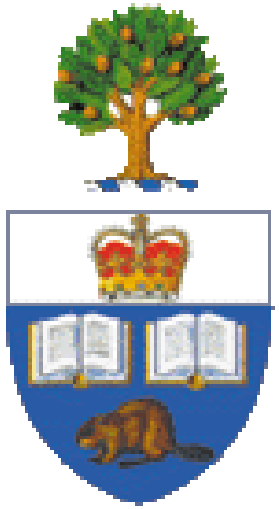
Heteroatom-Facilitated Lateral Lithiation: Generation and Application in Organic Synthesis



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Dept. of Chemistry
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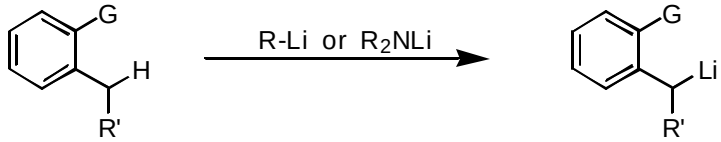
April 16, 2001

- Abstract -

Heteroatom-Facilitated Lateral Lithiation: Generation and Application in Organic Synthesis

Heteroatom-facilitated lithiation reactions play an important role in the elaboration of carbocyclic aromatic and heteroaromatic systems. The development of methodology for the lateral lithiation of alkyl-substituted aromatic systems promoted by an extensive array of heteroatomic substituents allows facile functionalization at benzylic positions.

Scheme 1: Lateral Lithiation



G = heteroatomic substituent
R = alkyl
R' = H, alkyl, aryl

Although organolithium reagents have been employed in organic synthesis for decades, little is known about the exact mechanism of their reactions. Predictions of the regioselectivity of lithiation reactions comes from mass records of empirical evidence. In an attempt to elucidate the mechanism, structural information about organolithium reagents gathered from IR and mass spectroscopy, and X-ray crystallography; theories of coordination chemistry; and theories of complex-induced proximity effects (CIPE) will be presented.

References:

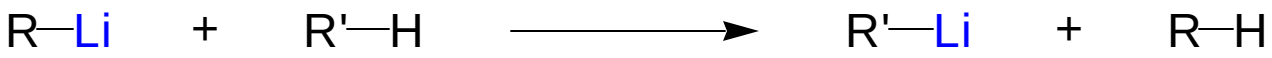
Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356-363.
Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1-314.
Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227-234.
Wakefield, B. J. *The Chemistry of Organolithium Compounds*, Pergamon Press, New York, 1974, pp. 3-18.
Wakefield, B. J. *Organolithium Methods*, Academic Press, London, 1998, pp. 3-4, 33-44.
Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Chem. Ber.* **1989**, *122*, 2303-2309.

Overview

1) Introduction to Organolithium Compounds
   - Structure of lithium aggregates in the solid phase
   - Reactivity: basicity and nucleophilicity
   - Ligand and solvent interactions
2) Types of Lithiation Reactions
   - α-, β(*ortho*)-Lithiations
   - Lateral lithiations
3) Lateral Lithiation Reactions
   - Mechanisms of lithiation
   - CIPE: complex-induced proximity effect
4) Application of Lateral Lithiations in Synthesis
5) Diastereoselective Lateral Lithiations
6) Conclusions and Future Work

Introduction

- The basic schematic of a lithiation shows replacement of hydrogen by lithium:



- Little is known about the structure of organolithium compounds, especially in the gaseous and solutions states.

- Known structural information comes from IR, mass spec., ^{1}H, ^{6}Li, ^{7}Li and ^{13}C-NMR, and X-ray crystallography.

- Although the formula "R-Li" is used to represent organolithium compounds, they are not found as monomeric structures.

- Organolithiums are usually encountered as aggregates with themselves or other electron donors.

Organolithium Aggregates in Solution

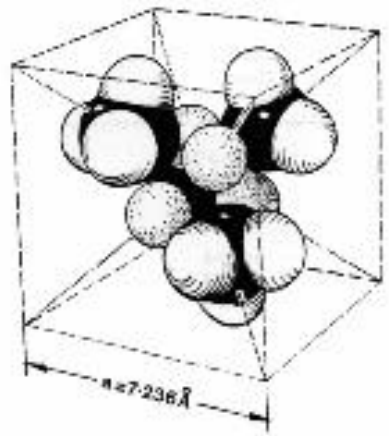


FIG. 1. 1. Model of tetrameric unit in crystal structure of methyl-lithium.[1961] (Reproduced by permission of Elsevier Co. and E. Weiss).

- MeLi and EtLi are insoluble in hydrocarbon solvents.
- X-ray crystal structures were obtained.
- Both compounds exist in tetrameric units in the crystalline state.

- Structures in other states examined indirectly:
  - IR shows little difference in C-Li stretching frequencies for spectra from mulls, in solution or in gas phase.
  - Mass spec. shows peaks for the tetrameric and hexameric particles.

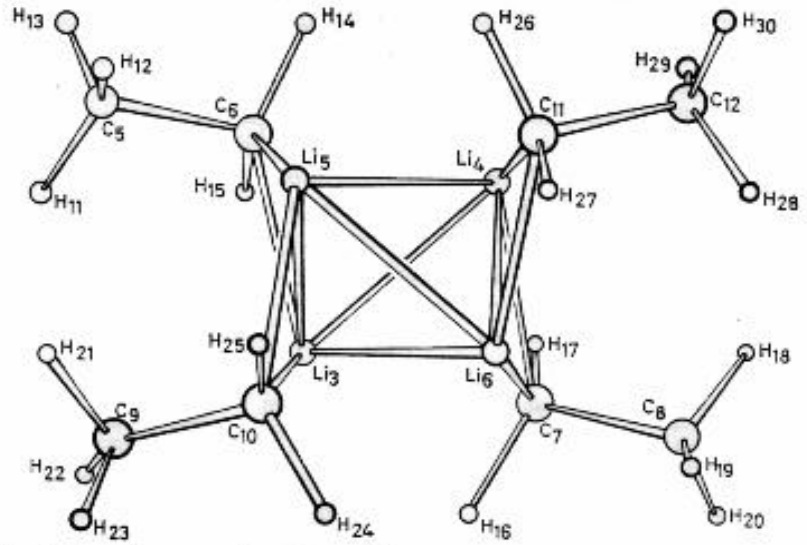
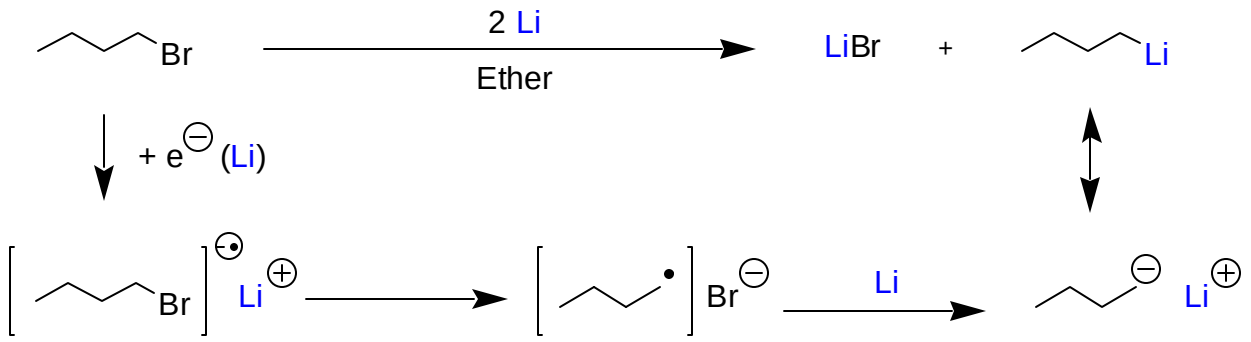


FIG. 1.2. Crystal structure of ethyl-lithium.[1963] (Reproduced by permission of the International Union of Crystallography and H. Dietrich)

Organolithium Compounds - 1

- Organolithium compounds generated from alkylhalides and lithium metal:



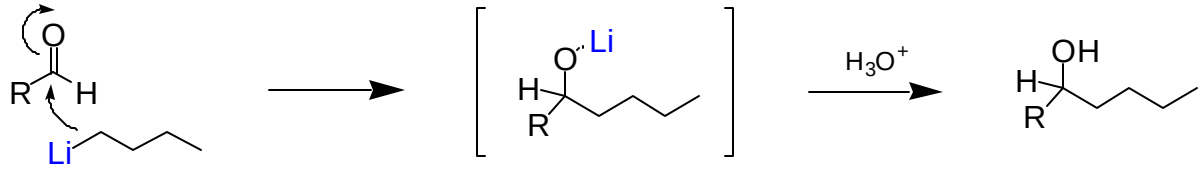
- Nature of the C-Li bond under debate:
  - IR shows low H-C-Li bending force constant which suggests ionic interaction.
  - Comparison of nuclei electronegativities, and extended Hückel molecular orbital calculations agree.
  - However, physical properties (m.p., b.p., solubility etc.) of many organolithium reagents are not characteristic of ionic compounds.

Organolithium Compounds - 2

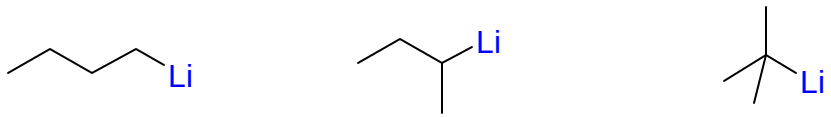
- Bonding in aggregated species is electron-deficient.

- Organolithiums behave as both electron-poor Lewis acids, and as nucleophilic Brrnsted bases.

- *n*-Butyllithium is so nucleophilic, it is usually incompatible with carbonyl groups:



- Steric hinderance helps to reduce the nucleophilicity of organolithium reagents:

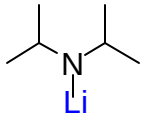


n-butyllithium *s*-butyllithium *t*-butyllithium

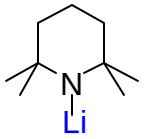
- The pKa of *n*-butane is around 45 - 50; other alkanes fall in the range of 42 - 60.

Organolithium Compounds - 3

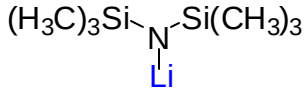
- Lithium amides are also employed in lithiations:



lithium diisopropylamide
(LDA)



2,2,6,6-tetramethylpiperidide
(LiTMP)



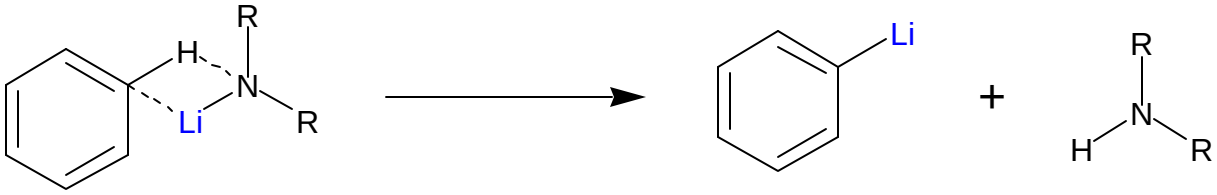
lithium bis(trimethylsilyl)amide
(LHMDS)

- Diminished Lewis acid character relative to uncomplexed lithium alkyls and aryls.

- Decreased thermodynamic basicity with pKa's ~ 30.

- High kinetic basicity due to free lone pair of electrons on the nitrogen.

- Coordination to the substrate generates a 4-membered transition state that avoids the need to stabilize a free carbanionic intermediate:



Ligand and Solvent Effects - 1

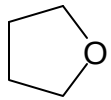
- Lewis bases interact with organolithium aggregates by coordinating with the electron-deficient framework.

  - Causes decrease in degree of association, and polarizes C-Li or N-Li bond.

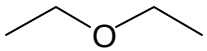
    Strong electron donor = Lower degree of association

  - *n*-Butyllithium is hexameric in hydrocarbons, tetrameric in Et_2O, and di- or trimeric in THF at -108°C.

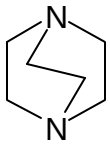
  - Very strong donors, like difunctional ligands, can give monomeric complexes.



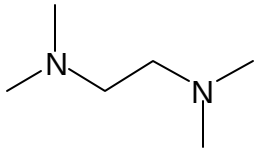
tetrahydrofuran
(THF)



diethyl ether
(Et_2O)



diazabicyclo-[2,2,2]-octane
(DABCO)



N,N,N',N'-tetramethyl-
1,2-diaminoethane
(TMEDA)

- Rate of reactions in different solvents: THF > Et_2O > hydrocarbons

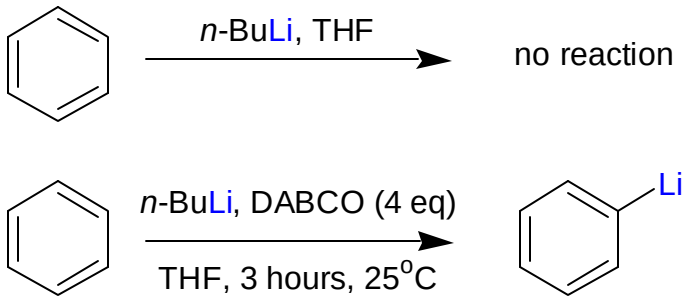
- Reactivity also enhanced by addition of electron-donating ligands.

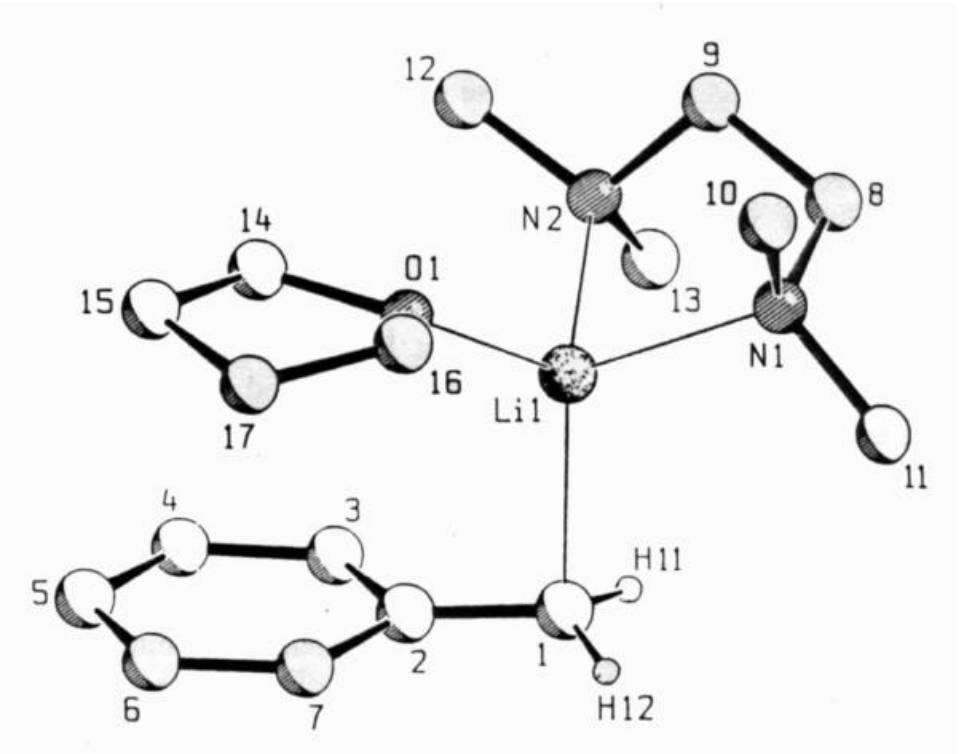
Ligand and Solvent Effects - 2

- Lithium prefers to be tetracoordinated.

- Variations in structure and complex formation influence reactivity.

- Some effects are dramatic:





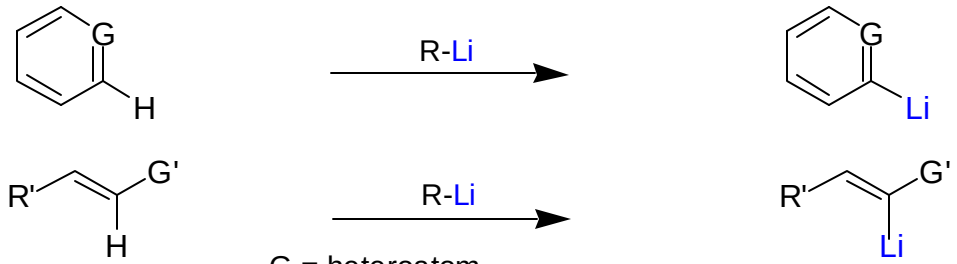
Zarges, W. *et al. Chem. Ber.* **1989**, *122*, 2303-2309.

- Ligand interaction allows for introduction of asymmetry into lithiations.

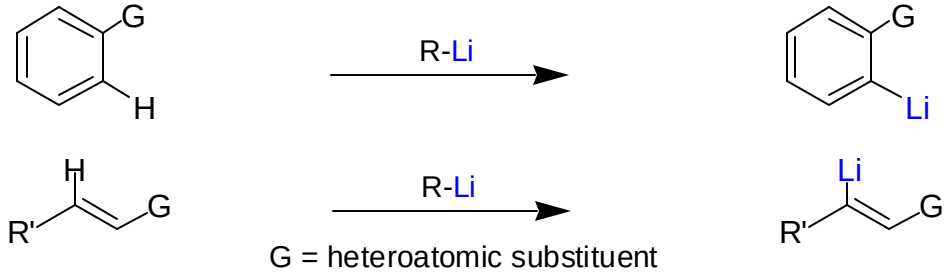
- Achiral organolithium reagents and substrates can give chiral products in the presence of a chiral ligand.

α- and β- (*ortho*-) Lithiations

- α-lithiations: the organolithium deprotonates the sp^2-carbon *alpha* to the heteroatom.



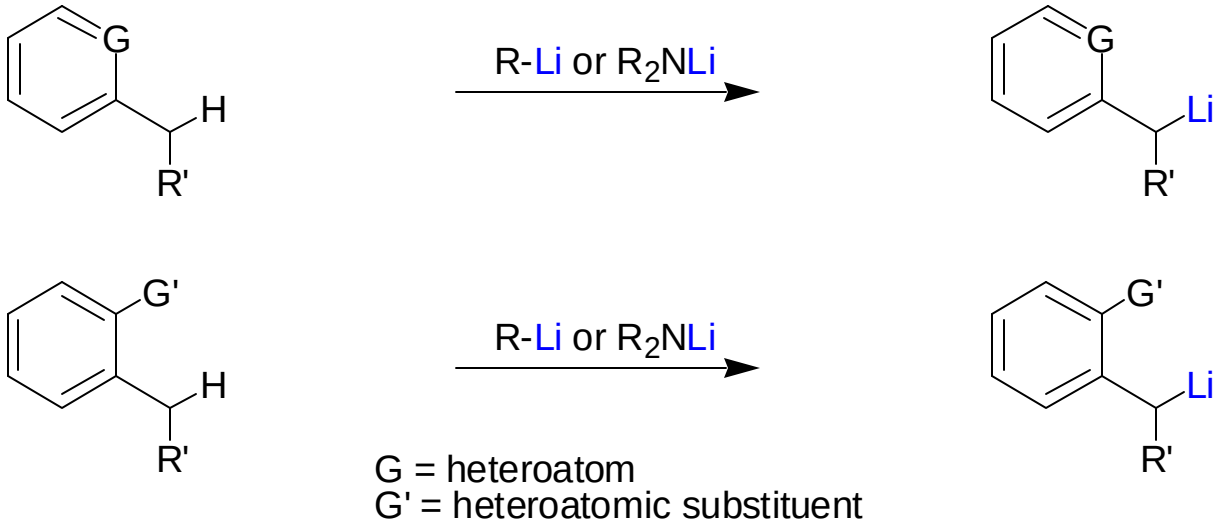
- β-lithiations: the organolithium is directed to deprotonate the sp^2-carbon *beta* to the heteroatomic substituent.



- The term "*ortho*" is reserved for the *beta* metallation of carbocyclic aromatic systems.

Lateral Lithiations

- Lateral lithiations deprotonate at a benzylic (side chain) position lateral to, or flanked by, a heteroatomic substituent.



G = heteroatom
G' = heteroatomic substituent

- The heteroatomic substituent facilitates lithiation relative to the unsubstituted substrate.

- The lithiated species are used for functionalization of benzylic sites; chain extensions; and synthesis of fused carbocylic and heterocyclic systems.

Mechanism of Lithiations - 1

- Heteroatomic substituents:
    1) Increase reactivity of substrates.
    2) Direct regioselectivity of deprotonation.

- Mechanistic proposals must explain both observations.

- Two major mechanisms theorized to drive *ortho*-lithiations:

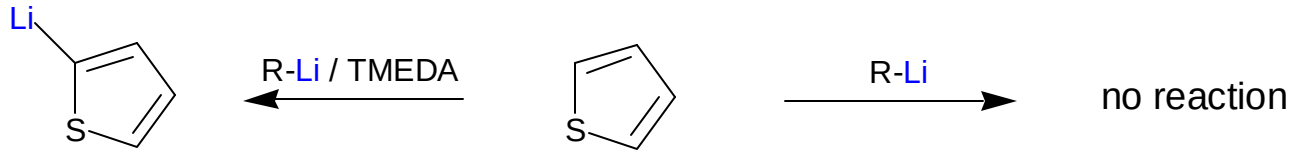
    1) "**Coordination only**" - substituent coordinates or "complexes" with organolithium reagent to increase kinetic basicity, and directs deprotonation to *ortho* position.

    2) "**Acid-base**" - inductive and/or resonance effects from heteroatomic substituent make *ortho* proton more acidic.

- Some lithiations are driven entirely by one factor or the other, but the majority of lithiations occur by a combination of both.

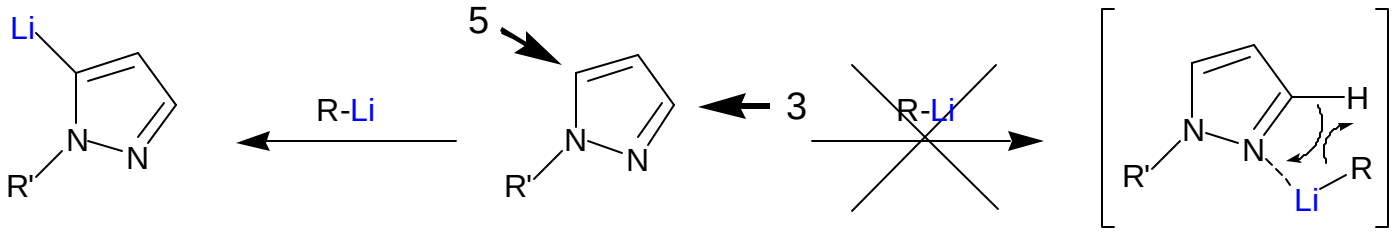
Mechanism of Lithiations - 2

- Organolithiums were thought to coordinate to heteroatoms in α-lithiation of heterocycles. However,



  - Sulfur atom of thiophene does not act as Lewis base to break up the lithium aggregates.
  - Rate enhancement and regioselectivty attributed to "**acid-base**" mechanism.

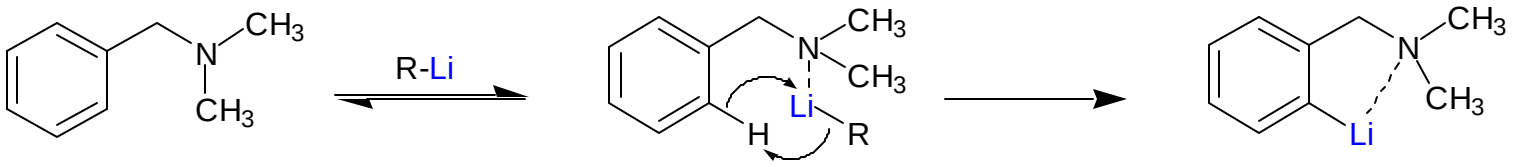
- Another example of "**acid-base**" mechanism from N-substituted pyrazoles:



Mechanism of Lithiations - 3

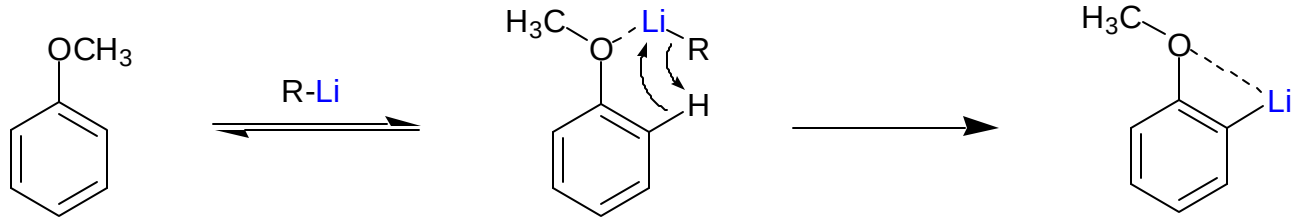
- Example of "**coordination only**" mechanism from *ortho*-lithiation of N,N-dimethyl-benzylamine:

  - Inductive effect from benzylic methylene lowers acidity of *ortho* proton, but deprotonation occurs exclusively at *ortho* position.



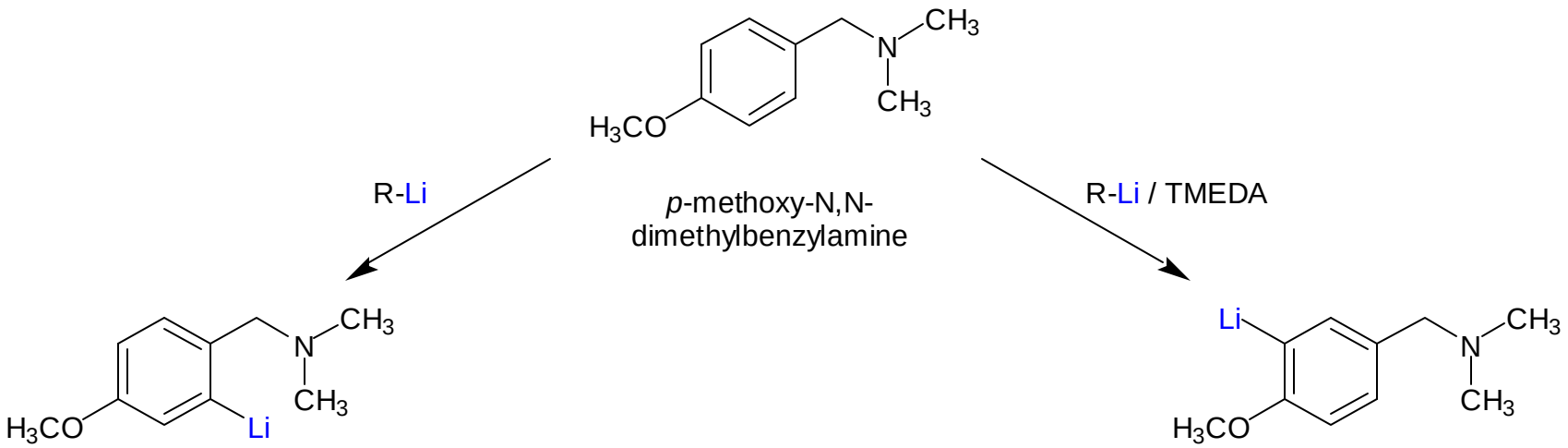
  - Excess lithiating reagent only gives monolithiated product.
  - Intramolecular model of the lithiation of benzene with R-Li/TMEDA.

- Lithiation of anisole shows combination of both "**coordination only**" and "**acid-base**" mechanisms:



Mechanism of Lithiations - 4

- Either mechanism can dominate depending on conditions:

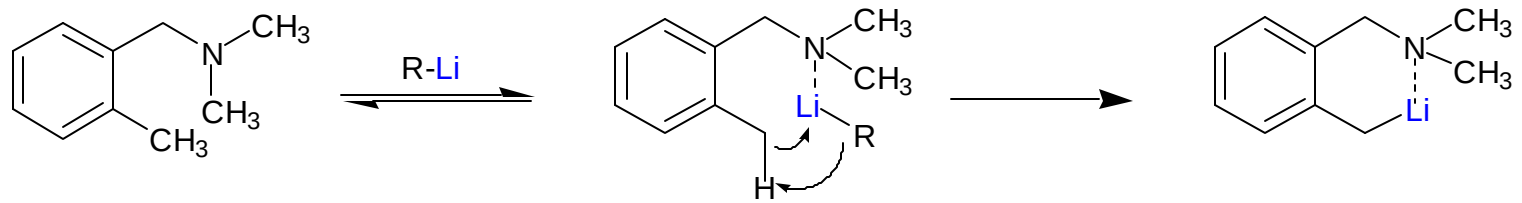


- Regioselectivity of multiple directing groups ranked similar to S_EAr.

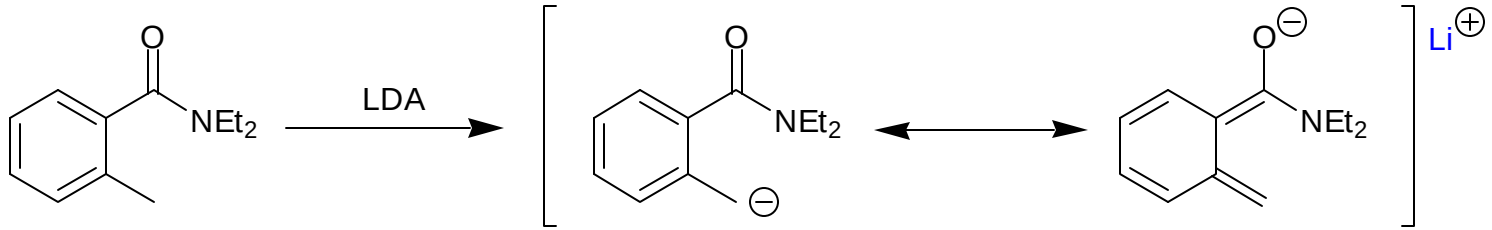
Mechanism of Lithiations - 5

- Same mechanistic approaches used to explain regioselectivity of lateral lithiations.
  - "Coordination-only" mechanism dominant.

- Complex-induced proximity effect (CIPE) presents unified coordination theory:
  - R-Li/substrate complex provides proper geometry for reaction.



  - Accounts for resonance, stereoelectronic, inductive and steric effects.



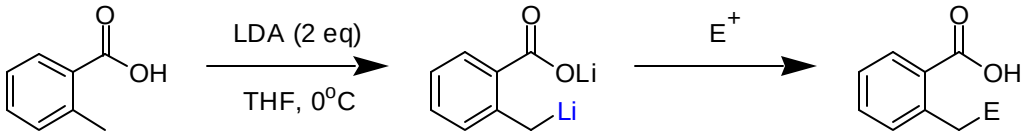
  - Explains why kinetic product is favoured over thermodynamic product.

Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356-363.

The Substrates - 1

Toluic Acid and Derivatives

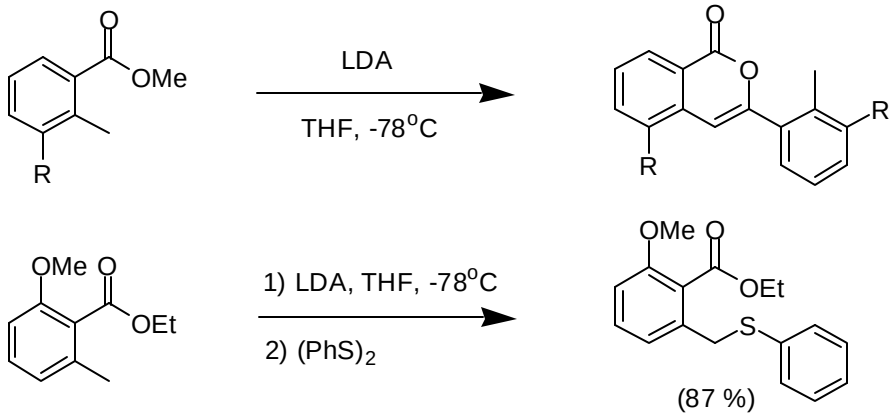
- Toluic acids:



Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396.

- Stronger bases require lower temperatures.
- Lateral lithiation due to electron-withdrawing properties of caroxylate.

- Toluate esters:

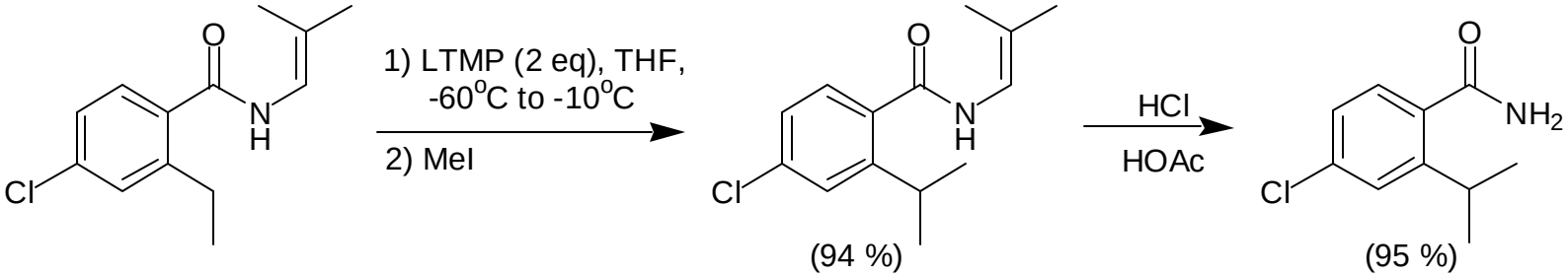


Hauser, F. M. *et. al*. *Synthesis* **1980**, 72.

The Substrates - 2

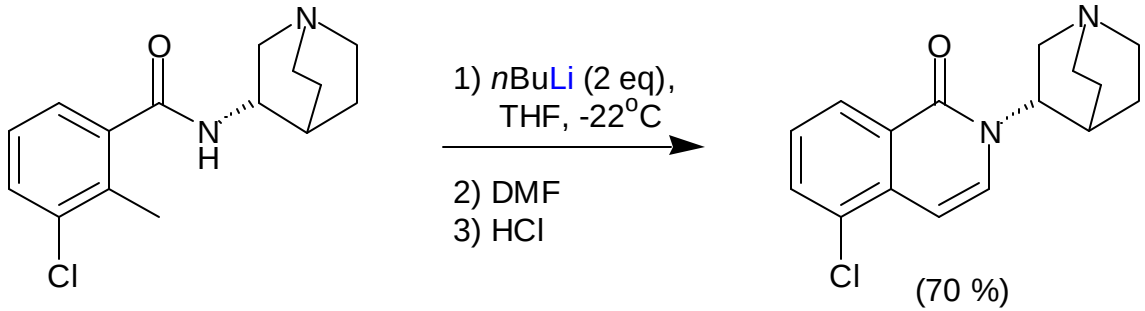
Toluamides

- 1^{o} toluamides show no regioselectivity.
  - Use acid labile protecting/activating group:



Clark, R. D. *et. al. Can. J. Chem.* **1994**, *72*, 23.

- 2^{o} and 3^{o} amides are powerful directing groups.
  - N-substituents can be any group not affected by organolithiums.

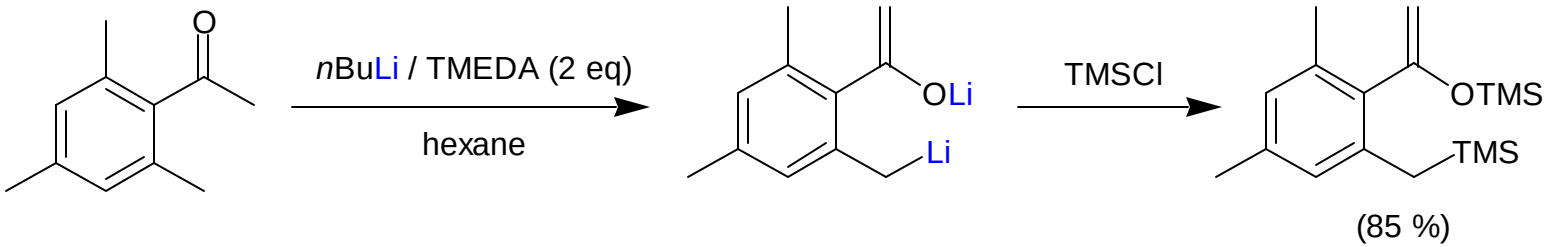


Clark, R. D. *et. al. J. Med. Chem.* **1993**, *36*, 2645.

The Substrates - 3

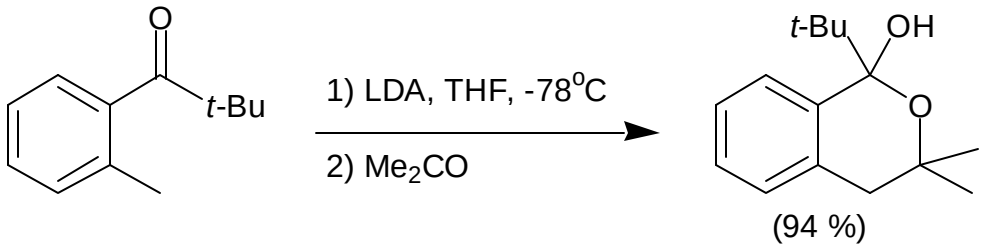
Tolyl Ketones

- Enolizable ketones facilitate lateral lithiations well:



Klein, J.; Medlik-Balan, A. *J. Org. Chem.* **1976**, *41*, 3307.

- Only one example of nonenolizable ketone:

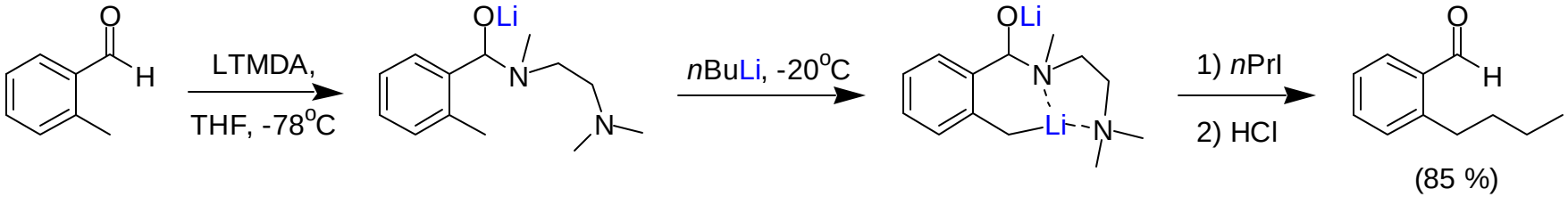


Kobayashi, K. *et. al. J. Chem. Soc., Perkin Trans. I* **1994**, 309.

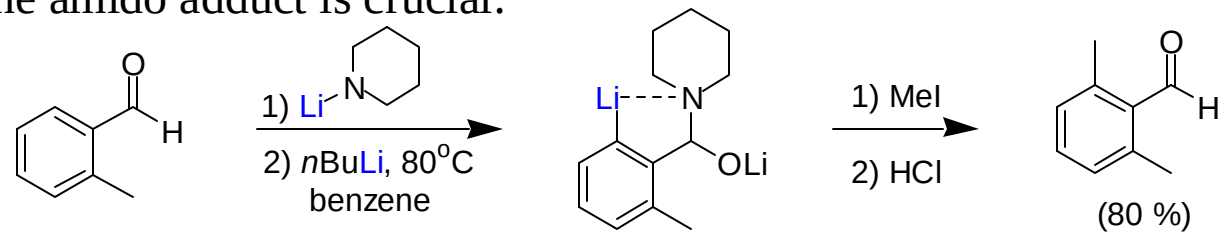
The Substrates - 4

Tolualdehydes

- Too electrophilic to lithiate directly.
  - Make amido adducts:

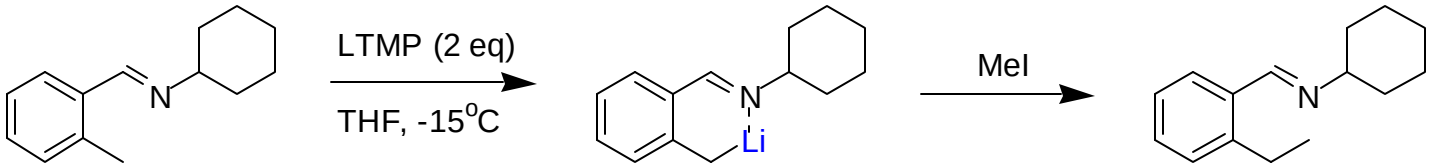


  - Diamine amido adduct is crucial:



Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1983,** *49*, 1078.

  - Can also make imines:

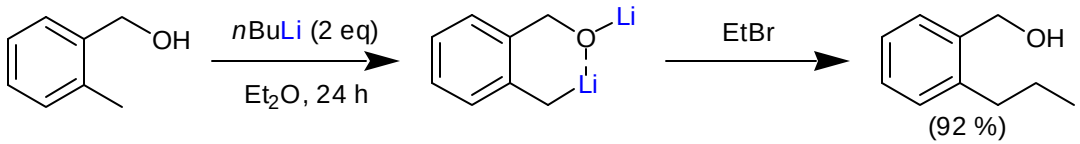


Flippin, L. A. *J. Org. Chem.* **1993**, *58*, 2463.

The Substrates - 5

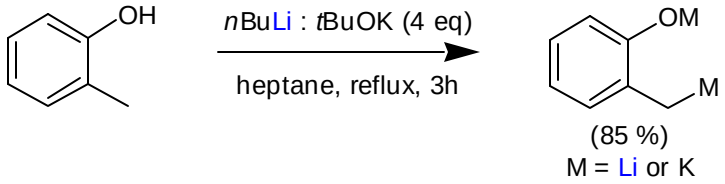
Alcohols and Cresols

- Benzyl alcohols show weak facilitation:



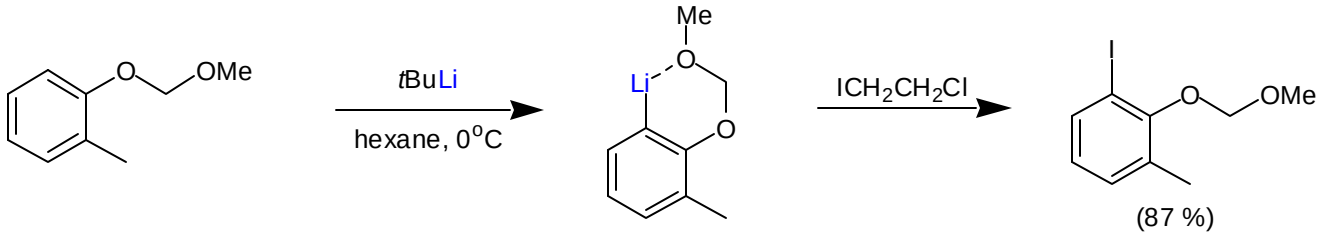
Braun, M; Ringer, E. *Tetrahedron Lett*. **1983**, *24*, 1233.

- *o*-Cresol requires "superbase" and vigorous conditions:



Bates, R. B.; Siahaan, T. J. *J. Org. Chem*. **1986**, *51*, 1432.

- MOM-protected *o*-cresol gives *ortho'*-lithiation exclusively:



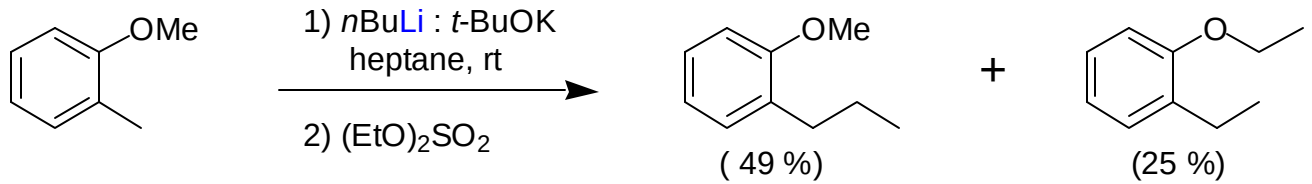
Winkle, M. R.; Ronald, R. C. *J. Org. Chem*. **1982**, *47*, 2101.

The Substrates - 6

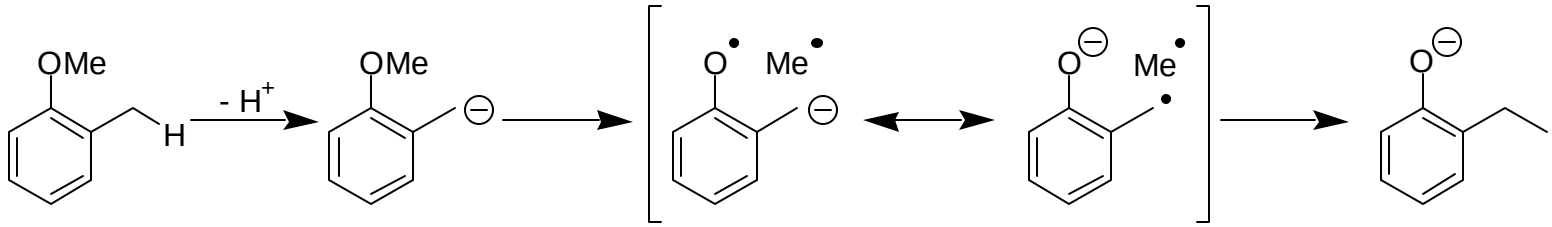
Aryl Ethers

- *o*-Methylanisole gives both *ortho*- and lateral lithiation with *n*BuLi.

- "Superbase" gives lateral lithiation, but also rearrangement products:



- Rearrangement through radical mechanism?

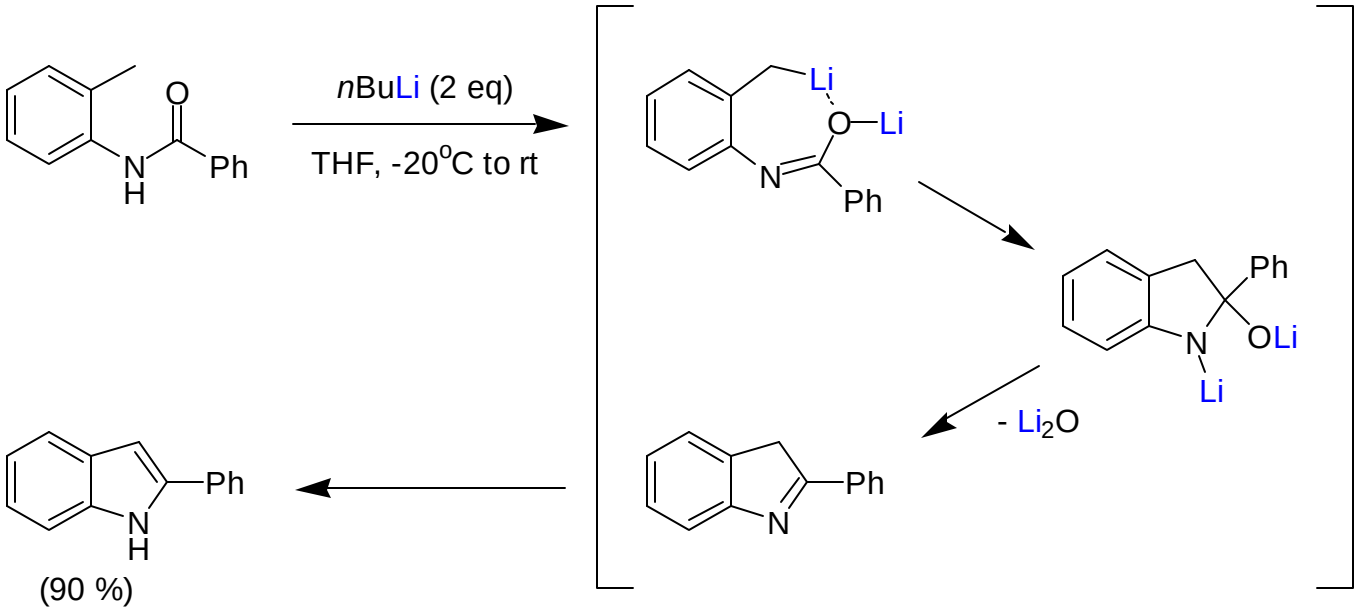


Bates, R. B.; Siahaan, T. J.; Suvannachut, K. *J. Org. Chem.* **1990**, *55*, 1328.

The Substrates - 7

Toluidines in Indole Synthesis

- Dilithiated *N*-acyl-*o*-toluidines can be trapped with electrophiles at low temperatures.
- Prolonged reaction at rt. allows intramolecular condensation/elimination to give indoles:

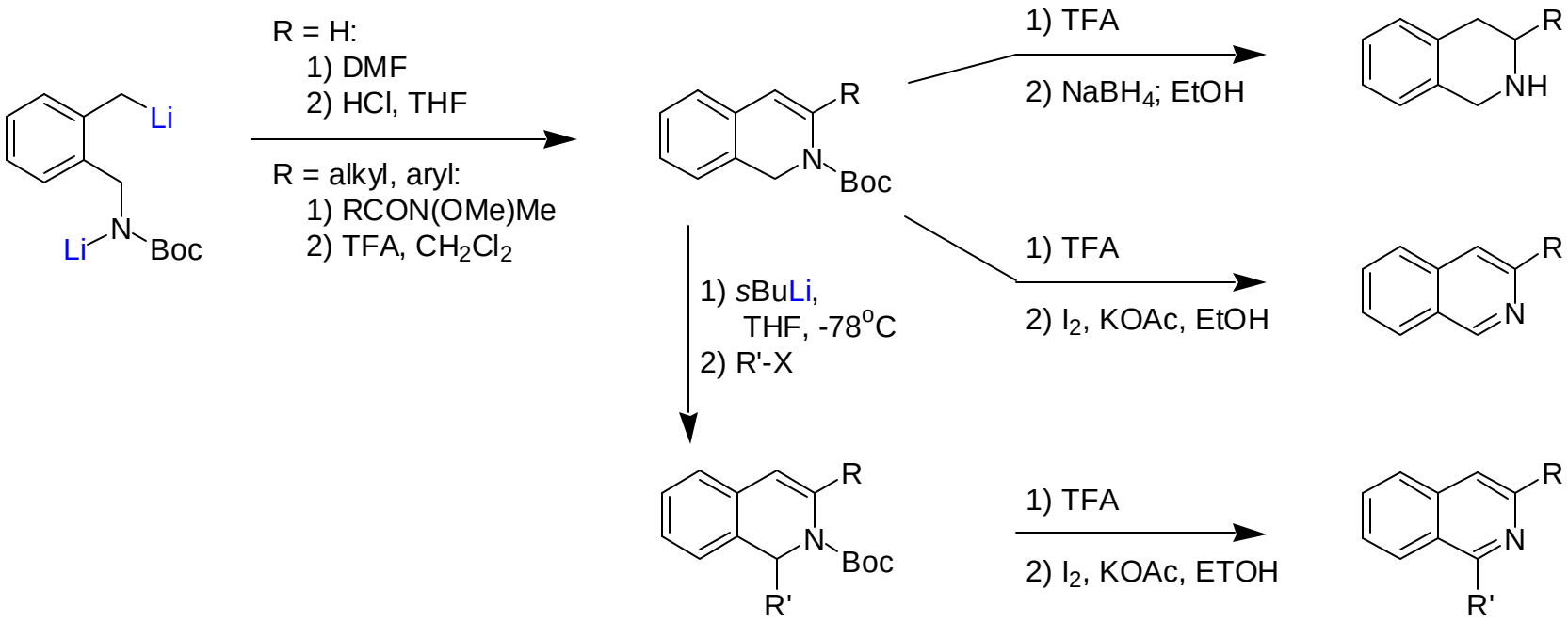


Allen, D. A. *Synth. Commun.*, **1999**, *29*, 447.
Fuhrer, W.; Gschwend, H. W. *J. Org. Chem*. **1979**, *44*, 1133.
Houlithan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511.

The Substrates - 8

Benzylamines in Isoquinoline Synthesis

- Lateral lithiation of Boc-2-methylbenzylamine provides access to a variety of isoquinoline derivatives:



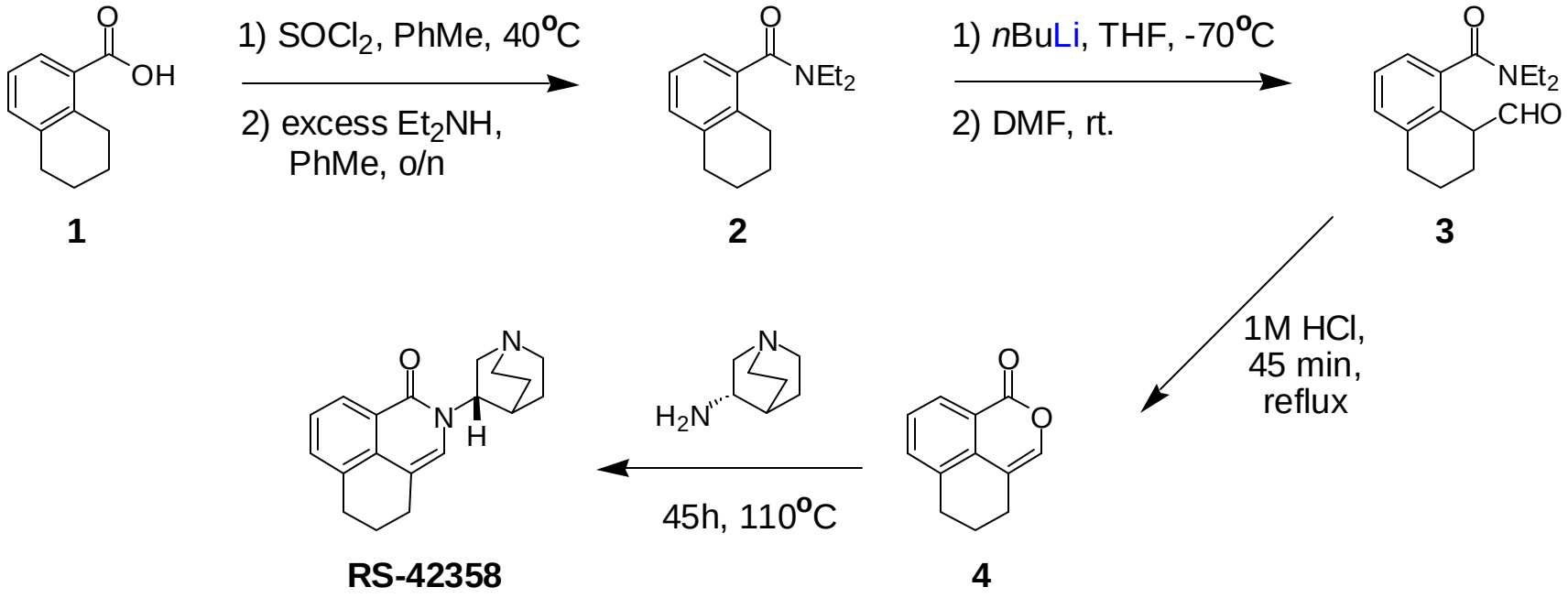
Clark, R. D. *et al. Can. J. Chem.*, **1994**, *72*, 23.

Total Synthesis of RS-42358

- RS-42358 and analogs are a class of 5-HT_3 receptor antagonists that show promise as anti-emetic agents.

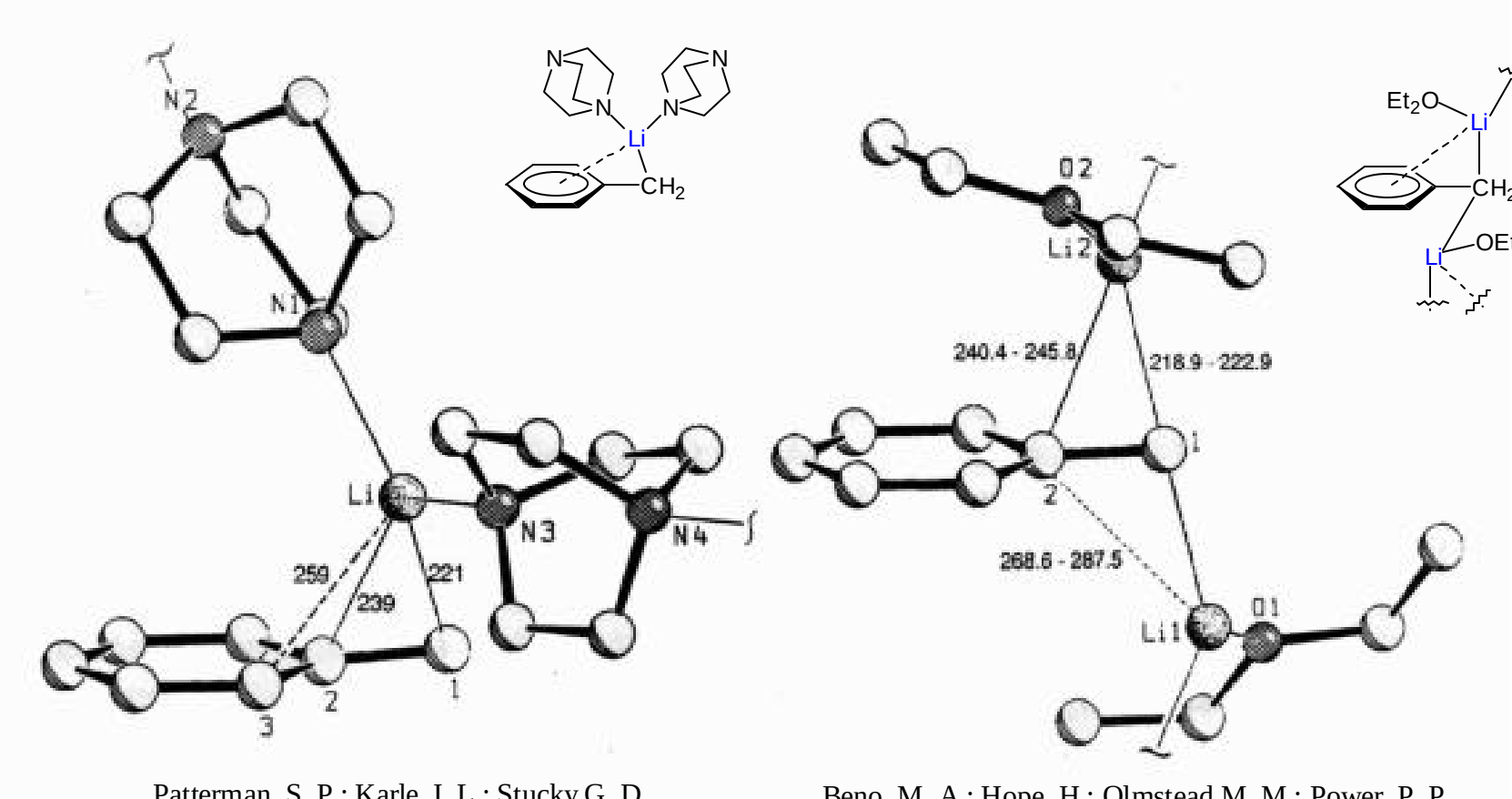
- Lateral lithiation is the key step towards closure of the intermediate **4**.

- Condensation of **4** with other amines allows facile generation of N-substituted amides.



Kowalczyk, B. A. *Synthesis* **2000**, *8*, 1113 - 1116.

The Lithiated Benzylic Carbanion



Patterman, S. P.; Karle, I. L.; Stucky G. D.
J. Am. Chem. Soc. **1970**, *92*, 1150-1157.

Beno, M. A.; Hope, H.; Olmstead M. M.; Power, P. P.
Organometallics **1985**, *4*, 2117-2121.

- Lithium cation was seen to be sp^2 hybridized, and was stabilized by projecting p-orbital into the π cloud of the aromatic ring.

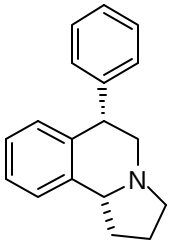
Deracemization of Diarylmethanes - 1

- Many bioactive molecules contain a chiral diarylmethane unit.

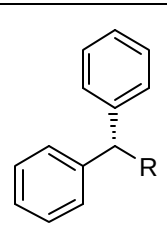
- Pharmocological interest due to ability to inhibit uptake of neutrotransmitters at post-synaptic receptors.

- Usually, only one enantiomer is biologically active, but synthesized in racemic form.

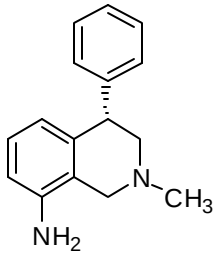
- Resolution of the crude products is inefficient, time-consuming, and expensive.



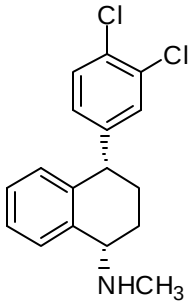
Hexahydropyrrolo [2,1-a] isoquinolines



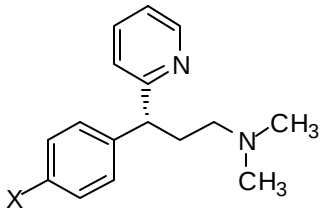
Diarylmethane Unit



4-aryltetrahydro-isoquinolines



Sertraline



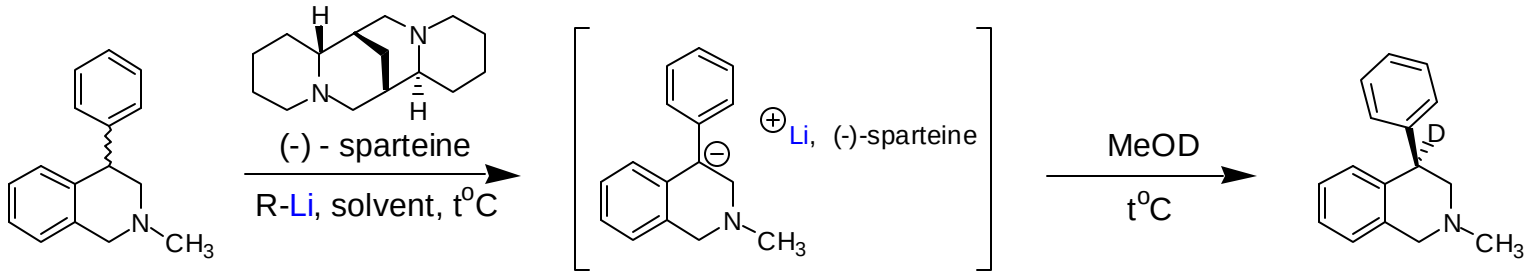
X = H, Cl, Br

Pheniramines

Deracemization of Diarylmethanes - 2

- Alternatives to resolution include asymmetric synthesis, or epimerization of chiral centers.

- Prat *et al.* discovered that deracemization of racemic diarylmethanes could be effected via lateral lithiation-protonation sequence with a chiral ligand.



Entry	Solvent	Li-Base (eq)	(-)-Spart eq	t (°C)	Time (h)	Ratio **1**-d_1 / **1**	e.e. (%)
1	PhMe	*s*BuLi (4)	4	-78	2	10 / 90	-
2	THF	*t*BuLi (4)	4	-78	2	90 / 10	4
3	THF	*s*BuLi (4)	4	-78	2	90 / 10	4
4	Et_2O	*s*BuLi (4)	4	-78	2	65 / 35	65
5	Et_2O	*s*BuLi (4)	4	-45	12	90 / 10	83
6	Et_2O	*s*BuLi (4)	4	-45	24	>95 / 5	88

Prat, L. *et al. Tetrahedron: Asymmetry* **1998**, *9*, 2509 - 2516.

Deracemization of Diarylmethanes - 3

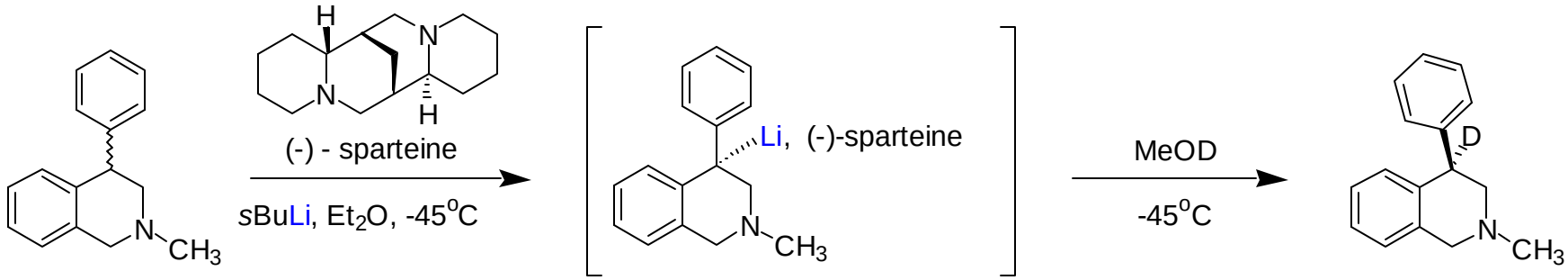
- Mechanism of enantioselectivity depends on confirgurational stability of benzylic carbanion. Two possibilities:

    1) Lithiation via asymmetric deprotonation.

    2) Post-lithiation dynamic resolution.

- Changing proton source (EtOH, *t*-BuOH, AcOH, H_2O, DMSO) did not change e.e.

- Conclusion: enantioselectivity through post-lithiation dynamic resolutionto form the diastereomeric **1**-Li/(-)-sparteine complexes of pyramidal benzylic carbanions.



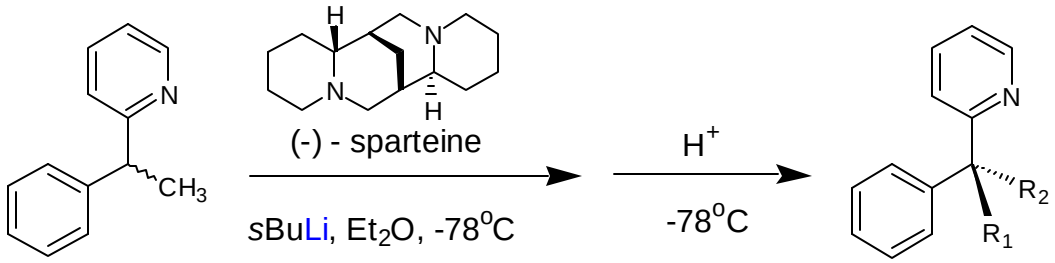
(*rac*) - 1

(*R*) - 1 - d_1

Prat, L. *et al. Tetrahedron: Asymmetry* **1998**, *9*, 2509 - 2516.

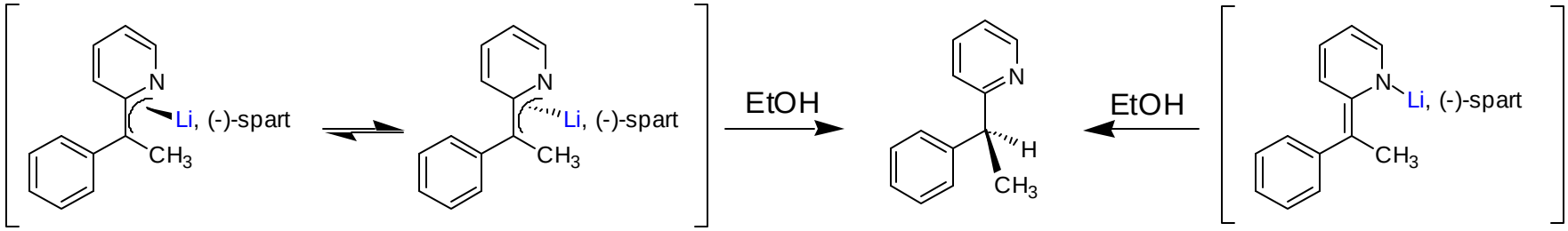
Deracemization of Diarylmethanes - 4

- Deracemization of pheniramine **2** displays changing enantioselectivity depending on the proton source:



Entry	R_1	R_2	H^+ Source	e.e. (%)
1	Me	H	EtOH	50 (*S*)
2	H	Me	*t*-BuOH	50 (*R*)

- Enantioselectivity can occur through dynamic resolution or asymmetric protonation:



Resolution of a 1,3-azaallyl complex

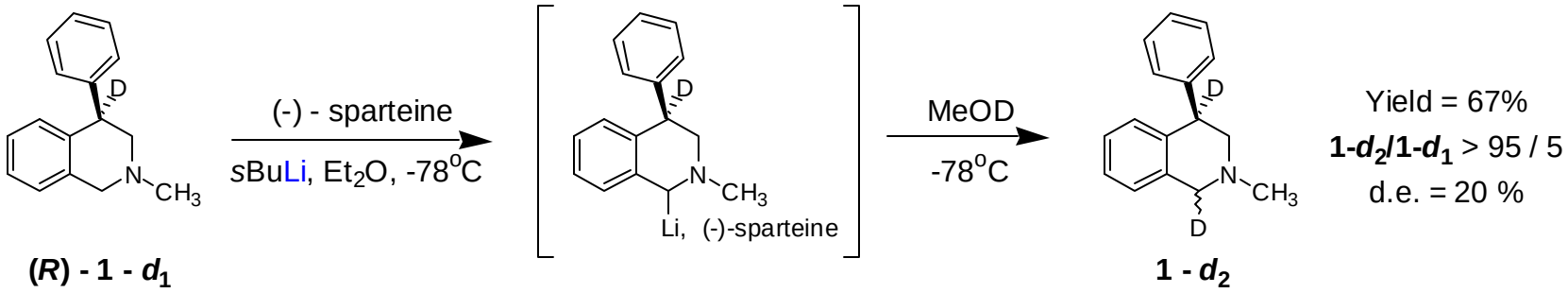
(*S*) - 2

Asymmetric protonation of an enamide

Prat, L. *et al. Tetrahedron: Asymmetry* **1998**, *9*, 2509 - 2516.

Kinetic Isotope Effects on Lithiations - 1

- Further lithiation of **1-d_1** resulted in deprotonation exclusively at C-1.



Prat, L. *et al. Tetrahedron: Asymmetry* **1998**, *9*, 2509 - 2516.

- Chiral HPLC of **1-d_2** indicated that no racemization at C-4.

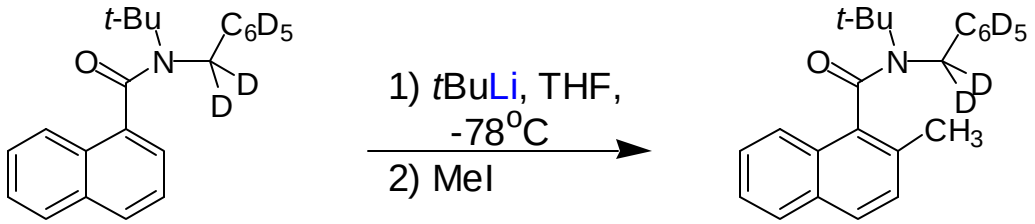
- Usually, deprotonation of 1,2,3,4-tetrahydroisoquinolines at C-1 requires a protecting group on nitrogen which activates through chelation and dipole stabilization.

- Conclusion: deuterium isotope effects can be used to direct regioselectivity of lithiations.

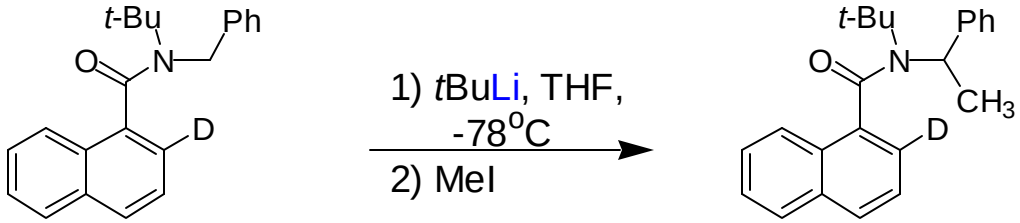
Kinetic Isotope Effects on Lithiations - 2

- Deuterium substitution at positions of high kinetic acidity can alter expected regio-selectivity of organolithium reagents.

- Deuterium can act as a protecting group for carbon.



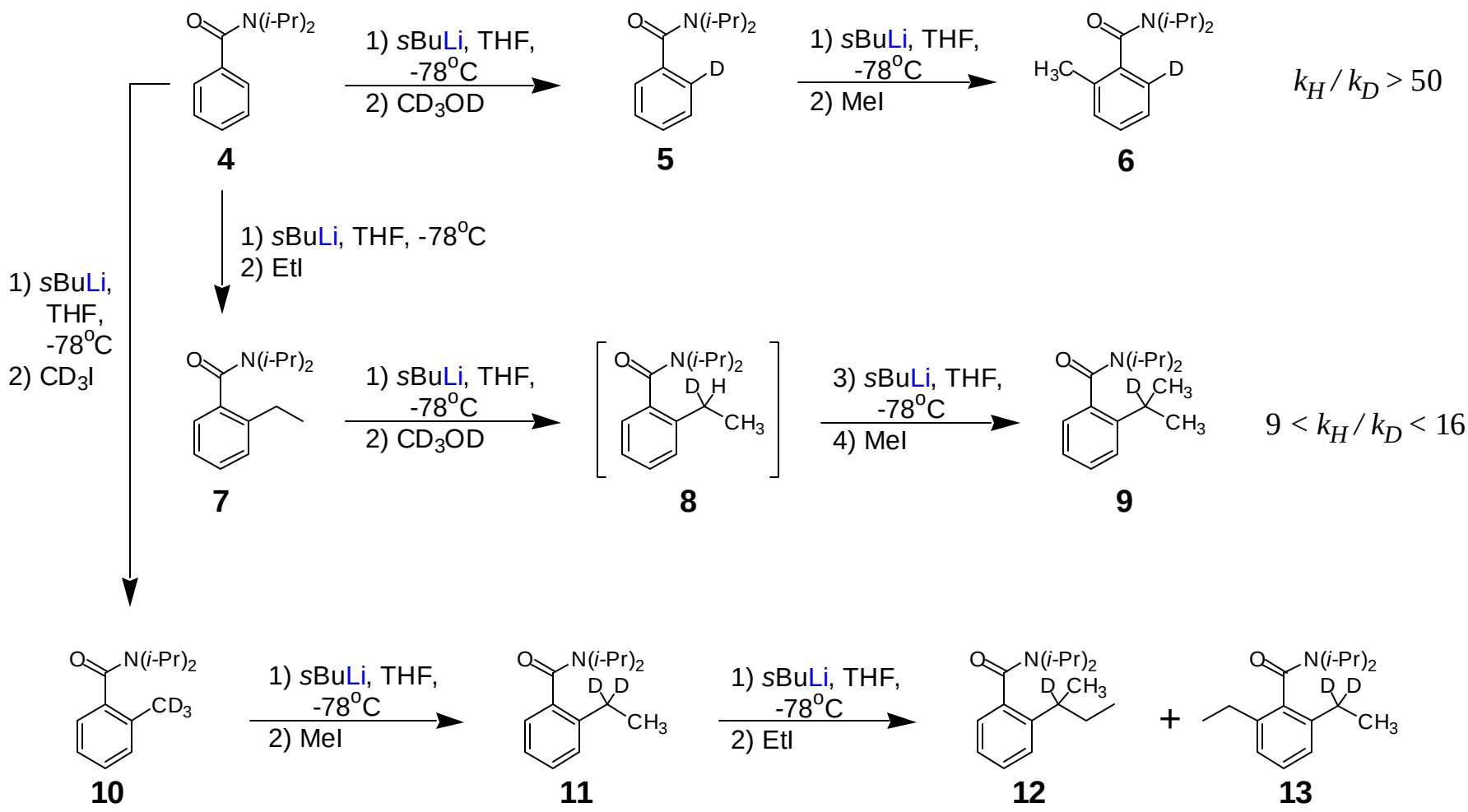
1 - *d_7-Bn* **2**



1 - *ortho-d_1* **3**

Clayden, J. *et al. Tetrahedron Letters* **1998**, *39*, 8377-8380.

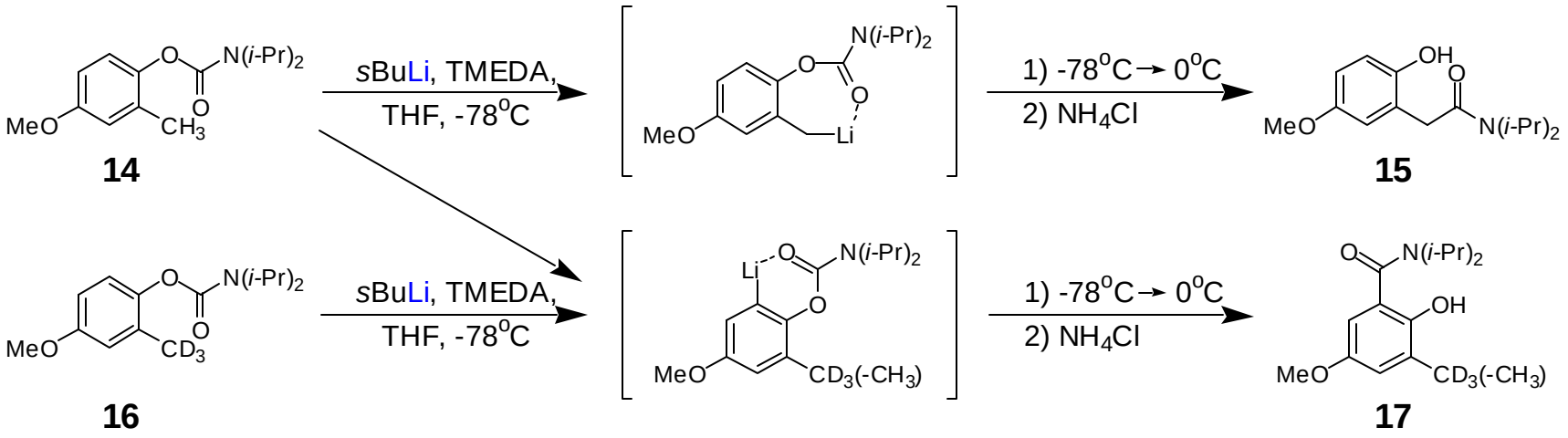
Kinetic Isotope Effects on Lithiations - 3



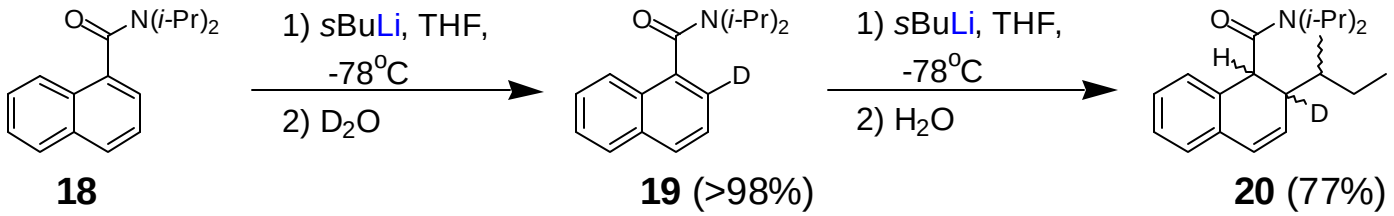
Clayden, J. *et al. Tetrahedron Letters* **1998**, *39*, 8377-8380.

Kinetic Isotope Effects on Lithiations - 4

- Effectiveness of deuterium isotope regioselectivity is substrate dependent:



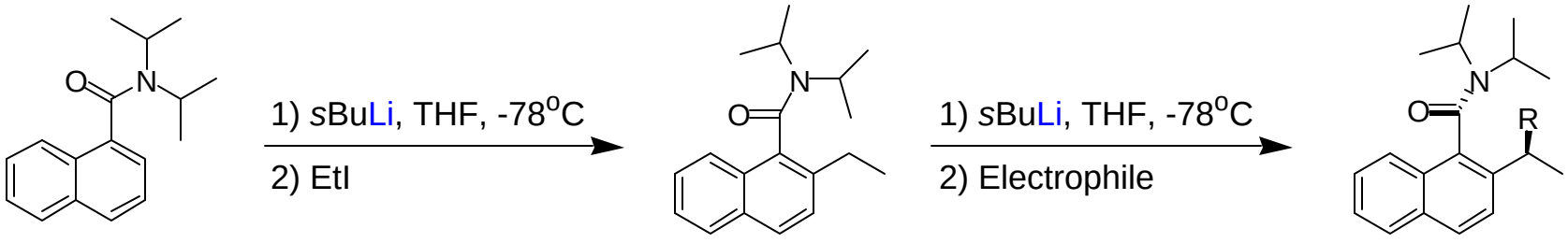
- In the absence of an acidic proton, substrate can undergo nucleophilic addition:



Clayden, J. *et al. Tetrahedron Letters* **1998**, *39*, 8377-8380.

Diastereoselective Deprotonation - 1

- Diastereoselective lateral lithiation can be accomplished without use of a chiral ligand.



1 **2** **3 - 7**

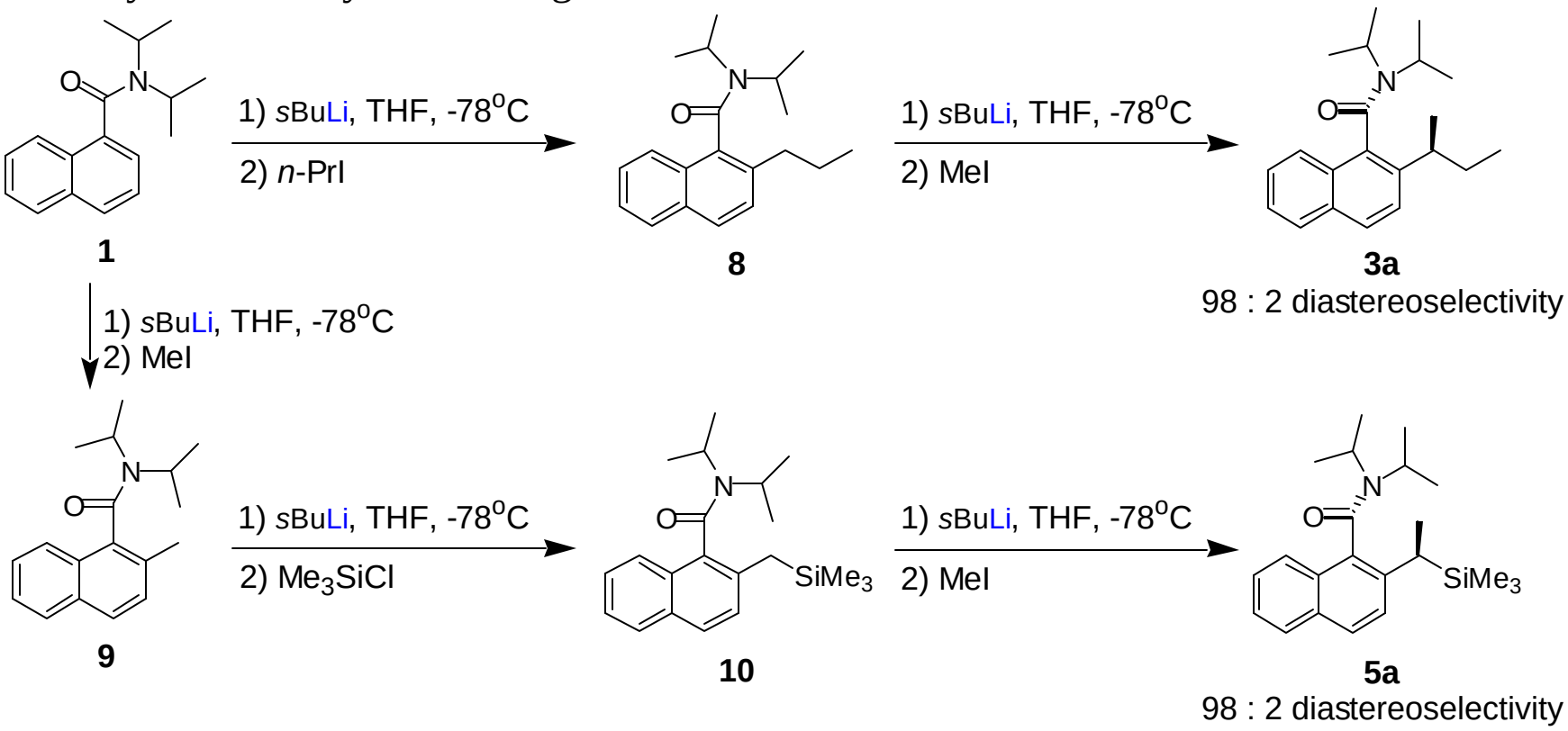
Entry	Eletrophile	R	Yield (%)	Diastereoselectivity
3	EtI	$-C_2H_5$	95	98 : 2
4	acetone	$-C(CH3)_2OH$	94	97 : 3
5	Me_3SiCl	$-SiMe_3$	88	98 : 2
6	$PhMe_2SiCl$	$-SiMe_2Ph$	93	97 : 3
7	CD_3OD	-D	97	90 : 10

Clayden, J.; Pink, J. H. *Tetrahedron Letters* **1997**, *38*, 2561 - 2564.

- All products showed *syn* relative stereochemistry giving evidence for oxygen direction of lithiating reagent.

Diastereoselective Deprotonation - 2

- To prove substituent directed stereoselectivity, diastereomers of **3** and **5** were synthesized by introducing substituents in reverse order.



Clayden, J.; Pink, J. H. *Tetrahedron Letters* **1997**, *38*, 2561 - 2564.

- Again, all products showed *syn* relative stereochemistry.

Conclusions and Future Work

- Lithiation offers facile method of functionalization of aromatic systems.

- Heteroatom-facilitated lateral and *ortho*-lithiations provide predictable regio- and stereoselectivities.

- Mechanistic picture still unclear, much work left to be done:

  - Developments in heteroatomic NMR will help to elucidate structures.

  - X-ray crystal structures of heteroatom coordination in lithiated species are needed.

  - Definitive data on relative strengths of substituent direction needs to be compiled.

Acknowledgements

Professor R. A. Batey

Batey Research Group