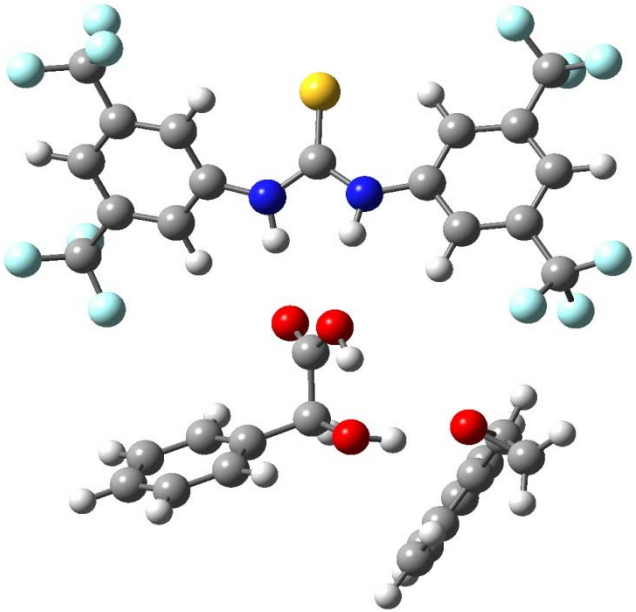
Organocatalytic Addition of Carbon and Oxygen Nucleophiles to C-O Electrophiles



JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

400 Jahre UNIVERSITÄT GIESSEN
1607–2007

Disputation zur Erlangung des Doktorgrades

der naturwissenschaftlichen Fachbereiche

(Fachbereich 08 – Biologie und Chemie)

der Justus-Liebig-Universität Giessen

Torsten Weil

October 17, 2008

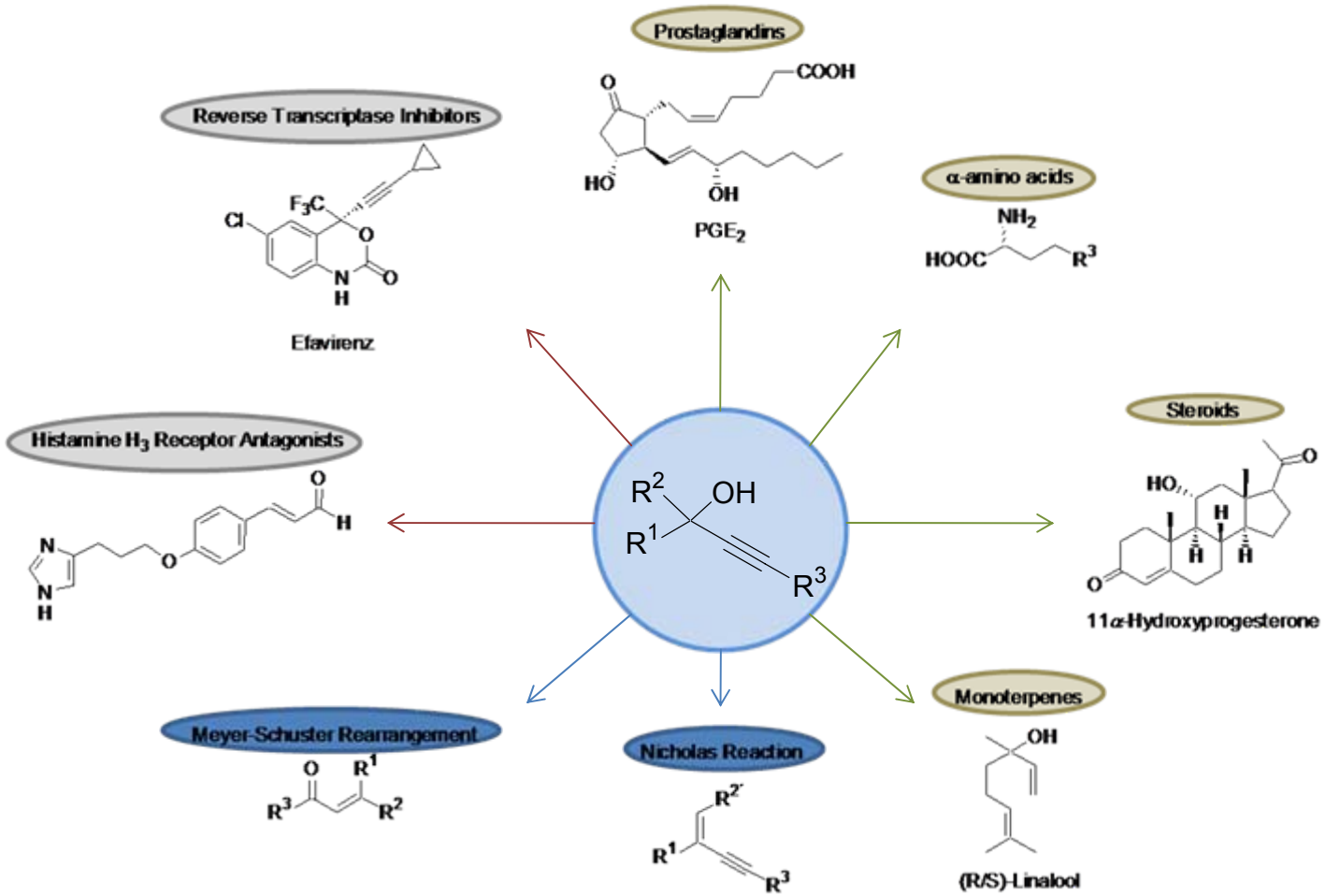
Contents

A. Organocatalytic Alkynylation of Aldehydes and Ketones under PTC-Conditions – Formation of Propargylic Alcohols

Contents

A. Organocatalytic Alkynylation of Aldehydes and Ketones under PTC-Conditions – Formation of Propargylic Alcohols

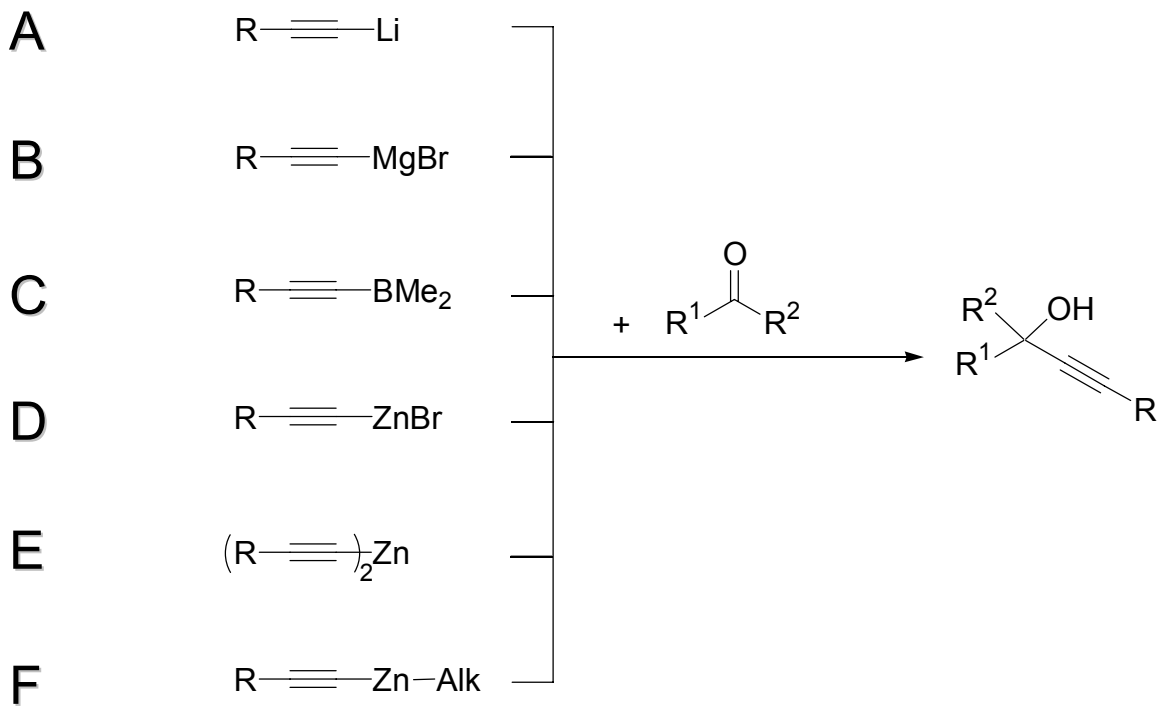
A.1 Propargylic Alcohols (prop-2-yn-1-ols): Applications



M. E. Pierce et al. *J. Org. Chem.* **1998**, *63*, 8536-8543; E. J. Corey, K. Niimura, Y. Konishi, S. Hashimoto, and Y. Hamada ,*Tetrahedron Lett*. **1986**, *27*, 2199-2202; B. Jiang, Y.-G. Si, *Adv. Synth. Catal*. **2004**, *346*, 669-674; H. Stark et al., *J. Med. Chem*. **2000**, *43*, 3987-3994; R. S. Brinkmeyer, V. M. Kapoor, *J. Am. Chem. Soc*. **1977**, 99, 8341-8343; K. H. Meyer, K. Schuster, *Ber*. **1922**, *55B*, 819-822; K. M. Nicholas, R. Petit, *J. Organomet. Chem*. **1972**, *44*, C21-C24.

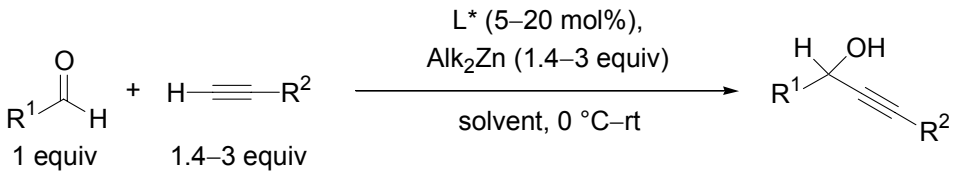
A.2 Additions of stoichiometric Amounts of Metal Acetylides to Aldehydes and Ketones

Method:

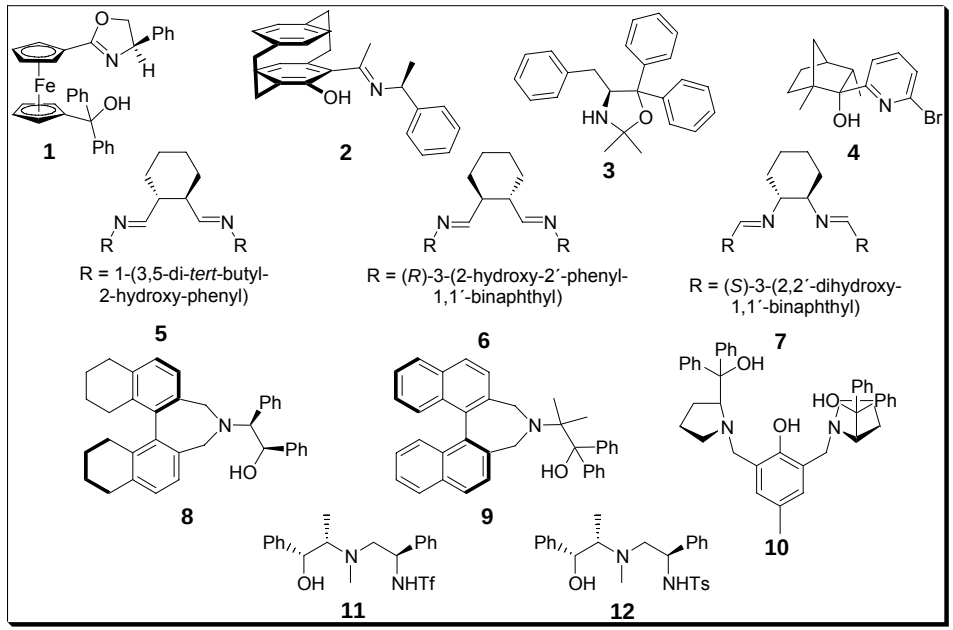


F.Diederich, P. J. Stang, R. R. Tykwinski, *Acetylene Chemistry. Biology and Material Science*, WILEY-VCH, Weinheim, 2005.

A.2.1 Established Protocols utilizing Dialkylzinc



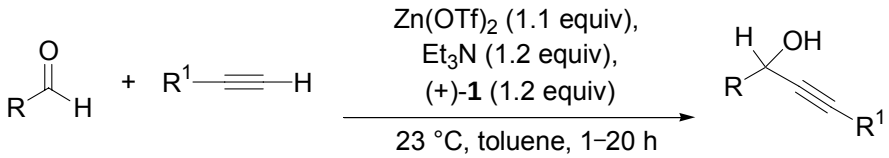
L* =



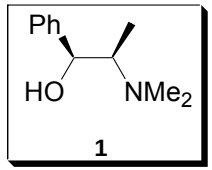
S. Dahmen, *Org. Lett*. **2004**, *6*, 2113-2116; M. Li, X.-Z. Zhu, K. Yuan, B.-X. Cao, X.-L. Hou, *Tetrahedron: Asymmetry* **2004**, *15*, 219-222; Z.-B. Li, L. Pu, *Org. Lett*. **2004**, *6*, 1065-1068; B. M. Trost, A. H. Weiss, A. J. Wangelin, *J. Am. Chem. Soc*. **2006**, *128*, 8-9; M. G. Pizzuti, S. Superchi, *Tetrahedron: Asymmetry* **2005**, *16*, 2263-2269; J. Ruan et al., *Adv. Synth. Catal*. **2008**, *350*, 76-84;

A.3 Established Protocols utilizing Zn(II) salts

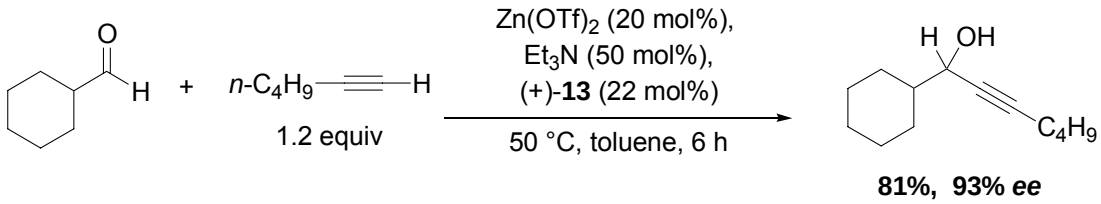
Carreira 2000



aldehyde	alkyne	yield [%]	*ee* [%]
c-C_6H_{11}	Ph	99	96
t-Bu	Ph	99	94
Ph	Ph	53	94



Carreira 2002

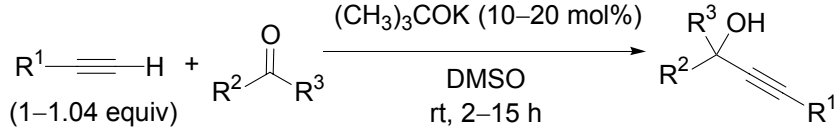


81%, 93% *ee*

D. E. Frantz, R. Fassler, E. M. Carreira, *J. Am. Chem. Soc*. **2000**, *122*, 1806-1807; N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc*. **2001**, *123*, 9687-9688.

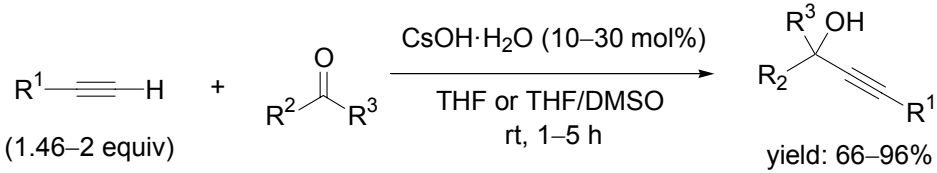
A.4 Alkaline Bases as Reaction Promoters

Babler 1996



	ketone	yield [%]
R^1=$CH_3(CH_2)_5$	*c*-hexanone	80
R^1=$HO(CH_3)_2$	3-pentanone	70
R^1=CH_2OTHP	*c*-hexanone	91

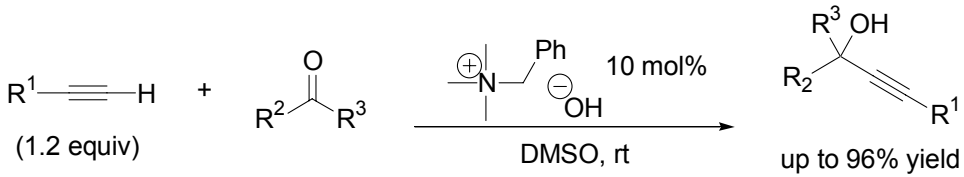
Knochel 1999



	carbonyl compound	yield [%]
R^1=Ph	cyclohexanone	88
R^1=Ph	*t*BuCHO	86
R^1=Bu	cyclohexanone	82

representative examples

Saito 2003



J. H. Babler, V. P. Liptak, and N. Phan, *J. Org. Chem*. **1996**, *61,* 416-417; D. Tzalis, P. Knochel, *Angew. Chem. Int. Ed*. **1999**, *38*, 1463-1465; T. Ishikawa, T. Mizuta, K. Hagiwara, T. Aikawa, T. Kudo, and S. Saito, *J. Org. Chem*. **2003**, *68*, 3702-3705.

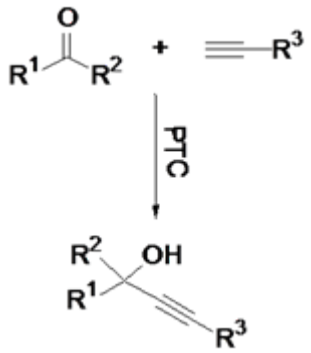
A.5 Why yet another Methodology?

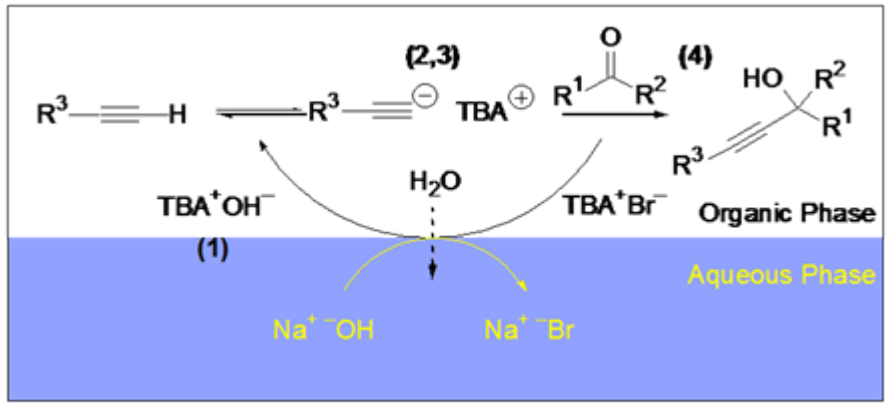
- Published protocols are limited to either aliphatic or aromatic aldehydes and ketones

- Straightforward procedures utilizing alkaline bases afford no chiral induction

➔ **Development of a universally applicable stereoselective organocatalytic alkynylation method**

A.6 Phase-Transfer-Catalytic Approach





Proposed four-step PTC alkynylation mechanism:

1) *in situ* generation of the ammonium base at the phase boundary,

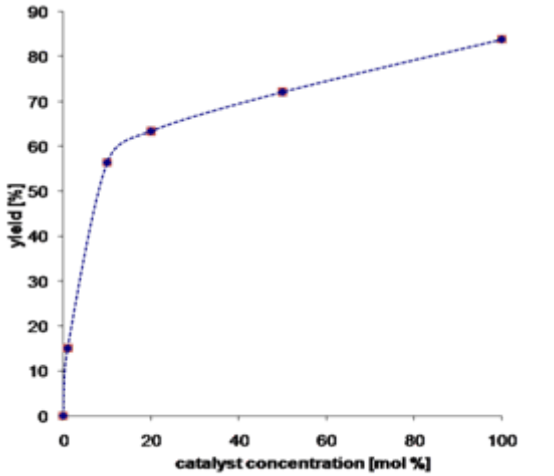
2) deprotonation of the alkyne,

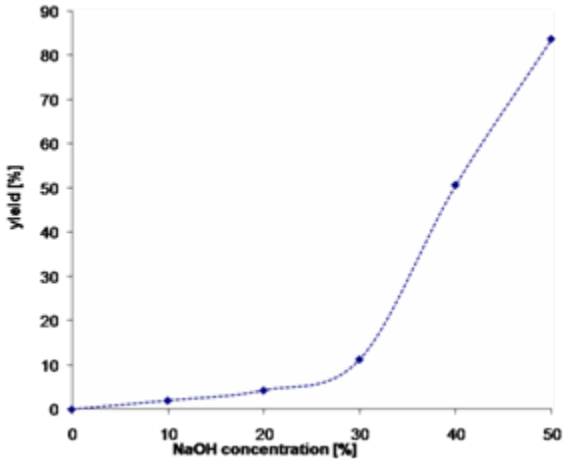
3) coordination to the PT-catalyst, and

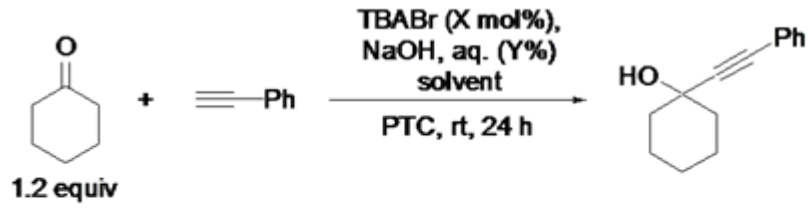
4) subsequent reaction with the carbonyl compound.

T. Weil, and P. R. Schreiner, *Eur. J. Org. Chem*. **2005**, 2213-2217.

A.6.1 Optimization of Reaction Conditions







yield [%]		
	PhF	88
	CH_2Cl_2	25

Minimum requirements:

- Catalyst Loading 20 mol%
- NaOH Concentration 35%
- Solvent: Fluorobenzene

T. Weil, and P. R. Schreiner, *Eur. J. Org. Chem*. **2005**, 2213-2217.

A. Alkynylation of Aldehydes and Ketones

A.6.1 Optimization of Reaction Conditions

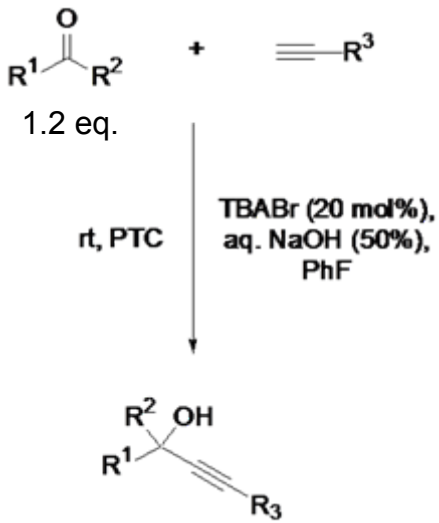
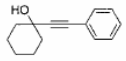
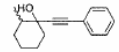
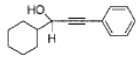
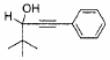
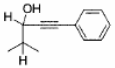
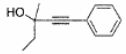
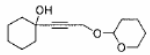
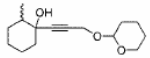
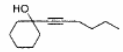
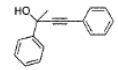
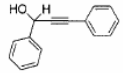
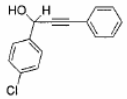


Table 1. PTC/organocatalytic alkynylation of selected aldehydes and ketones.

Entry	Carbonyl compound		Alkyne		Product		Cond.[a] (time [h])	Yield of isolated product [%]
1		1a		2a		3a	A (96)	88
2		1b		2a		3b	A (96)	87[b]
3		1c		2a		3c	B (72)	78
4		1d		2a		3d	A (48)	92
5		1e		2a		3e	A (48)	52
6		1f		2a		3f	A (96)	65
7		1a		2b		3g	A (96)	51
8		1b		2b		3h	A (96)	50
9		1d		2b		3i[11]	A (72)	72
10		1d		2c		3j	A (72)	57
11		1a		2c		3k	A (96)	53
12		1g		2a		3l	A (48)	35
13		1h		2a		3m[12]	B (36)	30
14		1i		2a		3n[12]	B (36)	31

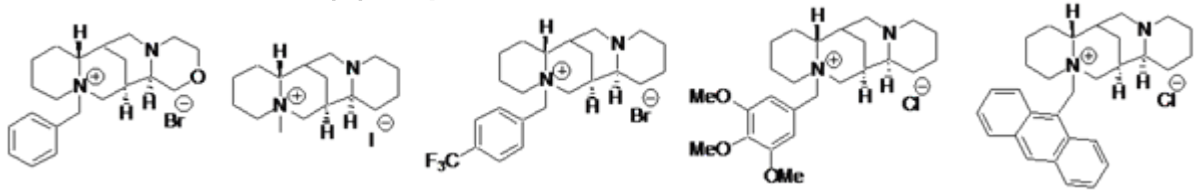
[a] Method A: 7 mmol alkyne, 8.4 mmol carbonyl compound, 1.4 mmol [20 mol-%] TBABr; method B: 14 mmol alkyne compound, 7 mmol carbonyl compound, 1.4 mmol [20 mol-%] TBABr. For details see experimental section. [b] 1:1 mixture of diastereomeric propargylic alcohols.

T. Weil, and P. R. Schreiner, *Eur. J. Org. Chem*. **2005**, 2213-2217; (11) M. Kimura, S. Tanaka, Y. Tamura *Bull. Chem. Soc. Jpn.,* **1995,** 68, 1689-1705; (12) Z. Li, L. Pu, *Org. Lett.,* **2004,** 6, (6), 1065-1068.

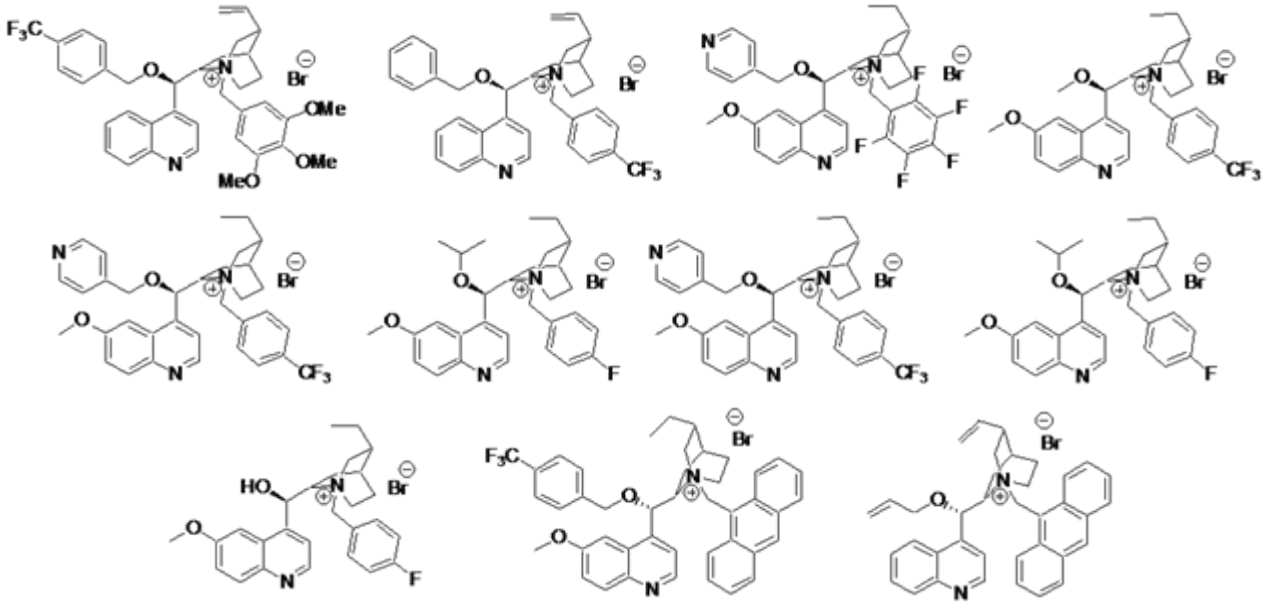
A.7 Stereoselective Alkynylations

Synthesized Potential Chiral PTC-Catalysts

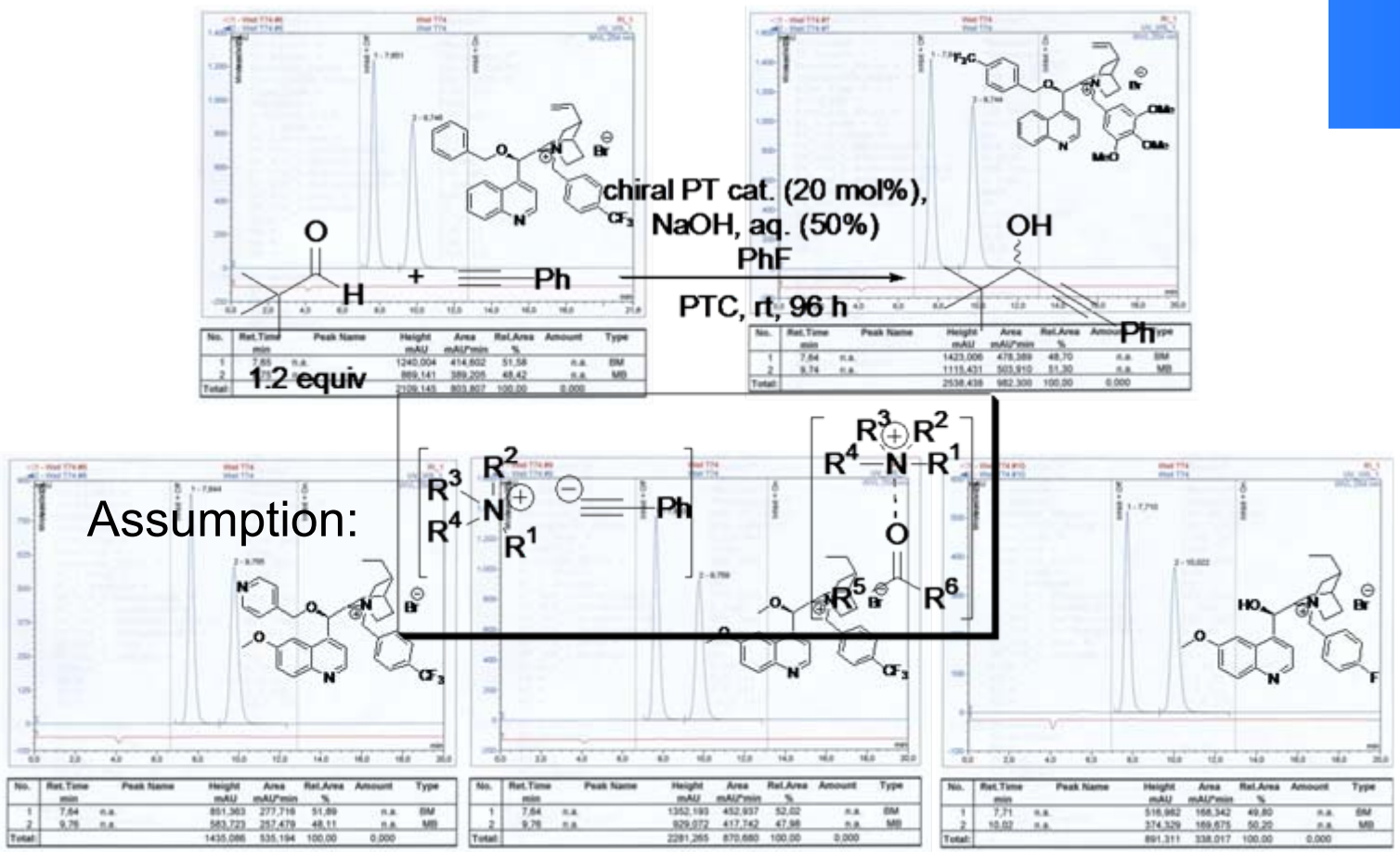
(-)-Sparteine Derivatives



Cinchona Alkaloid Derivatives



A.7 Stereoselective Alkynylations

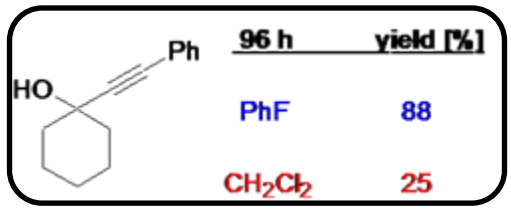


A.7.1 Stereoselective Alkynylations – Problems

- Low solubility of PTC catalysts

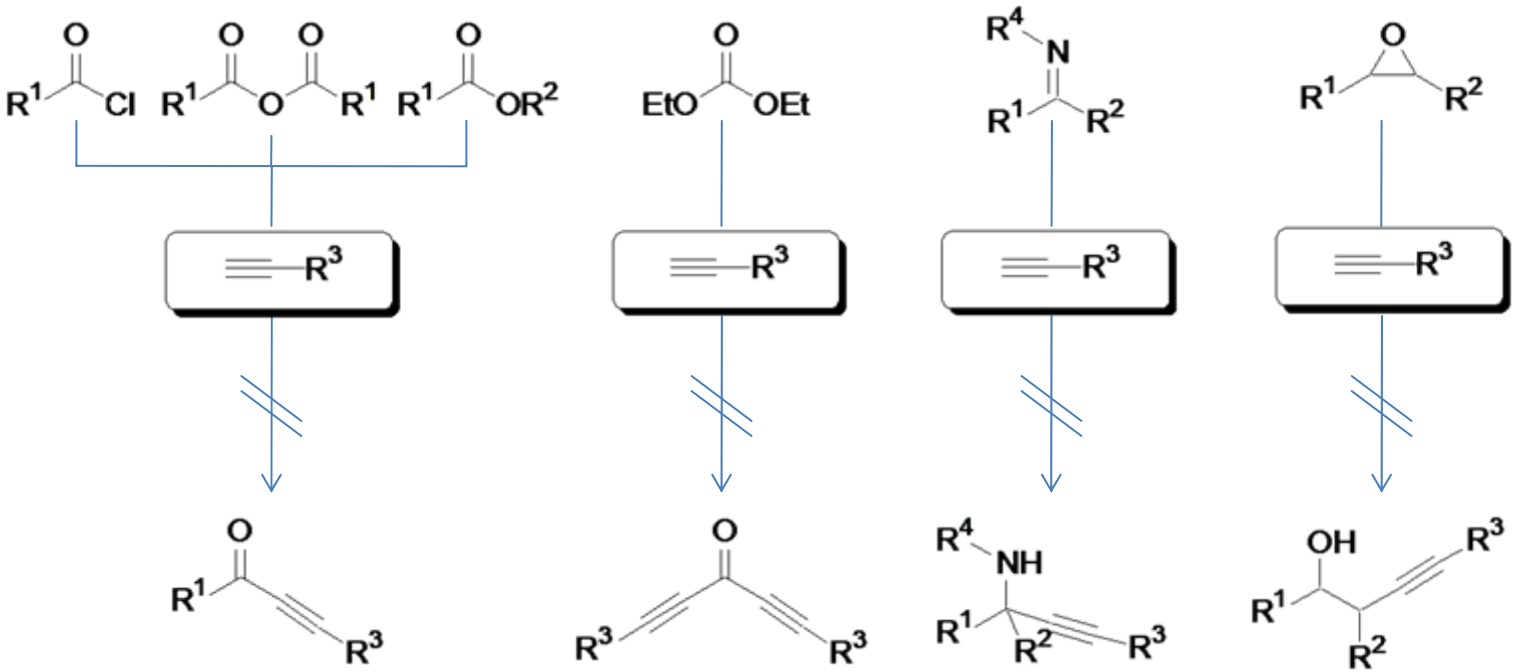
  → no conversion at low temperature

- Solvent effect



➔ **Low product yields and no chiral induction detectable!**

A.8 Additional Test Reactions

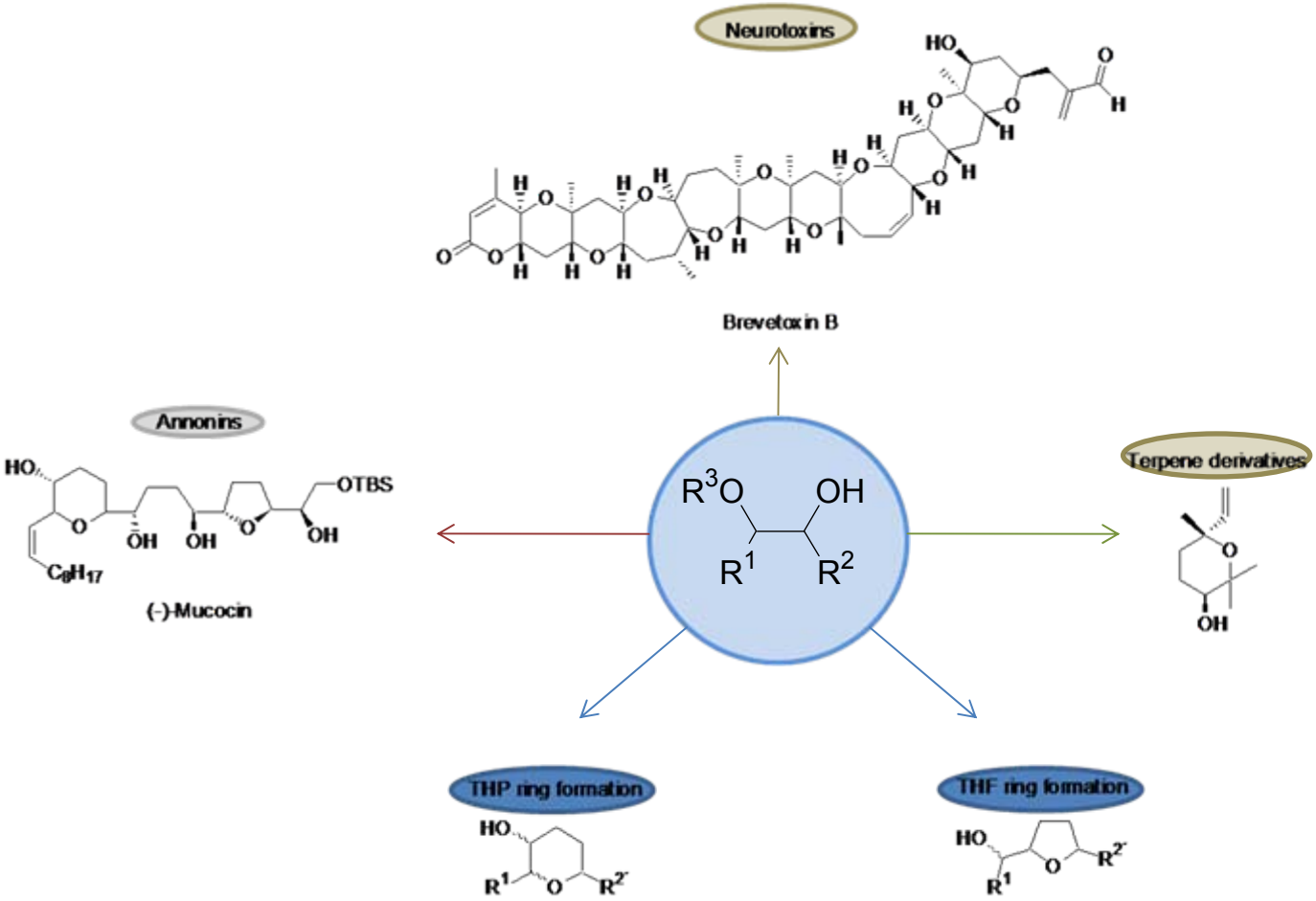


A.9 Summary A

- Development of a mild and effective non stereoselective organocatalytic PTC protocol for alkynylations of various aldehydes and ketones
- Best results are obtained for aliphatic ketones and non-enolizable aldehydes (reaction time, 48-96 h, up to 92% yield)
- Alkyne component can be varied widely and can be aromatic or aliphatic
- The development of an asymmetric PTC protocol failed

B. Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides – Formation of ß-Alkoxy Alcohols

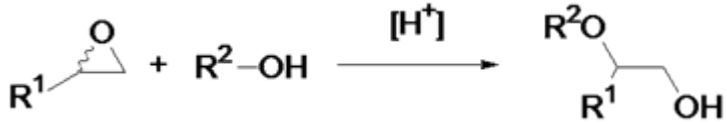
B.1 ß-Alkoxy Alcohols: Applications



P. Neogi, T. Doundoulakis, A. Yazbak, S. C. Sinha, E. Keinan, *J. Am. Chem. Soc*. **1998**, *120*, 11279-11284; K. C. Nicolaou, C. V. C. Prasad, P. K. Somers; C. K. Hwang, *J. Am. Chem. Soc*. **1989**, *111*, 5330-5334; D. Felix, A. Melera, J. Seibl, and S. Kovats, *Helv. Chim. Acta*. **1963**, *46*, 1531.

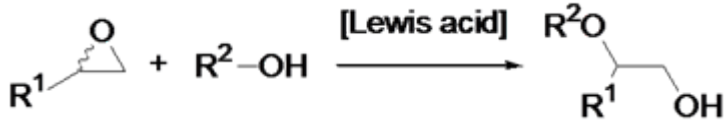
B.2 Established Methodologies

- Brønsted acid catalysis



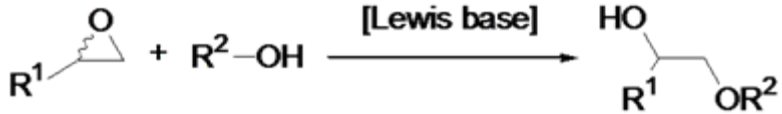
mostly 1° alcohol

- Lewis acid catalysis



1°/2° alcohol

- Lewis base catalysis



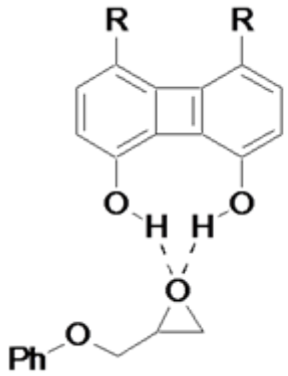
2° alcohol

B.3 Disadvantages

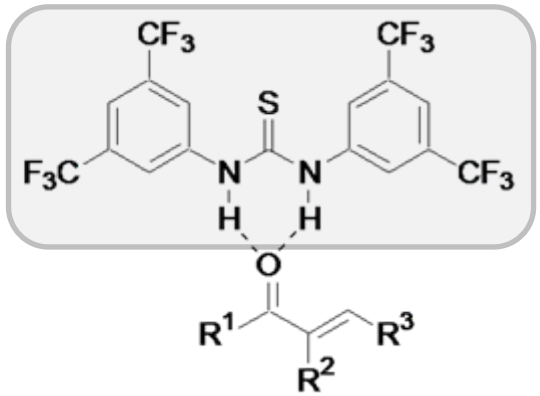
- Harsh reaction conditions
- Tolerates no acid-labile compounds
- Product inhibition
- Low TOF values
- Side reactions (polymerization, etc.)
- Lewis acids require stoichiometric quantities

B.4 Organocatalytic Approach

Double hydrogen-bonding



Hine 1985



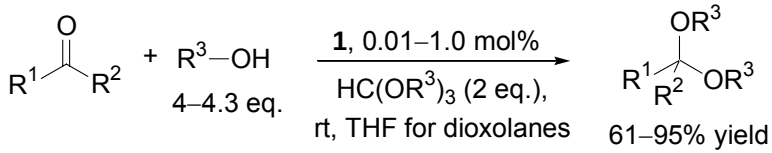
Schreiner 2003

J. Hine, S. M. Linden, V. M. Kanagasabapathy, *J. Am. Chem. Soc*. **1985**, *50*, 1082-1083; J. Hine, S. Hahn, D. E. Miles, K. Ahn, *J. Org. Chem*. **1985**, *50*, 5092-5096; P. R. Schreiner, *Chem. Soc. Rev*. **2003**, *32*, 289-296; A. Wittkopp, P. R. Schreiner, *Chem. Eur. J*. **2003**, *9*, 407-414.

B.4 Organocatalytic Approach

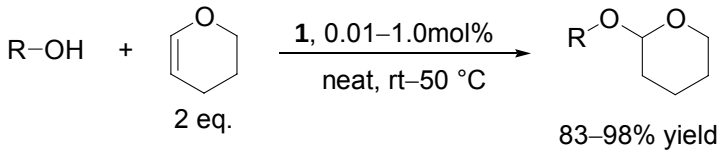
acetalization

Schreiner 2006



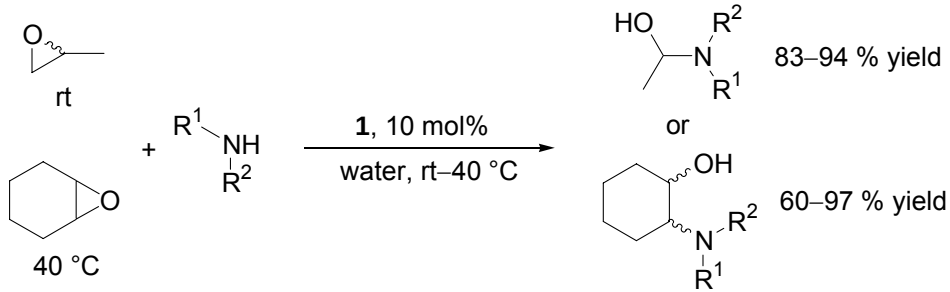
tetrahydropyranylation

Schreiner 2007



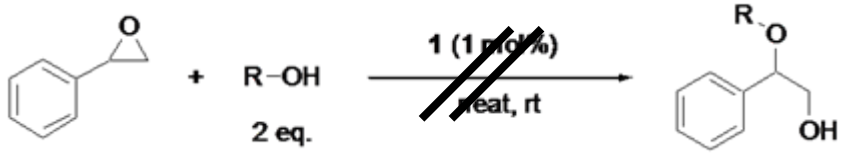
aminolysis of epoxides

Schreiner 2006



M. Kotke, P. R. Schreiner, *Tetrahedron* **2006**, *62*, 434-439; M. Kotke, P. R. Schreiner, *Synthesis* **2007**, 779-790; C. M. Kleiner, P. R. Schreiner, C*hem. Commun*. **2006**, 4315-4317. **1**: *N,N´*-bis-[3,5-bis-(trifluoromethyl)phenyl]thiourea

B.4 Organocatalytic Approach

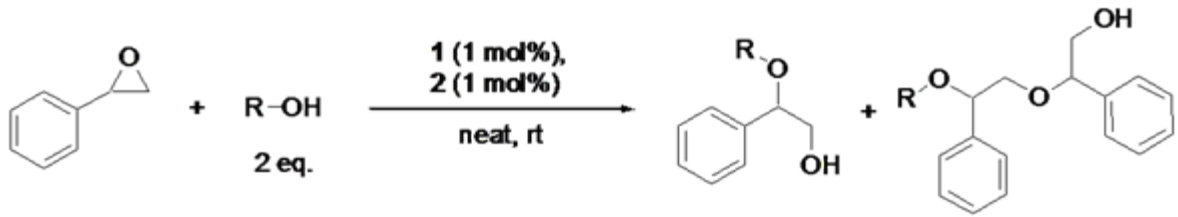


Observation:

- simple hydrogen-bond-activation failed

Solution:

- ´impurity´(identified as mandelic acid (**2**)) utilized as additive

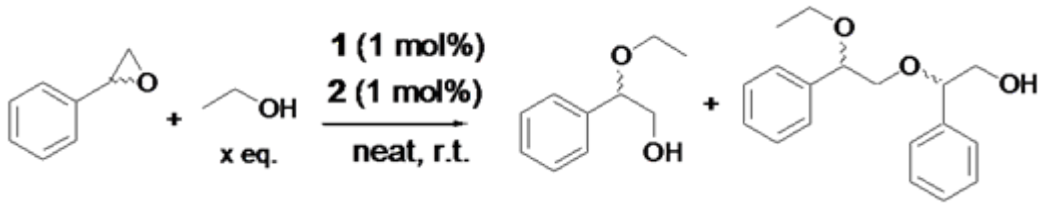


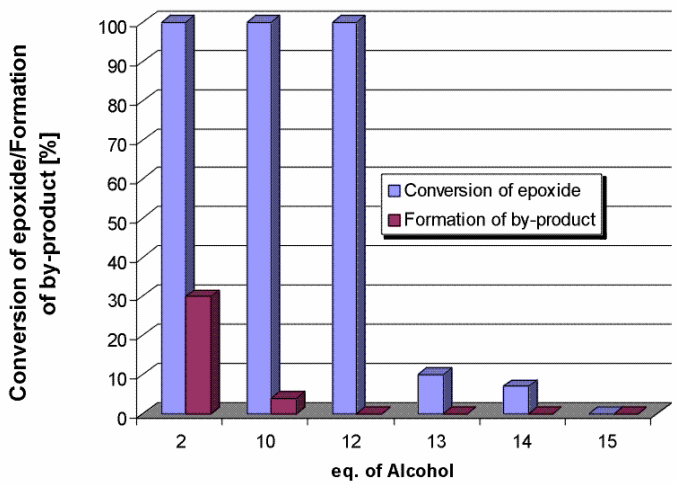
No conversion without 1 or 2!

T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett*. **2008**, *10*, 1513-1516. **1**: *N,N´*-bis-[3,5-bis-(trifluoromethyl)phenyl]thiourea; **2**: mandelic acid (2-hydroxy-2-phenyl acetic acid)

B.5 Protocol Optimization

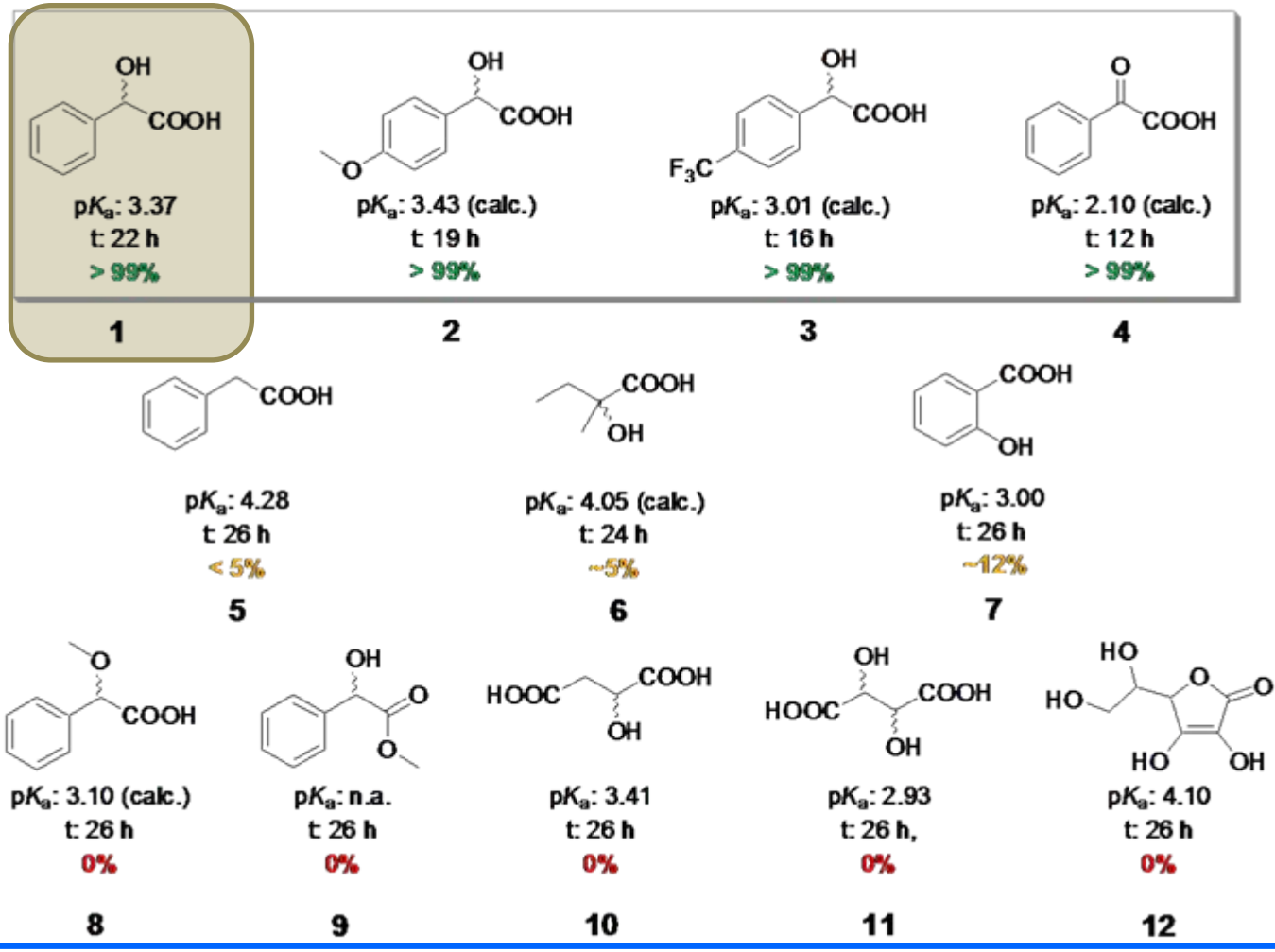
Minimization of by-Product Formation





T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett*. **2008**, *10*, 1513-1516. **1**: *N,N´*-bis-[3,5-bis-(trifluoromethyl)phenyl]thiourea; **2**: mandelic acid (2-hydroxy-2-phenyl acetic acid)

B.6 Brønsted-Acid Screening

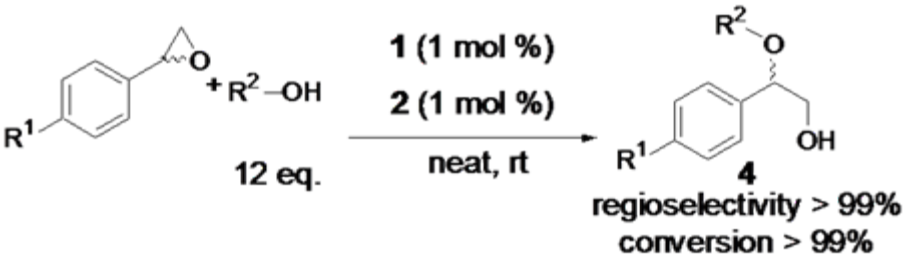


T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett*. **2008**, *10*, 1513-1516.

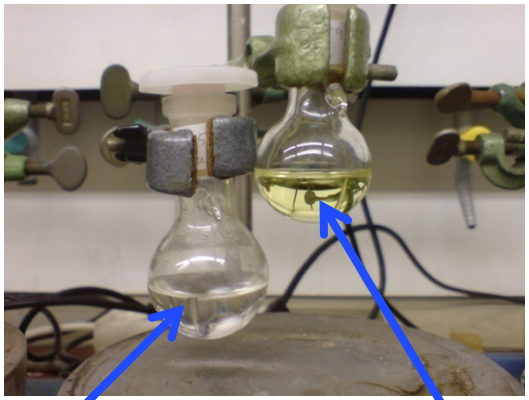
B. Alcoholysis of Styrene Oxides

B.7 Results

Optimized Protocol



no.[a]	R^1	1	alcohol (R^2-OH)	2	prod.	t [h]	%[d]
1	H	1a		2a	4a	18	85
2	H	1a		2b	4b	22	86
3	F	1b		2b	4c	24	57
4	*t*Bu	1c		2b	4d	15	65
5	H	1a		2c	4e	21	73
6[b]	H	1a		2d	4f	15	74
7[b]	F	1b		2d	4g	18	57
8[b]	*t*Bu	1c		2d	4h	16	65
9	H	1a		2e	4i	21	94
10	H	1a		2f	4j	20	73
11	H	1a		2g	4k	23	89
12	H	1a		2h	4l	18	80
13	H	1a		2i	4m	23	78
14[c]	H	1a		2j	4n	32	41
15	H	1a		2k	4o	16	65
16	F	1b		2k	4p	17	63
17	*t*Bu	1c		2k	4q	39	70
18[b]	H	1a		2l	4r	18	58



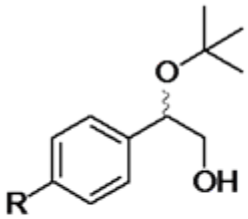
Reference reaction without **1**
→ **No conversion!**

Reaction utilizing **1** and **2** as cooperative catalysts
→ **Full conversion!**

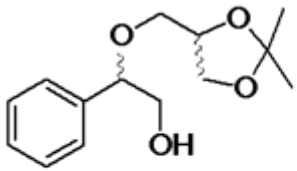
T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett.* **2008**, *10*, 1513-1516. **1**: *N,N´*-bis-[3,5-bis-(trifluoromethyl)phenyl]thiourea; **2**: mandelic acid (2-hydroxy-2-phenyl acetic acid)

B.7 Results

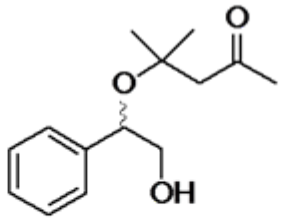
Selected Products:



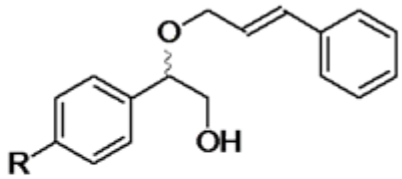
50 °C, 15 h
74% (R=H)
57% (R=F)
65% (R=*t*Bu)



50 °C, 46 h
41% (R=H)



50 °C, 40 h
61% (R=H)



r.t., 17 h
76% (R=H)
72% (R=F)
70% (R=*t*Bu)

sterically hindered

acid labile

B.8 Mechanistic Investigations

a) experimental

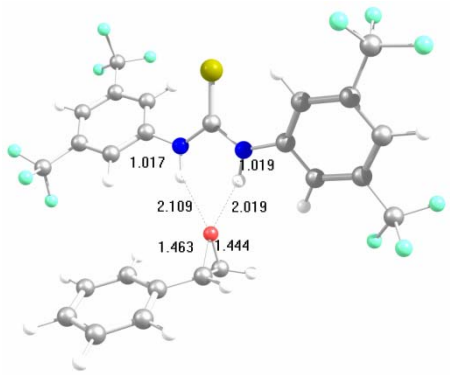
- NMR titration experiments

- DOSY-NMR spectroscopy

b) theoretical

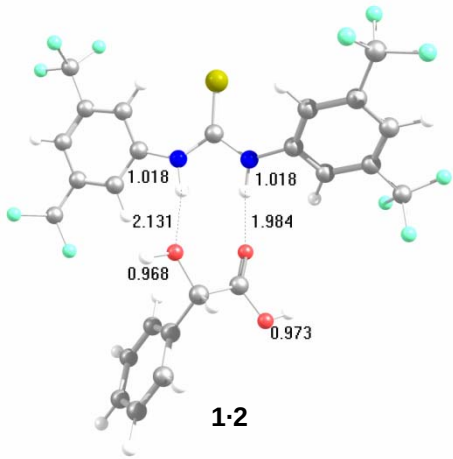
- DFT calculations

B.8 Mechanistic Investigations



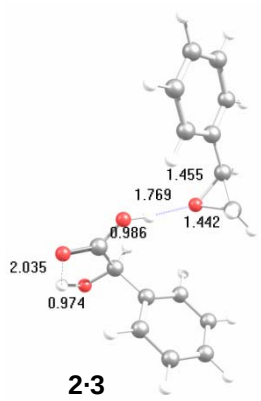
1·3

ΔH_0 [kcal/mol] -9.2



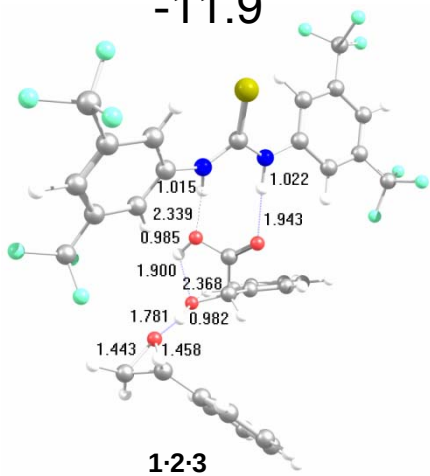
1·2

-11.9



2·3

-5.7

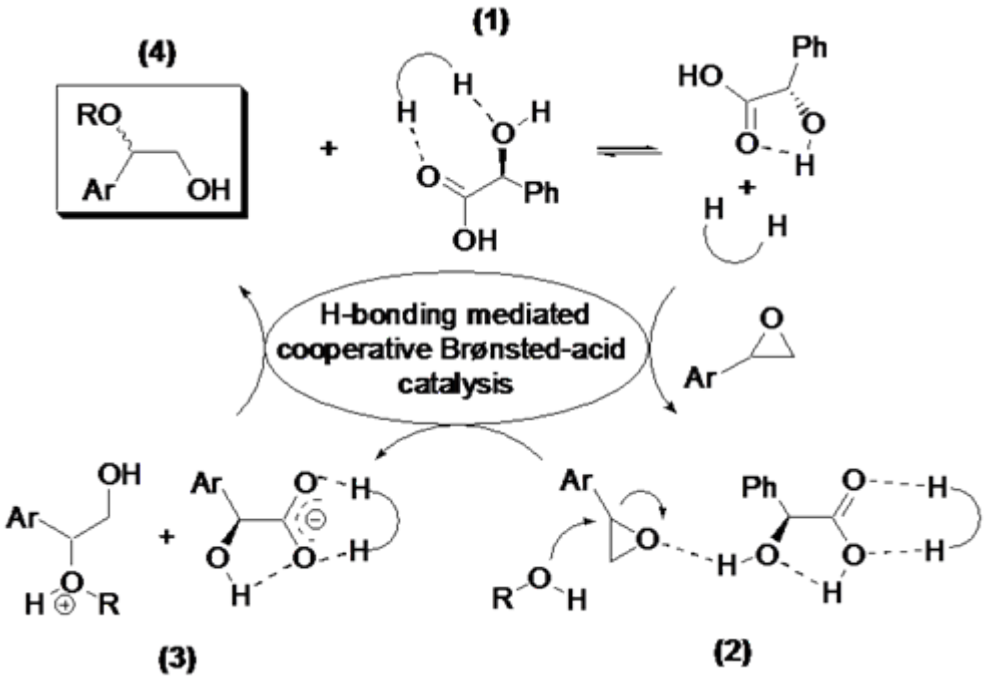


1·2·3

ΔH_0 [kcal/mol] -20.0

T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett*. **2008**, *10*, 1513-1516. Minimum energy structures of binary (**1·2**, **1·3,** and **2·3**) and ternary complexes (**1·2·3**) optimized at B3LYP/6-31+G(d,p).**1**: *N,N´*-bis-[3,5-bis-(trifluoromethyl)phenyl]thiourea; **2**: mandelic acid; **3**: styrene oxide

B.9 Mechanistic Investigations – Proposals



Key steps:

(1) Formation of binary catalyst complex

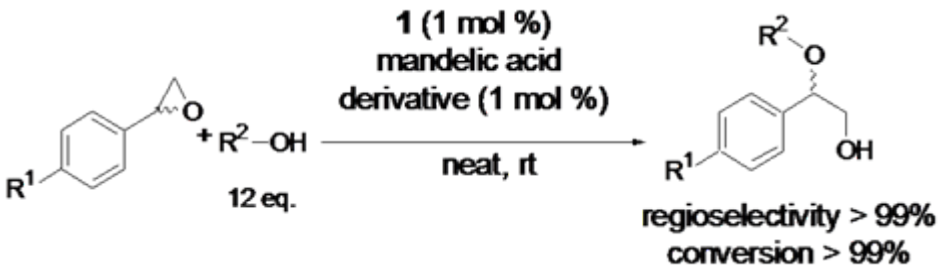
(2) Single-point hydrogen bond activation of styrene oxide and addition of the alcohol

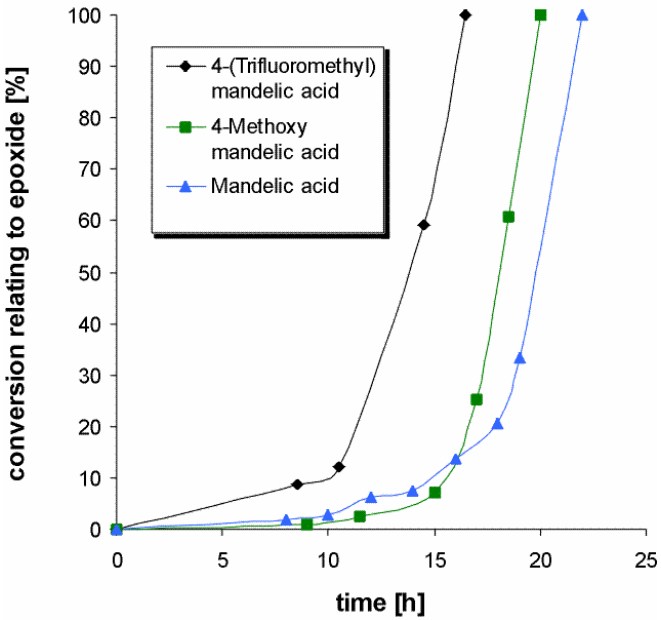
(3) Reprotonation of mandelate, and

(4) Product formation combined with liberation of binary catalyst complex

T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett*. **2008**, *10*, 1513-1516.

B.10 Mechanistic Investigations – Reaction Kinetics





Assumptions:

- autocatalysis
- kinetic resolution

both hypotheses could be vitiated by suitable experiments

T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett*. **2008**, *10*, 1513-1516. **1**: *N,N´*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea.

B.11 Summary B

- Various alcohols including acid-labile as well as sterically demanding derivatives react with styrene oxides within reasonable reaction times under mild reaction conditions (r.t./50 °C) with > 99% regioselectivity
- By-product is almost eliminated through dilution without influence on reaction time
- Low catalyst loading (1 mol%)
- Simple workup
- Brønsted-acid efficiency depends on structural aspects
- Thiourea derivative and Brønsted acid cooperate in **dual catalysis**

C. Outlook

- Investigation of reaction kinetics
- Development of a stereoselective and universally applicable protocol
- Application of developed protocol for further reactions

Acknowledgement

- My supervisor – an interesting topic
- Institute for Organic Chemistry – position as scientific coworker
- Deutsche Forschungsgemeinschaft (SPP 1179) and the Fonds der Chemischen Industrie
- My colleagues in the group
- The referees – reports for this thesis