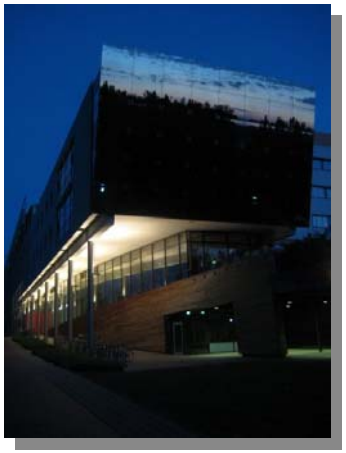
The Thin Red Line

Acidity and Activity in Silicon-Thiourea Catalysis

Gießen
AG Seminar

17.06.2011



Gergely Jakab

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Justus-Liebig-Universität
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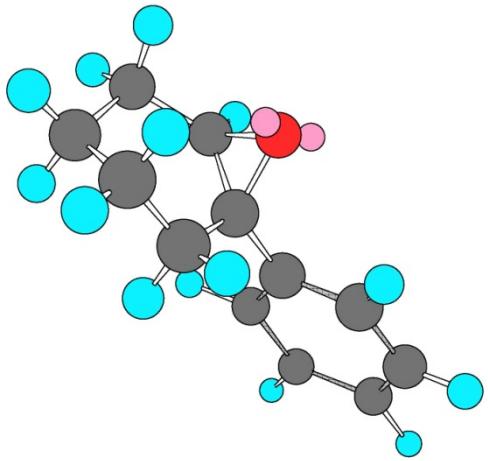
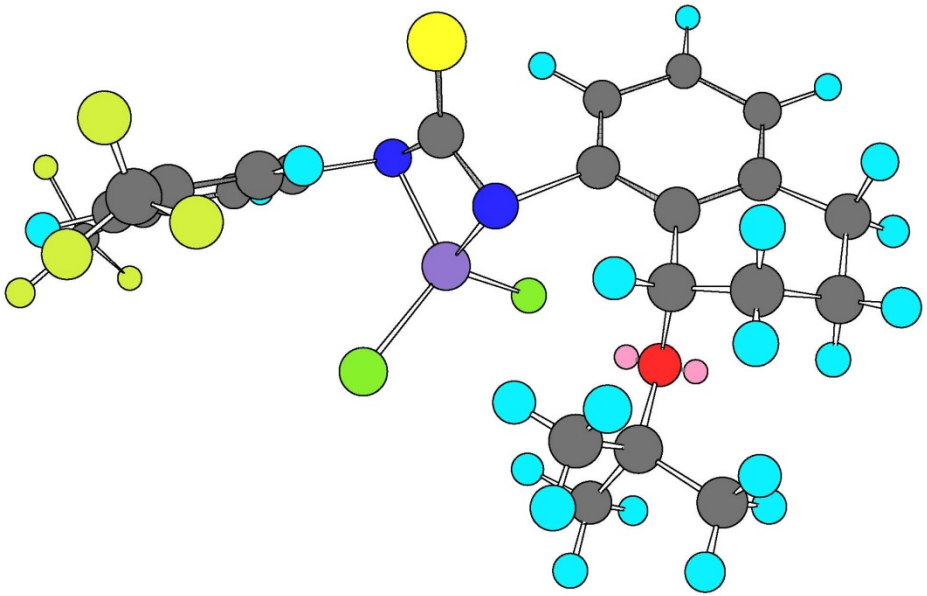
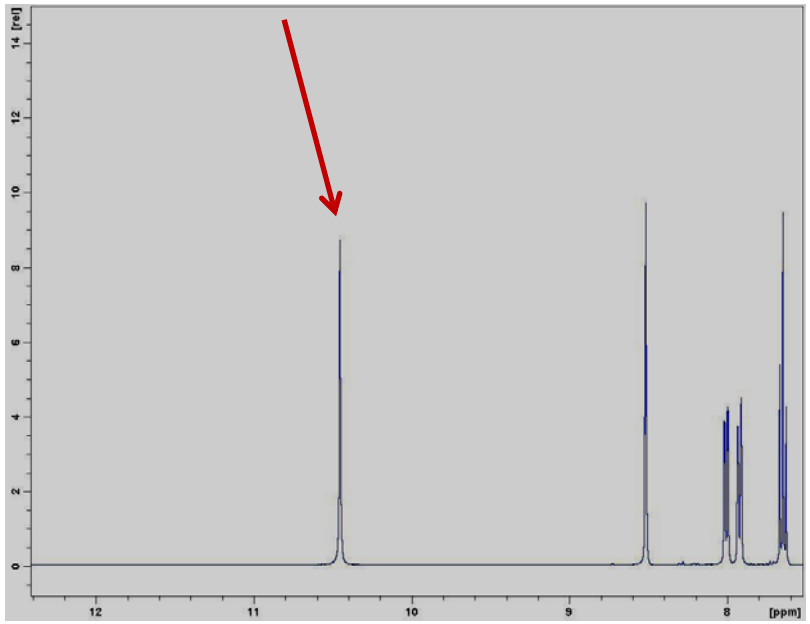
Introduction

Highlights



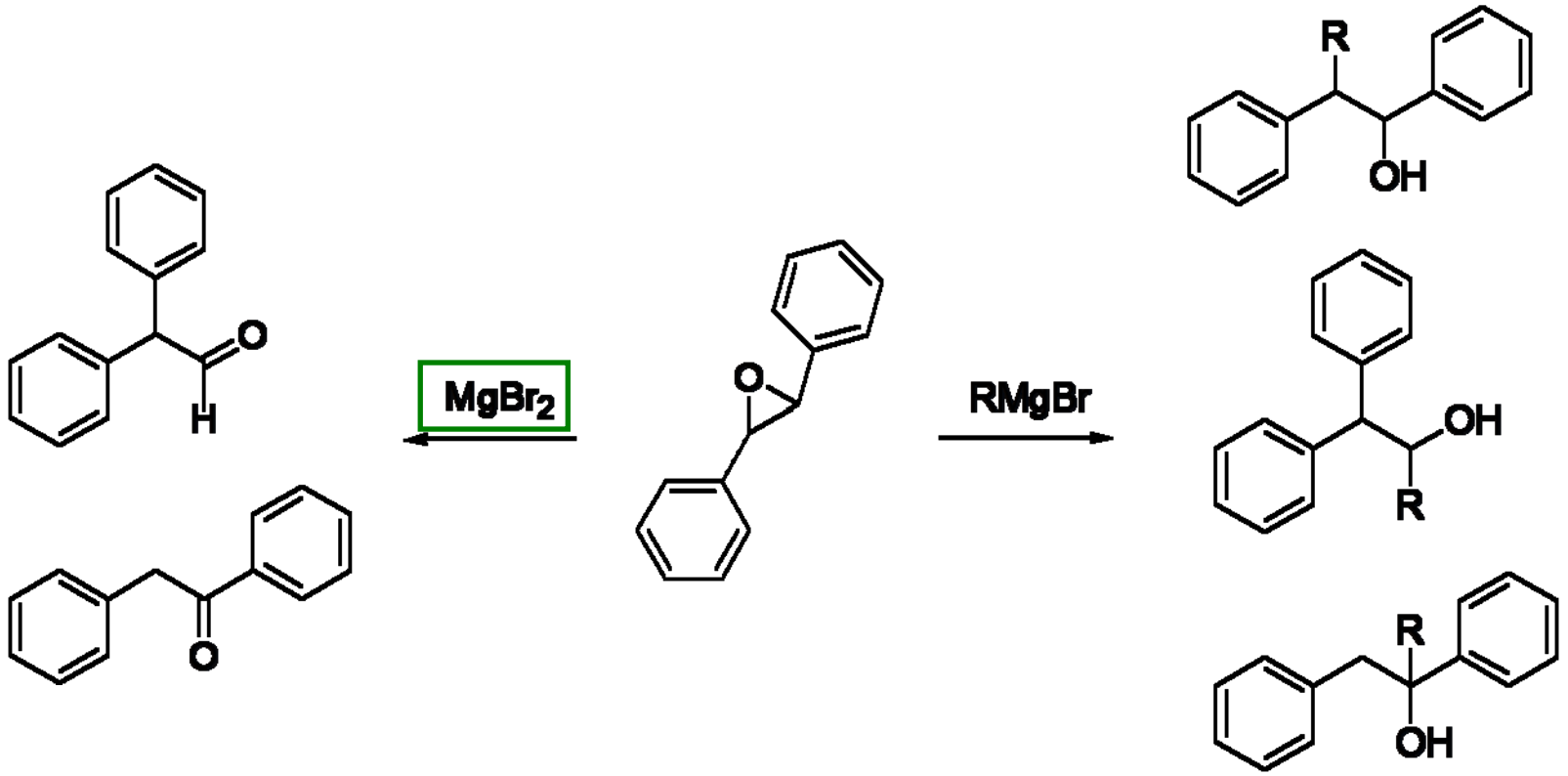




- Rearrangement of epoxides
- Structure & reactivity
- Search for chiral application

Introduction

An interesting observation

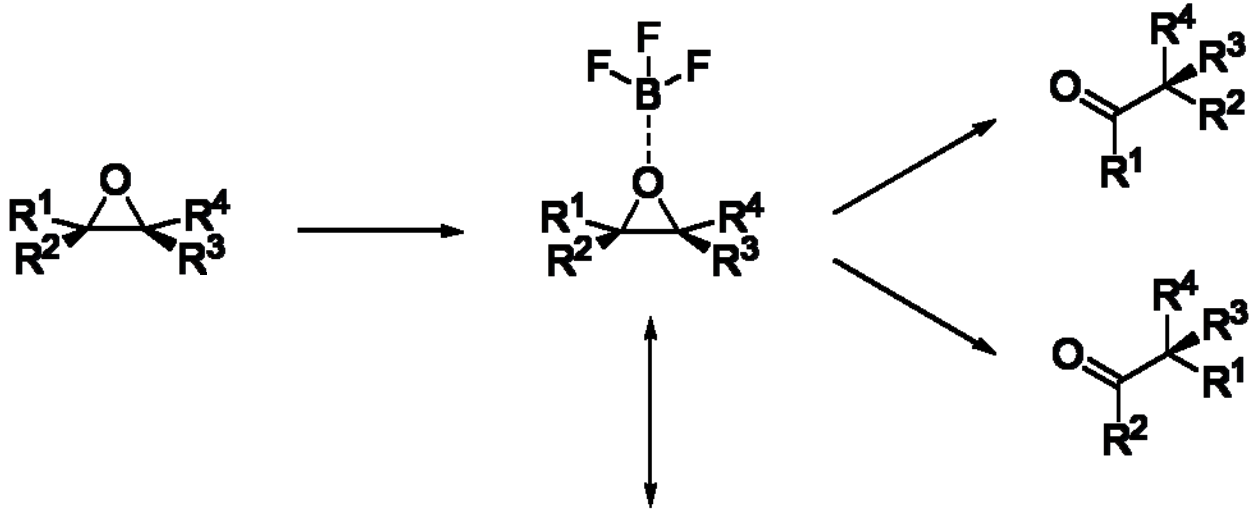


Unexpected sideproducts!

[1] N. G. Gaylord, E. I. Becker *Chem. Rev.* **1951**, *49*, 413
[2] H. O. House *J.Am.Chem.Soc.* **1955**, *77*, 3070.

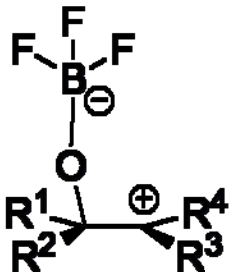
Introduction

Acid catalyzed rearrangement of epoxides



Often low selectivity

The more stable cation is favoured, substituents of the other carbon atom will migrate

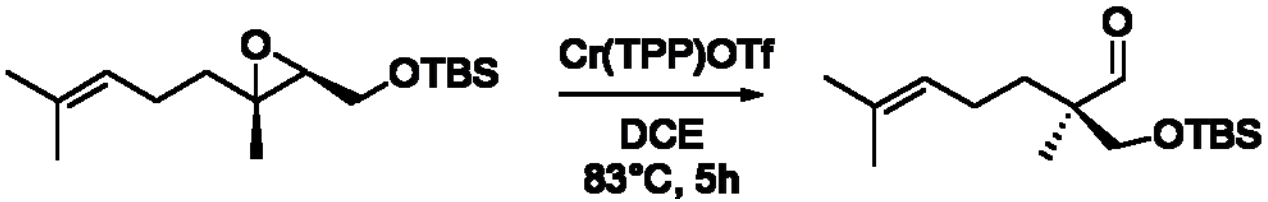


- Solvent
- Temperature
- Lewis-acid
- Substituents

R. E. Parker, N. S. Isaacs *Chem.Rev.* **1959**, *59*, 737.

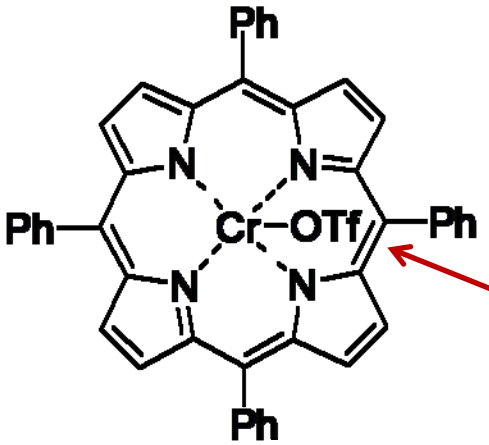
Introduction

Rearrangements via Alkyl-shift



99+% ee

99+% ee; <2% ketone



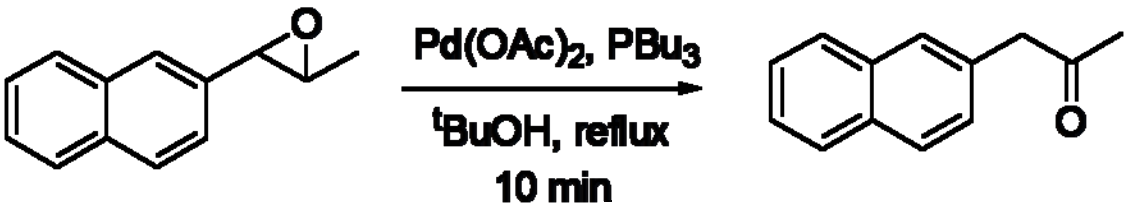
Al and **B** complexes also favouring alkyl shift: bulky catalyst is a prerequisite

Even the counter ion plays an important role

K. Suda, T. Kikkawa, S. Nakajima, T. Takanami *J.Am.Chem.Soc.* **2004**, *126*, 9554.

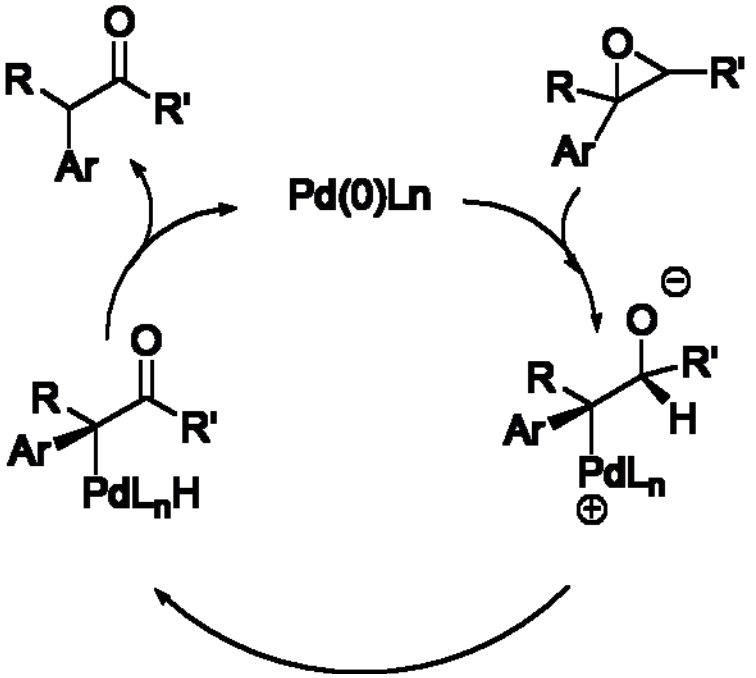
Introduction

Rearrangements via H-shift



96% isolated yield,
no aldehyde detected

Supports H-shift:
Bi, **Ir**, **In**, **V**, **Er**, **Fe**, **Cu**

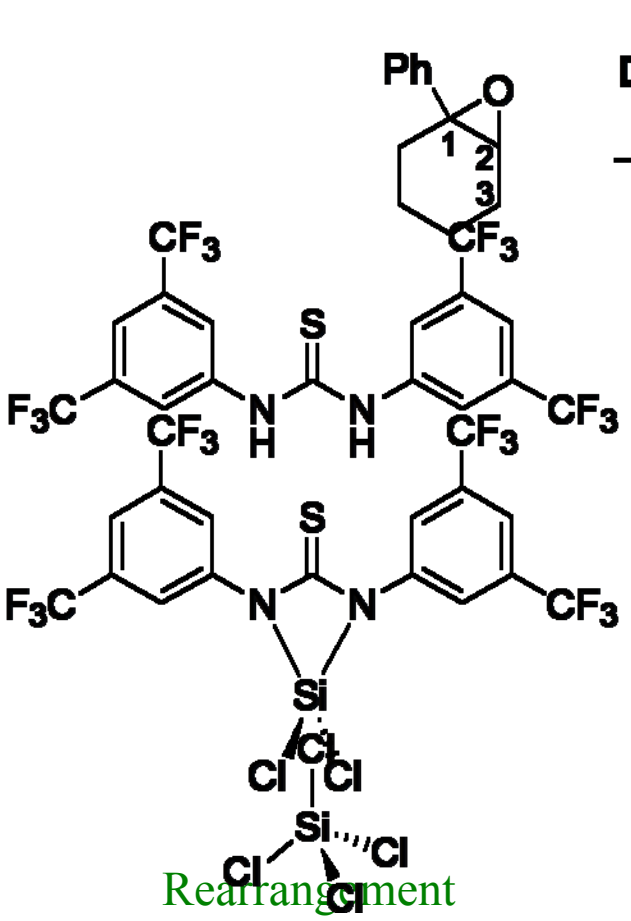


No reaction in the absence of β-H

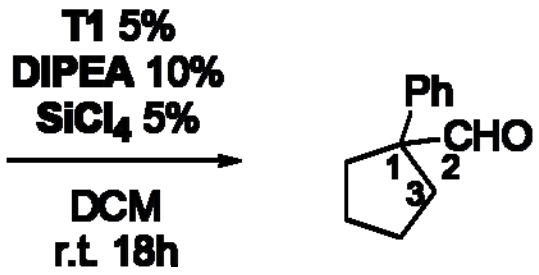
S. Kulasegaram, R. J. Kulawiec *J.Org.Chem.* **1997**, *62*, 6547.

A new approach

Radim and the silicon



Rearrangement



Ring opening when a nucleophile is present

- Polar aprotic solvents: DCM, Chloroform, Acetonitrile
- Room temperature
- $AllylSiCl_3$
- Selective C3 shift

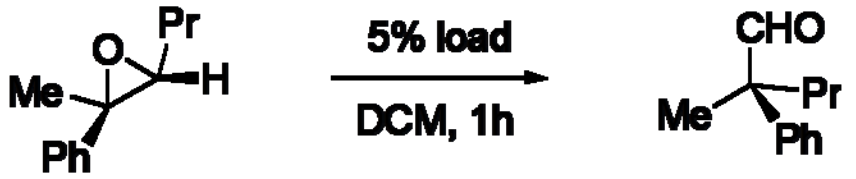
NMR and MS measurements support the proposed structure

Ring opening through halohydrine formation

R. Hrdina, C. E. Müller, R. C. Wende, K. M. Lippert, M. Benassi, B. Spengler, P. R. Schreiner *J.Am.Chem.Soc.* **2011**, *133*, 7624.

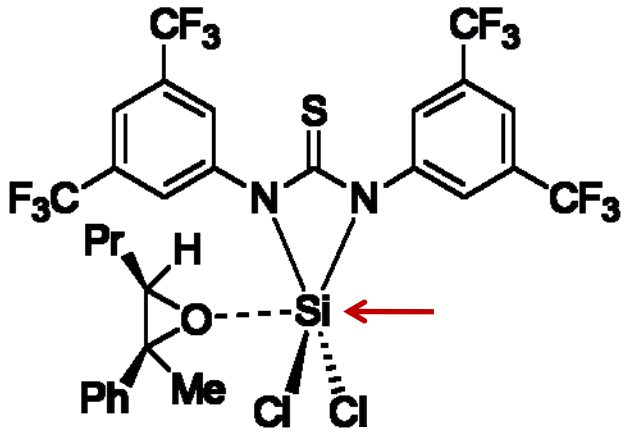
A new approach

The case of enantioenriched starting materials

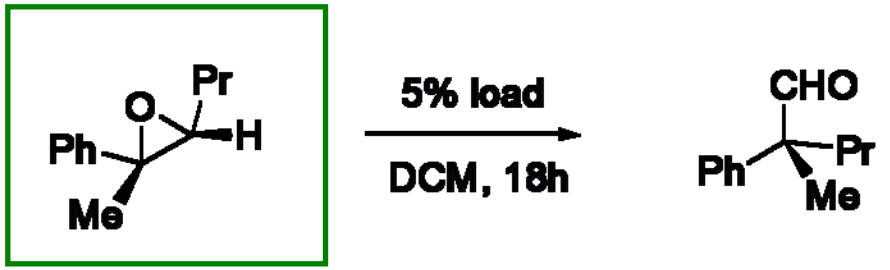


95% ee

93% ee, 86% yield



Six valent silicon
as active species



79% ee

76% ee, 85% yield

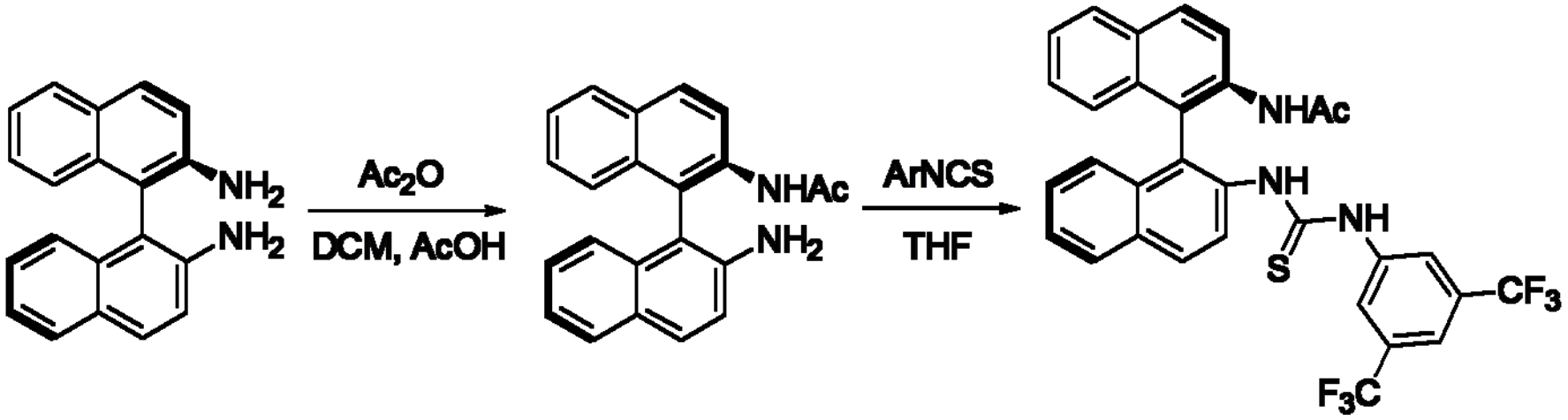
only 3% ketone

Enantiopurity increases over conversion!

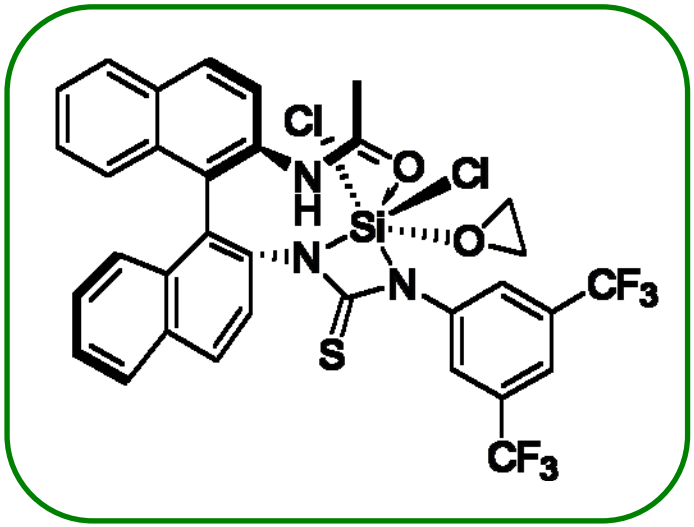
R. Hrdina, C. E. Müller, R. C. Wende, K. M. Lippert, M. Benassi, B. Spengler, P. R. Schreiner *J.Am.Chem.Soc.* **2011**, *133*, 7624.

Search for chiral catalysts

Binaphtyl amine framework 1.



1: 69% overall yield

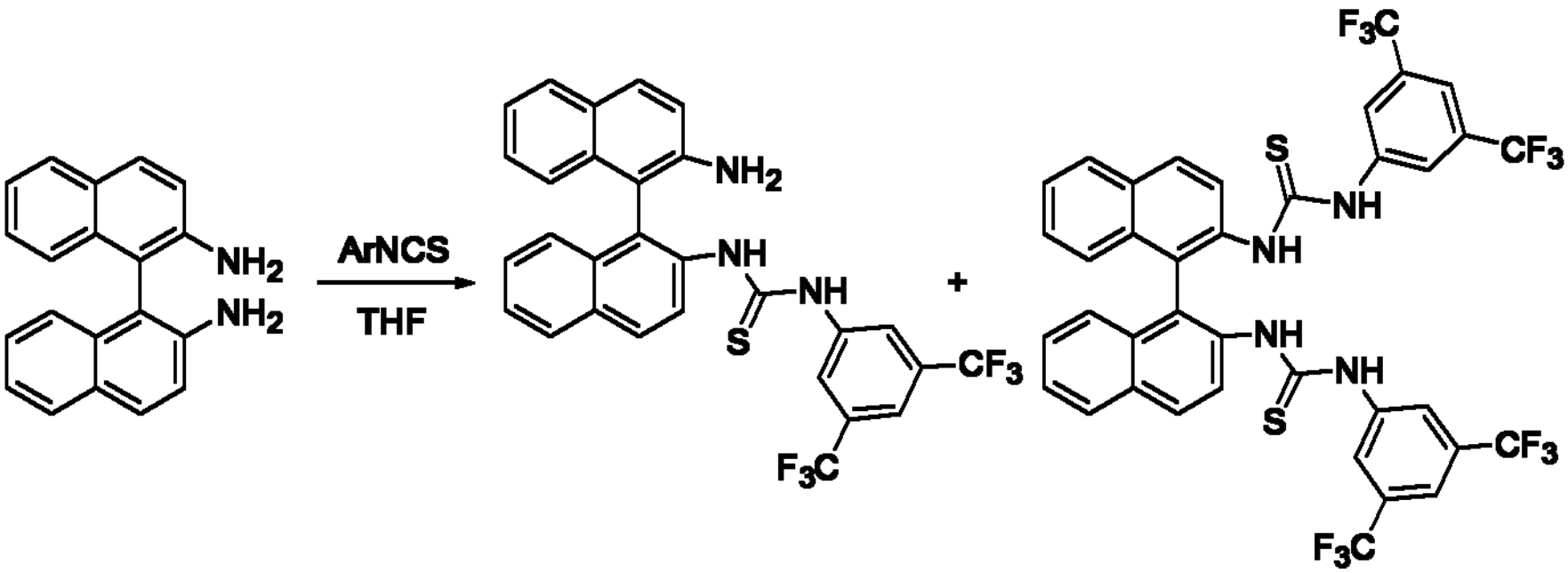


Rearrangement reaction:
11% conversion after 3 days (10% load)

C. Rampalakos, W. D. Wulff *Adv.Synth.Catal* **2008**, *350*, 1785.

Search for chiral catalysts

Binaphtyl amine framework 2.



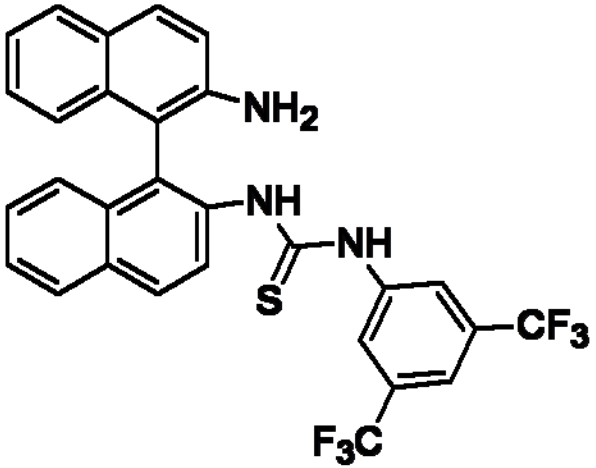
2: 47% yield

3: 48% yield

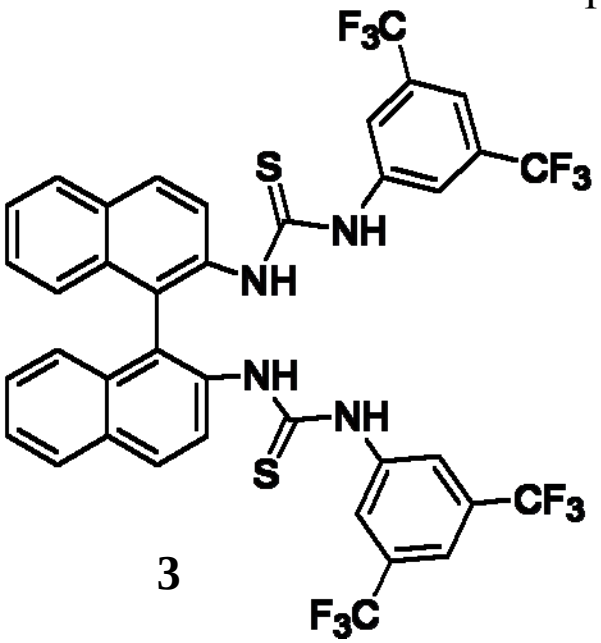
C. Rampalakos, W. D. Wulff *Adv.Synth.Catal* **2008**, *350*, 1785.

Search for chiral catalysts

Binaphtyl amine framework 2.



2



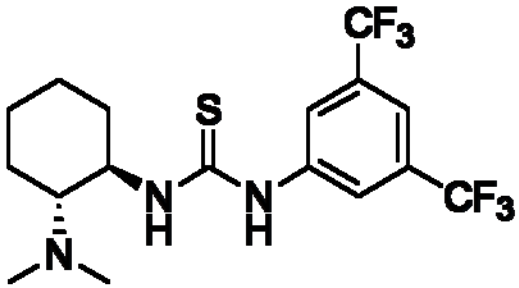
3

Catalyst[a]	Base (DIPEA)	$SiCl_4$	Conversion (GC)
2	1 eq	1 eq	12%
2	2 eq	1 eq	13%
3	4 eq	1 eq	10%
3	4 eq	2 eq	28%

[a] 10% load, r.t., DCM, 18h

Search for chiral catalysts

Catalysts from the shelf 1.



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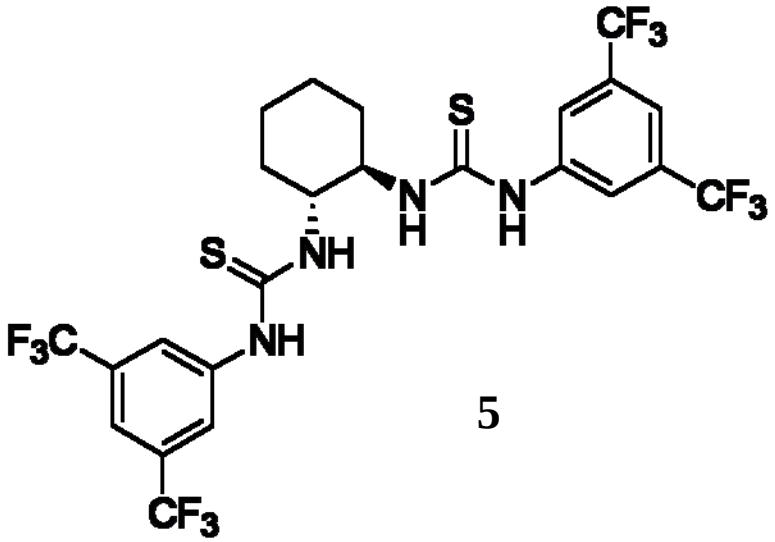
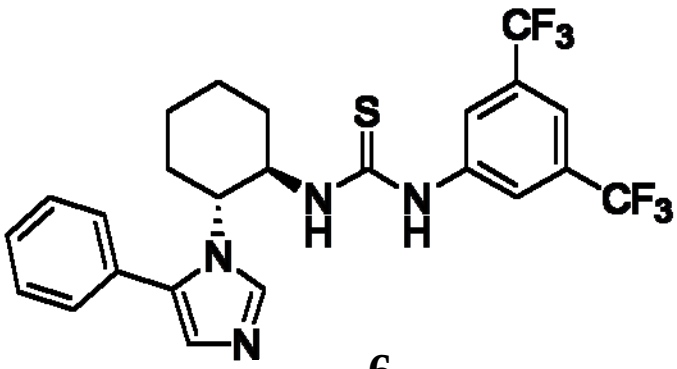


5



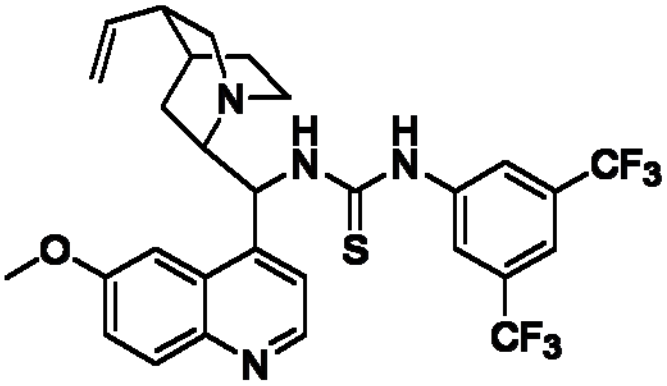
6

Catalyst[a]	Conversion (GC)
4	8%
5	11%
6	10%

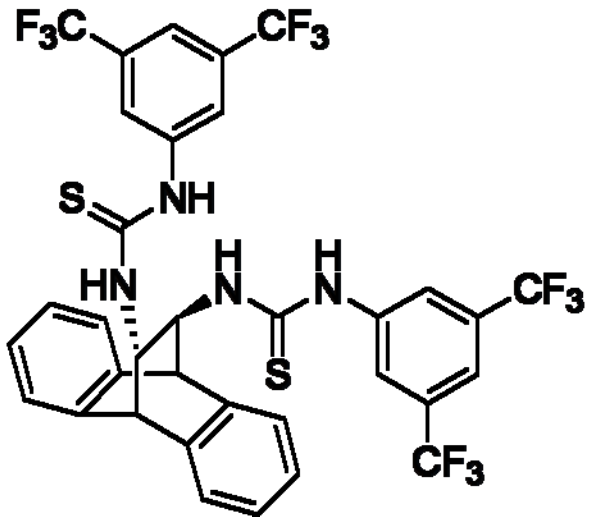
[a] 5% load (10% DIPEA, 5% $SiCl_4$), r.t., DCM, 18h

Search for chiral catalysts

Catalysts from the shelf 2.



7



8

Catalyst[a]	Conversion (GC)
7	trace
8	10%

[a] 5% load (10% DIPEA, 5% $SiCl_4$), r.t., DCM, 18h

Window of opportunity

Testing slightly different thioureas

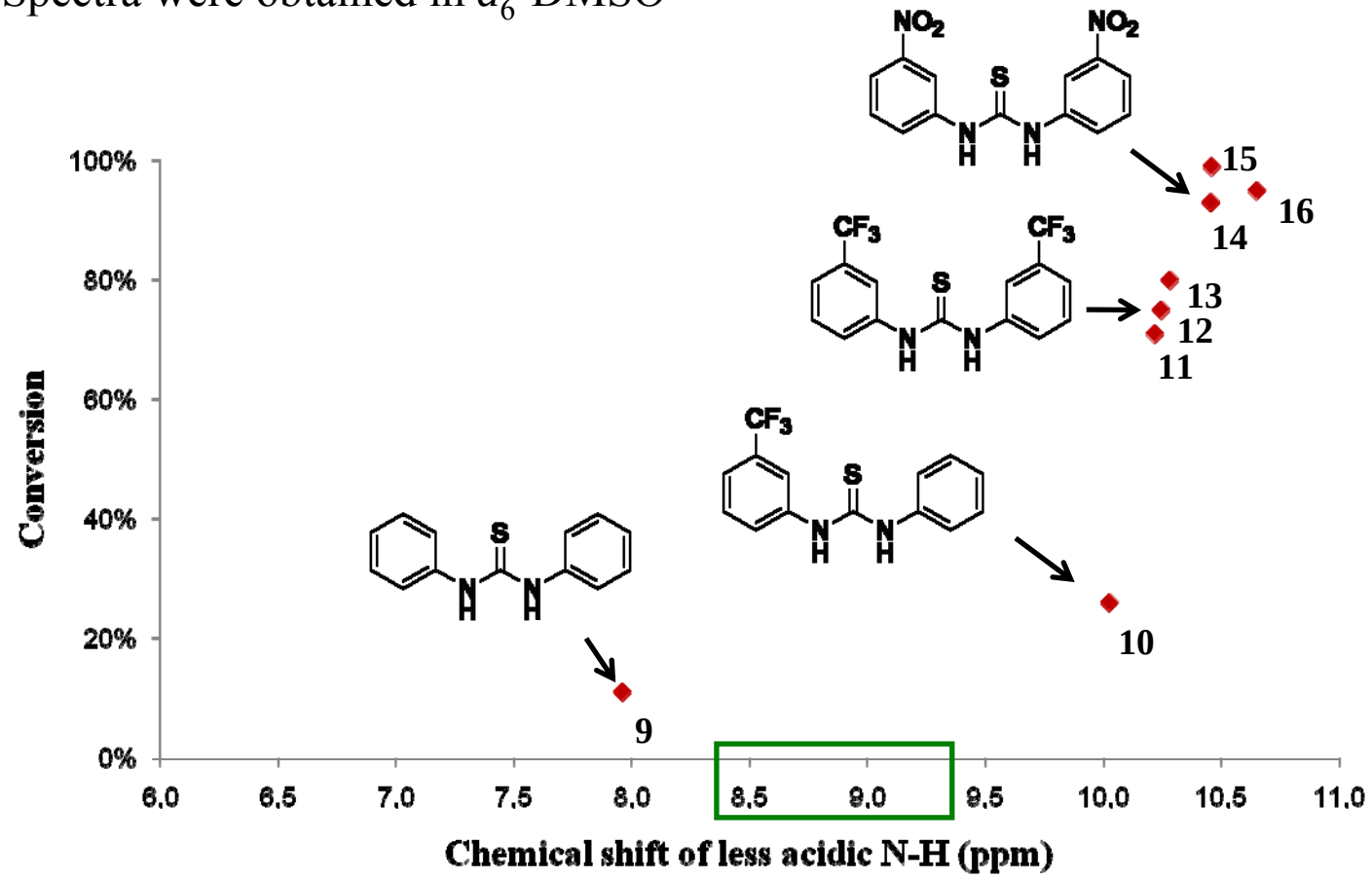
73-93% yield

Catalyst	R1	R2	R3	R4	Conversion (GC/NMR)
9	H	H	H	H	11%
10	CF_3	H	H	H	26%
11	CF_3	CF_3	H	H	71%
12	CF_3	H	CF_3	H	75%
13	Cl	Cl	Cl	Cl	80%
14	NO_2	H	NO_2	H	93%
15	CF_3	CF_3	CF_3	H	99+%
16	CF_3	CF_3	CF_3	CF_3	95+%

Window of opportunity

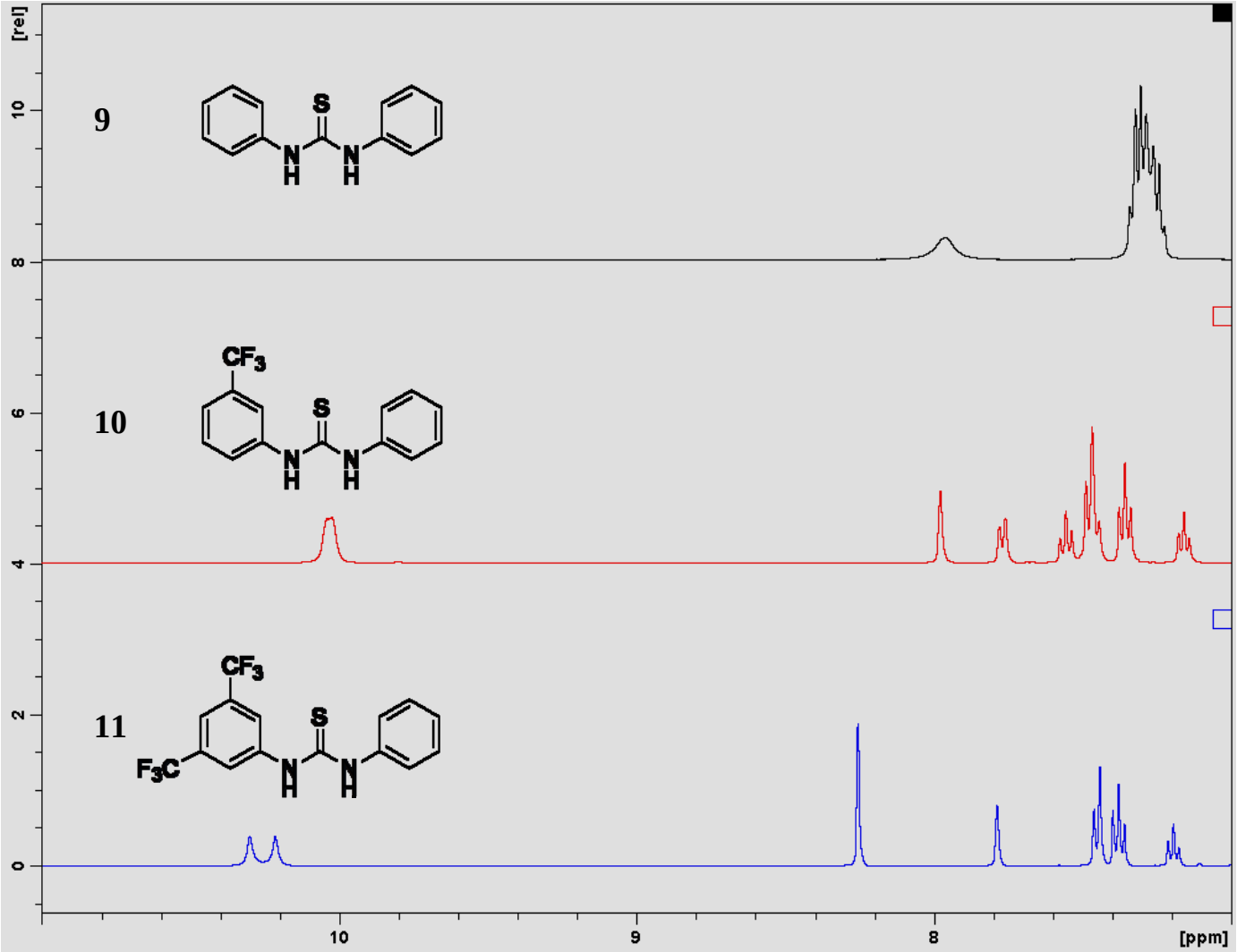
Performance related to N-H chemical shifts

Spectra were obtained in d_6-DMSO



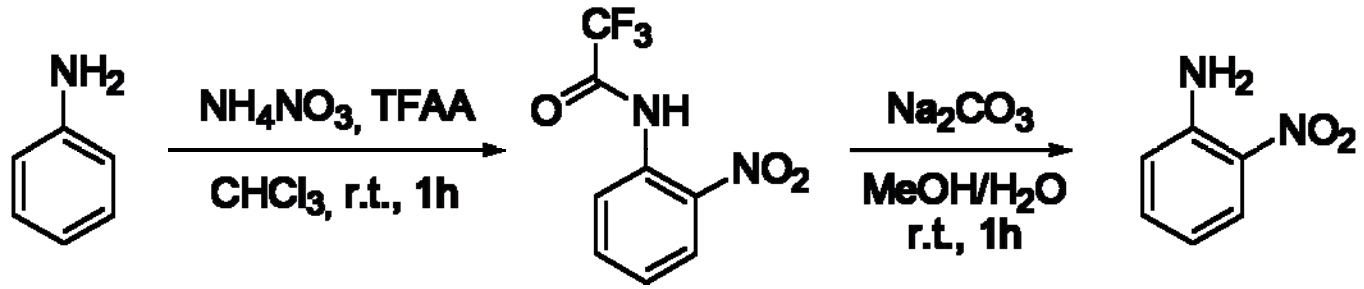
Window of opportunity

Previously tested chiral catalysts

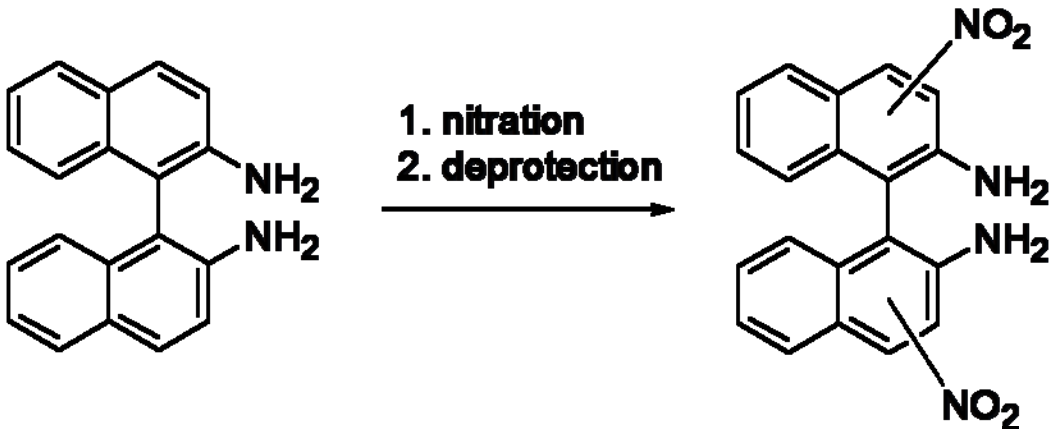


Window of opportunity

Mild nitration of aromatic amines



75% overall yield, small amounts of para- and dinitro derivative



At least 5 isomers!

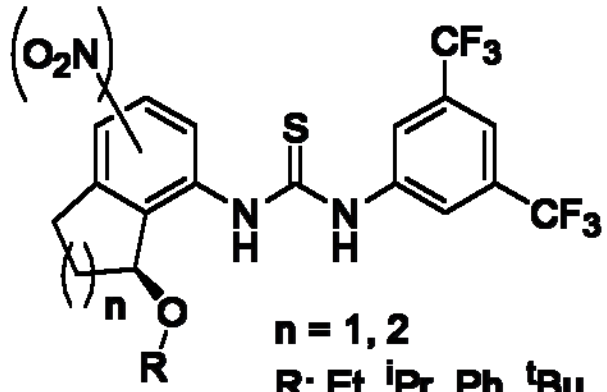
J. V. Crivello *J.Org.Chem.* **1981**, *46*, 3056.

Start from sketch

Designing a new framework

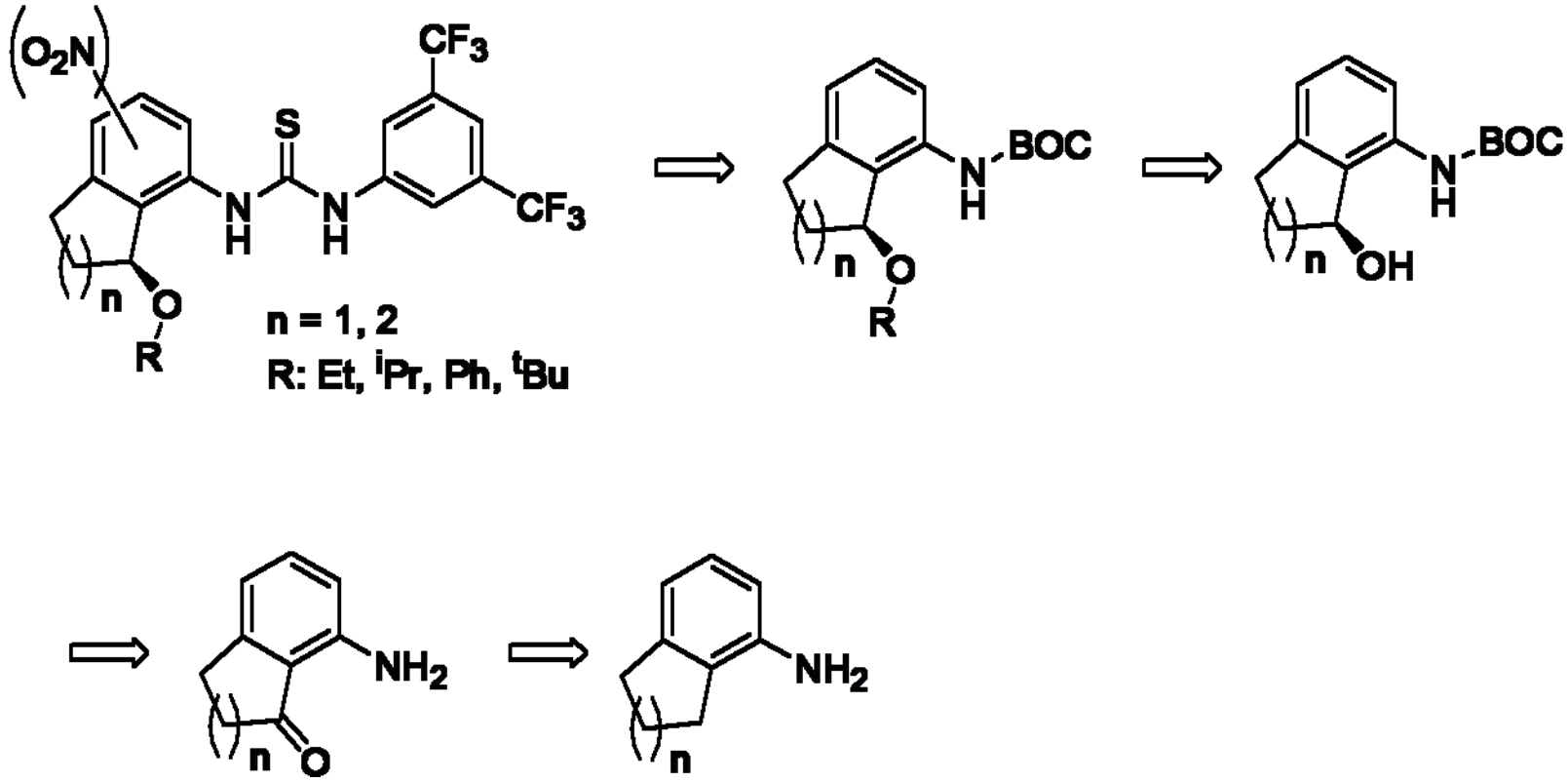
Requirements:

- Sufficient acidity
- Available enantiopure starting material
- Derivatization in late stage of synthesis



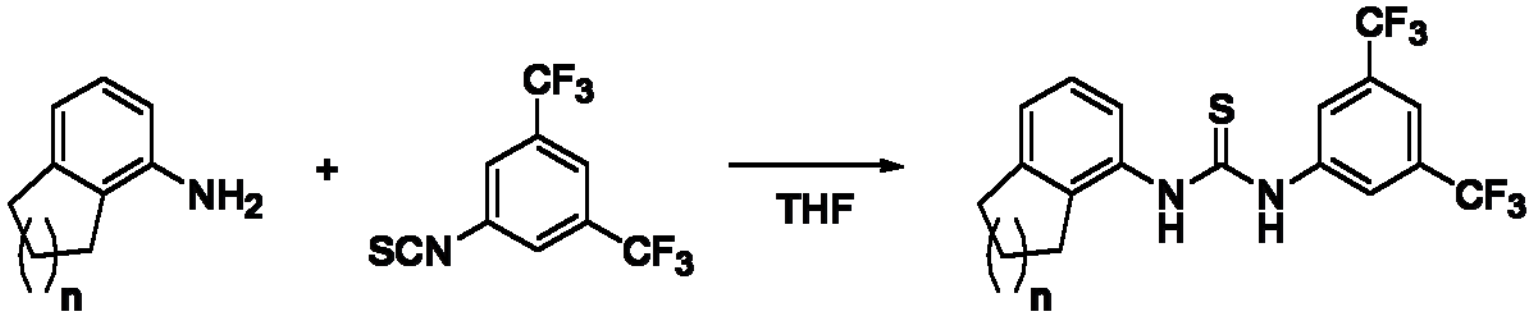
Start from sketch

The synthetic route



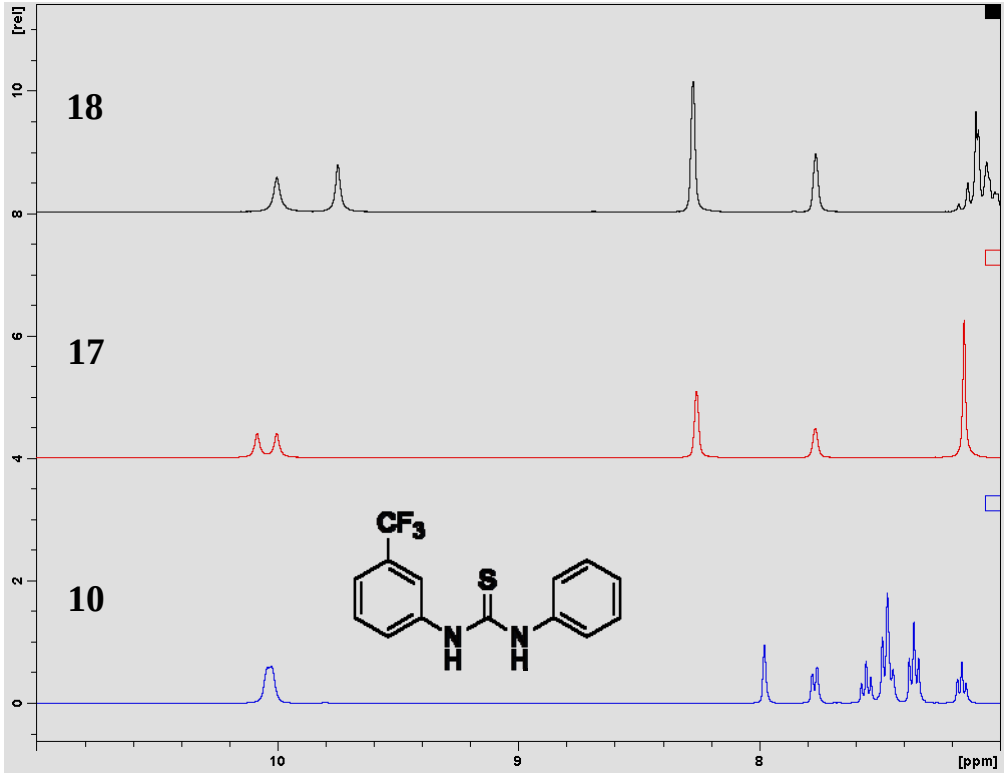
Start from sketch

Proof of concept



17: n = 1; 70% yield

18: n = 2; 92% yield

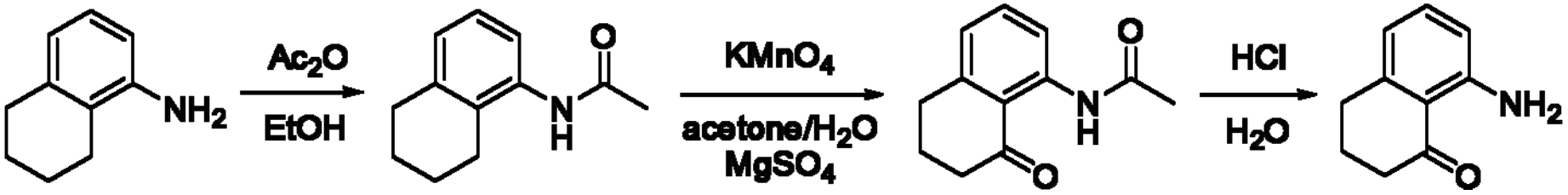


Catalyst[a]	Conversion (GC)
17	52%
18	61%

[a] 5% load (10% DIPEA, 5% $SiCl_4$), r.t., DCM, 18h

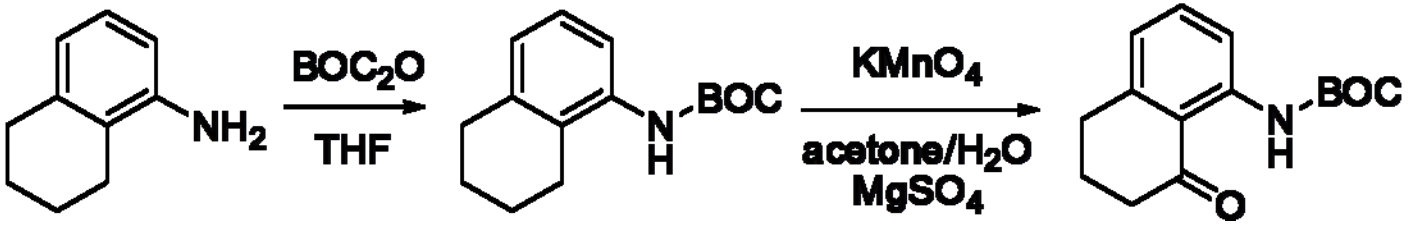
Start from sketch

Oxidation of the benzylic position



91% 48% 72%

Overall: 31%

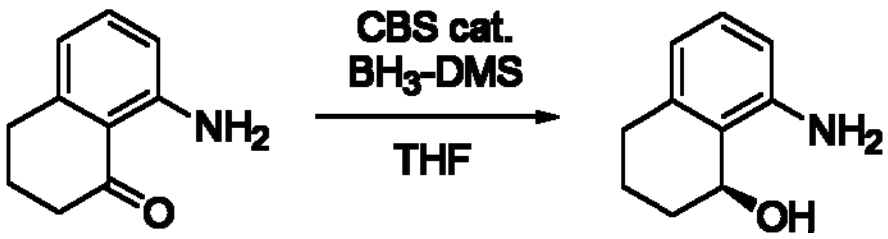


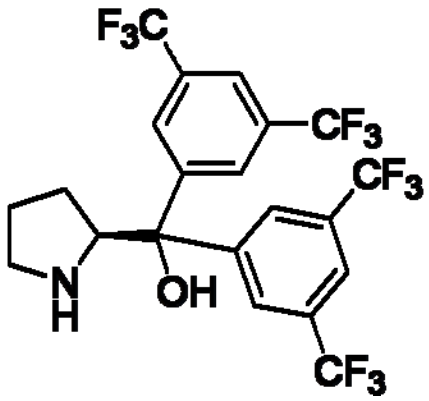
quantitative yield 32% (+10% dioxide)

P. Nguyen, E. Corpuz, T. M. Heidelbaugh, K. Chow, M. E. Garst *J.Org.Chem.* **2003**, *68*, 10195.

Start from sketch

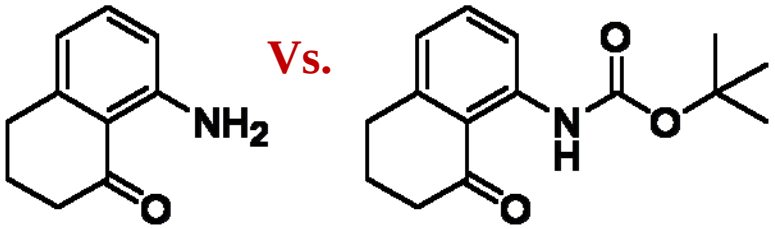
Asymmetric reduction





Enhanced separation properties

Key step of synthesis! Stereoselectivity?



Z. Dalicsek, F. Pollreisz, T. Soós *Chem.Commun.* **2009**, 7587.

Summary and Outlook

Results and future plans

- Synthesis and investigation of various T1 analogues
- Study of N-H acidity and reactivity relationship
- Design of two chiral platforms
- Proof of concept experiments

Acknowledgement

So long and thanks for all the fish!

Prof. Peter R. Schreiner

Radim Hrdina, Zhiguo Zhang
Katharina Lippert, Christian Müller
Christian Kleiner, Thorsten Weil

NMR and MS Department

Whole PRS Group