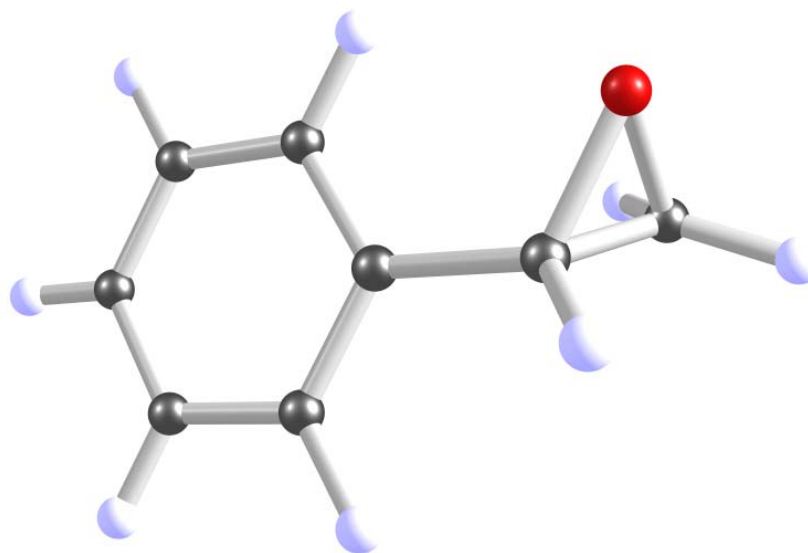


Mechanistic Studies on the Alcoholysis of Styrene Oxides



Kira Hof
30.01.2009

Contents

- Alcoholysis of Epoxides
- Addition of Carboxylic Acids to Alkynes
- Corey-Chaykovsky Reaction
- Summary
- Outlook
- Acknowledgement

Alcoholysis of Epoxides

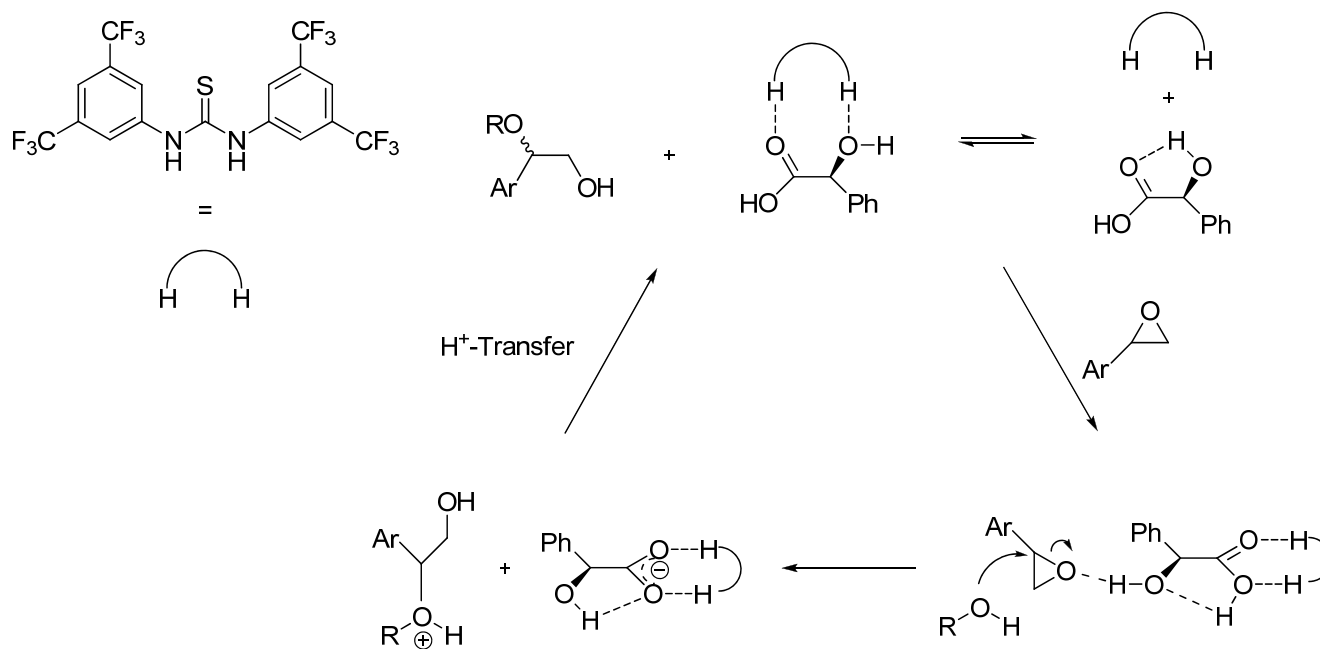
- Synthesis of β -alkoxy alcohols
- Strong acidic or basic conditions $\rightarrow$ limiting substrate scope
- Metal salts as catalysts: e.g. $\text{Al}(\text{OTf})_3$, LiClO_4 , Co-salen complexes

D. Bradley, G. Williams, M. Lawton, *Org. Biomol. Chem.* **2005**, 3, 3269-3272

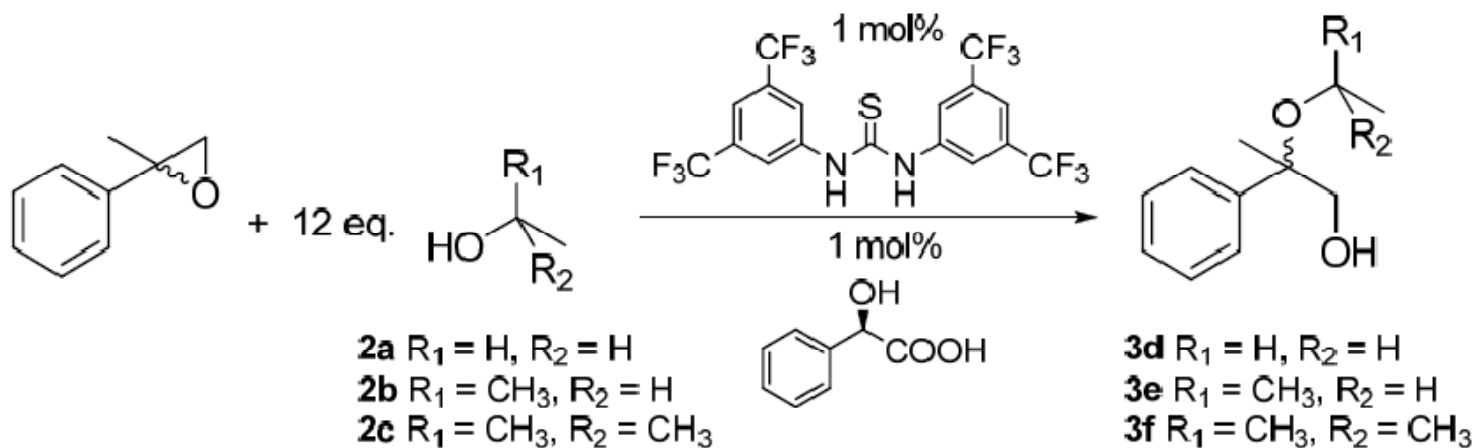
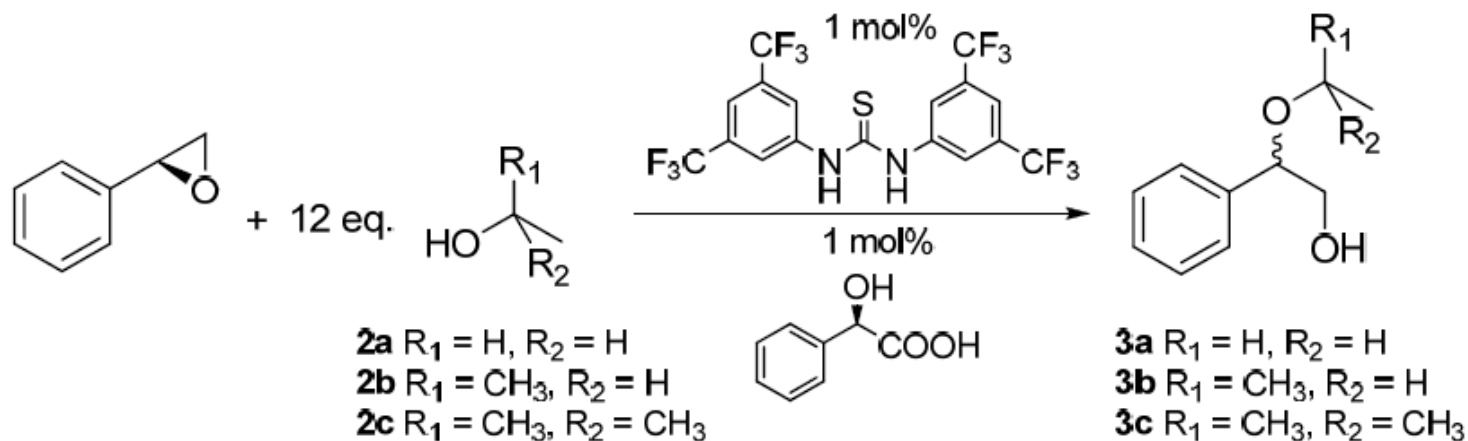
M. Chini, P. Crotti, C. Gardelli, F. Macchia, *Synlett* **1992**, 673-676

J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, 123, 2687-2688

Alcoholysis of Styrene Oxides

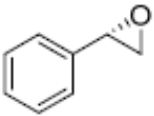
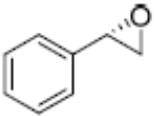
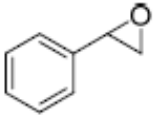


Task



Results

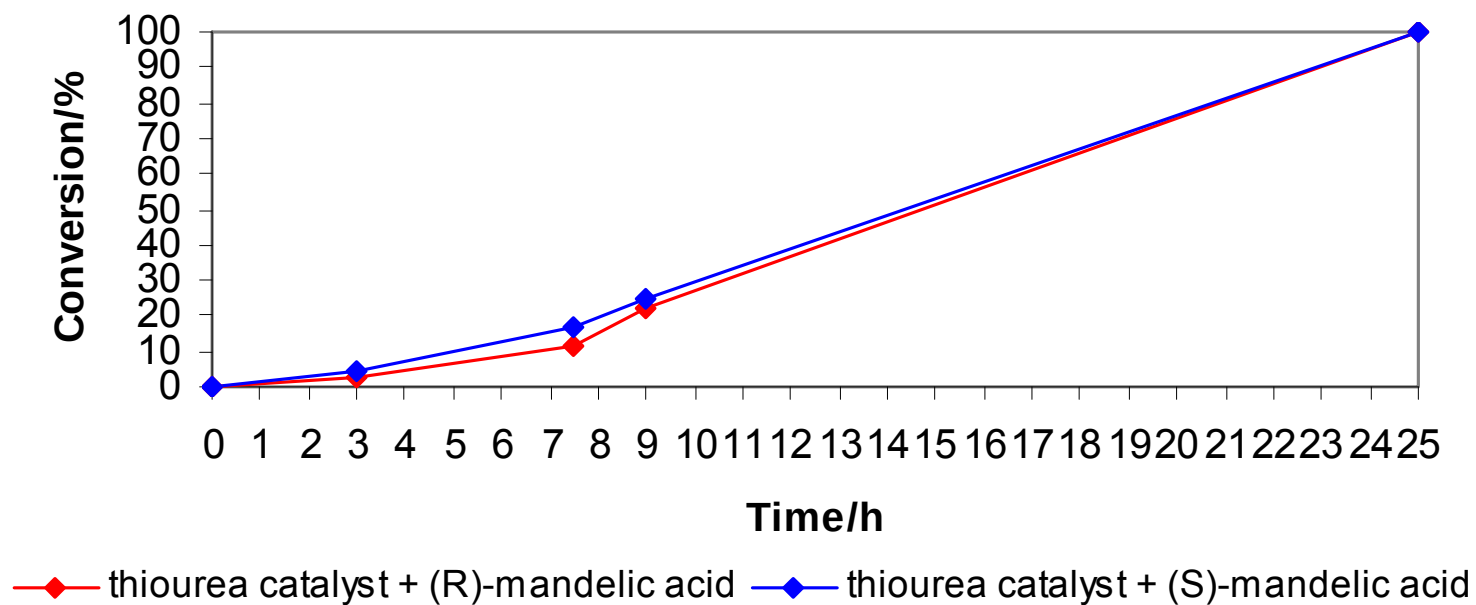
Alcoholysis of (*S*)-Styrene Oxide with Thiourea Catalyst and (*R*)-Mandelic Acid at Room Temperature

Entry	Epoxide	Alcohol	Conversion/% ^a	Time/h	Yield/% ^b	ee/% ^c
1			100	121,5 ^d	36	78
2			100	22	39	81 ^{e,f}
3			100	45 ^d	51	78
4			95	186 ^d	22	63 ^g
5			46	9,5	- ^h	0

^a GC/MS; ^b of isolated product; ^c chiral HPLC; ^d with impure thiourea catalyst; ^e with (*S*)-mandelic acid; ^f excess of same enantiomer as in experiment with (*R*)-mandelic acid; ^g at 50 °C; ^h not determined

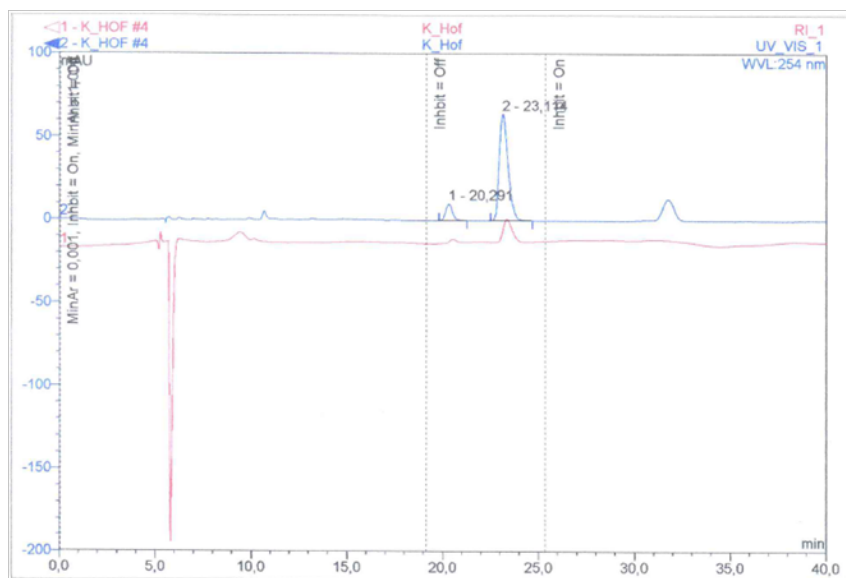
Results

Opening of (S)-Styrene Oxide with Ethanol at Room Temperature



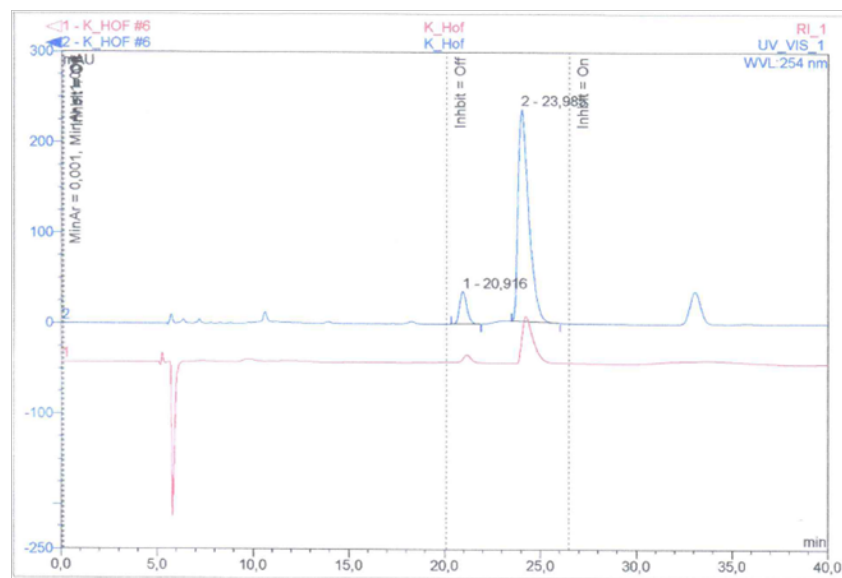
Results

Opening of (S)-Styrene Oxide with Ethanol at Room Temperature



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20,29	n.a.	9,983	4,121	10,69	n.a.	BMB
2	23,11	n.a.	64,081	34,434	89,31	n.a.	BMB
Total:			74,065	38,554	100,00	0,000	

(R)-mandelic acid

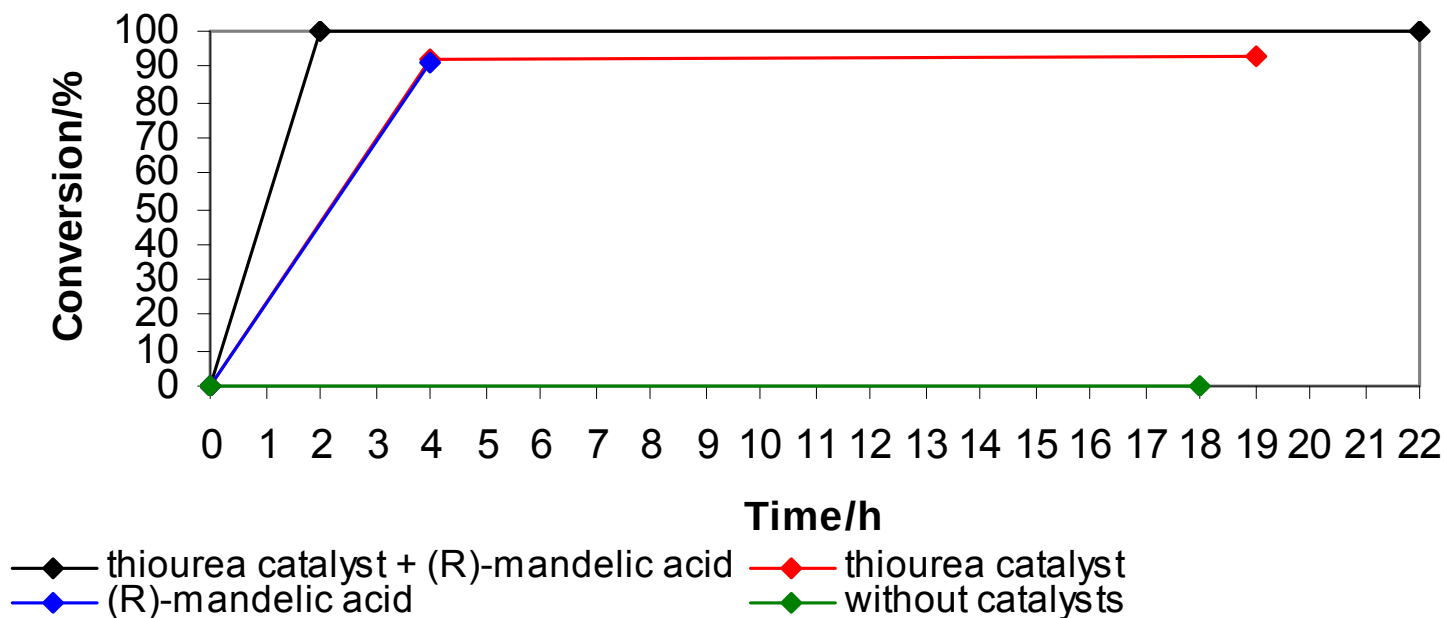


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20,92	n.a.	35,446	15,741	9,43	n.a.	BMB
2	23,98	n.a.	233,876	151,131	90,57	n.a.	BMB
Total:			269,322	166,872	100,00	0,000	

(S)-mandelic acid

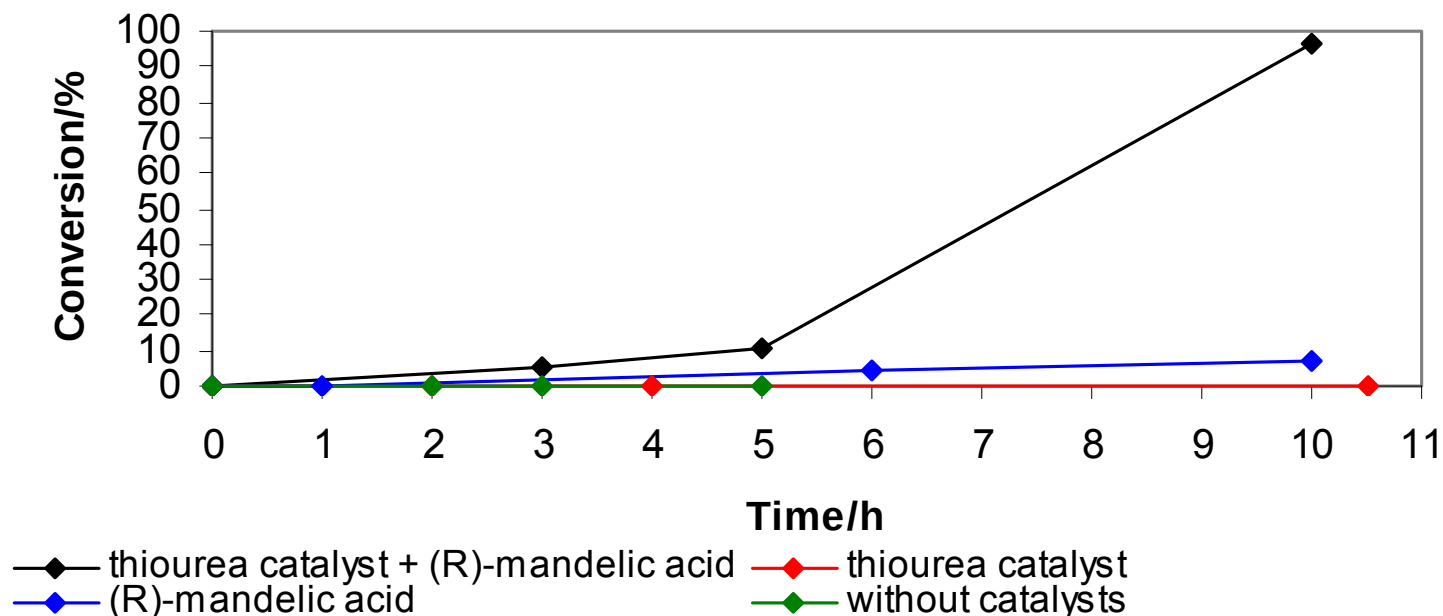
Results

Opening of *rac*-2-Methyl-2-phenyloxirane with Ethanol at Room Temperature



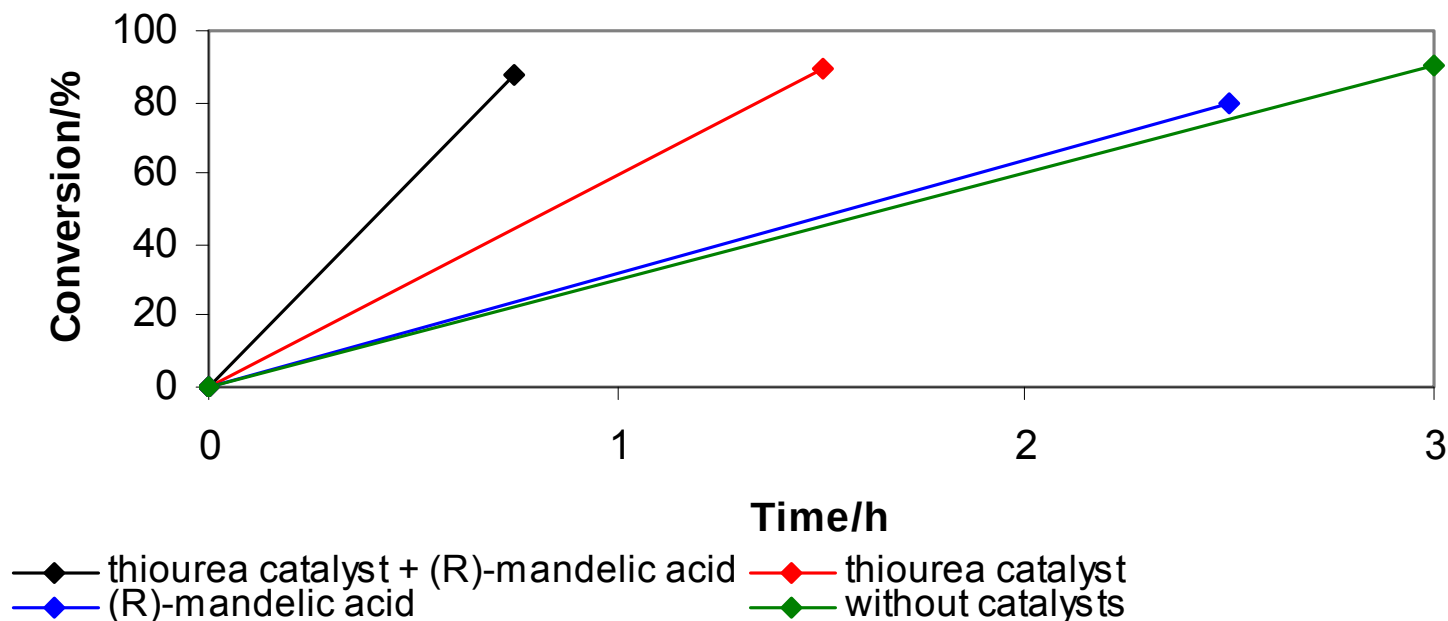
Results

Opening of *rac*-2-Methyl-2-phenyloxirane with
Ethanol at 0 °C



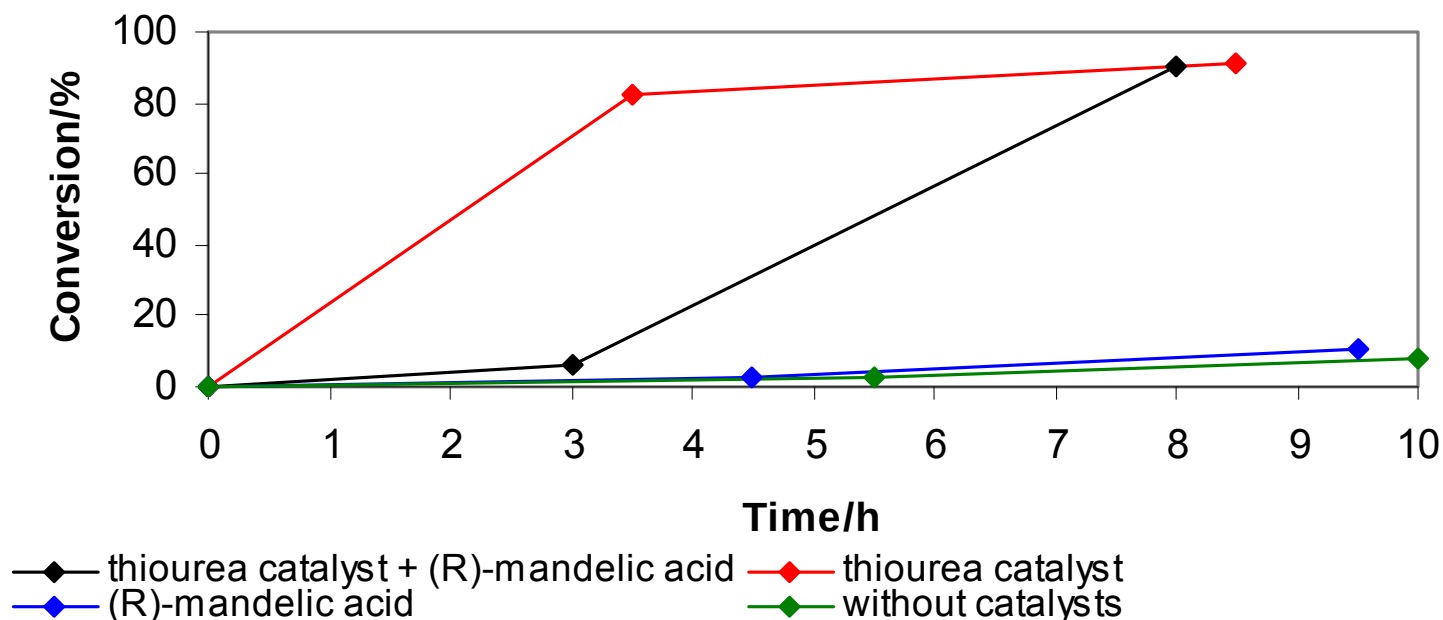
Results

Opening of *rac*-2-Methyl-2-phenyloxirane with 2-Propanol at Room Temperature



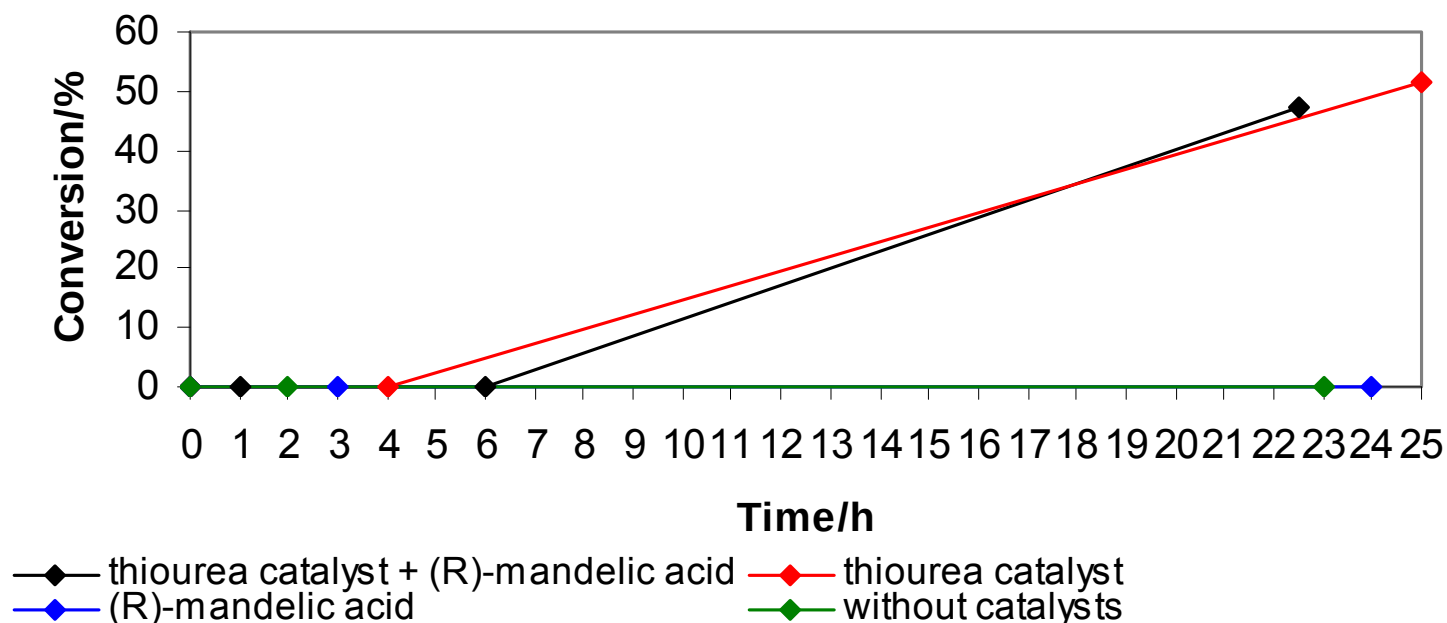
Results

Opening of *rac*-2-Methyl-2-phenyloxirane with 2-Propanol at 0 °C



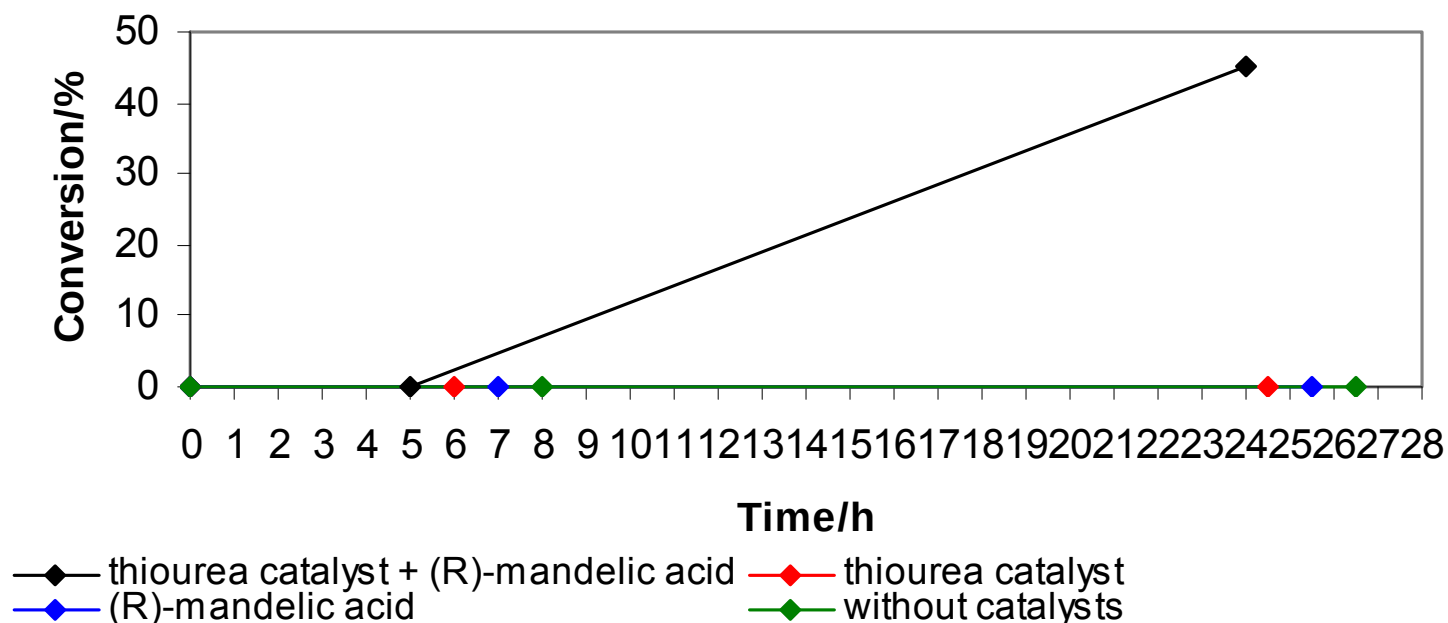
Results

Opening of *rac*-2-Methyl-2-phenyloxirane with *tert*-Butanol at Room Temperature



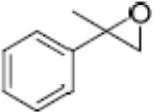
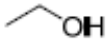
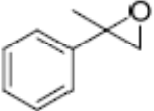
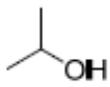
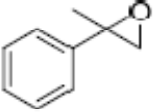
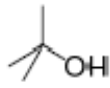
Results

Opening of *rac*-2-Methyl-2-phenyloxirane with
tert-Butanol at 0 °C



Results

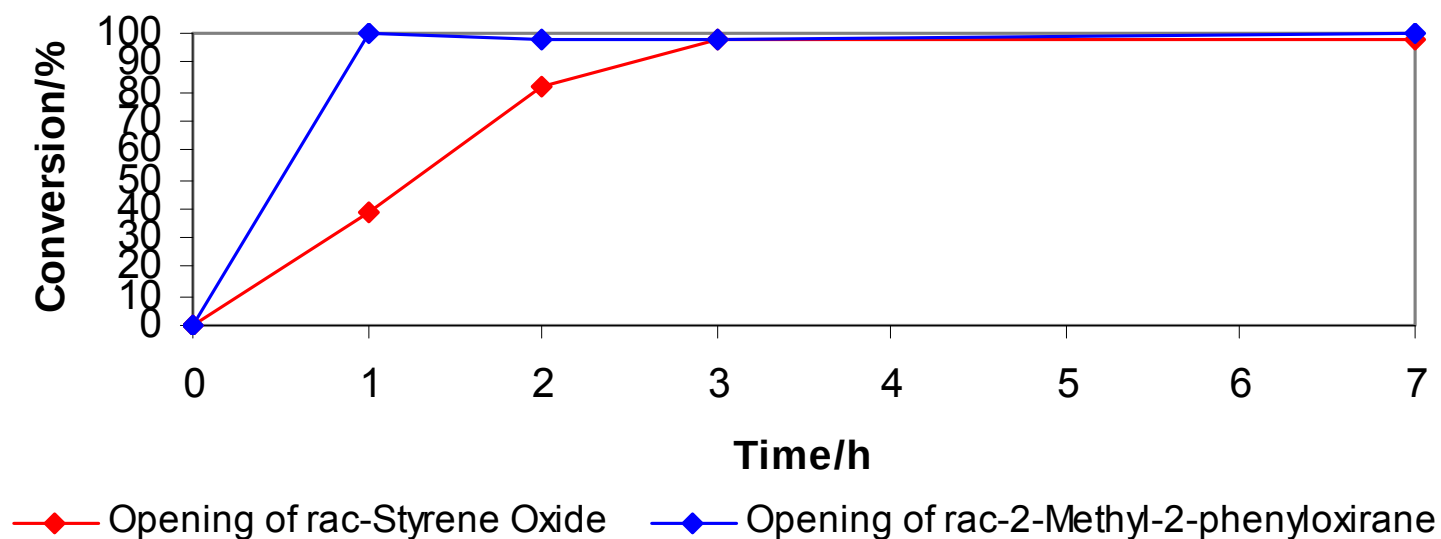
Alcoholysis of *rac*-2-Methyl-2-phenyloxirane with Thiourea Catalyst and (*R*)-Mandelic Acid at Room Temperature

Entry	Epoxide	Alcohol	Conversion/% ^a	Time/h	ee/% ^b
1			31	6,5 ^c	0
2			34	5,5 ^c	0
3			44	95	- ^d

^a GC/MS; ^b chiral HPLC; ^c at 0 °C; ^d product could not be isolated

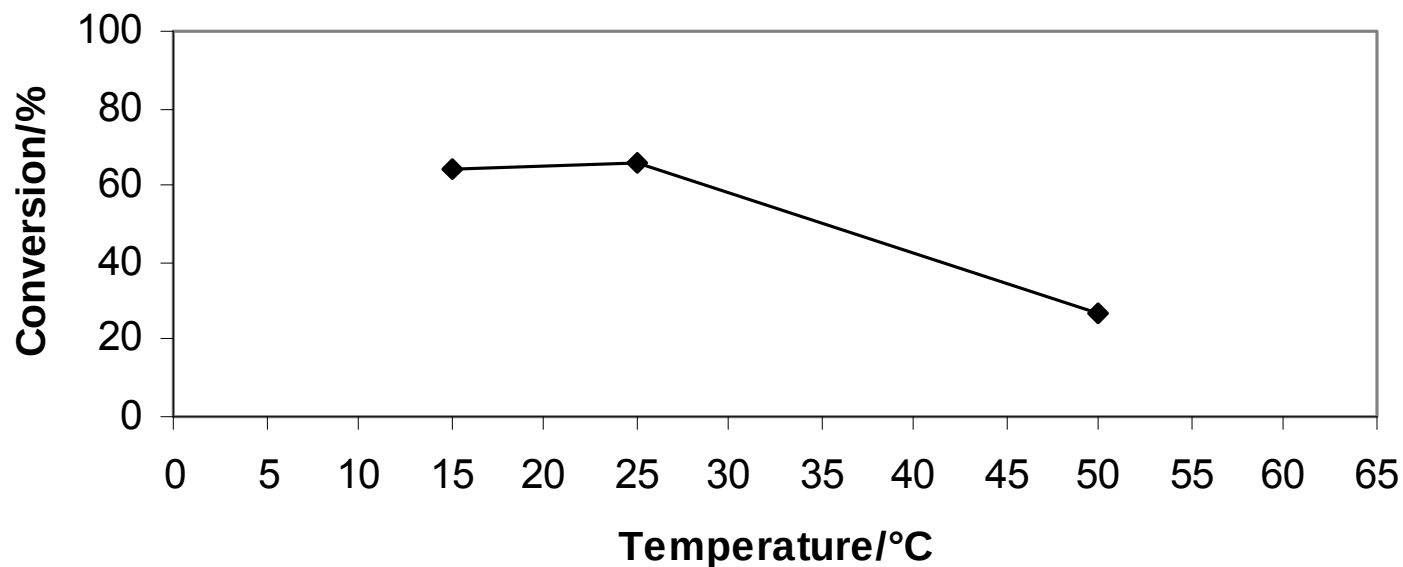
Results

Openings of *rac*-Styrene Oxide and *rac*-2-Methyl-2-phenyloxirane with Ethanol at Room Temperature



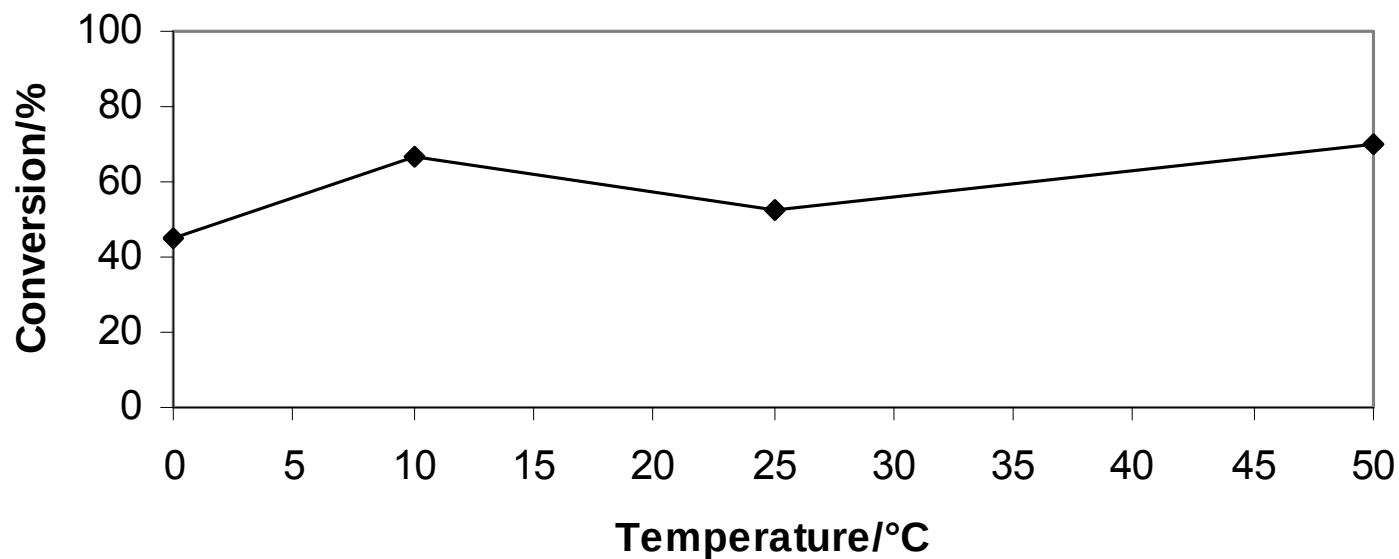
Results

Opening of *rac*-2-Methyl-2-phenyloxirane with
tert-Butanol after 24 hours



Results

Opening of *rac*-2-Methyl-2-phenyloxirane with
tert-Butanol after 24 hours



2 equivalents of *tert*-butanol

Addition of Carboxylic Acids to Alkynes

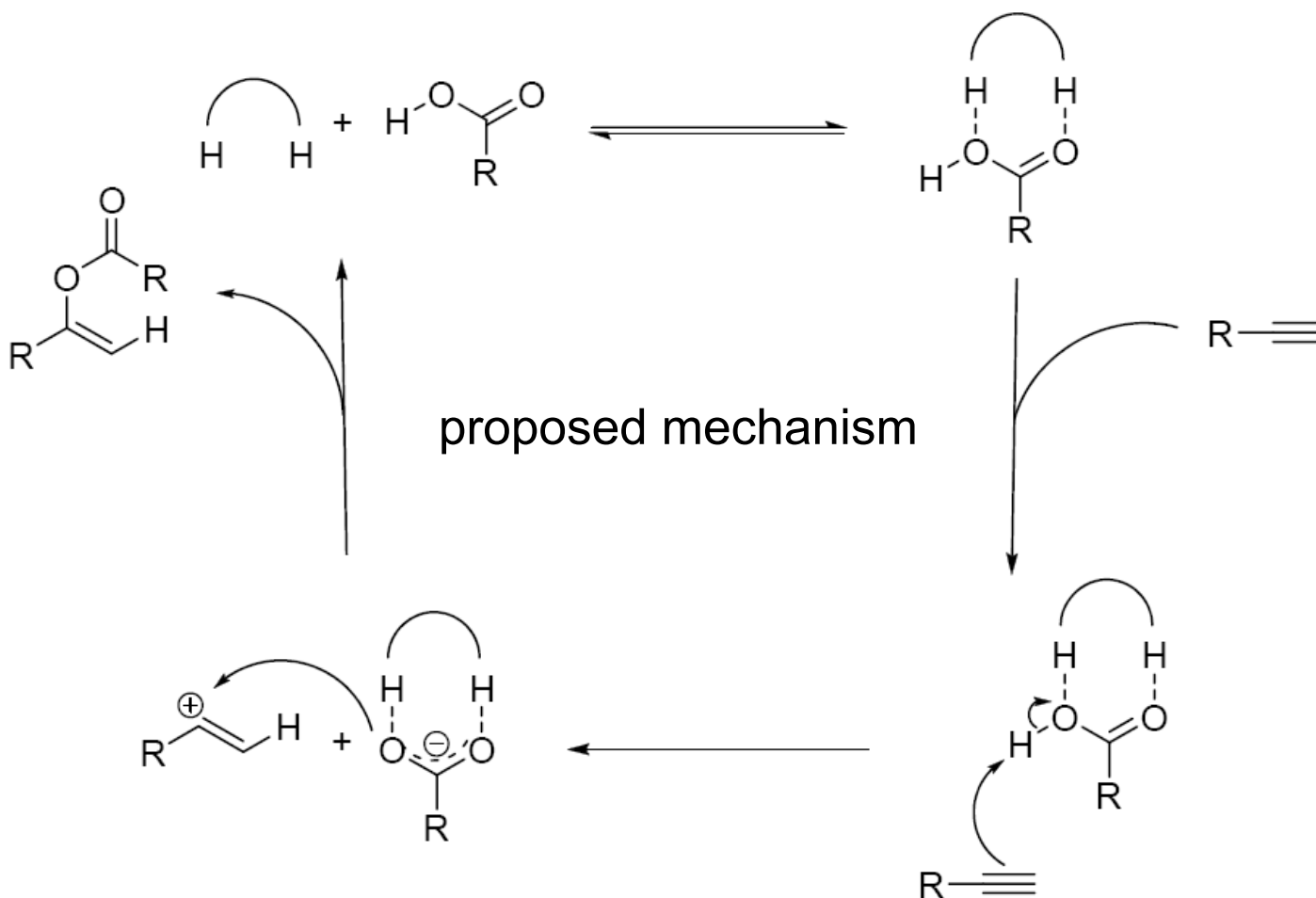
- Leads to enol or vinyl esters
- Until 1980s: mercury salts → toxic
- 1983, Rotem and Shvo: $\text{Ru}_3(\text{CO})_{12}$ as catalyst
- Up to now: other Ru catalysts → expensive

T. Mitsudo, Y. Hori, Y. Yamakawa, Y. Watanabe, *J. Org. Chem.* **1987**, 52, 2230-2239

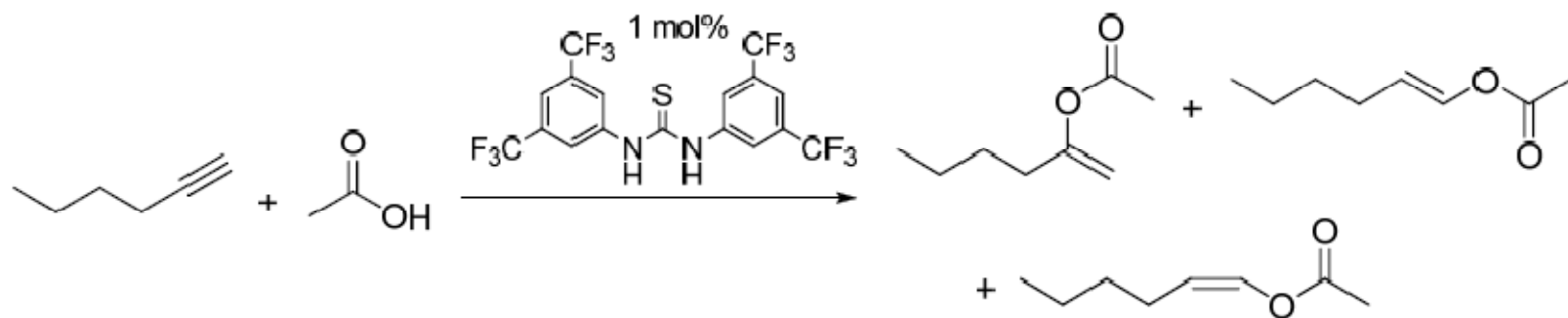
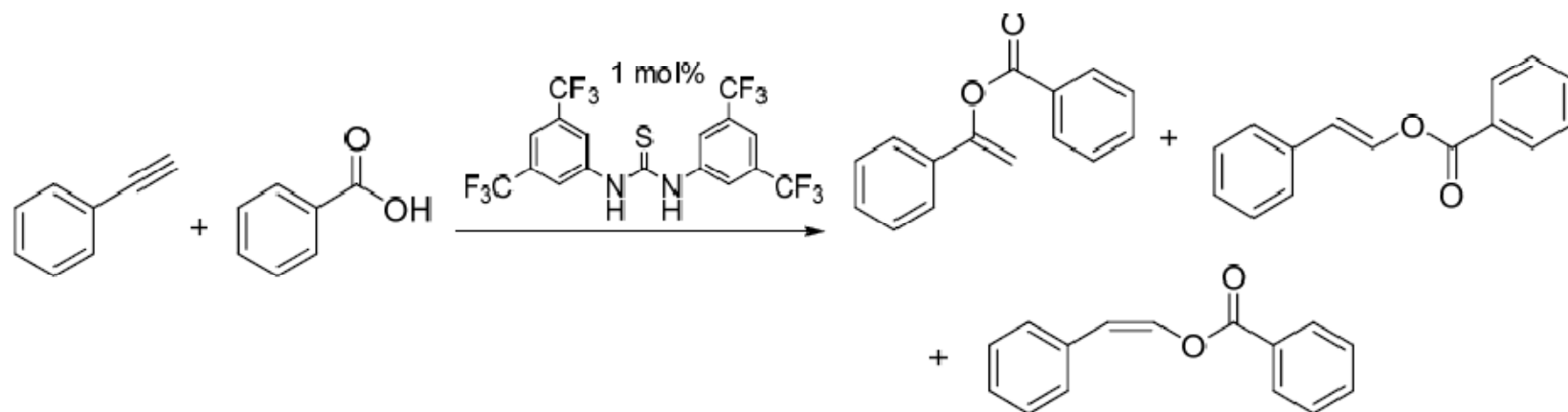
M. Rotem, Y. Shvo, *Organometallics* **1983**, 2, 1689-1691

L. J. Goossen, J. Paetzold, D. Koley, *Chem. Commun.* **2003**, 706-707

Addition of Carboxylic Acids to Alkynes

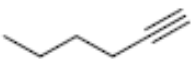
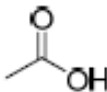
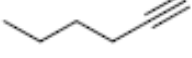
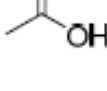
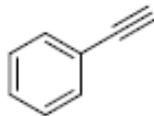
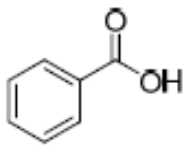
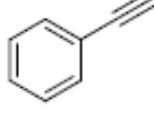
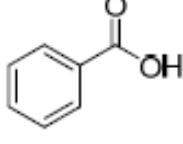
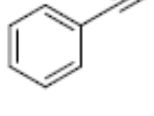
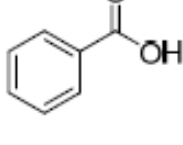


Task



Results

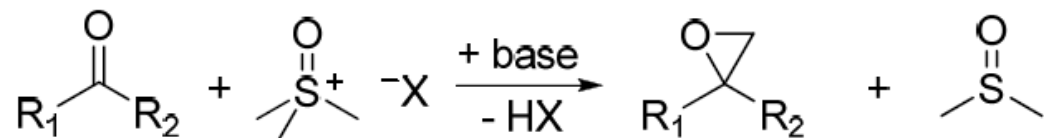
Attempted Addition of Carboxylic Acids to Alkynes

Entry	Alkyne	Carboxylic acid	Temperature	Solvent	Time/d	Conversion/% ^a
1			rt	DCM	15	0 ^e
2			rt	THF	15	0 ^e
3			rt	toluene	13	0 ^e
4 ^b			rt	toluene ^c	8	0 ^e
5 ^b			50 °C	toluene ^d	4	0 ^f

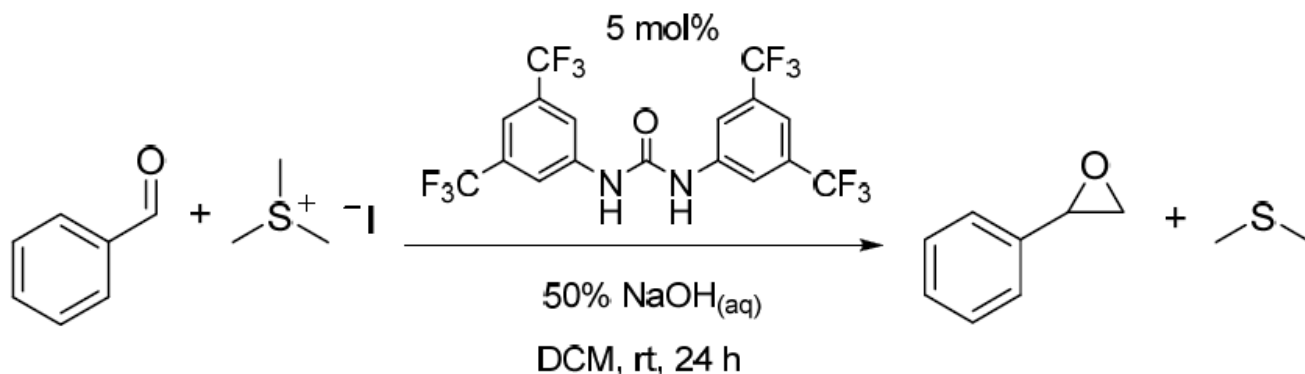
^a GC/MS; ^b addition of 1 mol% (*R*)-mandelic acid; ^c 8 mL solvent; ^d 10 mL solvent; ^e at rt; ^f at 50 °C

Corey-Chaykovsky Reaction

- Early 1960s, Corey and Chaykovsky:



- 2008, Connon *et al.*:

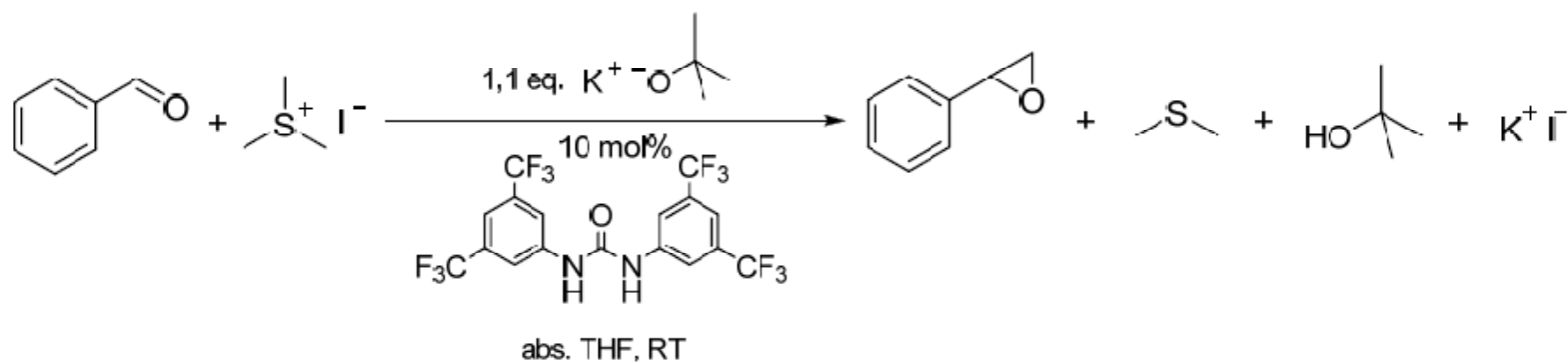
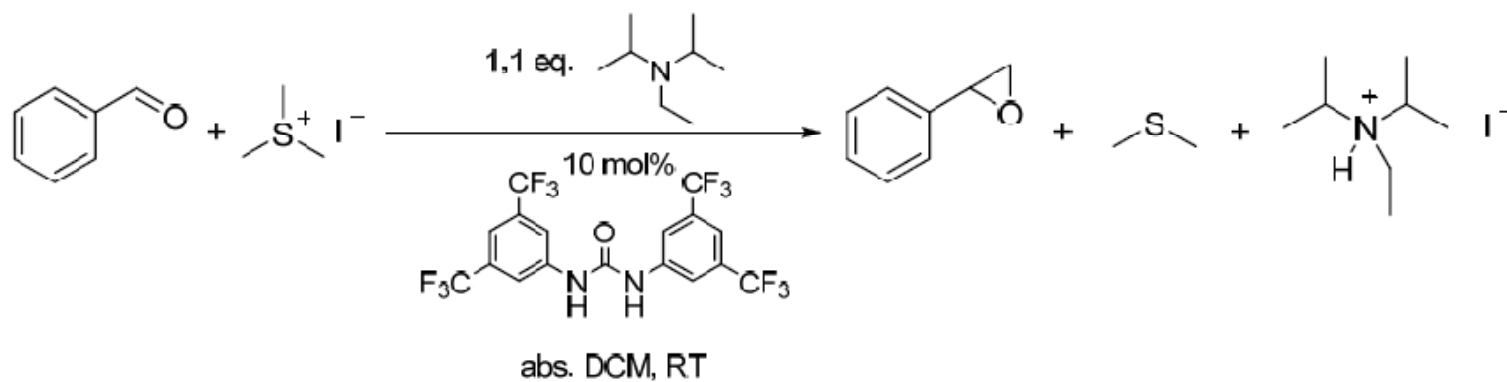


E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1962**, 84, 867-868

E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, 87, 1353-1364

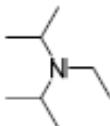
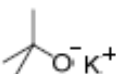
S. A. Kavanagh, A. Piccinini, E. M. Fleming, S. J. Connon, *Org. Biomol. Chem.* **2008**, 6, 1339-1343

Task



Results

Conversion of Benzaldehyde

Base	Time/h	Conversion/% ^a
	142,5	0 ^b
	113	0 ^c
	70	0 ^d
50% NaOH in H ₂ O	24	64
	24	100
	24	100 ^e

^a GC/MS; ^b approach a; ^c approach b; ^d approach c; ^e without catalyst

Approach a: DCM with a small amount of H₂O

Approach b: DCM/H₂O (1:1)

Approach c: DCM

Summary

- Opening of styrene oxide likely to be S_N2 -type
- Opening of 2-methyl-2-phenyloxirane probably S_N1 -like
- No kinetic resolution
- 2-methyl-2-phenyloxirane or corresponding β -alkoxy alcohol catalyst for alcoholysis of styrene oxide?

Summary

- Addition of carboxylic acids to alkynes failed
- DIPEA no suitable base for deprotonation of the sulfur ylide in Corey-Chaykovsky reaction
- Potassium *tert*-butoxide works, but even without any catalyst

Outlook

- Alcoholysis of enantiomerically enriched 2-methyl-2-phenyloxirane
- Alcoholysis of styrene oxide: catalytic amounts of 2-methyl-2-phenyloxirane or corresponding β -alkoxy alcohol

Outlook

- Addition of carboxylic acids to alkynes with stronger acids
- Corey-Chaykovsky reaction: one pot synthesis of β -alkoxy alcohols from aldehydes or ketones?

Acknowledgement

Thanks to

- Prof. Schreiner for providing the opportunity of making this diploma thesis
- Torsten Weil for the good mentoring, numerous discussions and his patience in answering all questions
- Mike Kotke, Katharina Lippert, Christian Müller, Daniela Zell, Volker Lutz, Mareike Machuy, and Nicole Graulich for the good cooperation and helpful advices