Crack Nuts – the Challenge of PTC Synthesis

Seminar talk presented by
Sascha Combe

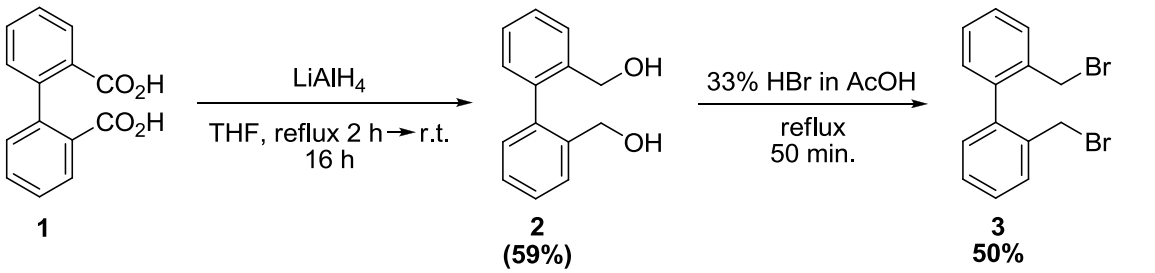
July 18th, 2014

Institute of Organic Chemistry
Justus-Liebig-University Giessen

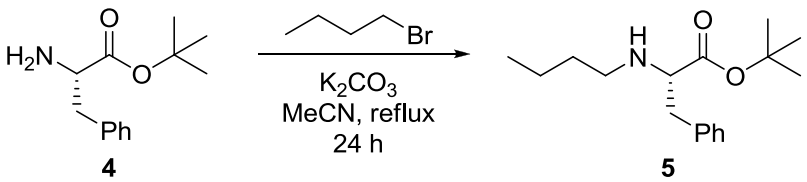
Outline

- Development of new catalyst
- Optimizations
- Catalyst analysis
- Journey of oxidation
- Further attempts of oxidation
- Summary and outlook

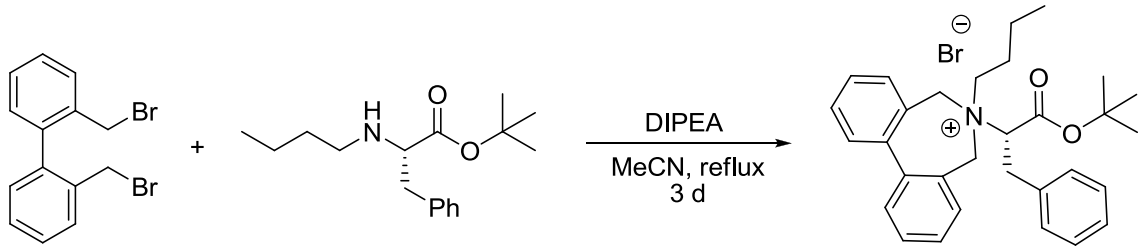
Diphenic acid related phase transfer catalyst



1 **2** **(59%)** **3** **50%**



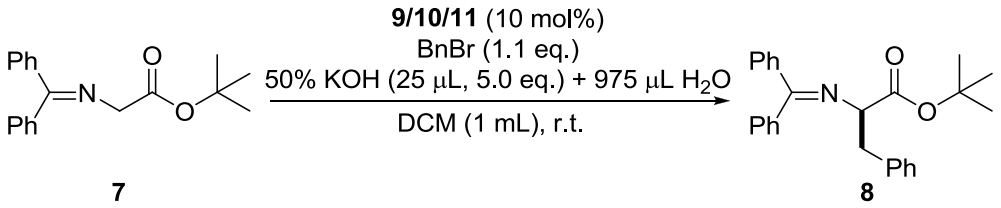
4 **5** **21%**



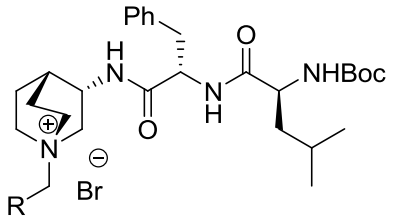
3 **5** **6**

Lygo, B.; Davison, C.; Evans, T.; Gilks, J. A. R.; Leonard, J.; Roy, C.-E. *Tetrahedron* **2011**, *67*, 10164–10170.

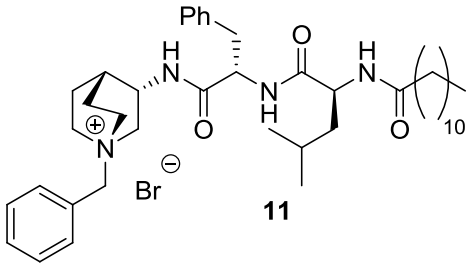
Screening



7 **8**



R = C_6H_5: **9**
R = $C_6H_4(3,5\text{-}CF_3)$: **10**

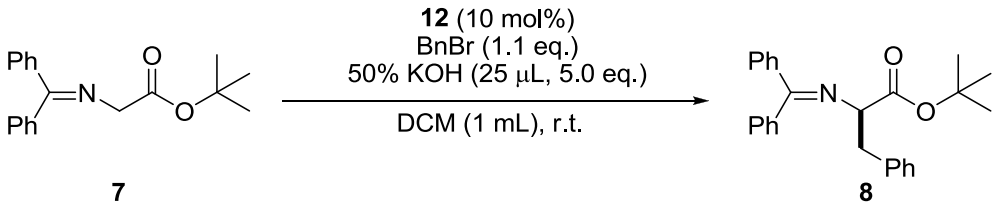


11

Time [h]	Conversion [%]	ee [%]	Catalyst
1	1	-17	a
4	3	-15	
48	14	-12	
1	1	7	b
4	2	8	
49	11	-2	
1	1	4	c
5	3	5	
28	9	1	
[1]5	8	2	c
28	22	-2	

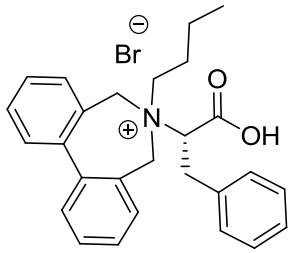
[1] Addition of 50 µL water.

Screening



7 8

Time [h]	Conversion [%]	ee [%]
1	1	-1
3	17	-2
28	65	-2

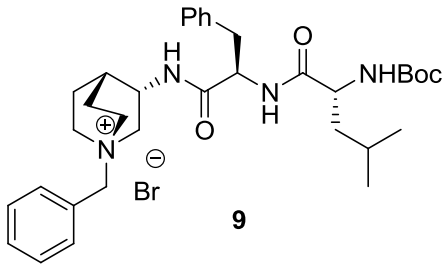


12

Optimization

1 4

Time [h]	Conversion [%]	ee [%]
[1]1	1	-17
4	3	-15
48	14	-12
[2]1	79	-5
4	99	4
49	99	4



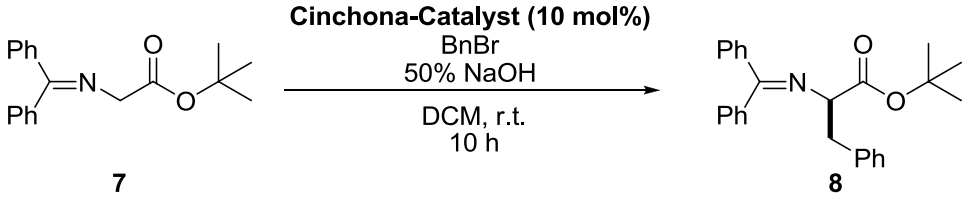
9

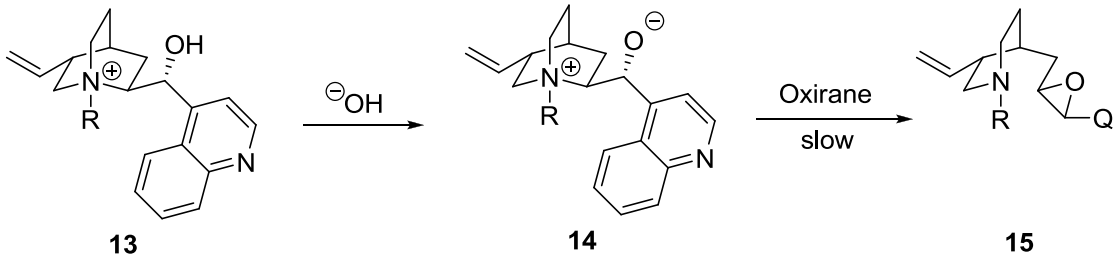
[1] 25 µL 50% KOH + 975 µL H_2O [2] KOH grinded

Problem: Solvation of OH^-

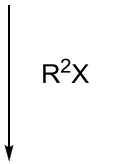
Hughes, D. L.; Dolling, U. H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745–4752.

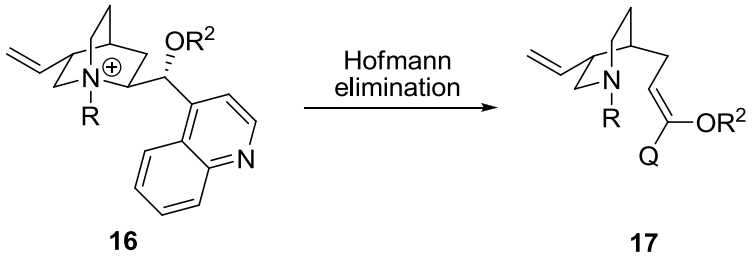
Problems





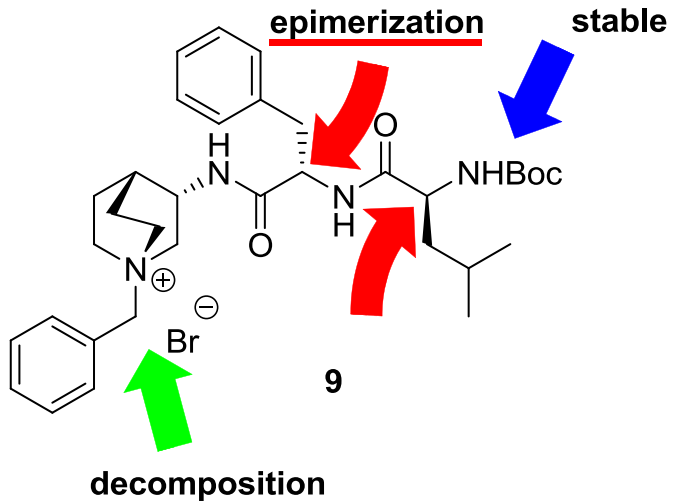
R, R^2 = -CH_2Ar





O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507.

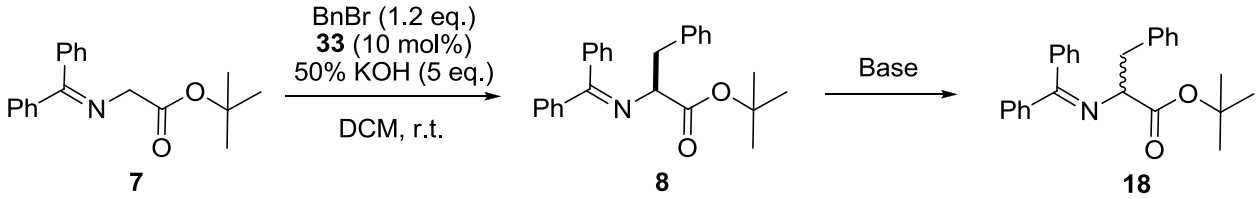
Catalyst



9

- Ee drops with time
  - Catalyst decomposes?
  - Catalyst-epimerization occurs?

Product

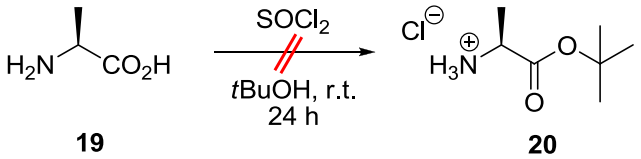


7 8 18

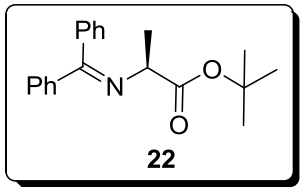
- Product racemizes (long reaction time)?
- double alkylation? (1.2 eq. BnBr – no)

Siebum, A. H. G.; Woo, W. S.; Lugtenburg, J. *Eur. J. Org. Chem.* **2003**, *2003*, 4664–4678.

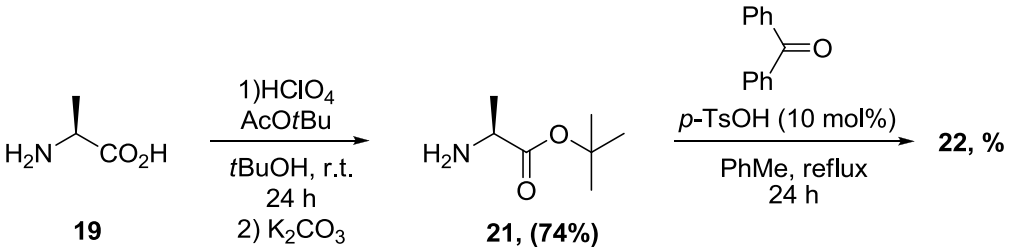
Substrate



19 20

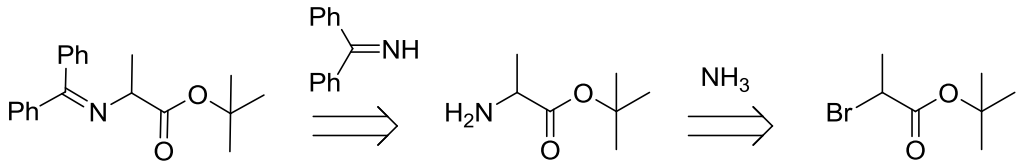


22



19 21, (74%) 22, %

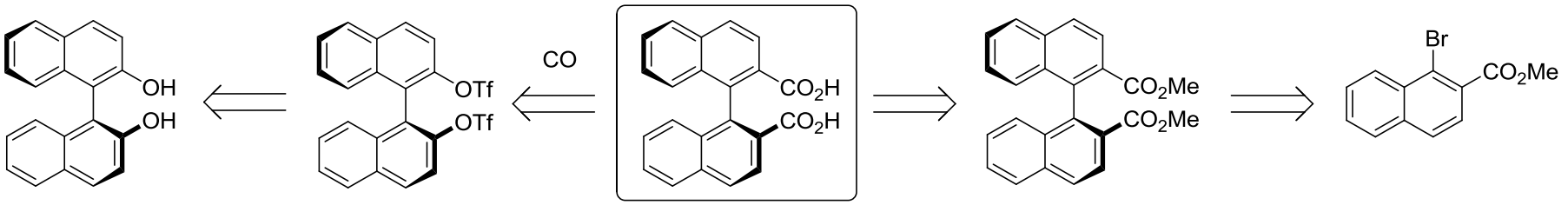
Alternative route



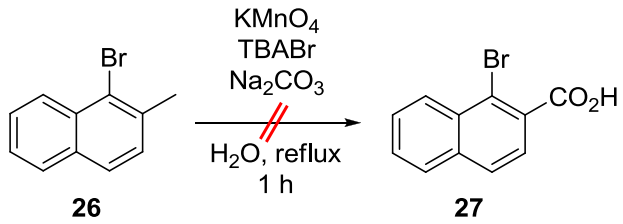
23 24 25

Virlouvet, M.; Goesmann, H.; Feldmann, C.; Podlech, J. *Monatsh. Chem.* **2010**, *141*, 177; Antoni, G.; Långström, B. *J. Label Compd. Radiopharm.* **1987**, *24*, 125; Siebum, A. H. G.; Woo, W. S.; Lugtenburg, J. *Eur. J. Org. Chem.* **2003**, *2003*, 4664–4678.

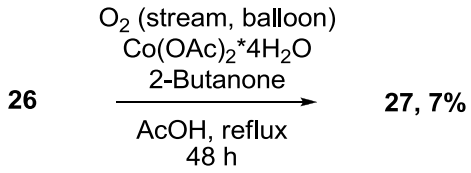
Synthesis of Maruoka related catalysts



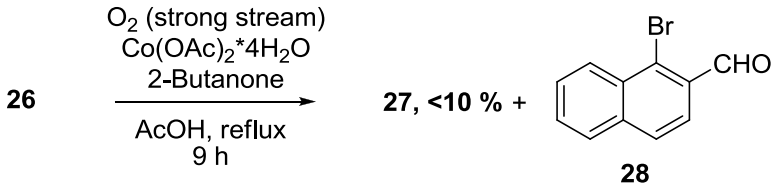
Important intermediate



26 **27**



26 **27, 7%**



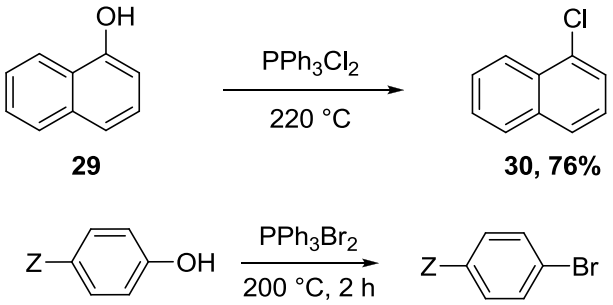
26 **27, <10 % +** **28**

Seki, M.; Yamada, S.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **31**, *2000*, 1677; Hellwinkel, D.; Bohnet, S. *Chem. Ber.* **1987**, *120*, 1151; Ohta, T.; Ito, M.; Inagaki, K.; Takaya, H. *Tetrahedron Lett.* **1993**, *34*, 1615.

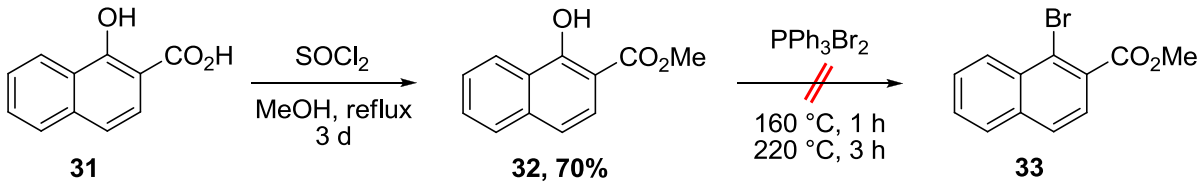
Synthesis of important Intermediates

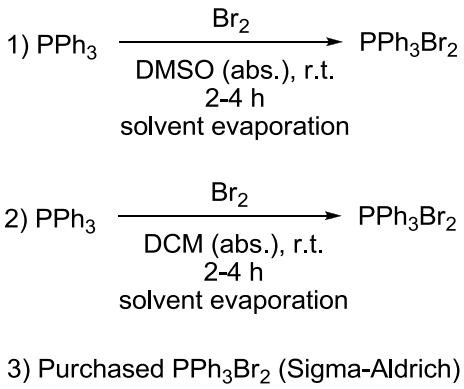
Can 

help?



Z = H, 92%; Cl, 90%, NO_2 60%; CH_3O, 59%

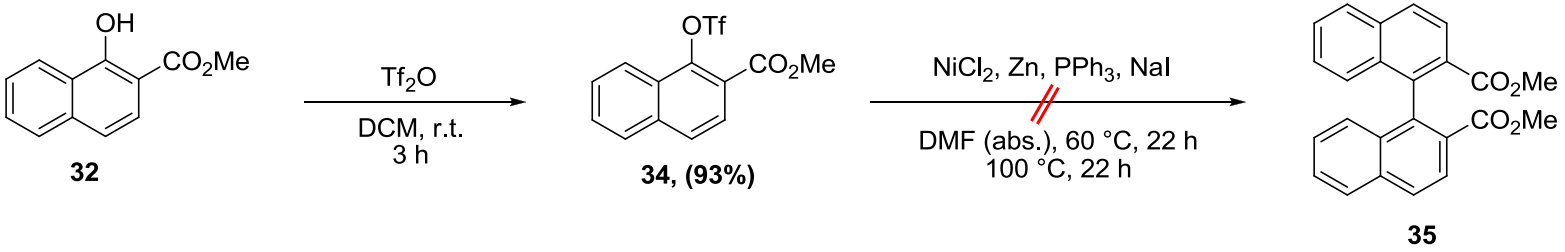


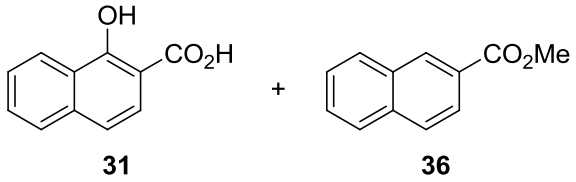


3) Purchased PPh_3Br_2 (Sigma-Aldrich)

Hoffmann, H.; Wippel, H. G.; Horner, L.; Michael, D. *Chem. Ber.* **1962**, *95*, 523; Cossío, F. P.; Ganboa, I.; Palomo, C. *Tetrahedron Lett.* **1985**, *26*, 3041; Kabachnik, M. I.; Lobanov, D. I.; Matveeva, A. G.; Kovsheva, O. E.; Terekhova, M. I.; Petrov, E. S.; Petrovskii, P. V.; Matrosov, E. I. *Phosphorus, Sulfur, and Silicon and the Related Elements* **1991**, *62*, 243; Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964.

Synthesis of important Intermediates

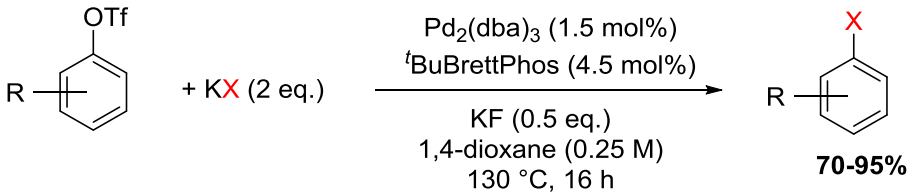


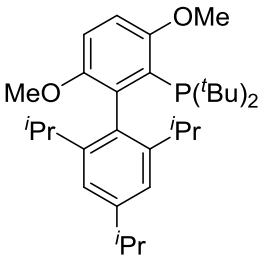


Problem: Group in ortho position

Yamashita, J.; Inoue, Y.; Kondo, T.; Hashimoto, H. *Chem. Lett.* **1986**, *15*, 407; Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176.

Alternative **Buchwald?**



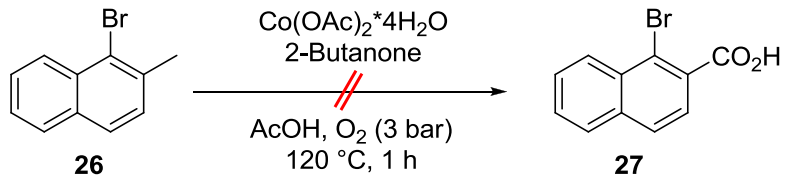


^{t}BuBrettPhos

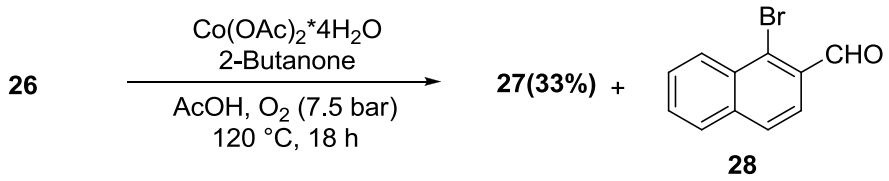
- Hard to synthesize (glove box)
- Sensitive to air

Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576–6583; Pan, J.; Wang, X.; Zhang, Y.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 4974–4976.

How to achieve oxidation?

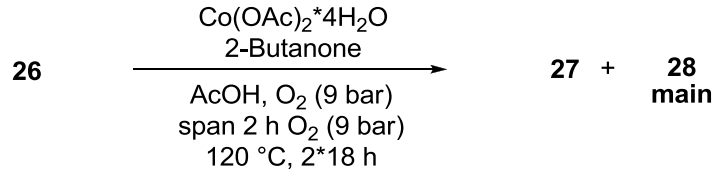


26 **27**



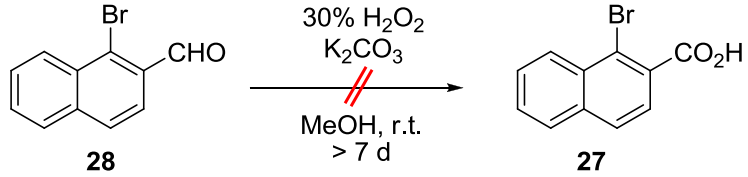
26 **27(33%)** + **28**

Oxygen comsumed?



26 **27** + **28 main**

- Recrystallization failed
- Transformation into Methylester not fruitful (Aldehyde nearly same R_f)

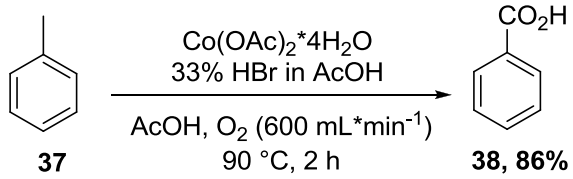


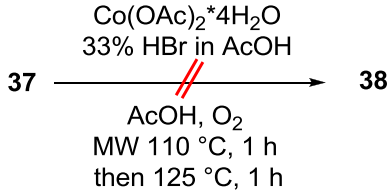
28 **27**

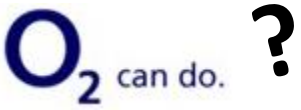
Check $KMnO_4$

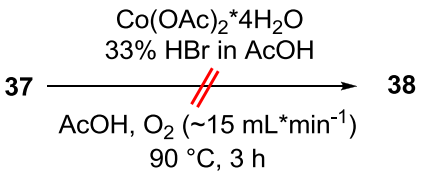
Seki, M.; Yamada, S.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **31**, *2000*, 1677; Ballini, R.; Petrini, M. *Synthesis* **2002**, *1986*, 1024.

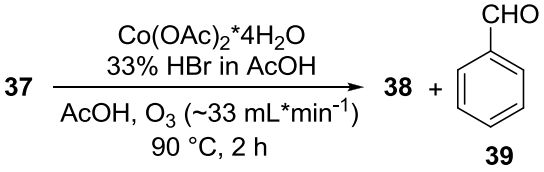
How to achieve oxidation?

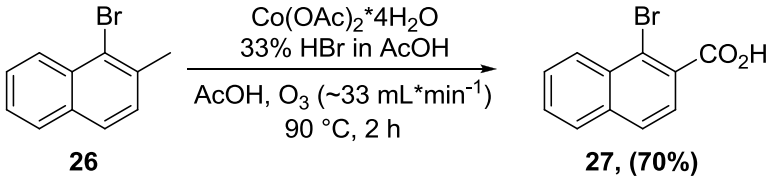






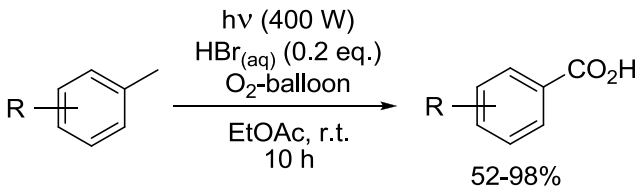


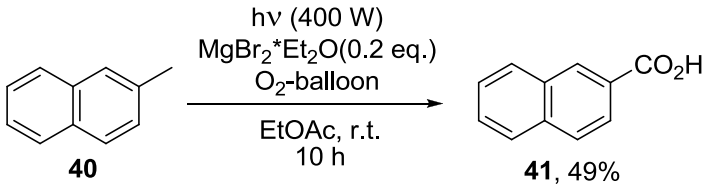


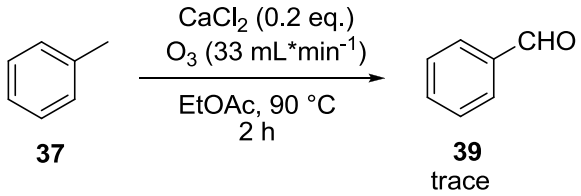


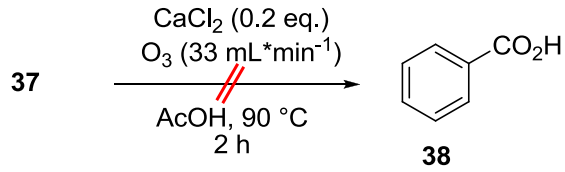
Hay, A. S.; Blanchard, H. S. *Can. J. Chem.* **1965**, *43*, 1306; Mamchur, A. V.; Galstyan, G. A. *Russ. J. Org. Chem.* **2004**, *40*, 1779.

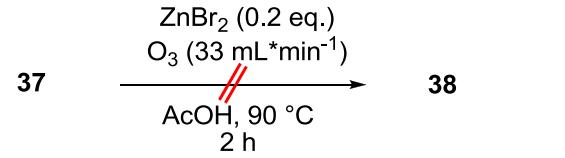
Further attempts in oxidation

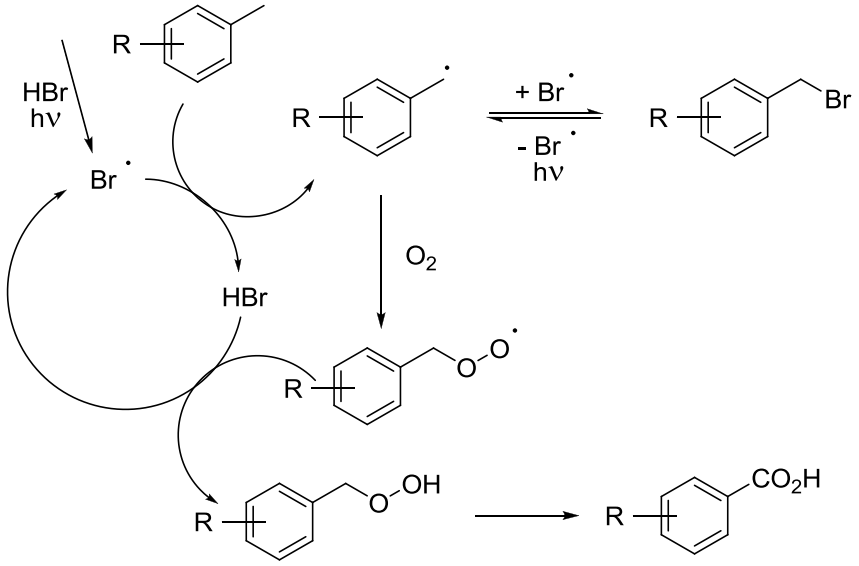








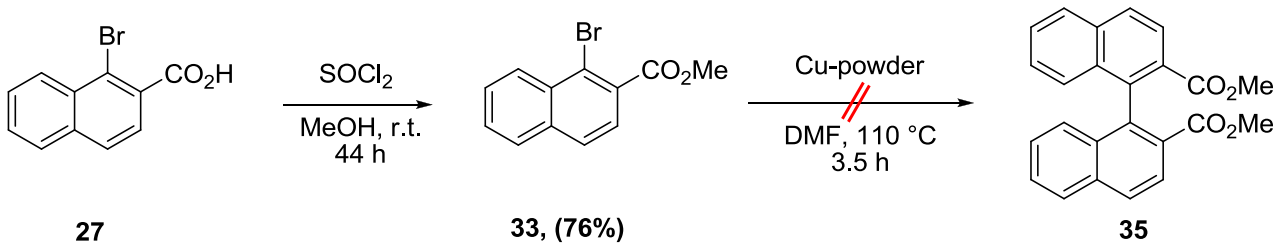




- Chlorination faster than bromination
- Reaction became green ⟶ Cl_2

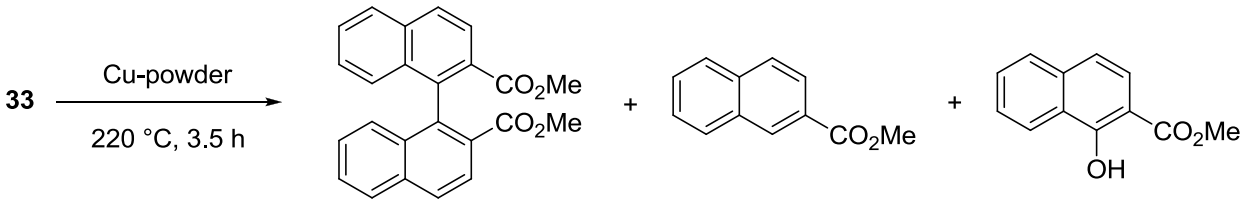
Hirashima, S.; Itoh, A. *Synthesis* **2006**, *2006*, 1757; Hirashima, S.; Itoh, A. *Photochem. Photobiol. Sci.* **2007**, *6*, 521.

Ullmann coupling

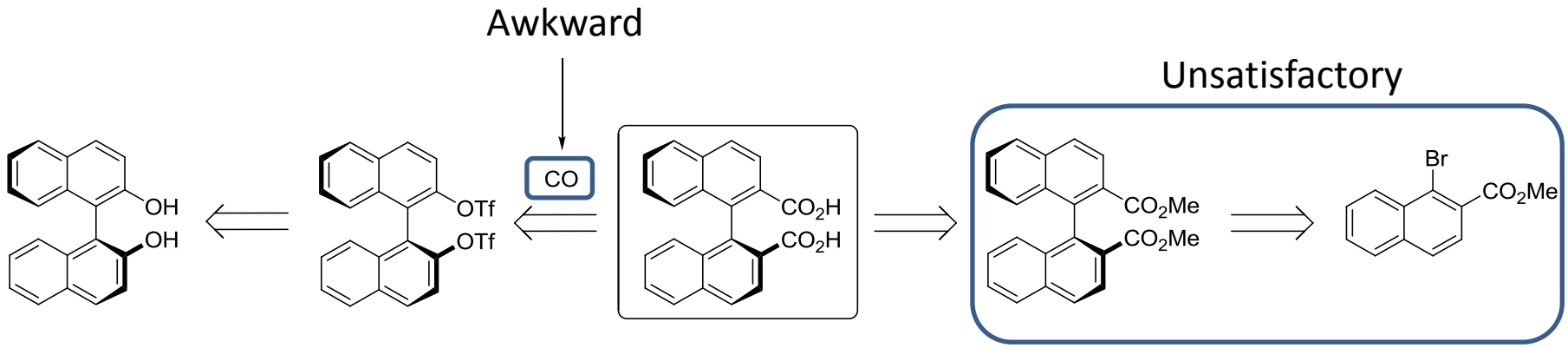


27 **33, (76%)** **35**

DMF: 0.5 ppm H_2O

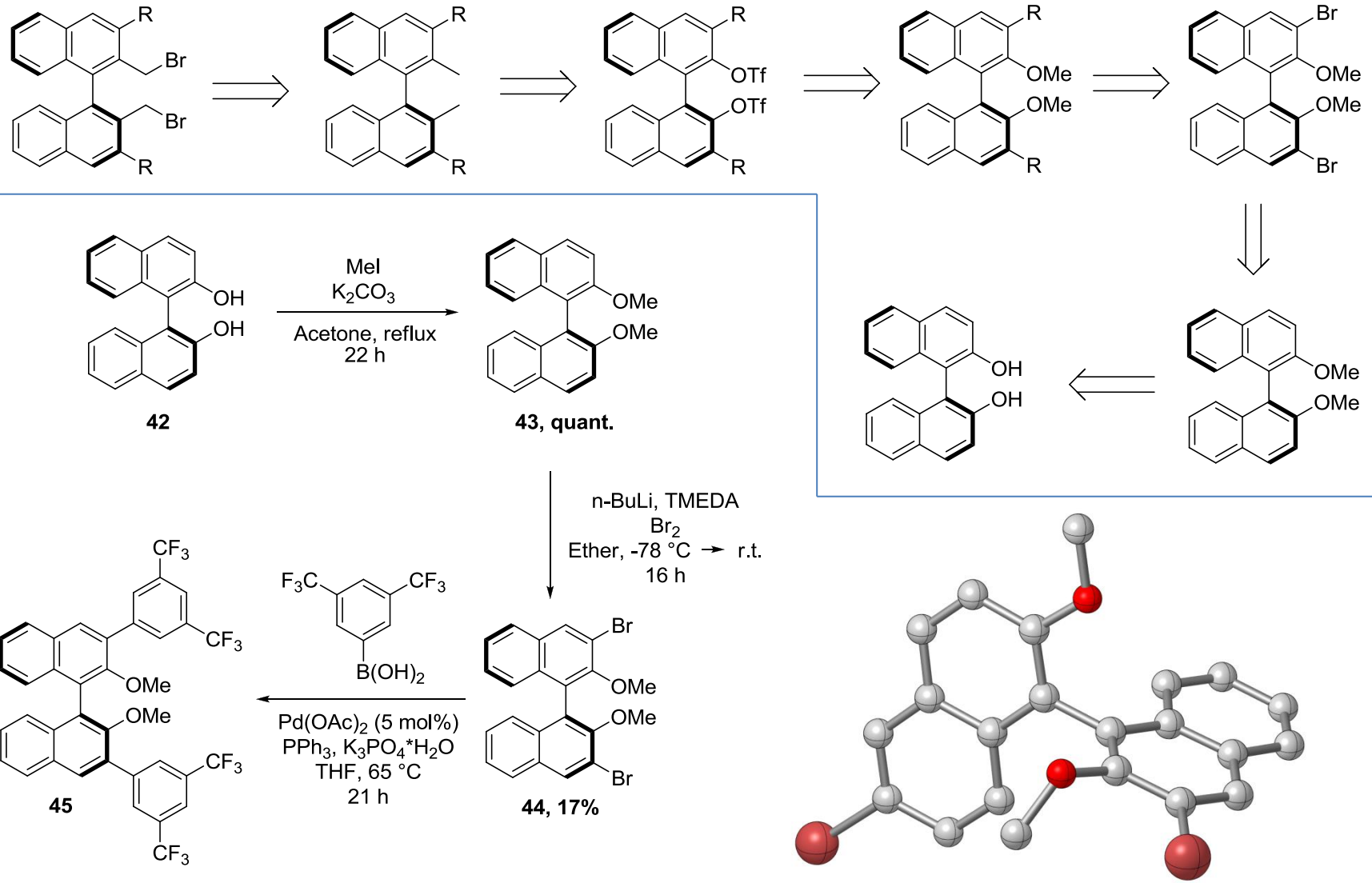


35, 26% **36, 30%** **31, 7%**



Seki, M.; Yamada, S.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **31**, *2000*, 1677.

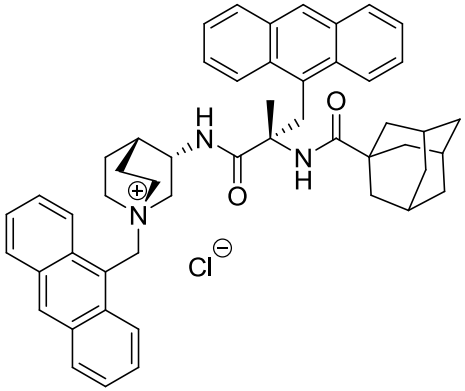
Future - switching strategy



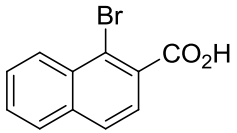
Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.

- Conversion was improved in the peptide catalysis: s-l instead of l-l
  BUT: ee decreased

- Peptide related PT catalysts seems to epimerize -> artificial amino acids
  - t-Butyl group seems to play import role (increased ee)



- Development of new oxidation method with ozone
  - Important intermediate could be synthesized with good yield*
    - Higher surface for better ozone absorption
- Starting with BINOL will be faster and more effective



27, (70%)

(*)Raw yield: NMR almost clean

… Prof. Schreiner

… Abolfazl Hosseini, Honman Yau

… Cesare Savarino

… PRS group

… Dr. Röcker, Anika Bernhardt

… Jonathan Becker

Thank you for your attention