Preparation and Reactions of Enantiomerically Pure α-Functionalized Grignard Reagents

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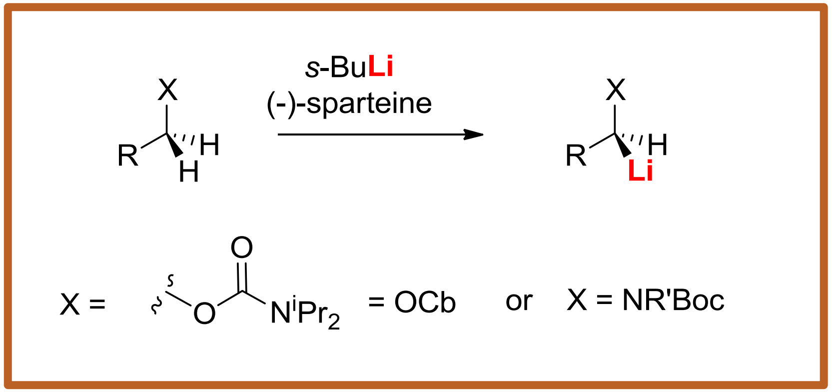
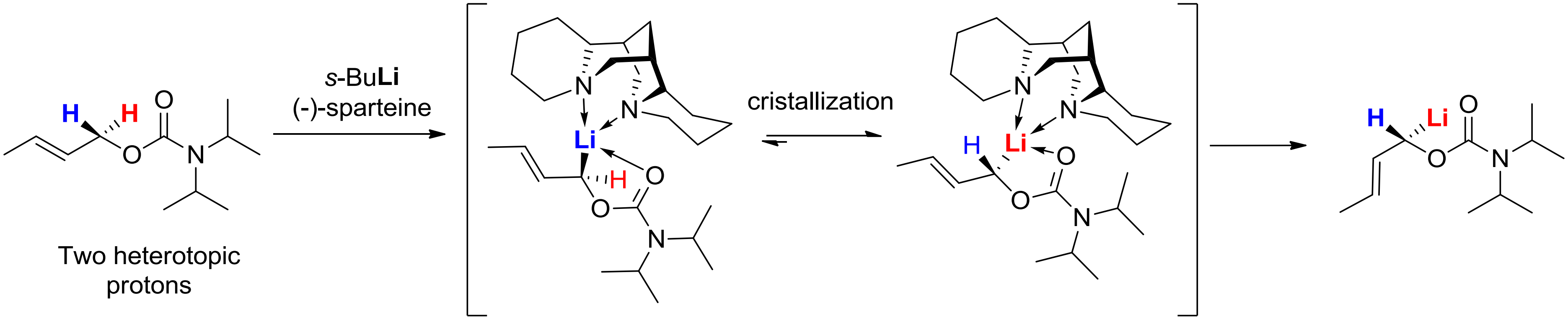
Jérémy Merad – 03/06/13

Pioneering Works



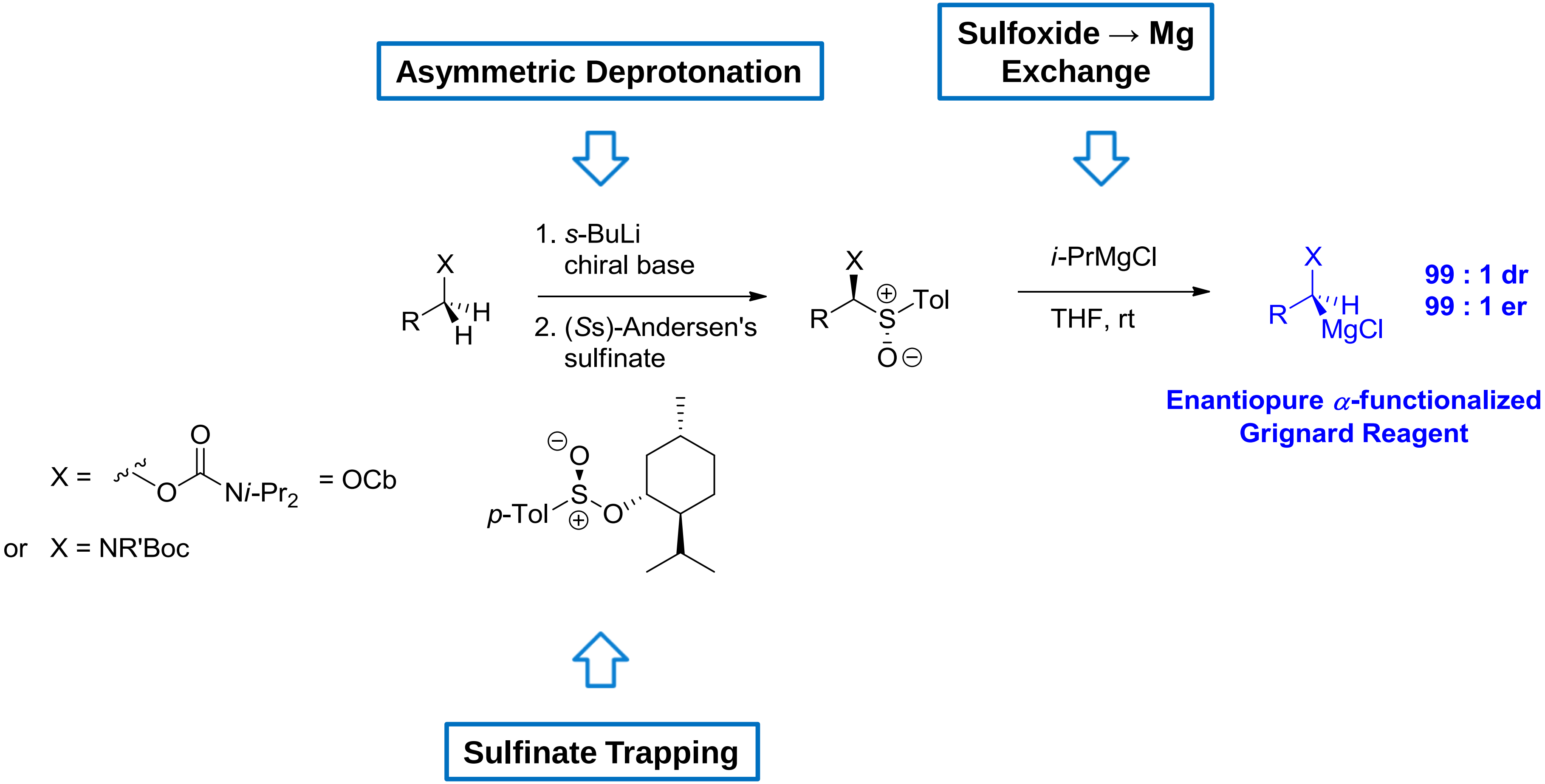
Hoppe's works



Two heterotopic
protons

- **er is substract depending and varies typically between 85:15 and 95:5**
- **only one enantiomer available**
- **variability of commmercial availability of (-)-sparteine**
- **configurational and chemical unstability of organolithium compounds above -78°C**

Toward a New Strategy



Asymmetric Deprotonation

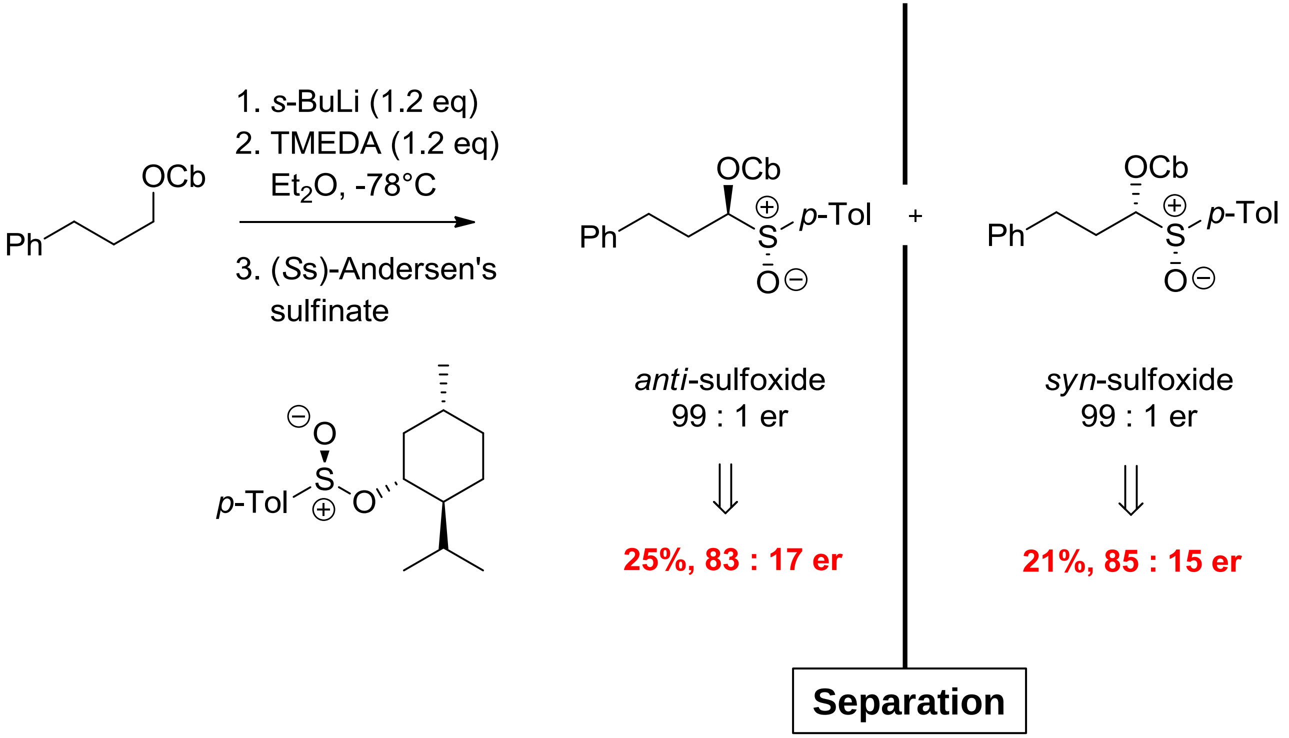
Sulfoxide → Mg Exchange

99 : 1 dr
99 : 1 er

Enantiopure α-functionalized Grignard Reagent

Sulfinate Trapping

Deprotonation/Sulfinate Trapping Sequence : Preliminar Studies



1. *s*-BuLi (1.2 eq)
2. TMEDA (1.2 eq) Et_2O, -78°C
3. (*S*s)-Andersen's sulfinate

anti-sulfoxide
99 : 1 er

⇓

25%, 83 : 17 er

syn-sulfoxide
99 : 1 er

⇓

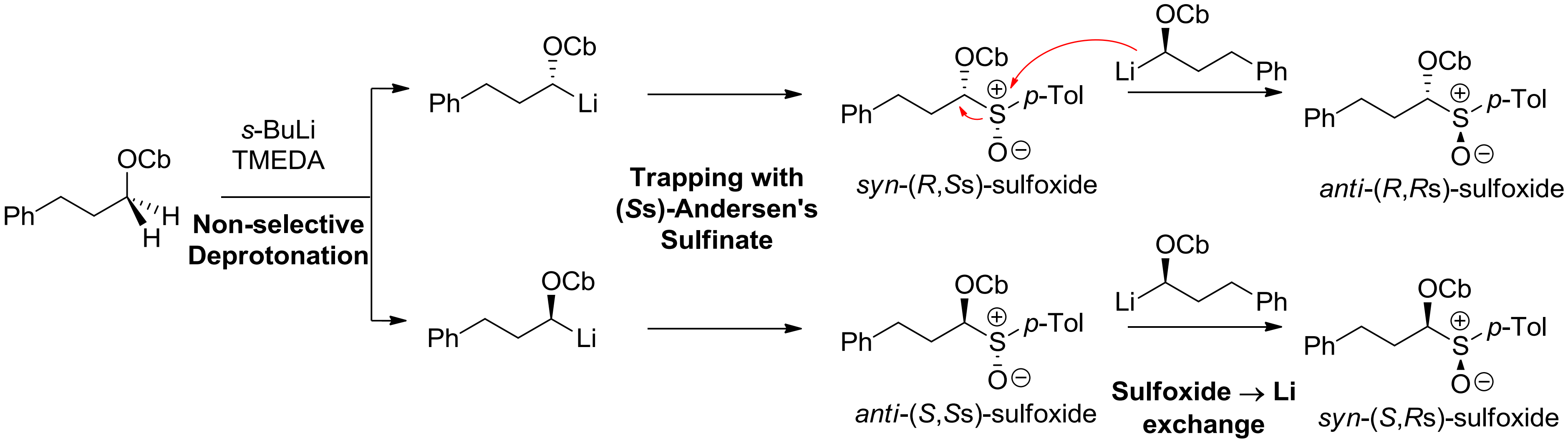
21%, 85 : 15 er

Separation

High stereospecificity expected

Disappointing Results

Proposed Mechanism For The Lack of Stereospecificity

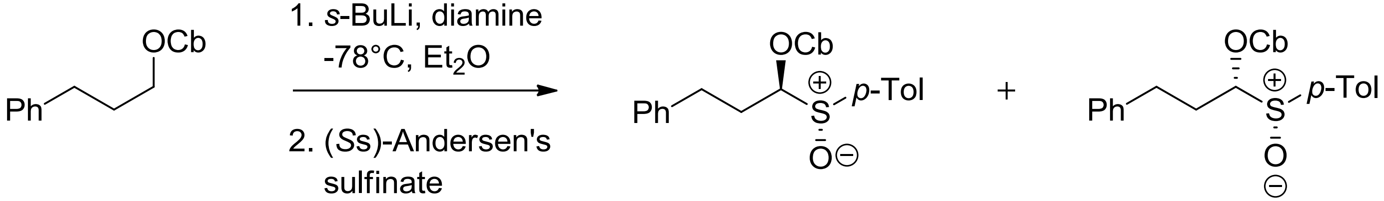


Racemic Mixture

Two Enantiopure Diastereoisomers

Enantiomers Of The Previous Sulfoxides

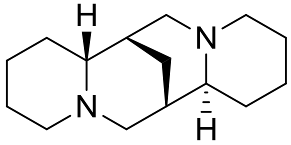
Optimization



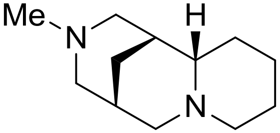
anti-sulfoxide

syn-sulfoxide

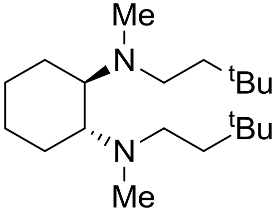
Normal Addition : addition of Andersen's sulfinate to organolithium
Reverse Addition : addition of organolithium to Andersen's sulfinate
Trapping conditions A : -78 to rt and 18h at rt
Trapping conditions B : -78°C for 5 min.



(-)-sparteine
((-)-sp)



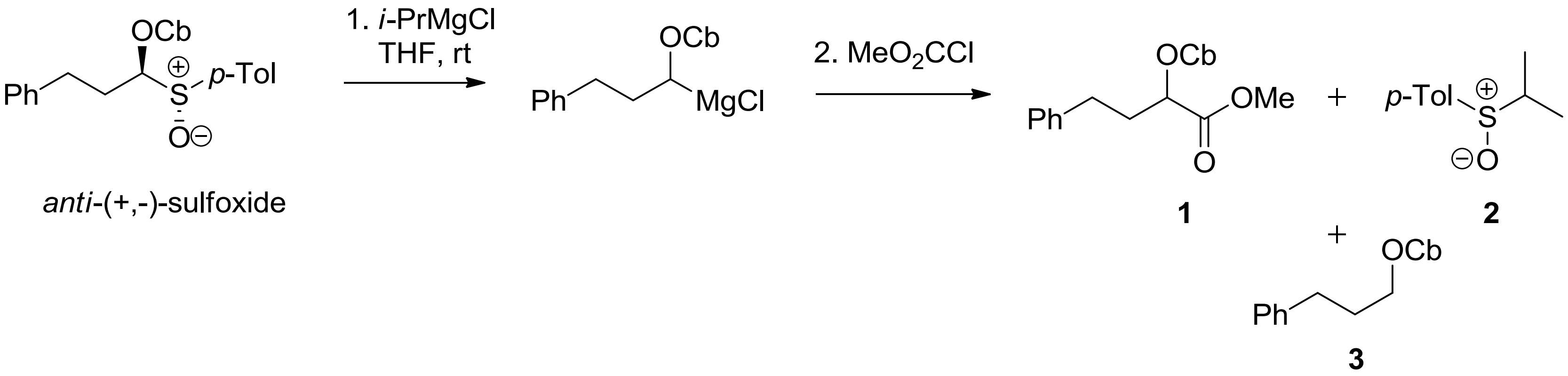
(+)-sparteine surrogate
((+)-sp surr)



(*R*,*R*)-diamine

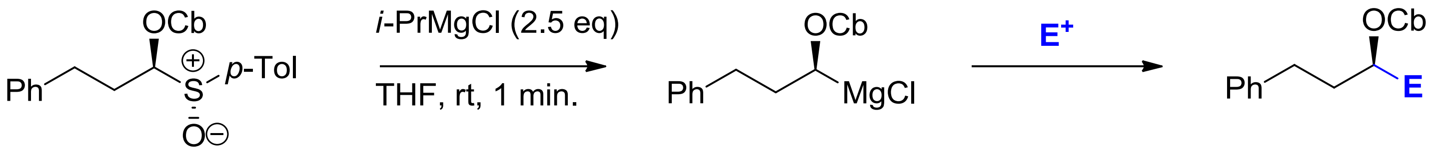
Diamine	Trapping cond.	Anti-sulf. %, er	Syn-sulf. %, er
TMEDA	Reverse, B	25, 87:13	29, 90:10
(-)-sp	Normal, A	53, 99:1	0.2, n.d.
(+)-sp surr	Normal, A	7, 87:13	45, 99:1
(*R*,*R*)-diamine	Reverse, B	56, 99:1	14, 93:7
(*S*,*S*)-diamine	Reverse, B	17, 95:5	54, 99:1

Sulfoxide → Mg Exchange

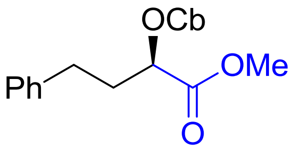


Equiv of *i*-PrMgCl	Time (min.)	1 (%)	2 (%)	3 (%)	Starting (%)
1.3	5	48	81	14	4
1.3	1	65	73	6	8
1.5	5	42	82	17	0
1.5	1	67	84	9	0
2.5	1	75	84	5	0

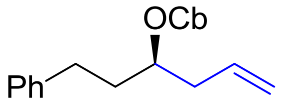
Examples of Enantiopure Carbamates Obtained



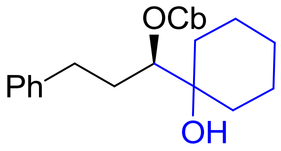
anti-sulfoxide
99:1 er



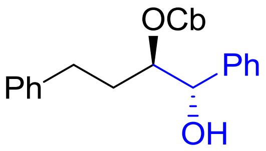
(*S*)-carbamate
73%, 99:1 er
E^+ = MeO$_2$CCl



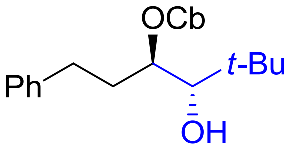
(*S*)-carbamate
70%, 99:1 er
E^+ = CuBr.Me$_2$S
then allyl bromide



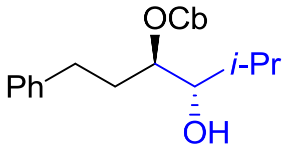
(*S*)-carbamate
71%, 99:1 er
E^+ = cyclohexanone



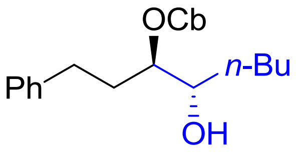
(*R*,*S*)-diol, 99:1 er
71%, 90:10 dr
E^+ = PhCHO



(*R*,*S*)-diol, 99:1 er
78%, 70:30 dr
E^+ = *t*-BuCHO

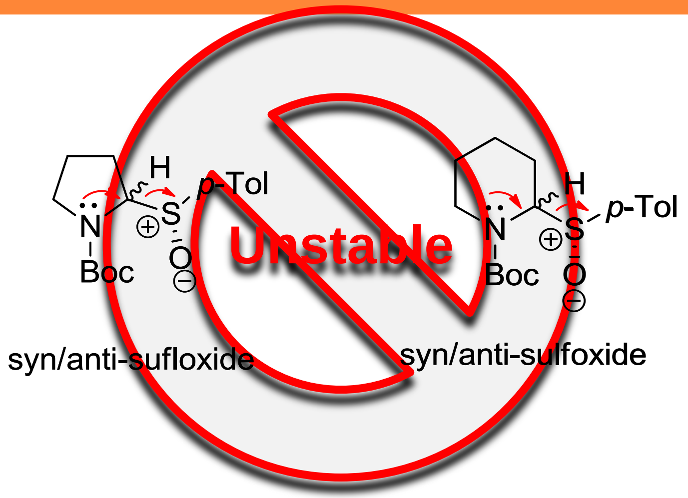


(*R*,*S*)-diol, 99:1 er
70%, 99:1 dr
E^+ = *i*-PrCHO



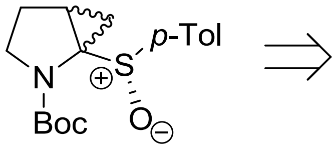
(*R*,*S*)-diol, 99:1 er
65%, 90:10 dr
E^+ = *n*-BuCHO

Toward the α–Amino Sulfoxides

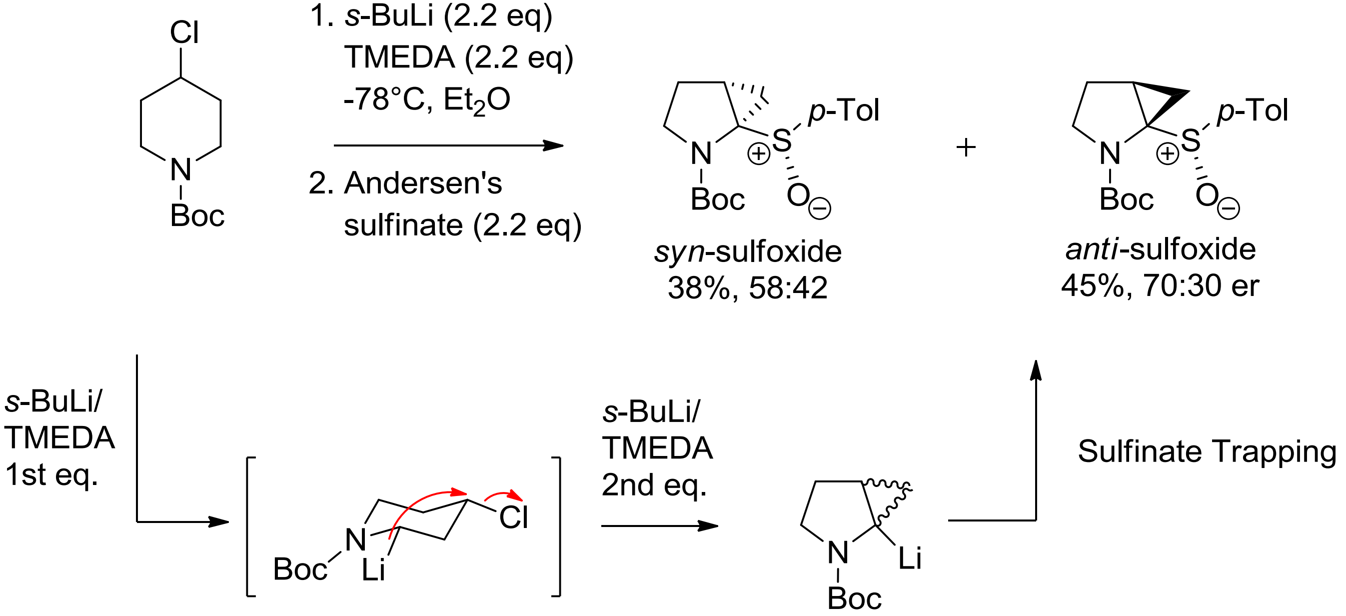


syn/anti-sufloxide

syn/anti-sulfoxide



α-elimination disfavoured by the [3:1:0] bicyclic system



1. *s*-BuLi (2.2 eq) TMEDA (2.2 eq) -78°C, Et_2O

2. Andersen's sulfinate (2.2 eq)

syn-sulfoxide
38%, 58:42

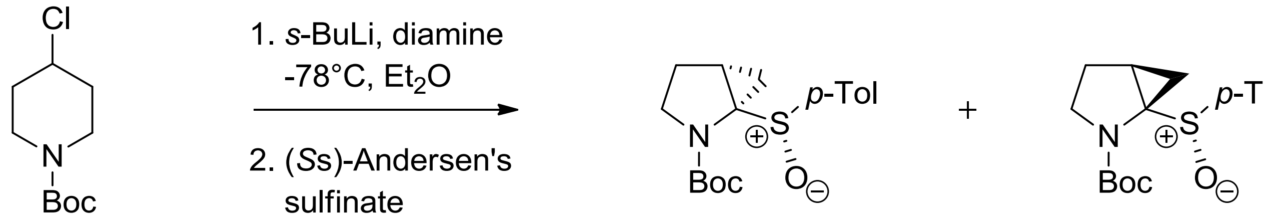
anti-sulfoxide
45%, 70:30 er

s-BuLi/ TMEDA 1st eq.

s-BuLi/ TMEDA 2nd eq.

Sulfinate Trapping

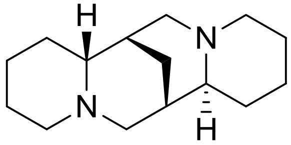
Toward the α–Amino Sulfoxides : Optimization



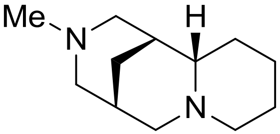
syn-sulfoxide

anti-sulfoxide

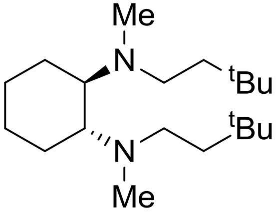
Normal Addition : addition of Andersen's sulfinate to organolithium
Reverse Addition : addition of organolithium to Andersen's sulfinate
Trapping conditions A : -78 to rt and 18h at rt
Trapping conditions B : -78°C for 5 min.



(-)-sparteine
((-)-sp)



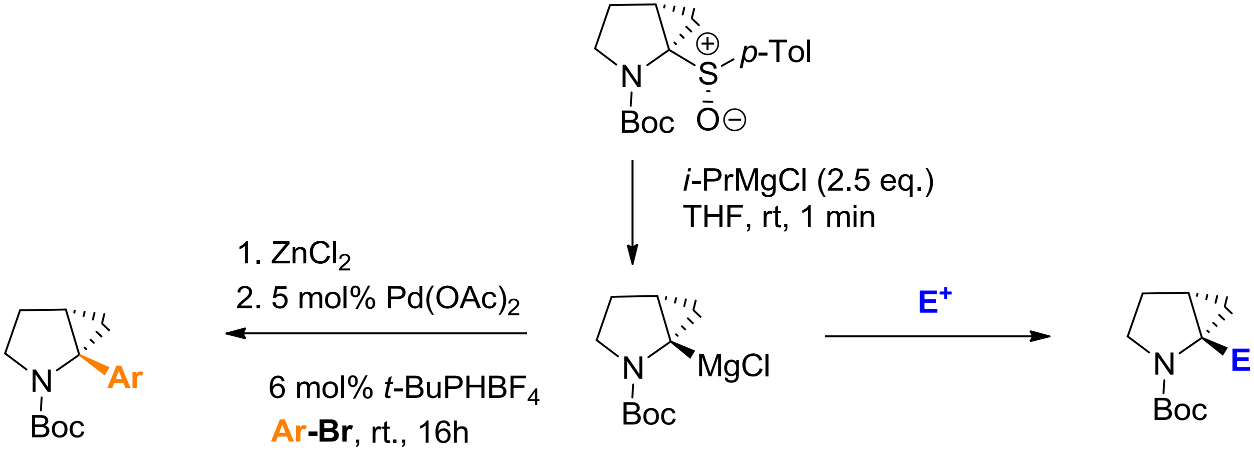
(+)-sparteine surrogate
((+)-sp surr)



(*R*,*R*)-diamine

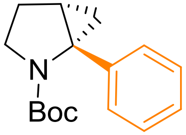
Diamine	Trapping cond.	*Syn*-sulf. %, er	*Anti*-sulf. %, er
TMEDA	Reverse, B	39, 88:11	44, 88:12
(-)-sp	Reverse, B	27, 96:4	24, 89:11
(+)-sp surr	Reverse, B	26, 99:1	27, 93:7
(*R*,*R*)-diamine	Reverse, B	51, 99:1	25, 87:13
(*S*,*S*)-diamine	Reverse, B	17, 89:11	54, 87:13

Enantiopure Amines Obtained

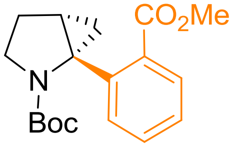


(*R*,*R*)-Grignard Reagent

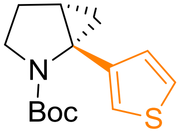
Negishi Coupling



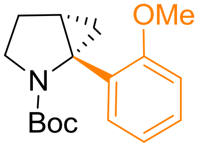
(*S*,*R*)-amine
68%, 99:1 er



(*S*,*R*)-amine
74%, 99:1 er

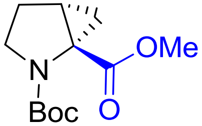


(*S*,*R*)-amine
72%, 99:1 er

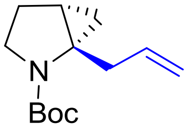


(*S*,*R*)-amine
68%, 99:1 er

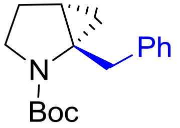
Electrophilic Trapping



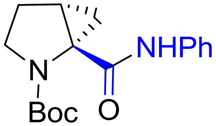
(*S*,*R*)-amine
89%, 99:1 er
E^+ = MeO$_2$CCl



(*S*,*R*)-amine
69%, 99:1 er
E^+ = CuBr.Me$_2$S
then allyl bromide



(*S*,*R*)-amine
64%, 99:1 er
E^+ = CuBr.Me$_2$S
then benzyl bromide



(*S*,*R*)-amine
67%, 99:1 er
E^+ = PhCNO

Conclusion

- New simple strategy to prepare enantiopure α–alkoxy and α–amino Grignard reagents

Perspectives :

- Improve the asymmetric deprotonation selectivity
- Increase the scope of the reaction