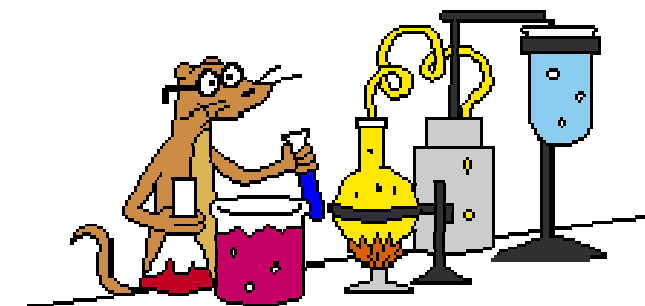


Malonoyl peroxides, potential organocatalysts for the stereospecific dihydroxylation of alkenes

PRS Group Seminar

28.03.2014

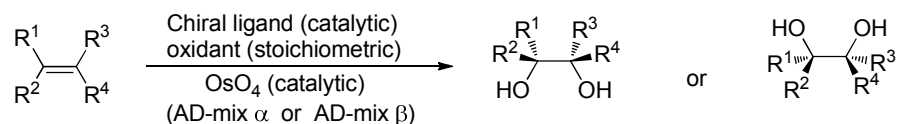
Afsaneh Pilevar



*Institut für Organische Chemie
Justus-Liebig-Universität
35435 Gießen, Germany*

Sharpless asymmetric *syn*-dihydroxylation

➤ More than 20 years after its introduction, development of organocatalytic version of this reaction still remains a challenge



R¹⁻⁴ = H, alkyl, aryl

AD-mix α : (DHQD)₂PHAL + K₂OsO₂(OH)₄ + K₃Fe(CN)₆ + K₂CO₃

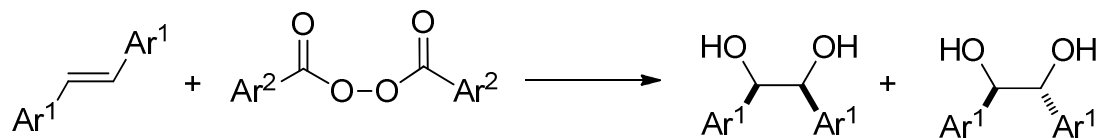
AD-mix β : (DHQD)₂PHAL + K₂OsO₂(OH)₄ + K₃Fe(CN)₆ + K₂CO₃

➤ Metal-free *syn*-dioxxygenation

- Hypervalent iodine
- Selenium
- Sulphur
- **Peroxides**

➔ Early attempts for metal free *syn* dihydroxylation:

✓ The use of acyclic peroxide for alkene dihydroxylation

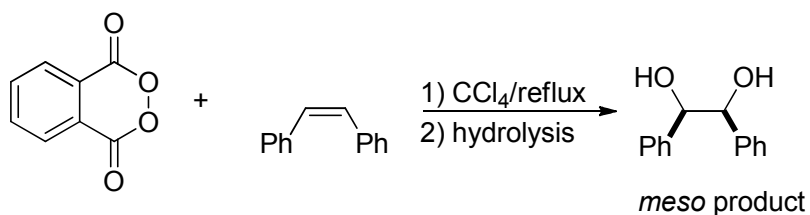
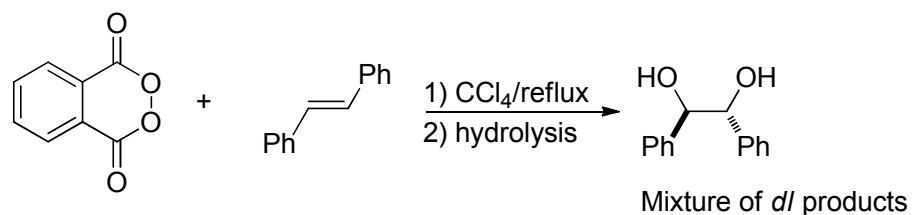


Mixture of *syn* and *anti* products

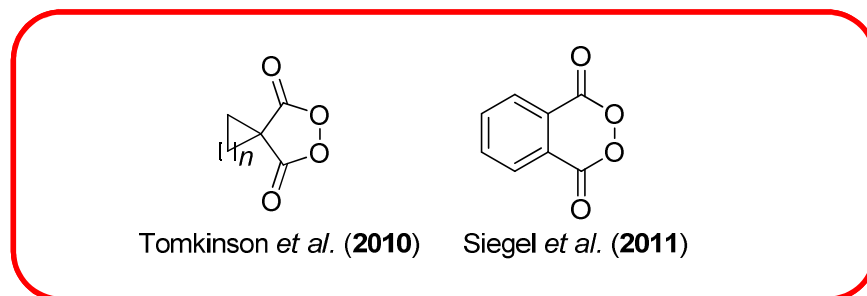
Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, 94, 2483.

Greene, F. D.; Adam, W.; Cantrill, J. E. *J. Am. Chem. Soc.* **1961**, 83, 3461.

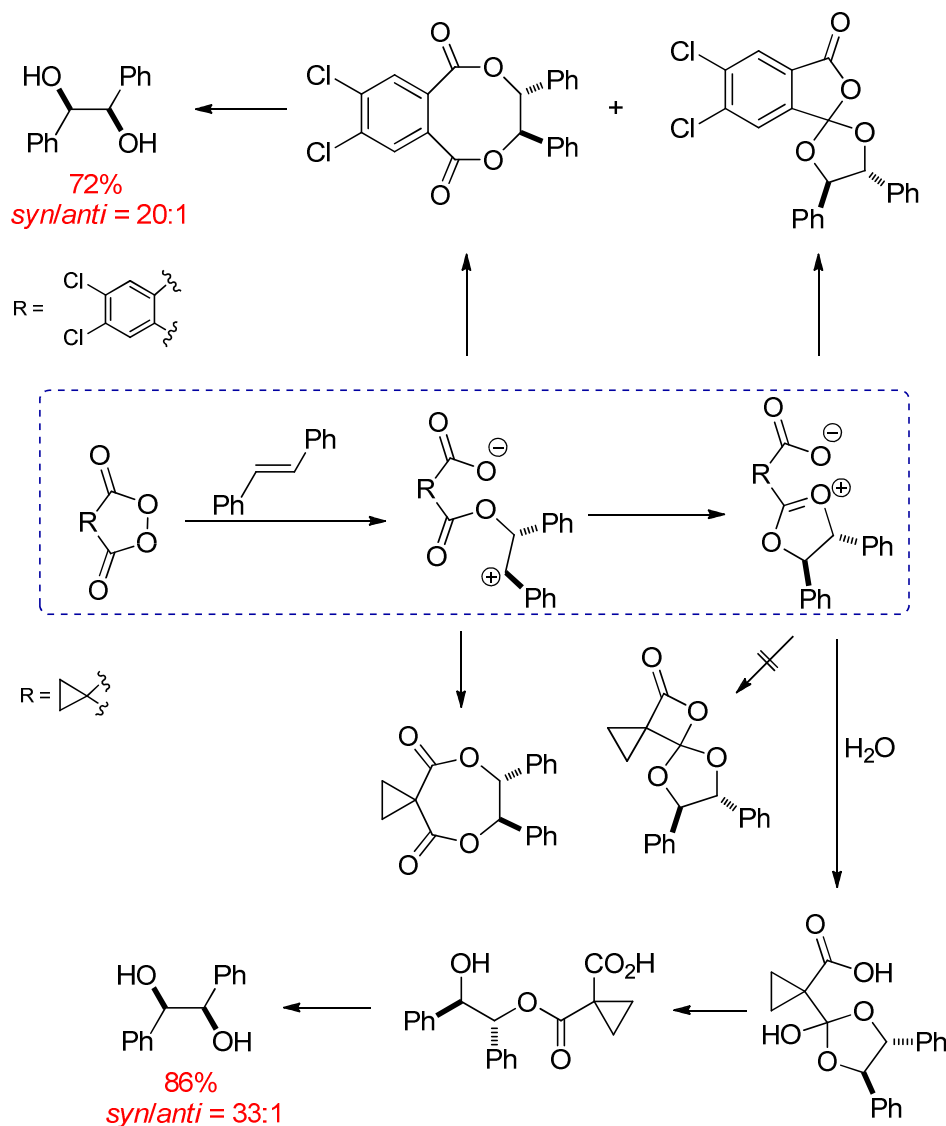
✓The use of cyclic peroxide for alkene dihydroxylation



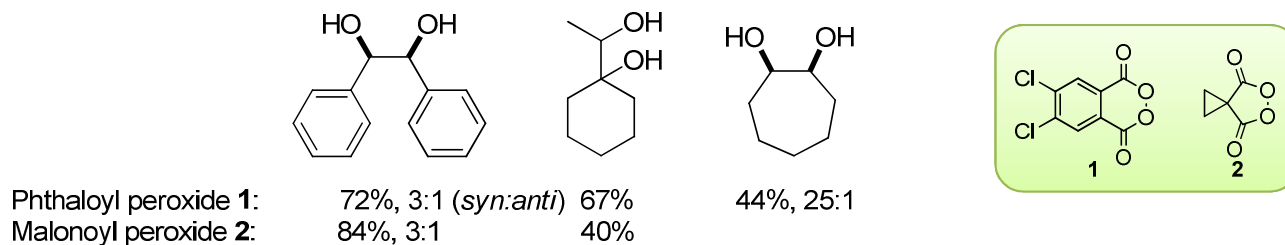
✓Use of cyclic peroxides for alkene *syn* dihydroxylation



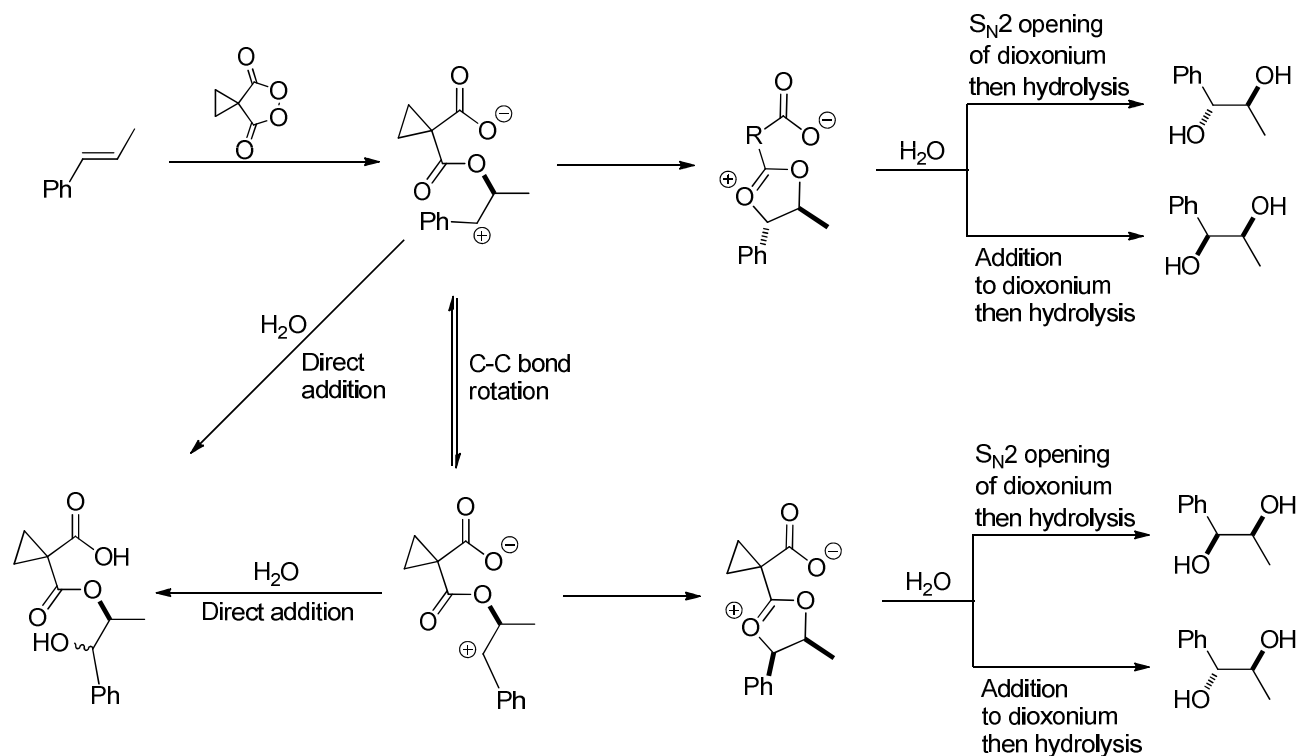
➤ Possible mechanistic pathway for the dihydroxylation of alkenes



➤ Comparison of the stereospecificity and reactivity of cyclic peroxides 1 and 2 in the reactions of selected alkenes



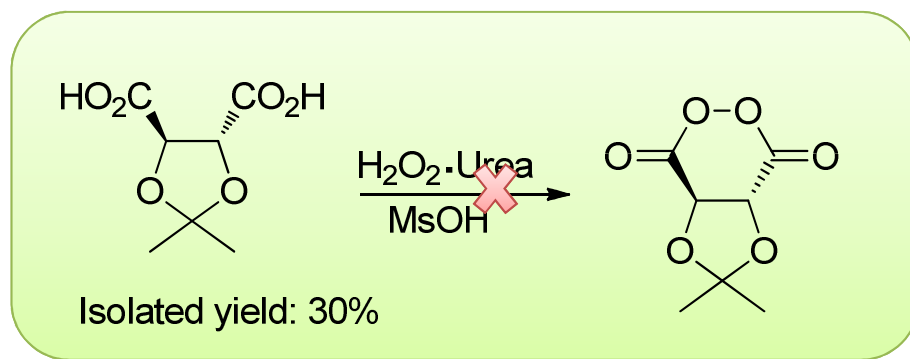
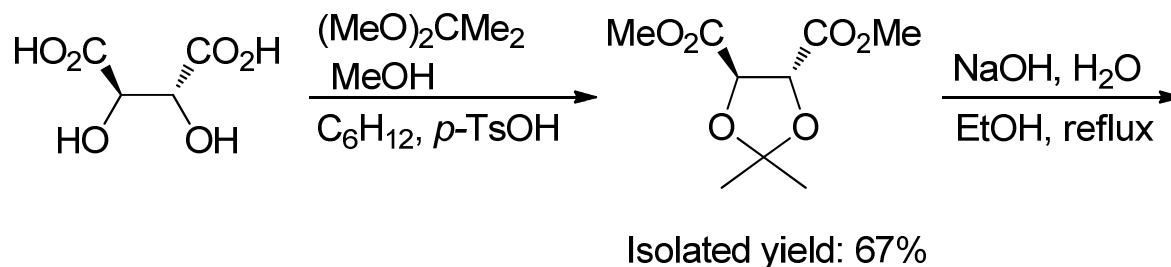
➤ Potential mechanistic pathways for the *syn*- and *anti*-dioxxygenation of 1,2-disubstituted alkenes



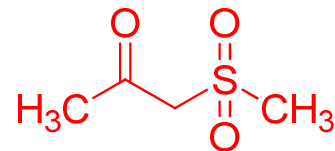
Schwarz, M.; Reiser, O. *Angew. Chem., Int. Ed.* **2011**, 50, 10495.

Rawling, M. J.; Rowley, J. H.; Campbell, M.; Kennedy, A. R.; Parkinson, J. A.; Tomkinson, N. C. O. *Chem. Sci.* **2014**.

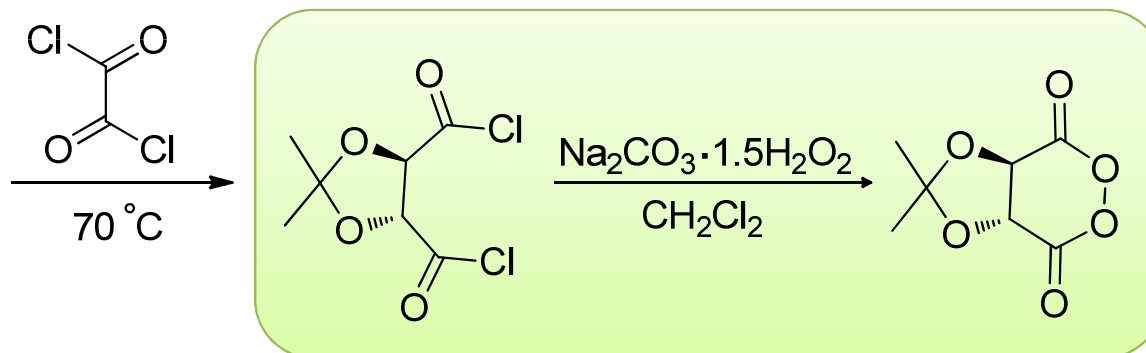
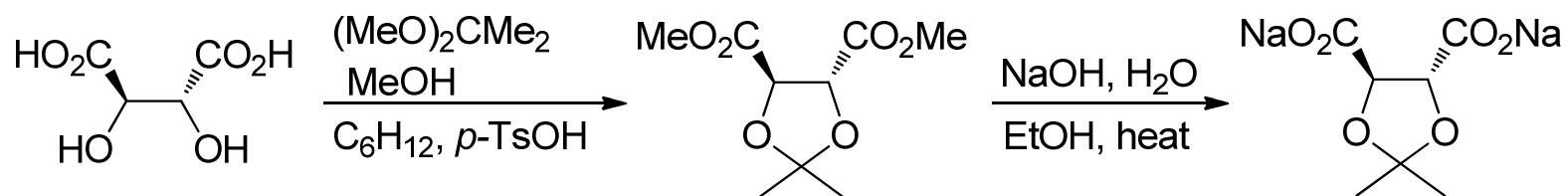
➤ Attempts to synthesis of chiral peroxide using tartaric acid



Proposed product by NMR & MS:



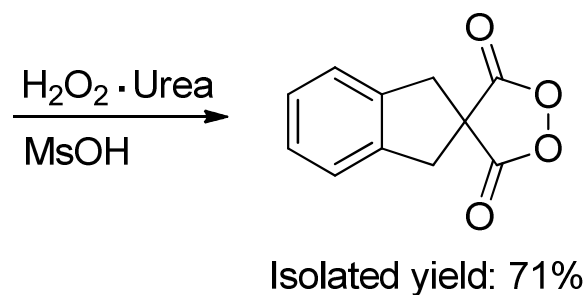
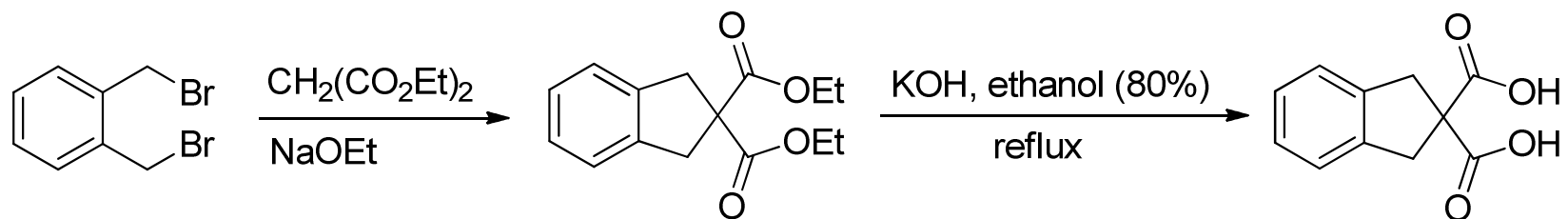
➤ Future work: use of basic condition



Delaney, E. J.; Massil, S. E.; Shi, G.-Y.; Klotz, I. M. *Arch. Biochem. Biophys.* **1984**, 228, 627.

Yuan, C.; Axelrod, A.; Varela, M.; Danysh, L.; Siegel, D. *Tetrahedron Lett.* **2011**, 52, 2540.

➤ Attempts to synthesize new peroxide with potentially higher activity



Not stable on the bench

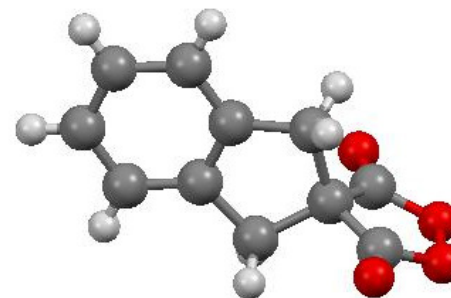
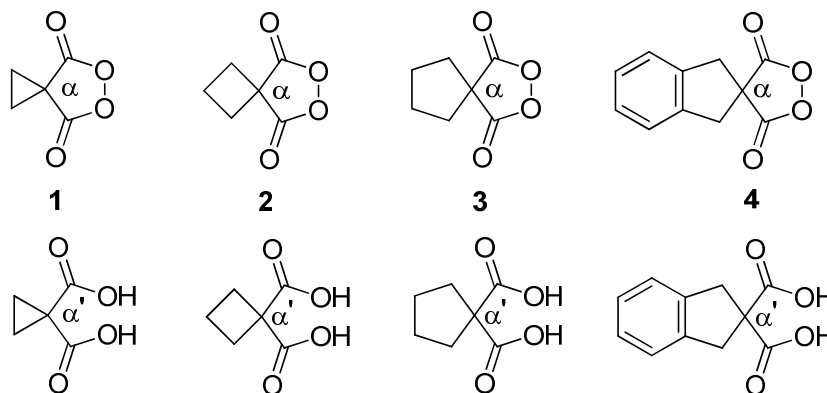
Stable in -25°C (in Fraser)

Jamrozik, J.; Zak, G.; Grochowski, J.; Markiewicz, M.; Serda, P. *J. Mol. Struct.* **2004**, 687, 79.

Tomiyama, T.; Wakabayashi, S.; Yokota, M. *J. Med. Chem.* **1989**, 32, 1988.

Brill, W. K-D.; Furet, P.; Traxler, P. U.S. Patent No. 5686457, **1997**.

➤ X-ray structural data for peroxides



Comparison of calculated α angles of the closed acyl peroxides and their corresponding open dicarboxylic acids.^[a]

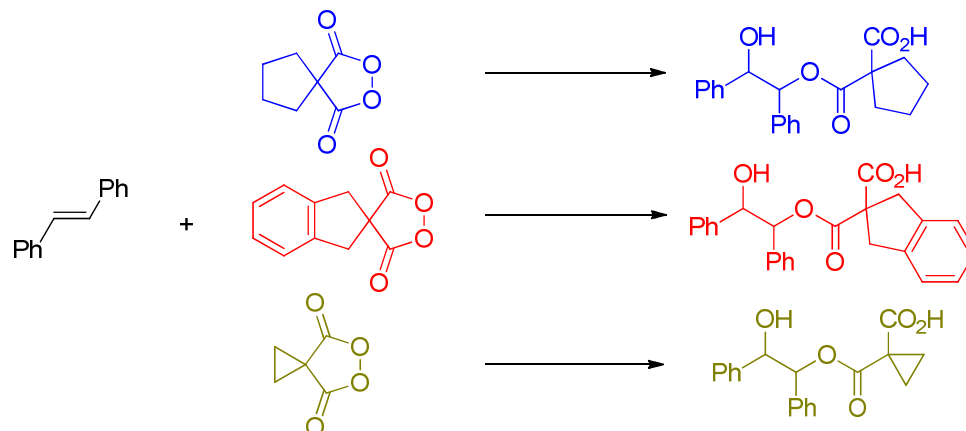
Peroxide	α	α'	$\alpha' - \alpha$	O-O bond (Å)
1	105.2° (107.6°) ^[b]	119.6°	14.4°	1.476
2	102.3° (104.0°) ^[b]	116.2°	14.1°	1.476
3	101.5° (102.3°) ^[b]	104.6°	3.1°	1.471
4	(102.5°)			1.466

[a] Hartree–Fock 6-31G* calculation; equilibrium geometry at ground state. [b] Bond angles α derived from X-ray structure analysis.

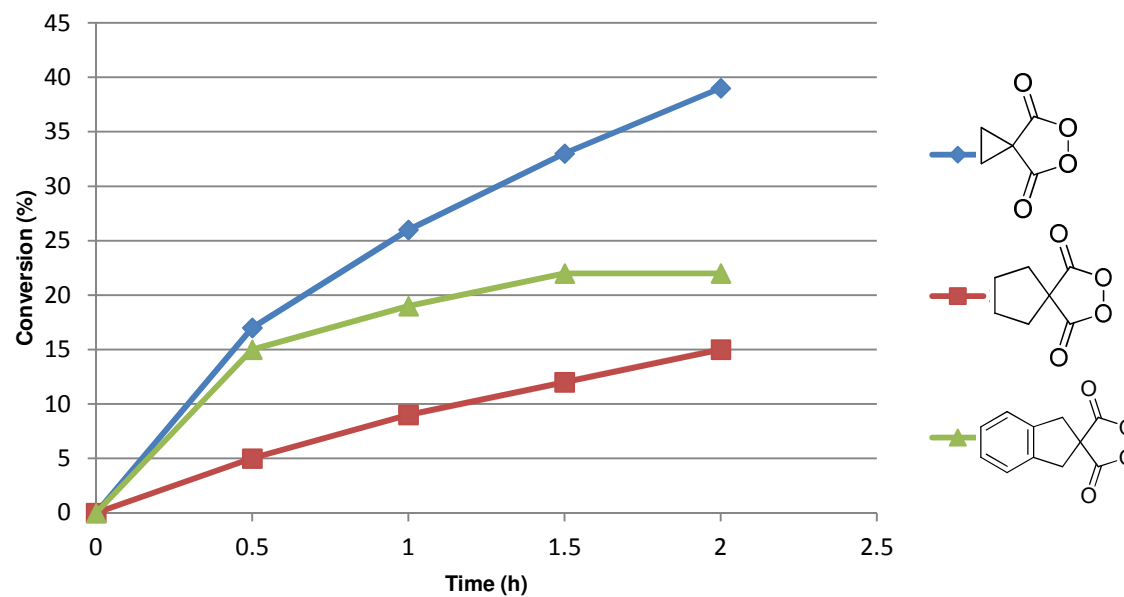
Griffiths, J. C.; Jones, K. M.; Picon, S.; Rawling, M. J.; Kariuki, B. M.; Campbell, M.; Tomkinson, N. C. O. *J. Am. Chem. Soc.* **2010**, *132*, 14409.

Schwarz, M.; Reiser, O. *Angew. Chem., Int. Ed.* **2011**, *50*, 10495.

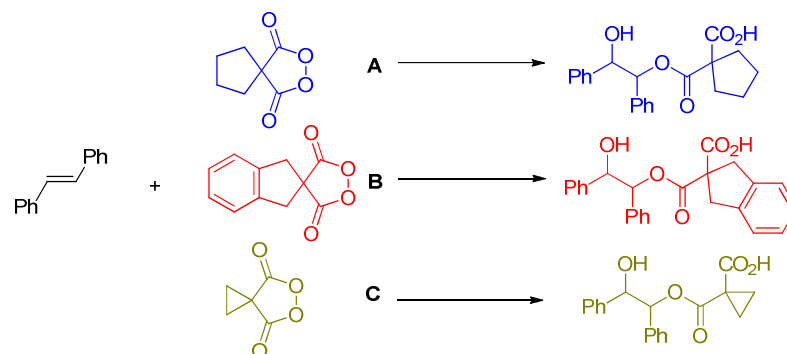
➤ Relative rates for the reaction of various cyclic peroxides with stilbene



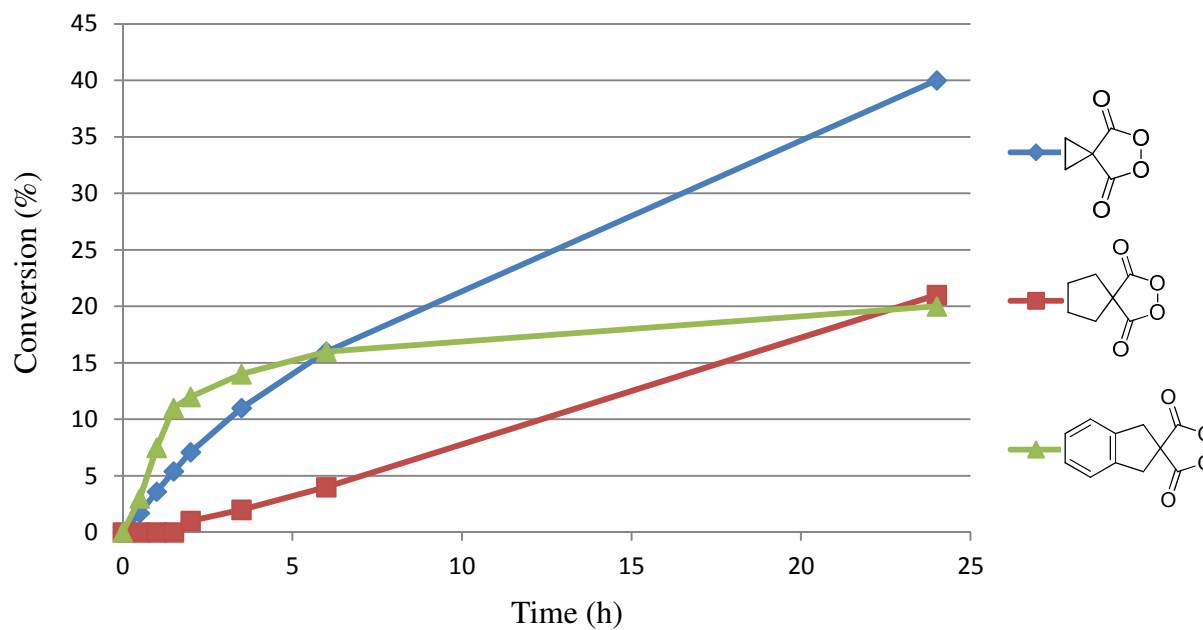
Reaction condition: stilbene (1.0 equiv.), peroxide (1.0 equiv.), H₂O (1.0 equiv.) in **CDCl₃** at RT.



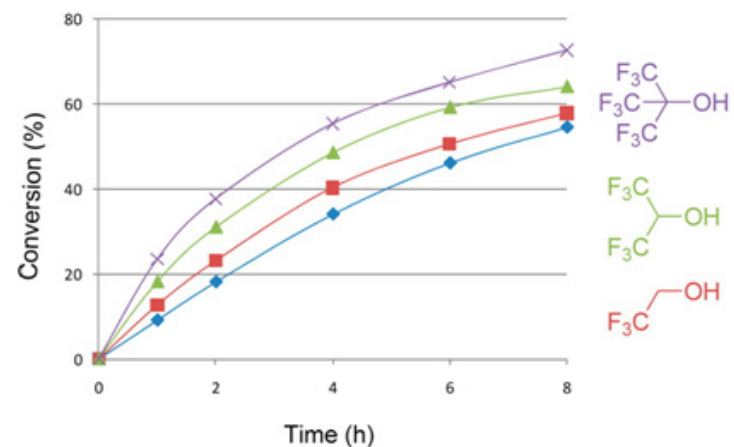
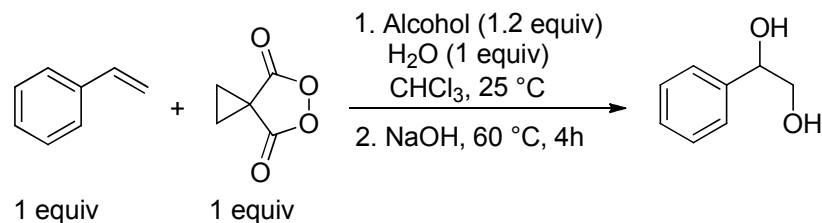
- Relative rates for the reaction of various cyclic peroxides with stilbene
- ✓ Effect of nonpolar solvent on decomposition rate of new peroxide **B**



Reaction condition: stilbene (1.0 equiv.), peroxide (1.0 equiv.), H₂O (1.0 equiv.) in **Toluene** at RT.

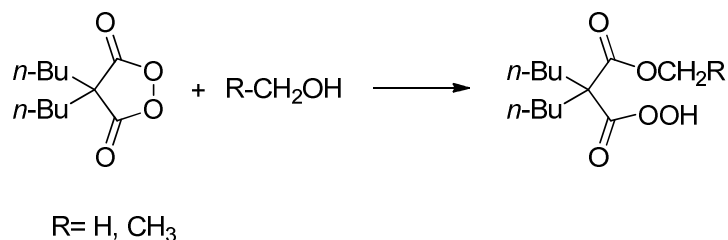


➤ Increase the rate of reaction and stereoselectivity of dihydroxylation using fluorinated alcohols



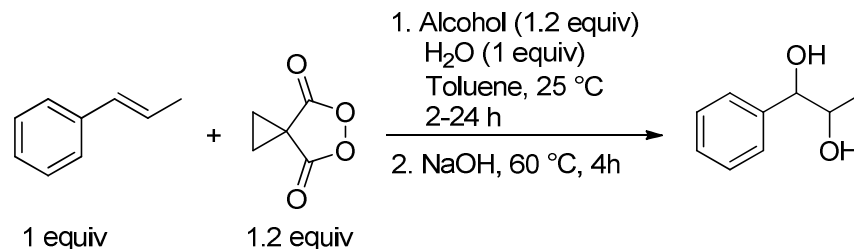
(◆) No alcohol; (■) trifluoroethanol (TFE); (▲) hexafluoroisopropanol (HFP); (x) perfluoro-*tert*-butyl alcohol (PFB).

➤ Why fluorinated alcohols?



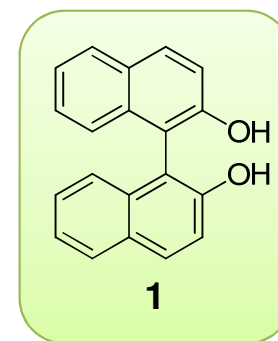
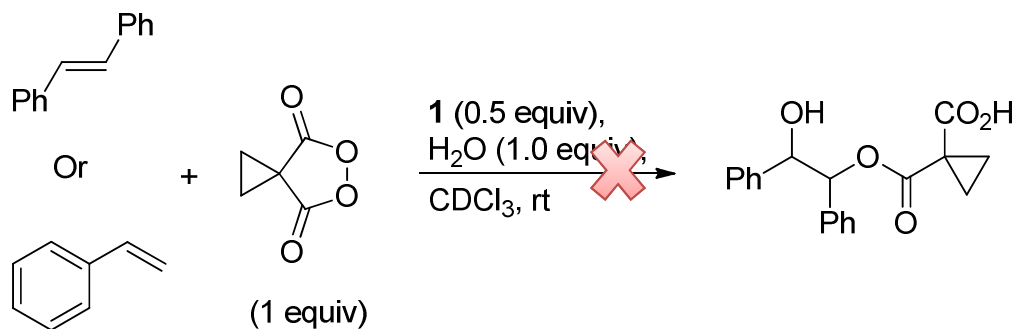
Fluorinated alcohols are less nucleophilic and stronger H-bond donor. Increasing the acidity of the alcohol TFE→HFP→PFB will increase the rate of reaction.

➤ Effect of fluorinated alcohols on stereoselectivity of dihydroxylation using malonoyl peroxide

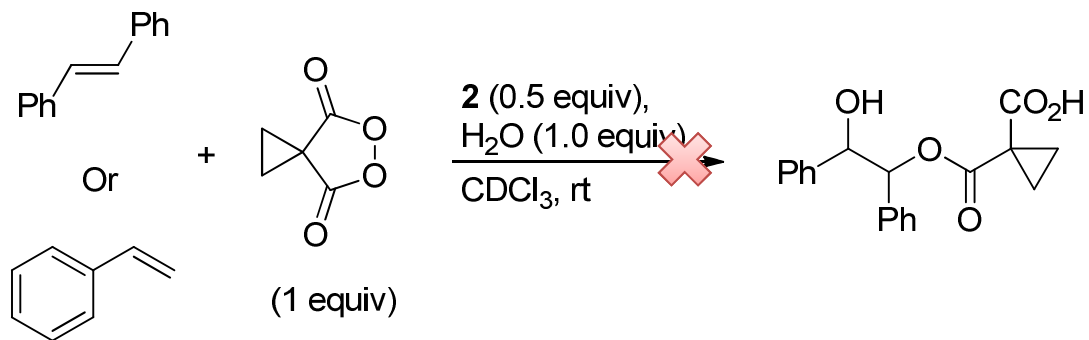


entry	alcohol	<i>syn/anti</i>	% yield
1	none	13:1	78
2	TFE	17:1	84
3	HFP	17:1	81
4	PFB	19:1	85

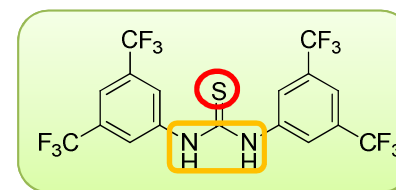
✓Is there any possibility for asymmetric induction using chiral H-bond donor catalysts ?



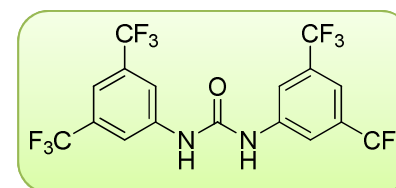
Picon, S.; Rawling, M.; Campbell, M.; Tomkinson, N. C. O. *Org. Lett.* **2012**, *14*, 6250.



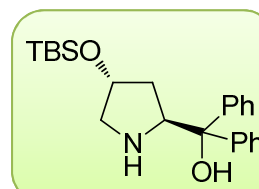
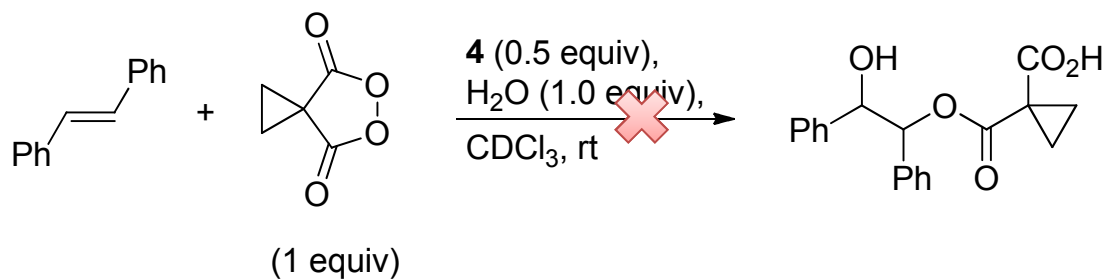
T1 was destroyed in presence and absence of water



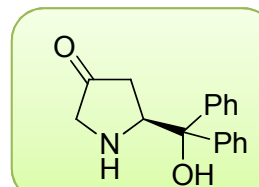
2



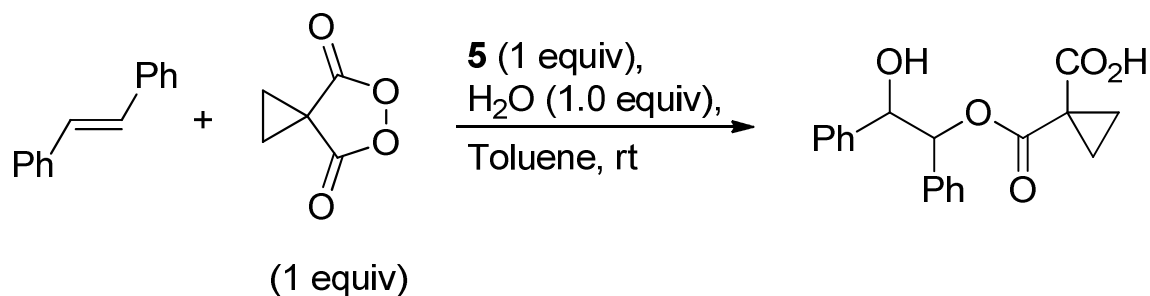
3



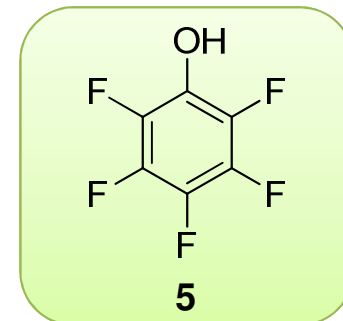
4



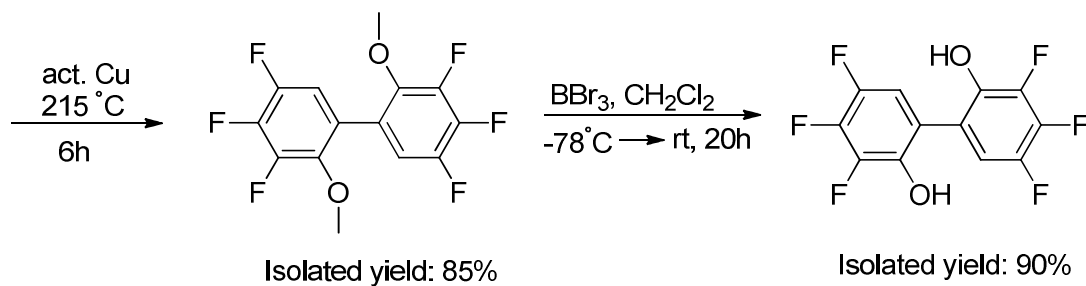
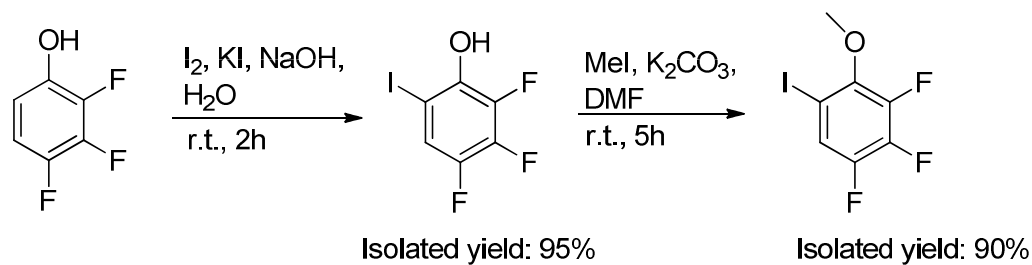
ESI (M+H)⁺: 268



Yield by NMR after 2h: **without catalyst:** 7%
with catalyst: 29%

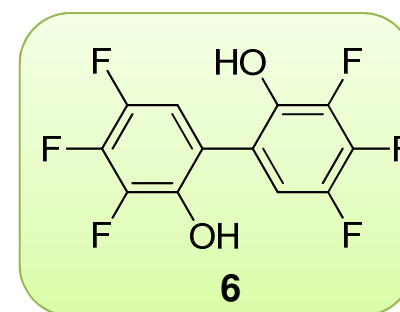
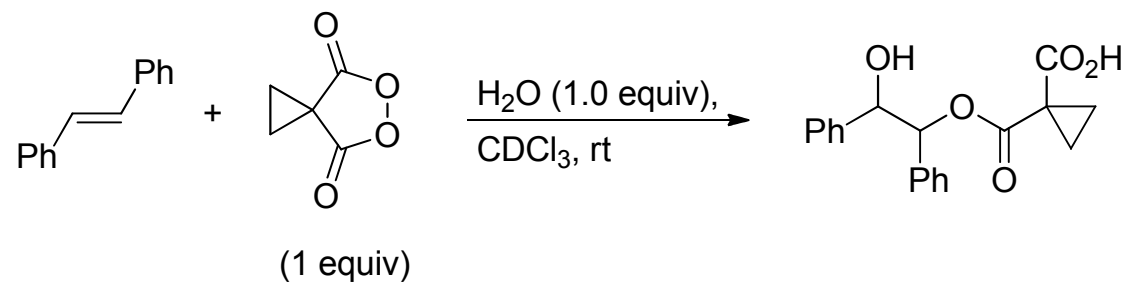
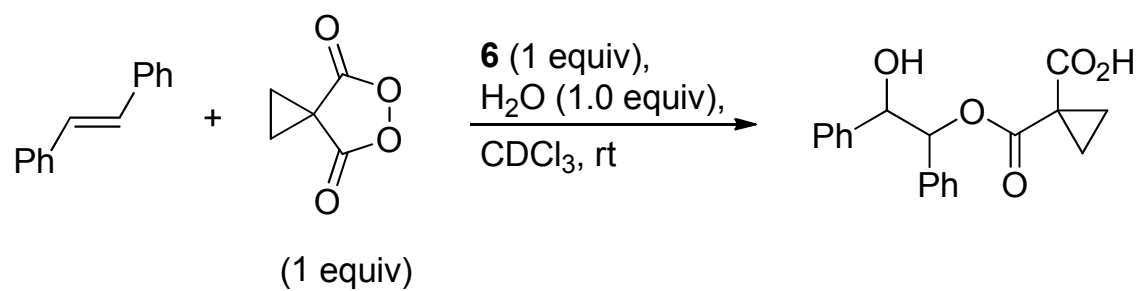


➤ Synthesis of fluorinated biphenols



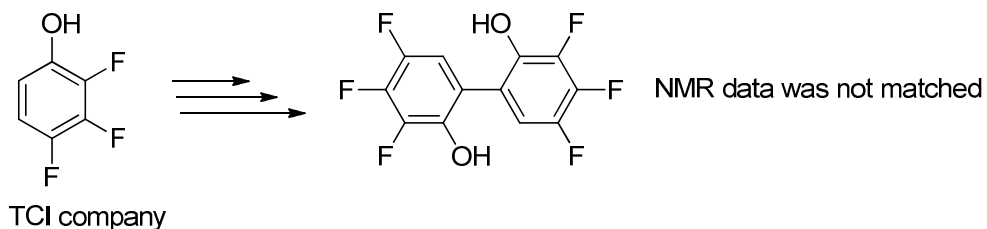
Francke, R.; Schnakenburg, G.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2010**, 2357.

Francke, R.; Schnakenburg, G.; Waldvogel, S. R. *Org. Lett.* **2010**, 12, 4288.

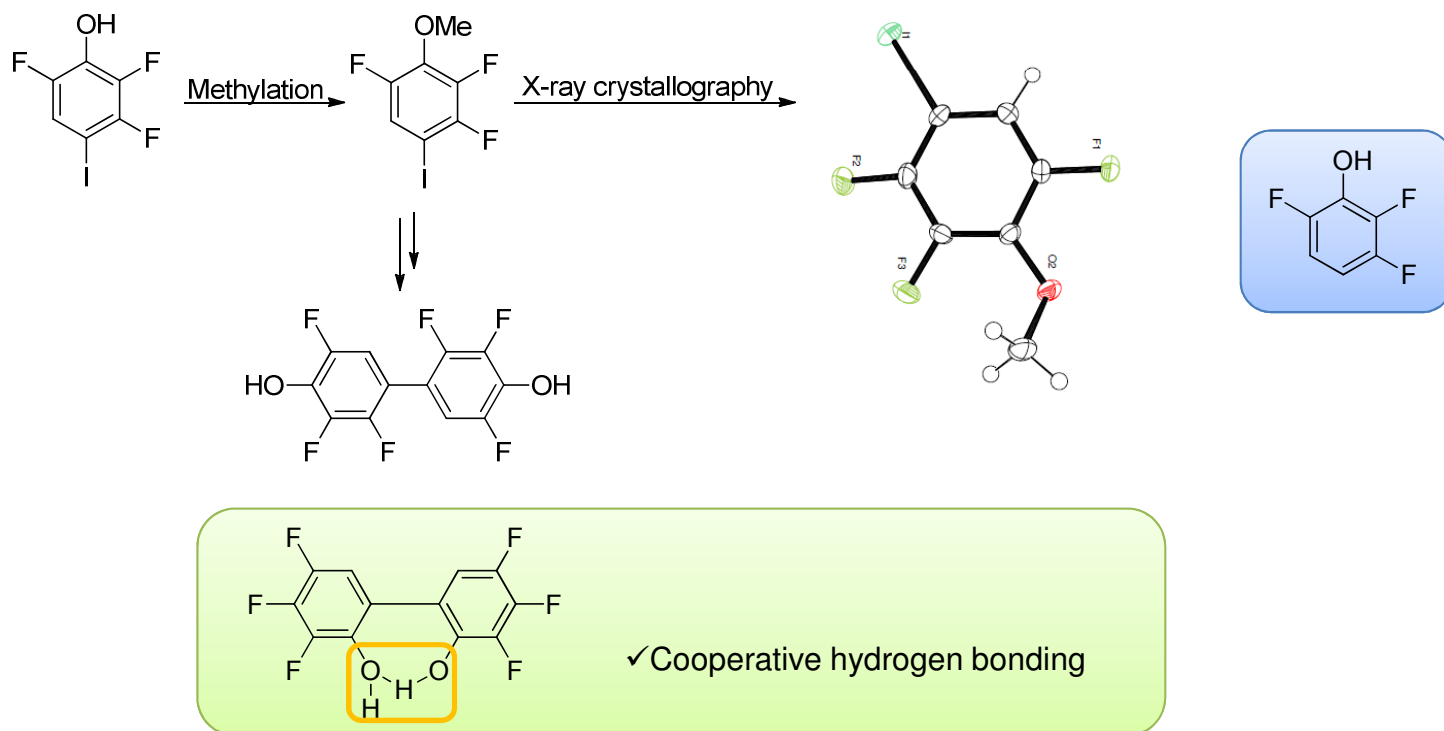


Catalyst	Time	Yield (%)
----	1h:45	32
1 equiv	1h:45	56
----	6h	69
1 equiv	6h	67

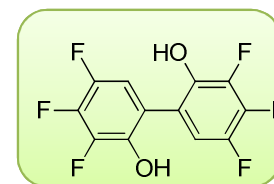
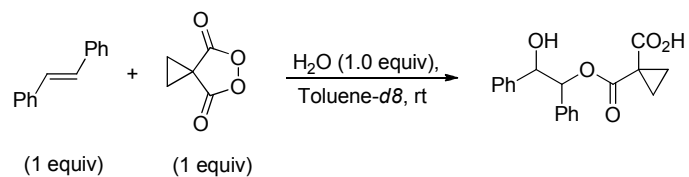
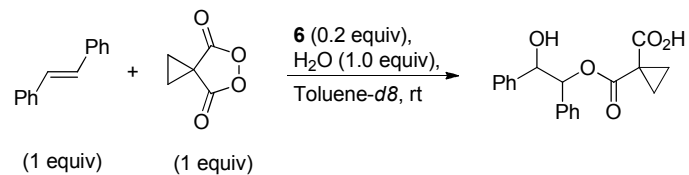
➤ Attempts to scale up the synthesis of fluorinated biphenols



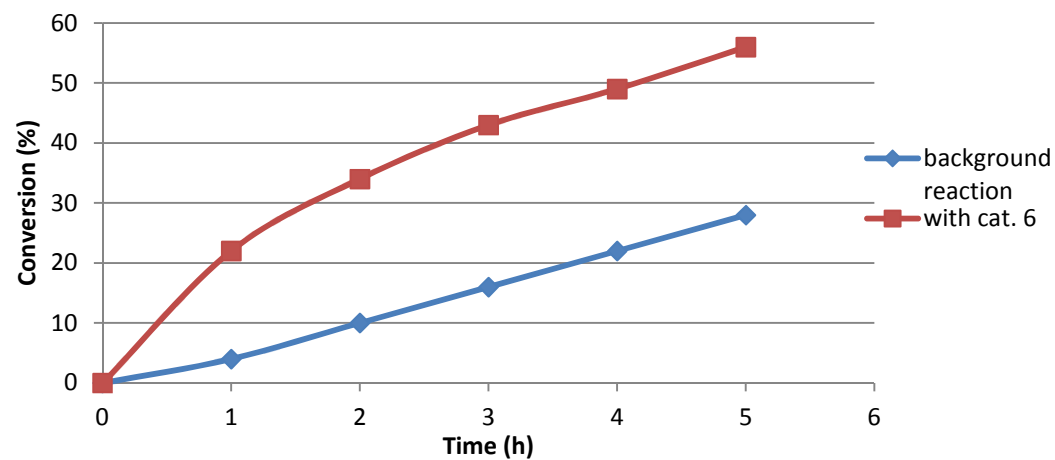
✓ TCI sent a wrong chemical two times, both were another isomer of fluorinated phenol and the structure was confirmed by X-ray crystallography



➤ Increase the rate of reaction using catalytic amount of fluorinated alcohols



6



Acknowledgement

- Special thanks to Professor Schreiner for his support, helpful discussions and suggestions
- Thanks to Jan-Philipp Berndt for the preparation of the catalyst
- The whole group for pleasant work environment

Thanks for your attention!