Chiral Brønsted Acid-catalyzed Enantioselective House-Meinwald Rearrangement

Group Seminar

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25.02.2022

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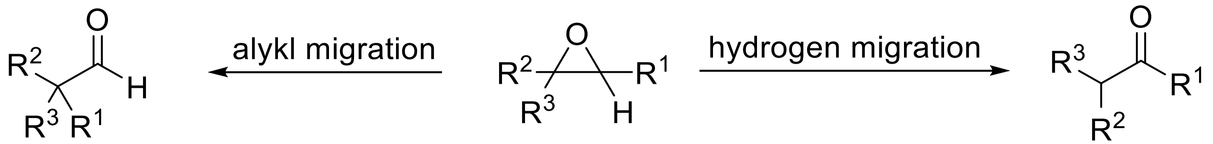
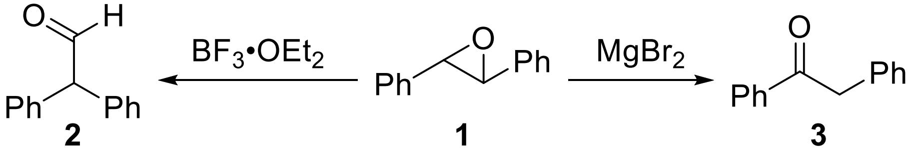
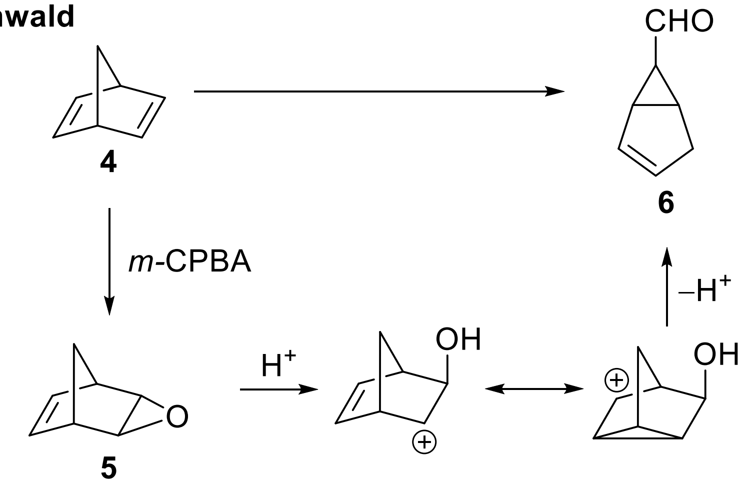
The House-Meinwald Rearrangement



House

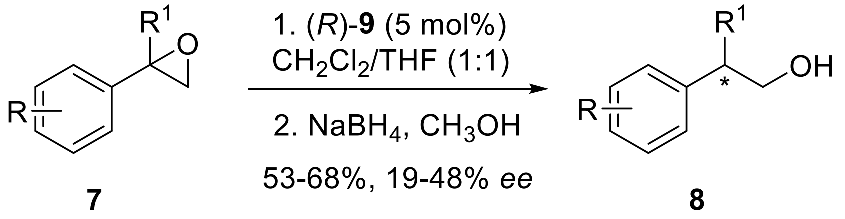


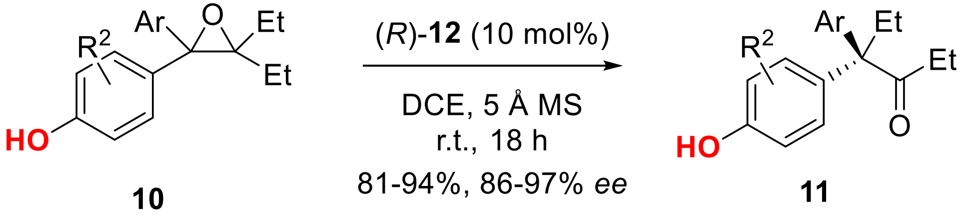
Meinwald

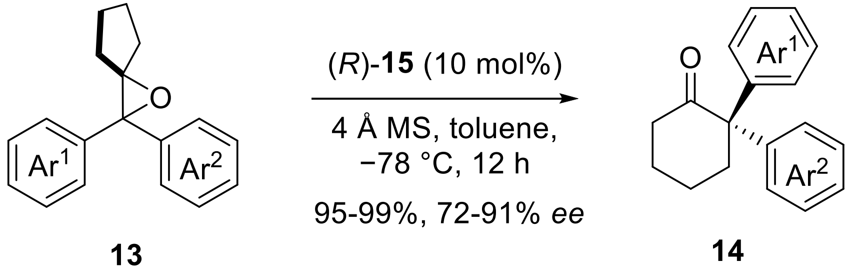


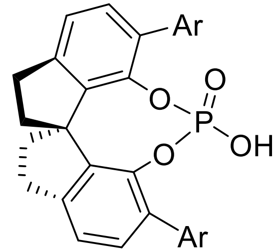
H. O. House, *J. Am. Chem. Soc.* 1955, *77*, 3070; J. Meinwald, S. S. Labana, M. S. Chadha, *J. Am. Chem. Soc*. 1963, *85*, 582.

Current State of the Art

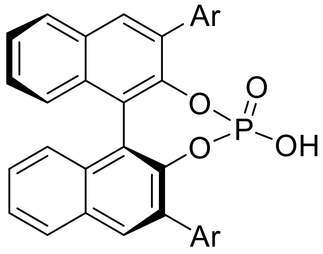




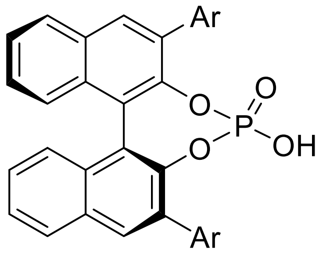




(*R*)-**9**
Ar = 2,4,6-*i*PrC$_6$H$_2$



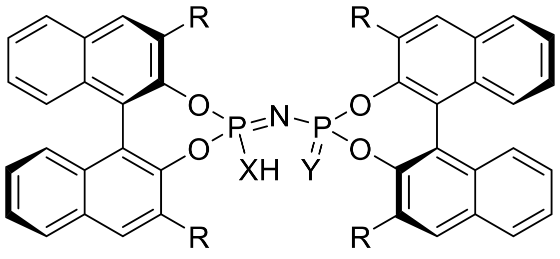
(*R*)-**12**
Ar = 1-naphthyl



(*R*)-**15**
Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$

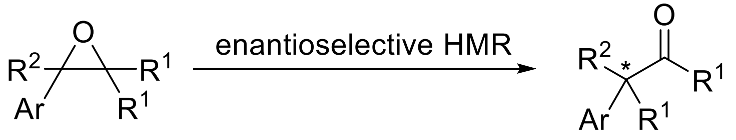
J. Sun *et al. J. Am. Chem. Soc.* **2019**, 141, 13783.; M. Zhuang, H. Du, *Org. Biomol. Chem.* **2013**, *11*, 1460.; H. Wu, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2019**, *141*, 11372.

Goal of the Project

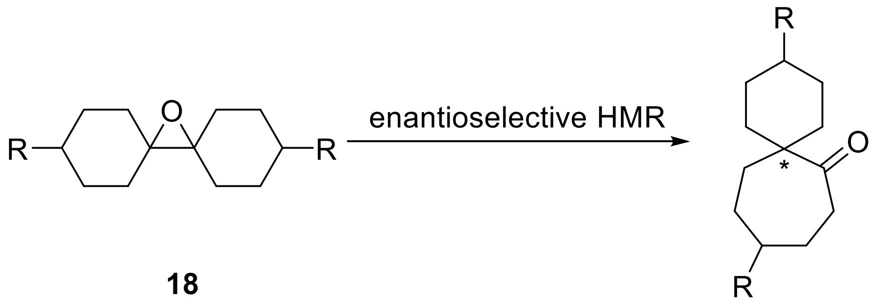


X = Y = O : IDP
X=NTf, Y = O : iIDP
X = Y = NTf : IDPi

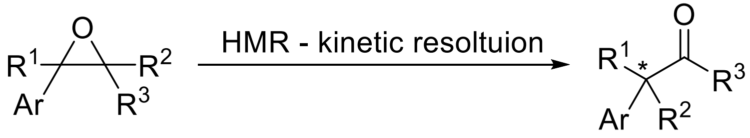
Influence of Dispersion Energy Donors



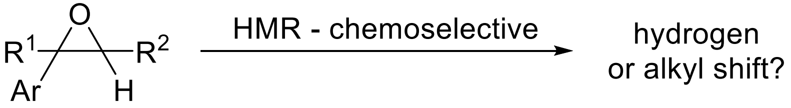
16 **17**



18 **19**



20 **21**



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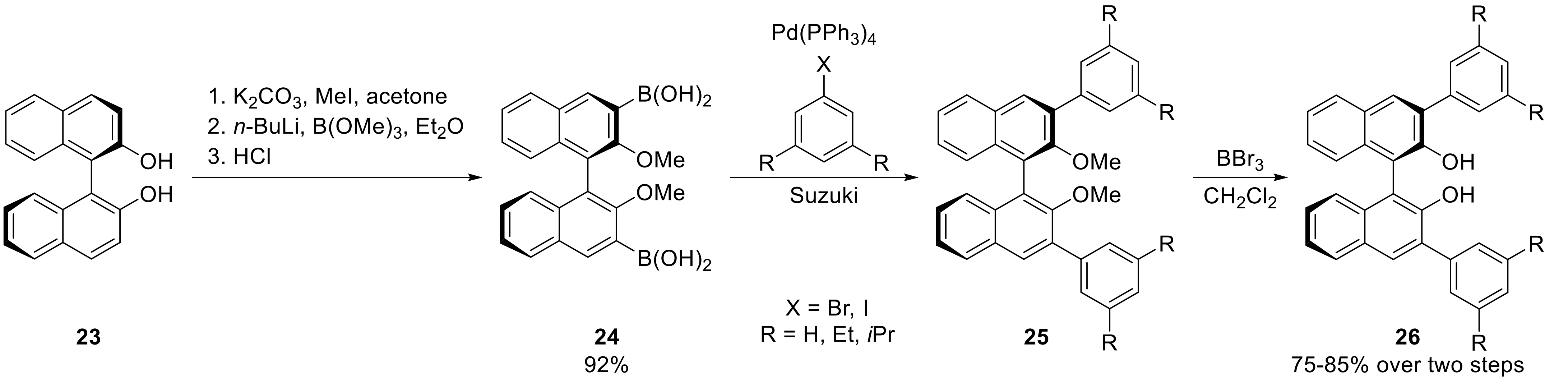
B. List *et al. J. Am. Chem. Soc.* **2021**, 143, 14835.

Synthesis of the Catalysts

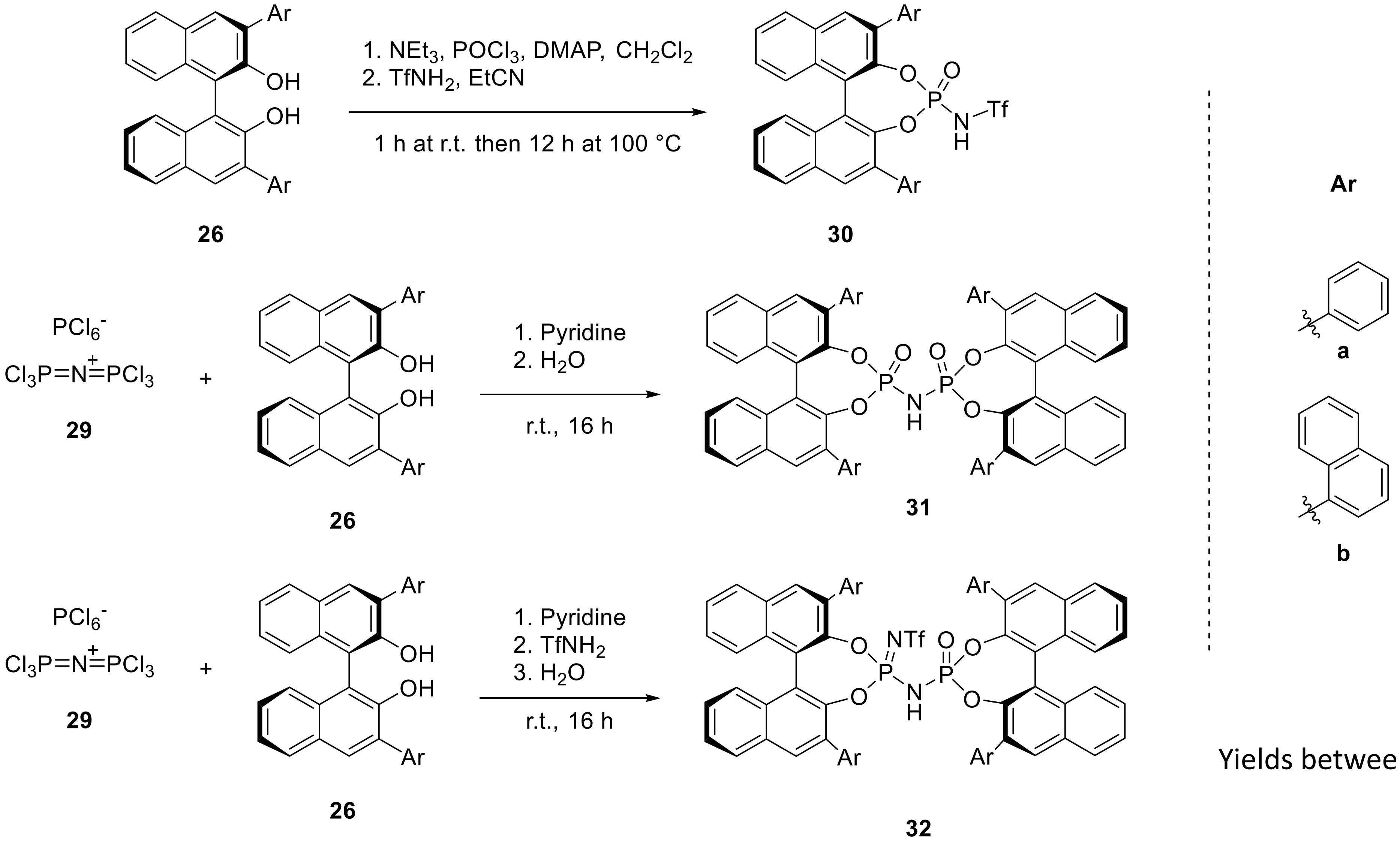


$$\underset{\mathbf{27}}{PCl_5} + \underset{\mathbf{28}}{NH_4Cl} \xrightarrow[\text{130 °C, 5.5 h}]{\text{Nitrobenzene}} \underset{\mathbf{29}}{PCl_6^- \; Cl_3P{=}\overset{+}{N}{=}PCl_3}$$

29
HCPP

B. List *et al. J. Am. Chem. Soc.* **2021**, 143, 14835.

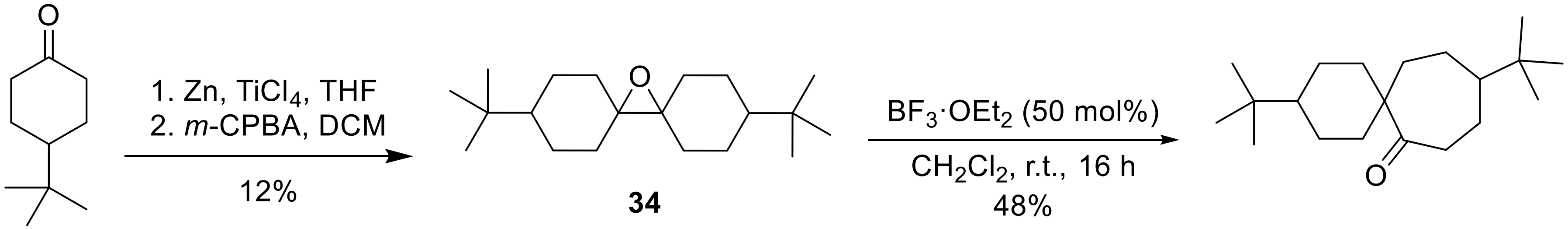
Synthesis of the Catalysts



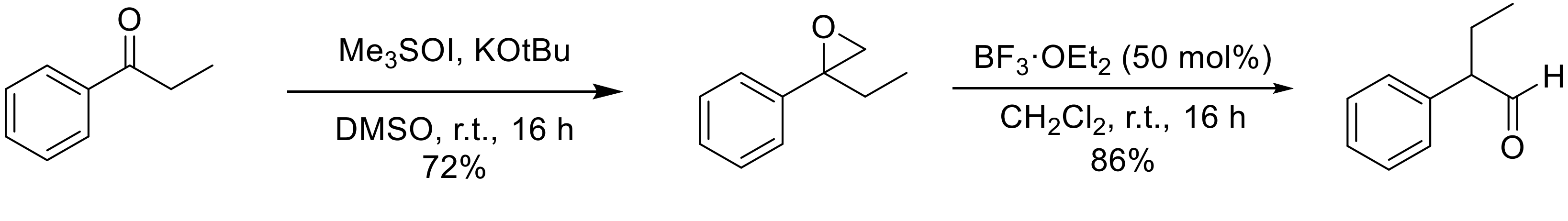
Yields between 72-82%

B. List *et al. J. Am. Chem. Soc.* 2021, 143, 14835.

Synthesis of Substrates and Model Reactions



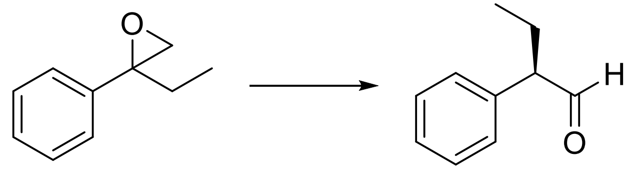
33 **34** ***rac*-35**



36 **37** ***rac*-38**

M. Zhuang, H. Du, *Org. Biomol. Chem.* 2013, *11*, 1460.

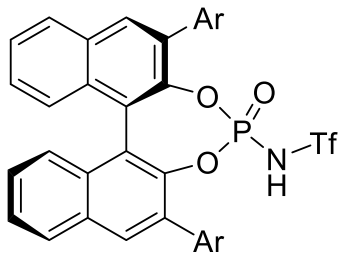
First Test Reactions



37 38

Entry	Solvent	Catalyst (mol%)	Temperature (°C)	Time (h)	*ee* (%)
1	CH_2Cl_2/THF (1:1)	**30b** (10)	r.t.	3	1
2	CH_2Cl_2/THF (1:1)	**30b** (10)	−78	8	1
3	CH_2Cl_2/THF (1:1)	**31b** (5)	−78 to −40	10	**16**
4[a]	PhMe	**31a** (5)	−30	50	2
5	CH_2Cl_2/THF (1:1)	**31b** (5)	−30	50	4

All reactions were carried out on a 0.2 mmol scale and 0.5 M concentrations.
[a]4 Å MS were added to the reaction mixture.



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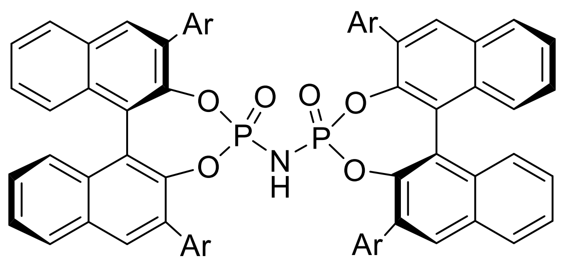

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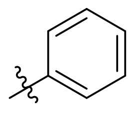
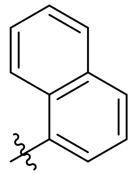
Ar



a



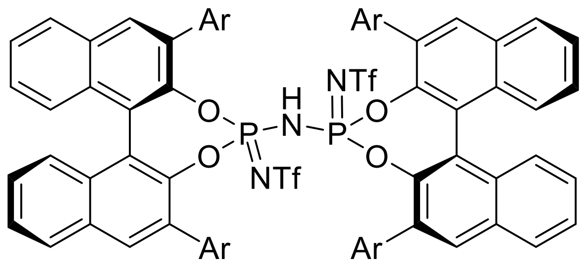
b

M. Zhuang, H. Du, *Org. Biomol. Chem.* **2013**, *11*, 1460.

Summary

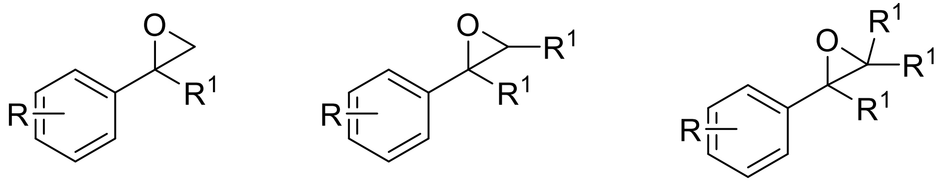
- Synthesis of multiple BINOL derivatives and different catalysts
- Synthesis of the substrates
- Synthesis of the standards through BF_3-catalyzed rearrangement
- First promising test reaction

Outlooks



IDPi

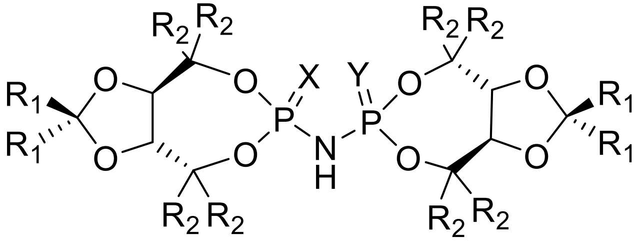
- Application of IDP and iIDP catalysts in the rearrangement
- Synthesis of IDPi
  - Does the yield/*ee* depend on catalyst‘s acidity



R = EDG
R^1 = alkyl

- Synthesis of different substrates
- Scope of the reaction and optimization of reaction conditions (DoE)
- Investigation of the influence of dispersion energy donors (DED)
- Synthesis and application of a new TADDOL-based catalyst

TADDOL-based IDP?



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R_1 = Me
R_2 = EWG and DED
X = Y = O
X = O and Y = NTf
X = Y = NTf

- Cheaper alternative to BINOL
- IDP analogues
- Tuning of acidity through R groups and influence of DED
- Confinement?
- Flexibility?

B. List *et al. J. Am. Chem. Soc.* **2021**, *143*, 14835.; D. Seebach *et al.*, *Helv. Chim. Acta* **2012**, *95*, 1303.;
A. C. O'Donoghue *et al.* , *Chem. Eur. J.* **2011**, *17*, 8524.

Acknowledgements

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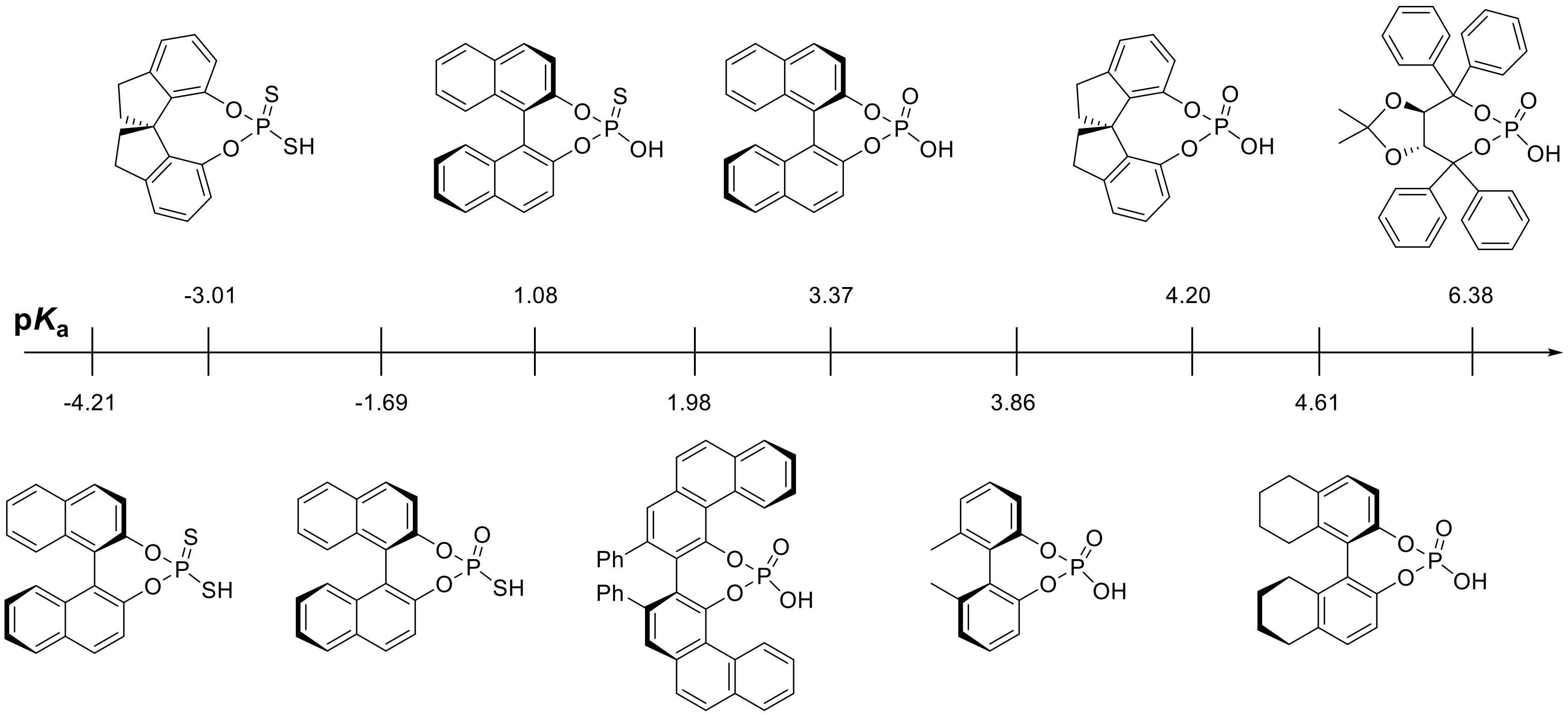
- Friedhelm
- Labs B204 and B205
- PRS Group

Acidity Scale



Theoretical study on the acidities of some chiral phosphoric acids in DMSO.

C. Yang, X.-S. Xue, J.-L. Jin, X. Li, J.-P. Cheng, *J. Org. Chem.* **2013**, *78*, 7076.