(–)-Sparteine-mediated deprotonations

Some new insight and applications in enantioselective synthesis

Ischia Advanced School of Organic Chemistry (IASOC) 2004

September 18 - 23, Ischia Porto (Napoli, Italy)

Outline

- Asymmetric Deprotonation of Alkyl Carbamates
- Synthesis of (–)-Slaframine
- Asymmetric Deprotonation of Allyl Carbamates
- Enantioselective Homoaldol Reaction
- Enantioselective Cycloalkylation
- Synthesis of (–)-Kainic Acid
- Homoenolate Reagents by Asymmetric γ-Deprotonation
- Cyclopropane Synthesis via Carbamoyl Migration

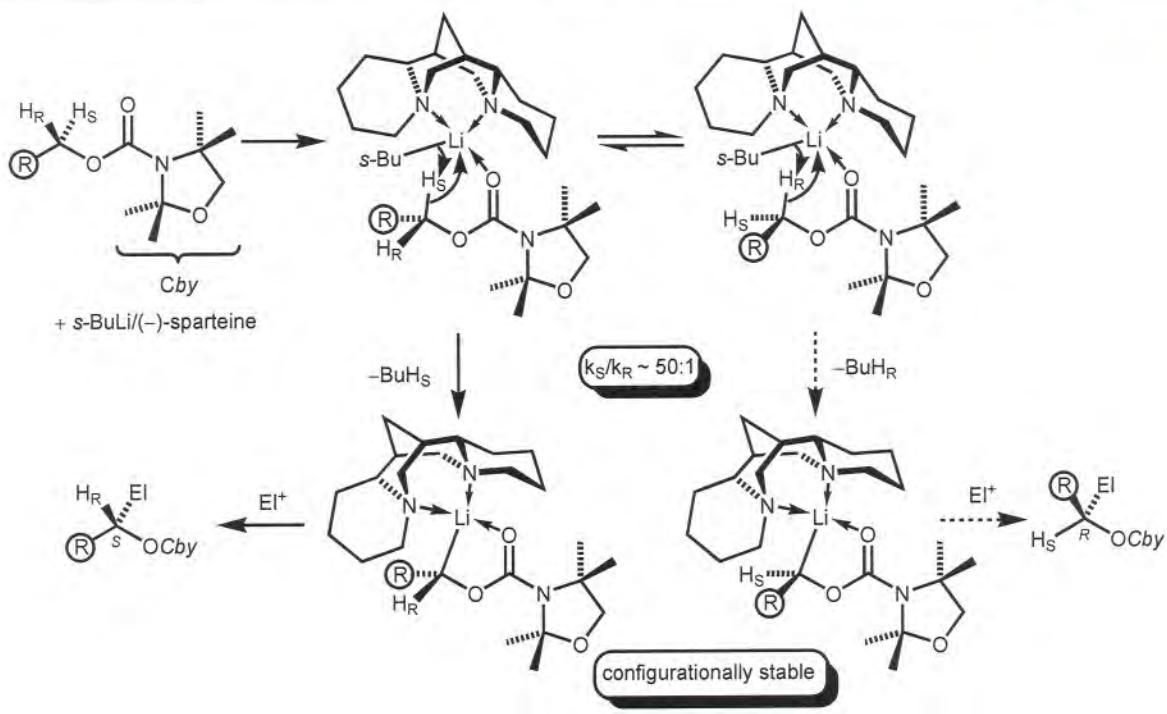
D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376; *Int. Ed. Engl.* **1997**, *36*, 2282.

A. Basu, S. Thayumanavan, *Angew. Chem. Int. Ed.* **2002**, *41*, 717.

D. Hoppe, F. Marr, M. Brüggemann, in *Organolithiums in Enantioselective Synthesis* (Ed. D. M. Hodgson), *Topics in Organometallic Chemistry*, Vol 5, **2003**, 61-138.
P. Beak, T. A. Johnson, D. D. Kim, S. H. Lim, *ibid*, 139.
Further contributions in this volume by: D. M. Hodgson, B. Goldfuss, T. Toru, J. Clayden, J. F. Normant.

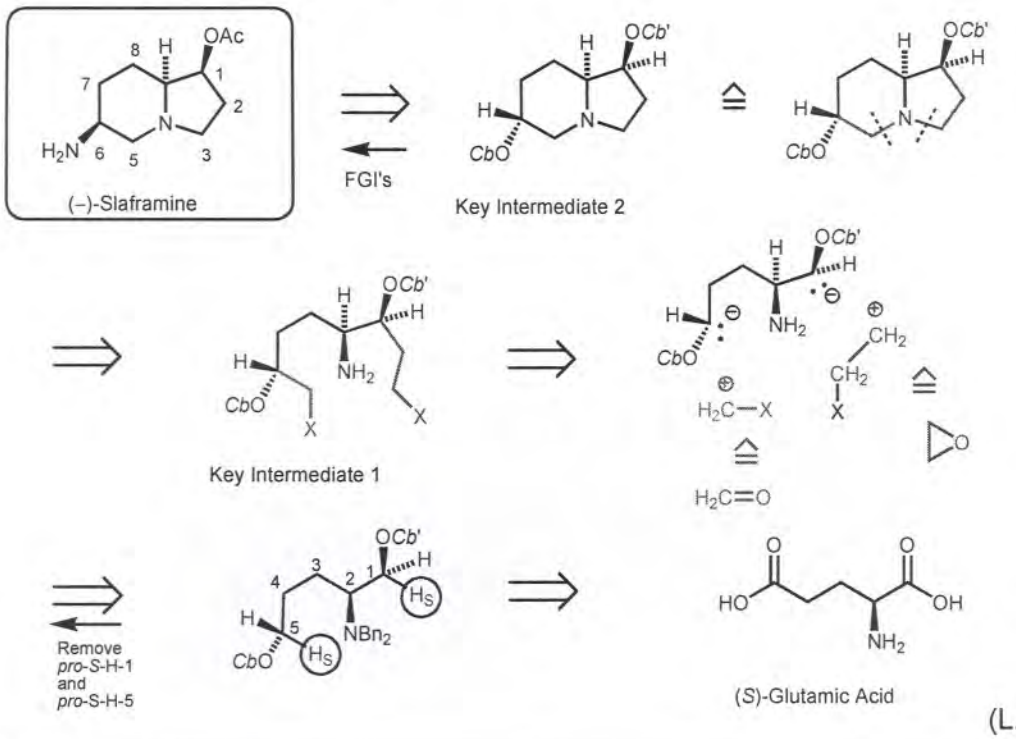
D. Hoppe, G. Christoph, „*Asymmetric deprotonation with alkyllithium – (–)-sparteine*", in *The Chemistry of Organolithium Compounds* (Eds. Z. Rappoport, I. Marek), in Patai Series *The Chemistry of Functional Groups*, p. 1055-1164, Wiley, **2004**.

Kinetic Control by Selection between Enantiotopic Protons



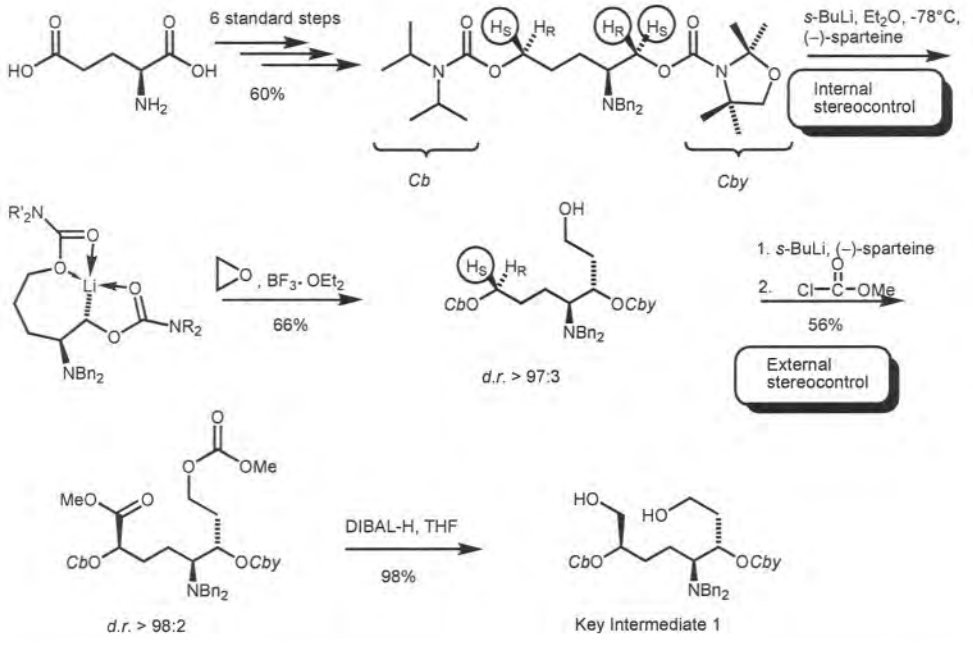
D. Hoppe, F. Hintze, P. Tebben, *Angew. Chem.* **1990**, *102*, 1457; *Int. Ed.* **1990**, *29*, 1422.
Mechanism of deprotonation: E.-U. Würthwein, K. Behrens, D. Hoppe, *Chem. Eur. J.* **1999**, *5*, 3459.

1. Retrosynthetic Scheme



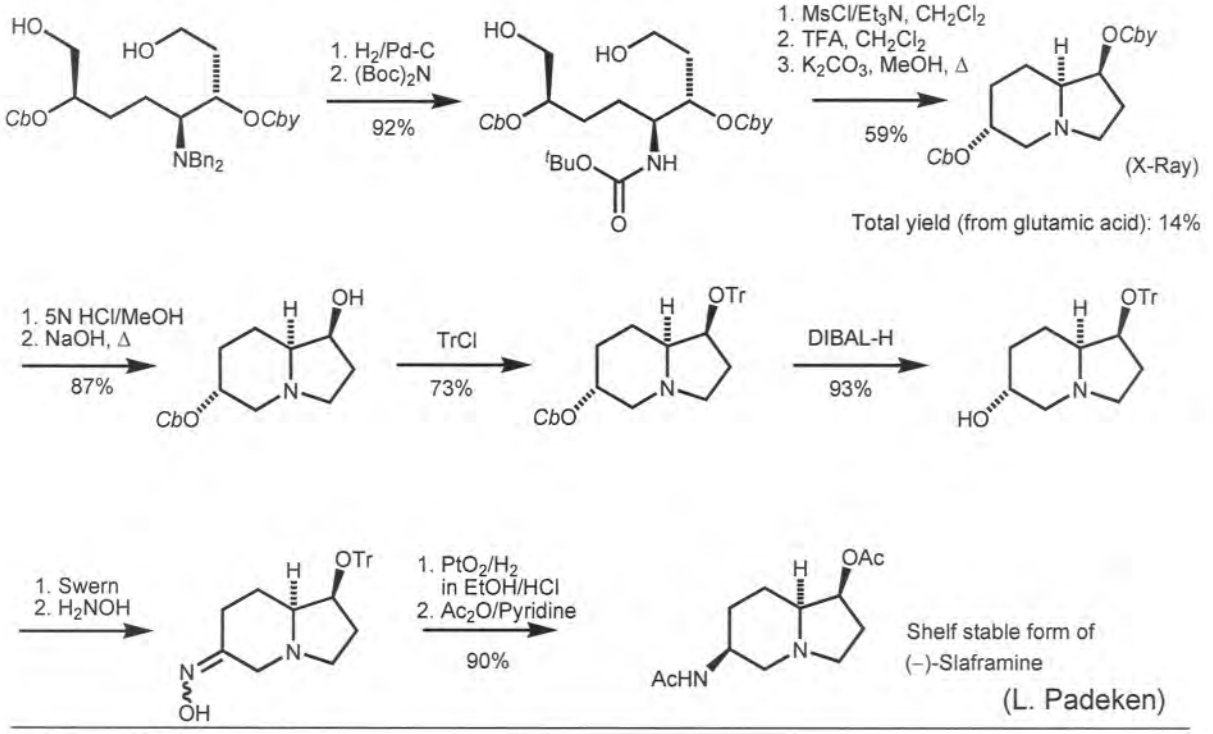
(L. Padeken)

2. Highly Diastereoselective Disubstitution of a *N,N*-Dibenzyl-(*S*)-glutamindiol Dicarbamate

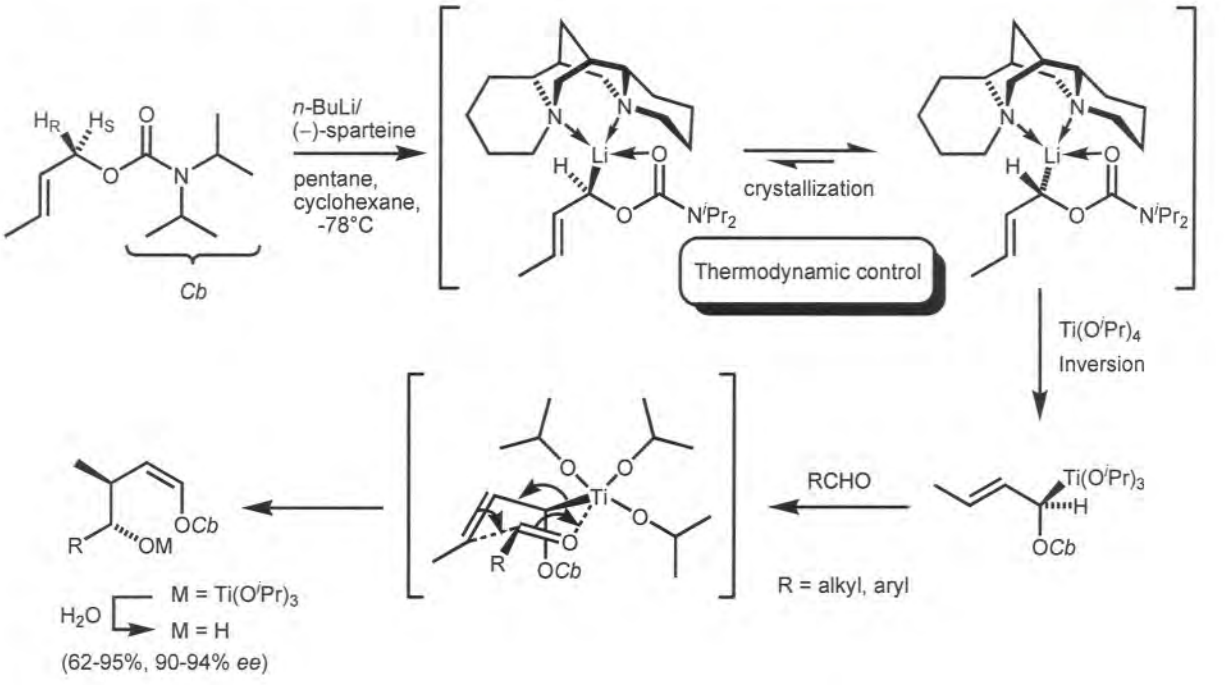


(L. Padeken)

3. Bicyclization and Final Steps

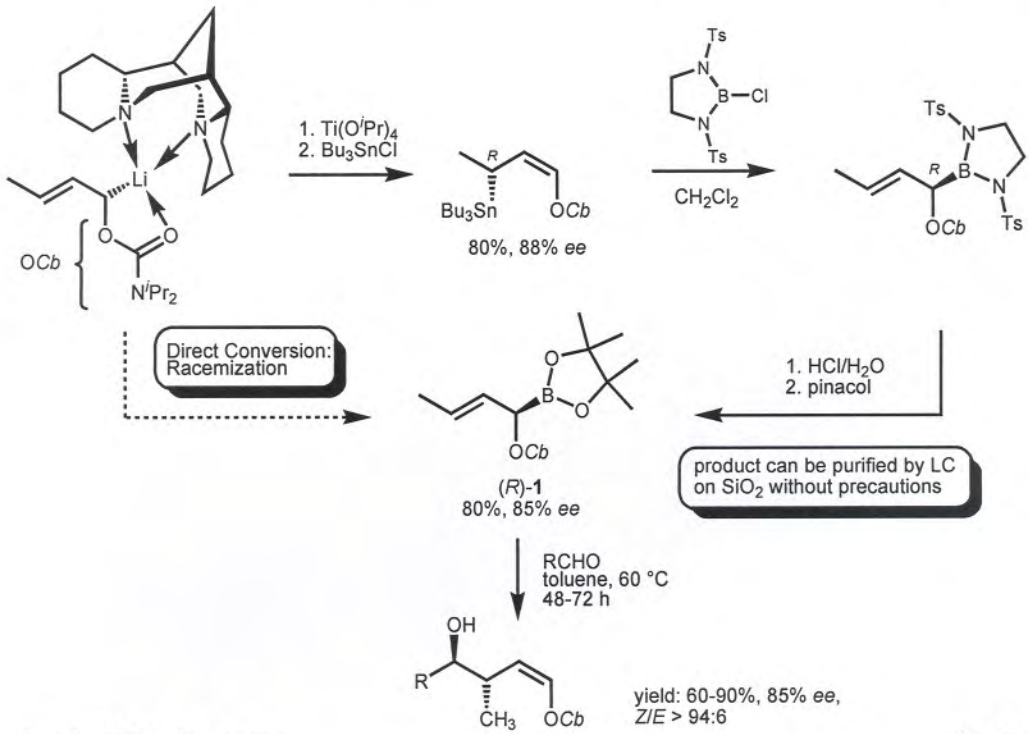


Enantioselective Homoaldol Reaction of (*E*)-Crotyl Carbamate



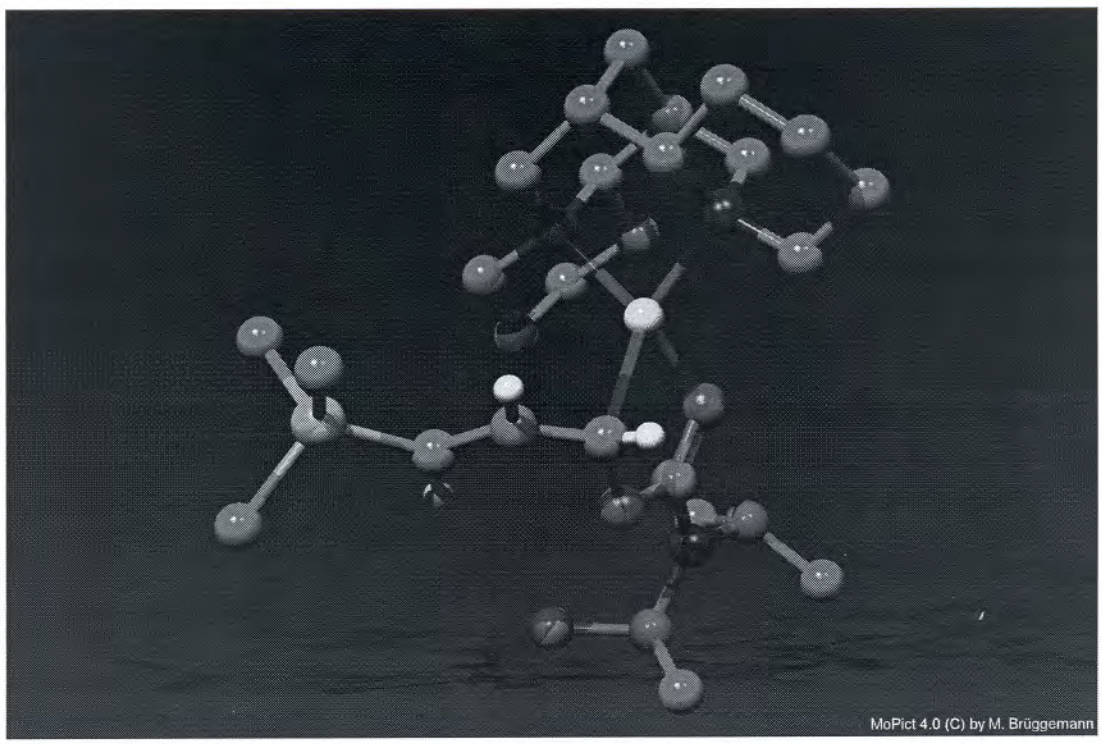
O. Zschage, *Angew. Chem.* **1989**, *101*, 67; H. Paulsen, C. Graeve, *Synthesis* **1996**, 141.

(*S*)-1-Lithiocrotyl Carbamate – Conversion into an Air- and Water-Stable, Chiral Boron Homoenolate Reagent



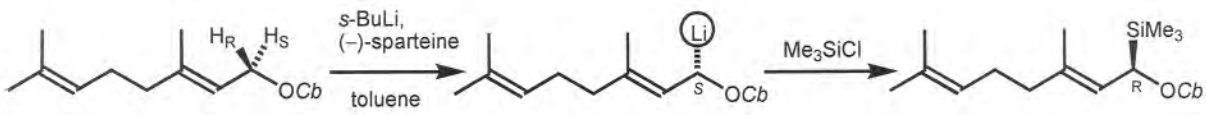
Synthesis **2004**, in press. (E. Beckmann)

X-Ray Structure of [(CH$_3$)$_3$Si(CH)$_3$OC(O)N*i*Pr$_2$Li(Sparteine)]



M. Marsch, K. Harms, O. Zschage, D. Hoppe, G. Boche*, *Angew. Chem.* **1991**, *103*, 338-339.

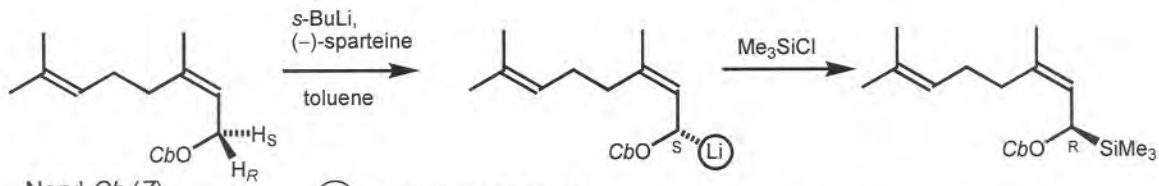
Configurational Stability of Lithiated 3,3-Disubstituted Allyl Carbamates



Geranyl-*Cb* (*E*)

-70° to -40°C

in situ	41%, 82% *ee*
15 min, -78°C	47%, 73% *ee*
240 min, -78°C	85%, 16% *ee*



Neryl-*Cb* (*Z*)

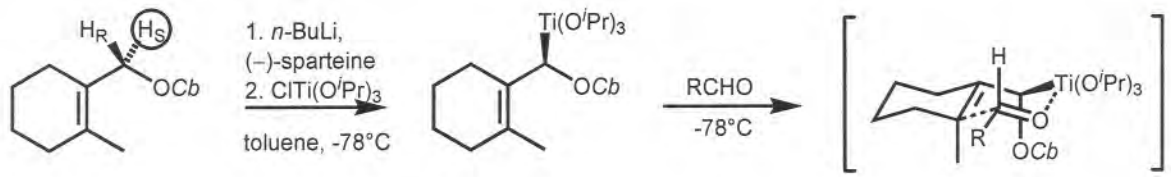
(Li) = Li • (–)-sparteine

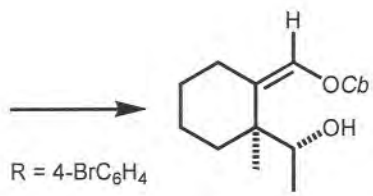
in situ	43%, 76% *ee*
15 min, -78°C	75%, 69% *ee*
240 min, -78°C	87%, 12% *ee*

Conclusions
- No torsion of allylic double bond
- Medium configurational stability of the stereogenic center

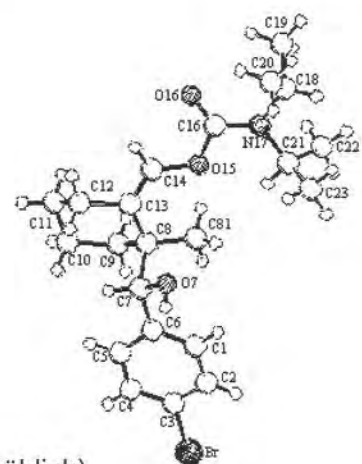
(W. Zeng)

Enantioselective Homoaldol Reaction of (1-Cycloalkenyl)methyl Carbamates

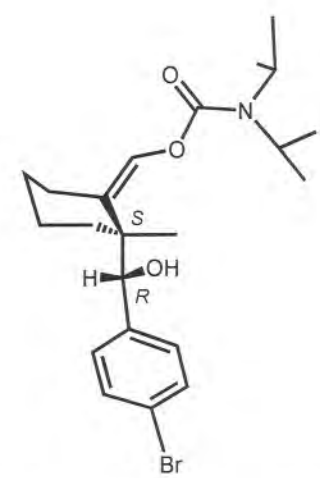




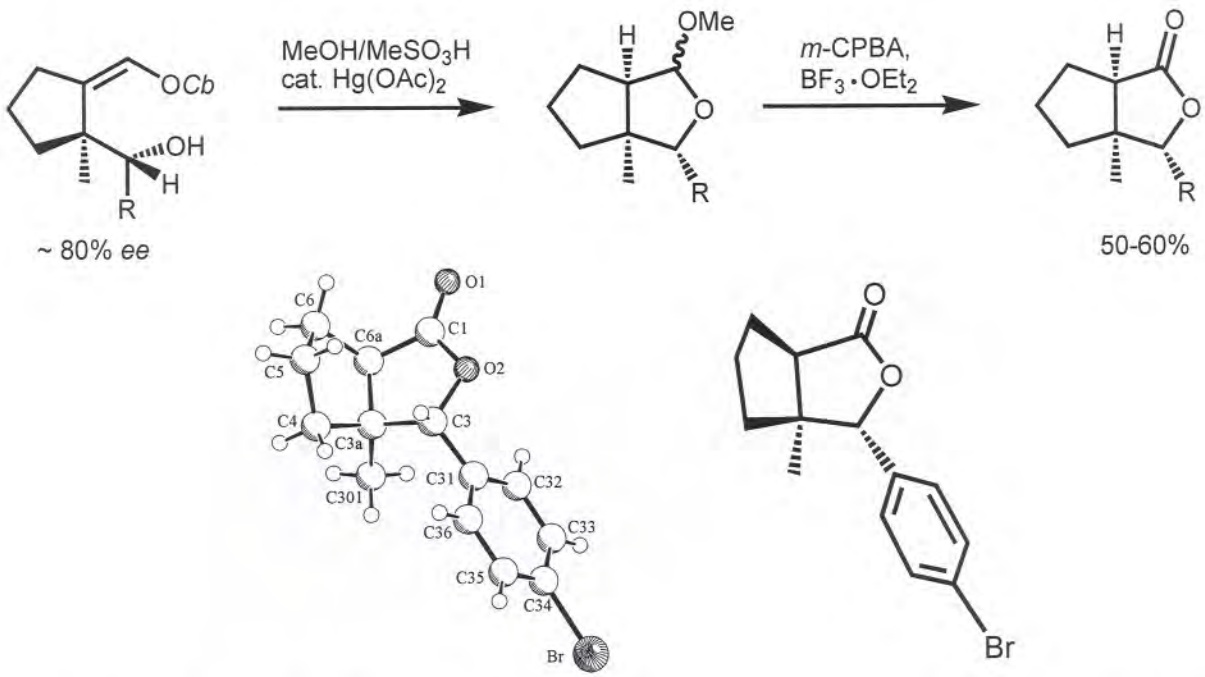
35%, 87% *ee*
d.r. > 97:3
Many further examples



(R. Fröhlich)

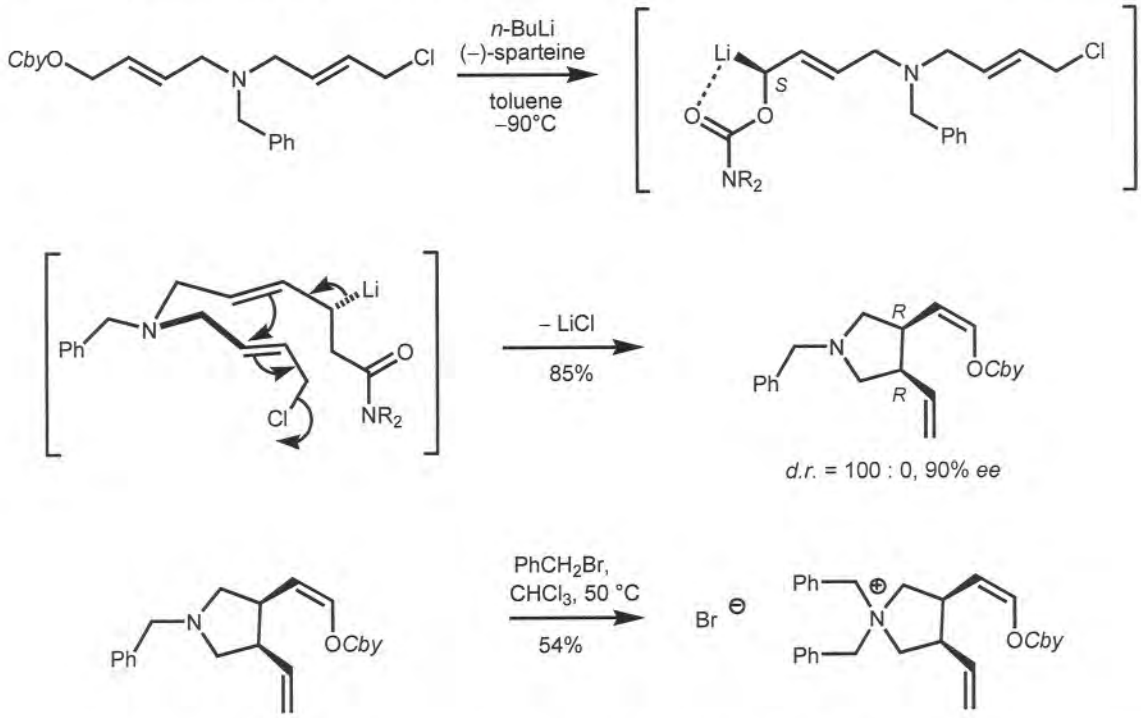


Eur. J. Org. Chem. **2002**, 414-427. (J. Kristensen, M. Özlügedik)

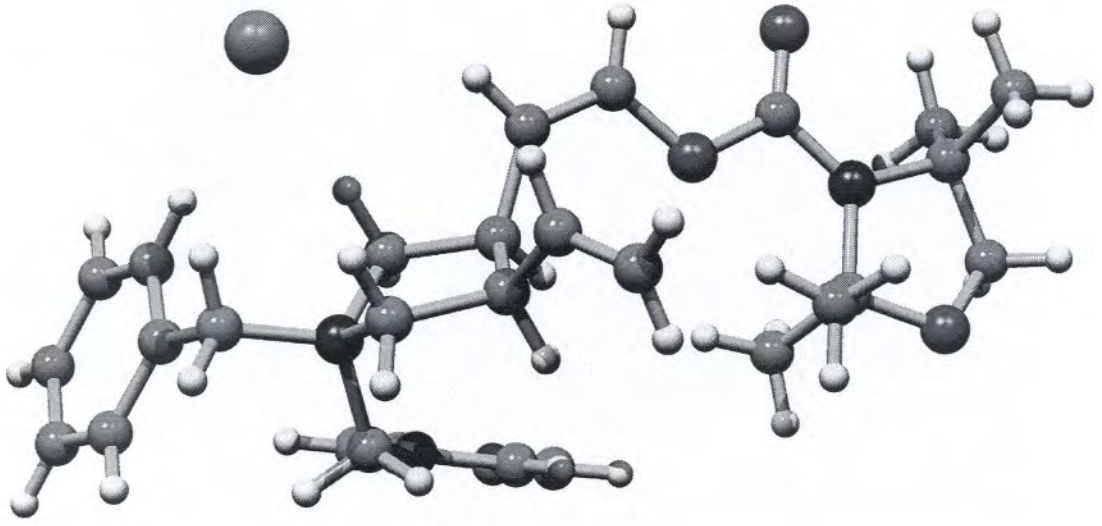


Many further examples: *Synthesis* **2004**, in press. (M. Özlügedik)

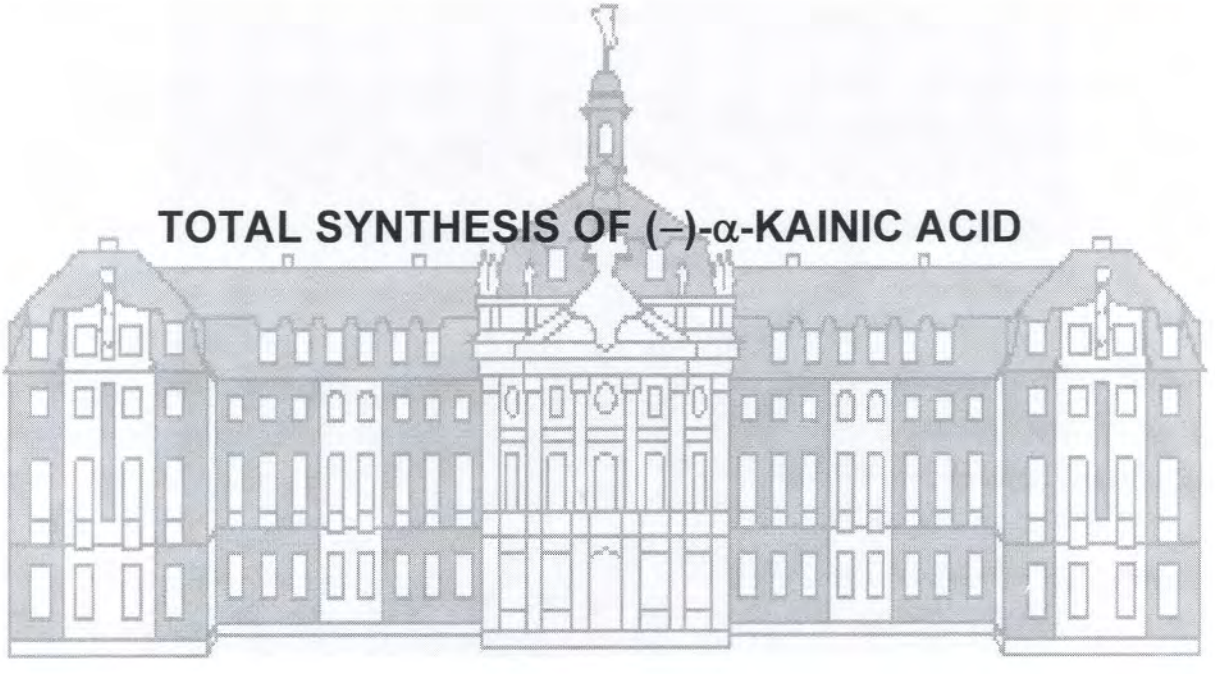
Synthesis of a 3,4-Divinylpyrrolidine via Asymmetric Deprotonation and Cycloalkylation



A. Deiters, B. Wibbeling, D. Hoppe, *Adv. Synth. Catal.* **2001**, *343*, 181.



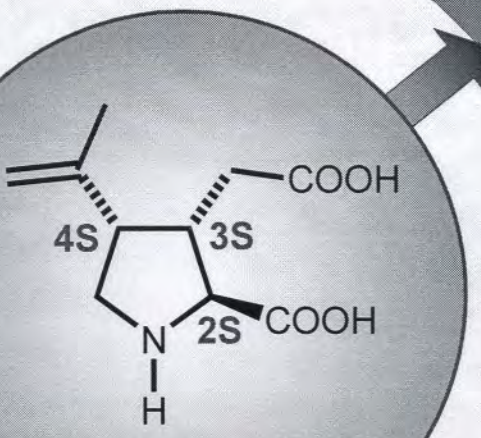
(A. Deiters, B. Wibbeling)



Montserrat M. Martínez, *Org. Lett.* **2004**, in press.

Firstly isolated (1953) from alga *Digenea Simplex* by Takemoto

Potent neurotransmitting activity in the central nervous system



(–)-α-Kainic acid

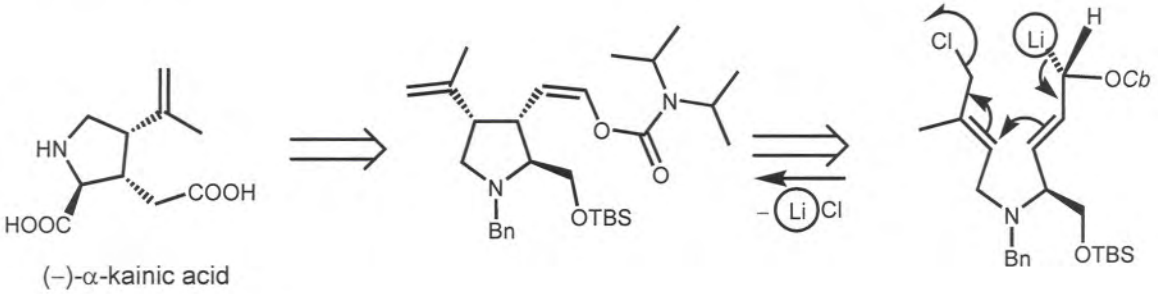
Limited availability
Expensive product
(10 mg ~ 157 Eur)

Applications

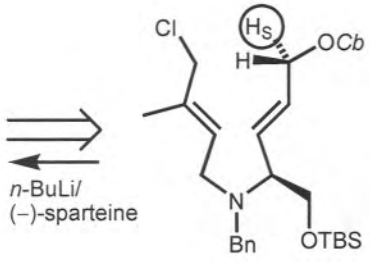
- **Anthelmintic (intestinal worm).**
- **Neuroscience research:**
  - **modeling of epilepsy, Alzheimer and others.**

Retrosynthesis of (–)-α-Kainic Acid

Cyclization Step



(–)-α-kainic acid

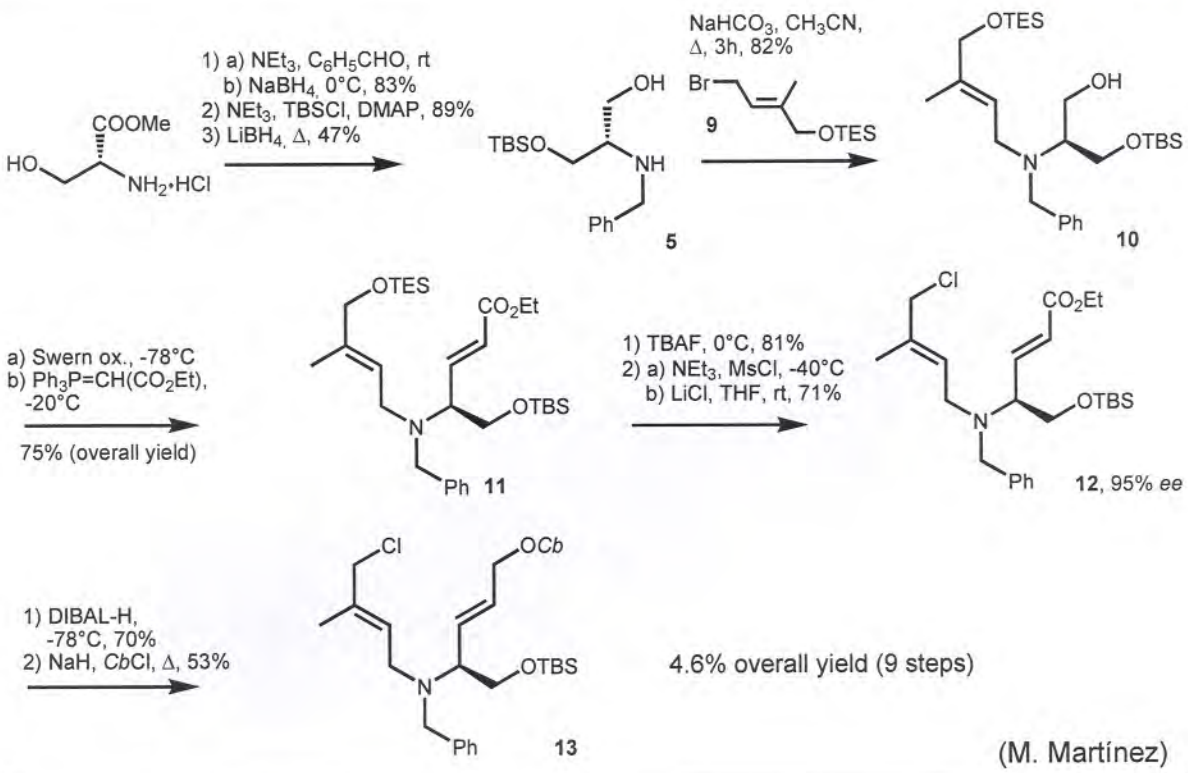


n-BuLi/
(–)-sparteine

Key intermediate

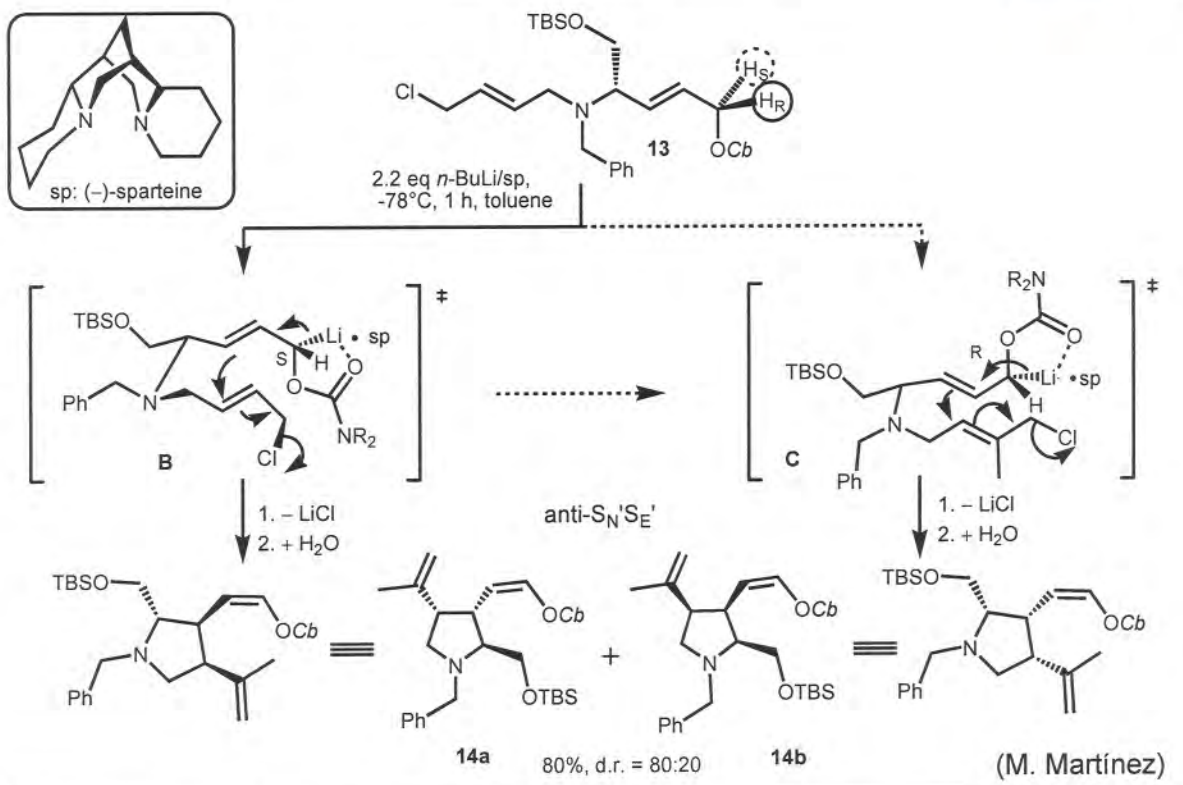
(M. Martínez)

Synthesis of Key Intermediate



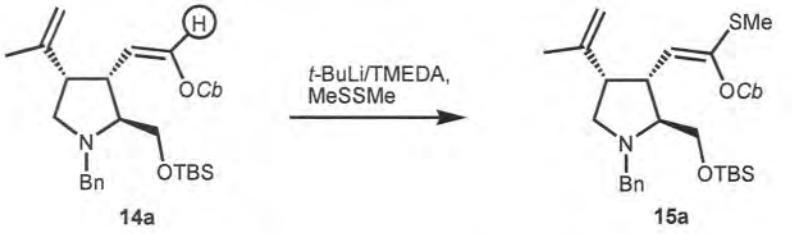
(M. Martínez)

Key Step: (–)-Sparteine-mediated Cycloalkylation

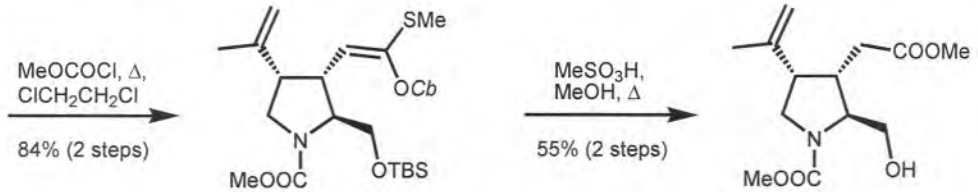


(M. Martínez)

Completion of the Synthesis to (–)-α-Kainic Acid



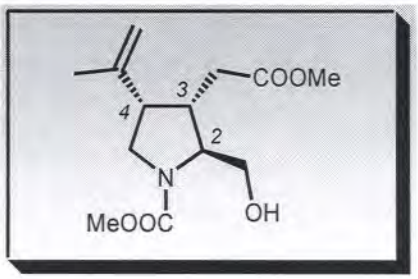
14a **15a**



18a **19a**

$[\alpha]_D^{20}$ = –41.2 (c 0.52, CH_2Cl_2)

Lit.[1] $[\alpha]_D^{20}$ = –43.0 (c 1.25, CH_2Cl_2)



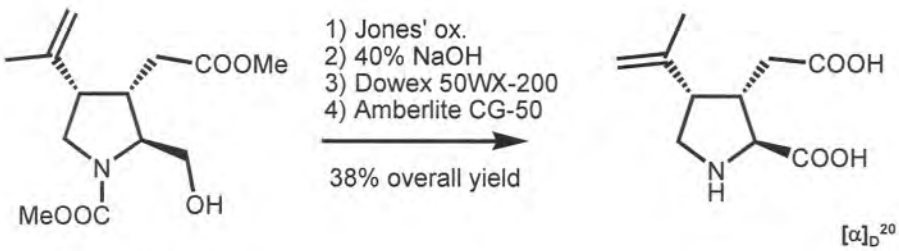
NOE studies at low T[a] show:

C2/C3 → *trans* configuration

C3/C4 → *cis* configuration

(M. Martínez)

Completion of the Synthesis to (–)-α-Kainic Acid

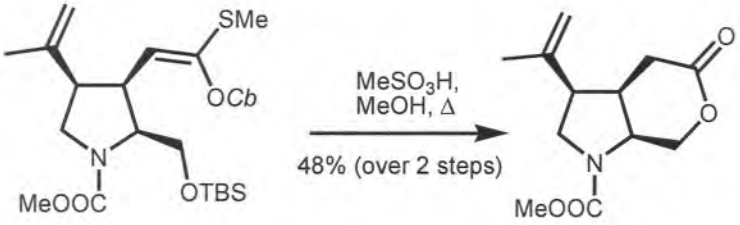


19a

$[\alpha]_D^{20}$ = –14.3 (c 0.40, H_2O)

Lit.[2] $[\alpha]_D^{20}$ = –15.0 (c 0.50, H_2O)

[2] W. Oppolzer, K. Thirring, *J. Am. Soc.*, **1982**, *104*, 4978.



14b **20b**

NOE studies at low T[a] shows:

C2/C3 → *cis* configuration

C3/C4 → *cis* configuration

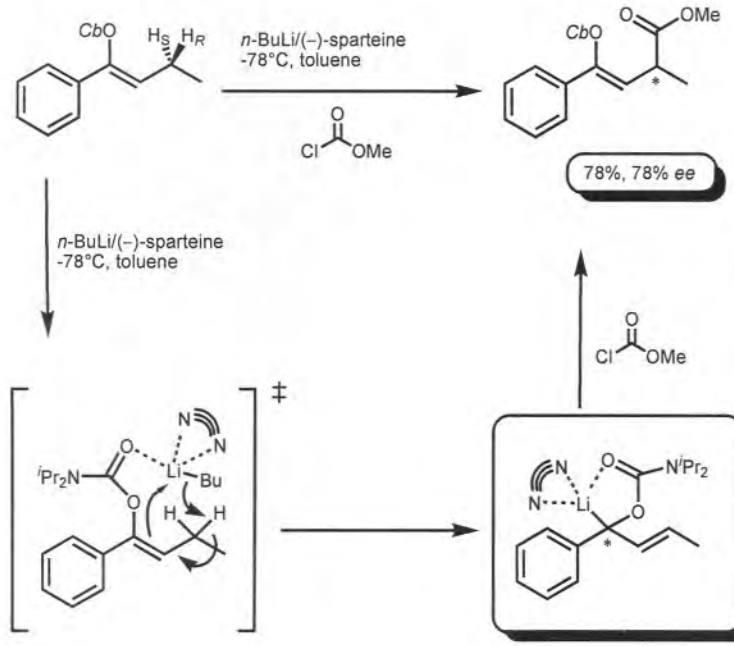
$[\alpha]_D^{20}$ = –28.1 (c 0.30, $CHCl_3$)

Lit.[3] $[\alpha]_D^{20}$ = +32.1 (c 1.20, $CHCl_3$)
***ent*-20b**

[3] D. A. Campbell, M. T. Raynham, J. K. Taylor, *Perkin I*, **2000**, *19*, 3194.

(M. Martínez)

First Results



Conclusions:

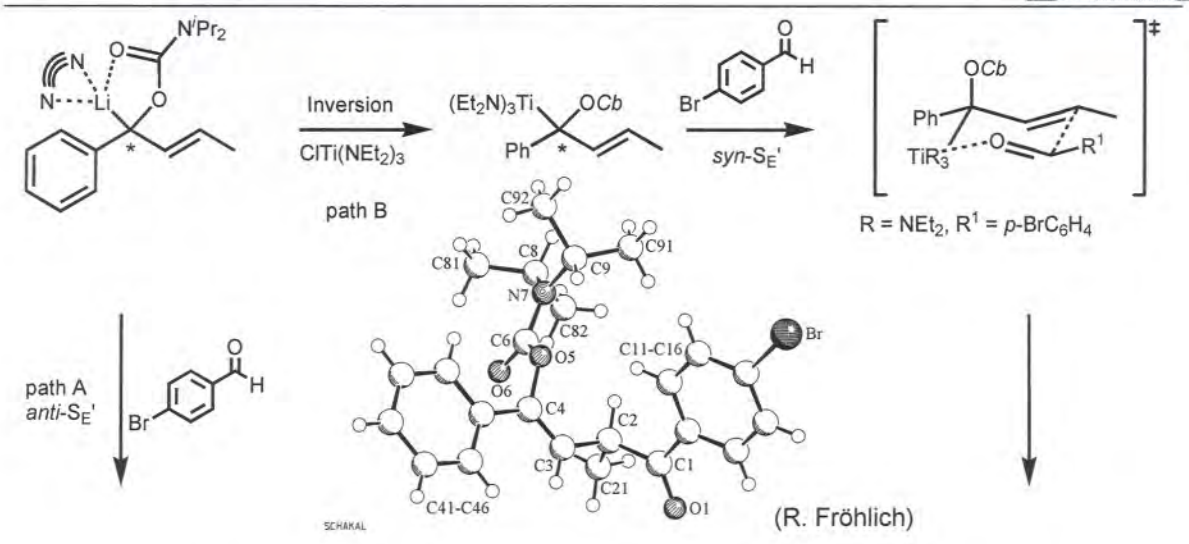
Enantiotopos differentiating γ-deprotonation with *n*-BuLi/(–)-sparteine

Enantioenriched ion pair is configurationally stable

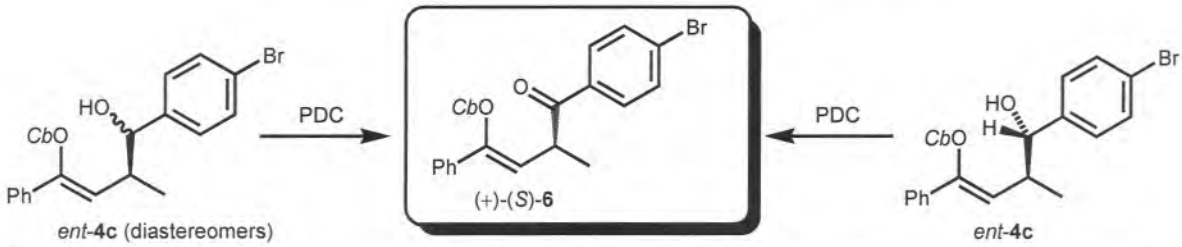
Configurations still unknown at this stage

(M. Seppi)

Stereochemistry of Aldehyde Addition (1)

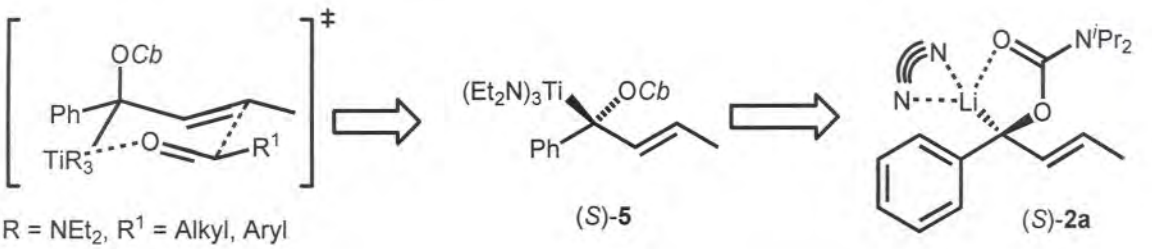


(R. Fröhlich)



ent-**4c** (diastereomers)

ent-**4c**



R = NEt_2, R^1 = Alkyl, Aryl

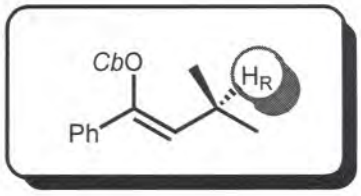
(*S*)-**5**

(*S*)-**2a**

Transmetallation Li→Ti in all known cases: Inversion

⇨ Lithium intermediate **2a** has (*S*)-configuration

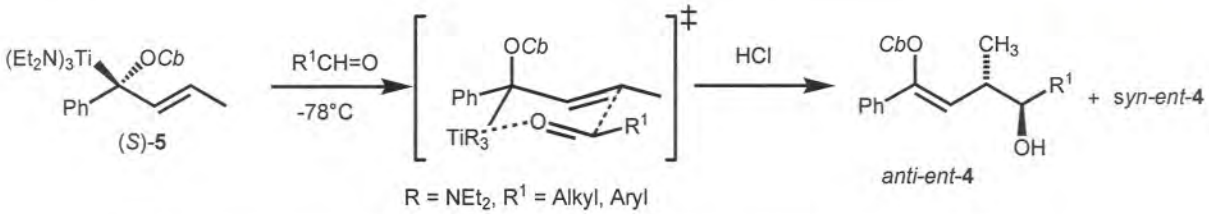
⇨ (–)-Sparteine/*n*-butyllithium removes the γ-*pro-R* proton



[1] Titanation, reviews: M. T. Reetz, *Organotitanium Reagents in Organic Synthesis*, Springer, Berlin, **1986**; „Organotitanium Chemistry": M. T. Reetz in *Organometallics in Synthesis* (Ed. M. Schlosser), Wiley, Chichester, **2002**, 817.

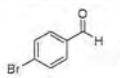
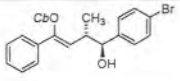
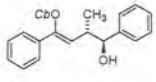
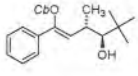
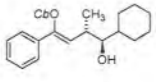
(R. Kalkofen)

Highly Stereoselective Homoaldol Reactions



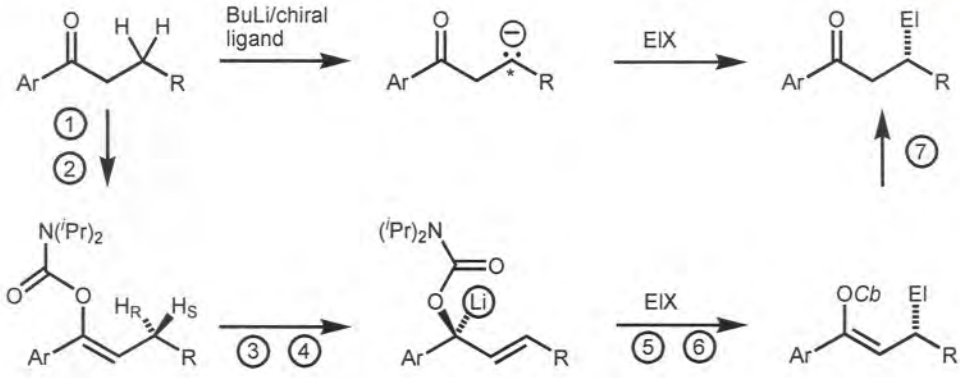
anti-ent-**4**

R = NEt_2, R^1 = Alkyl, Aryl

Entry	Aldehyde	Product	Yield[%]	*d.r.*	*e.e.* [%]	$[\alpha]_D^{20}$
1			66	95:5	97	–135
2			71	98:2	95	–133
3			75	99:1	96	–73
4			77	99:1	95	–85

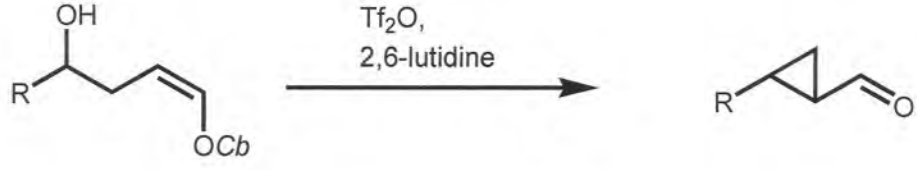
Angew. Chem. Int. Ed. **2004**, *43*, 1423-1427.

(R. Kalkofen)



1. Enolization via abstraction of the most acidic proton.
2. Activation of the allylic protons.
3. Enantiotopos differentiation by *n*-BuLi/(–)-sparteine for R = Ar, or Me_3Si.
4. Enhancement of the configurational stability in five-membered chelate.
5. Stereospecific S_E'-substitutions (with few exceptions *syn*).
6. Inversion via Li/Ti exchange possible.
7. Liberation of the ketone from the enol ester (e.g. TMSOTf/Nu).

Cyclization of Racemic Homoaldol Products – Cyclopropane Carboxaldehydes



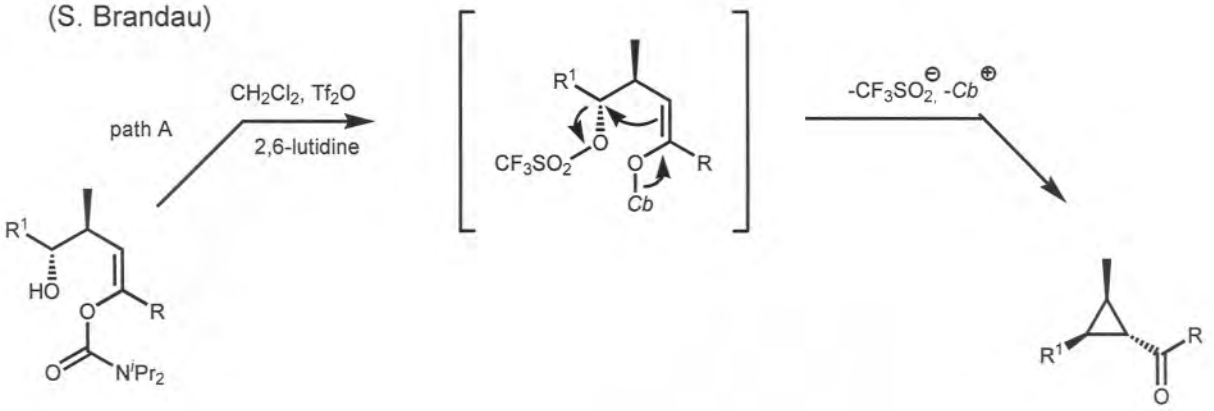
R = CH_2CH_2Ph 84%

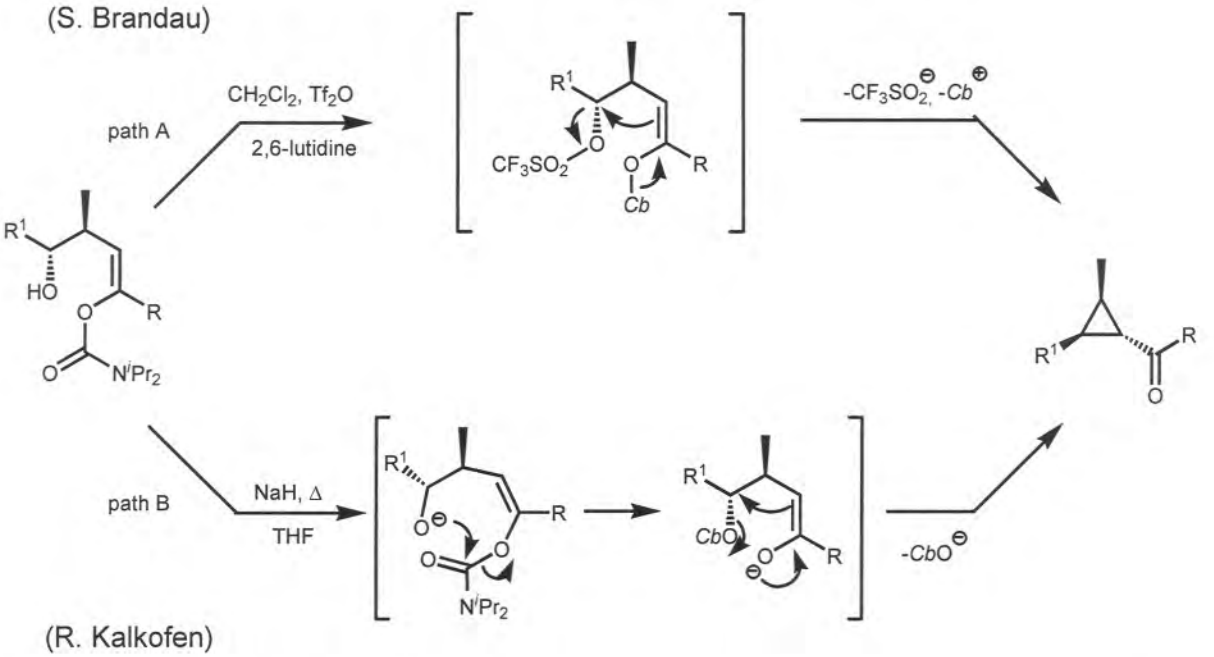
R = C_6H_{11} 89%

R = CH_2CH_2Ph 97%, 89:11 *trans/cis*

R = C_6H_{11} 97%, 98:2 *trans/cis*

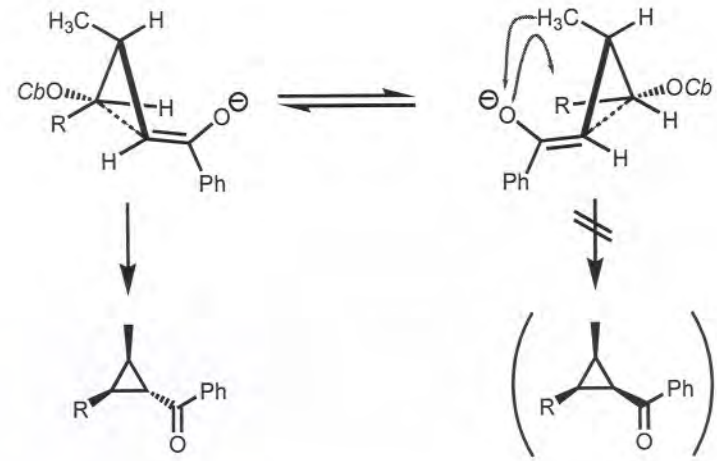
R. E. Taylor, C. A. Risatti, C. Engelhardt, M. Schmidt *Org. Lett.* **2003**, *5*, 1377.





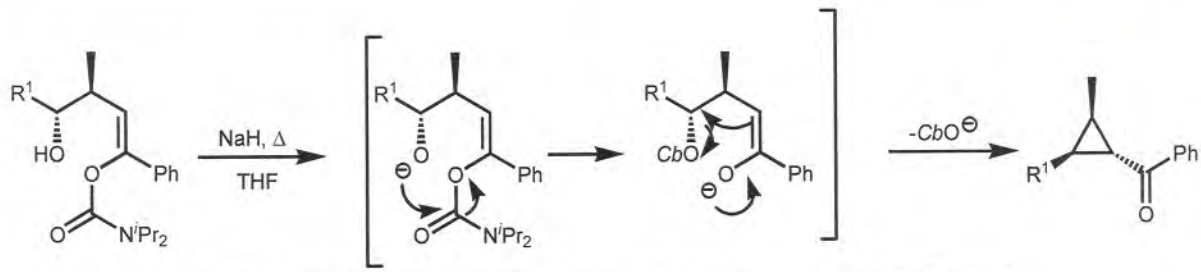
Angew. Chem. Int. Ed. **2004**, in press.

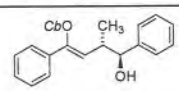
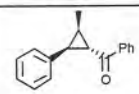
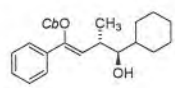
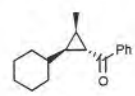
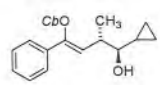
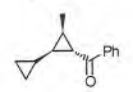
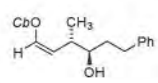
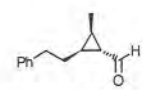
(Based on Proposal of R. E. Taylor)



(R. Kalkofen)

Synthesis of Stereohomogeneous Cyclopropanes (3)



Entry	Starting Material	Product	Yield[%]	*e.e.* [%]	*d.r.*
1			98	91	98:2
2			78	95	>98:2
3			74	96	97:3
4			58	87	>98:2

(R. Kalkofen, S. Brandau)

1. Activation by the carbamate group in the deprotonation step for the homoaldol reaction

2. Directing of regio- and stereochemistry in the addition step

3. One-step liberation of the enolate and activation of the hydroxy group by migration in the cyclopropane-forming step

Acknowledgements

To all former and present group members

Presented results by:

Homoenolates
Mustafa Özlügedik
Jesper Kristensen
Michael Seppi
Rainer Kalkofen
Sven Brandau
Wenbin Zeng
Edith Beckmann

Cycloalkylation
Alexander Deiters
Lars Padeken
Dr. Montserrat M. Martínez

X-Ray
Dr. Roland Fröhlich and his coworkers

Funding
Deutsche Forschungsgemeinschaft, SFB 424
Fonds der Chemischen Industrie
Humboldt Foundation
NRW Graduate School of Chemistry
German-Dutch Graduate Kolleg
Ministerio de Educacíon, Cultura y Deporte of Spain