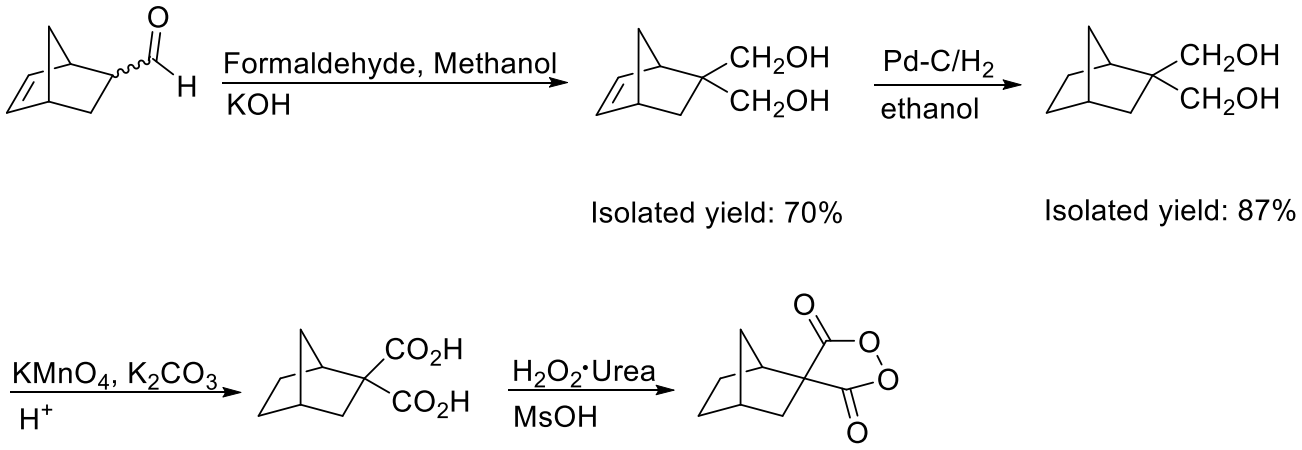
Efforts Toward Stereoselective Oxidation of Alkenes and Arenes

2nd December 2016

Afsaneh Pilevar

Institute of Organic Chemistry
Justus-Liebig University
35392 Giessen, Germany

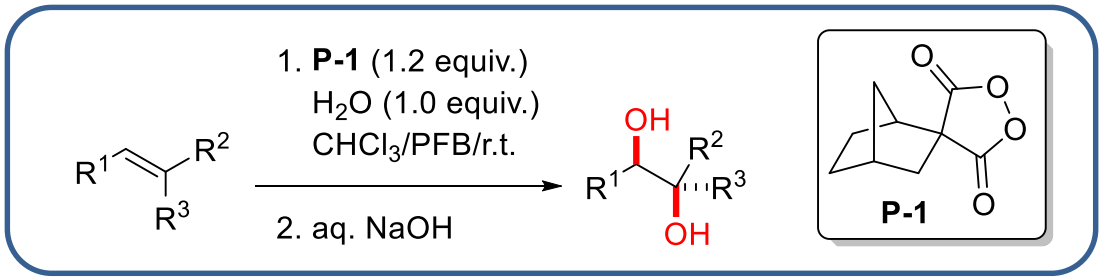
Synthesis of chiral cyclic peroxide

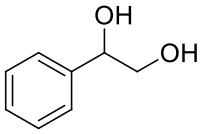


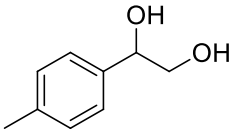
Total yield: 46%

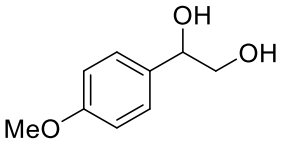
Murayama, M.; Sanda, F.; Endo, T. *Macromolecules* **1998**, *31*, 919.; Nemoto, N.; Kakimoto, K.; Endo, T. *J. Polym. Sci. Part A Polym. Chem*. **2002**, *40*, 1698.; Griffith, J. C.; Jones, K. M.; Picon, S.; Rawling, M. J.; Kariuki, B. M.; Campbell, M.; Tomkinson, N. C. O. *J. Am. Chem. Soc.* **2010**, *132*, 14409.

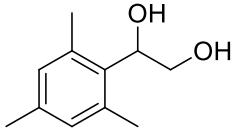
Alkene *syn* dihydroxylation

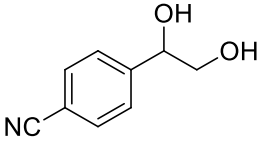


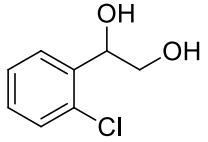

94%

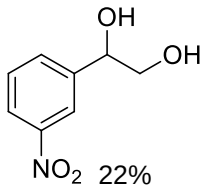

93%

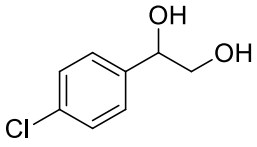

72%

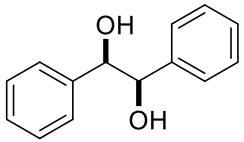

65%

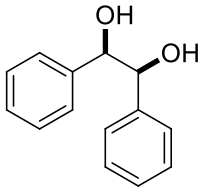

29%

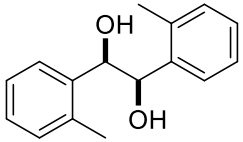

71%

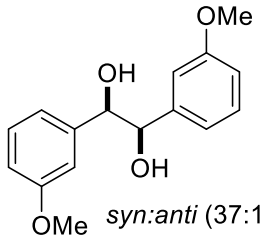

22%

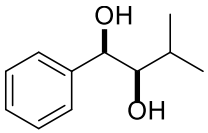

80%

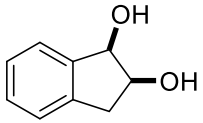

syn:anti (38:1)
93% (94% d.e.)

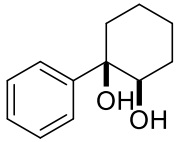

syn:anti (4:1)
91% (60% d.e.)


syn:anti (45:1)
82% (95% d.e.)

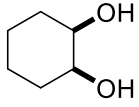

syn:anti (37:1)
64% (94% d.e.)

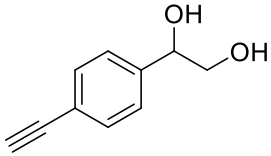

Syn:anti (12:1)
81% (84% d.e.)

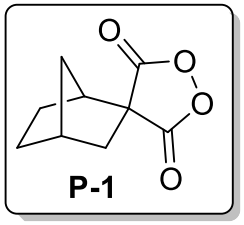

74%
100% *syn* addition


61%
100% *syn* addition


41%

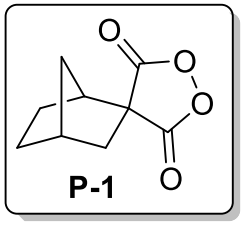

23%


27%



chiral but enantiopure?

- Diasteromerization using chiral acid or alcohol
- Racemic Resolution of Bicyclo [2.2.1] heptane-2,2-dicarboxylic acid
- The use of enantiopure terpene derivatives as precursors for synthesis of chiral cyclic peroxides



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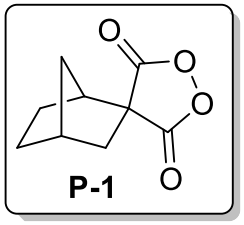

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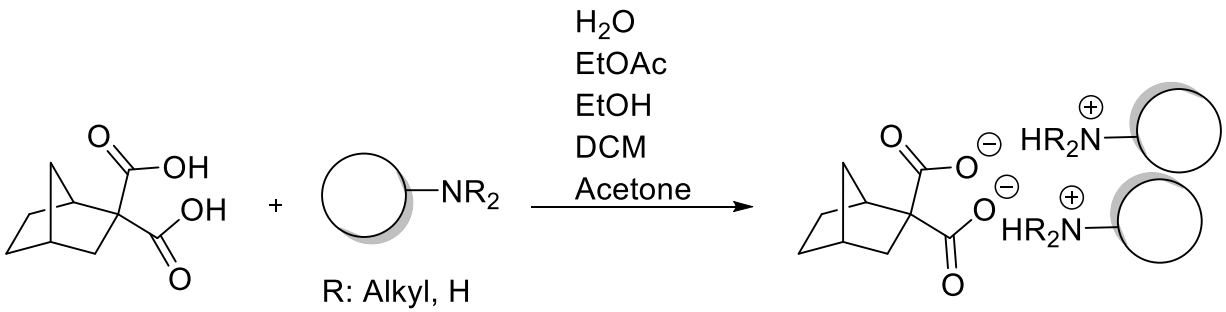
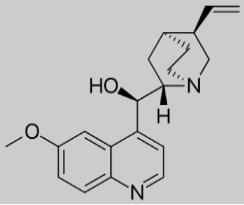
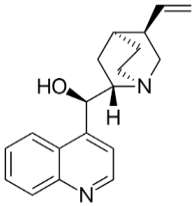
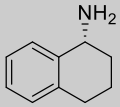
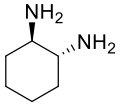
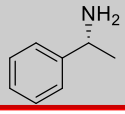
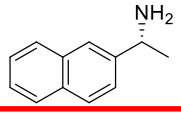
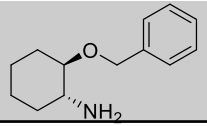
Racemic resolution



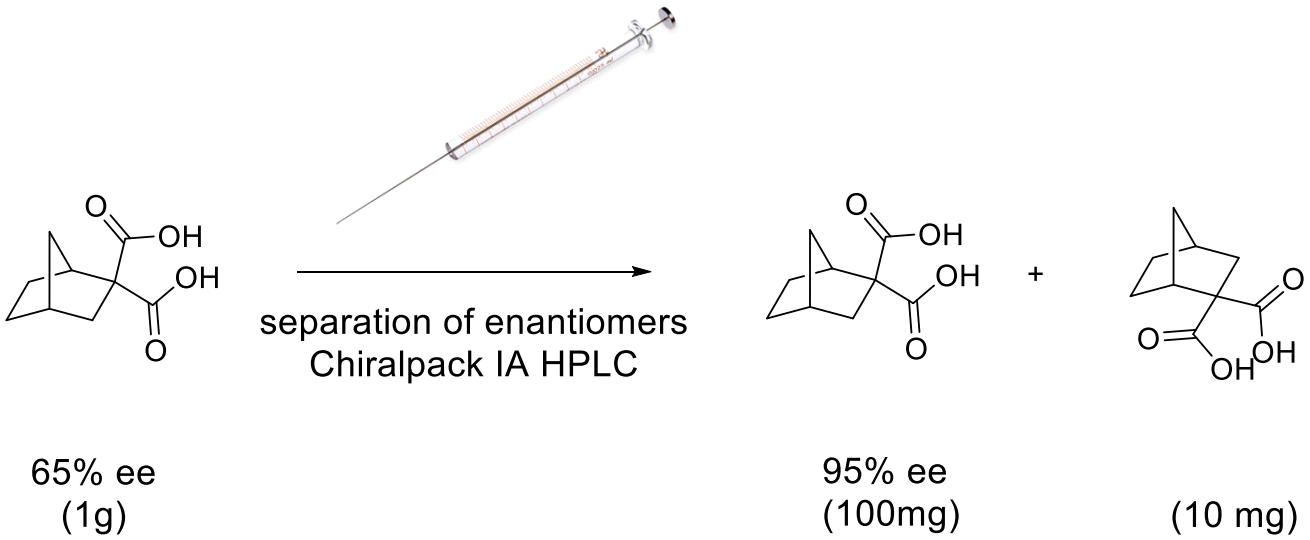
- No Crystallized in H_2O and EtOAc
- Crystallization in DCM and EtOH = 10-25% *ee*

Racemic resolution

Entry	Amine	Solvent	Yield	*ee*
1		Acetone	-	12%
2		Acetone	40%	54%
3		Acetone	-	10%
4		Acetone	10-20%	71%
5		Acetone	-	14%
6		Acetone	45%	65%*
7		Acetone	-	-

* With Second crystallization **70%** enantiomeric excess was obtained.

Separation of enantiomers through preparative chiral HPLC

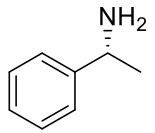


65% ee
(1g)

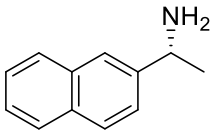
95% ee
(100mg)

(10 mg)

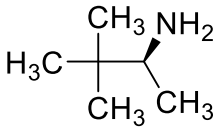
Outlook



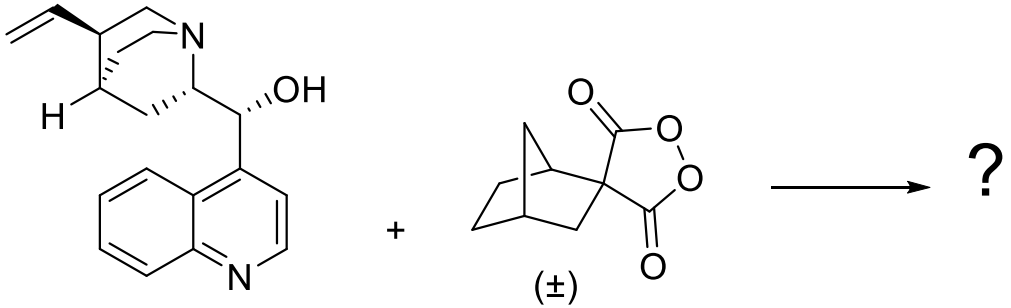
14% *ee*

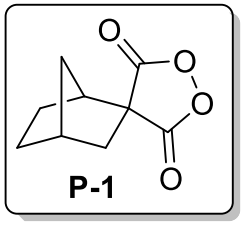


65% *ee*



?





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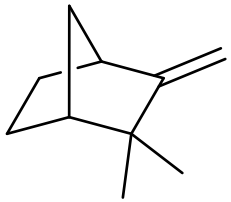
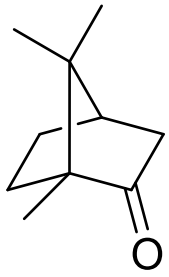


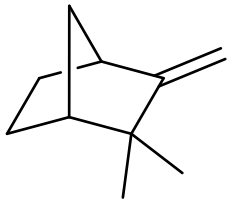
(1R)-(+)-Camphene, 80%

Größe: 100 g
Preis (€): 34.00



(1R)-(+)-Camphor, 98%

Größe: 100 g
Preis (€): 37.00



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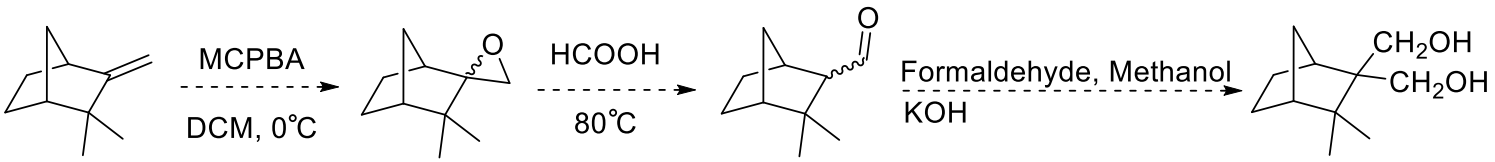
Synthesis of chiral enantiopure cyclic peroxide



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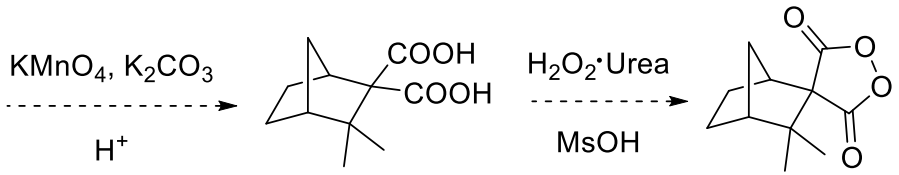

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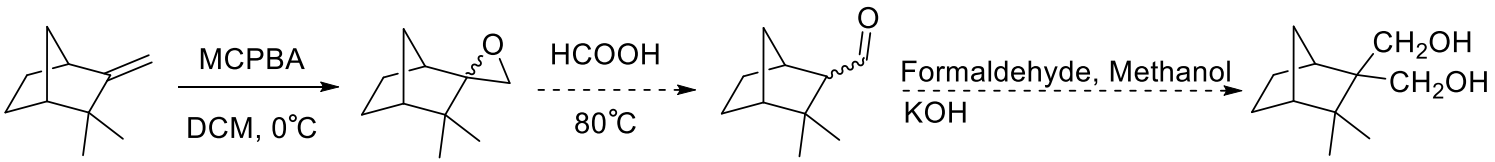

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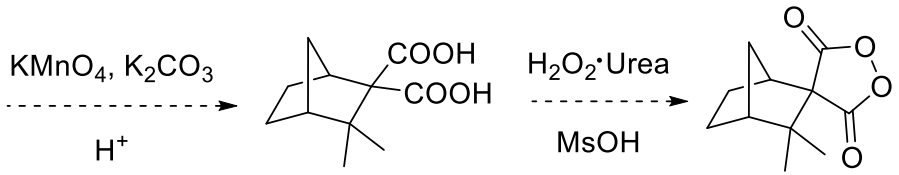

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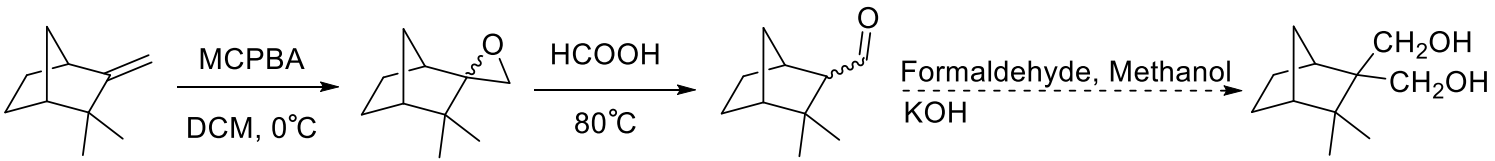

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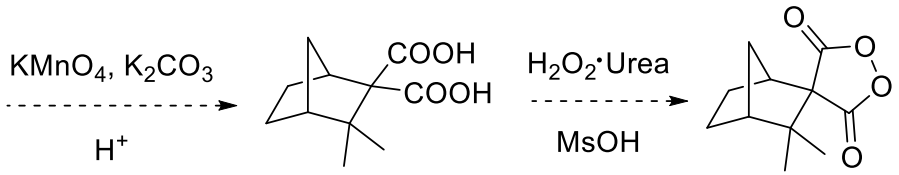

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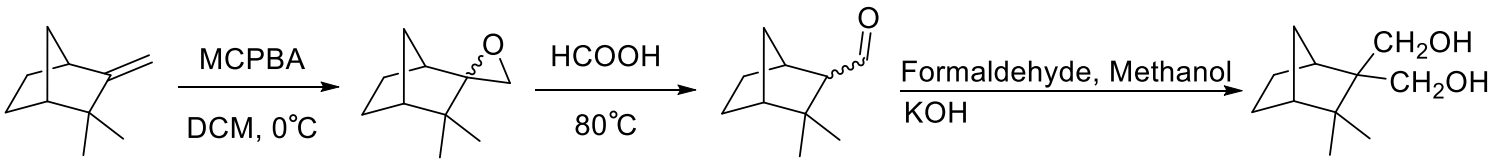
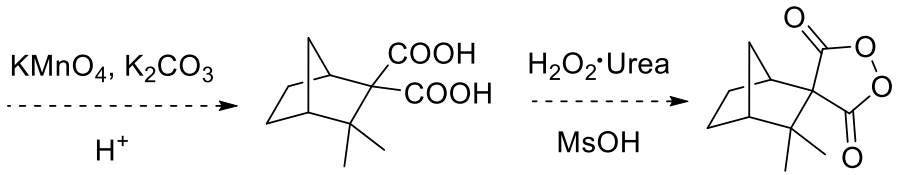
Synthesis of chiral enantiopure cyclic peroxide



(1R)-(+)-Camphene

total yield (3 steps): 50%



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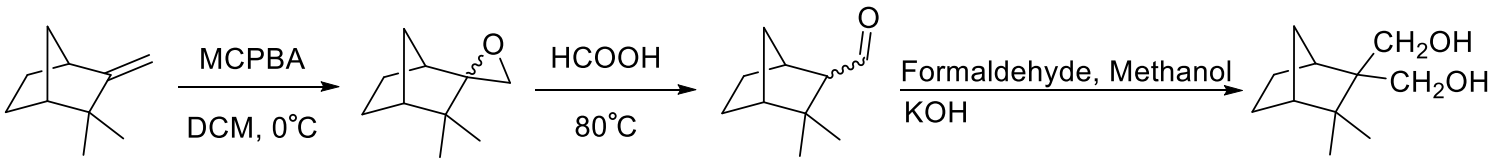
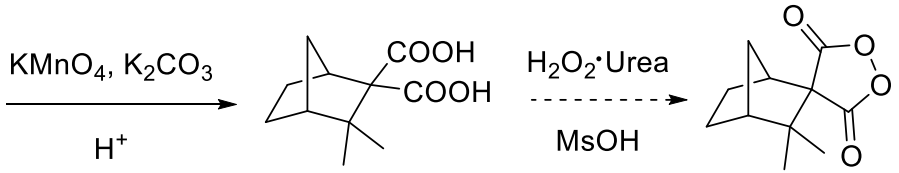


(1R)-(+)-Camphene

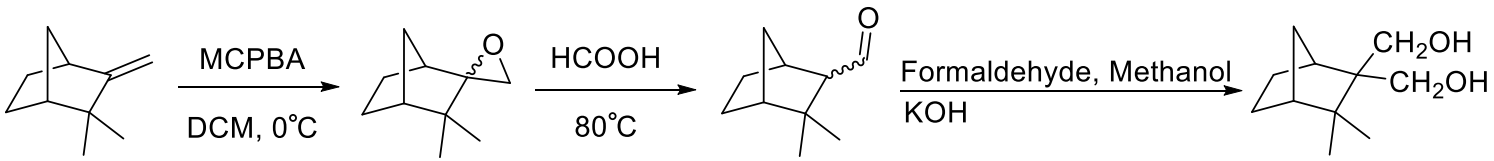
total yield (3 steps): 50%



Isolated yield: 70%

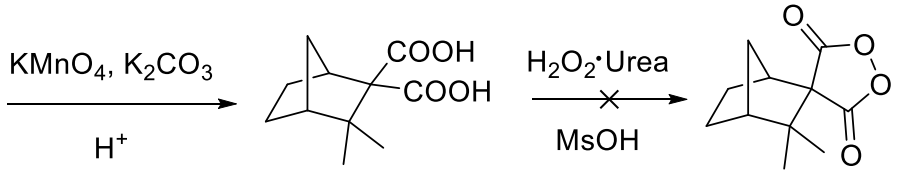
Ghavtadze, N.; Melkonyan, F. S.; Gulevich, A. V.; Huang, C.; Gevorgyan, V. *Nature* **2004**, *6*, 122.
Crivello, J. V. *J. Polym. Sci., Part A: Polym. Chem*. **2014**, *52*, 2934.
Yarovaya, O. I.; Korchagina, D. V.; Gatilov, Y. V.; Barkhash, V. A. *Russ. J. Org. Chem*. **2002**, *38*, 810.

Synthesis of chiral enantiopure cyclic peroxide



(1R)-(+)-Camphene

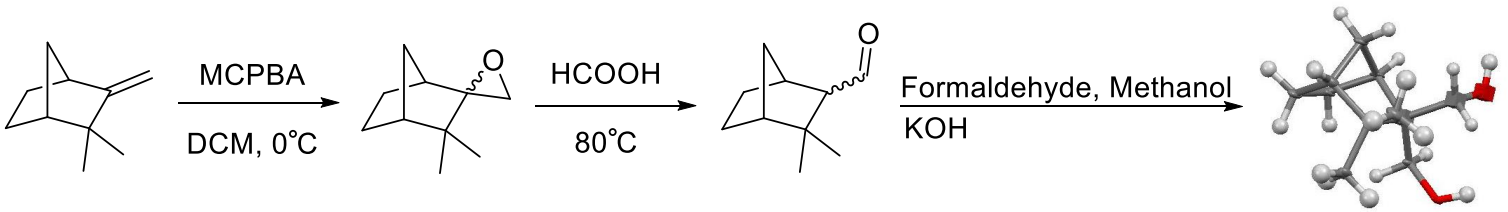
total yield (3 steps): 50%



Isolated yield: 70%

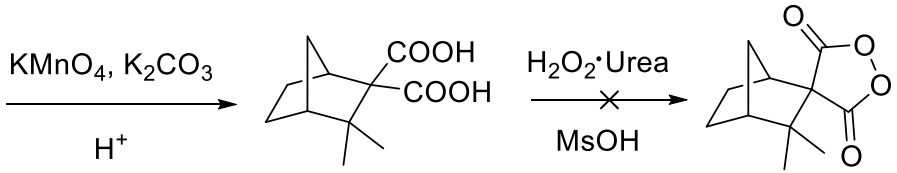
Ghavtadze, N.; Melkonyan, F. S.; Gulevich, A. V.; Huang, C.; Gevorgyan, V. *Nature* **2004**, *6*, 122.
Crivello, J. V. *J. Polym. Sci., Part A: Polym. Chem*. **2014**, *52*, 2934.
Yarovaya, O. I.; Korchagina, D. V.; Gatilov, Y. V.; Barkhash, V. A. *Russ. J. Org. Chem*. **2002**, *38*, 810.

Synthesis of chiral enantiopure cyclic peroxide



(1R)-(+)-Camphene

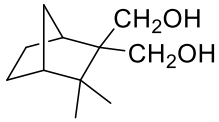
total yield (3 steps): 50%



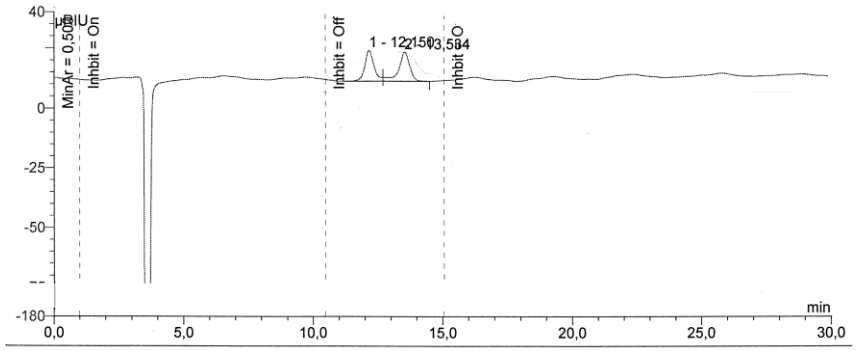
Isolated yield: 70%

Ghavtadze, N.; Melkonyan, F. S.; Gulevich, A. V.; Huang, C.; Gevorgyan, V. *Nature* **2004**, *6*, 122.
Crivello, J. V. *J. Polym. Sci., Part A: Polym. Chem*. **2014**, *52*, 2934.
Yarovaya, O. I.; Korchagina, D. V.; Gatilov, Y. V.; Barkhash, V. A. *Russ. J. Org. Chem*. **2002**, *38*, 810.

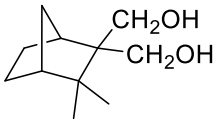
HPLC results



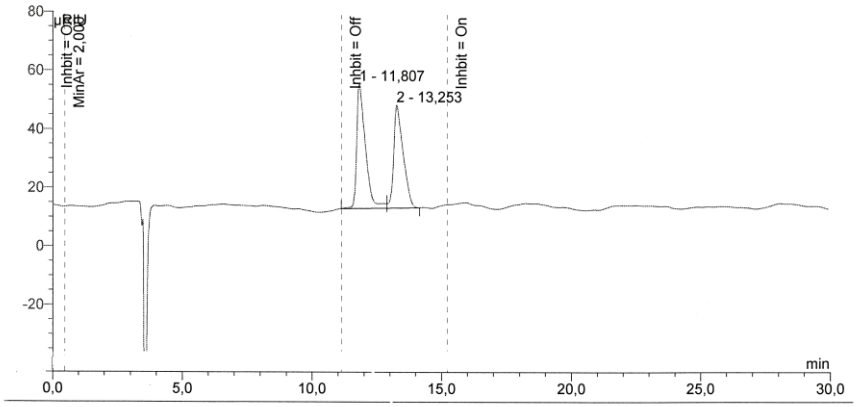
(±)- Camphen alcohol



No.	Ret.Time min	Peak Name	Height µRIU	Area µRIU*min	Rel.Area %	Amount	Type
1	12,15	n.a.	12,846	5,294	46,76	n.a.	BM
2	13,53	n.a.	12,040	6,028	53,24	n.a.	MB
Total:			24,886	11,322	100,00	0,000	



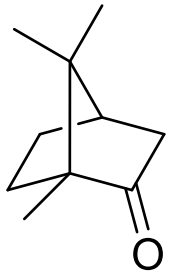
(1*R*)-(+)-Camphen alcohol



No.	Ret.Time min	Peak Name	Height µRIU	Area µRIU*min	Rel.Area %	Amount	Type
1	11,81	n.a.	42,465	16,591	52,47	n.a.	BM
2	13,25	n.a.	35,139	15,027	47,53	n.a.	MB
Total:			77,604	31,618	100,00	0,000	

(1R)-(+)-Camphene, 80%

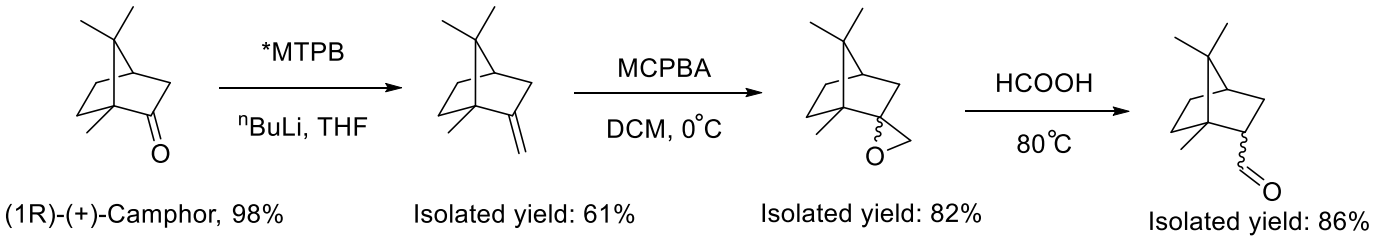
Größe: 100 g
Preis (€): 34.00



(1R)-(+)-Camphor, 98%

Größe: 100 g
Preis (€): 37.00

Synthesis of chiral enantiopure cyclic peroxide

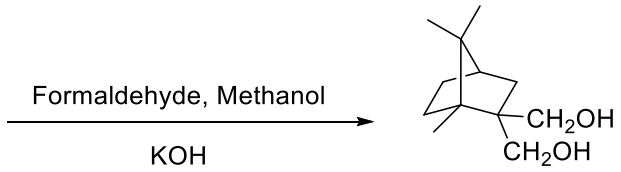


(1R)-(+)-Camphor, 98%

Isolated yield: 61%

Isolated yield: 82%

Isolated yield: 86%

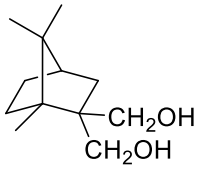


Isolated yield: 63%

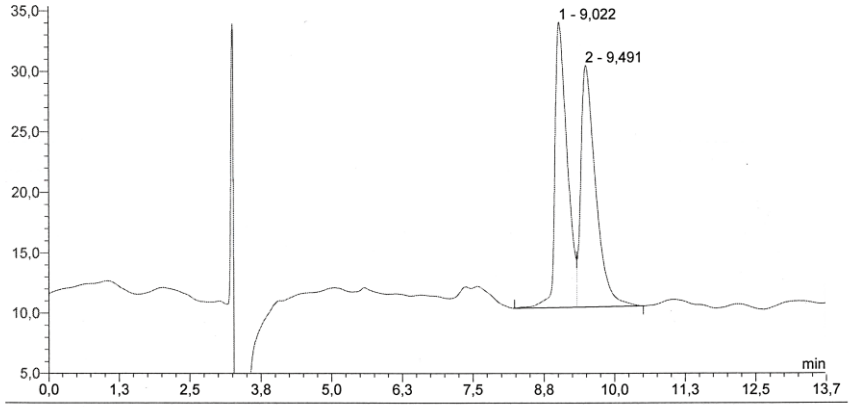
Ghavtadze, N.; Melkonyan, F. S.; Gulevich, A. V.; Huang, C.; Gevorgyan, V. *Nat. Chem.* **2014**, *6*, 122.

*Methyltriphenylphosphonium bromide

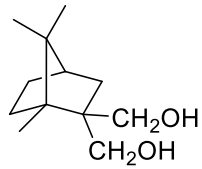
HPLC results



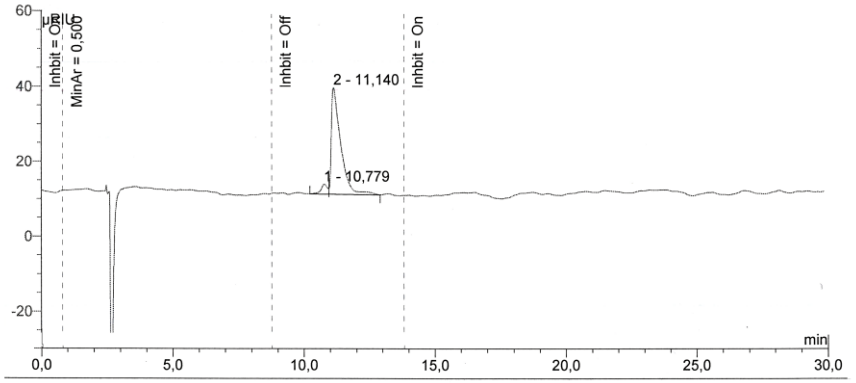
(±)- Camphor alcohol



No.	Ret.Time min		Peak Name	Height µRIU	Area µRIU*min	Rel.Area %	Amount	Type
1	9,02	n.a.		23,574	5,920	49,30	n.a.	BM
2	9,49	n.a.		19,992	6,087	50,70	n.a.	MB
Total:				43,565	12,008	100,00	0,000	

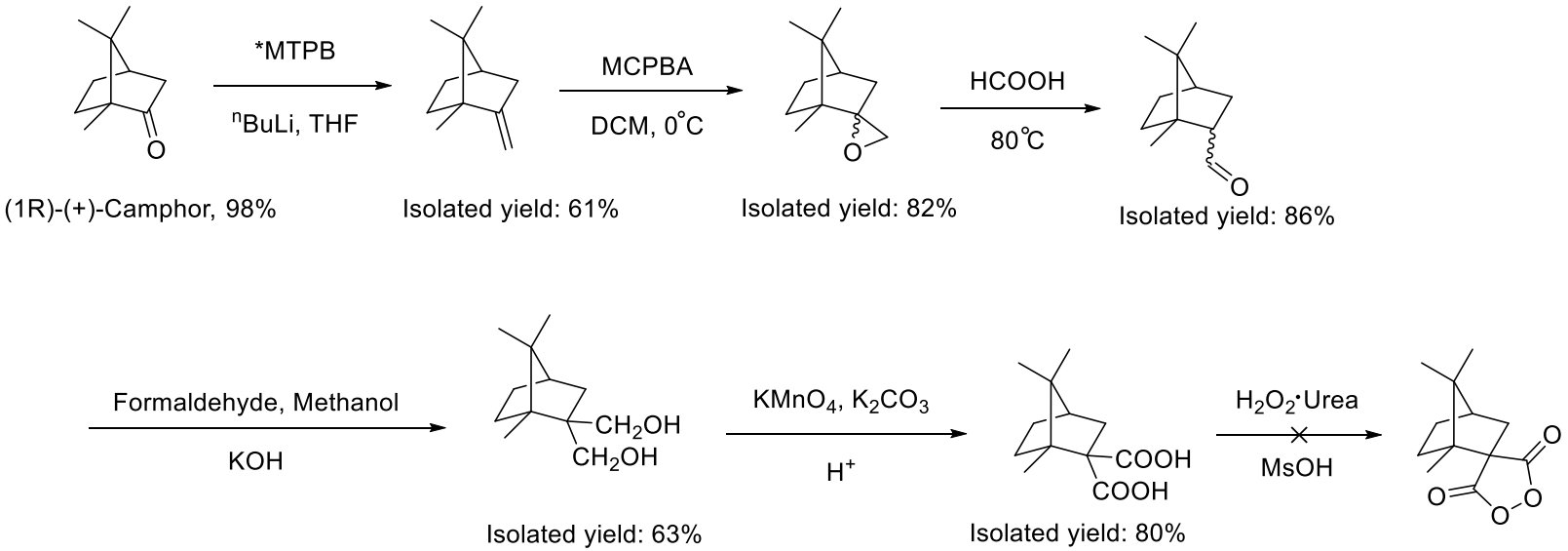


(1*R*)-(+)-Camphor alcohol



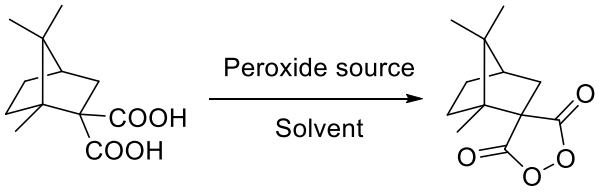
No.	Ret.Time min		Peak Name	Height µRIU	Area µRIU*min	Rel.Area %	Amount	Type
1	10,78	n.a.		2,591	0,725	5,83	n.a.	BM
2	11,14	n.a.		28,364	11,713	94,17	n.a.	MB
Total:				30,955	12,438	100,00	0,000	

Synthesis of chiral enantiopure cyclic peroxide



- Impurity increased by heating, therefore all extraction steps like acidification and removing the solvent was done in an ice-salt bath
- The use of silica and basic alumina column chromatography was unsuccessful
- Crystallization was successful using ether/petroleum ether

Synthesis of peroxide

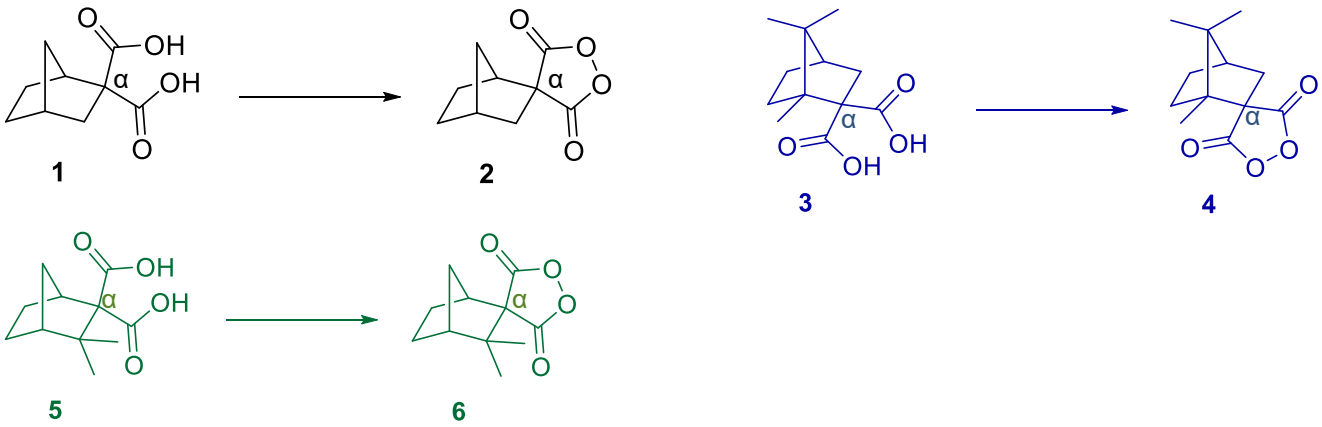


Entry	Temp.	Time (h)	Solvent	Peroxide source	yield
1	0 °C	72	$MeSO_3H$	Urea H_2O_2	-
2	17 °C	72	$MeSO_3H$	Urea H_2O_2	Mixture*
3	r.t.	48	$MeSO_3H$	Urea H_2O_2	Mixture*
4	40°C	24	$MeSO_3H$	Urea H_2O_2	Mixture*
5	r.t.	24	$MeSO_3H/CH_2Cl_2$	Urea H_2O_2	Mixture*
6	r.t.	24	$MeSO_3H$/TfOH	Urea H_2O_2	-
7	r.t.	24	$MeSO_3H$	Na_2O_2	?

❖ Dissolving sodium peroxide in methane sulfonic acid is an extremely exothermic reaction; insufficient cooling resulting in ignition of the reaction mixture.

70-80% of starting material was recovered. Remaining mixture was decarboxylated acid and the corresponding peroxide.

X-ray structural data



Compound	α from X-ray / °	α from computation / °
1	n. d.	111.2
2	102.0	102.7
3	103.8	101.0
4	n. d.	100.9
5	n. d.	102.8
6	n. d.	102.1

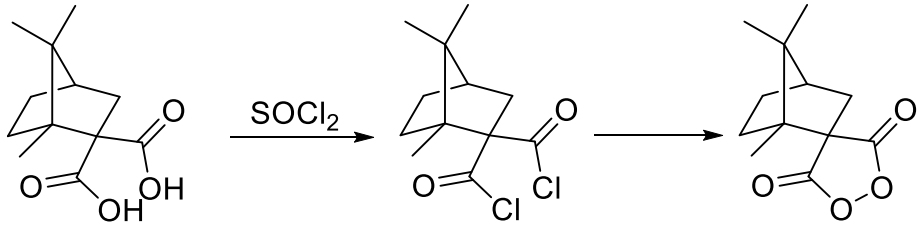
Relevant OC-C-CO bond angles obtained from the X-ray structures and from geometrics optimized at B3LYP-D3(BJ)/6-311+G(d.p)level of theory.

Outlook

- These peroxides were prepared treating a substituted acid with 98% hydrogen peroxide in methanesulfonic acid.

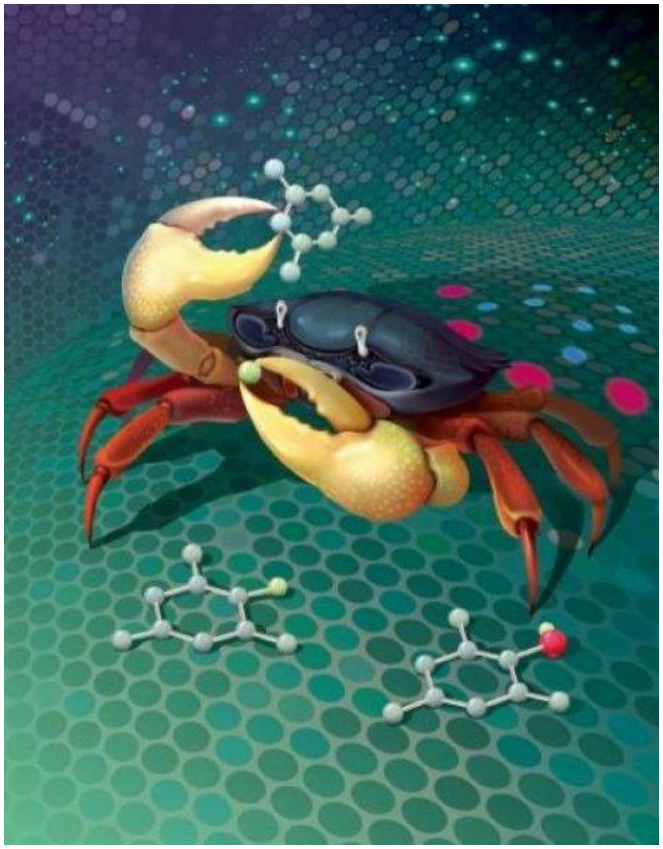
- The same result avoiding the dangerous hydrogen peroxide can be achieved by using a solution of sodium peroxide in methanesulfonic acid.

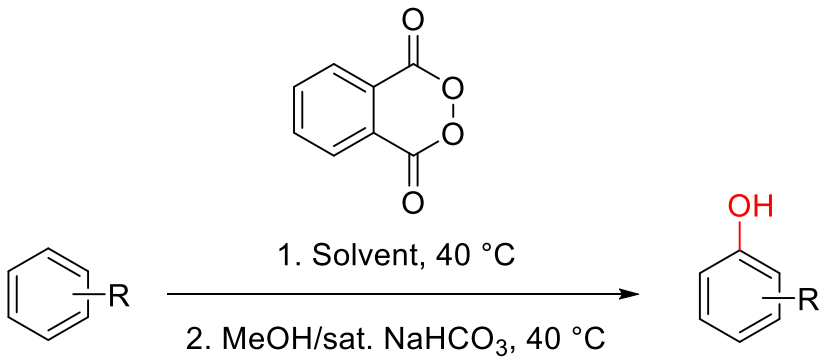
- Synthesis of camphor chloride as an alternative starting material



Arene Oxidation

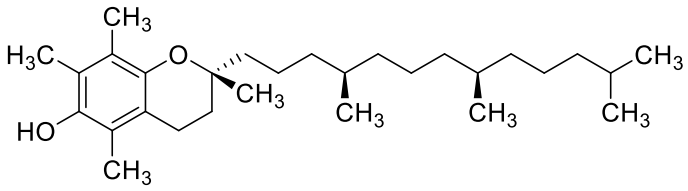
Arene Oxidation



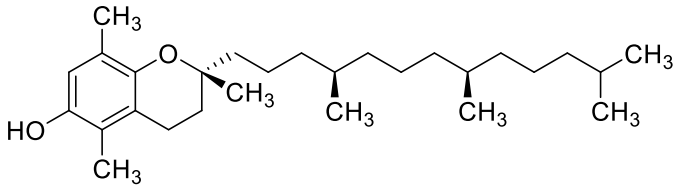


The crab represents the chemical phthaloyl peroxide. The claws are the reactive regions of the molecule that undergo the reaction. The crab is grabbing a molecule (forming the carbon-oxygen bond) then tearing a hydrogen atom off.

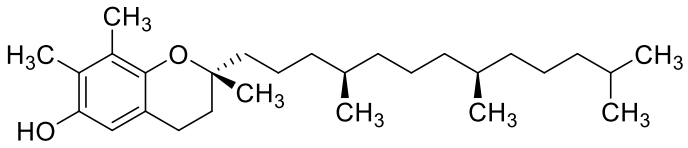
Yuan, C.; Liang, Y.; Hernandez, T.; Berriochoa, A.; Houk, K. N.; Siegel, D. *Nature* **2013**, *499*, 192.
http://www.robaid.com/



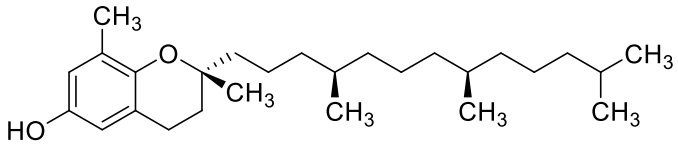
alpha-Tocopherol



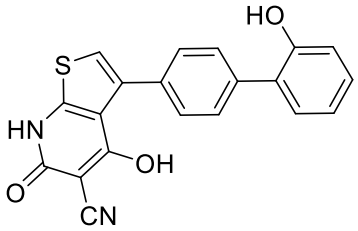
beta-Tocopherol



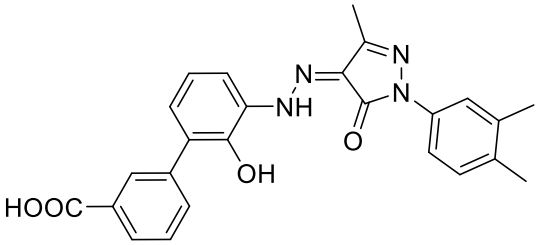
gamma-Tocopherol



delta-Tocopherol

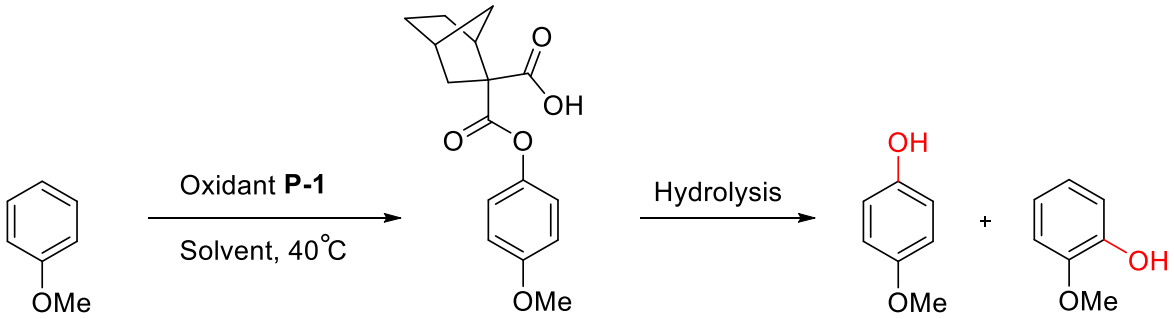


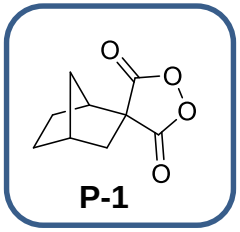
A-769662
Diabetes



Eltrombopag
Blood disease

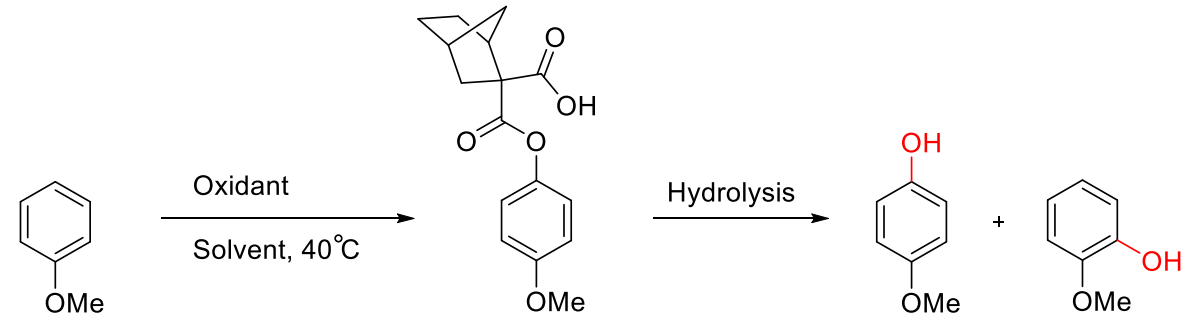
Arene Oxidation



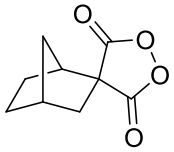


Entry	oxidant/equiv.	solvent	yield
1	**1/** 1.2 equiv.	DCM	28
2	**1/** 1.2 equiv.	EtOAC	-
3	**1/** 1.2 equiv.	1,4-dioxane	15
4	**1/** 1.2 equiv.	Toluene	16
5	**1/** 1.2 equiv.	Benzene	14
6	**1/** 1.2 equiv.	MeCN	8
7	**1/** 1.2 equiv.	TFE	65
8	**1/** 1.2 equiv.	HFIP	82

Arene Oxidation



Entry	oxidant/equiv	solvent	yield
1	**P-1/** 1.2 equiv	HFIP	82
2	**P-2/** 10 equiv	HFIP	-
3	**P-3/** 10 equiv	HFIP	-
4	**P-4/** 5 equiv	HFIP	-
5	**P-5/** 1.3 equiv	HFIP	45
6	**P-6/** 2 equiv	HFIP	63



P-1

10% *t*BuOOH

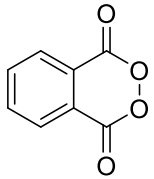
P-2

30% H_2O_2

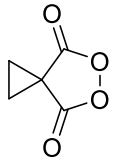
P-3

BPO

P-4



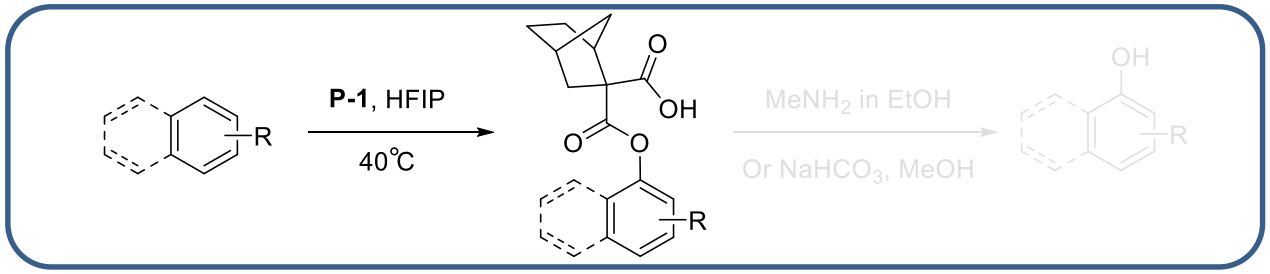
P-5

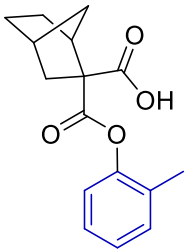


P-6

Yuan, C.; Liang, Y.; Hernandez, T.; Berriochoa, A.; Houk, K. N.; Siegel, D. *Nature* **2013**, *499*, 192. Dragan, A.; Kubczyk, T. M.; Rowley, J. H.; Sproules, S.; Tomkinson, N. C. O. *Org. Lett*. **2015**, *17*, 2618.

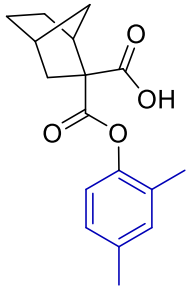
Arene Oxidation





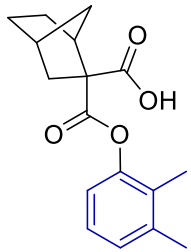
71%

(46%)



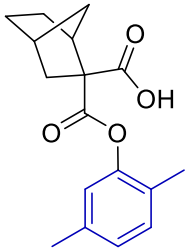
85%

(94%)



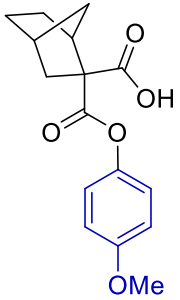
78%

(62%)



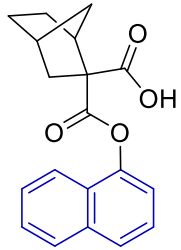
98%

(86%)



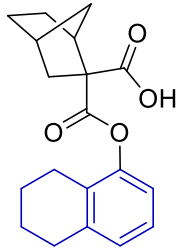
86%

(45%)



79%

(63%)

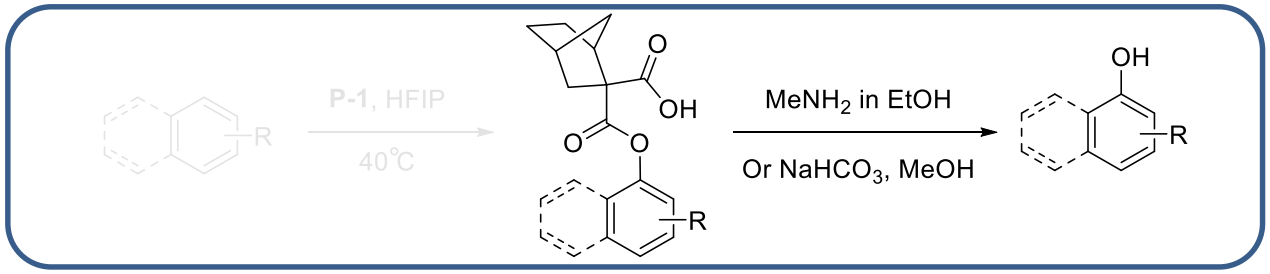


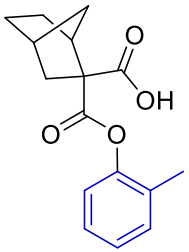
84%

(70%)

*The numbers in parenthesis refers to isolated yield of phenol using phthaloyl peroxide.

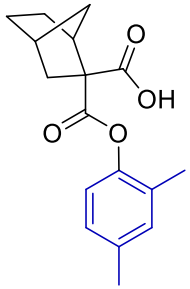
Arene Oxidation





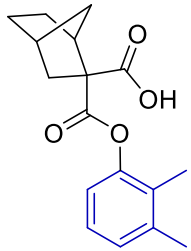
71%

(46%)



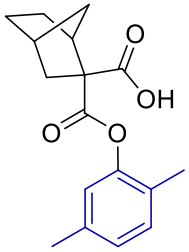
85%

(94%)



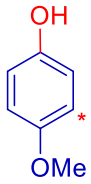
78%

(62%)



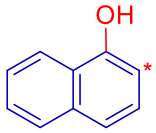
98%

(86%)



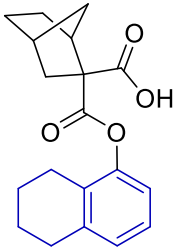
82%
[2.8:1]*

(45%, 1:1.4) **



75%
[14.7:1]*

(63%, 5.8:1) **



84%

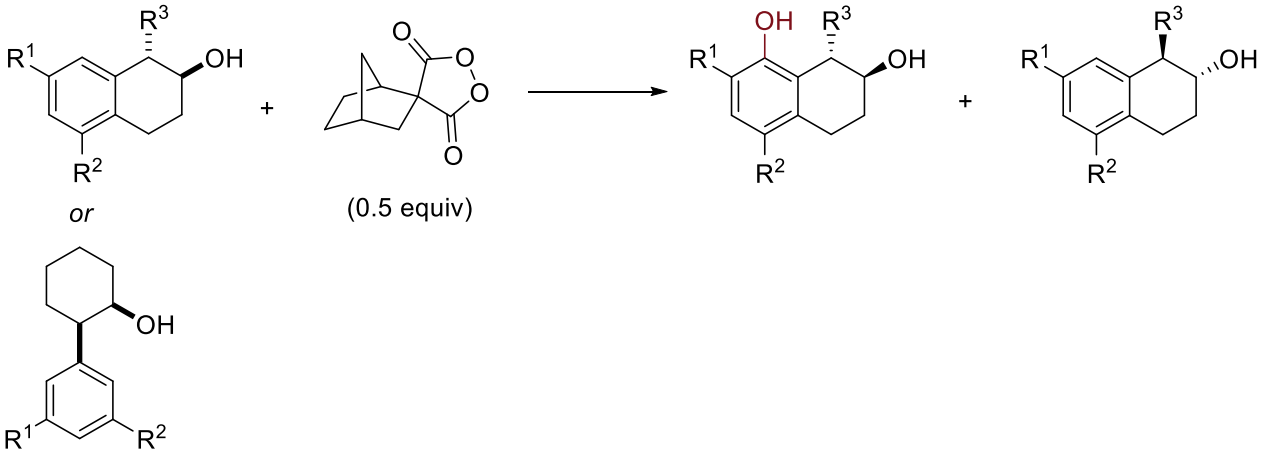
(70%)

*The minor regioisomeric position is labelled with the corresponding carbon atom.

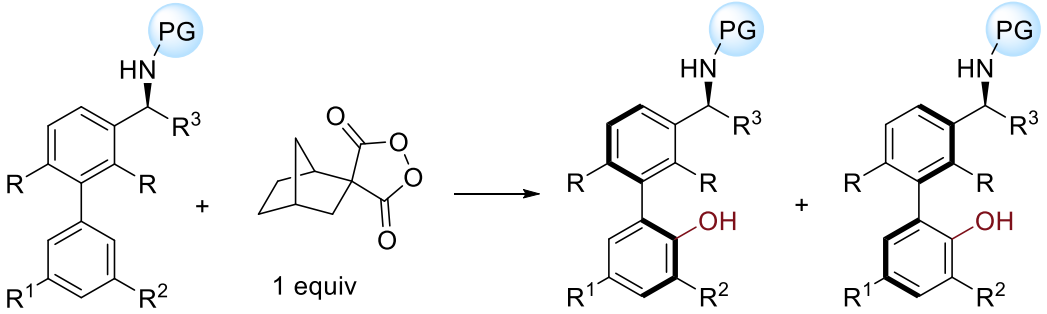
**Isolated yield of phenol using phthaloyl peroxide.

Outlook

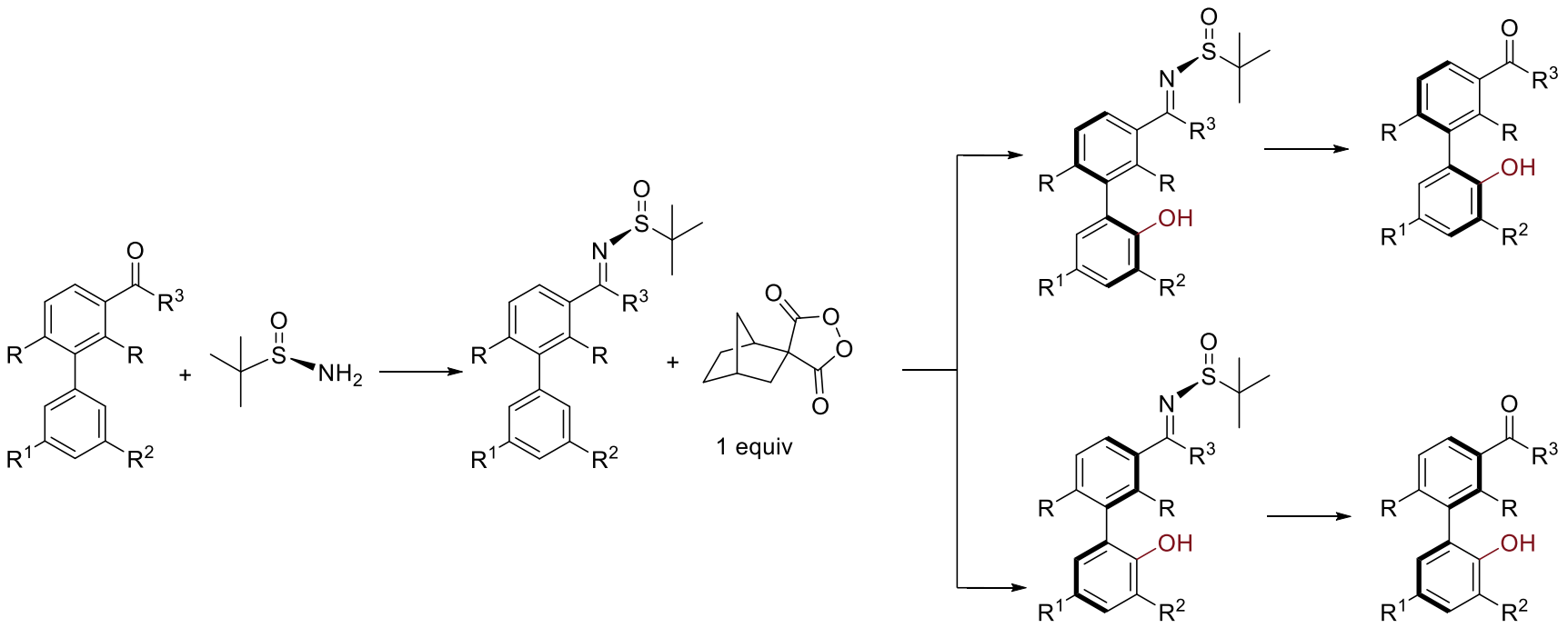
- Kinetic resolution using enantiopure peroxide



- Diastereomerization of chiral biphenyls using racemic peroxide



- Use of chiral auxiliaries for enantioselective preparation of 2-Hydroxybiphenyl



Prof. Dr. Peter R. Schreiner

Dr. Marina Šekutor

Sören Rösel and our organocatalysis group

Analytical department

the whole group!

Thank You for Your Attention

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