

Lewis-Säure-Aktivierung *via* Thioharnstoffderivaten – Neue Synthesestrategien in der House-Meinwald-Umlagerung

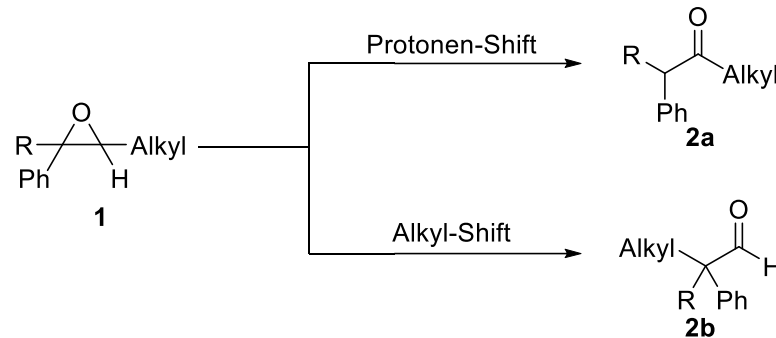
Friedemann Dreßler

16.11.2018

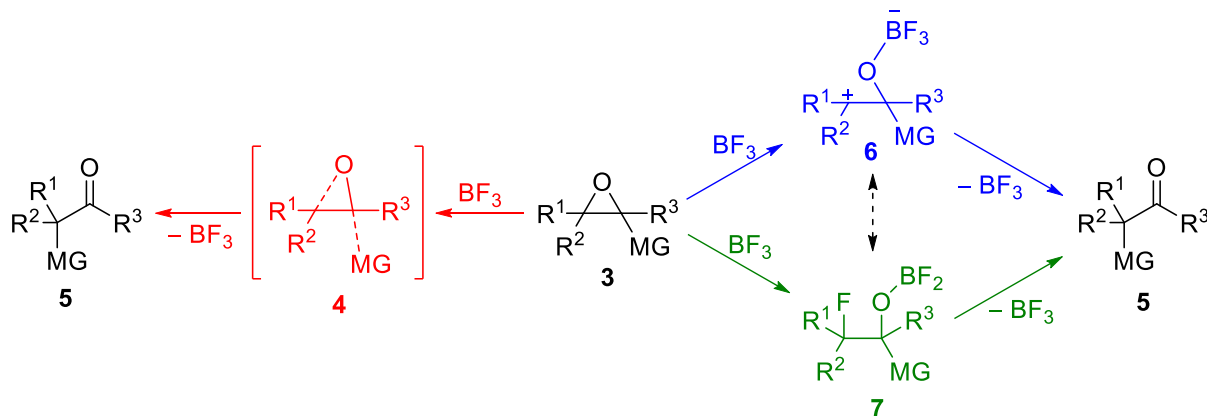
*Institute of Organic Chemistry
Justus-Liebig University Giessen*



- 1955 von H. O. House und 1966 von J. Meinwald beschrieben
- Darstellung von Aldehyden oder Ketonen



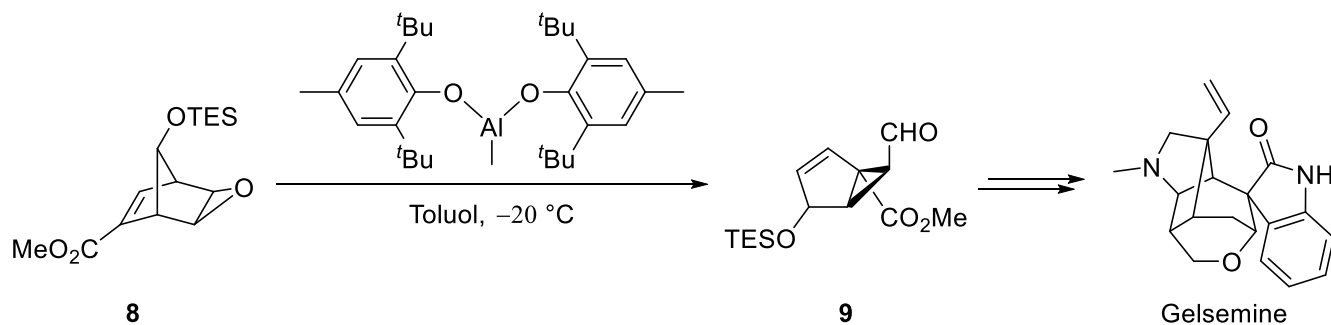
- Verschiedene Mechanismen untersucht: stereospezifisch





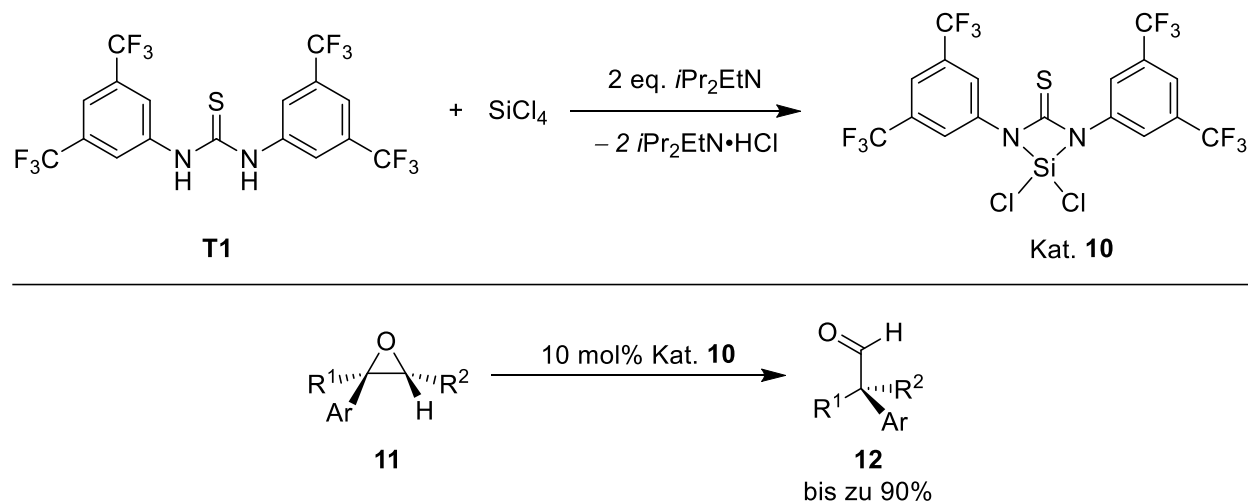
- Brønsted- und Lewis-Säuren als Katalysator
 - H, B, Al, Co → Alkyl-Shift
 - Pd, Ir, In → H-Shift

- Anwendung in verschiedenen Totalsynthesen





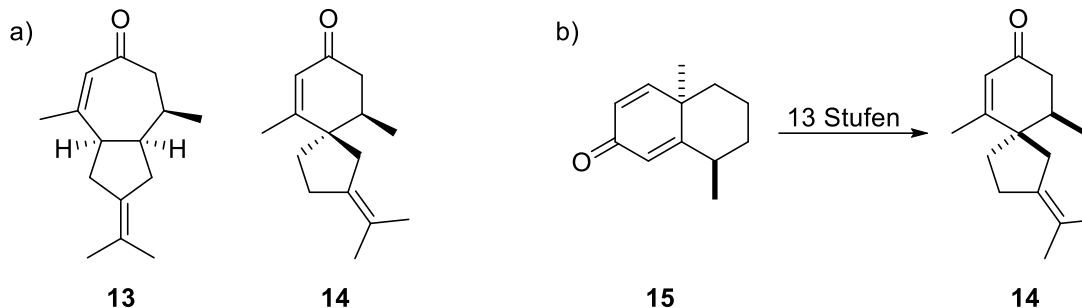
- Aufbau quartärer Kohlenstoffe möglich



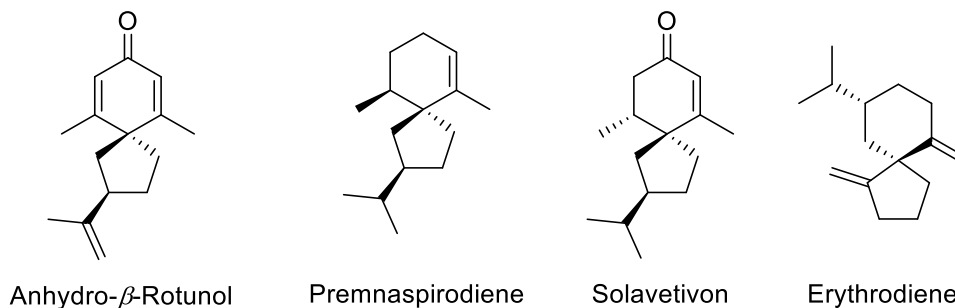
- Asymmetrische Synthese von quartären Kohlenstoffen große Herausforderung



- Erste Spiroverbindung von Pfau und Plattner 1939: β -Vetivon
 - Falsche Struktur eines Hydroazulens angenommen
 - 1967 korrekte Struktur und erste Totalsynthese von Marshall



- Zahlreiche weitere Naturstoffe mit Bioaktivität

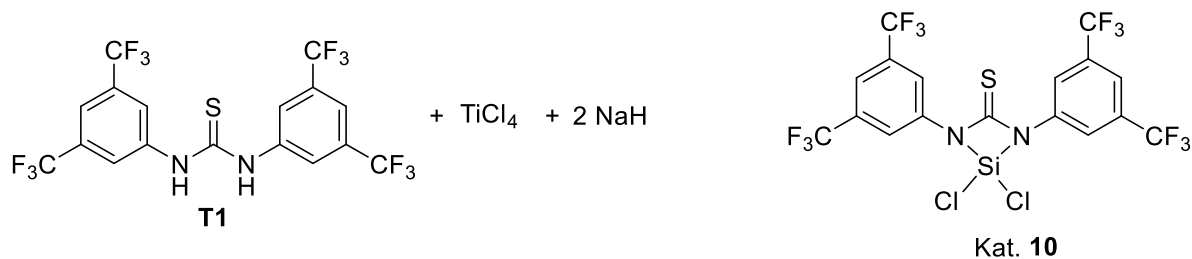




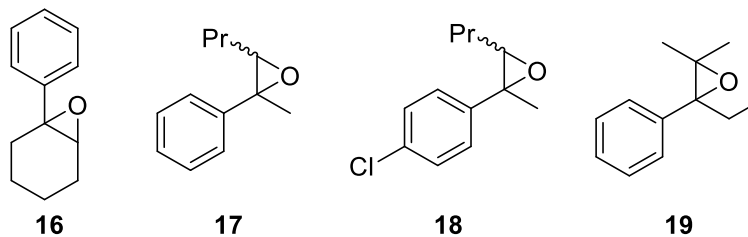
- Verschiedene Synthesestrategien
 - Aldol-Reaktionen
 - Ringschluss-Metathese
 - Diels-Alder-Reaktion
 - [3,3]-sigmatrope Umlagerungen



- Synthese quartärer Carbonylverbindungen *via* HMU
- Katalysatoren auf Si- und Ti-Thioharnstoff-Basis

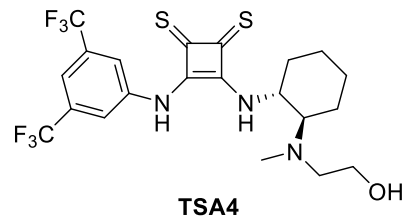
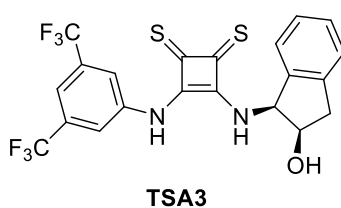
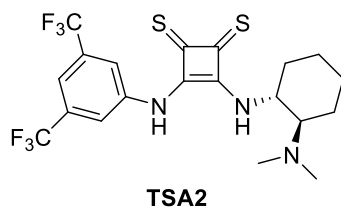
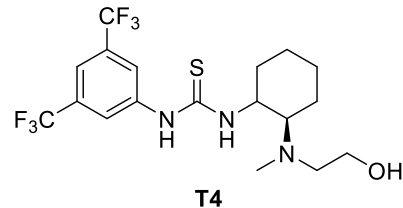
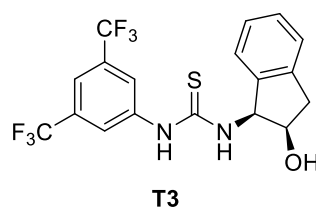
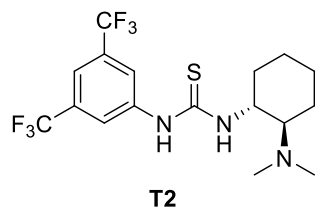
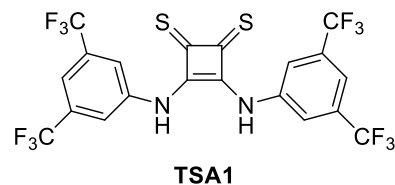
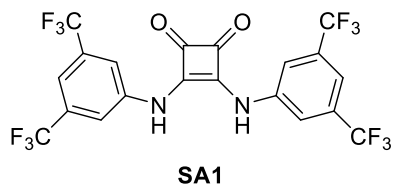


- Testsubstrate



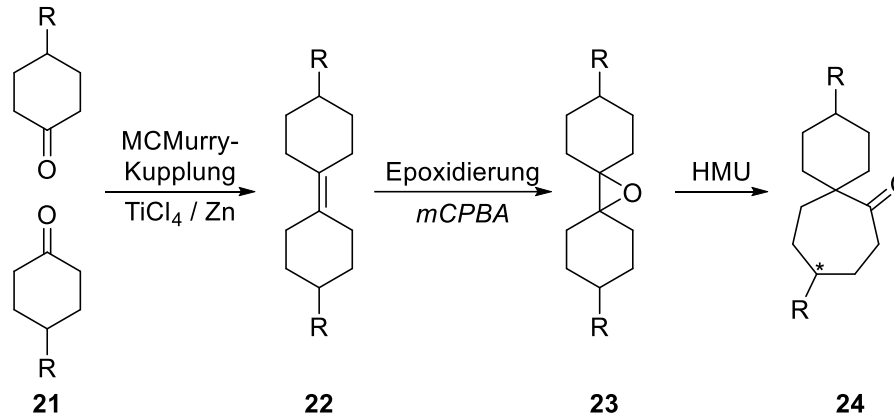


- Synthese weiterer Liganden





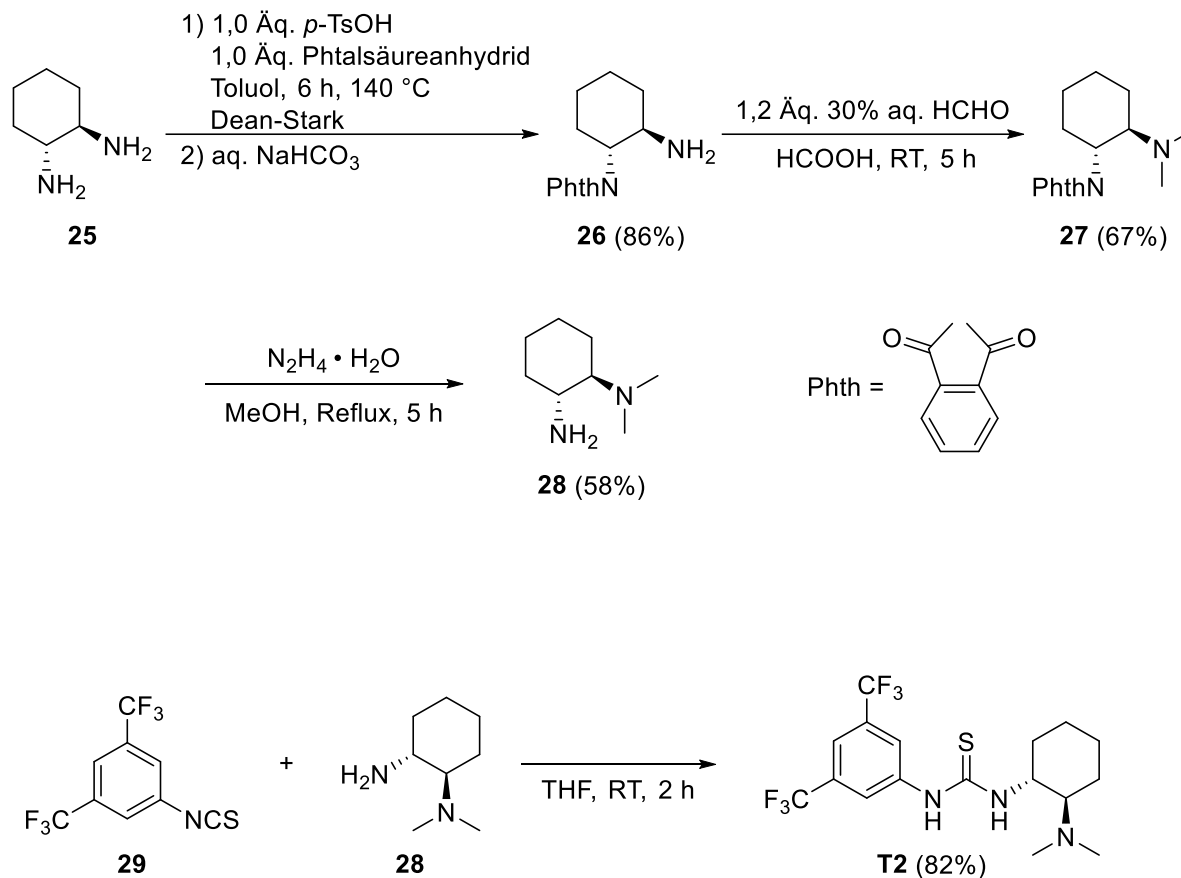
- Asymmetrische Liganden → Enantioselektive HMU



- Strukturaufklärung der Katalysatorspezies

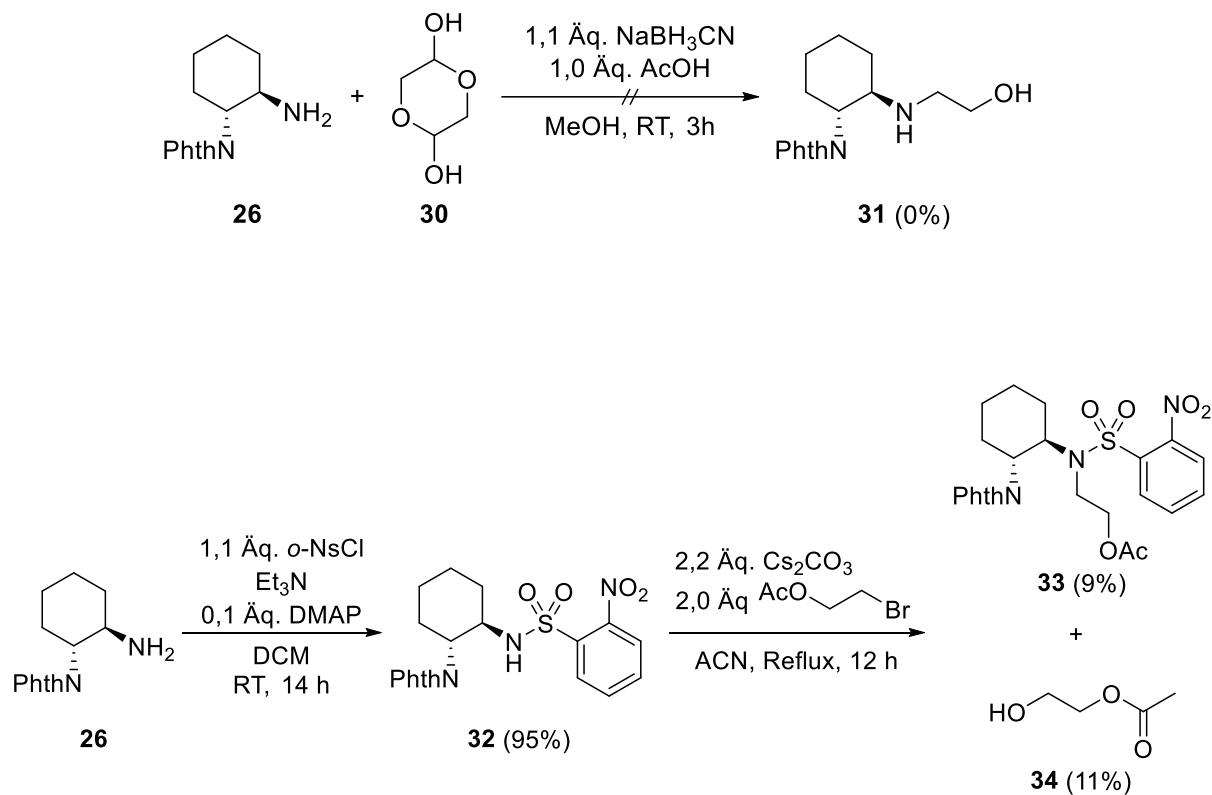


Takemoto-Thioharnstoff **T2**



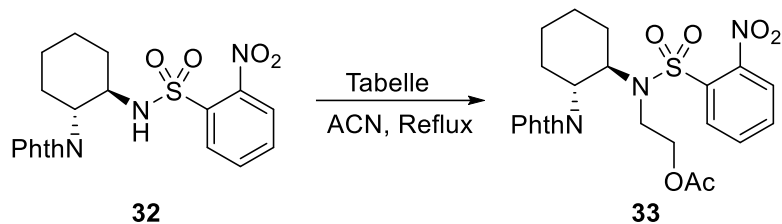


- Takemoto-Thioharnstoff **T4**



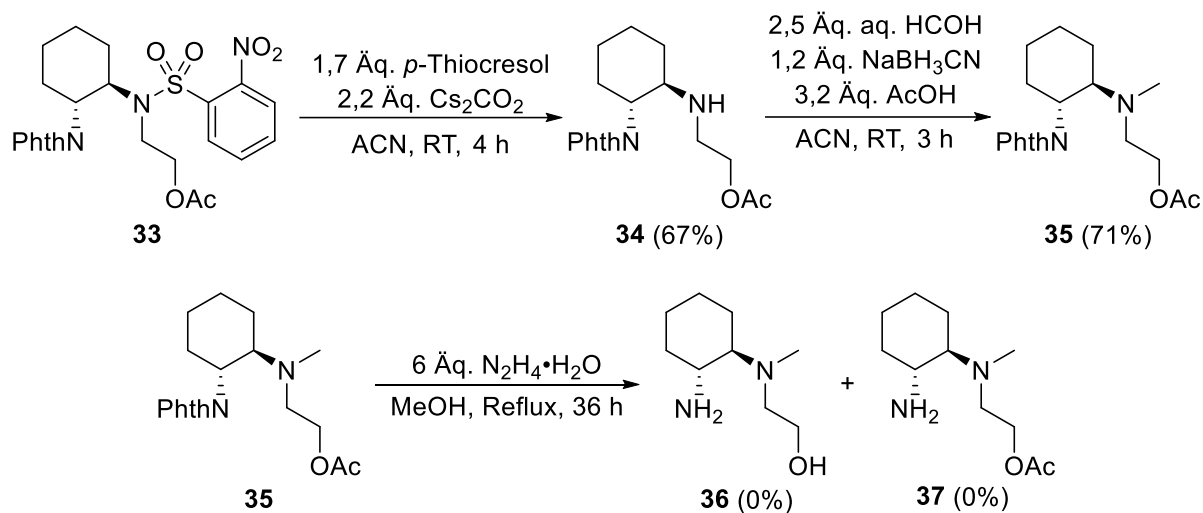


- Reaktionsoptimierung



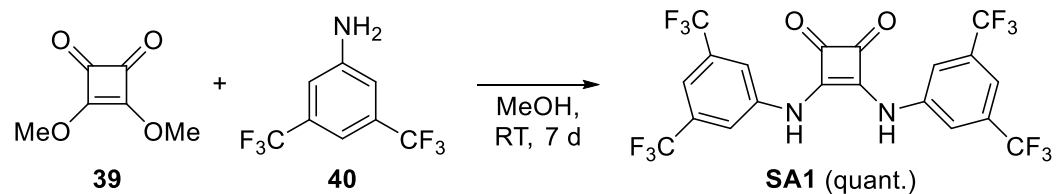
Eintrag	Äq.	Base (Äq.)	MgSO ₄ (Äq.)	t / h	33 / %
	BrCH ₂ CH ₂ OAc				
1	2,0	Cs ₂ CO ₃ (2,2)	–	12	9
2^a	2,0	NaH	–	6	0
3^b	2,2	Cs ₂ CO ₃ (2,4)	–	12	11
4	3,3	Cs ₂ CO ₃ (3,2)	2,3	24	15
5	4,0	Cs ₂ CO ₃ (5,7)	4,4	24	17
6	3,1	Na ₂ CO ₃ (6,0)	–	24	7
7	3,4	K ₂ CO ₃ (3,2)	–	24	13
8	4,7	K ₂ CO ₃ (9,2)	15,1	36	21

^a THF als Lösungsmittel. ^b Verwendung von Cs₂CO₃ nach 24 h Trocknen in Trockenpistole.

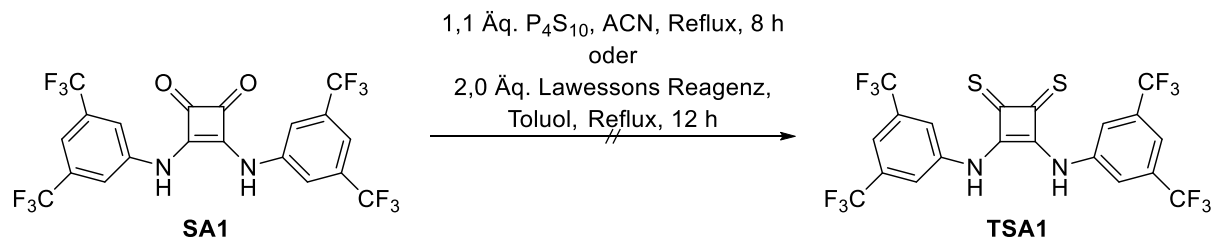




- SA1

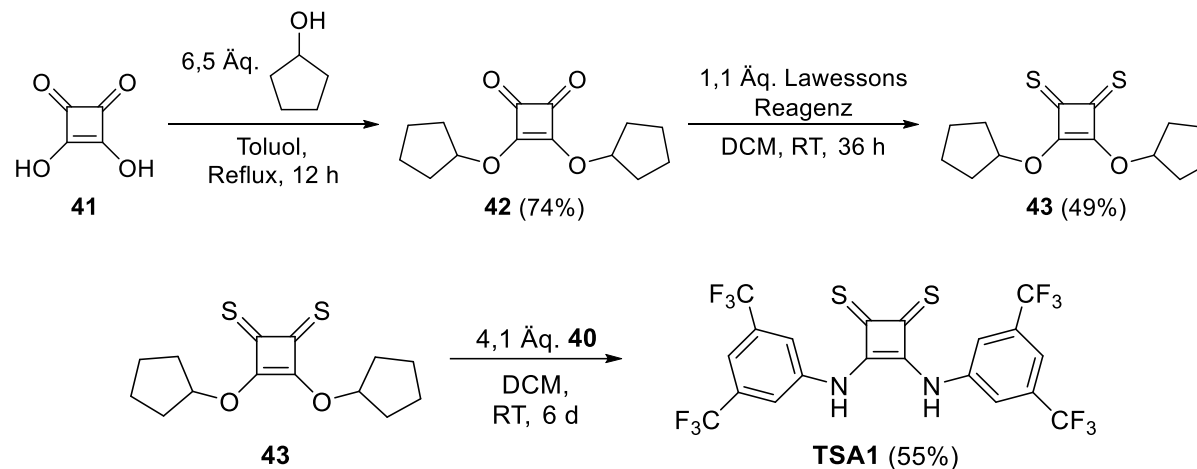


- TSA1

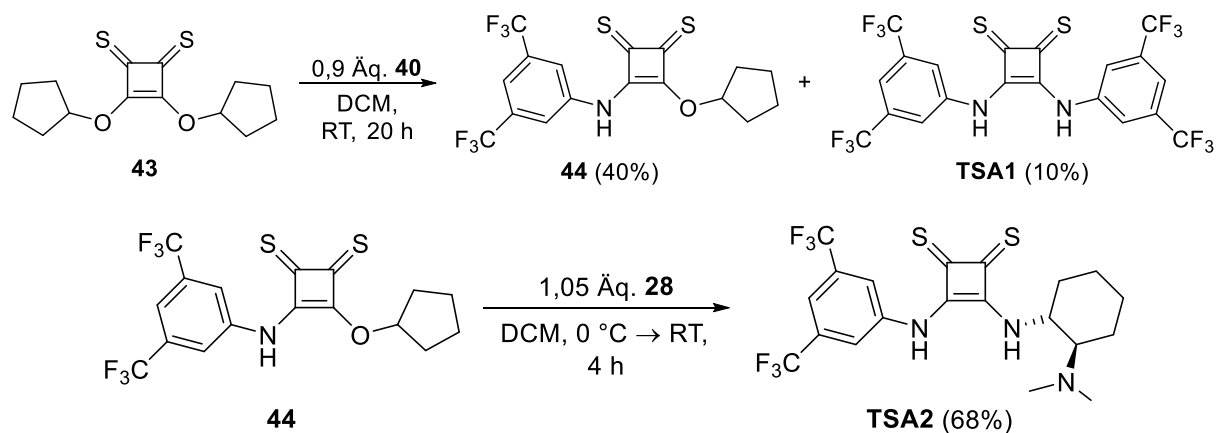




• TSA1

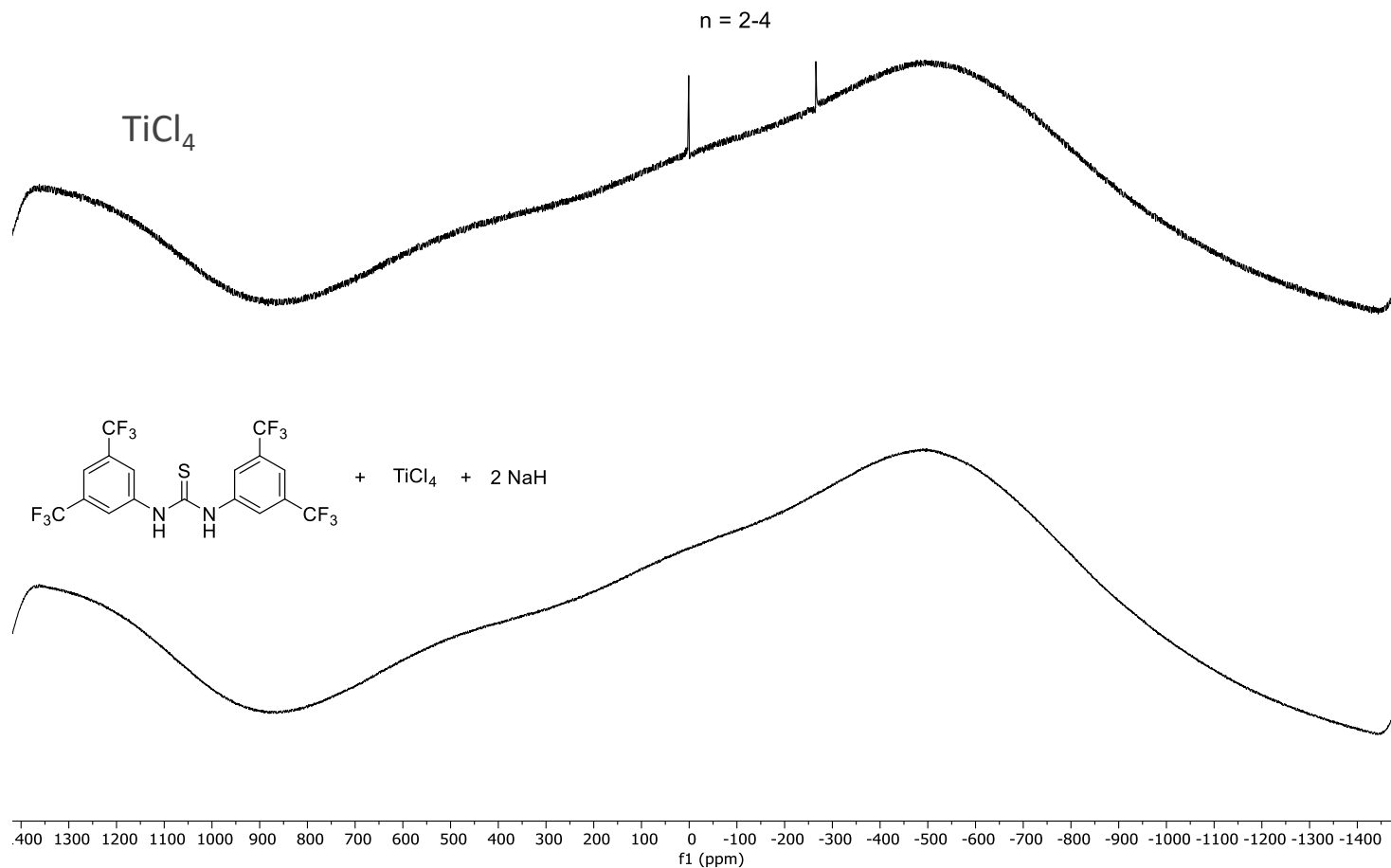
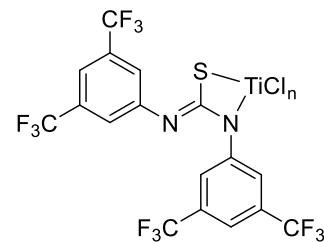
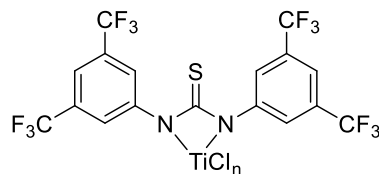


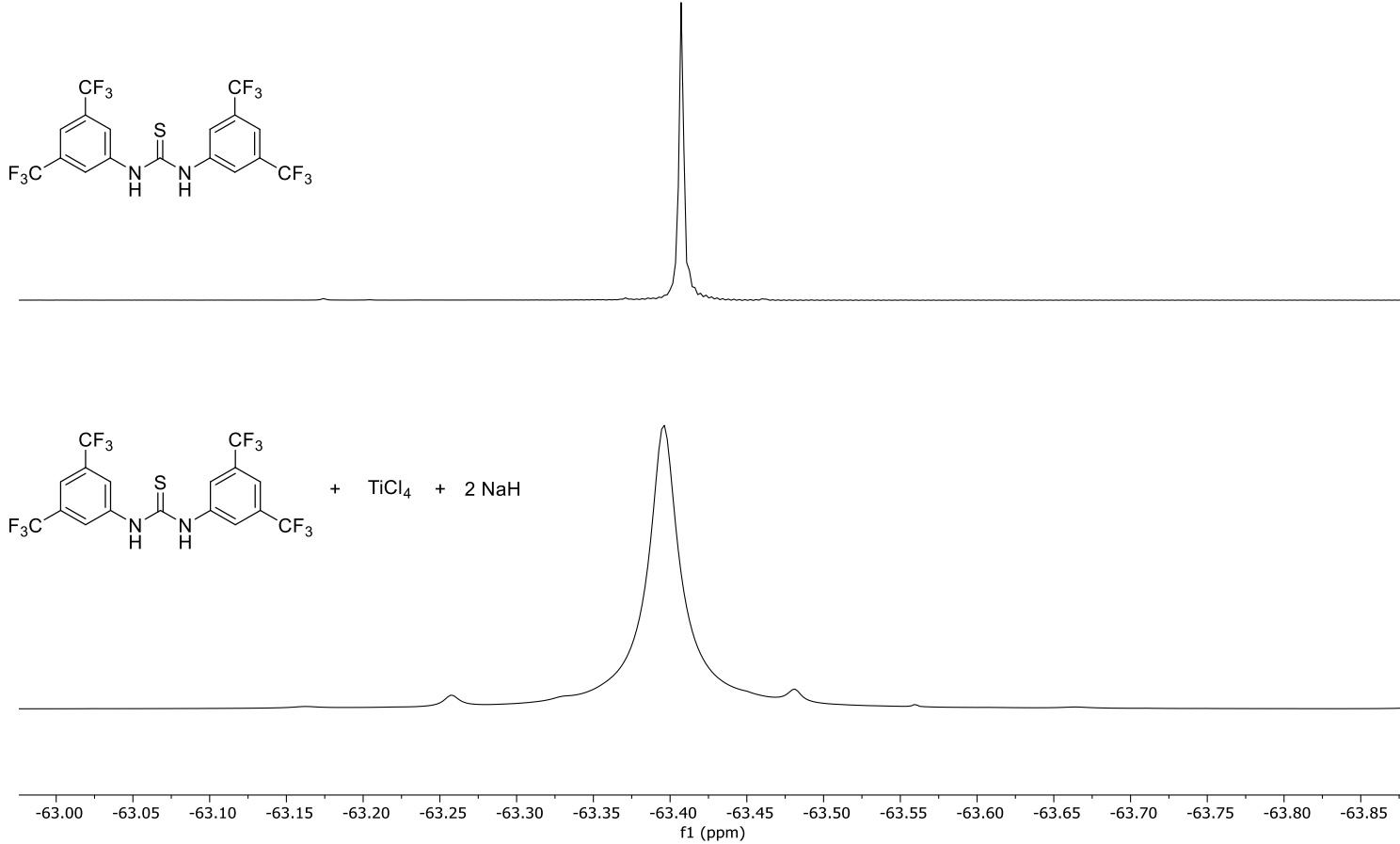
• TSA2

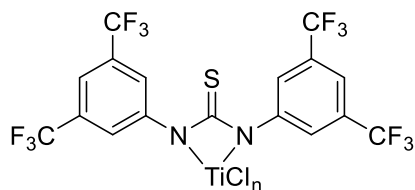
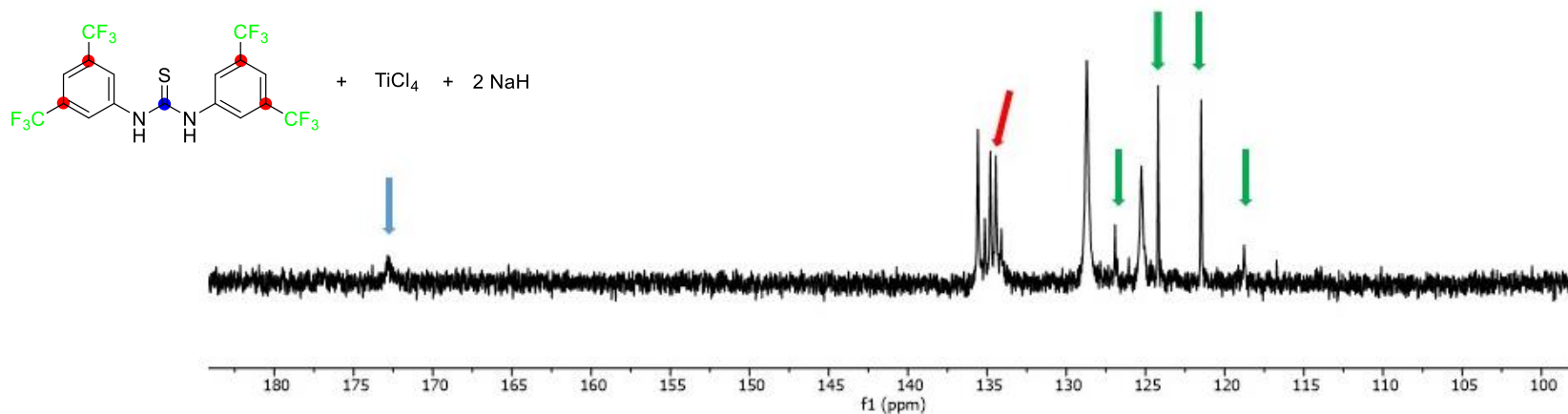
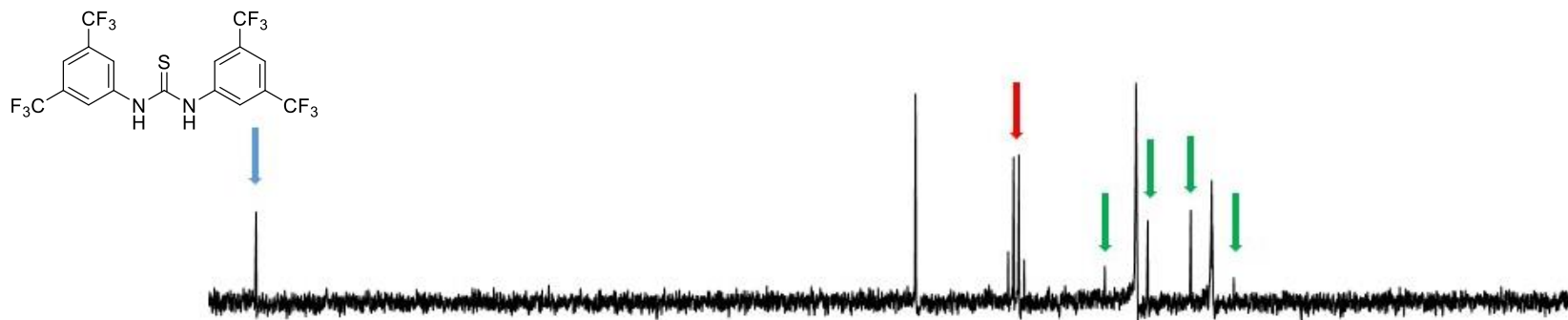


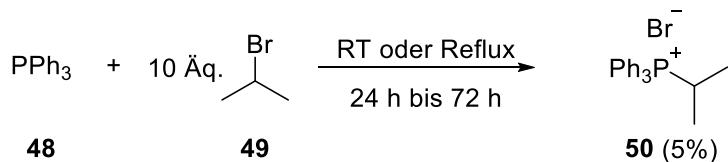
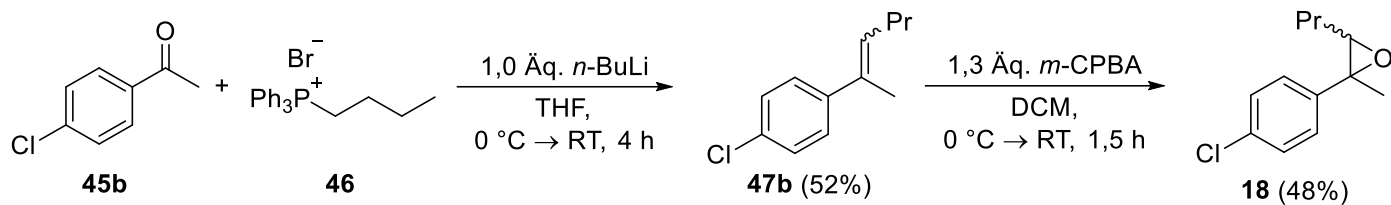


- Mögliche Strukturen

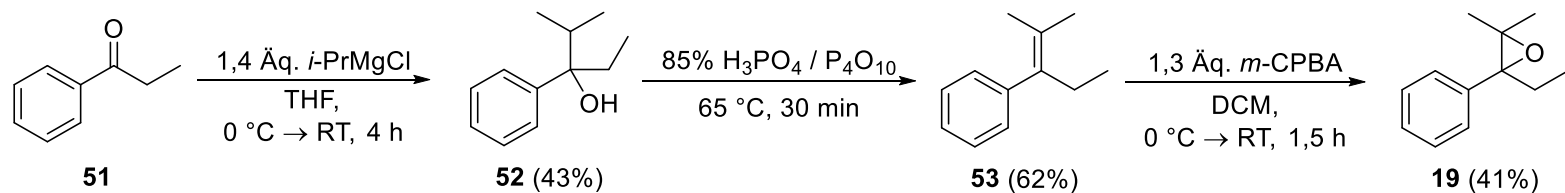


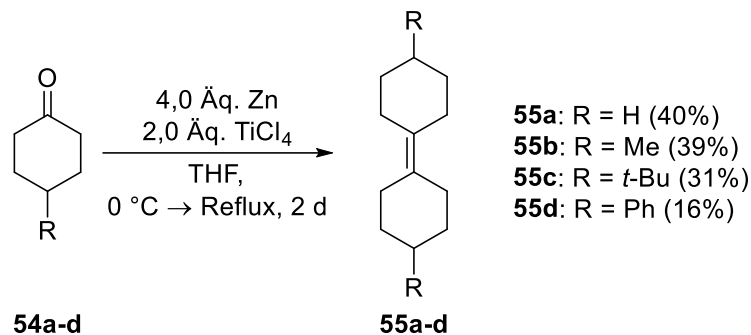




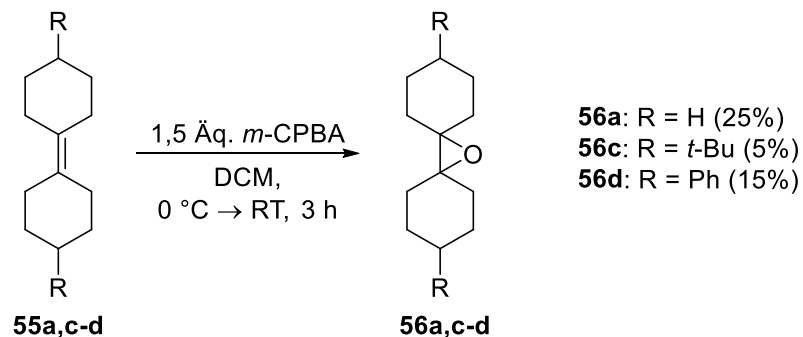


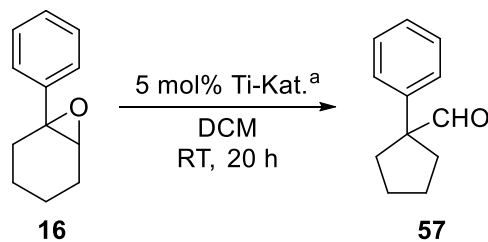
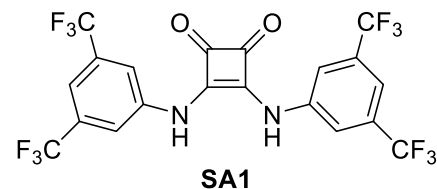
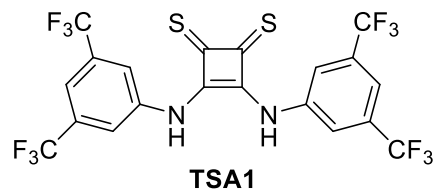
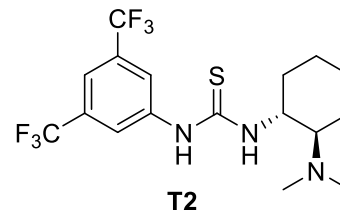
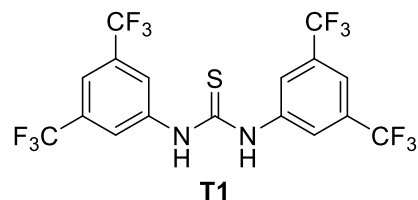
- Synthese der tetrasubstituierten Epoxide nicht über Wittig möglich





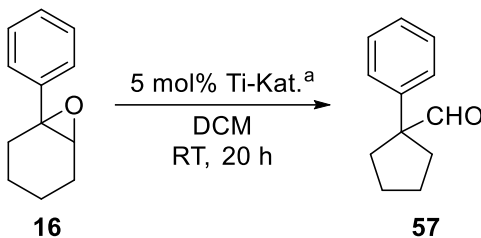
- Optimierung der McMurry-Kupplung schwierig
 - Nebenprodukte
 - Niedrigere Ausbeute





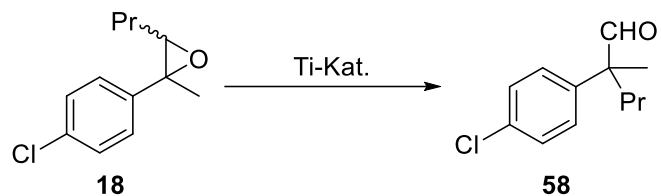
Eintrag	Ligand	57 / % ^b	16 / % ^b
1	T1	84	–
2	T2	23	14
3	TSA1	44	0
4	SA1	<5	>90

^a 5 mol% TiCl_4 , 10 mol% NaH, 5 mol% Ligand. ^b Ausbeute wurde *via* $^1\text{H-NMR}$ mit *p*-Nitrobenzaldehyd als interner Standard bestimmt.



Eintrag	Base	57 / % ^b	16 / % ^b
1	–	26	7
2	D/PEA	16	45
3	NaH	84	0
4	LiH	36	0
5	<i>n</i> -BuLi	47	0

^a 5 mol% TiCl₄, 10 mol% Base, 5 mol% **T1**. ^b Ausbeute wurde *via* ¹H-NMR mit *p*-Nitrobenzaldehyd als interner Standard bestimmt.

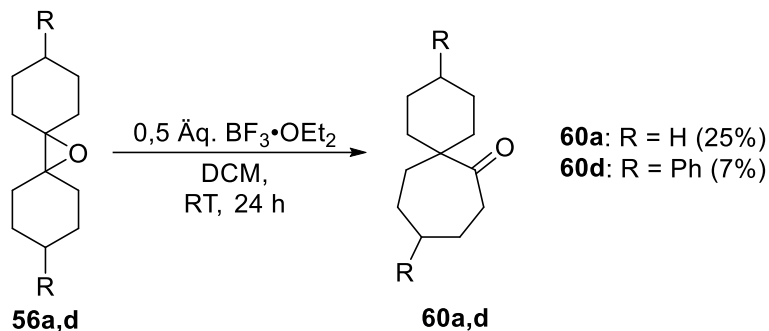


Eintrag	mol% Kat.	Ligand	Lösungsmittel	T / °C	t / h	58 / % ^a
1	5	–	DCM	RT	20	<1
2	5	T1	DCM	RT	20	28
3	5	T1	Toluol	RT	20	15
4	5	T1	THF	RT	20	<1
5	5	SA1	DCM	RT	20	6
6	10	T1	DCM	RT	20	35
7	10	T1	DCE	RT	20	33
8	10	T1	DCM	–10 °C	42	<1
9	10	T1	DCE	–10 °C	42	<1

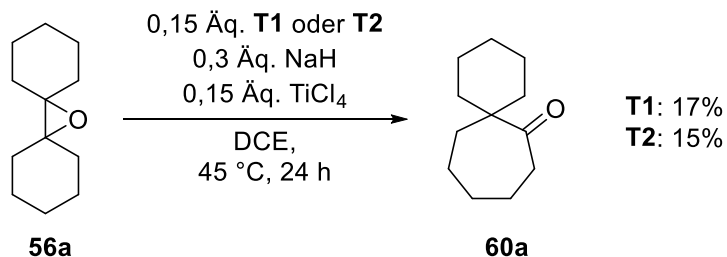
^a Ausbeute wurde *via* ¹H-NMR mit *p*-Nitrobenzaldehyd als interner Standard bestimmt.



- Umlagerung zu Spiroverbindungen mit $\text{BF}_3 \cdot \text{OEt}_2$ analog zu Sands:



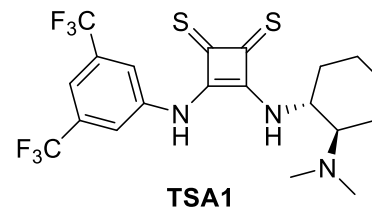
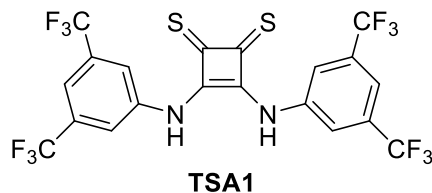
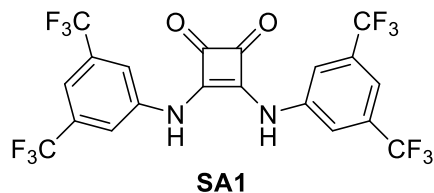
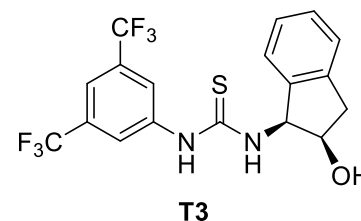
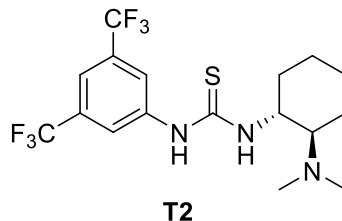
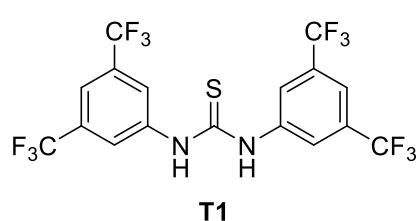
- Titan-Thioharnstoff-Katalysator



- 4,4'-Phenyl-Derivat: Unbekannte Substanz isoliert → Kristallstrukturanalyse steht aus



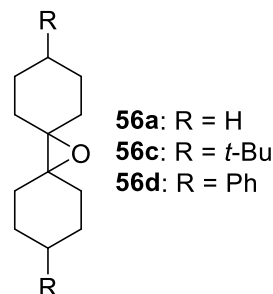
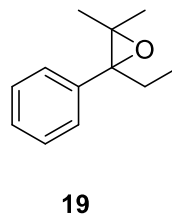
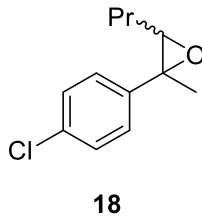
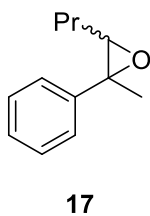
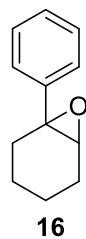
- Synthese verschiedener Liganden



→ Katalysen mit bisher nicht verwendeten Liganden

→ Verwenden des Silicium-Thioharnstoff-Katalysators

- Synthese verschiedener Epoxide





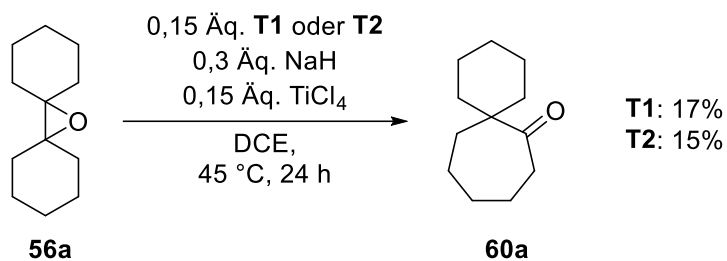
- Voroptimierungen für „*Design of Experiment*“-Ansatz

→ DCE als Lösungsmittel

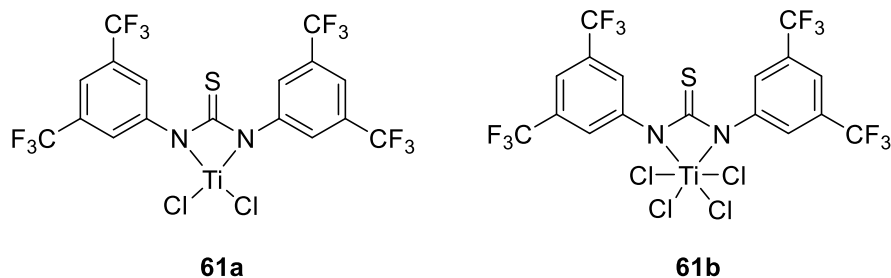
→ leichtes Erhitzen

→ vollständiges „*Design of Experiment*“

- Synthese von Spiroverbindungen mit asymmetrischer Lewis-Säure



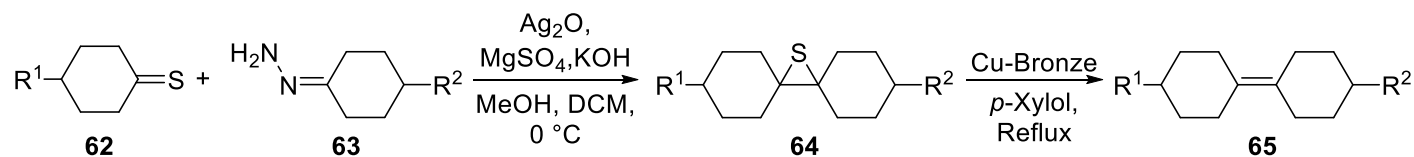
- Strukturanalyse



→ Kristallisationsversuche in Glovebox

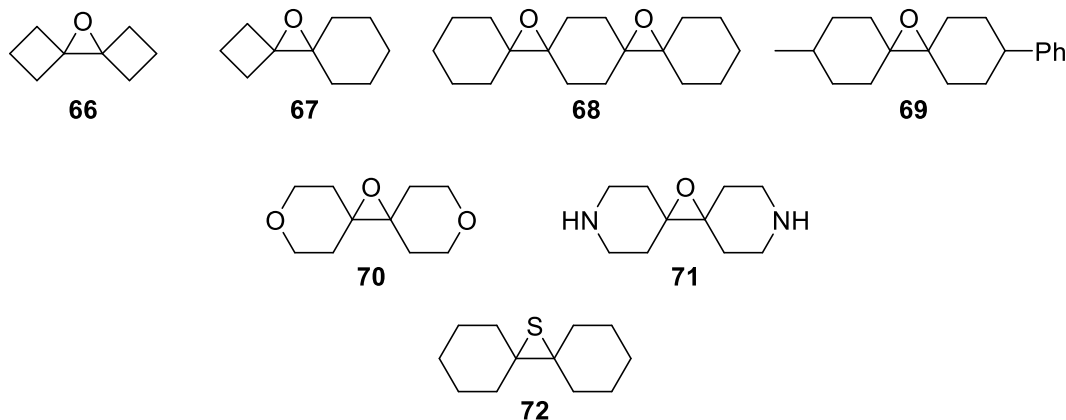


- Optimierung der McMurry-Kupplung
 - TiCl_3 als Titanspezies
 - LiAlH_4 , Lithium, Natrium oder Kalium als Reduktionsmittel
 - Diazo-Thioketon-Kupplung



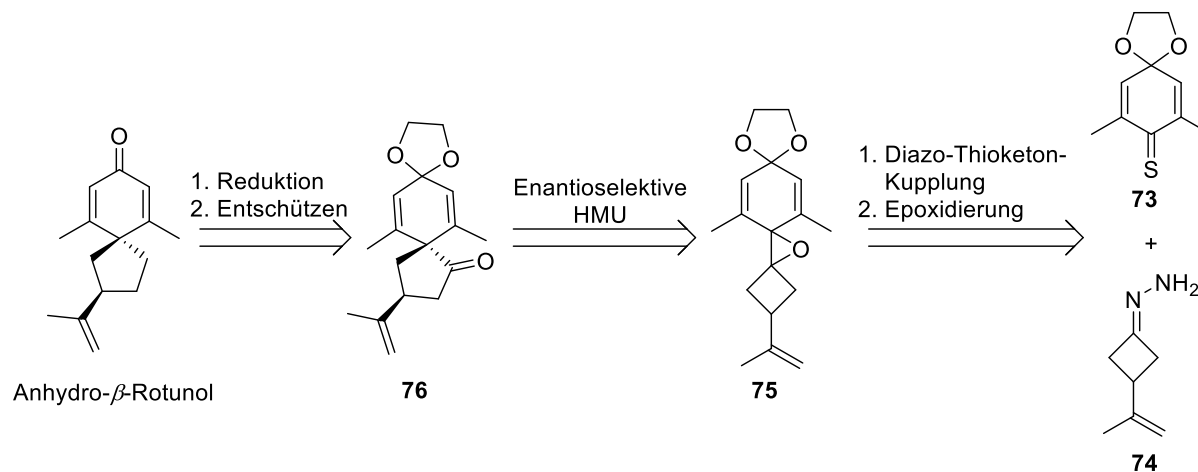
→ unterschiedliche Substituierte Olefine

- Substratpool

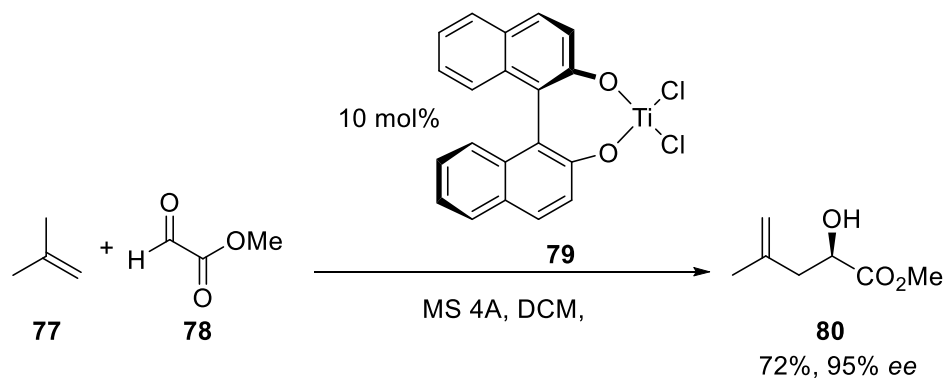




- Totalsynthese von Anhydro- β -Rotunol



- Andere Katalysatoren und Reaktionen





- Prof. Dr. P. R. Schreiner
- Christian Eschmann
- Dr. Raffael C. Wende
- Dr. Heike Hausmann, Dr. Jonathan Becker, Simon Becher
- Labore 204, 205, 207
- AG Schreiner

