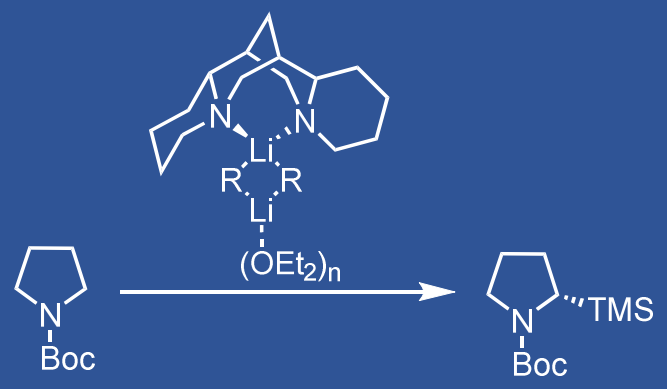
Enantioselective Lithiation-Substitution of Nitrogen-Containing Heterocycles

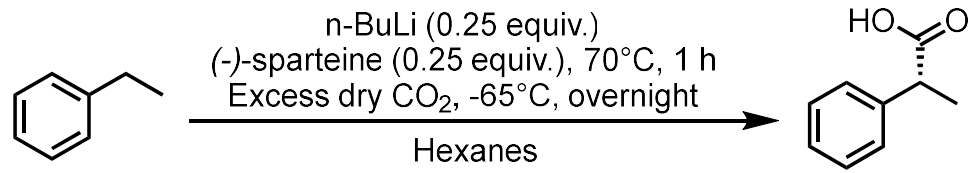
Emily M. Mumford

February 25, 2020



Historical Context: Asymmetric lithiation-substitutions using *(-)*-sparteine as a chiral ligand

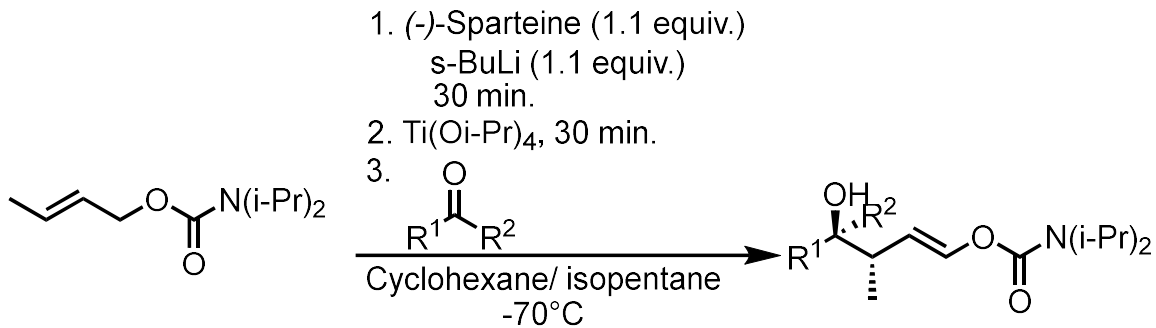
Noyori et al. (1971)



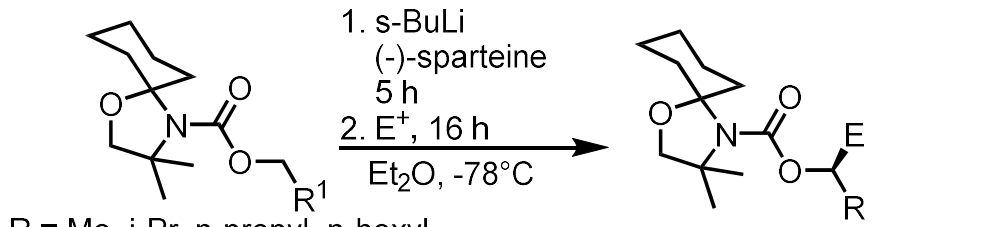
18% NMR yield
70:30 e.r.
(calculated from optical rotation of mixture)

Hoppe et al. (1989-1990)

"Dipole-stabilized carbanions"
high levels of enantioselectivity
achieved using *s*-BuLi/ sparteine



92 -95% yield
80 - 84% e.e.



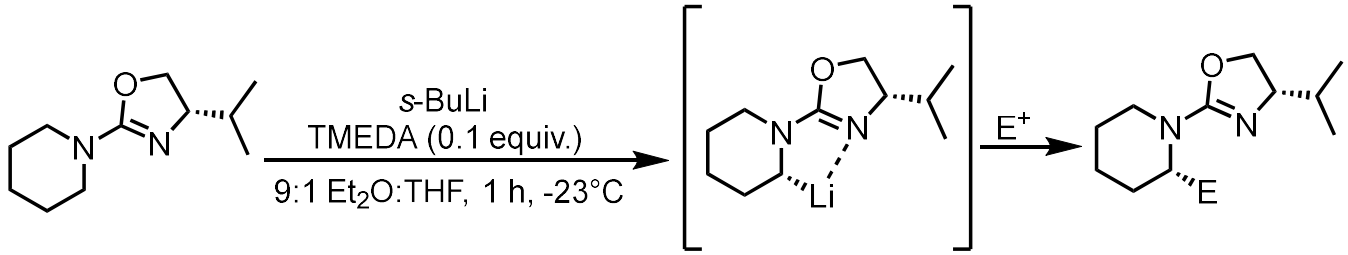
R = Me, i-Pr, n-propyl, n-hexyl

E = Me, TMS, COOH, Me_3Sn
52 - 86% yield
> 95% e.e.

Noyori, R. *et al. Tetrahedron* 1971, 27, 905; Hoppe, D. *et al. Angew. Chem. Int. Ed.* 1989, 28, 69; Hoppe, D. *et al. Angew. Chem. Int. Ed.* 1990, 29, 1422

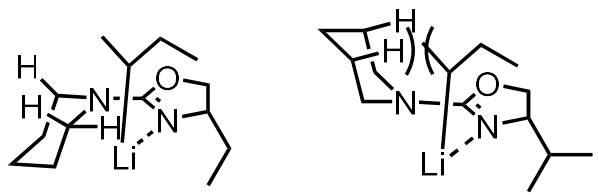
Diastereoselective lithiation-substitutions of nitrogen-containing heterocycles

Gawley and Bartolotti et al (1989)



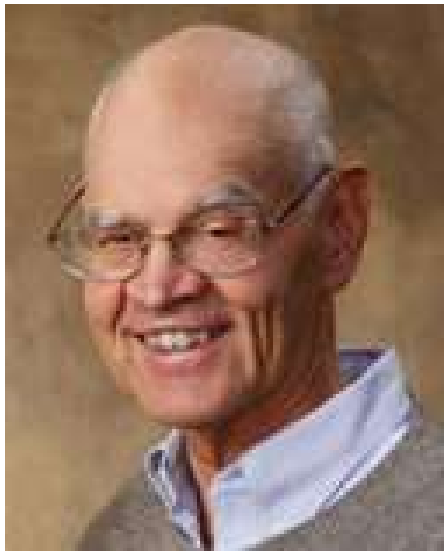
E = Me (96% yield), TMS (30% yield)
Single diastereomer

Diastereoselective deprotonation proposed

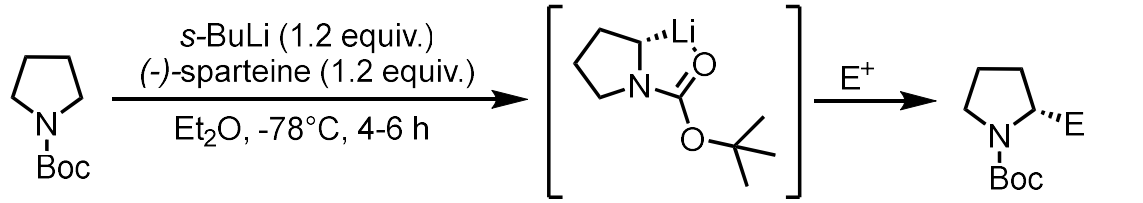


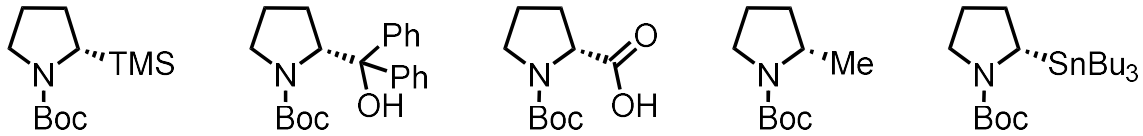
Favored Disfavored

Seminal (Synthetically Useful) Example: Peter Beak, 1991



Peter Beak





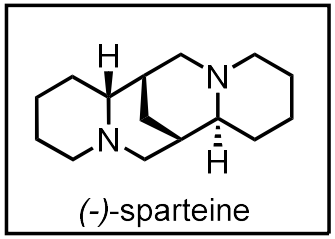
76% yield
96% e.e.

75% yield
90% e.e.

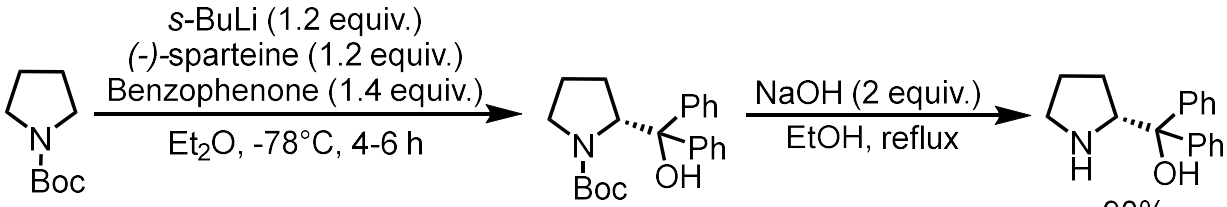
55% yield
88% e.e.

76% yield
95% e.e.

76% yield
95% e.e.



Synthetic utility: alternative route to proline derivatives



70% yield
99.3% e.e.
after single recrystallization

90%

Beak, P. *et al. J. Am. Chem. Soc.* 1991, 113, 25, 9708-9710; Image from http://www.nasonline.org/member-directory/members/62818.html

Outline and scope of presentation

1. Asymmetric Deprotonation
2. Asymmetric Substitution
3. Functionalization of 3, 4, and 7- membered rings
4. Comparison to other methods
5. Future directions

Outline and scope of presentation

1. **Asymmetric Deprotonation**
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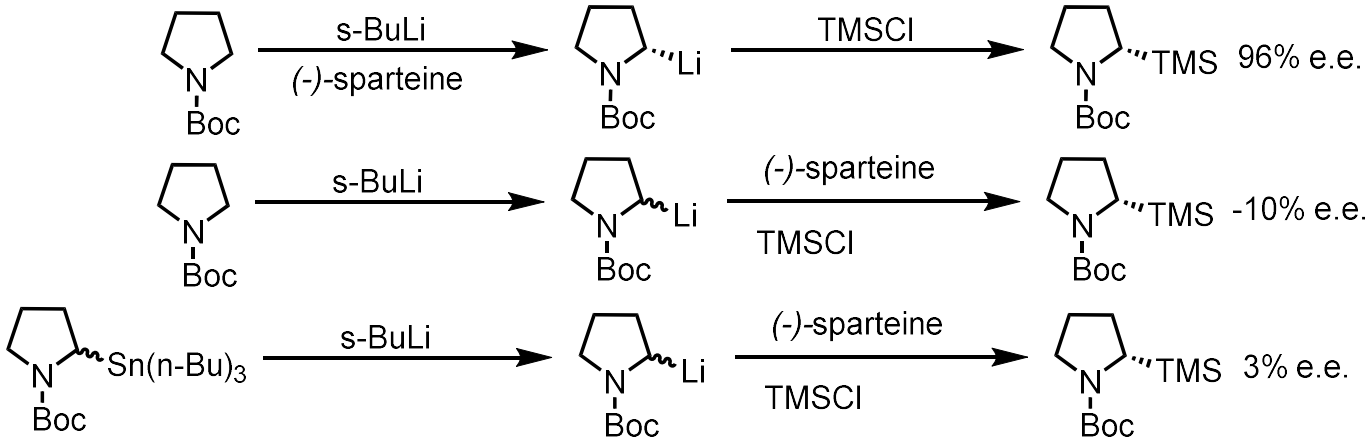
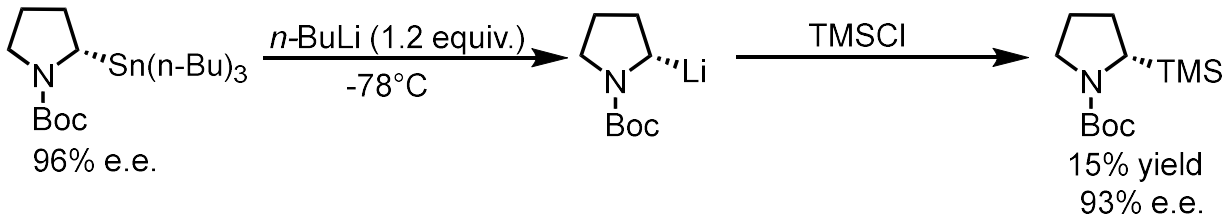
Evidence for asymmetric deprotonation



Generation of racemic organolithium followed by trapping with electrophile in the presence of *(-)*-sparteine fails to match the levels of enantioenrichment observed when sparteine is present for lithiation step

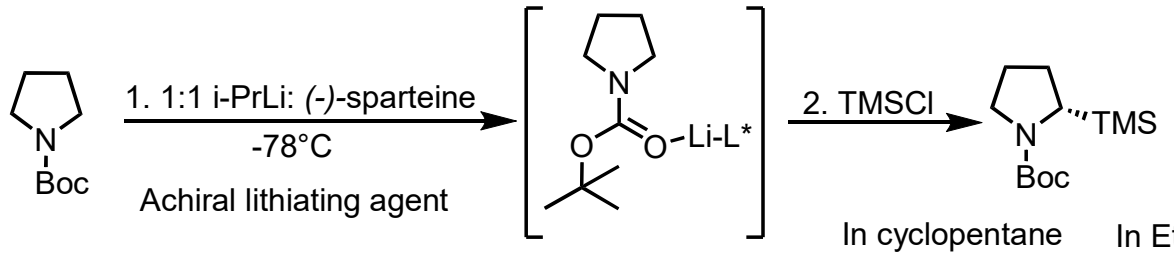


α-lithiopyrrolidine is configurationally stable under reaction conditions

Beak, P. *et al. J. Am. Chem. Soc.*. 1994, 116, 3231

Understanding stereoselectivity: structure and reactivity of isopropyllithium complex

Isopropyllithium shows similar reactivity and selectivity to s-BuLi



In cyclopentane
80% yield
80% e.e.

In Et_2O
67% yield
95% e.e.

With *s*-BuLi in Et_2O
76% yield
96% e.e.

^1H, ^{13}C, ^6Li NMR at -80°C of 1:1 i-Pr^{6}Li: (-)-sparteine in **Et2O-d$_{10}$**
(*in absence of N-Boc pyrrolidine)*

Diagnostic resonances

- ^1H: 2 types of iPr methines
- ^{13}C: 2 types of iPr methine carbons, with Li-C coupling suggesting each C is attached to 2 Li atoms → Li dimer
- ^6Li: 2 resonances: either 2 kinds of dimer or nonsymmetrical Li dimer

Beak, P. *et al. J. Am. Chem. Soc.* 1992, 114, 5872

Understanding stereoselectivity: structure and reactivity of isopropyllithium complex

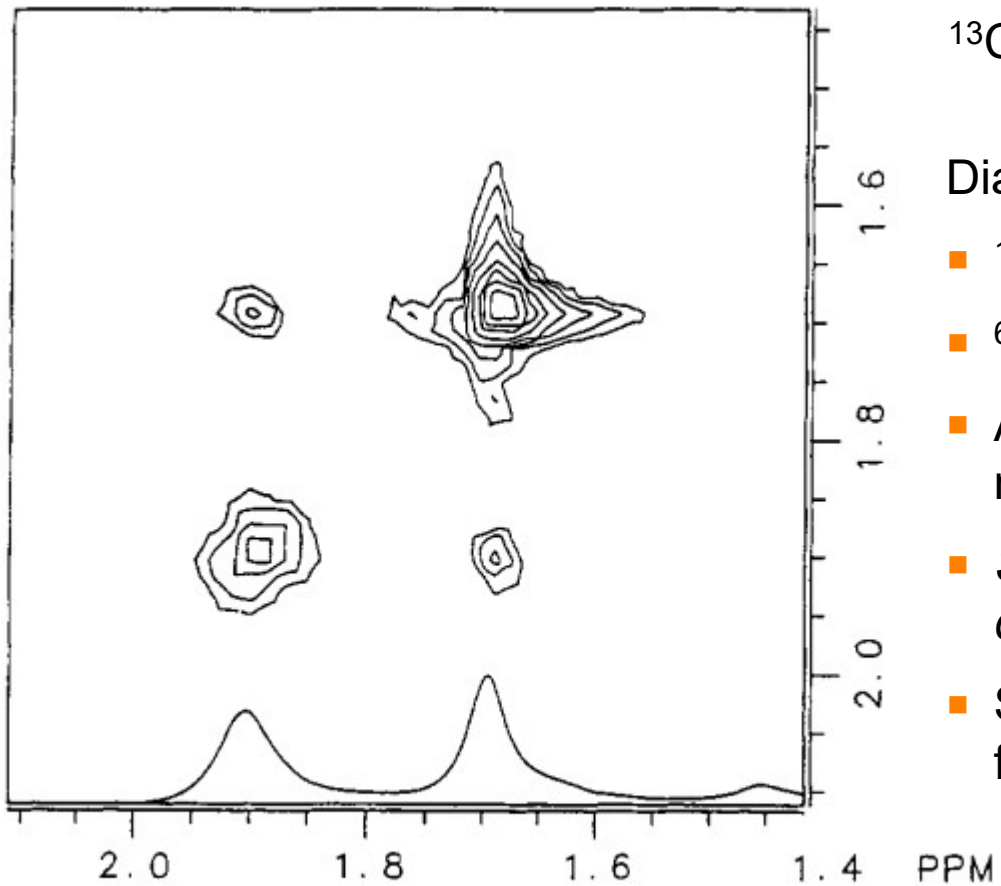


Figure 1. ^{6}Li–^{6}Li COSY spectrum of *i*-Pr^{6}Li/sparteine in Et_2O at −80 °C (0.2 M).

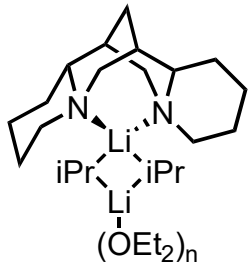
Cross peaks in COSY support nonsymmetrical dimer

^{13}C, ^{6}Li NMR at -80°C of 1:1 i-Pr^{6}Li: (-)-sparteine in **cyclopentane**

Diagnostic resonances

- ^{13}C: single broad iPr methine
- ^{6}Li: single broad peak
- Addition of 2.5 equiv. diethyl ether: resembles spectra in Et_2O_{d10}
- *Suggests incorporation of Et_2O in dimer*
- Spectra in cyclopentane attributed to fluxional sparteine coordination

Proposed dimer structure



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Understanding stereoselectivity: structure and reactivity of isopropyllithium complex

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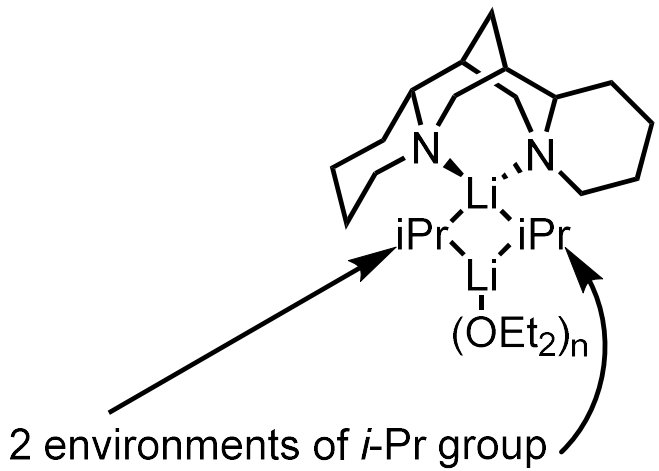

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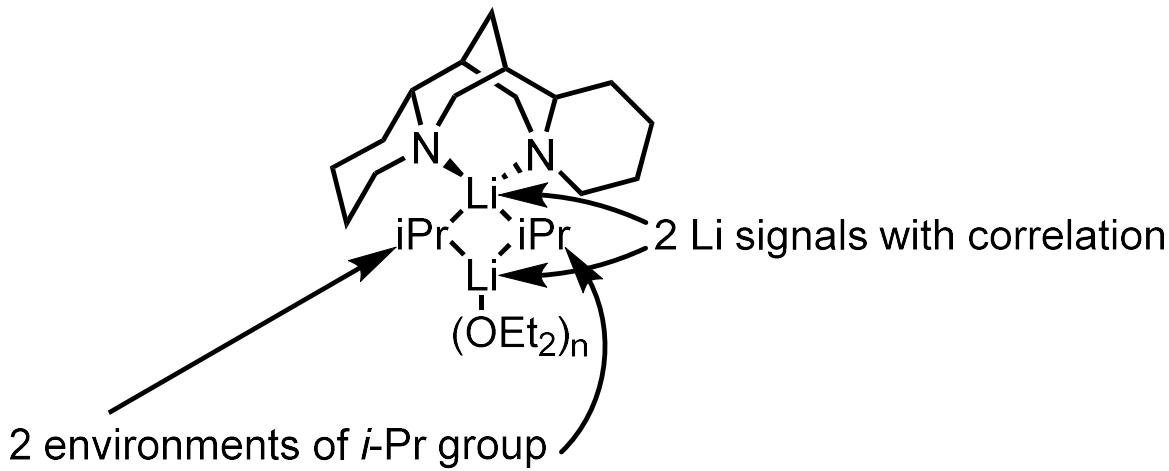
Understanding stereoselectivity: structure and reactivity of isopropyllithium complex

Proposed dimer structure

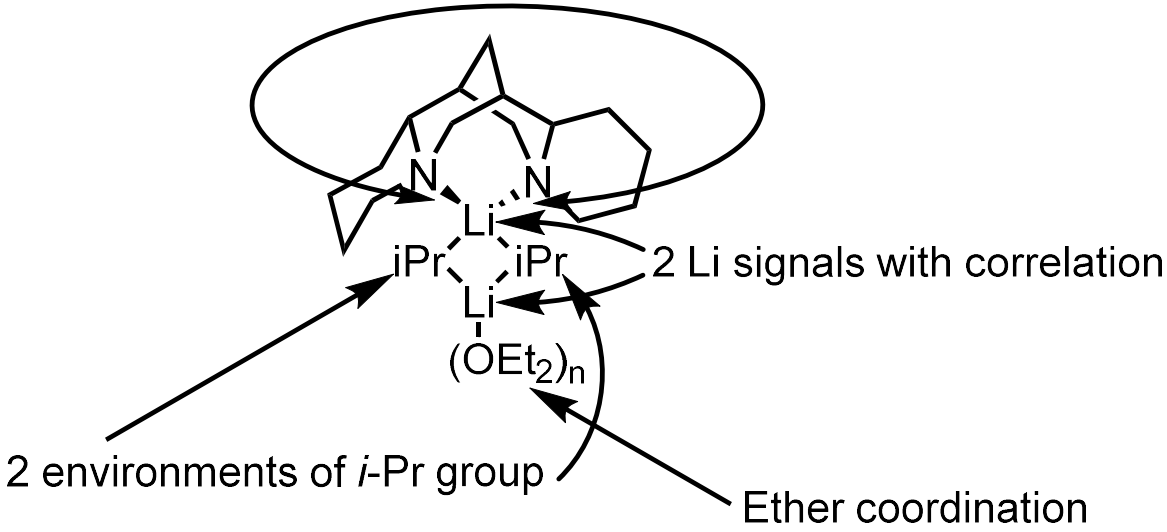


Beak, P. *et al. J. Am. Chem. Soc.* 1992, 114, 5872

Understanding stereoselectivity: structure and reactivity of isopropyllithium complex

Proposed dimer structure

Fluxional η_1 / η_2 sparteine binding in cyclopentane



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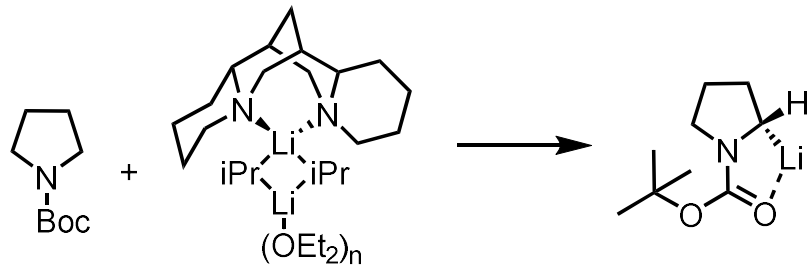
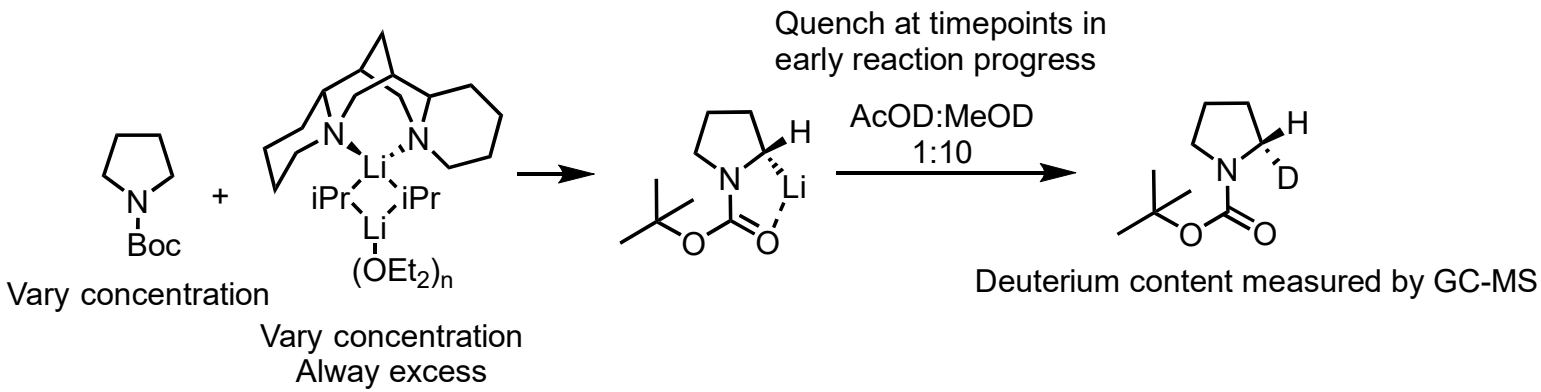
Understanding stereoselectivity: structure and reactivity of isopropyllithium complex

Plausible mechanism



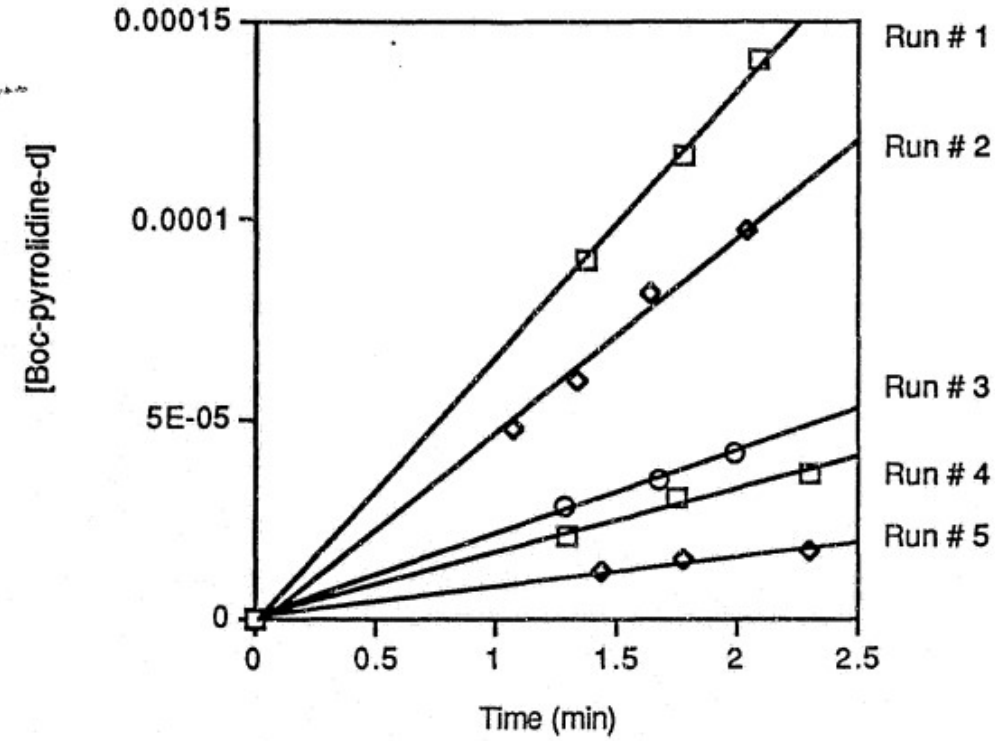
- Is the dimer a reactive species or does reaction proceed through a monomer?
- Kinetics: Order in lithium dimer
  - Reaction with dimer: should be 1st order
  - Dimer breakdown to monomer: should be 0.5 order

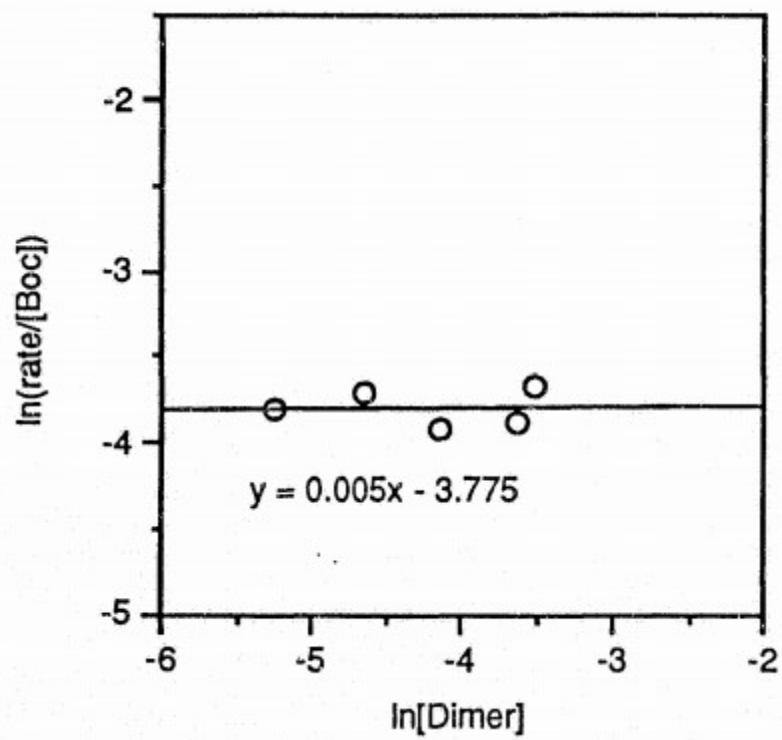
Initial rate kinetics; pseudo-first-order conditions (different excesses dimer)



Beak, P. *et al. J. Org. Chem.* 1995, 60, 7092

Understanding stereoselectivity: structure and reactivity of isopropyllithium complex



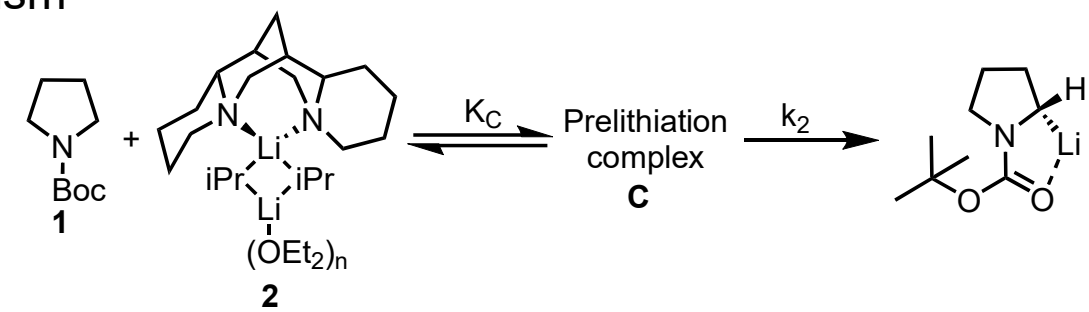


- Pseudo-first order conditions (excess dimer) initial rates: zero order!
- Fast, reversible prelithiation complex formation with rate-determining deprotonation?

Beak, P. *et al. J. Org. Chem.* 1995, 60, 7092

Understanding stereoselectivity: structure and reactivity of isopropyllithium complex

Revised mechanism



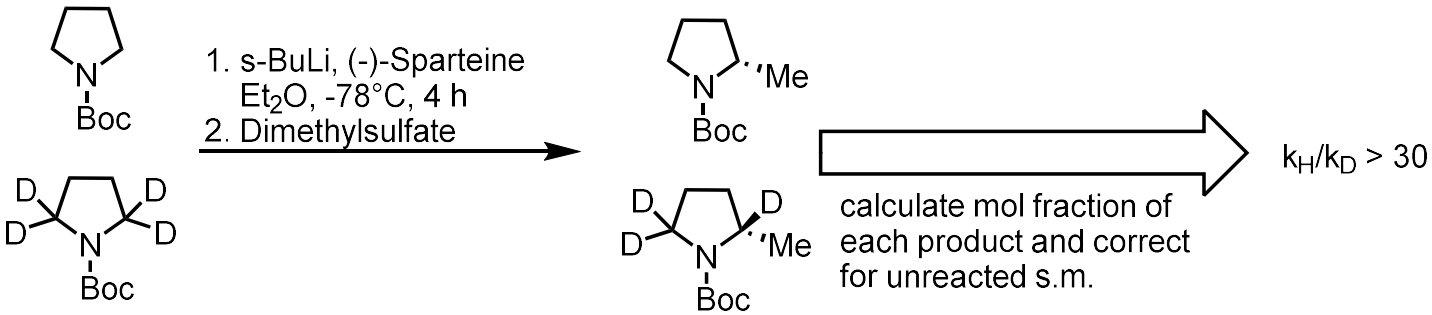
THEN:

- $dP/dt = k_2[C]$
- $K_C = \frac{[C]}{[2_i-C][1_i-C]}$
- Excess dimer: $K_C = \frac{[C]}{[2_i][1_i-C]}$
- Solve for [C] then $dP/dt = \frac{k_2K_c\,[2_i][1_i]}{1+K_c[2_i]}$
- If K_c large (>300) then **$dP/dt = k_2[1_i]$** → ***zero order in 2***

Beak, P. *et al. J. Org. Chem.* 1995, 60, 7092

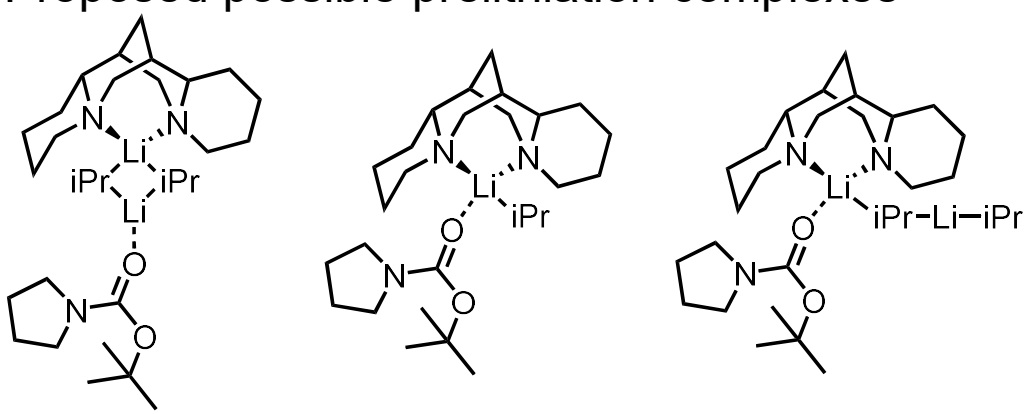
Understanding stereoselectivity: structure and reactivity of isopropyllithium complex

KIE support for rate-determining deprotonation: Intermolecular competition experiment



Proposed possible prelithiation complexes

- Ligated ether displaced on unsymmetrical dimer
- Distance might be too far to transmit stereochemical information

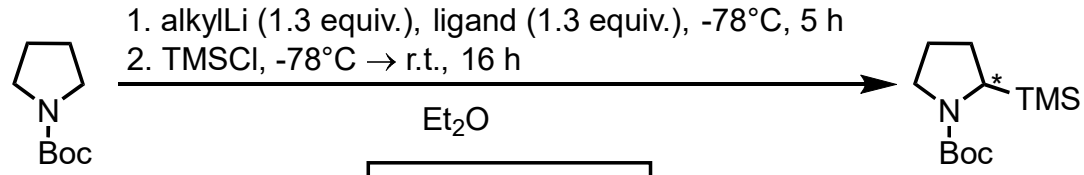


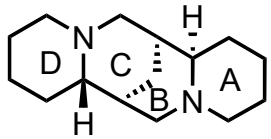
- Pyrollidine in closer proximity to chiral information
- Dimer similar to dimer proposed by Collum et al. for lithium dialkylamide transition structures

Beak, P. *et al. J. Org. Chem.* 1995, 60, 7092

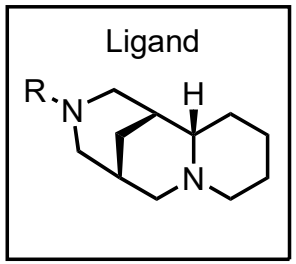
Sparteine SAR: What structural features are necessary for high enantioselectivity?

Effect of N-alkyl substituent

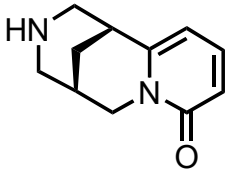




(-)-sparteine



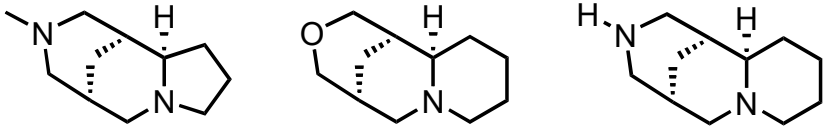
Derived from (-)-cytisine



(-)-cytisine

Alkyllithium	Ligand	Yield	e.r.	recovered s.m.
s-BuLi	(-)-sparteine	87	95:5 (S)	N/A
iPr-Li	(-)-sparteine	78	99:1 (S)	N/A
s-BuLi	R = Me	84	5:95 (R)	N/A
iPr-Li	R = Me	66	6:94 (R)	N/A
s-BuLi	R = Et	73	10:90 (R)	N/A
s-BuLi	R = nBu	27	11:89 (R)	20%
s-BuLi	R = CH_2tBu	35	51:49 (R)	36%
s-BuLi	R = i-Pr	0	N/A	58%

Examined computationally with lower selectivities predicted

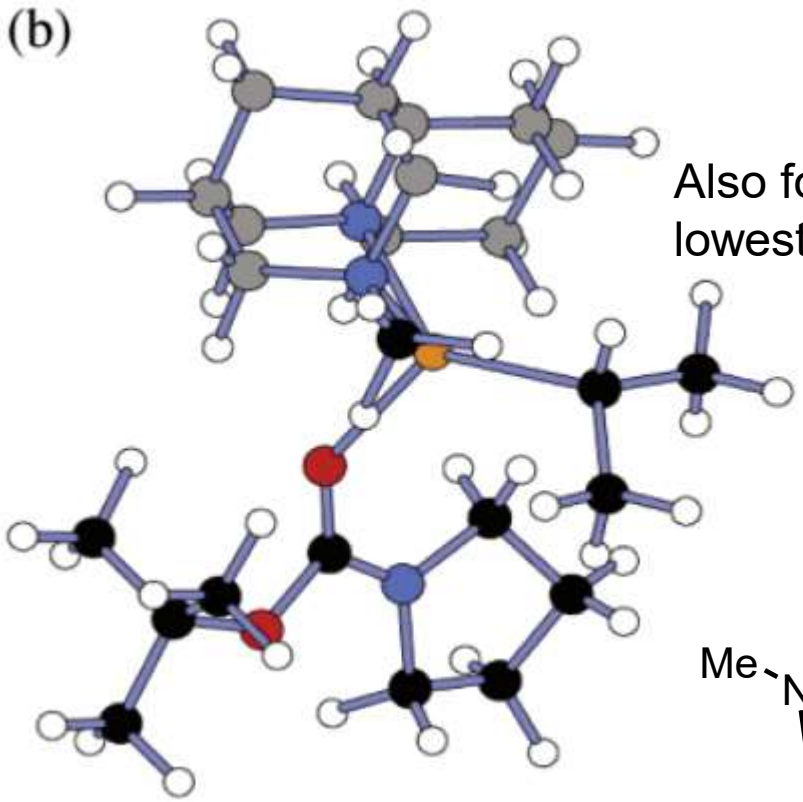


A, B, C rings and N-alkyl substituent important

O'Brien, P; Wiberg, K.B.; Bailey, W.S. *et al. J. Am. Chem. Soc.* 2004, 126, 15480

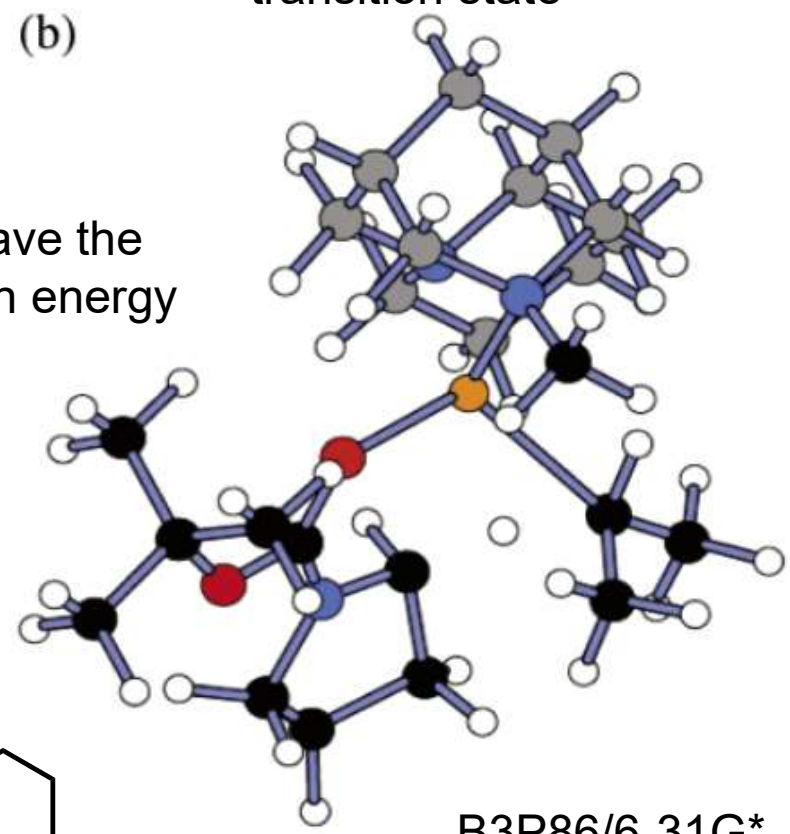
Computational investigations on origin of enantioselectivity

Calculated lowest energy pre-lithiation complex

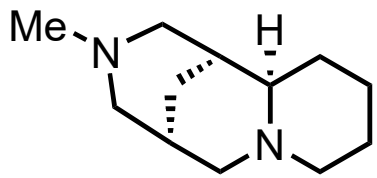


Also found to have the lowest activation energy

transition state



Ligand



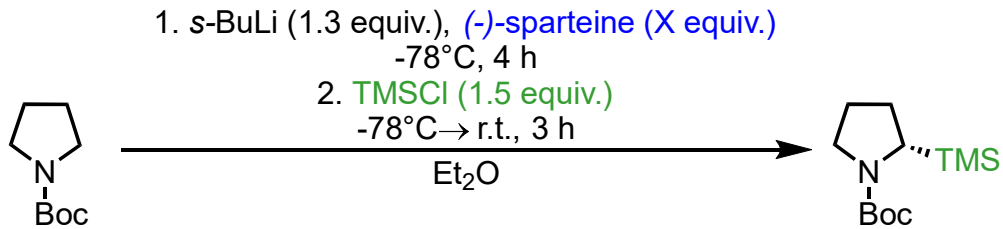
B3P86/6-31G*

"These computational results indicate that the **etiology of the high enantioselectivity observed in lithiations mediated by (-)- sparteine** involves **steric interactions within the prelithiation complex** (isopropyllithium/diamine/N-Boc-pyrrolidine) **engendered by the A-, B-, and C-rings of the ligand**."

O'Brien, P; Wiberg, K.B.; Bailey, W.S. *et al. J. Am. Chem. Soc.* 2004, 126, 15480

Early attempt at use of substoichiometric *(-)*-sparteine

Beak (1994)



Equivalents sparteine	% Yield	% e.e.
1.3	87	96
0.25	33	64
0.5	48	78
0.1 (with 0.9 equiv. TMEDA)	65	-3

- Decreased yields and enantioselectivites suggest that sparteine continues to bind the organolithium after deprotonation: no regeneration of the reactive diamine/ s-BuLi complex

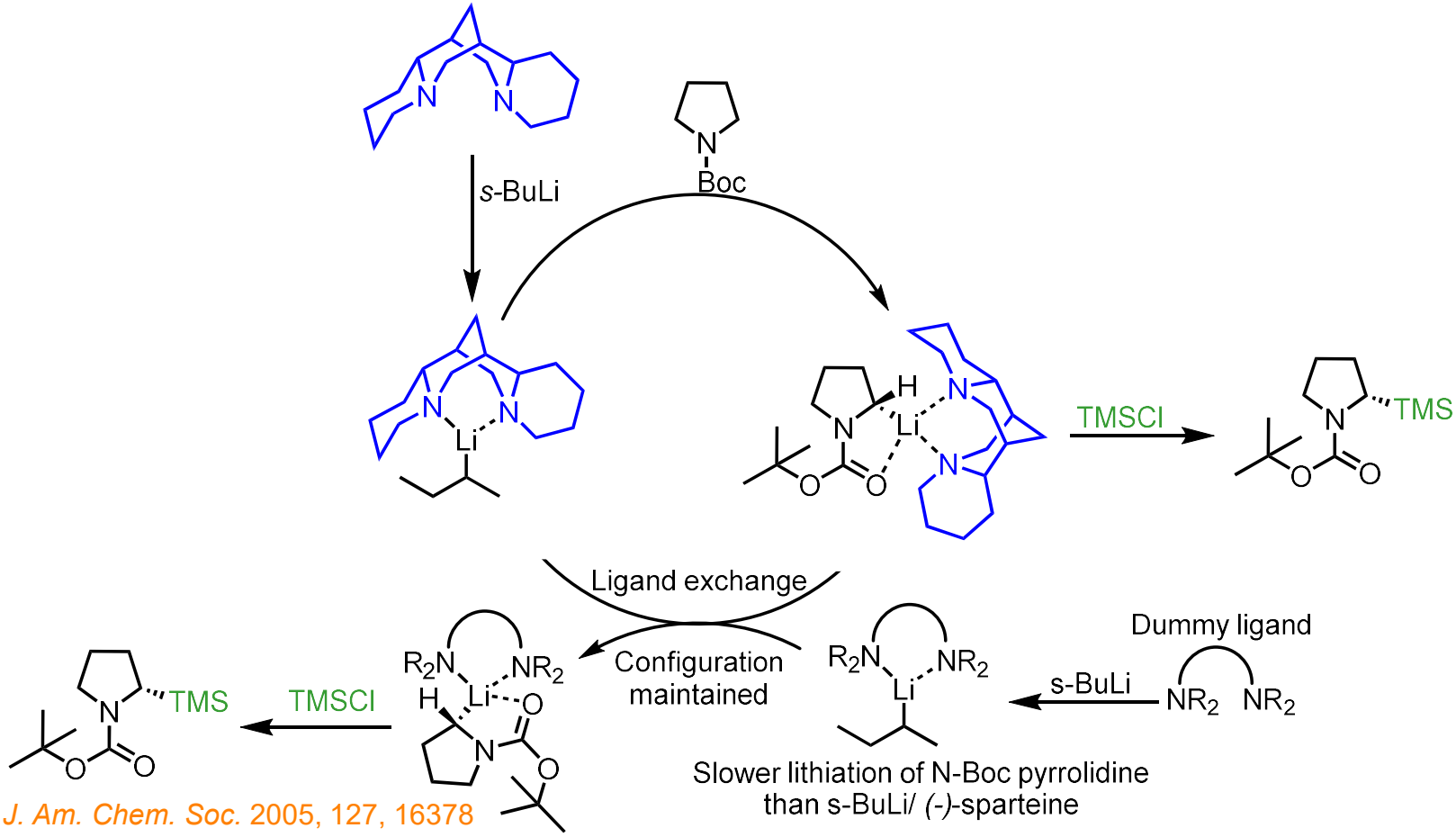
- TMEDA/ s-BuLi complex has a competitive rate of (racemic) lithiation to *(-)*-sparteine/ *s*-BuLi complex

Beak, P. *et al. J. Am. Chem. Soc.*. 1994, 116, 3231; O'Brien *et al. J. Am. Chem. Soc.* 2005, 127, 16378

Diamine switch strategy enables use of catalytic sparteine

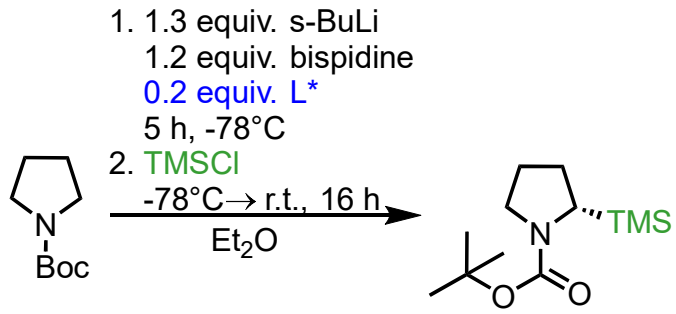
Successful catalytic variant will meet the following criteria

- Ligand exchange from sparteine to a “dummy ligand” must occur following lithiation
- Configuration of organolithium must be maintained during ligand exchange
- Rate of lithiation with chiral diamine/ s-BuLi complex must be faster than with dummy ligand/ s-BuLi complex

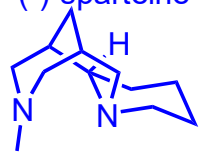


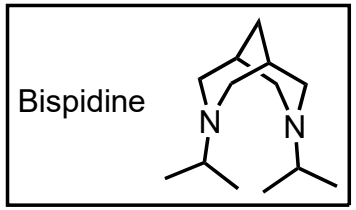
O‘Brien *et al. J. Am. Chem. Soc.* 2005, 127, 16378

Diamine switch strategy enables use of catalytic sparteine



L*	Yield	e.r.
(-)-sparteine	76%	90:10 (S)
(+)-sparteine surrogate	66%	4:96 (R)



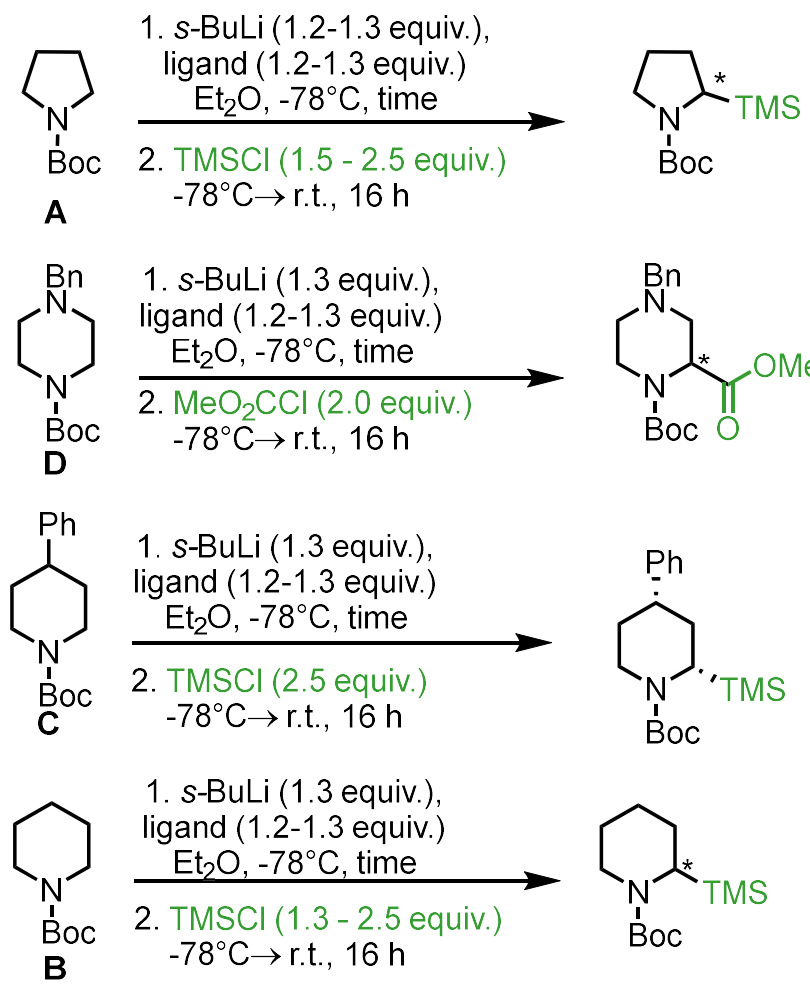


Original Beak conditions with stoichiometric (-)-sparteine: 87% yield, 96% e.e.

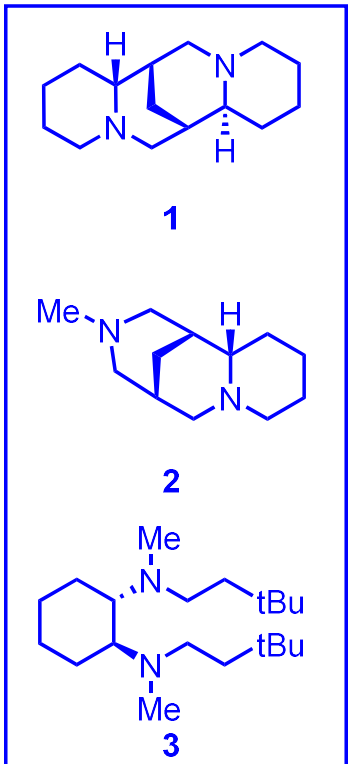
- Approaching reactivity and selectivity observed with stoichiometric chiral ligand
- Applicable to other asymmetric deprotonations with high enantioselectivities

O'Brien *et al. J. Am. Chem. Soc.* 2005, 127, 16378

Heterocycle and ligand reactivity trends



Ligand	time	% yield	e.r.
1	4	87	98:2 (S)
2	5	84	5:95 (R)
3	3	72	95:5 (S)
1	1.5	71	88: 12 (R)
2	1	88	15: 85 (S)
1	6	6	78:22 (S,S)
3	6	48	87:13 (S,S)
1	16	8	87:13 (S)
2	6	73	14:86 (R)
3	6	13	90:10 (S)



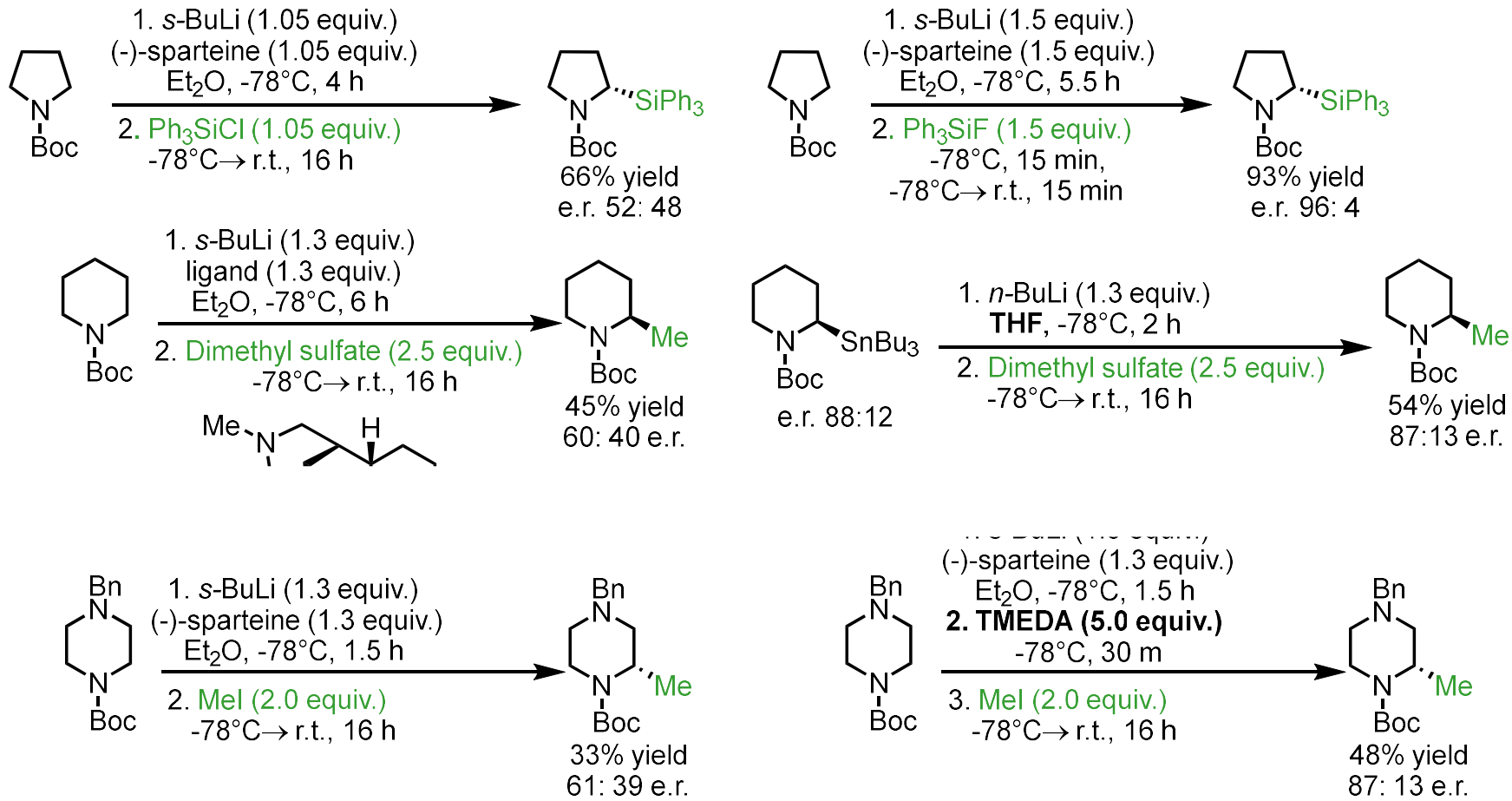
Reactivity: 2 > 3 > 1
Selectivity: 1≈ 2 ≈ 3

Reactivity: A ≈ B > C > D

Beak, P. *et al. J. Am. Chem. Soc.* 1994, 116, 3231; Firkin, C. R. and O'Brien, P. *et al. J. Am. Chem. Soc.* 2002, 124, 11870; O'Brien, P. *et al. Org. Lett.* 2008, 10, 1409; Bailey, W. F.; Beak, P.; Wiberg, K. B. *et al. J. Am. Chem. Soc.* 2002, 124, 1889; O'Brien, P. *et al. J. Am. Chem. Soc.* 2010, 132, 7260; Coldham, I.; O'Brien, P. *et al. Tetrahedron: Asymmetry* 2007, 18, 2113; O'Brien, P. *et al. J. Am. Chem. Soc.* 2016, 138, 651.

Asymmetic deprotonation: problems and solutions

Low enantioselectivities obtained when lithiated substrate is not reactive at -78 and rate of trapping is competitive with rate of interconversion

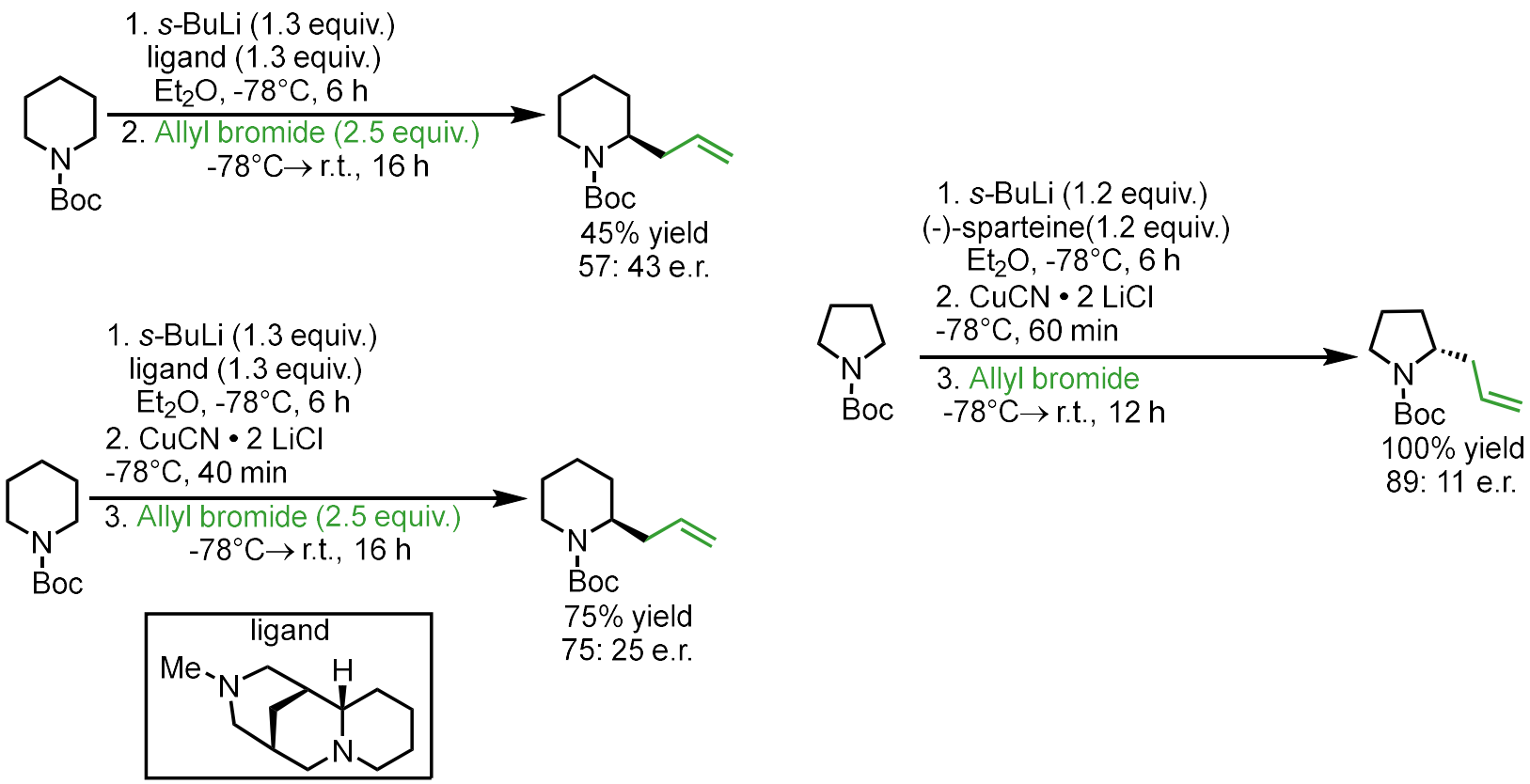


Tunability: Electrophile and organolithium/ ligands can be modified for higher reactivity and enantioselectivity

Franz, A. K. *et al. J. Org. Chem.* 2011, 76, 7065; O'Brien, P. *et al. J. Am. Chem. Soc.* 2010, 132, 7260; O'Brien, P. *et al. J. Am. Chem. Soc.* 2016, 138, 651.

Asymmetic deprotonation: problems and solutions

- Low enantioselectivities for certain electrophiles proposed to arise from competing SET mechanism
- Solution: transmetalation to copper

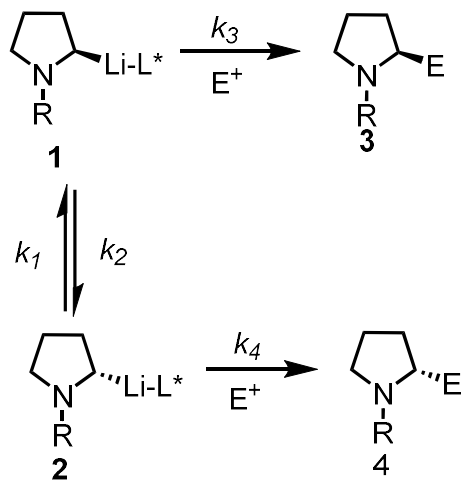


O'Brien, P. *et al. J. Am. Chem. Soc.* 2010, 132, 7260 ; Dieter, R. K. *et al. J. Org. Chem.* 2004, 69, 3076

Outline and scope of presentation

1. Asymmetric Deprotonation
2. **Asymmetric Substitution**
3. Functionalization of 3, 4, and 7 membered rings
4. Comparison to other methods
5. Future directions

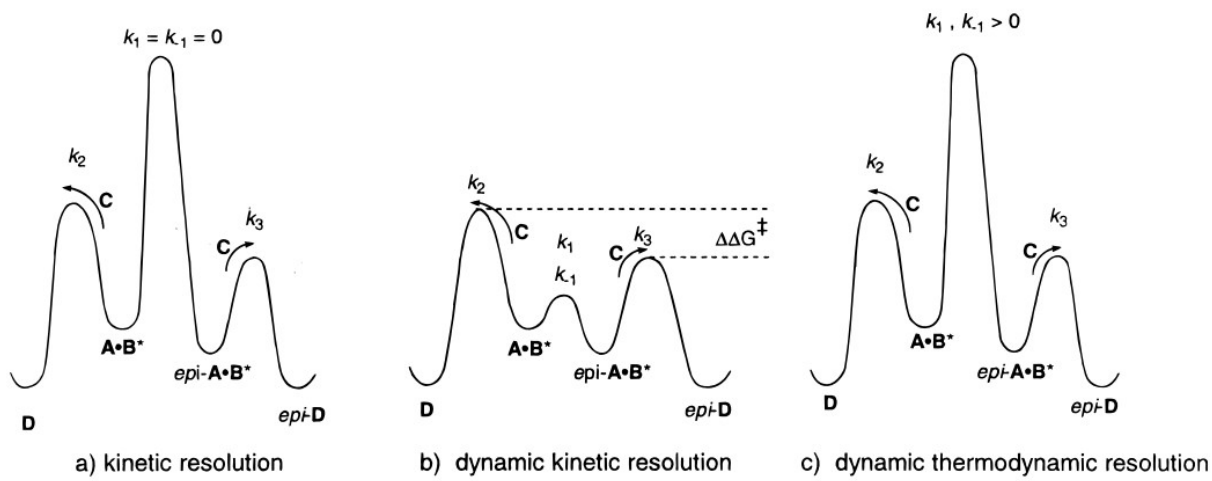
Asymmetric substitution: Dynamic Resolutions



k_1, k_2 = 0: stereodetermining deprotonation or kinetic resolution
Barrier to interconversion

Product ratio in DKR is based on the difference in barrier heights

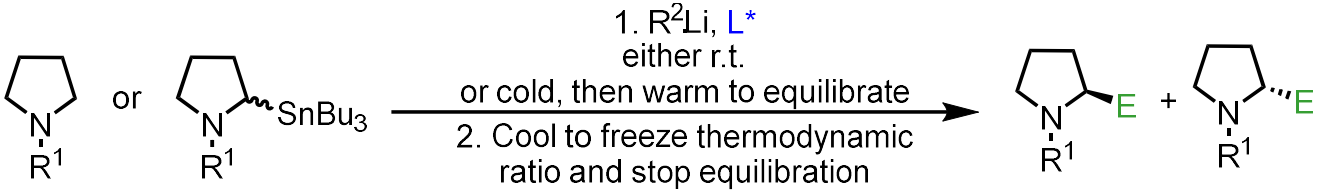
Product ratio in DTR is based on the difference in diastereomer populations



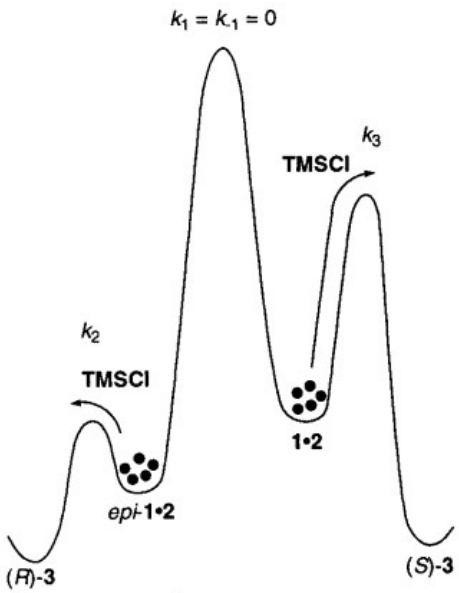
Coldham, I. *et al. J. Am. Chem. Soc.* 2006, 128, 10943; Beak, P. *et al Acc. Chem. Res.* 2000, 33, 715-727

Asymmetric substitution: Dynamic Resolutions

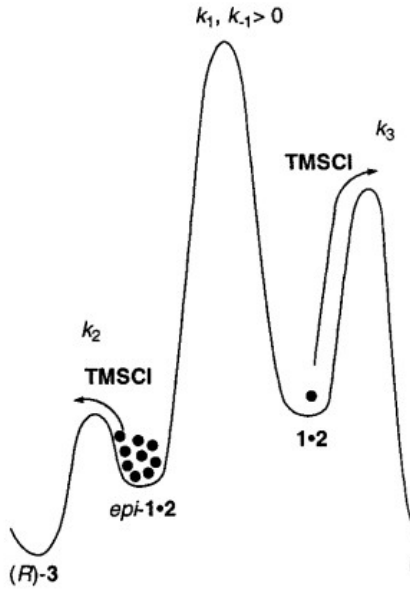
General procedure for nitrogen-containing heterocycles:



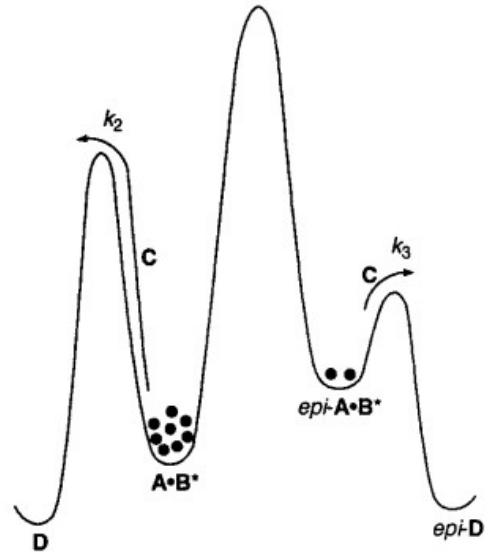
Capture thermodynamic ratio of organolithium/L* diasteromers



Entire Reaction at –78 °C



Reaction under dynamic thermodynamic c
equilibration at –25 °C is enantiodetermini



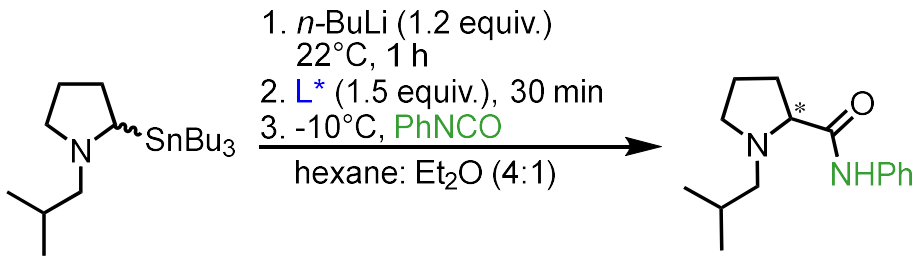
c-2) 4:1 population of diastereomers

Warming the mixture to equilibrate is necessary for dynamic thermodynamic resolution, otherwise only kinetic resolution possible. Freezing the thermodynamic ratio is necessary when higher energy diastereomer also has lower barrier.

Beak, P. *et al Acc. Chem. Res.* 2000, 33, 715-727

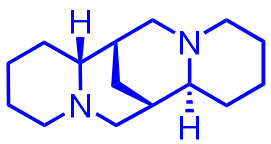
Dynamic thermodynamic resolution of N-alkyl pyrrolidine

Ligand optimization

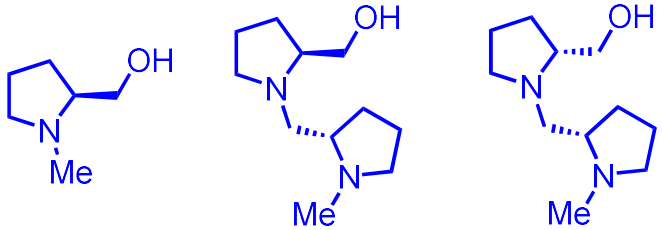


L*

(-)-Sparteine



57% yield
82:18 (*S*)

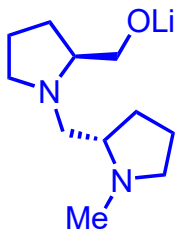


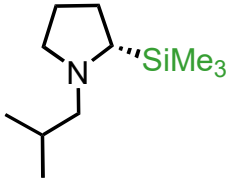
Pretreated with n-BuLi

76% yield 41:59 (*R*)	61% yield 3:97 (*R*)	74% yield 96:4 (*S*)

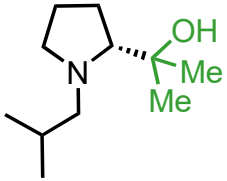
Electrophile scope

with

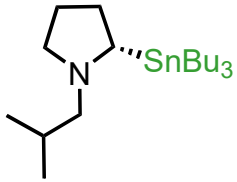




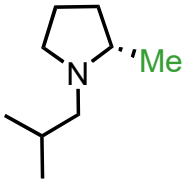
from TMSCl
75% yield
> 96:4 e.r.



from Acetone
54% yield
> 96:4 e.r.



from $SnBu_3Cl$
71% yield
96:4 e.r.



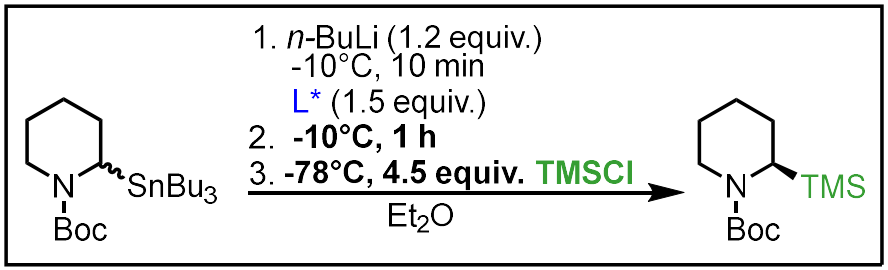
from dimethyl sulfate
(added at -78°C)
54% yield
> 96:4 e.r.

Coldham, I. *et al. Angew. Chem. Int. Ed.* 2002, 41, 3887

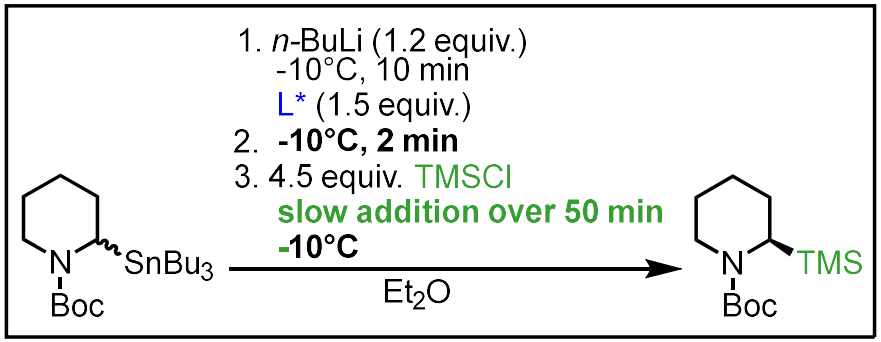
Dynamic resolution of N-Boc piperidine

Ligands screened for DKR and DTR

DTR

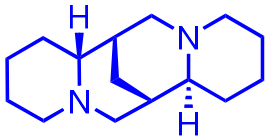


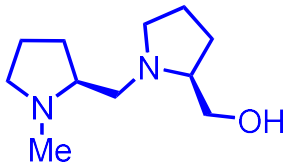
DKR

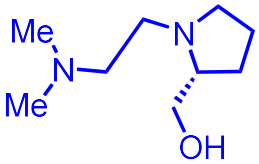


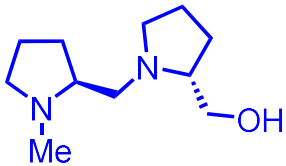
L*

(-)-Sparteine









			Pretreated with n-BuLi and TMEDA used for Sn-Li exchange		
DTR	86% yield 55:45 (*R*)	88% yield 50:50	46% yield 23:77 (*S*)	39% yield 59:41 (*R*)	41% yield 58:42 (*R*)
DKR	55% yield 53:46 (*R*)	86% yield 51:49 (*R*)	45% yield 72:28 (*R*)	60% yield 11:89 (*S*)	**62% yield** **7:93 (*S*)**

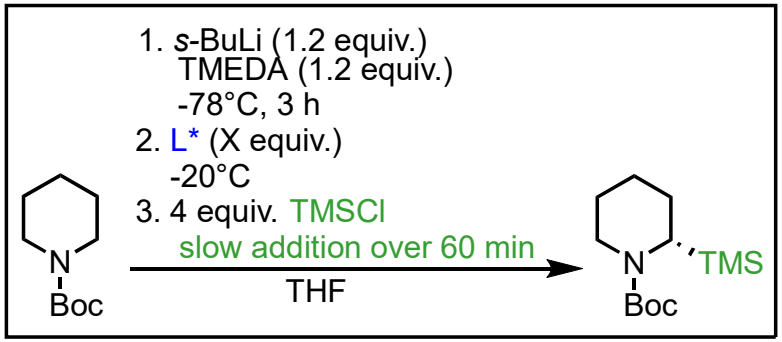
However little to no enantioselectivity with this ligand observed in DKR with Bu_3SnCl, allyl bromide, DMF, Dimethyl sulfate

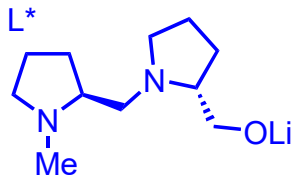
Coldham, I. *et al. Chem. Commun.*, 2007, 4534

Difference in mechanism?

Improvements in procedure:

- Stannane not required
- Catalytic ligand possible

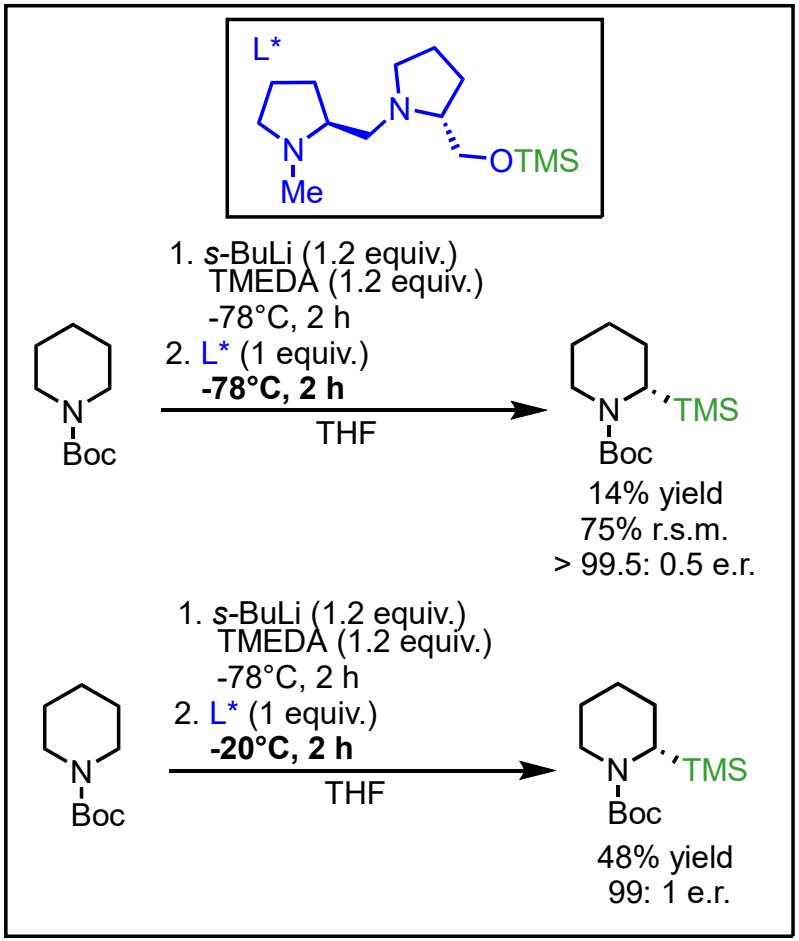




1.5 equiv.
60% yield
95:5 e.r.

0.1 equiv.
54% yield
96:4 e.r.

Low enantioselectivity of non-silyl electrophiles still observed

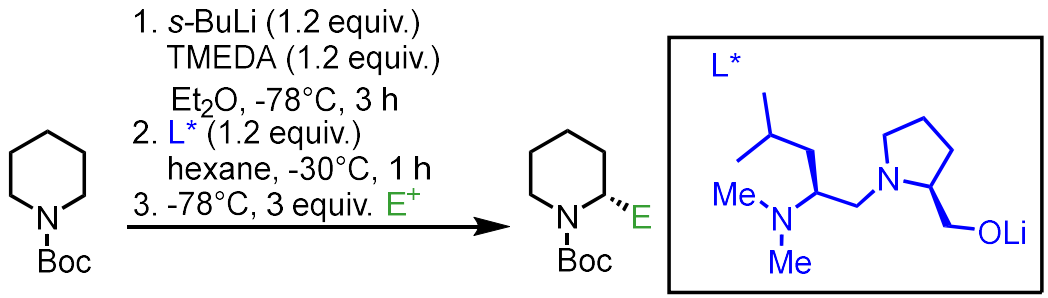


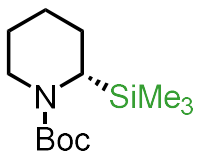
Possibly intermolecular retro-Brook, or double asymmetric induction with α-lithiopiperidine coordinated to Li alkoxide with delivery from L*

Coldham, I. *et al. Chem. Eur. J.* 2010, 16, 4082

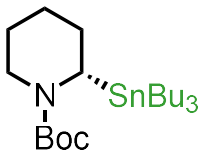
Dynamic resolution of N-Boc piperidine

Further screening of diamino-alkoxide ligands

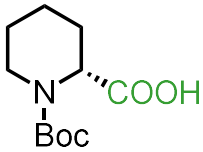




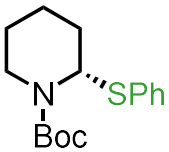
From TMSCl
65% yield
85:15 e.r.



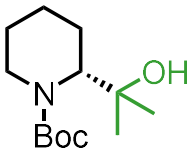
From Bu_3SnCl
67% yield
84:16 e.r.



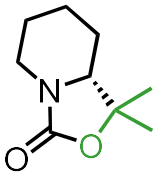
From CO_2
62% yield
87:13 e.r.



From PhSSPh
62% yield
87:13 e.r.



From MeOH, then acetone
38% yield
74:26 e.r.

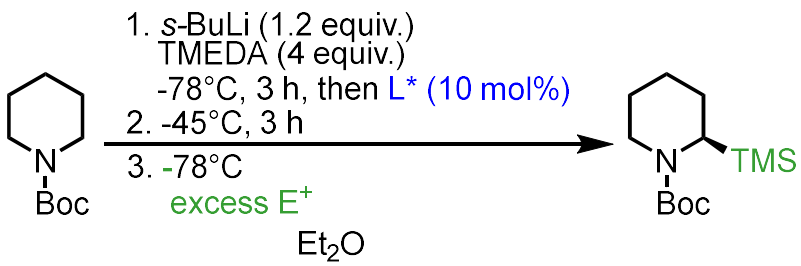


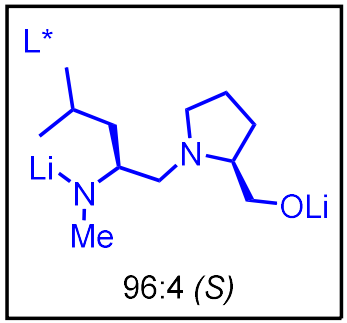
From acetone
39% yield
77:23 e.r.

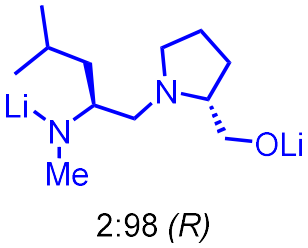
Coldham, I. *et al. Chem. Commun.*, 2008, 4174; Coldham, I. *et al. Chem. Commun.*, 2009, 5239

Catalytic dynamic resolution of N-Boc piperidines

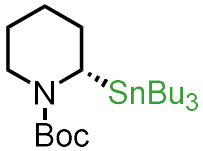
- Substoichiometric chiral ligand possible?



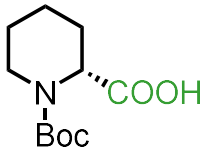




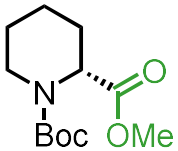
Electrophile scope



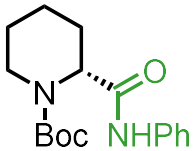
From Bu_3SnCl
74% yield
96:4 e.r.



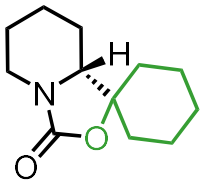
From CO_2
78% yield
98:2 e.r.



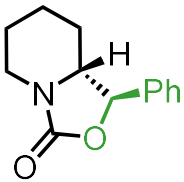
From $ClCO_2Me$
88% yield
> 99:1 e.r.



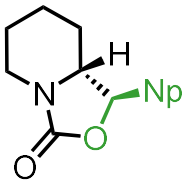
From PhNCO
68% yield
98:2 e.r.



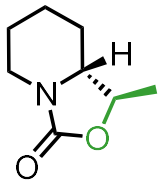
60% yield
94:6 e.r.



74% yield
62:38 d.r.
> 99:1/ 98:2 e.r.

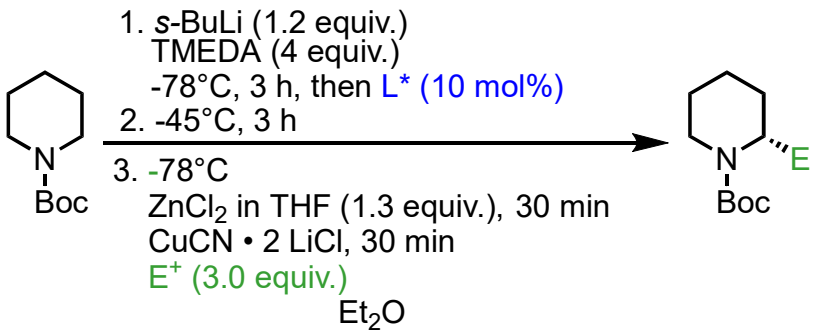


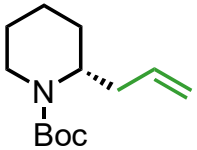
66% yield
82:18 d.r.
> 94:6/ 93:7 e.r.



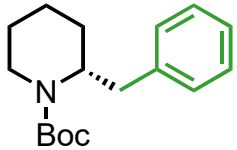
78% yield
85:15 d.r.
> 99:1 each

Required transmetallation





From allyl bromide
63% yield
95:5 e.r.



From benzyl bromide
65% yield
> 99:1 e.r.

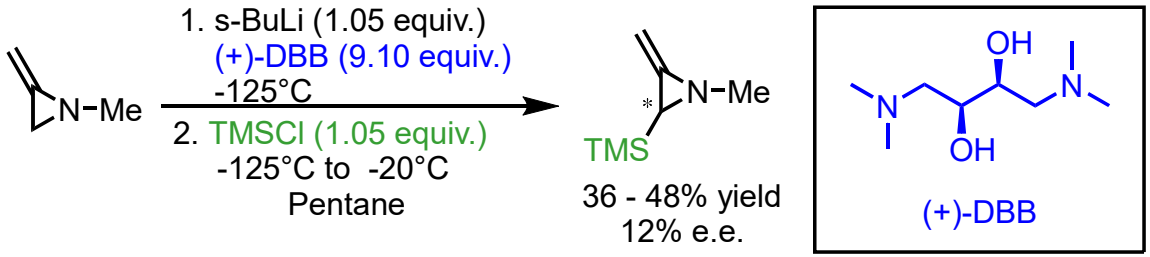
Gawley, R.E. *et al. J. Am. Chem. Soc.* 2010, 132, 12216

Outline and scope of presentation

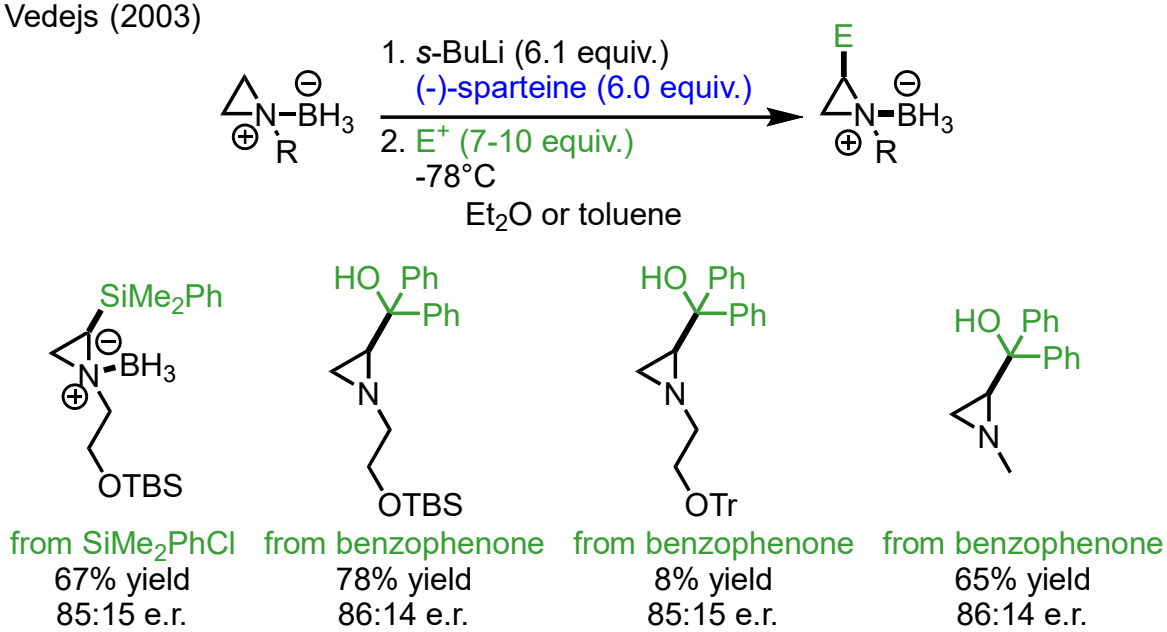
1. Asymmetric Deprotonation
2. Asymmetric Substitution
3. **Functionalization of 3, 4 and 7 membered rings**
4. Comparison to other methods
5. Future directions

Aziridines

Quast and Vélez (1978)



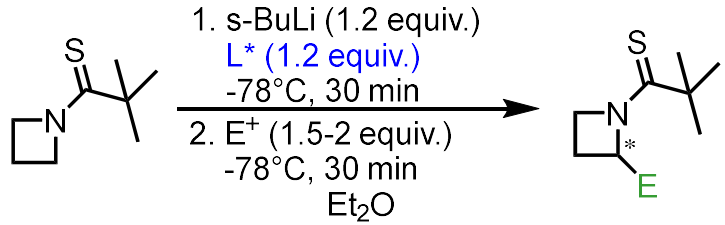
Vedejs (2003)

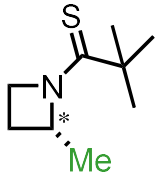


- N-BOC aziridines poor substrates: lithiated species undergoes N- to C-BOC migration

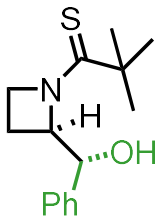
Quast, H. and Vélez, C. A. W. *Angew. Chem. Int. Ed.* 1978, 17, 213; Vedejs, E. *et al. Tetrahedron* 2003, 59, 9849

N-thiopivaloyl Azetidines

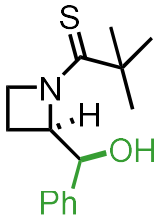




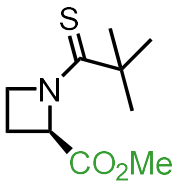
59:41 e.r. *(R)*
91% yield



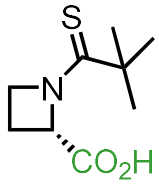
75:25 e.r. *(R, R)*
75% yield



58:42 e.r. *(S, R)*
9% yield

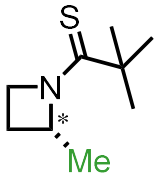


67:33 e.r. *(R)*
45% yield

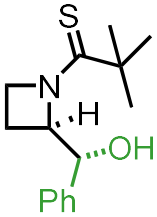


75:25 e.r. *(S)*
96% yield

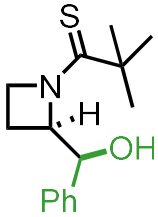
(-)-Sparteine



80: 20 *(R)*
96% yield

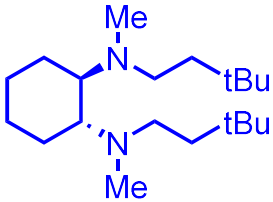


53:47 *(S, S)*
73% yield



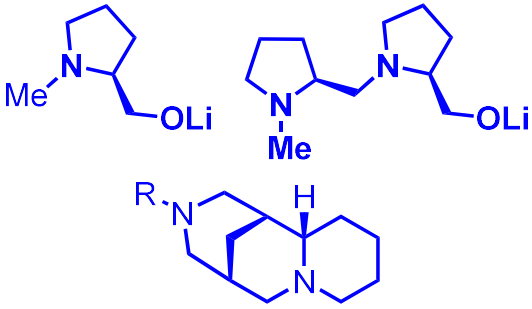
From benzaldehyde

65:35 *(R, S)*
20% yield



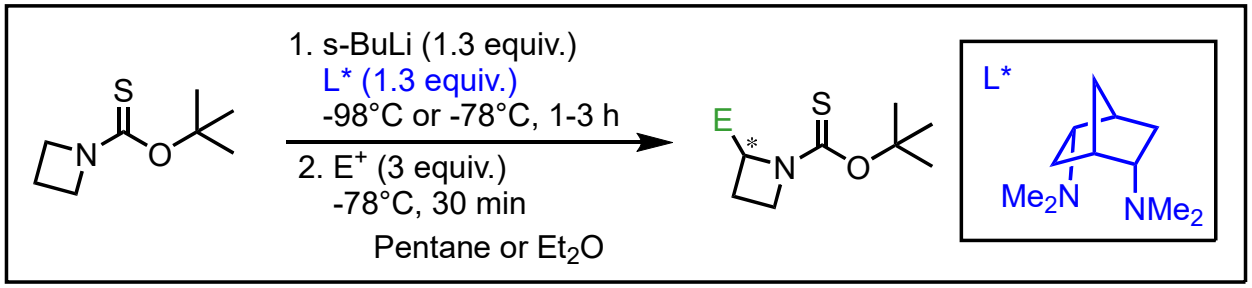
Alexakis Diamine

Less successful ligands

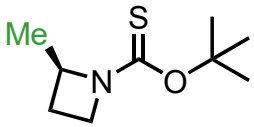


O'Brien, P. *et al. Chem. Commun.*, 2016, 52, 1354; Hodgson, D. M. et al. Angew. Chem. Int. Ed. 2010, 49, 2900

N-tert-butoxythiocarbonyl Azetidines

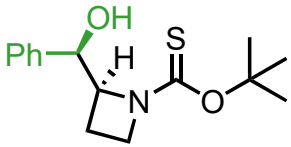


From MeI



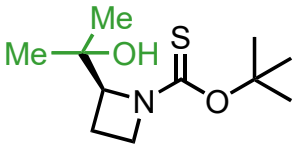
45% yield
91:9 e.r.

From benzaldehyde

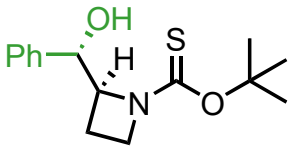


53% yield
86: 14 e.r.

From acetone



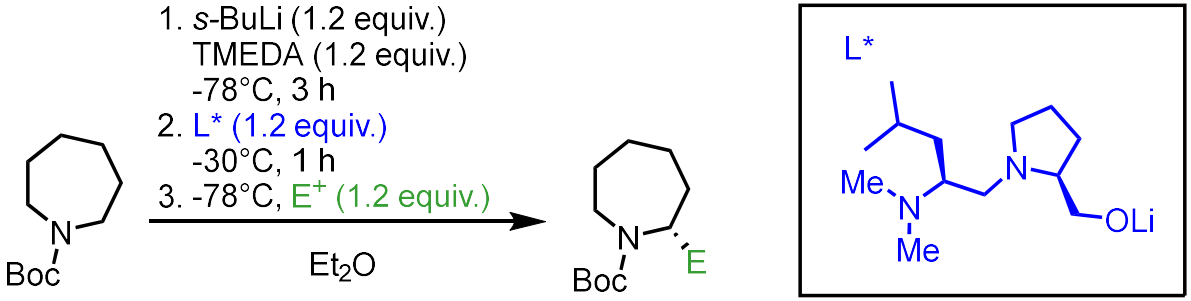
64% yield
92:8 e.r.

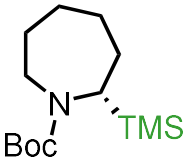


35% yield
85: 15 e.r.

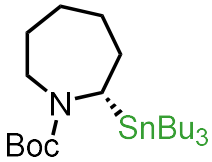
Hodgson, D. M. *et al*. *Org. Lett.* 2015, 17, 330

N-Boc Azepine

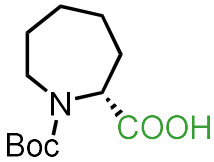




From TMSCl
33% yield
92:8



From $SnBu_3Cl$
29% yield
90:10



From CO_2
18% yield
87:13

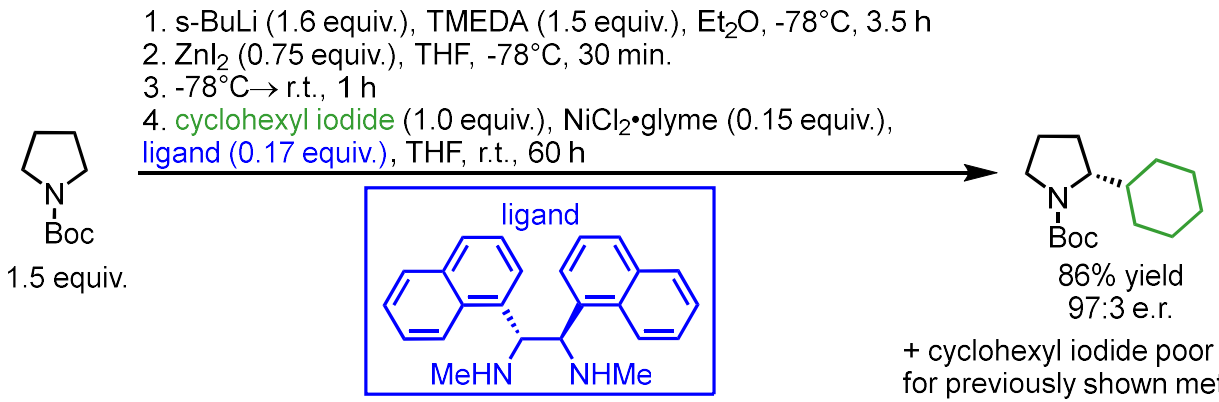
Coldham, I. *et al Chem.—Eur. J.* 2010, 16, 4082.

Outline and scope of presentation

1. Asymmetric Deprotonation
2. Asymmetric Substitution
3. Functionalization of 3, 4, and 7 membered rings
4. **Comparison to other methods**
5. Future directions

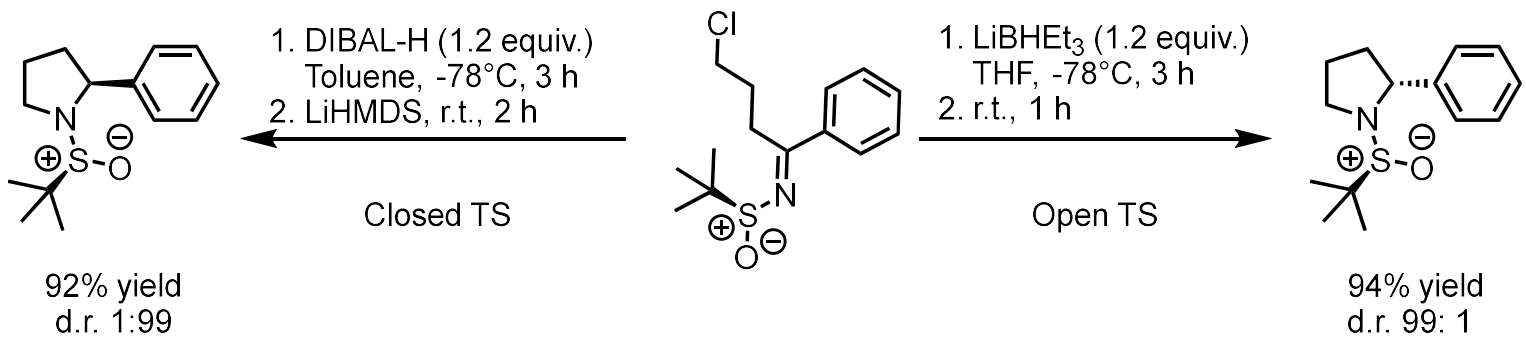
Comparison to other methods

Enantioconvergent Negishi cross-coupling (Fu, 2013)



+ cyclohexyl iodide poor electophile for previously shown methods
- longer reaction time

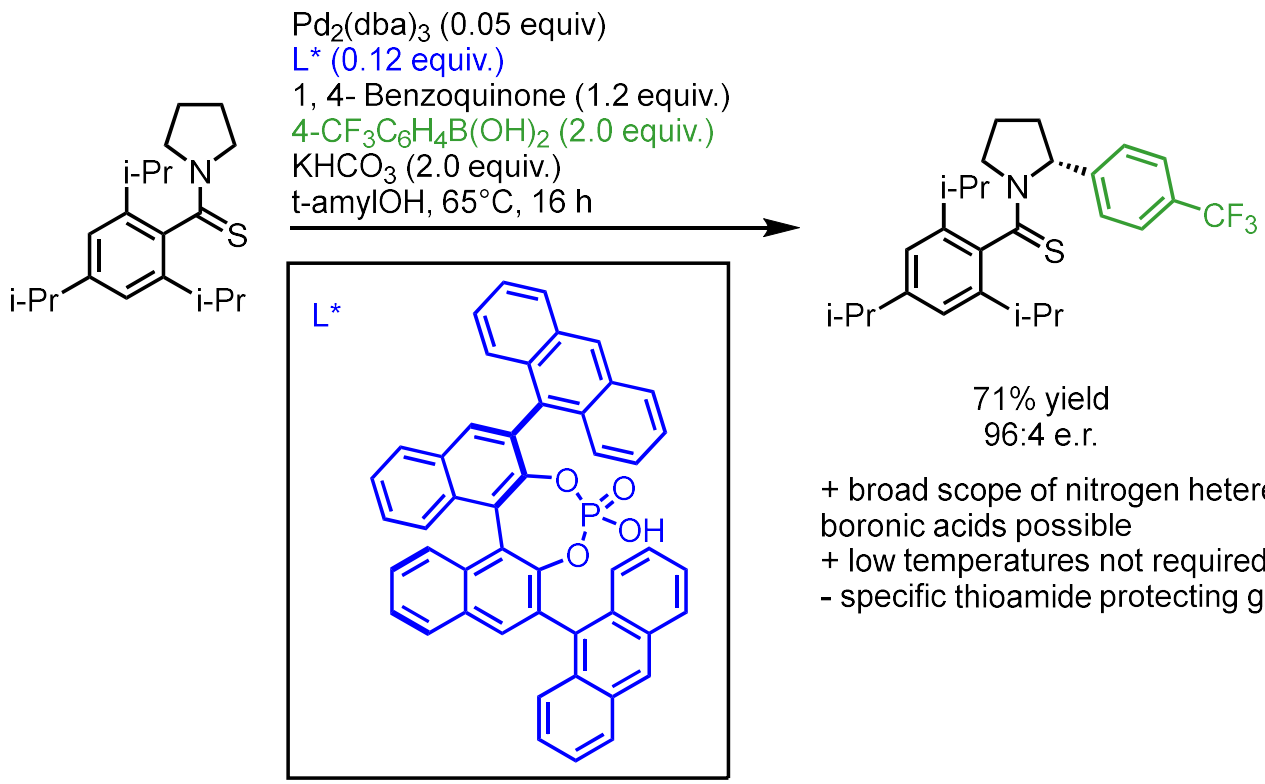
Reduction and in-situ cyclization with Ellman auxiliary (Reddy, 2010)



Fu, G. *et al. J. Am. Chem. Soc.* 2013, 135, 30, 10946; Reddy, L. R. *et al. J. Org. Chem.* 2010, 75, 2236.

Comparison to other methods

Enantioselective C-H arylation (Yu, 2017)



71% yield
96:4 e.r.

+ broad scope of nitrogen hetereocycles and boronic acids possible
+ low temperatures not required
- specific thioamide protecting group required

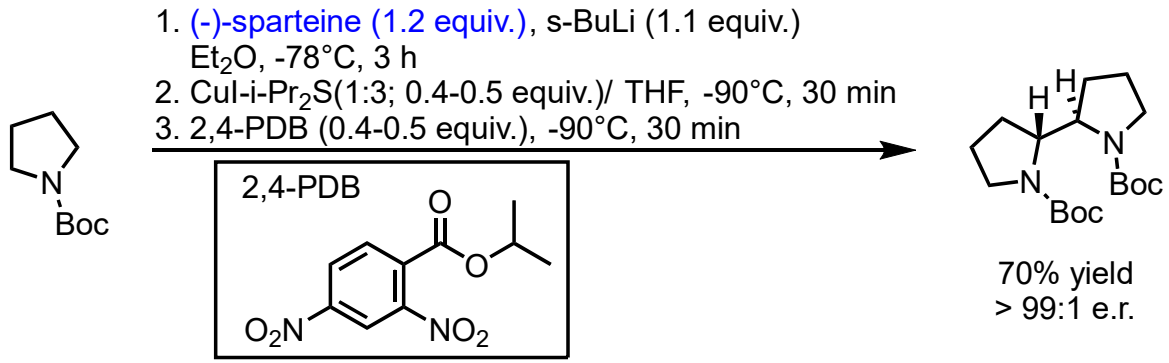
Yu, J.-Q. *et al. Nat. Chem.* 2017, 9, 140

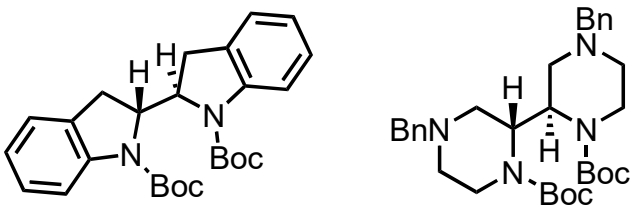
Outline and scope of presentation

1. Asymmetric Deprotonation
2. Asymmetric Substitution
3. Functionalization of 3. 4, and 7- membered rings
4. Comparison to other methods
5. **Future directions**

Current directions & applications of method

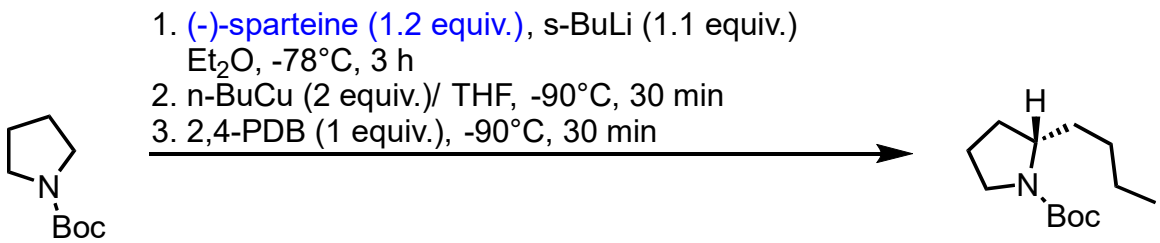
Coupling (Corey, 2017)





6 h deprotonation
68% yield
> 99:1 e.r.

5 h deprotonation
60% yield
95:5 e.r.

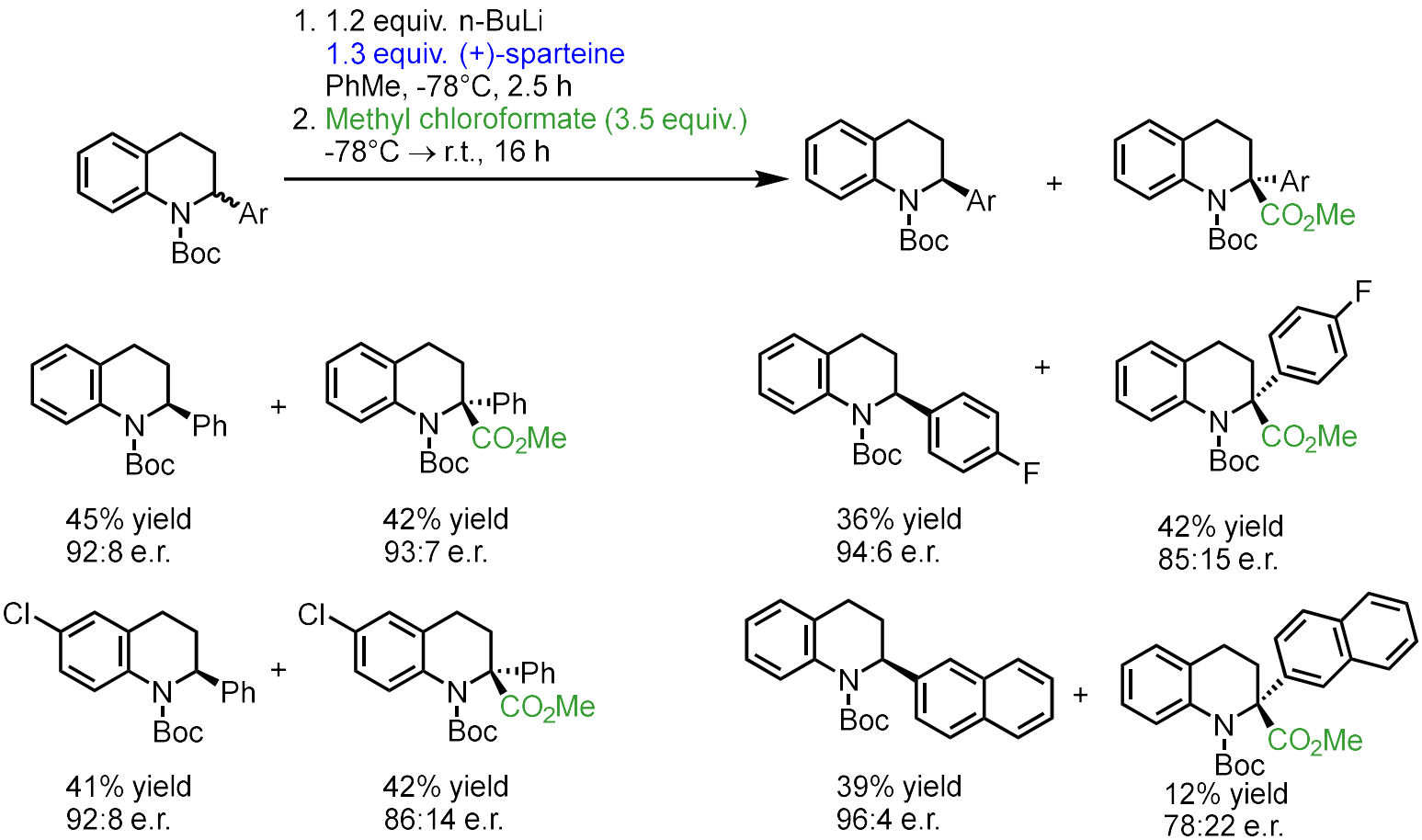


70% yield
> 98:2 e.r.

Corey, E. J. *et al. J. Am. Chem. Soc. 2017*, 139, 11044

Current directions & applications of method

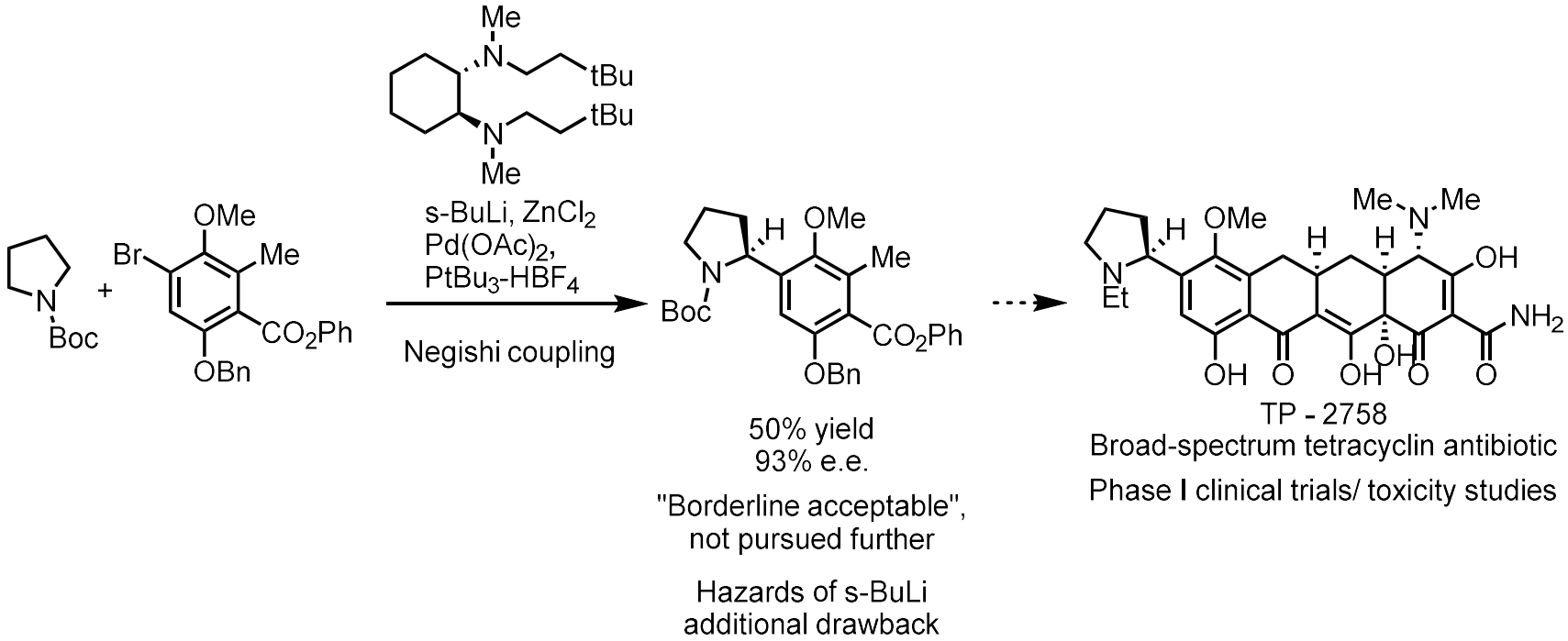
Kinetic resolutions of tetrohydroquinolines (Coldham, 2018)



Coldham, I. *et al Chem. Sci.*, 2018, **9**, 1352

Current directions & applications of method

Application/ investigation in industry (Zhang *et al.*, 2016)



- CDR not well understood!
- Search for sparteine surrogates

Zhang, W.-Y. *et al. Org. Process Res. Dev.* 2016, 20, 284

Image from https://cen.acs.org/articles/95/i17/sparteine-gone.html

Beak Kinetics

Table 1. Initial Rate of Appearance of 2-Deuterio-Boc-pyrrolidine (1-*d*)

[1][a] (M)	[dimer][b] (M)	Δ[1-*d*]/Δ*t* (M min^{-1})[c]	ln[dimer]	ln(Δ[1-*d*]/Δ*t*/[1]
3.22×10^{-3}	0.0264	6.65×10^{-5}	−3.63	−3.88
1.90×10^{-3}	0.0299	4.86×10^{-5}	−3.51	−3.67
1.06×10^{-3}	0.0160	2.11×10^{-5}	−4.14	−3.91
6.57×10^{-4}	0.00970	1.37×10^{-5}	−4.63	−3.88
3.45×10^{-4}	0.00525	7.63×10^{-6}	−5.24	−3.81

[a] Initial concentration of **1**. [b] Initial concentration of dimer **2**, calculated as 1/2 *i*-PrLi concentration. [c] Estimated initial rates (see supporting information).

Beak, P. *et al*. J. Org. Chem. 1995, 60, 7092