Deprotonative metalation for the preparation of diversely-functionalized organometallic reagents

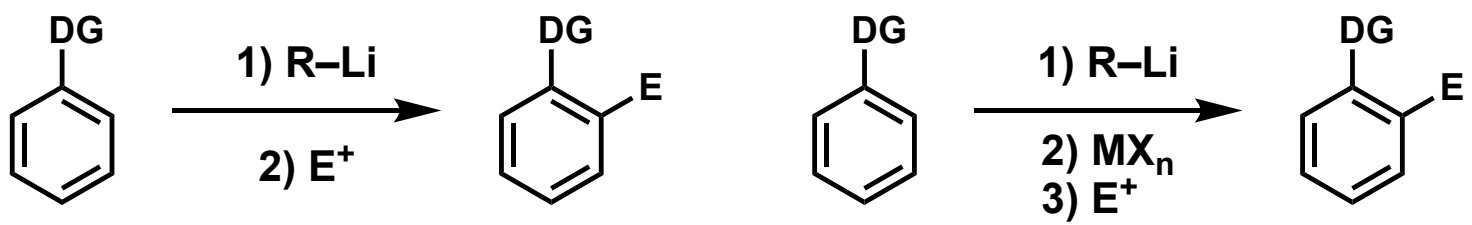
Brad Gilbert

SED Group Meeting

9/26/2017

Proton-metal exchange

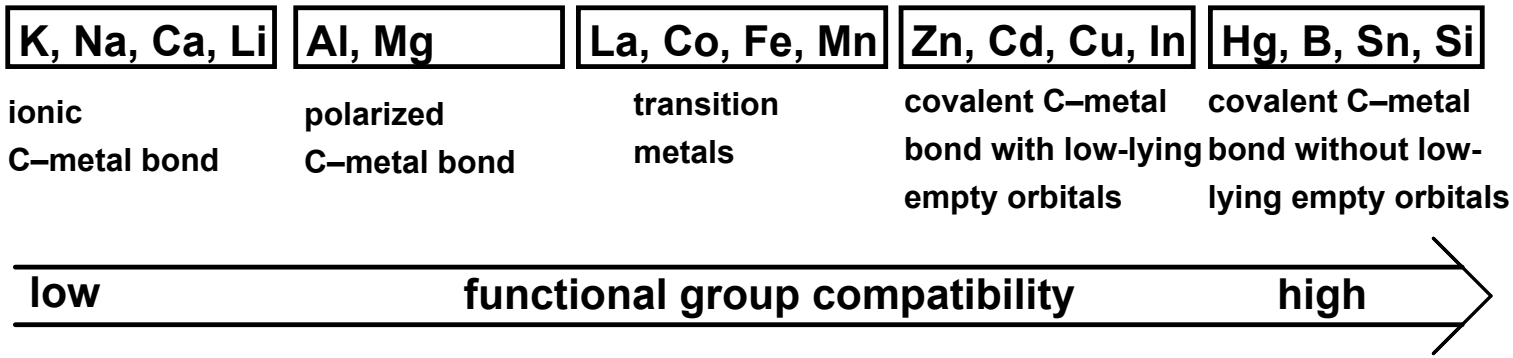
- Frequently employed by organic chemists as Directed *ortho*-Metalation (DoM)
- Bases employed are typically R–Li (*n-, s-,* or *t*-BuLi, less frequently PhLi, MeLi) or R_2N–Li (LiHMDS, LDA, LiTMP), K- and Na- bases are also used.



- Organolithium reagents have relatively low functional group tolerance

Organometallic reagent compatibility

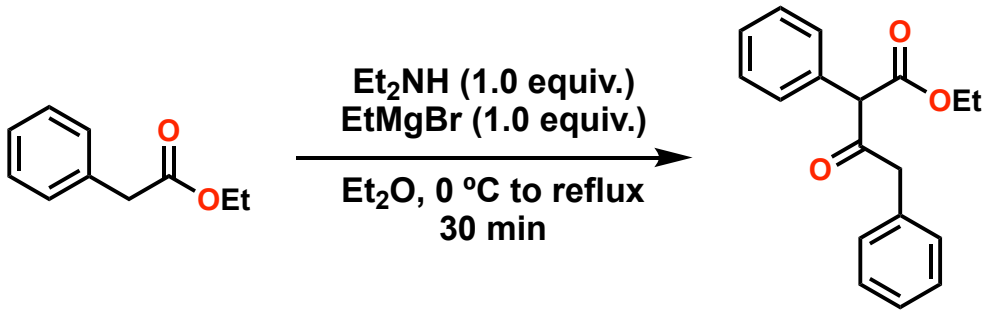
- Organozinc reagents are more compatible with a variety of functional groups than are organomagnesium reagents, which are still more compatible than organolithium reagents.



- However, traditional means of RMgX and RZnX preparation often involve elevated temperatures and/or transmetalation from a less compatible metal
- Can a mild deprotonation to generate organometallic reagents compatible with a broad range of functional groups be achieved?

Reproduced from: Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 9794-9824.

Magnesium amide reagents



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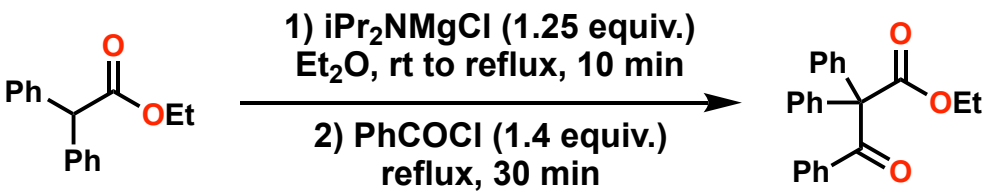
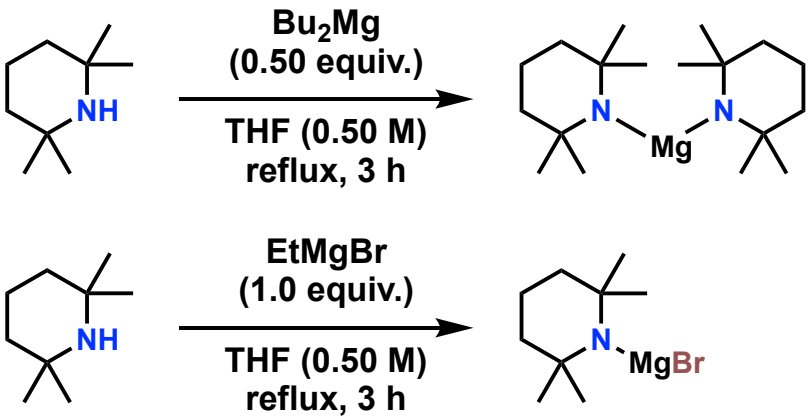


38%

Charles R. Hauser
Duke University

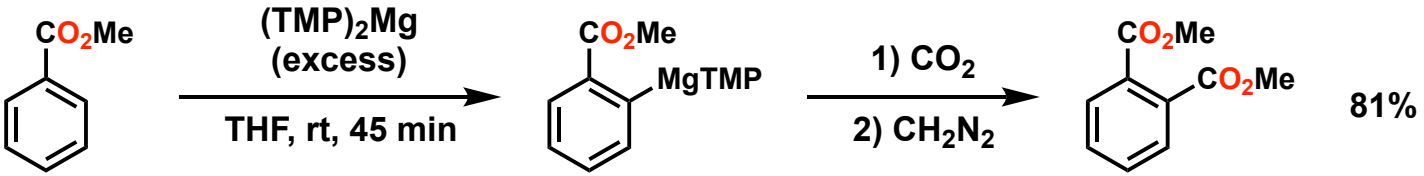
Hauser, C. R.; Walker, H. G. *J. Am. Chem. Soc.* **1947**, *69*, 295-297.
Frostick, F. C.; Hauser, C. R. *J. Am. Chem. Soc.* **1949**, *71*, 1350-1352.

Directed metalation by $(TMP)_2Mg$



Both reagents are, unlike TMPLi and LDA, stable for >24 h in refluxing THF

Philip E. Eaton
U. Of Chicago

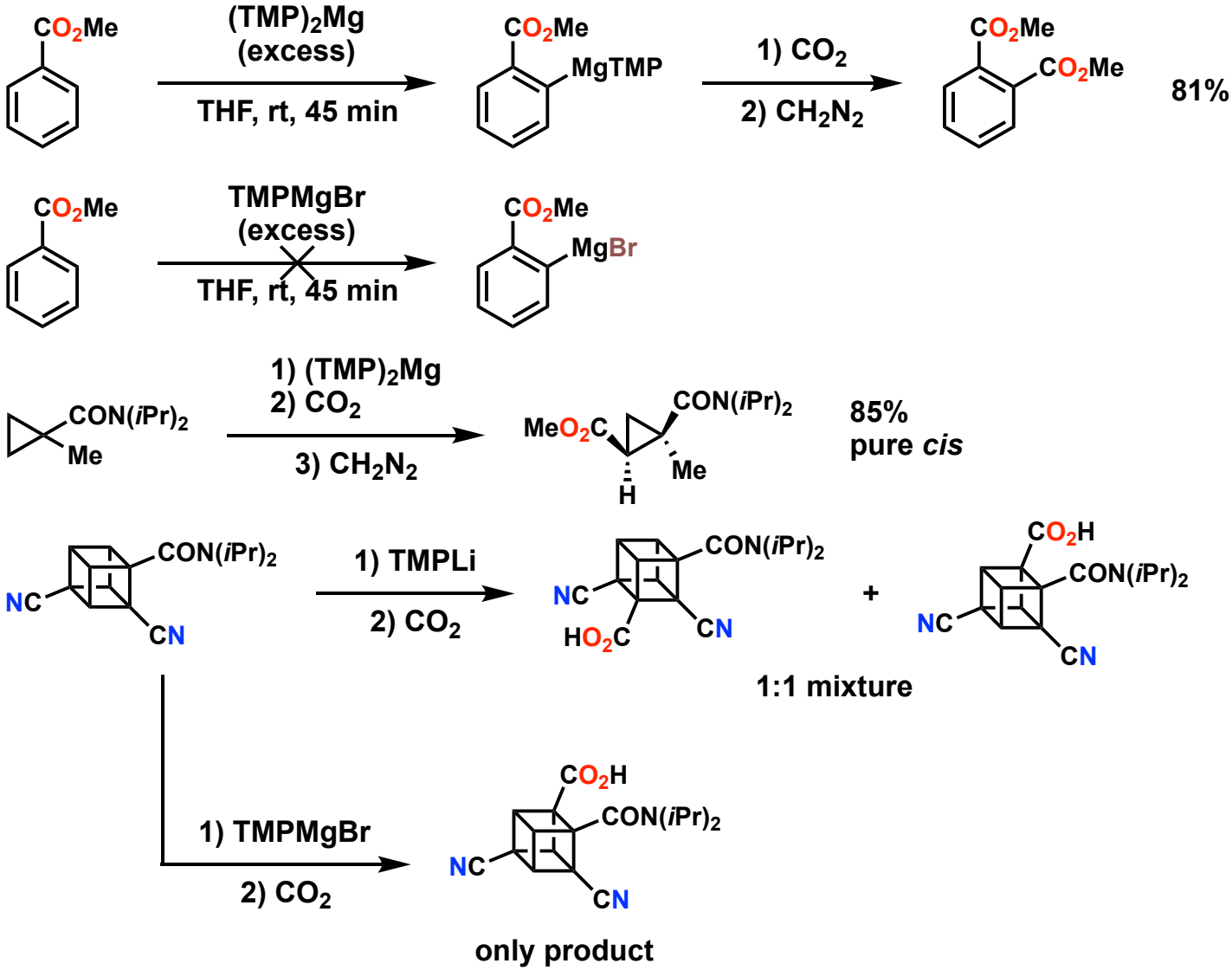


81%

"Hauser bases and magnesium diamides are known, but their uses in organic synthesis have barely been explored."
"To our knowledge, it has always ben assumed that the initial metalation depended crucially, if not exactly explicably, on the properties of lithium. To the contrary, as we show here, direct "ortho magnesiation" can be accomplished readily."

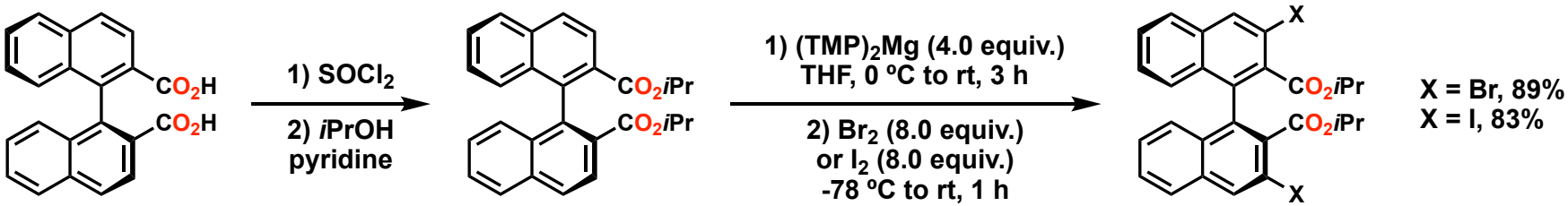
Eaton, P. E.; Lee, C. -H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016-8018.

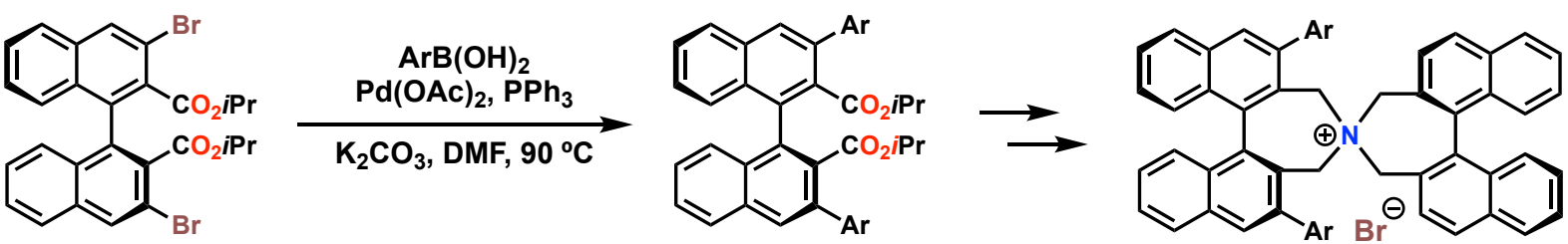
Scope of metalation with $(TMP)_2Mg$



Eaton, P. E.; Lee, C. -H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016-8018.

Scope of metalation with $(TMP)_2Mg$

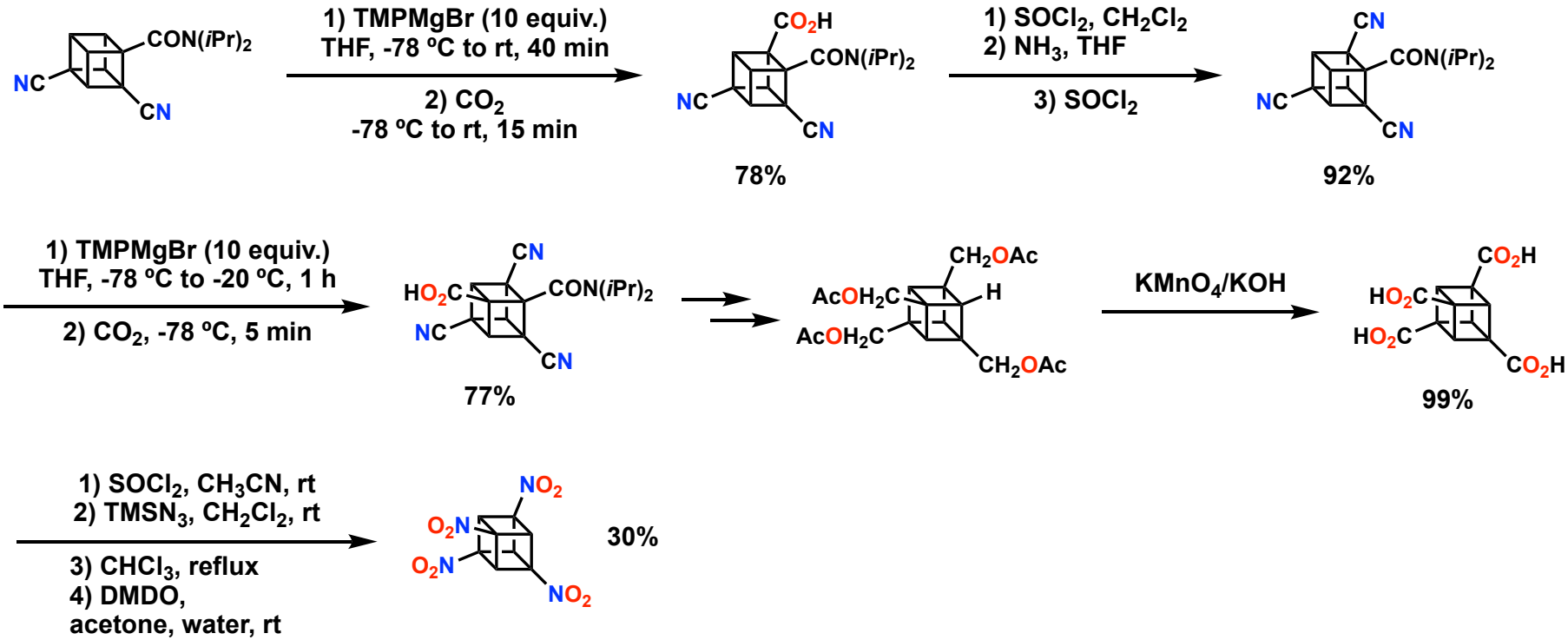




Ar = 3,5-Me_2Ph, 91%
Ar = 3,4,5-F_3Ph, 90%

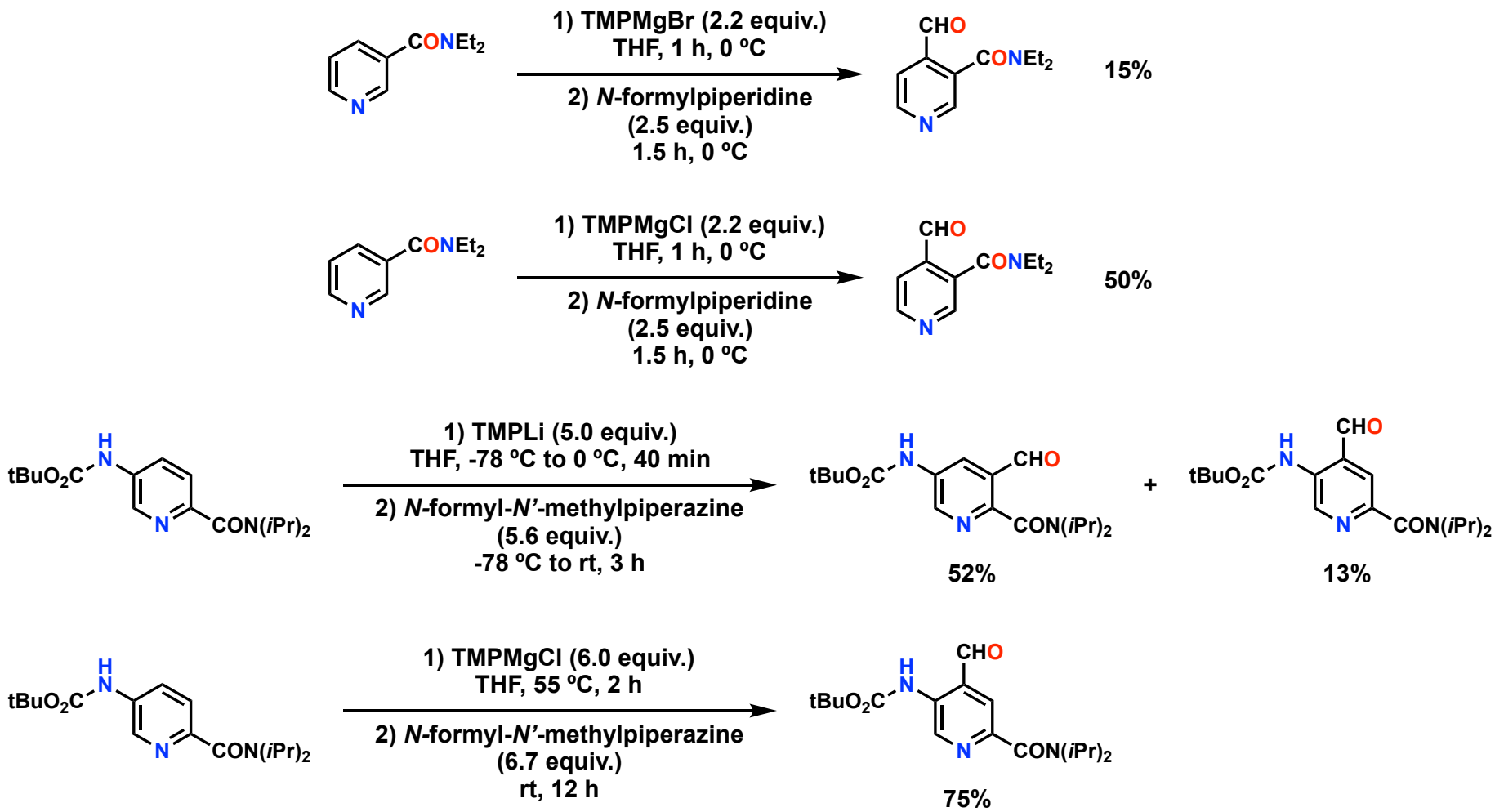
Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Org. Chem.* **2003**, *68*, 4576-4578.

Scope of metalation with TMPMgBr



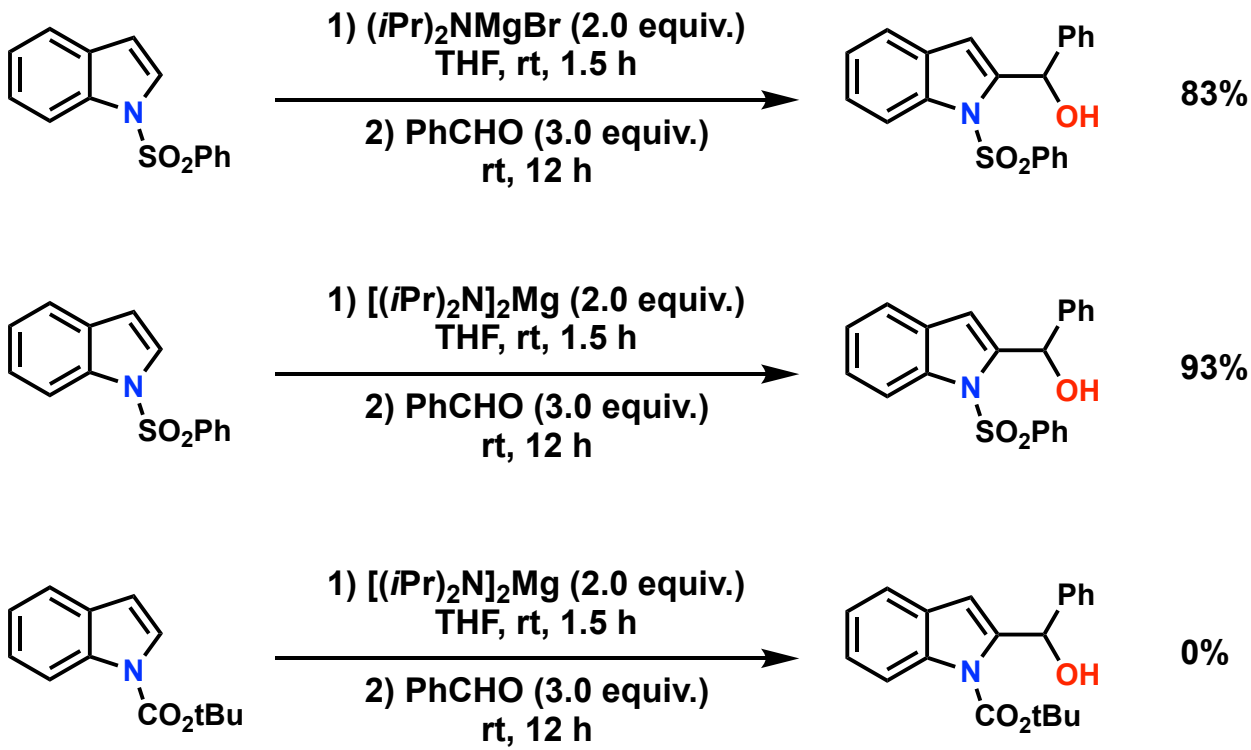
Eaton, P. E.; Xiong, Y.; Gilardi, R. *J. Am. Chem. Soc.* **1993**, *115*, 10195-10202.

Importance of the halide



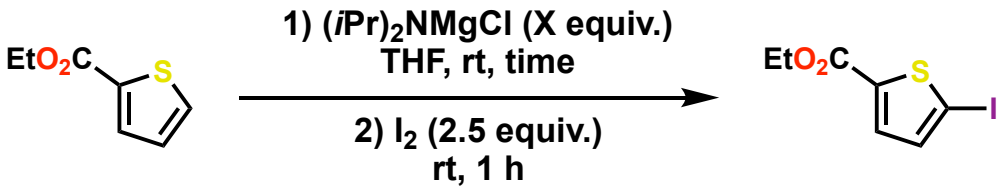
Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *J. Org. Chem.* **1995**, *60*, 8414-8416.

Deprotonation of heterocycles

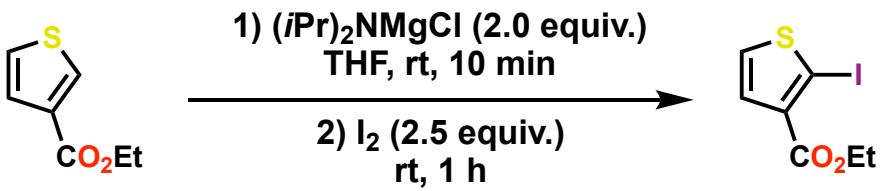


Kondo, Y.; Yoshida, A.; Sakamoto, T. *J. Chem. Soc. Perkin Trans. 1*. **1996**, 2331-2332

Deprotonation of heterocycles



Equiv. iPr_2MgCl	time	yield
1.0	1 h	21% (73% rsm)
1.0	24 h	0% (90% rsm)
2.0	10 min	77%
2.0	30 min	60%
2.0	1 h	52%
2.0	24 h	0%

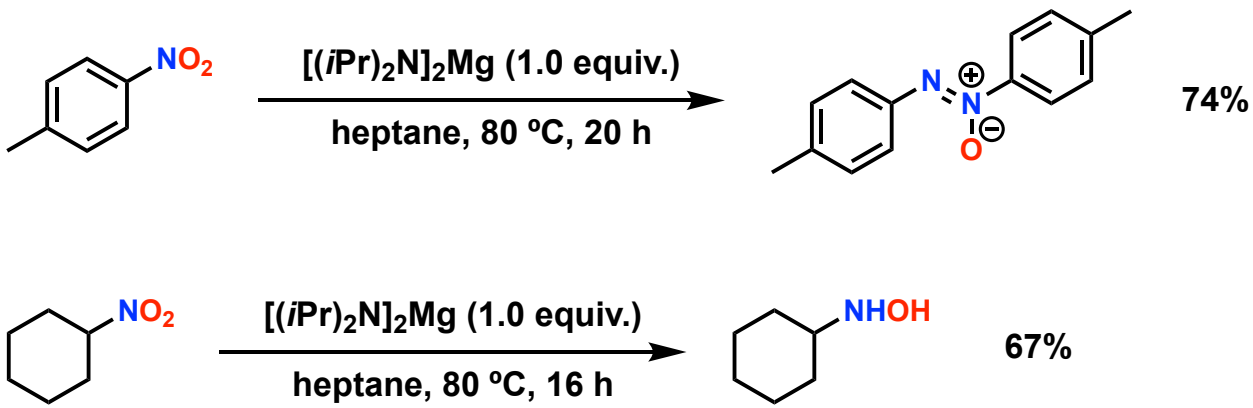


94%

Shilai, M.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc. Perkin Trans. 1.* **2001**, 442-444.

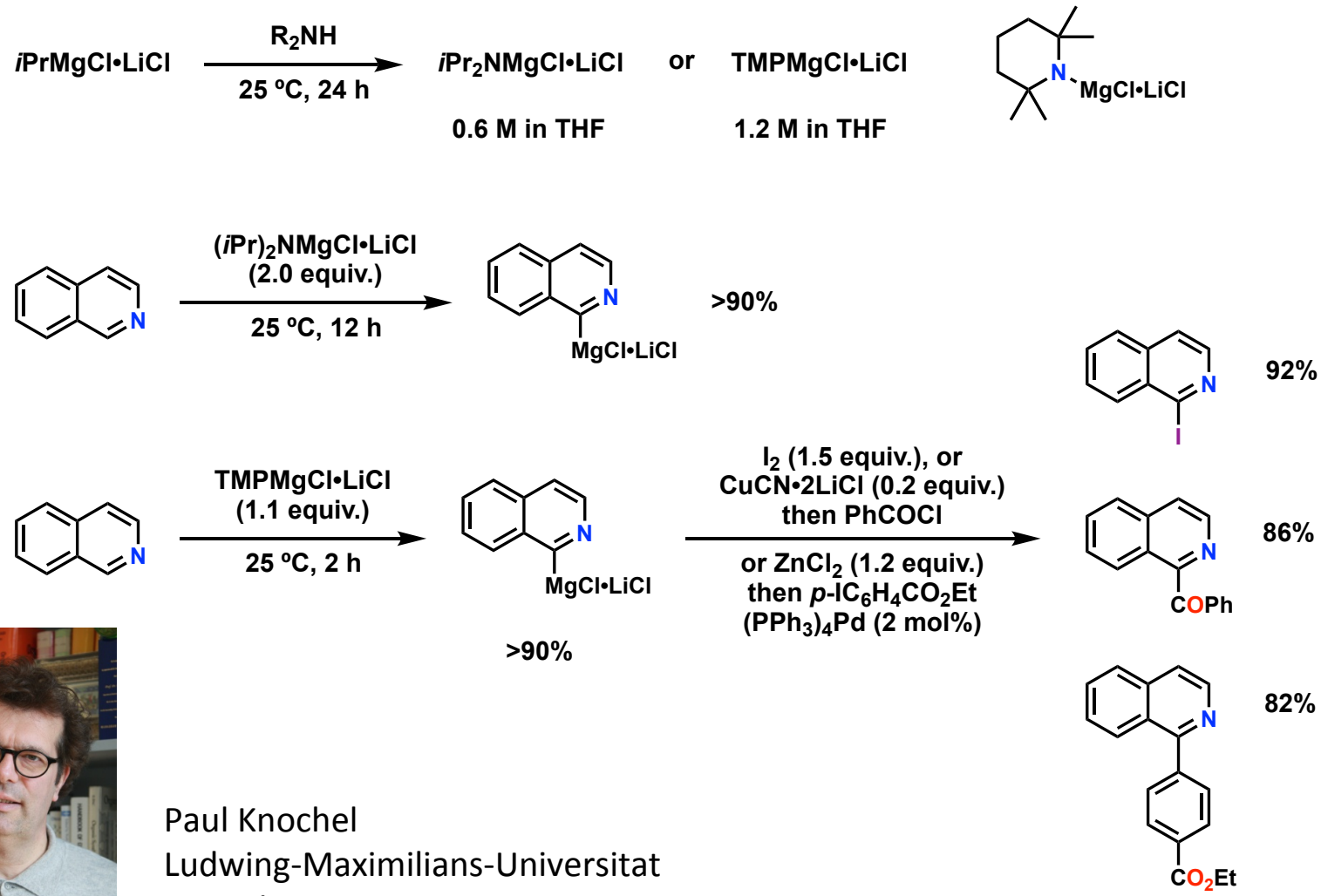
Shortcomings of the original methodology

- Reagents of the type R_2N-MgX and R_2N-Mg-NR_2 are only partially soluble in THF and insoluble in most others – large excess is often employed at 25 ºC or greater
- Insoluble magnesium amides can behave as reducing agents



Sanchez, R.; Vest, G.; Scott, W. *J. Org. Chem.* **1989**, *54*, 4026-4027.

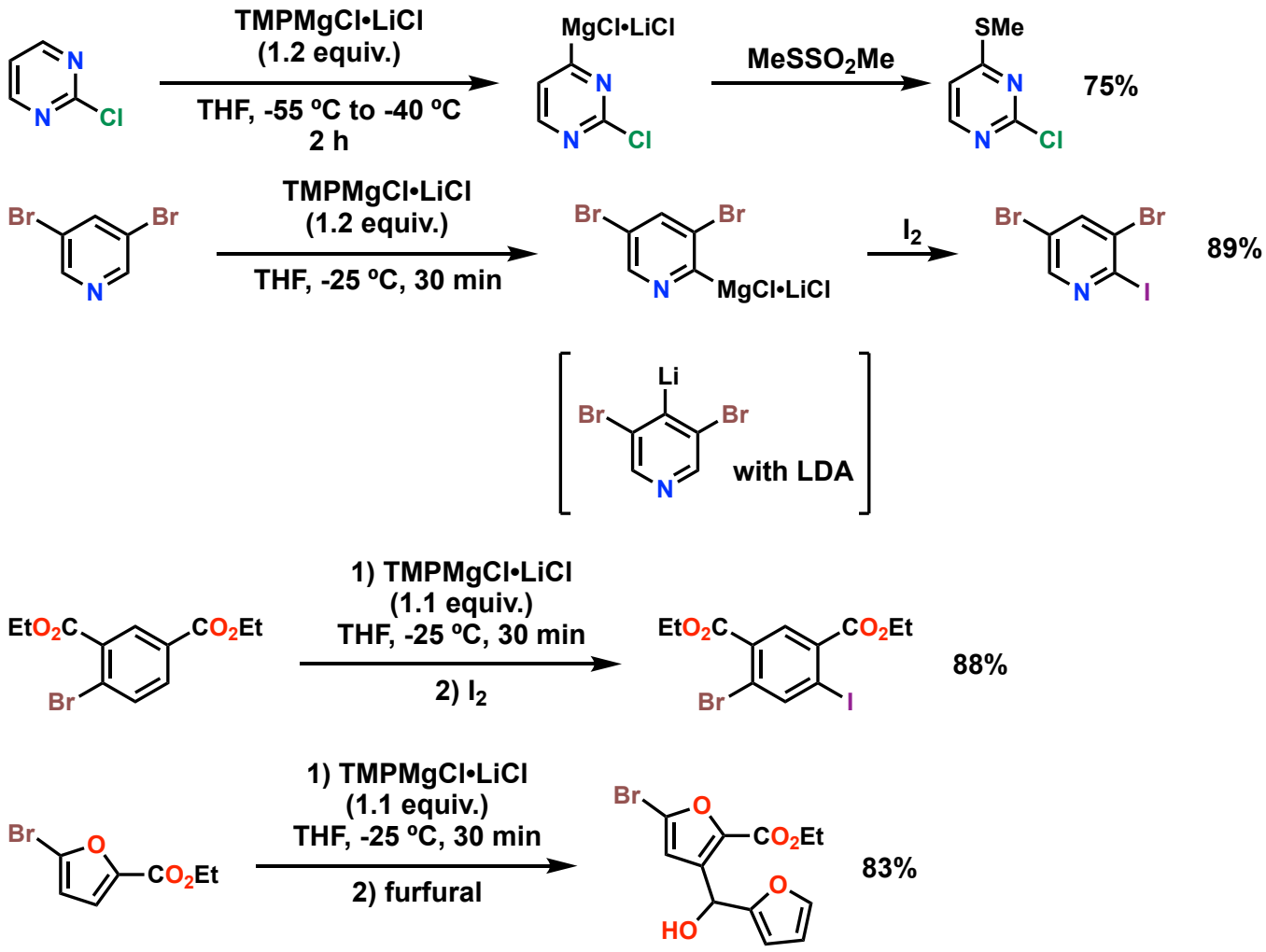
Lithium chloride complexes



Paul Knochel
Ludwing-Maximilians-Universitat
Munich, Germany

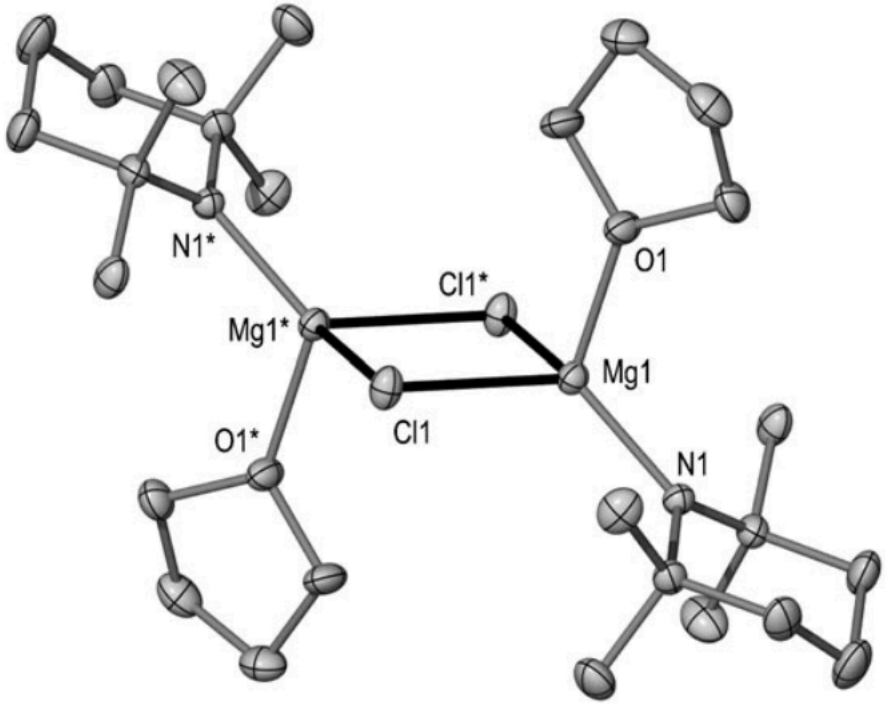
Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958-2961.

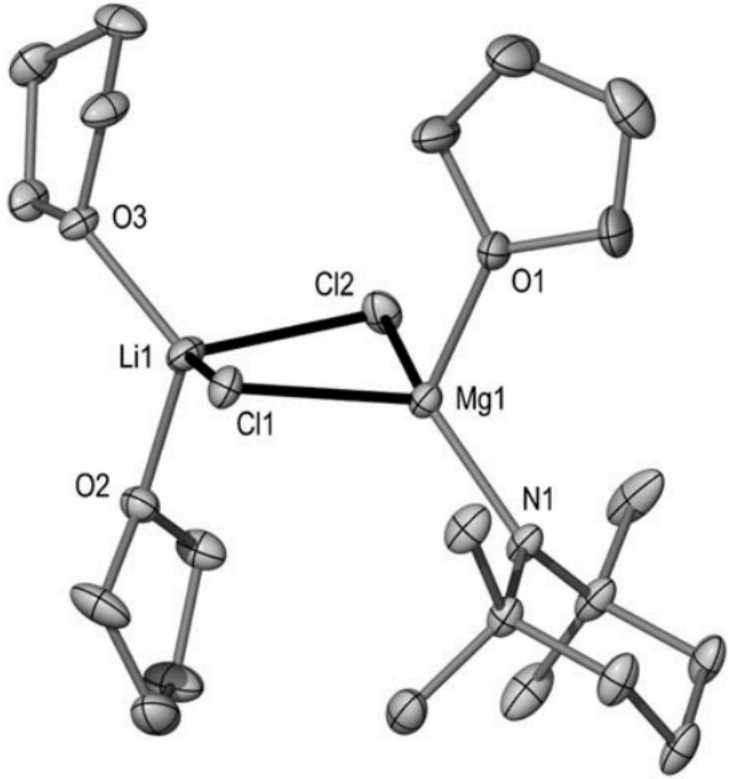
TMPMgCl•LiCl – mild and selective



Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958-2961.

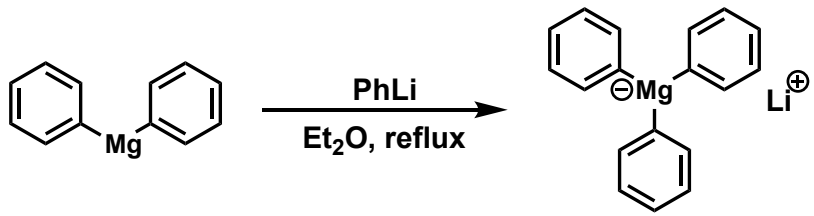
Structure of TMPMgCl•LiCl

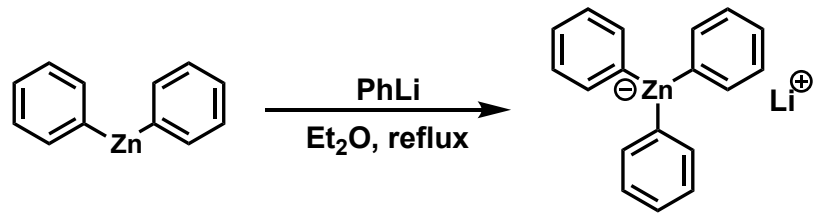


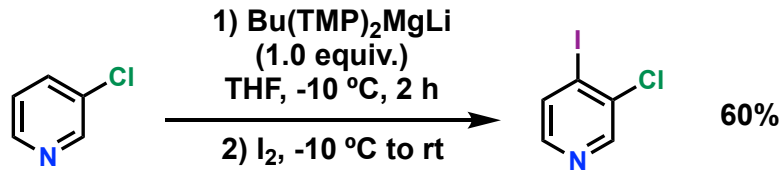


Garcia-Alvarez, P.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Weatherstone, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 8079-8081

“Ate” complexes as metalating agents







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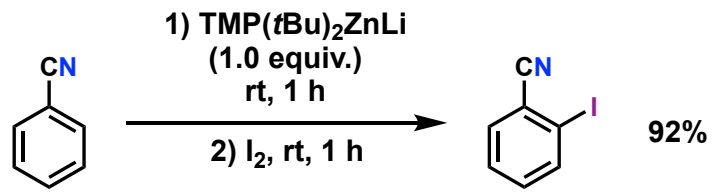

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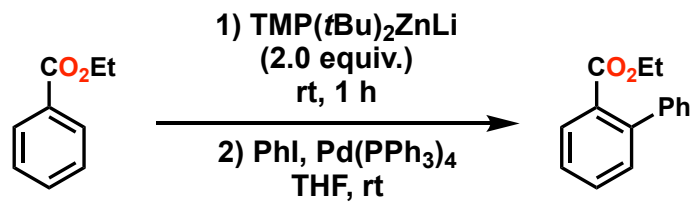

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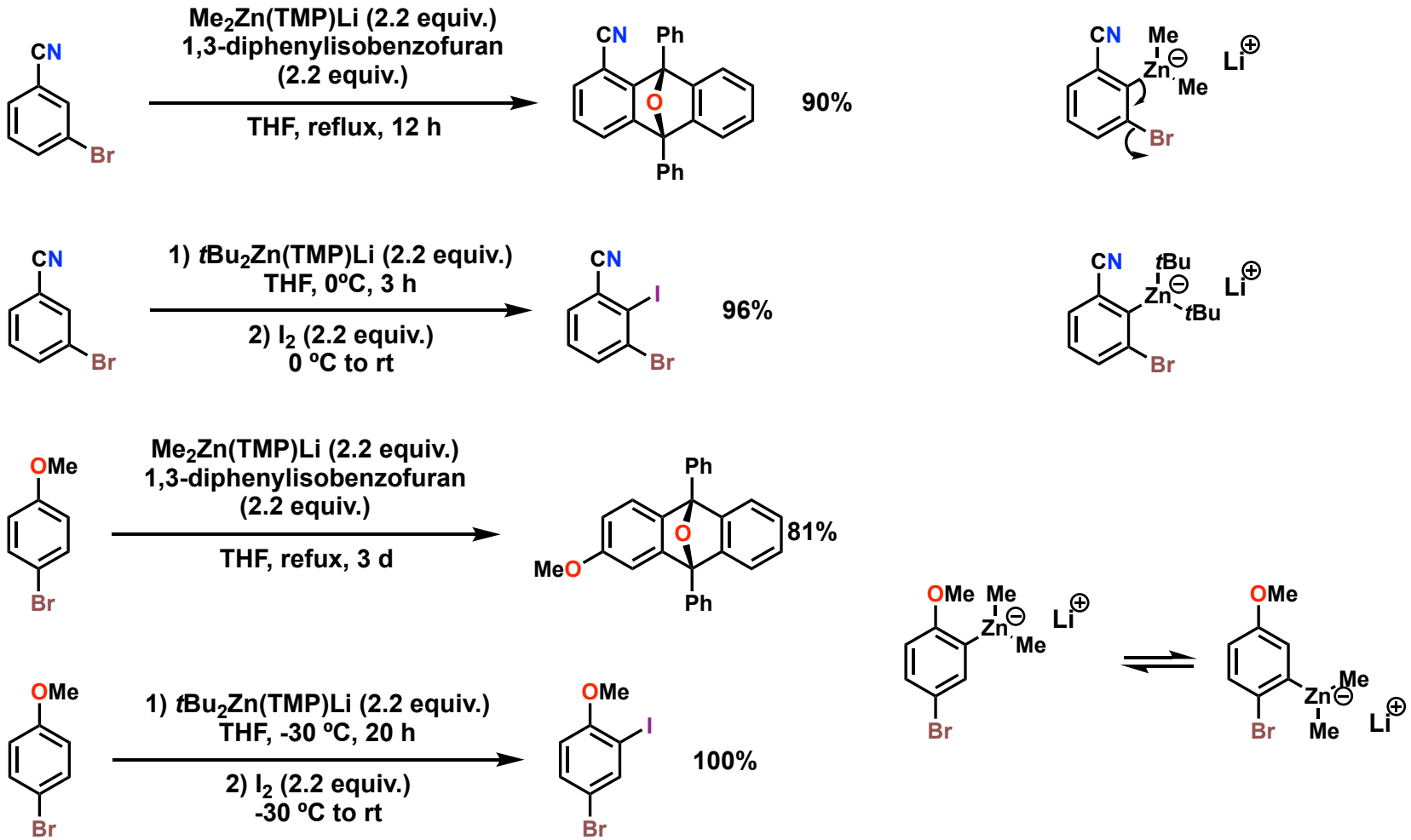
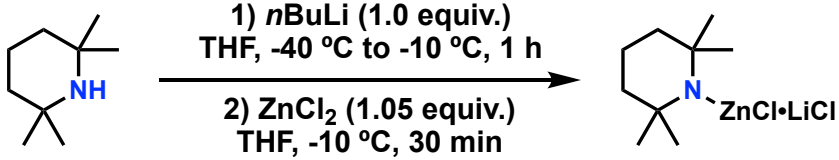
Wittig, G.; Meyer, F. J.; Lange, G. *Justus Liebigs Ann. Chem*. **1951**, *571,* 167-201.
Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Marsais, F. *Tetrahedron Lett.* **2004**, *45*, 7873-7877.
Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539-3540.

Zincates as metalating reagents

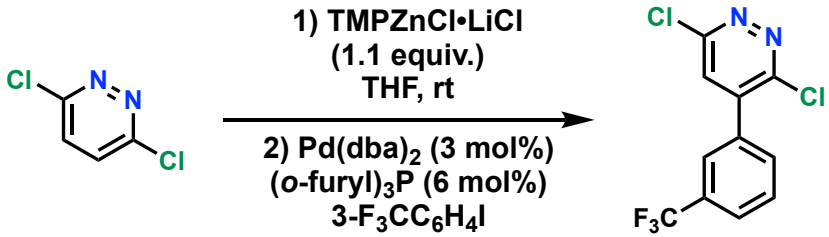


Uchiyama, M.; Kobayashi, Y.; Furuyama, T.; Nakamura, S.; Kajihara, Y.; Miyoshi, T.; Sakamoto, T.; Kondo, Y.; Morokuma, K. *J. Am Chem. Soc.* **2008**, *130*, 472-480.

Zincation with TMPZnCl•LiCl



>97%, 1.35 M



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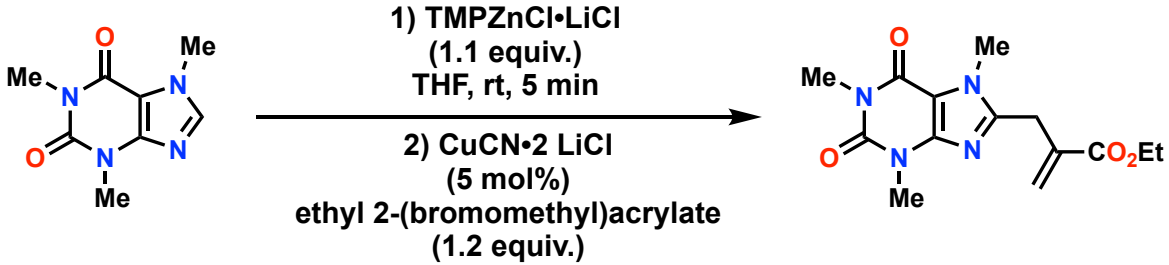

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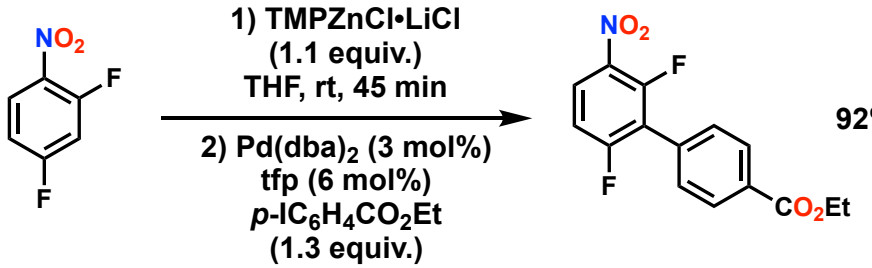

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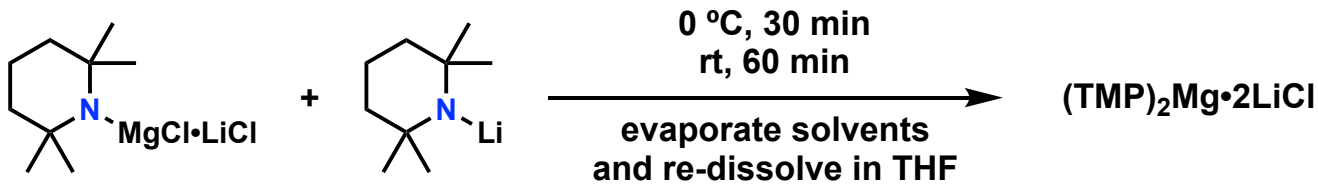
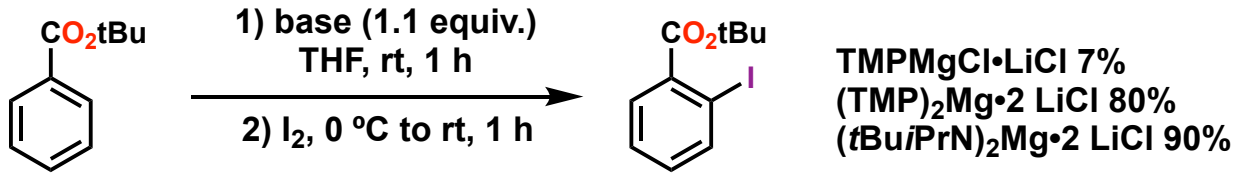
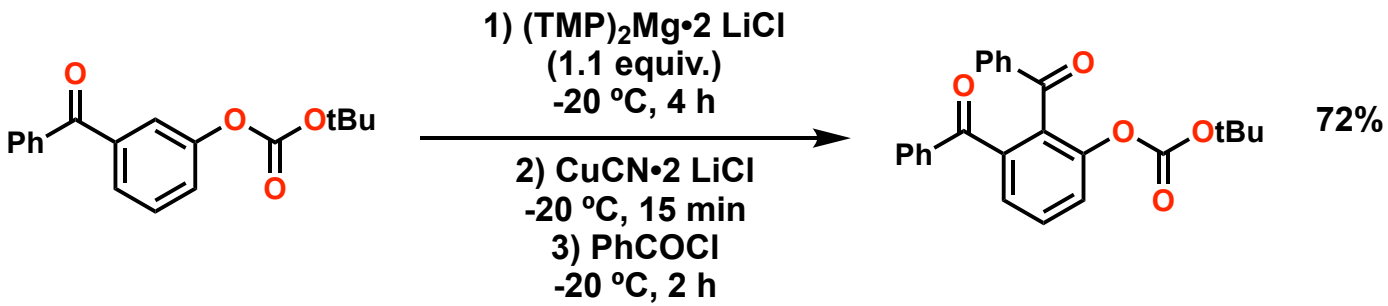
Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837-1840.

$(TMP)_2Mg\bullet 2\ LiCl$ – for reluctant C–H acids

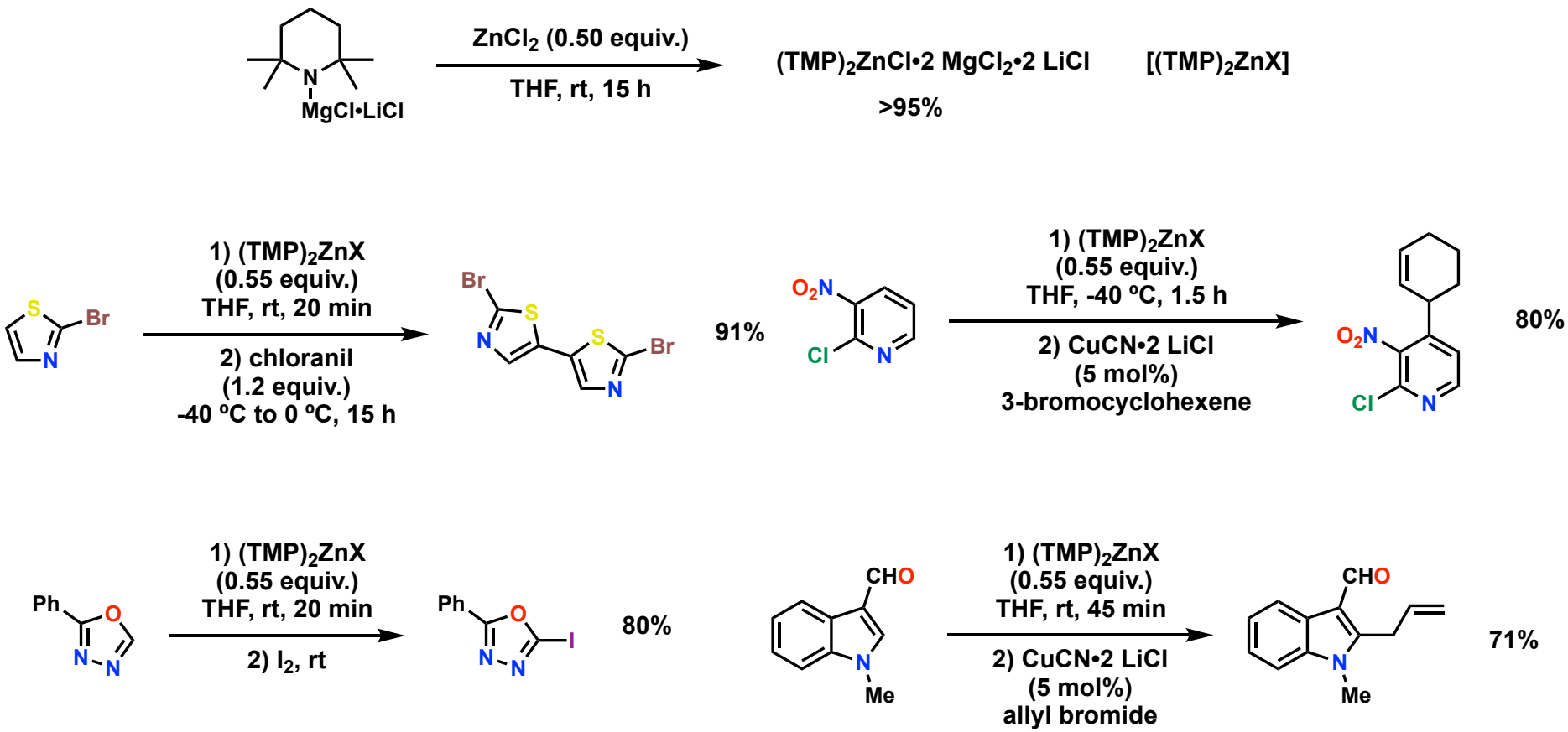






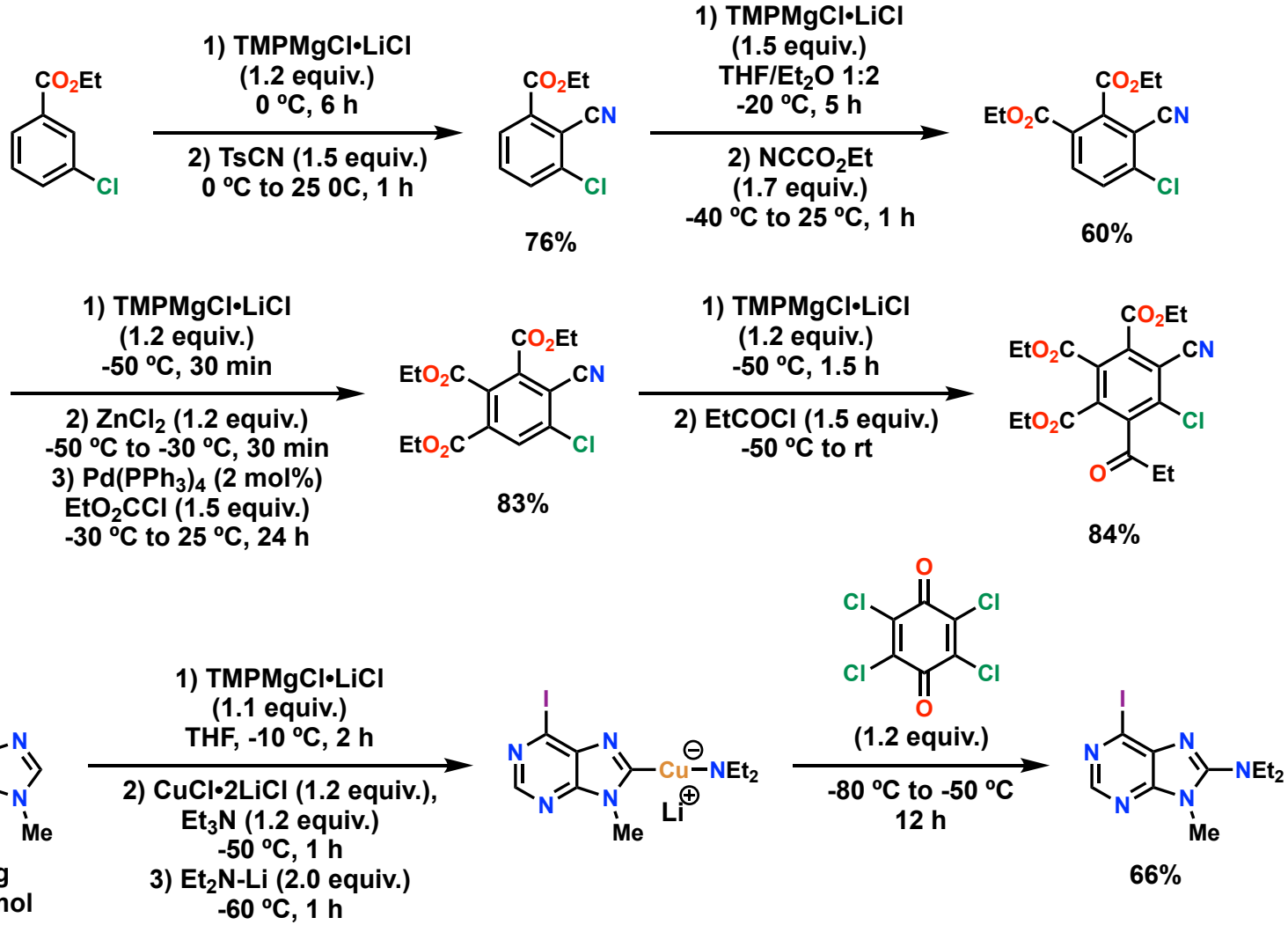
Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681-7684.

$(TMP)_2Zn \bullet 2\ MgCl_2 \bullet 2\ LiCl$



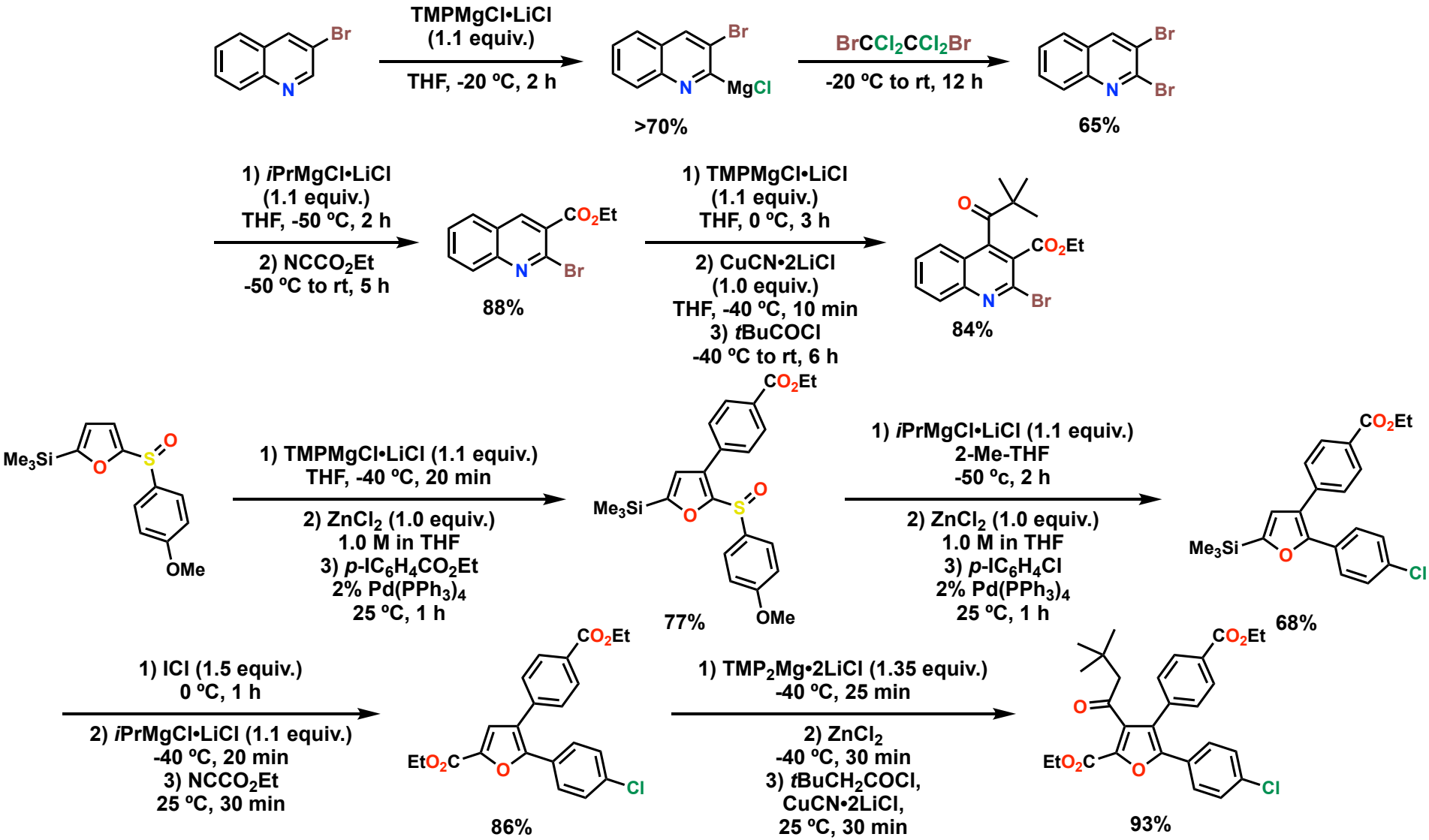
Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7685-7688.

Applications



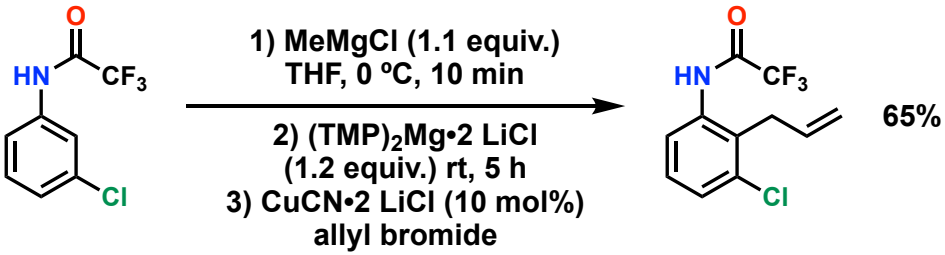
Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673-5676.
Boudet, N.; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2008**, *10*, 1715-1718.

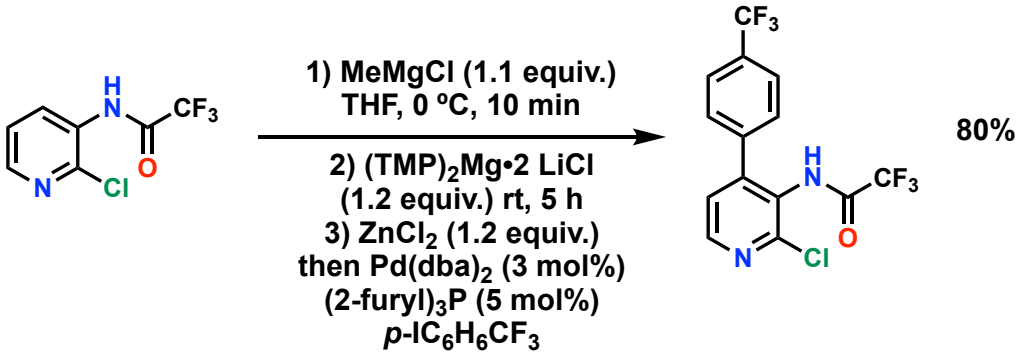
Applications

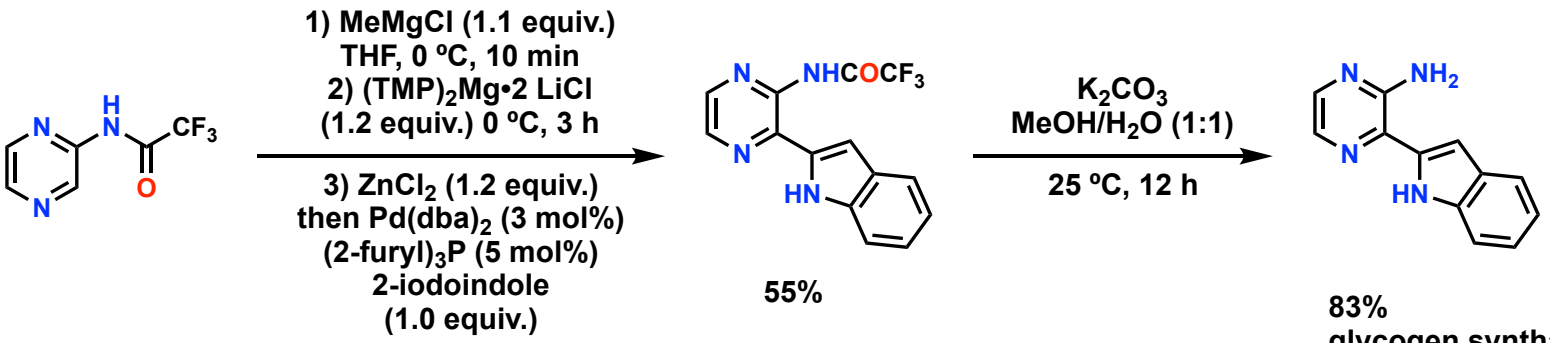


Boudet, N.; Lachs, J. R.; Knochel, P. *Org. Lett.* **2007**, *9*, 5525-5528.
Melzig, L.; Rauhut, C. B.; Knochel, P. *Chem. Commun.* **2009**, 3536-3538.

Aminoarenes



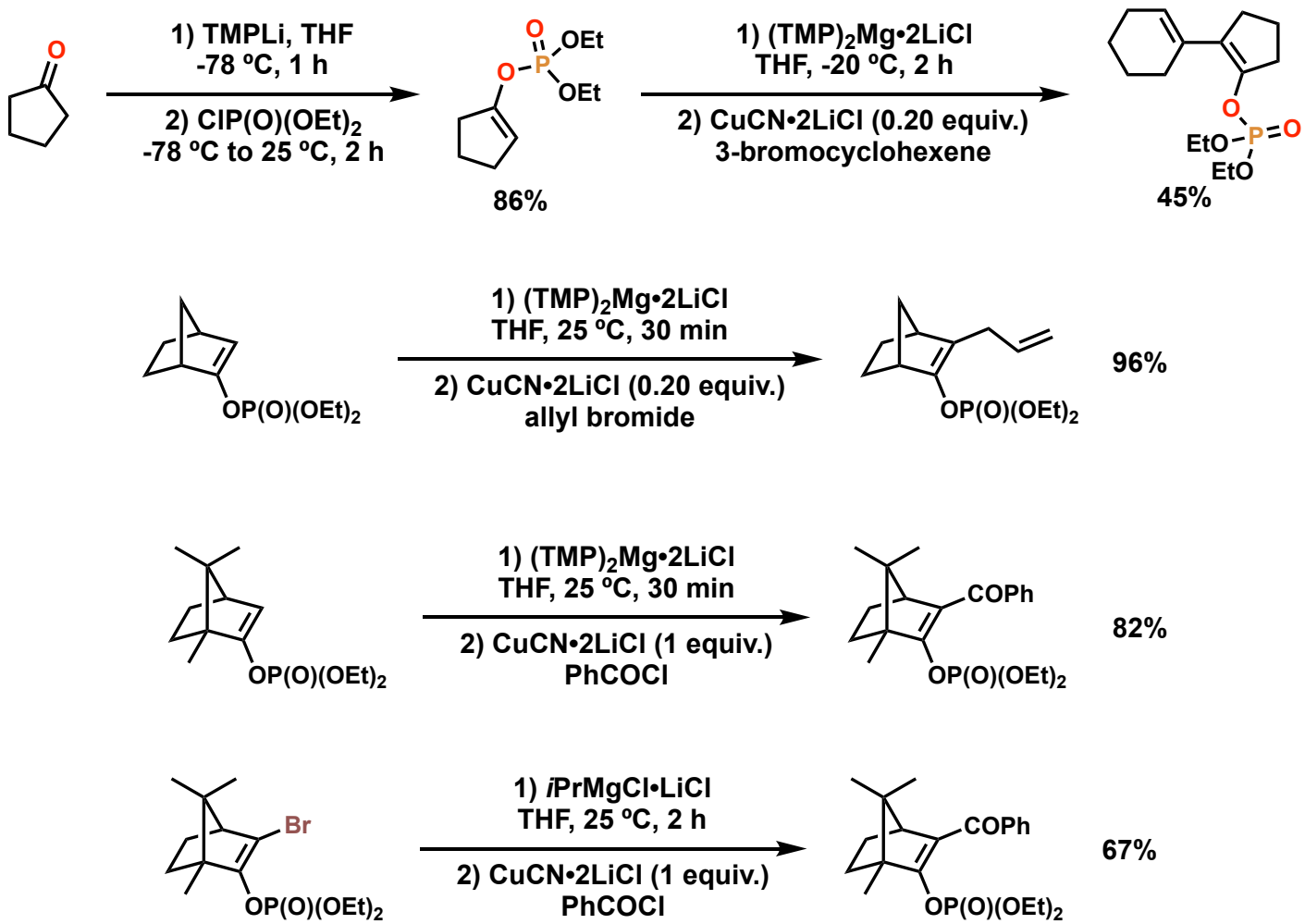




83%
glycogen synthase kinase 3 and lymphocyte-specific protein tyrosine kinase inhibitor

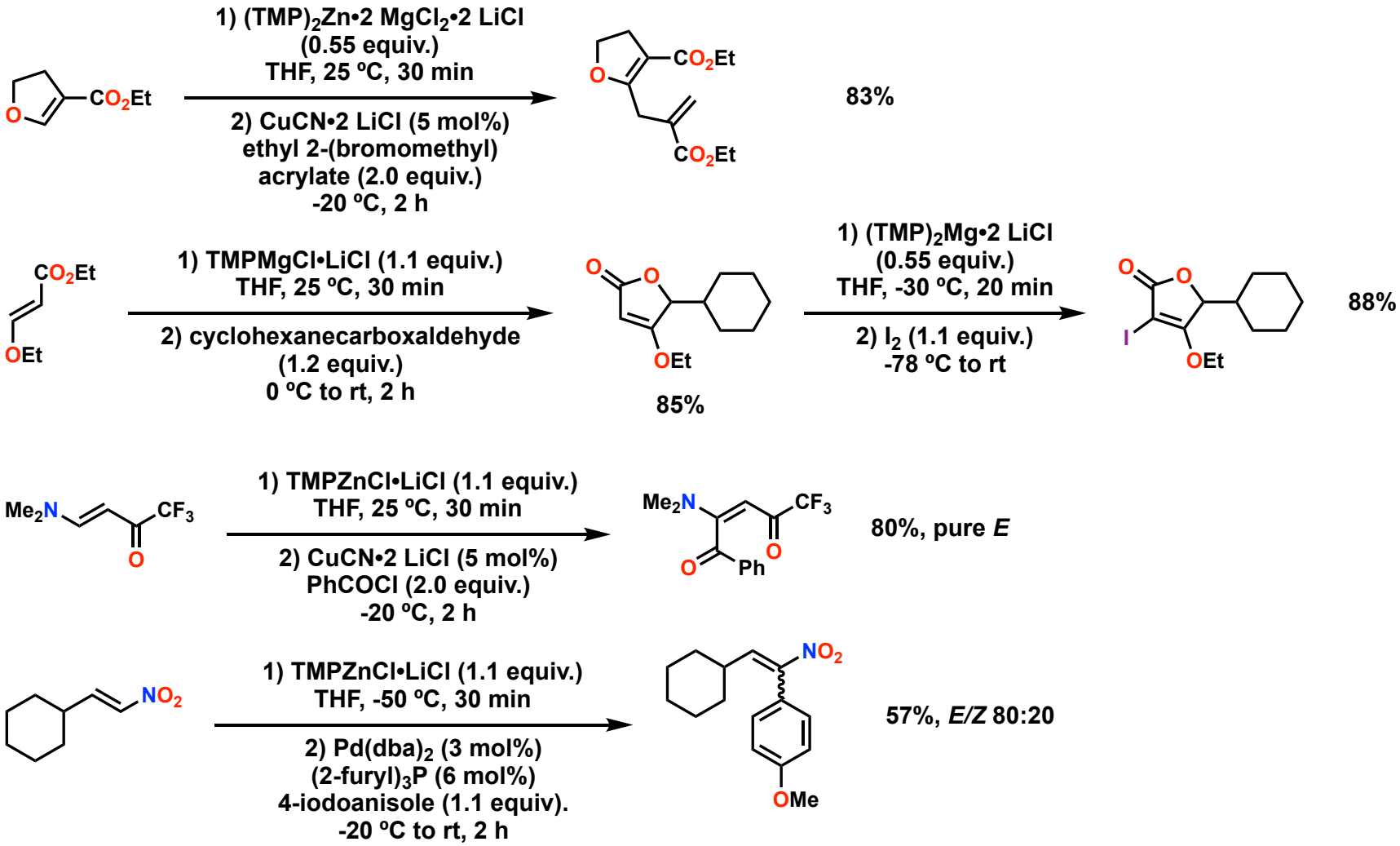
Monzón, G.; Tirotta, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 10624-10627.

Nonaromatic substrates



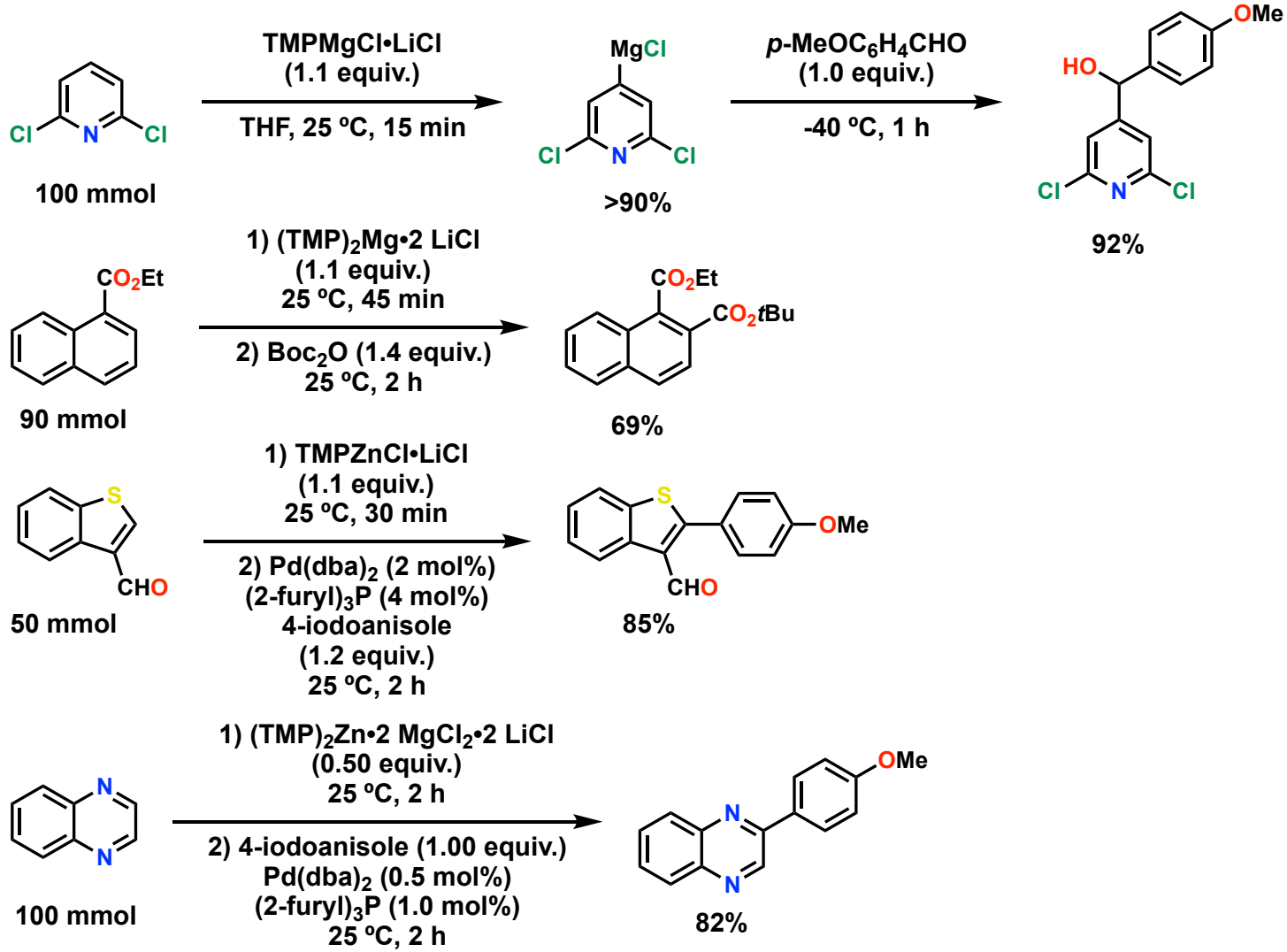
Piller, F. M.; Bresser, T.; Fischer, M. K. R.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4365-4375.

Nonaromatic substrates



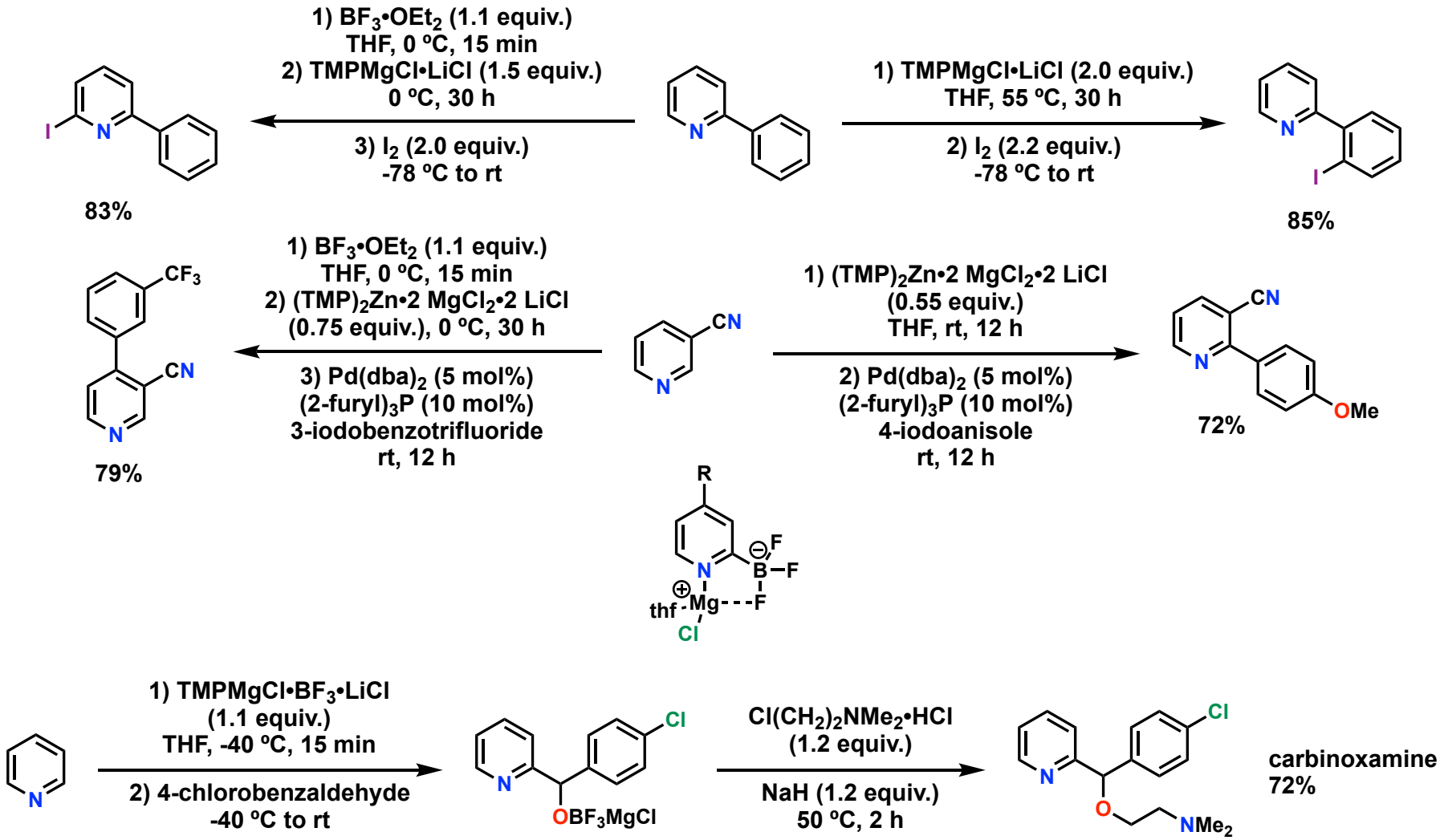
Bresser, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 1914-1917.

Large-scale transformations



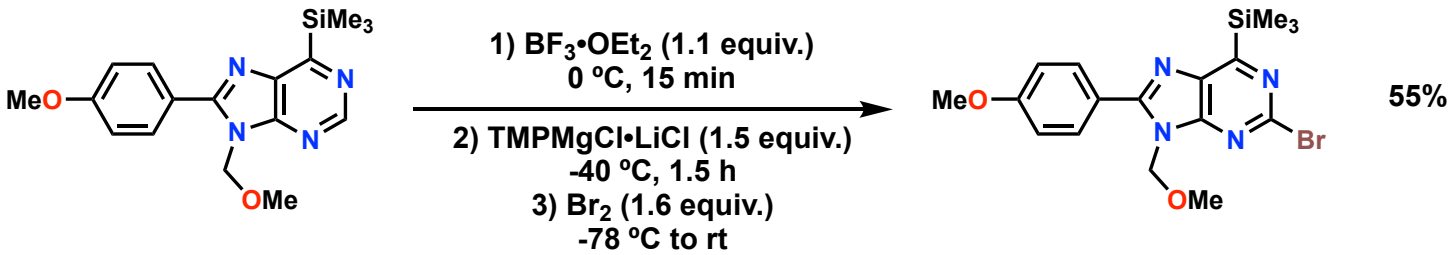
Wunderlich, S. H.; Rohbogner, C. J.; Unsinn, A.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 339-345.
Bresser, T.; Monzon, G.; Mosrin, M., Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 1299-1303.

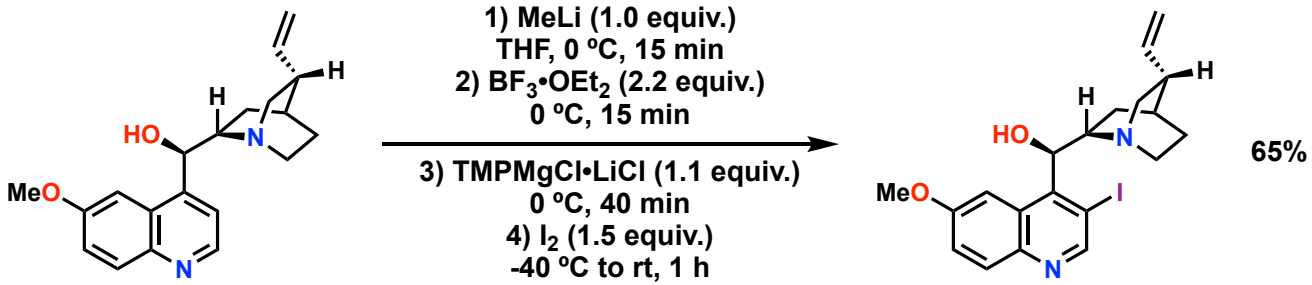
Lewis acid cooperativity

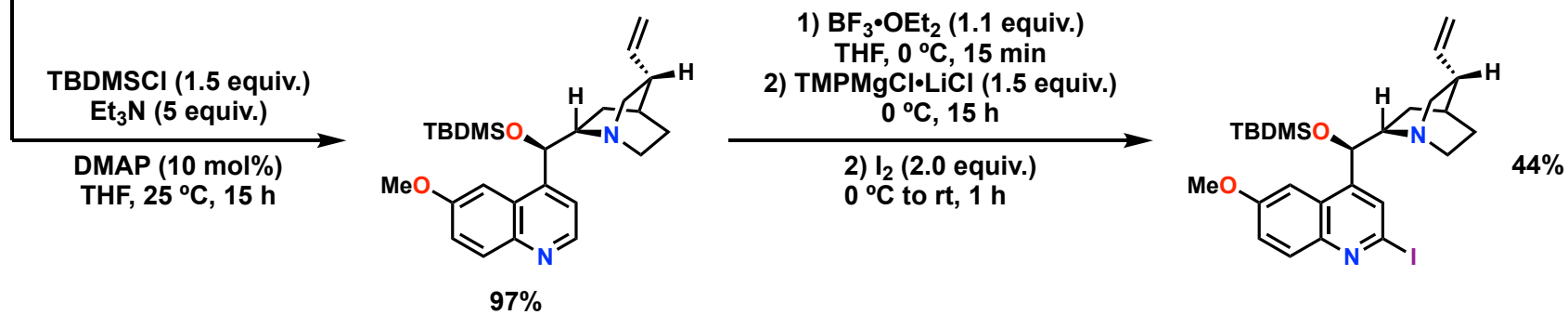


Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 5451-5455.

Complex substrates

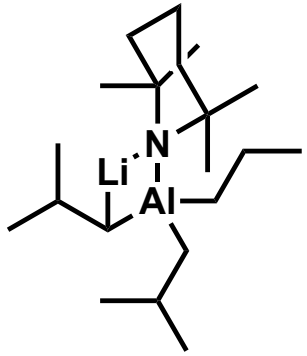




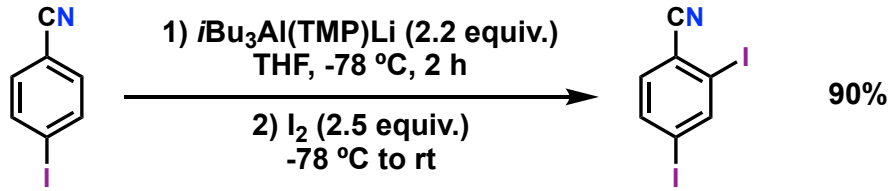


Groll, K.; Manolikakes, S. M.; Mollat du Jourdin, X.; Jaric, M.; Bredihhin, A.; Karaghiosoff, K.; Carell, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 6776-6780.
Jaric, M.; Haag, B. A.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2011**, *13*, 2306-2309.

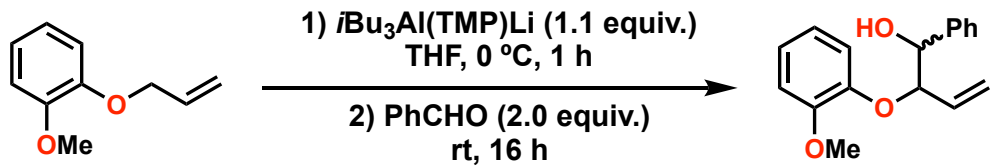
Other metals: Al



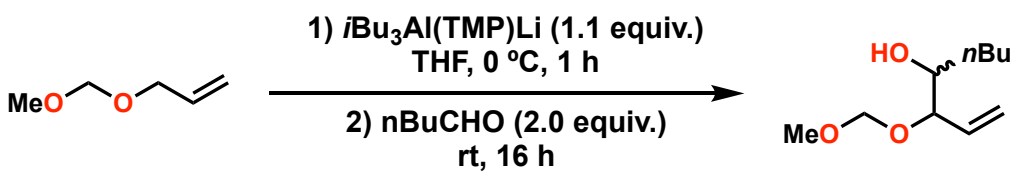
Single, novel species by
^{1}H, ^{13}C, ^{7}Li, ^{15}N, ^{27}Al-NMR



90%



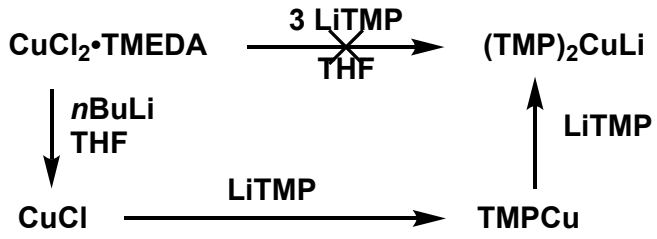
82%
α:γ >99:1

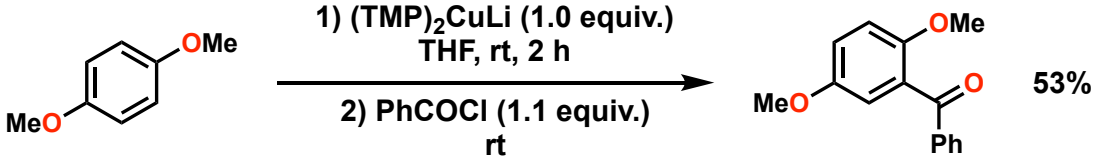


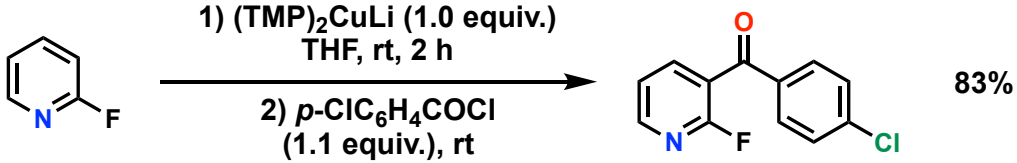
97%
α:γ >99:1

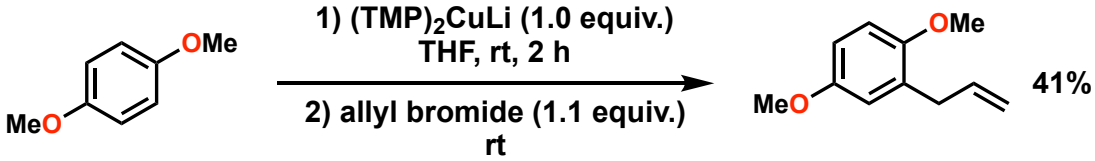
Uchiyama, M.; Naka, H.; Matsumoto, Y.; Ohwada, T. *J. Am. Chem. Soc.* **2004**, *126*, 10526-10527.

Other metals: Cu



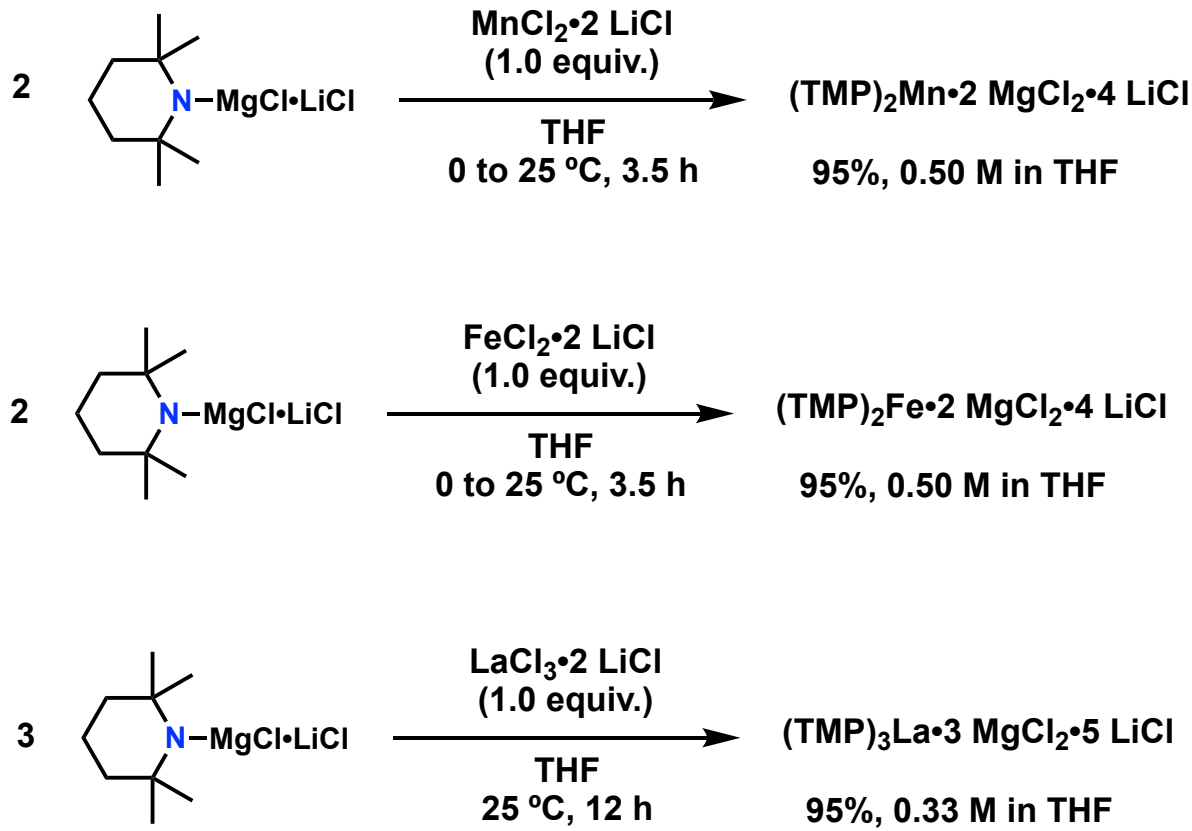






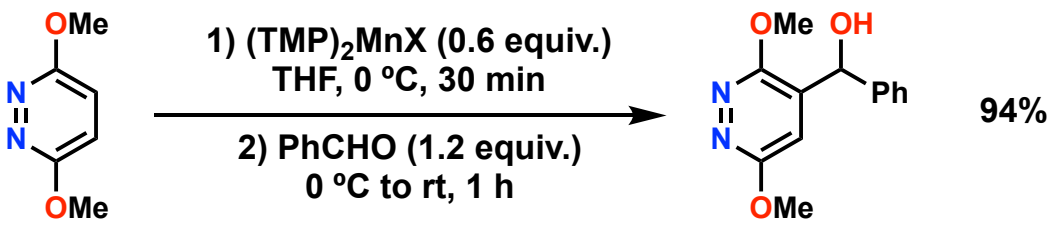
Nguyen, T. T.; Chevallier, F.; Jouikov, V.; Mongin, F. *Tetrahedron Lett.* **2009**, *50*, 6787-6790.

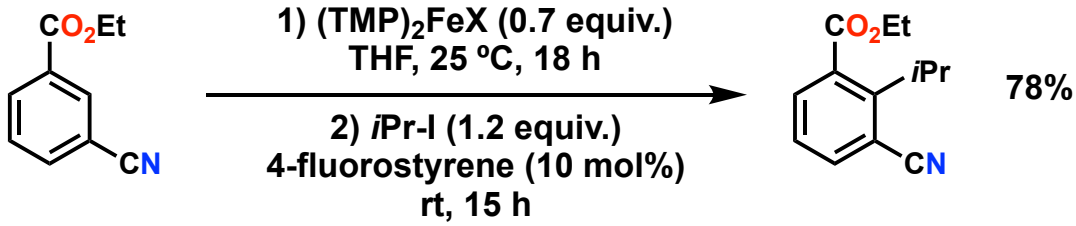
Other metals: Mn/Fe/La

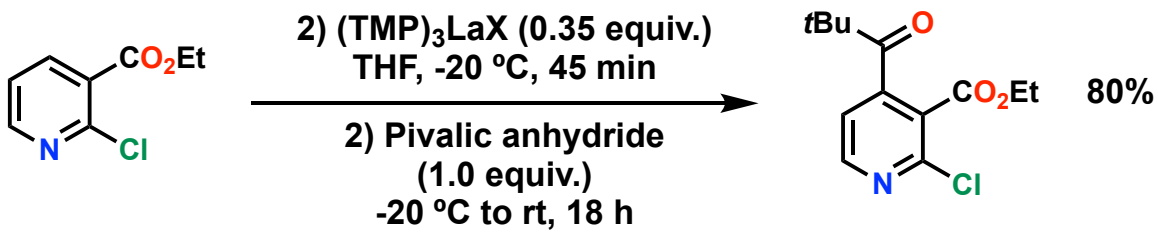


Wunderlich, S. H.; Bresser, T.; Dunst, C.; Monson, G.; Knochel, P. *Synthesis*, **2010**, 2670-2678.

Other metals: Mn/Fe/La







Wunderlich, S. H.; Bresser, T.; Dunst, C.; Monson, G.; Knochel, P. *Synthesis*, **2010**, 2670-2678.

Conclusion

- Organometallic reagents can be readily prepared by deprotonation, without transmetalation from an organolithium intermediate
- TMP-Mg and TMP-Zn bases are stable in THF solution at room temperature for months
- Fragile and highly functionalized aromatic and heterocyclic structures can be metalated and captured in good to excellent yields

- While the methodologies are very selective, only the kinetically most acidic C–H will be deprotonated
- TMP bases are soluble in very few solvents other than THF
- Some metalation/transmetalation/cross-coupling methodologies are very technically sophisticated

Important Reviews

(1) Klatt, T.; Markiewicz, J. T.; Sämann, C.; Knochel, P. Strategies To Prepare and Use Functionalized Organometallic Reagents. *J. Org. Chem.* **2014**, *79*, 4253-4269.

(2) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. Regio- and Chemoselective Metalation of Arenes and Heteroarenes Using Hindered Metal Amide Bases. *Angew. Chem. Int. Ed.* **2011**, *50*, 9794-9824.

(3) Mulvey, R. E.; Robertson, S. D. FascinATES: Mixed-Metal Ate Compounds That Function Synergistically. *Top. Organomet. Chem.* Vol. 47. **2014**, Springer-Verlag: Berlin; pp 129-158.

(4) Mulvey, R. E.; Avant-Garde Metalating Agents: Structural Basis of Alkali-Metal-Mediated Metalation. *Acc. Chem. Res.* **2009**, *42*, 743-755.

(5) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. Deprotonative Metalation Using Ate Compounds: Synergy, Synthesis, and Structure Building. *Angew. Chem. Int. Ed.* **2007**, *46*, 3802-3824.