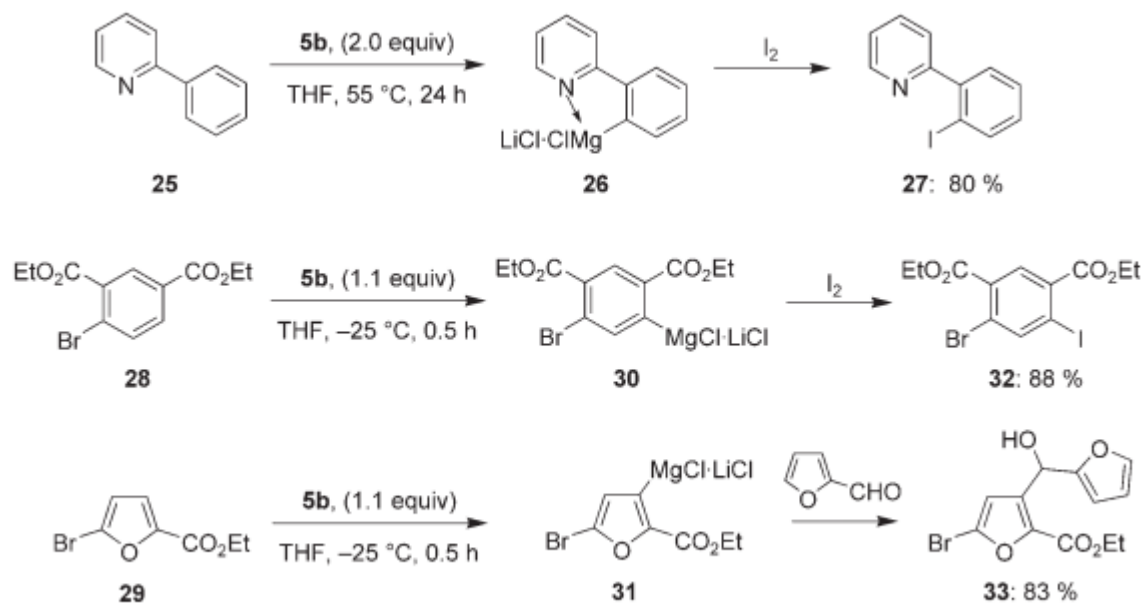
Development of Knochel-Hauser base (TMPMgCl.LiCl) has helped address some of these problems.

Scope

| Entry | Magnesium reagent ^[a] | T [°C], t [h] ^[b] | Electrophile | Product | Yield [%] ^[c] |
|-------|----------------------------------|------------------------------|-----------------------|---|--------------------------|
| | | | | | |
| 1 | 6 | 25, 2 | I ₂ | 7a : R = I | 92 |
| 2 | 6 | 25, 2 | PhCOCl ^[d] | 7b : R = COPh | 86 |
| 3 | 6 | 25, 2 | | 7c : R = 4-EtO ₂ CC ₆ H ₄ | 82 |
| | | | | | |
| 4 | 8 | -25, 0.3 | I ₂ | 9a : R = I | 87 |
| 5 | 8 | -25, 0.3 | DMF | 9b : R = CHO | 91 |
| | | | | | |
| 6 | 10 | 25, 0.1 | I ₂ | 11a : R = I | 93 |
| 7 | 10 | 25, 0.1 | DMF | 11b : R = CHO | 90 |
| 8 | 10 | 25, 0.1 | PhCHO | 11c : R = CH(OH)Ph | 84 |
| | | | | | |
| 9 | 12 | -25, 0.5 | I ₂ | 13a : R = I | 89 |
| 10 | 12 | -25, 0.5 | DMF | 13b : R = CHO | 85 |
| | | | | | |
| 11 | 14a : X = O, Y = CH | 25, 24 | DMF | 15a : R = CHO | 81 |
| 12 | 14b : X = S, Y = CH | 25, 24 | DMF | 15b : R = CHO | 90 |
| 13 | 14c : X = S, Y = N | 0, 0.1 | PhCHO | 15c : R = CH(OH)Ph | 94 |
| | | | | | |
| 14 | 16a : X = S, Y = CH | 25, 24 | DMF | 17a : R = CHO | 93 |
| 15 | 16b : X = S, Y = N | 0, 0.1 | I ₂ | 17b : R = I | 98 |

[a] Lithium chloride and TMPH are complexed to the Grignard reagent. [b] Reaction conditions for the deprotonation with **5b** (1.1 equiv). [c] Yield of isolated, analytically pure product. [d] A transmetalation with CuCN·2 LiCl (0.2 equiv) was performed. [e] Obtained by palladium-catalyzed cross-coupling after transmetalation with ZnCl₂.

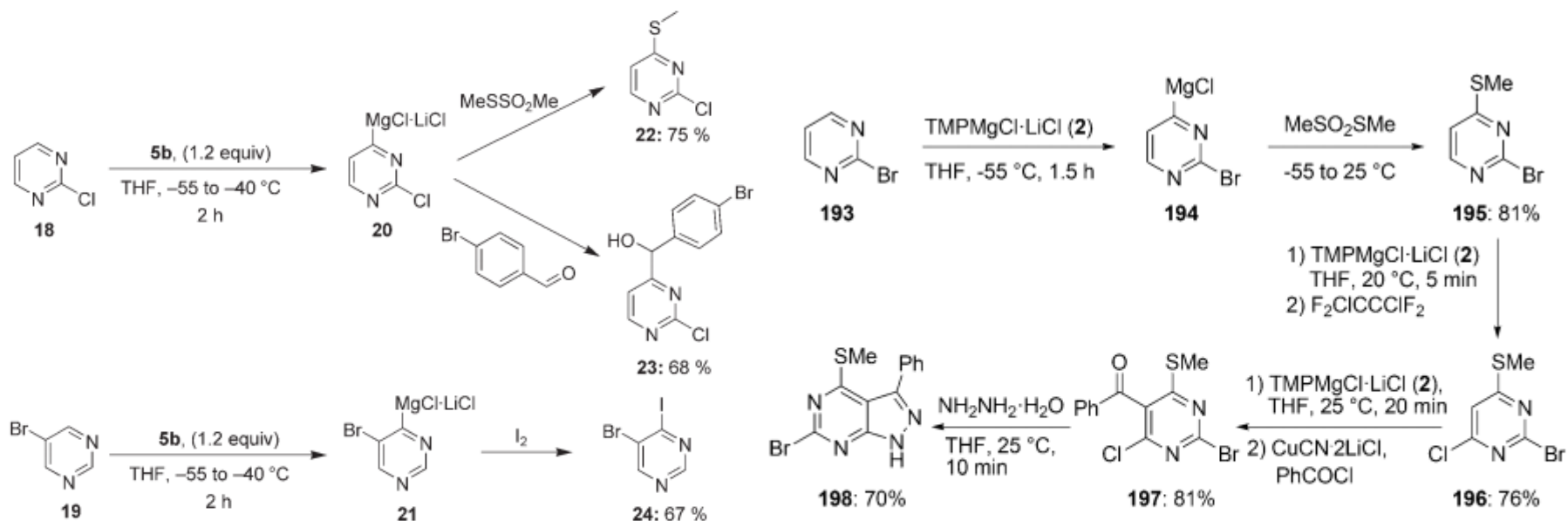
Examples of Regioselectivity



Scheme 4. Regioselective magnesiation of polyfunctional aromatic systems.

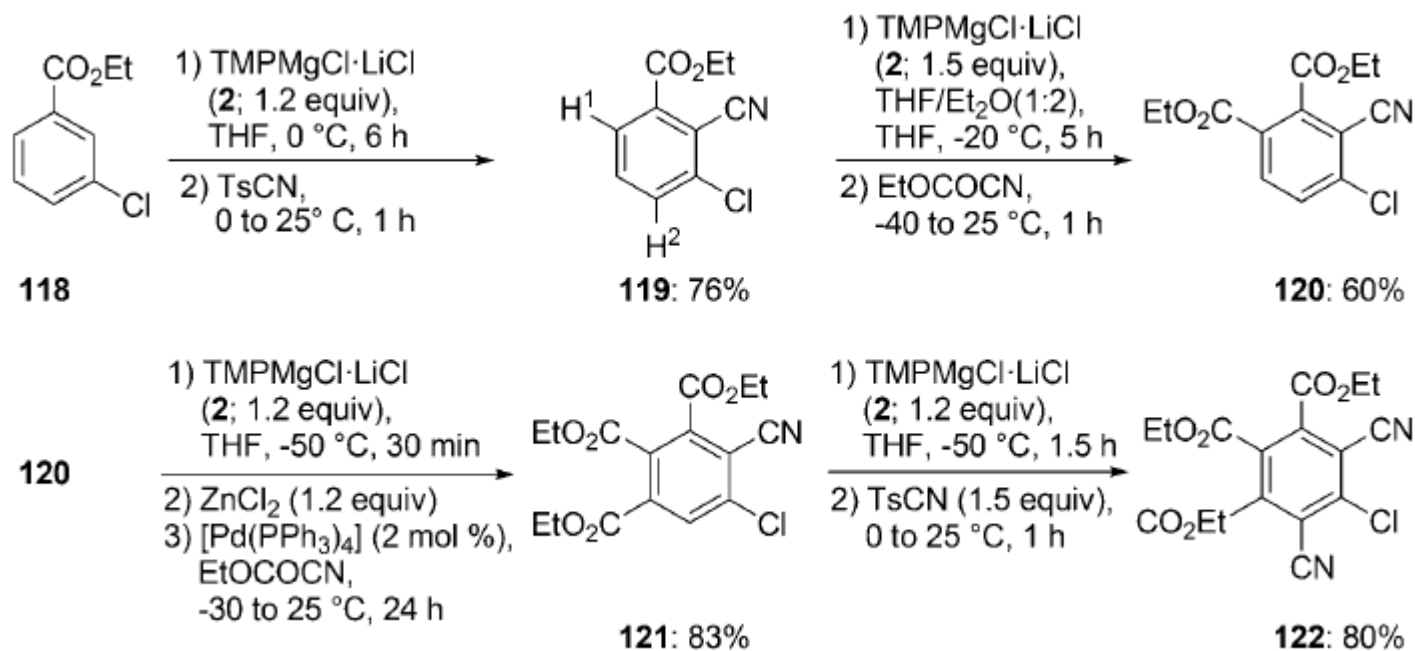
Examples above show preferential deprotonation of the arene ring over pyridine and also high levels of regioselectivity on substituted heteroaryls.

Applications to Pyrimidines



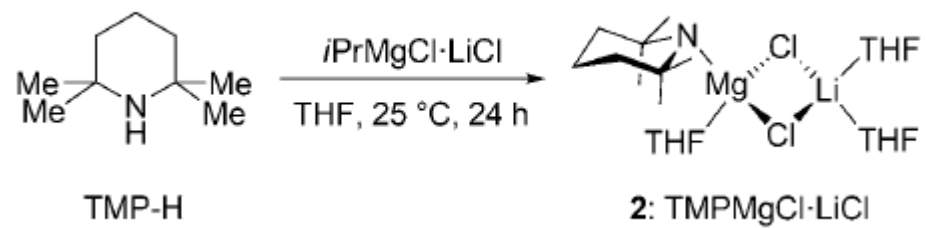
Traditionally difficult to deprotonate pyrimidines (due to their propensity to react with organometallic reagents) are successfully deprotonated and quenched with a number of electrophiles. The methodology was showcased with the synthesis of a fully substituted pyrimidine.

Preparation of Fully Substituted Benzene



Showcases how this methodology can be used to synthesis very highly substituted aryl systems by successive deprotonations. It is also shown to be applicable to the synthesis of fully substituted thiophenes and furans. Note the transmetalation and cross coupling to synthesis **121**.

Why?



Summary

Two new reagents to consider when making organometallics:

1. Halogen/Magnesium exchange

- Increased functional group compatibility
- Mild reaction conditions, including a convenient range of temperatures
- Side reactions inhibited
- Allows for preparation of functionalized heteroaryl organometallics
- Large-scale production of Grignard reagents possible

2. Selective Deprotonation

- High functional group tolerance
- High kinetic activity due to LiCl
- Solubility in THF
- No Chichibabin reactions, less side reactions in general
- Regioselective metalation of arenes and heteroarenes