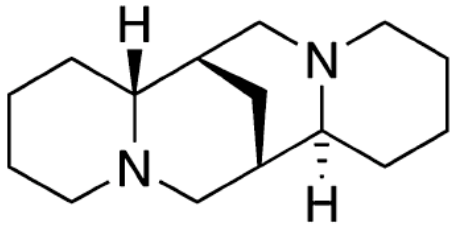
# Asymmetric deprotonation using *s*-BuLi or *i*-PrLi and chiral diamines in THF: The diamine matters

Carbone, G.; O'Brien, P.; Hilmersson. G.

J. Am. Soc. Chem. 2010, ASAP.

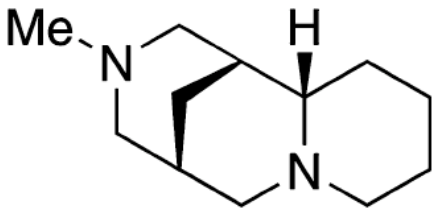
DOI: 10.1021/ja107672h

# Sparteine and sparteine surrogate




(–)-sparteine = (–)-sp

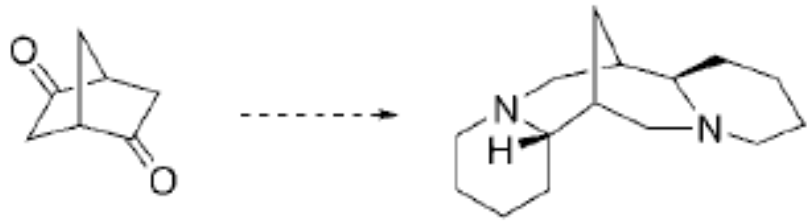
Not commercially available
Not readily accessible




(+)-sparteine surrogate

Not commercially available
Easily accessible

# First asymmetric total synthesis of (+)-sparteine



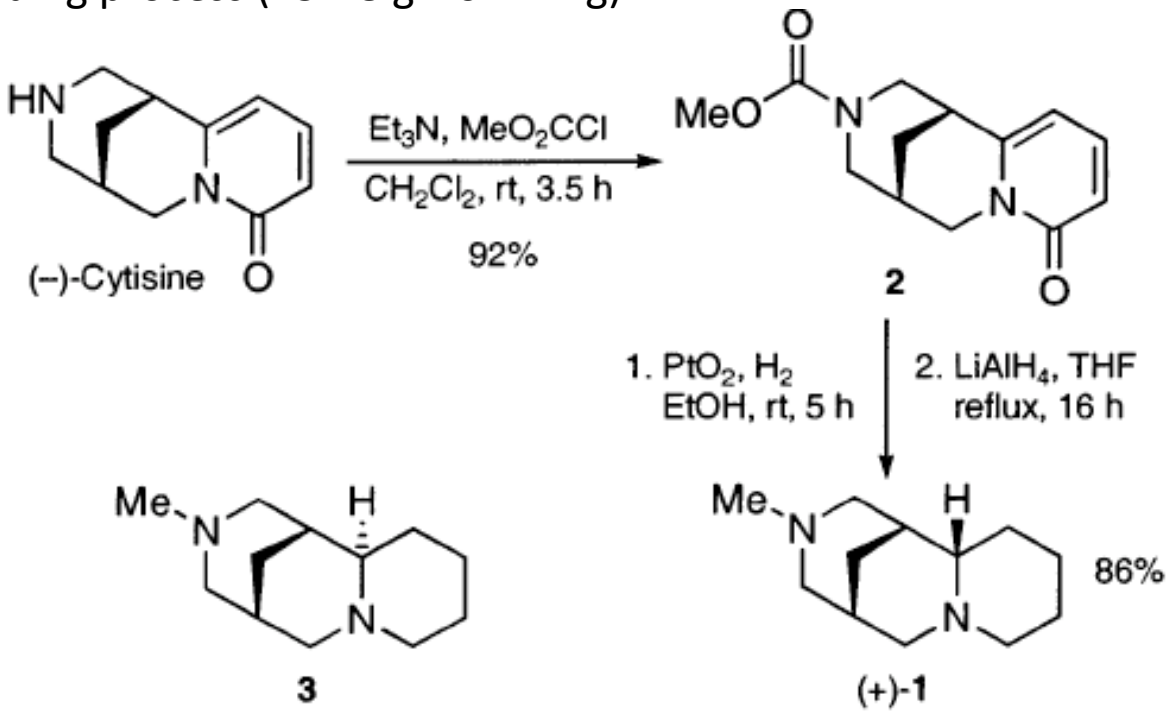

(+)-Sparteine

Starting from the chiral ketone
15 steps
Overall yield: 15.7%.

Smith, B. T.; Wendt, J. A.; Aube, J. Org. Lett. 2002, 4, 2577.

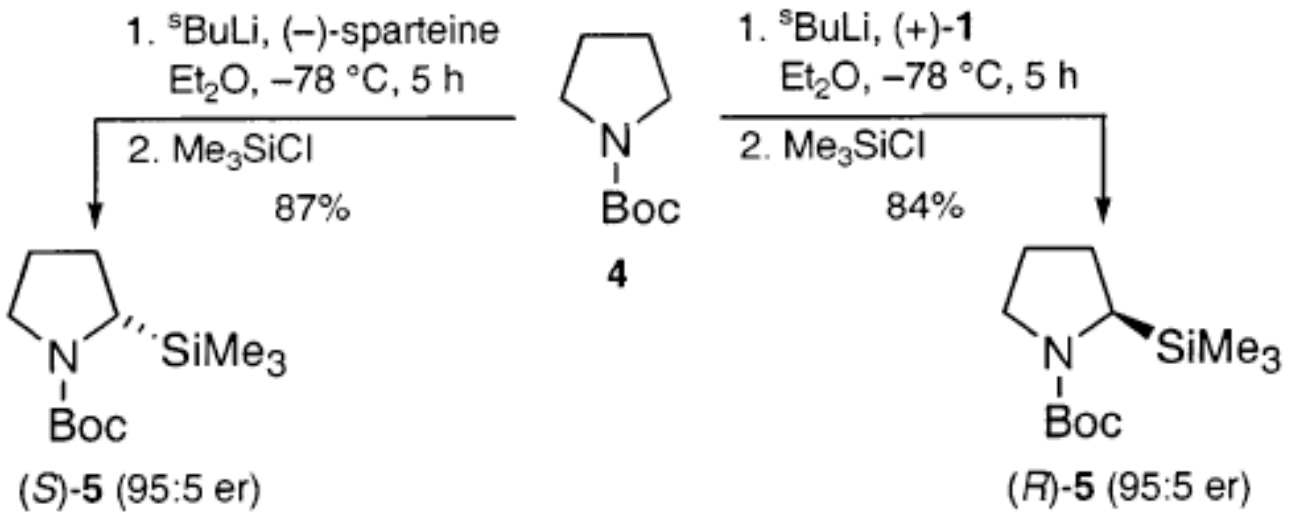
# Access to (+)-sparteine surrogate

From Laburrum anagyroides seeds (ca. £35 per kg from Vilmorin, France)
Simple and high yielding process (15-18 g from 1 kg)



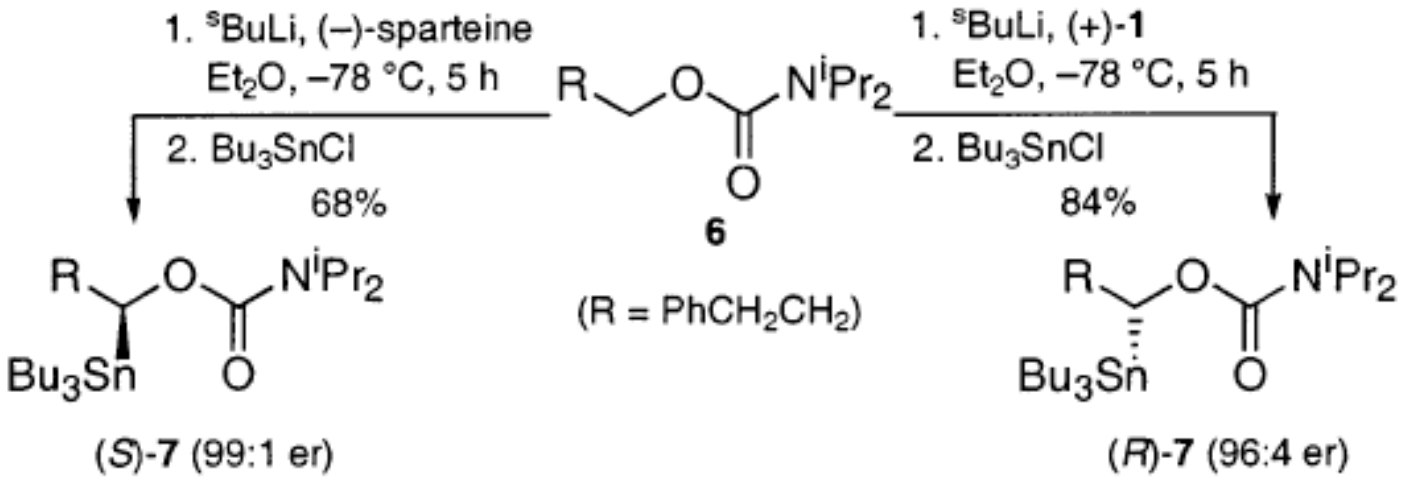

Dearden, M. J.; Firkin, C. R.; Hermet, J-P. R.; O'Brien, P. J. Am. Chem. Soc. 2002, 124, 11870.

# Sparteine and its surrogate in the reactions



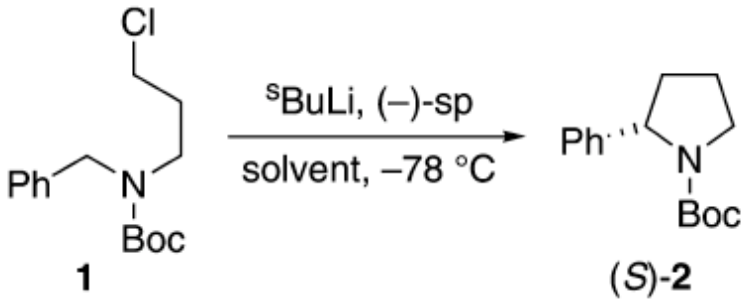

Dearden, M. J.; Firkin, C. R.; Hermet, J-P. R.; O'Brien, P. J. Am. Chem. Soc. 2002, 124, 11870.

# Sparteine and its surrogate in the reactions




Dearden, M. J.; Firkin, C. R.; Hermet, J-P. R.; O'Brien, P. J. Am. Chem. Soc. 2002, 124, 11870.

# Asymmetric deprotonation



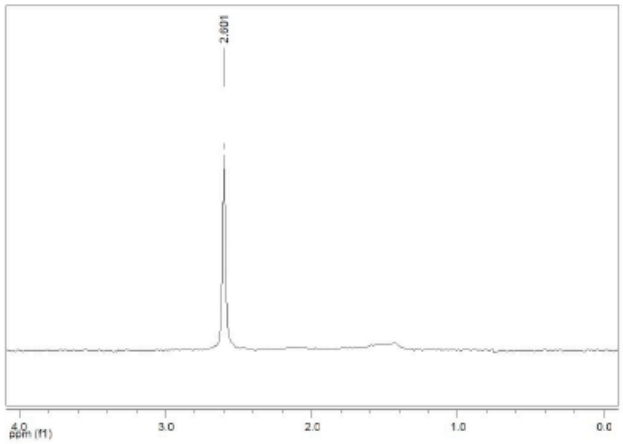

| solvent | yield (%) | ee[a] (%) |
|---|---|---|
| THF | 58 | 3 |
| *t*-BuOMe | 64 | 58 |
| $Et_2O$ | 59 | 64 |
| $Et_2O$:pentane (1:1) | 40 | 70 |
| pentane | 54 | 80 |
| toluene | 72 | 96 |

Will sparteine surrogate behave the same?

Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.

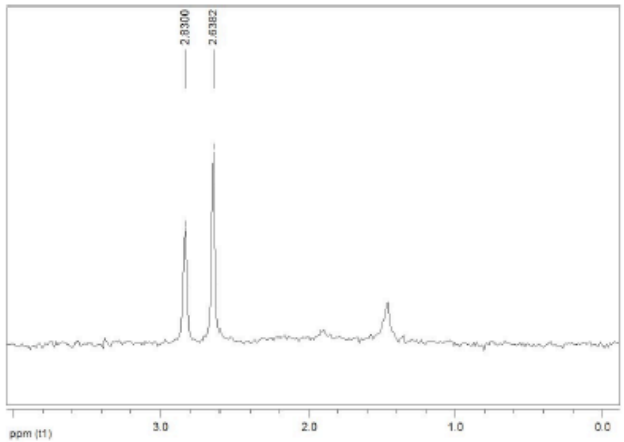
# the complexes of organolithium reagents

$^{6}$Li NMR of $^{6}$[Li]i-PrLi and sparteine $Et_2O$-$d_{10}$



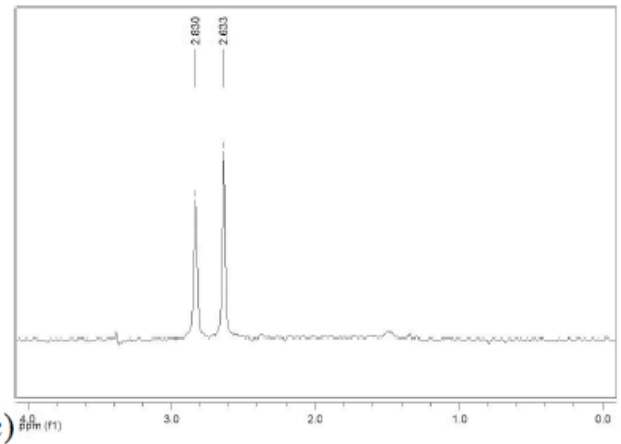

(a)

No (–)-sparteine



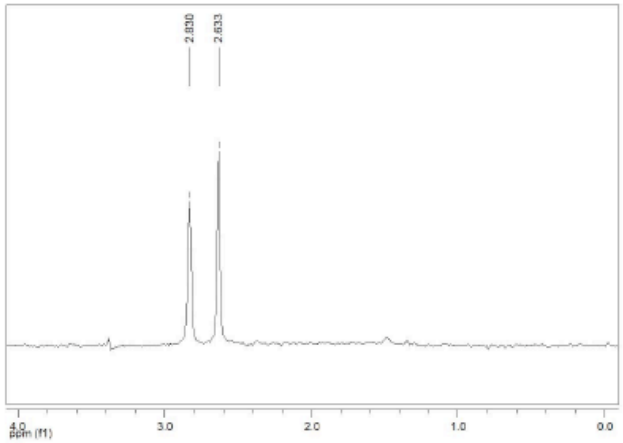

(b)

0.5 eq. (–)-sparteine




(c)

1.0 eq. (–)-sparteine

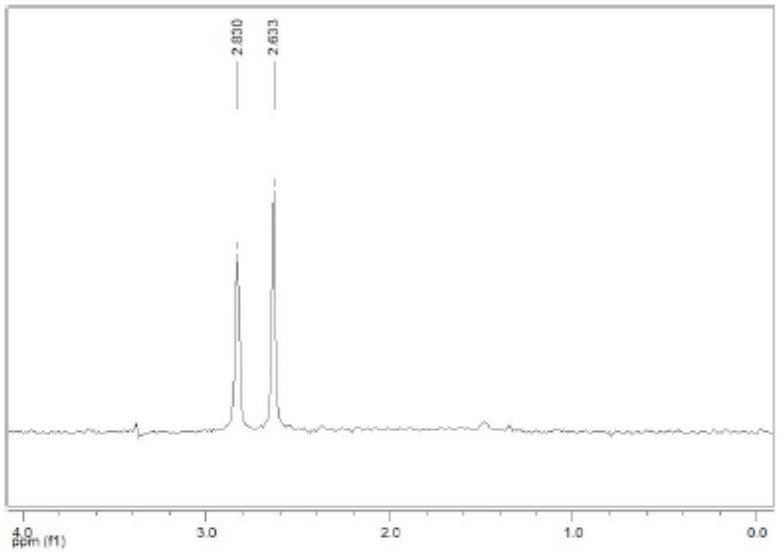



(d)

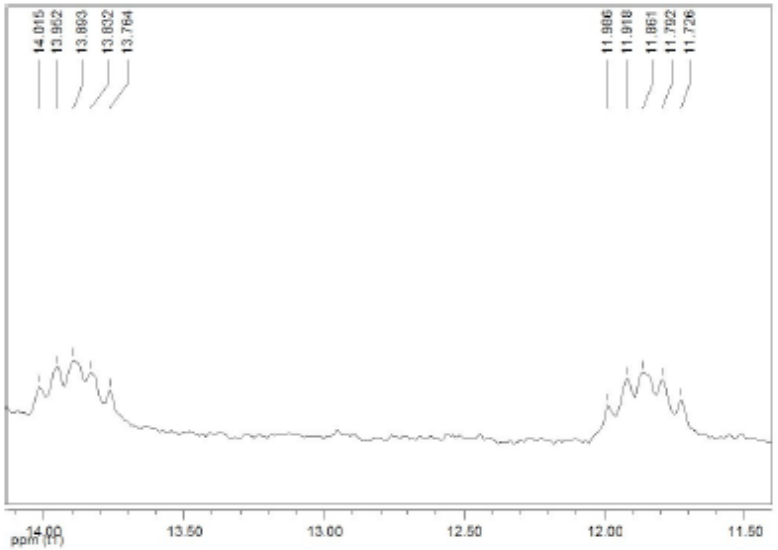
2.0 eq. (–)-sparteine

# the complexes of organolithium reagents

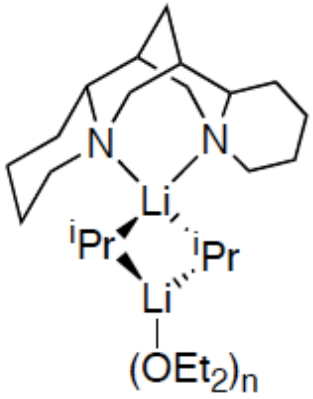
$^{6}$Li NMR of $^{6}$[Li]i-PrLi and sparteine in $Et_2O$




$^{13}$C NMR of $^{6}$[Li]i-PrLi and sparteine




Two different Lithium environment




$\delta$ 13.89 ppm ($^{1}J(^{6}Li,^{13}C) = 8.0$ Hz)

$\delta$ 11.86 ppm ($^{1}J(^{6}Li,^{13}C) = 8.5$ Hz)

Empirical Bauer-Winchester-Schleyer rule

$J(^{6}Li, ^{13}C) = (17+/-2)/n_c$

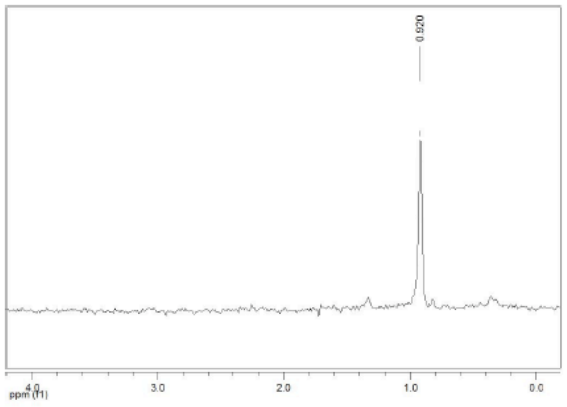
$n_c$: # of $^{6}$Li cation

$n_c = 2$

2 Different CH environment

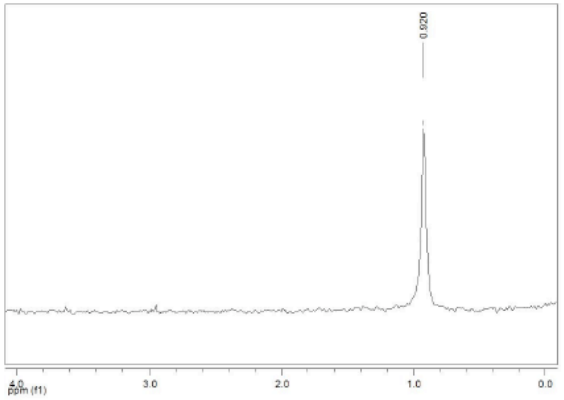
# Sparteine-Li complex in THF

$^{6}$Li NMR of $^{6}$[Li]i-PrLi and sparteinein THF-$d_8$



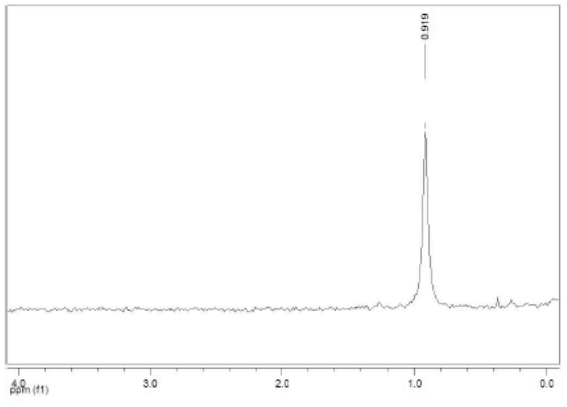

(a)

No (–)-sparteine



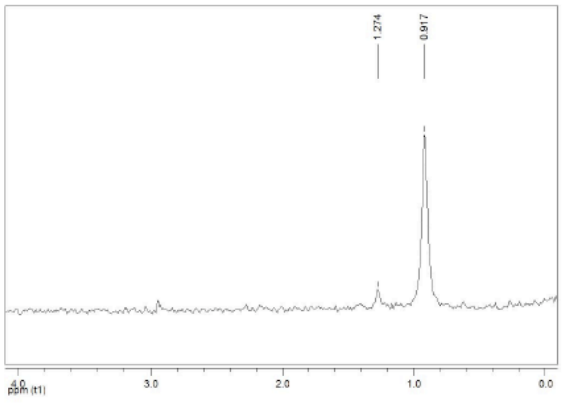

(b)

0.5 eq. (–)-sparteine




(c)

1.0 eq. (–)-sparteine

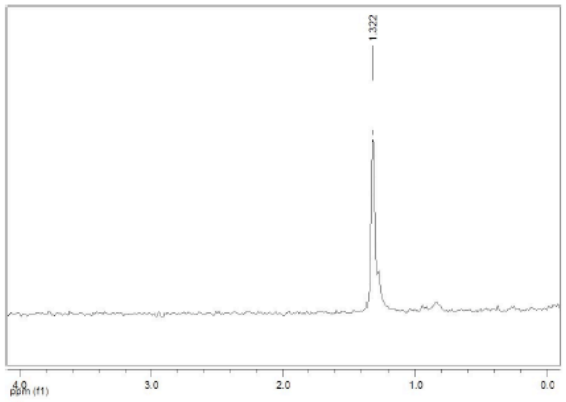



(d)

3.0 eq. (–)-sparteine

# Sparteine-Li complex in THF

$^{6}$Li NMR of $^{6}$[Li]i-PrLi and sparteinein in THF-$d_8$

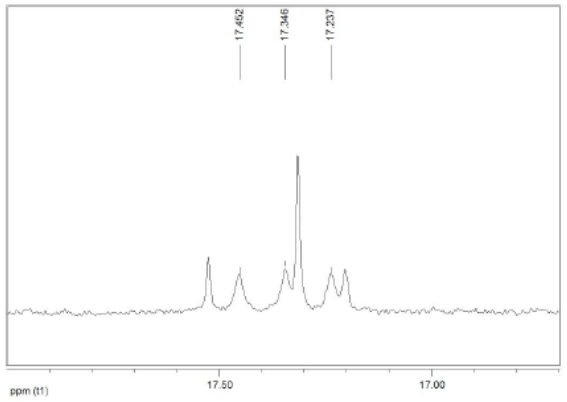



(e)

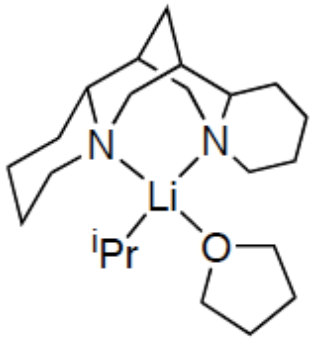
6.0 eq. (–)-sparteine

1 Li environment

$^{13}$C NMR of $^{6}$[Li]i-PrLi and sparteinein in THF-$d_8$



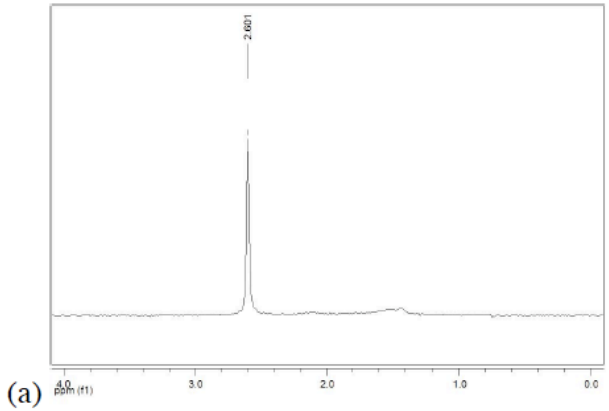

δ 17.35 ppm 1:1:1 triplet ($^{1}J(^{6}Li,^{13}C)$ = 13.5 Hz)




1 CH environment
1 Li cation

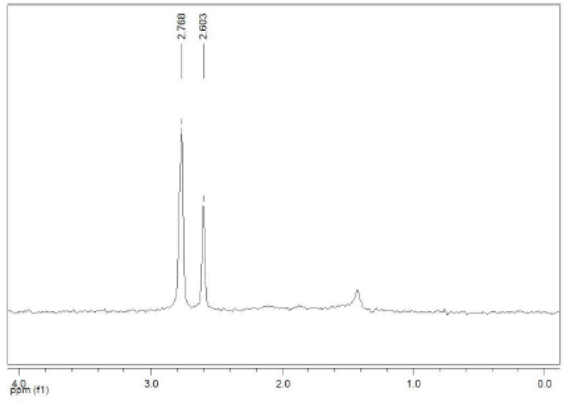
# the complexes of organolithium reagents

$^{6}$Li NMR of $^{6}$[Li]i-PrLi and sparteine surrogate in $Et_2O$-$d_{10}$



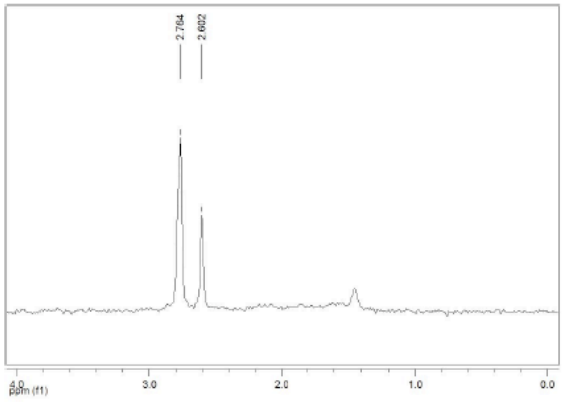

(a)

No (+)-sparteine surrogate



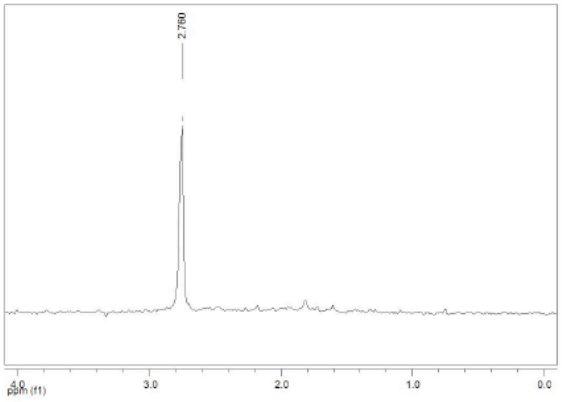

(b)

0.5 eq. (+)-sparteine surrogate




(c)

1.0 eq. (+)-sparteine surrogate

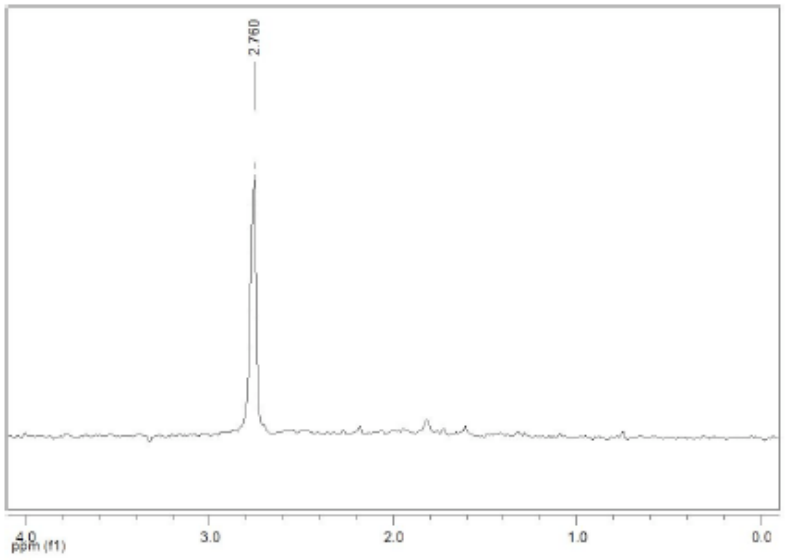



(d)

1.5 eq. (+)-sparteine surrogate

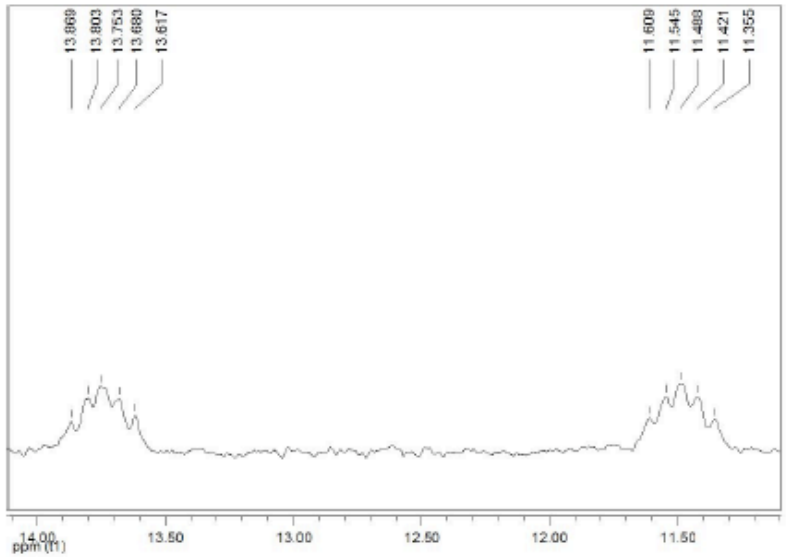
# the complexes of organolithium reagents

$^{6}$Li NMR of $^{6}$[Li]i-PrLi and sparteine surrogatein $Et_2O$




1 Lithium environment

$^{13}$C NMR of $^{6}$[Li]i-PrLi and sparteine surrogate




$\delta$ 13.75 ppm ($^{1}J(^{6}Li,^{13}C) = 8.0$ Hz)

$\delta$ 11.49 ppm ($^{1}J(^{6}Li,^{13}C) = 8.0$ Hz)

$J(^{6}Li, ^{13}C) = (17+/-2)/n_c$

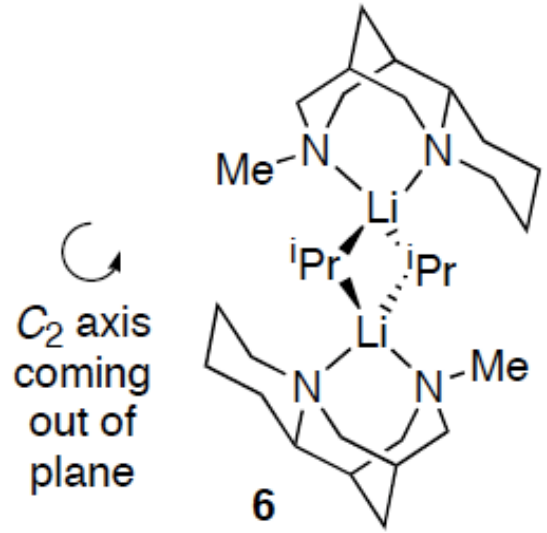
$n_c$: # of $^{6}$Li cation

$n_c = 2$

2 Different CH environment

# Proposed structure in $Et_2O$

Head-to-tail homodimer

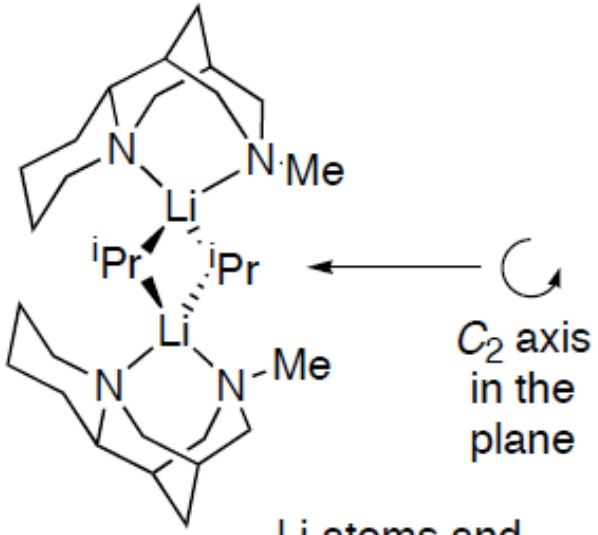



$C_2$ axis coming out of plane

**6**

Li atoms equivalent
C atoms different

Head-to-head homodimer

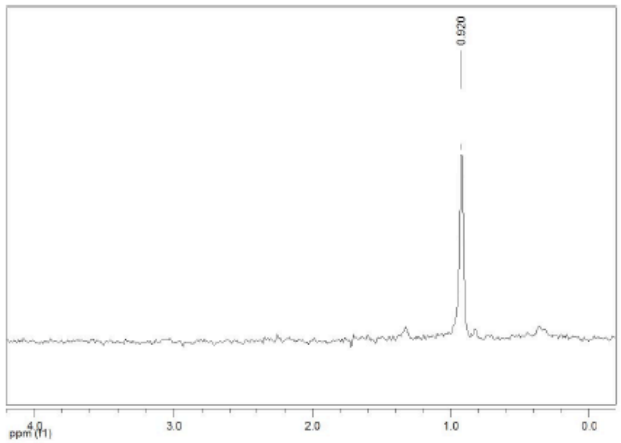



$C_2$ axis in the plane

Li atoms and
C atoms are
equivalent

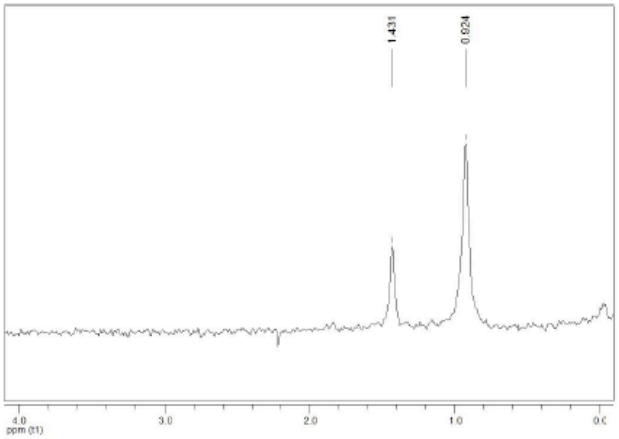
# Sparteine surrogate-Li complex in THF

$^{6}$Li NMR of $^{6}$[Li]i-PrLi and sparteinein surrogate THF-$d_8$



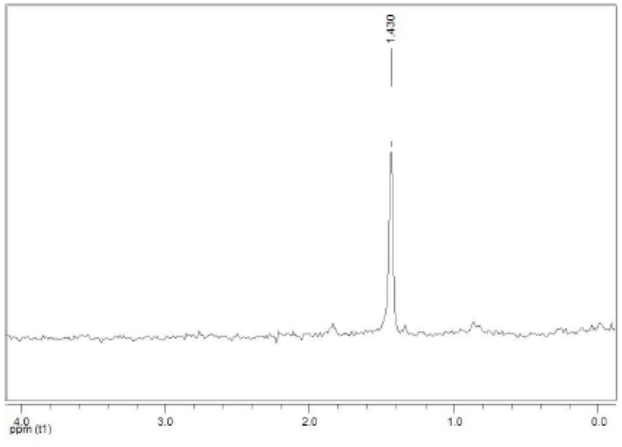

(a)

No (+)-sparteine surrogate



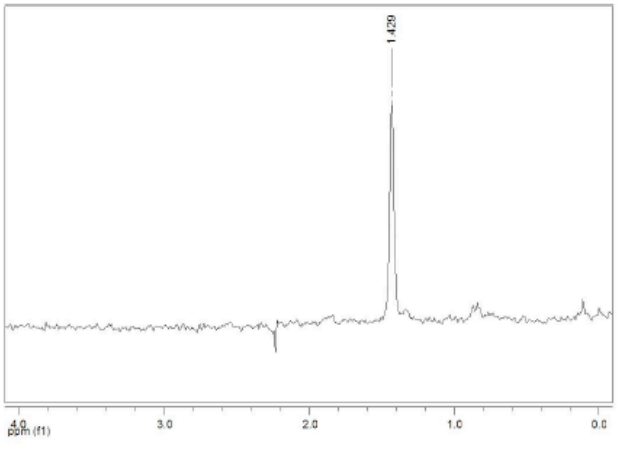

(b)

0.5 eq. (+)-sparteine surrogate




(c)

1.0 eq. (+)-sparteine surrogate

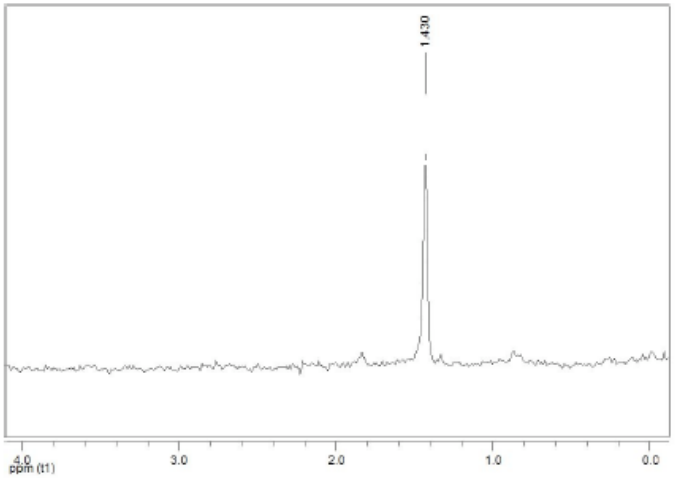



(d)

1.5 eq. (+)-sparteine surrogate

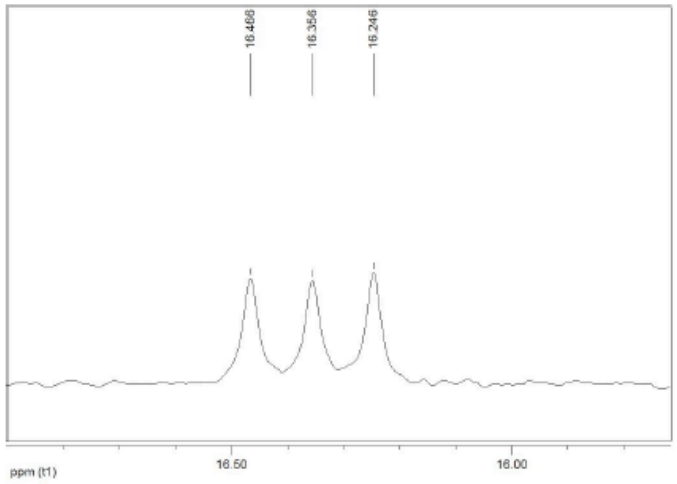
# Sparteine surrogate-Li complex in THF

$^{6}$Li NMR of $^{6}$[Li]i-PrLi and sparteinein surrogatein THF-$d_8$




1 Li environment

$^{13}$C NMR of $^{6}$[Li]i-PrLi and sparteinein surrogate in THF-$d_8$

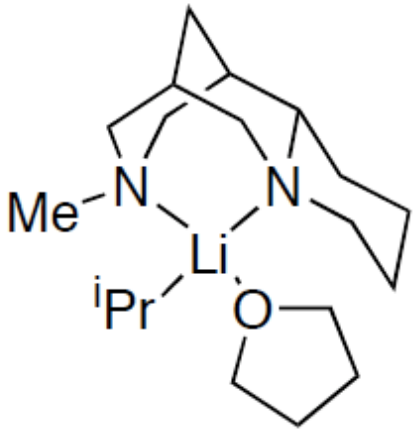


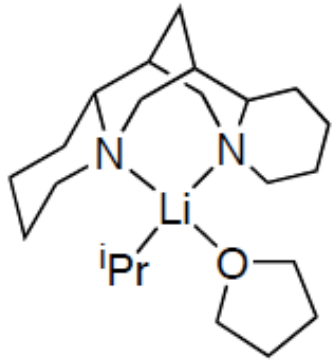

δ 16.36 ppm 1:1:1 triplet ($^{1}J(^{6}\mathrm{Li},^{13}\mathrm{C})$ = 14.0 Hz)

1 CH environment
1 Li cation

# Proposed structure in THF

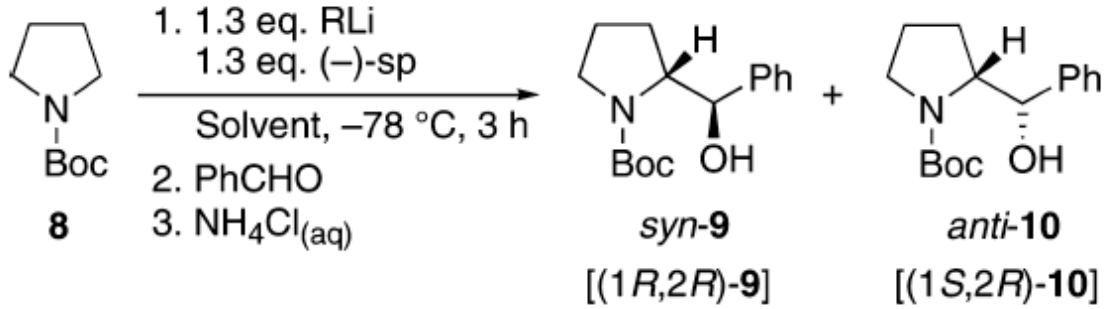
Sparteine surrogate (1.0 equiv) with i-PrLi (1.0 equiv.) in THF



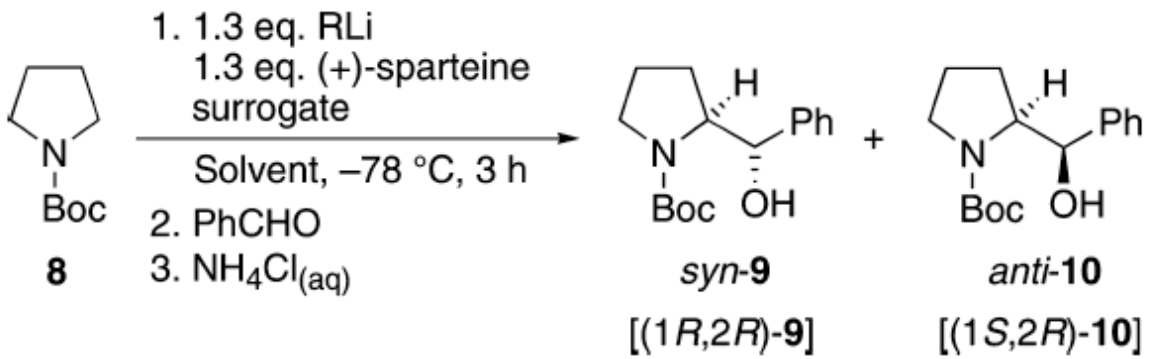

Sparteine (6.0 equiv.) with i-PrLi (1.0 equiv.) in THF
No complex was formed when 1.0 equiv. sparteine

# Tests in the reactions




| RLi | solvent | yield of *anti*-**10** (%)[a] | er of *anti*-**10**[b] |
|---|---|---|---|
| *i*-PrLi | $Et_2O$ | 22 | 95:5 |
| *s*-BuLi | $Et_2O$ | 23 | 97:3 |
| *s*-BuLi | TBME | 24 | 98:2 |
| *i*-PrLi | THF | 22 | 60:40 |
| *s*-BuLi | THF | 14 | 51:49 |
| *s*-BuLi | 2-methyl-THF | 29 | 55:45 |

# Tests in the reactions




| RLi | solvent | yield of *anti*-10 (%)[a] | er of *anti*-10[b] |
|---|---|---|---|
| *i*-PrLi | $Et_2O$ | 23 | 95:5 |
| *s*-BuLi | $Et_2O$ | 23 | 94:6 |
| *s*-BuLi | TBME | 31 | 93:7 |
| *i*-PrLi | THF | 21 | 97:3 |
| *s*-BuLi | THF | 20 | 95:5 |
| *s*-BuLi | 2-methyl-THF | 22 | 93:7 |

# Why do we about this at all?

| property | MeTHF | THF | $Et_2O$ |
|---|---|---|---|
| dielectric const | 6.97 | 7.5 | 4.42 |
| dipole moment, Debye | 1.38 | 1.69 | 1.11 |
| water solubility, g/100 g | 4 | mis | 1.2 |
| Hildebrand, $MPa^{1/2}$ | 16.9 | 18.7 | 15.5 |
| solvation energy, kcal/mol | 0.6 | 0 | 2.3 |
| donor number | 18 | 20.5 | 19.2 |

MeTHF provides clean organic-water phase separation

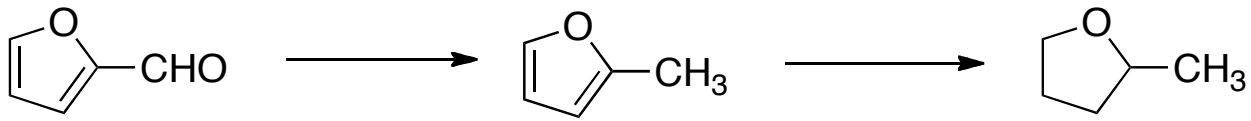
MeTHF has even lower melting point (-136 $^{o}$C) than THF (-108 $^{o}$C)

MeTHF and THF has higher bp than $Et_2O$, which makes them attractive in industrial process.

Aycock, D. F. Org. Process. Res. Dev. 2007, 11, 156.

# Even better of MeTHF: from a renewable source

Agriculture waste
Such as corncobs, bagasse




MeTHF production process

# Thank you!