

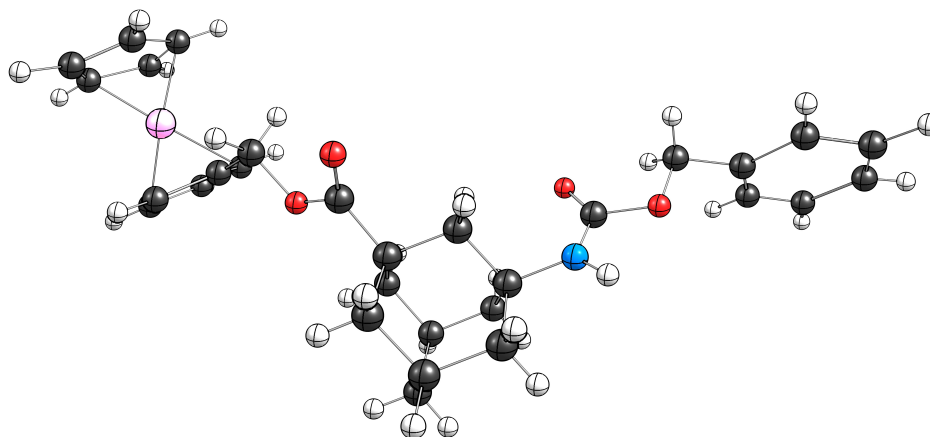
Synthesestudien für die Ortsselektive Hydroborierung

Bachelor Thesis Verteidigung

Victoria Öhler

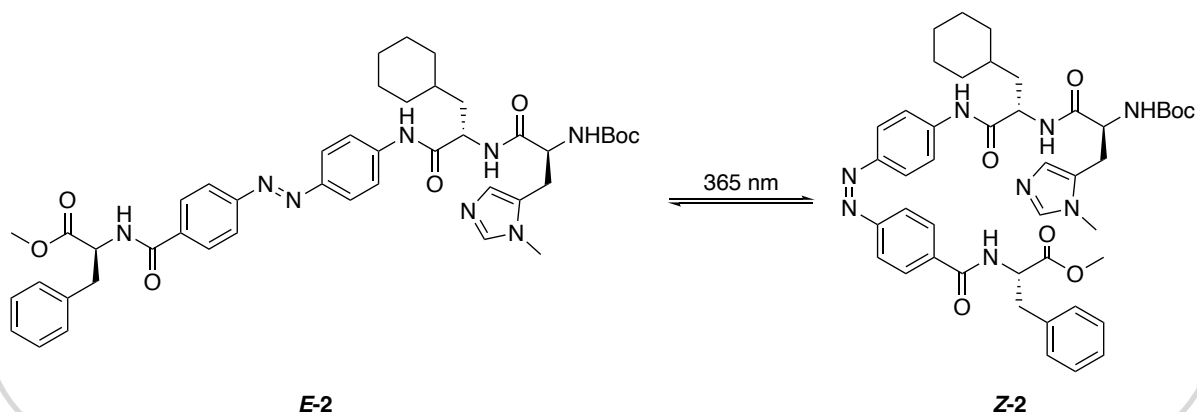
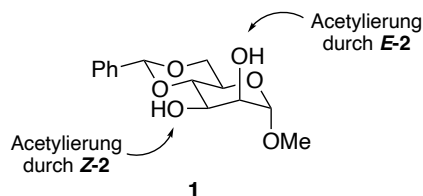
28.05.2021

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



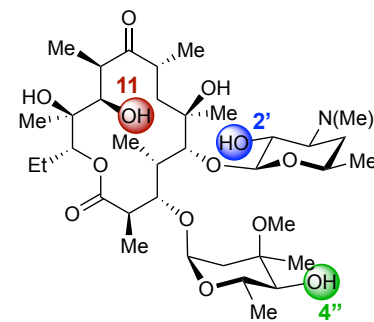


- Selektive Funktionalisierung von Naturstoffen
- Totalsynthese
- Umgehung der kinetischen Präferenz

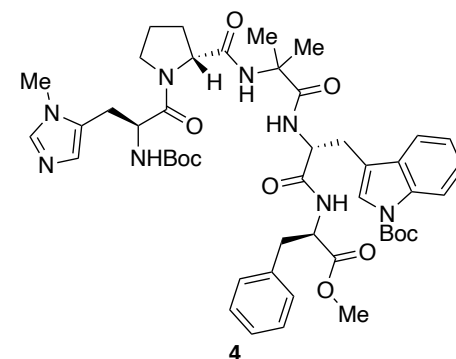


Photokatalytisch kontrolliert (Schreiner *et al.*)

Inhärente Reaktivität
2'-OH > 4''-OH > 11-OH



Erythromycin A

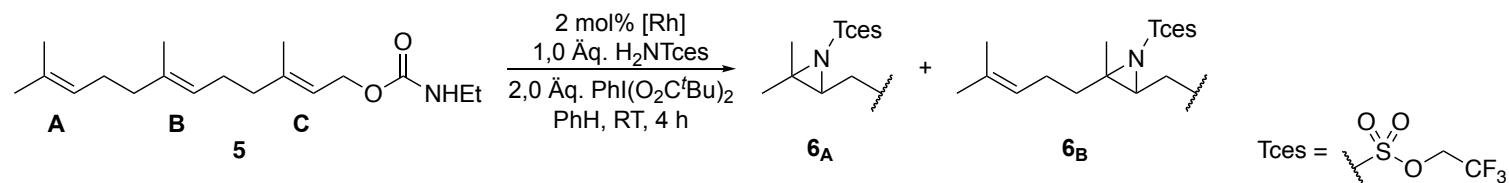


Acetylierung von 11-OH

Katalysator-kontrolliert (Lewis und Miller)

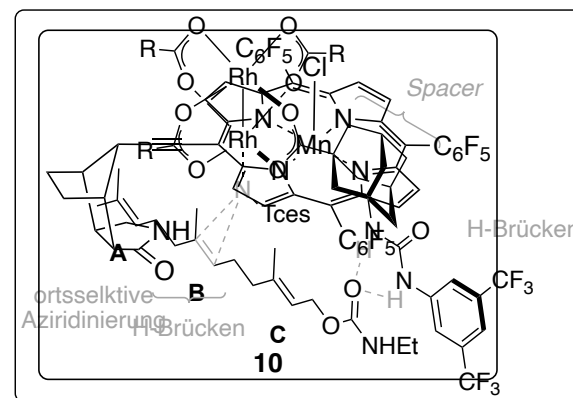
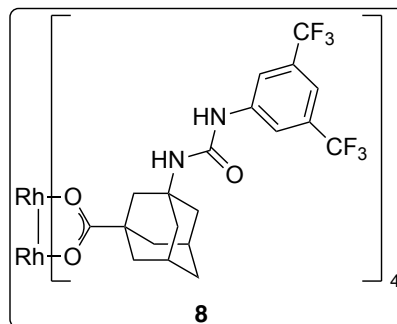
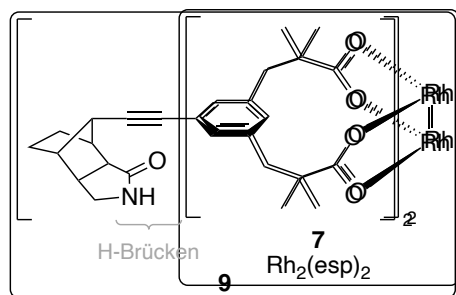


- Konzept der definierten Abstände:



[Rh]	6 _A : 6 _B	Ausbeute (6 _A + 6 _B) /%	Umsatz /%
Rh ₂ (esp) ₂ ^a	2,0:1,0	29	81
8 ^b	1,0:5,0	23	73

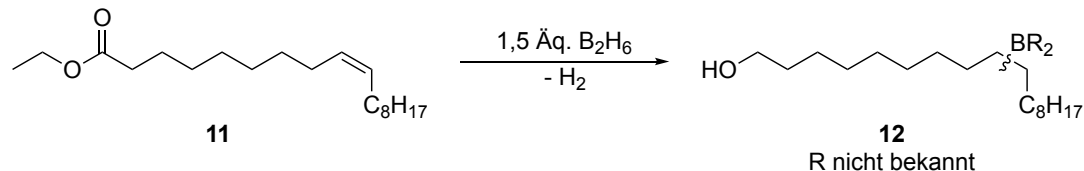
^a c = 1,0 M. ^b c = 0,01 M.



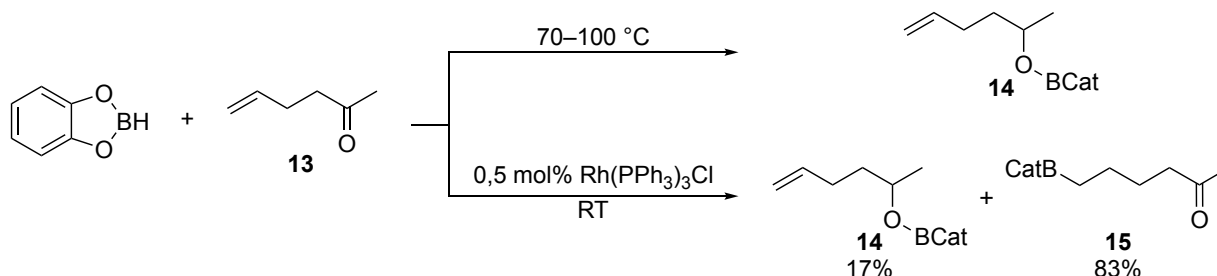
➤ Umkehr der intrinsischen Selektivität



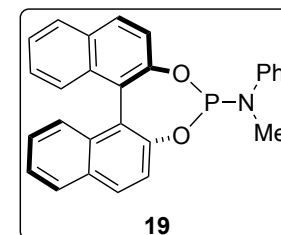
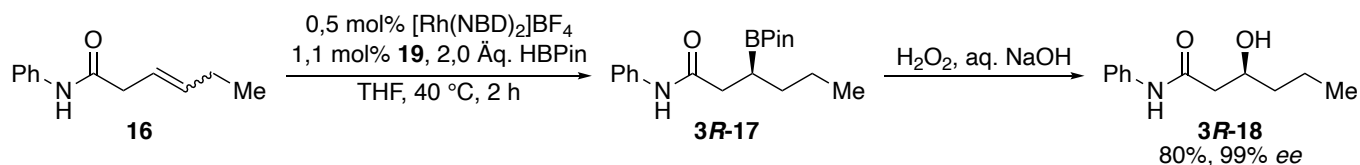
- Reduktion von Carbonylen und Doppelbindungen (Brown und Rao, 1956):



- Rh(I)-katalysierte Hydroborierung (Manning und Nöth, 1985):



- Enantioselektive Hydroborierung (Takacs *et al.*, 2008):

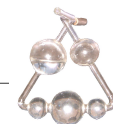


- Phosphinliganden auf Basis von Ferrocenyl, Binaphthyl, Biphenyl, TADDOL etc.

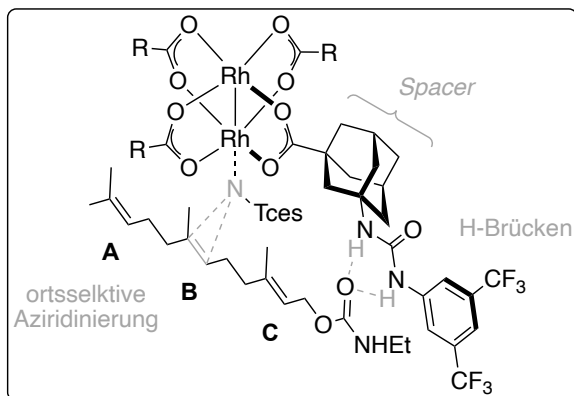
H. C. Brown, B. C. S. Rao, *J. Am. Chem. Soc.* **1956**, 78, 2582–2588.

D. Manning, H. Nöth, *Angew. Chem. Int. Ed.* **1985**, 24, 878–879.

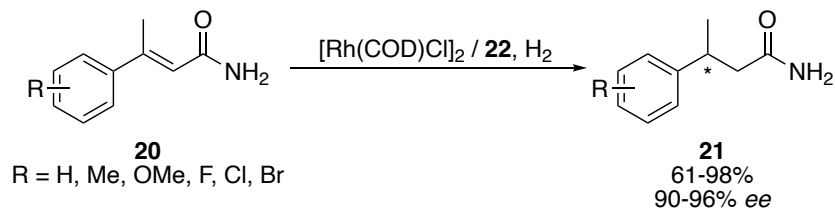
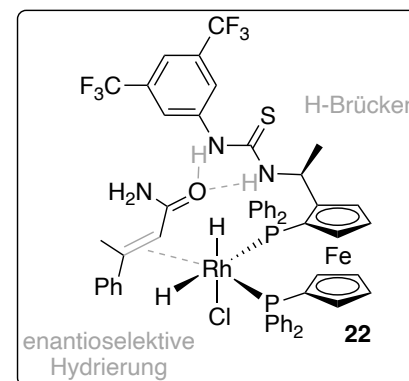
S. M. Smith, N. C. Thacker, J. M. Takacs, *J. Am. Chem. Soc.* **2008**, 130, 3734–3735.



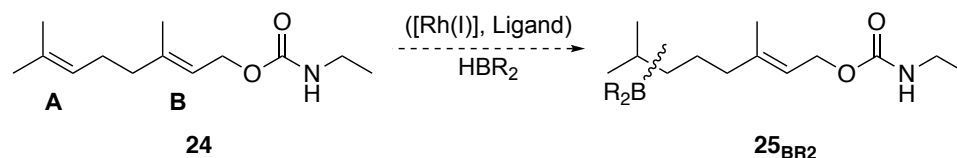
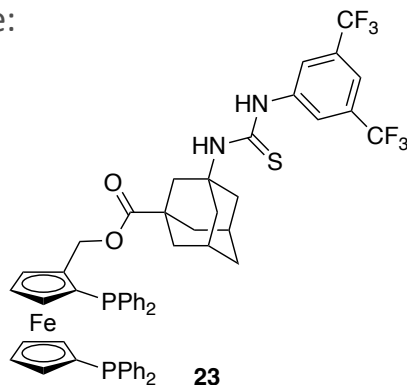
- Definierte Abstände $\leftrightarrow$ H-Brücken-Donor:



- Phosphinligand $\leftrightarrow$ Kooperative Katalyse:

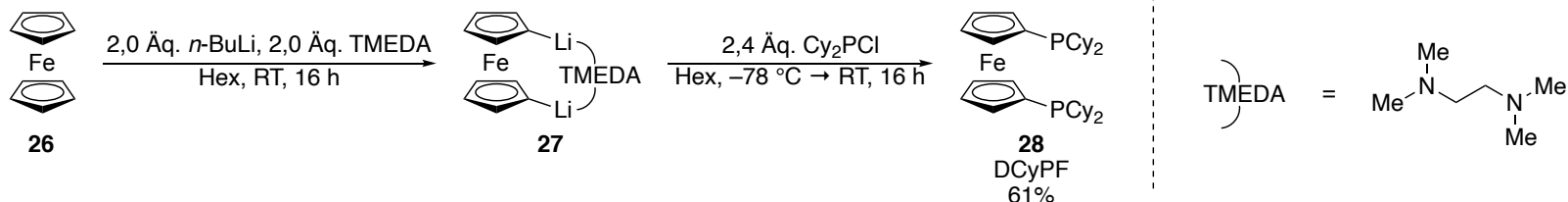


- Synthese:

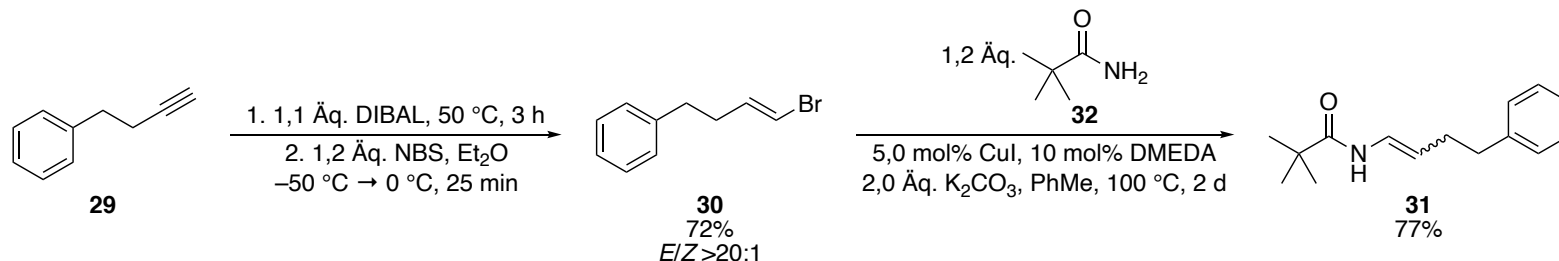




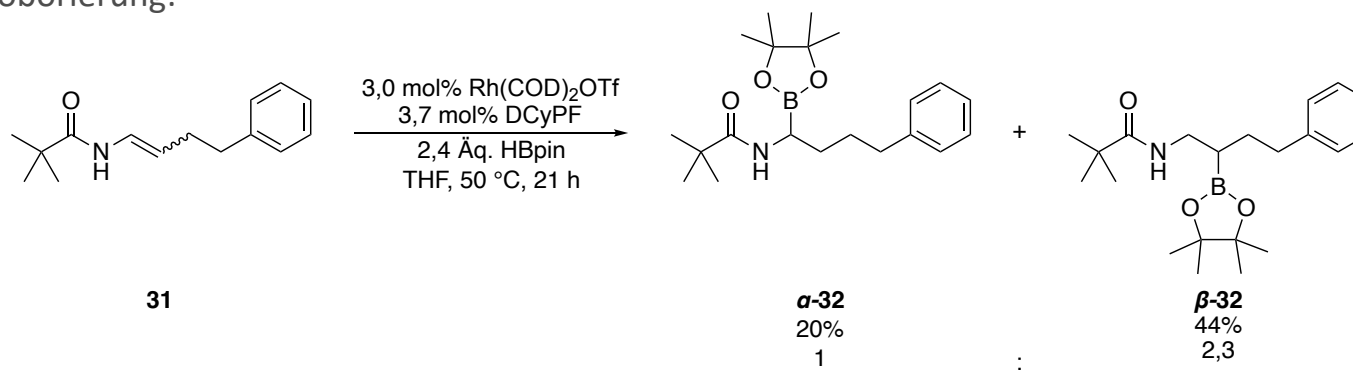
- Phosphorylierung:

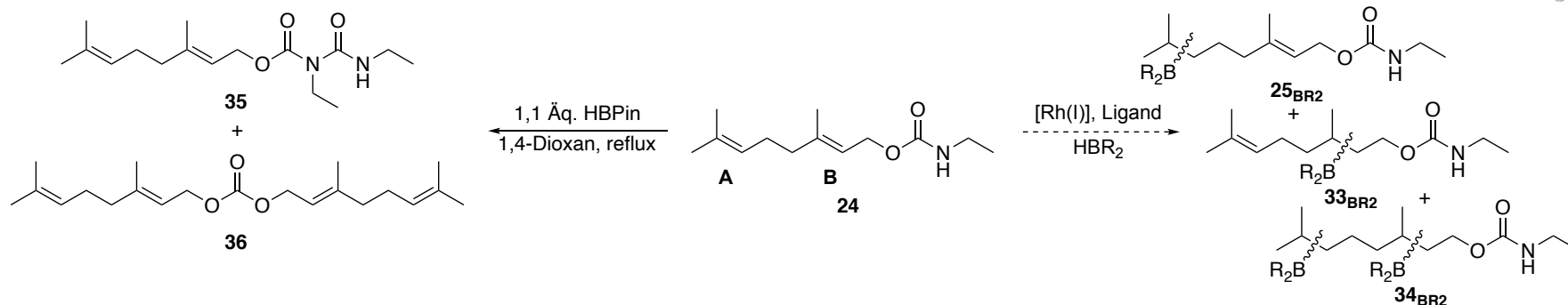
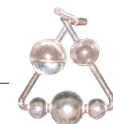


- Synthese des Testsubstrats:



- Hydroborierung:





Eintrag	Reagenzien & Bedingungen	Rh-Vorläufer + Ligand	t / d	Produkt
1	1,1 Äq. HBPIn, 1,4-Dioxan, 100 °C	-	2	Edukt + 35 + Spuren 36
2	1,0 Äq. HBPIn, THF, 60 °C	2,4 mol% [Rh(COD)Cl] ₂ 5,4 mol% DCyPF	4	Edukt + Hydrierungsprodukt
3	1,0 Äq. HBCat, THF, RT	1,7 mol% [Rh(COD) ₂]BF ₄ 1,9 mol% DPPF	5	Edukt + Hydrierungsprodukt
4	2,0 Äq. HBPIn, THF, 50 °C	3,0 mol% [Rh(COD) ₂]OTf 3,6 mol% DCyPF	1	Edukt + Hydrierungsprodukt
5	1,2 Äq. HBPIn, THF, 50 °C	3,0 mol% [Rh(COD) ₂]BF ₄ 3,5 mol% DCyPF	8	Edukt + 25 _{BR2} bzw. 33 _{BR2} + 34 _{BR2}

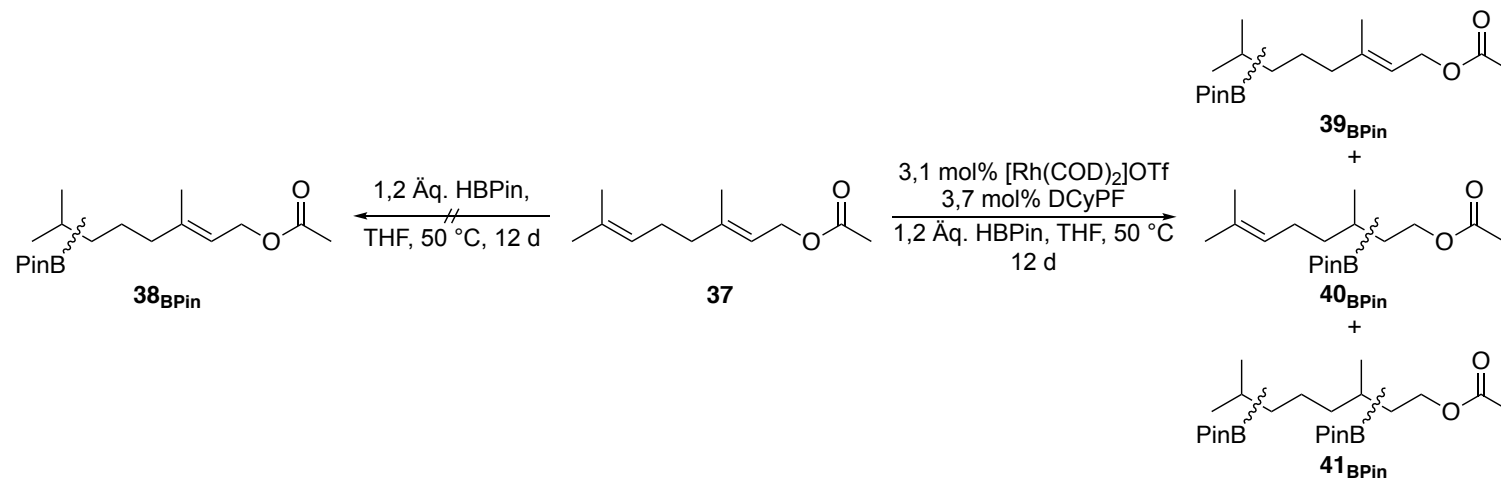
➤ N–H-Proton → Problem?

C. Stock, R. Brückner, *Adv. Synth. Catal.* **2012**, 354, 2309–2330.

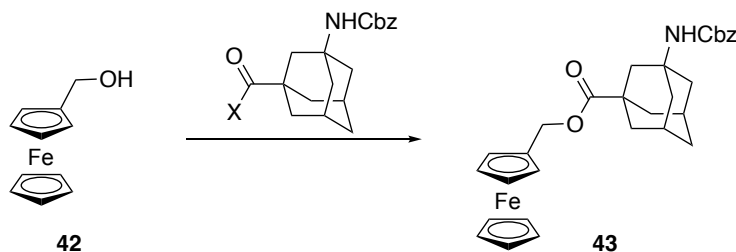
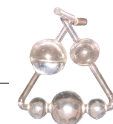
X.-Y. Bai, W. Zhao, X. Sun, B.-J. Li, *J. Am. Chem. Soc.* **2019**, 141, 19870–19878.

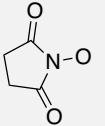


- Alternatives Substrat:



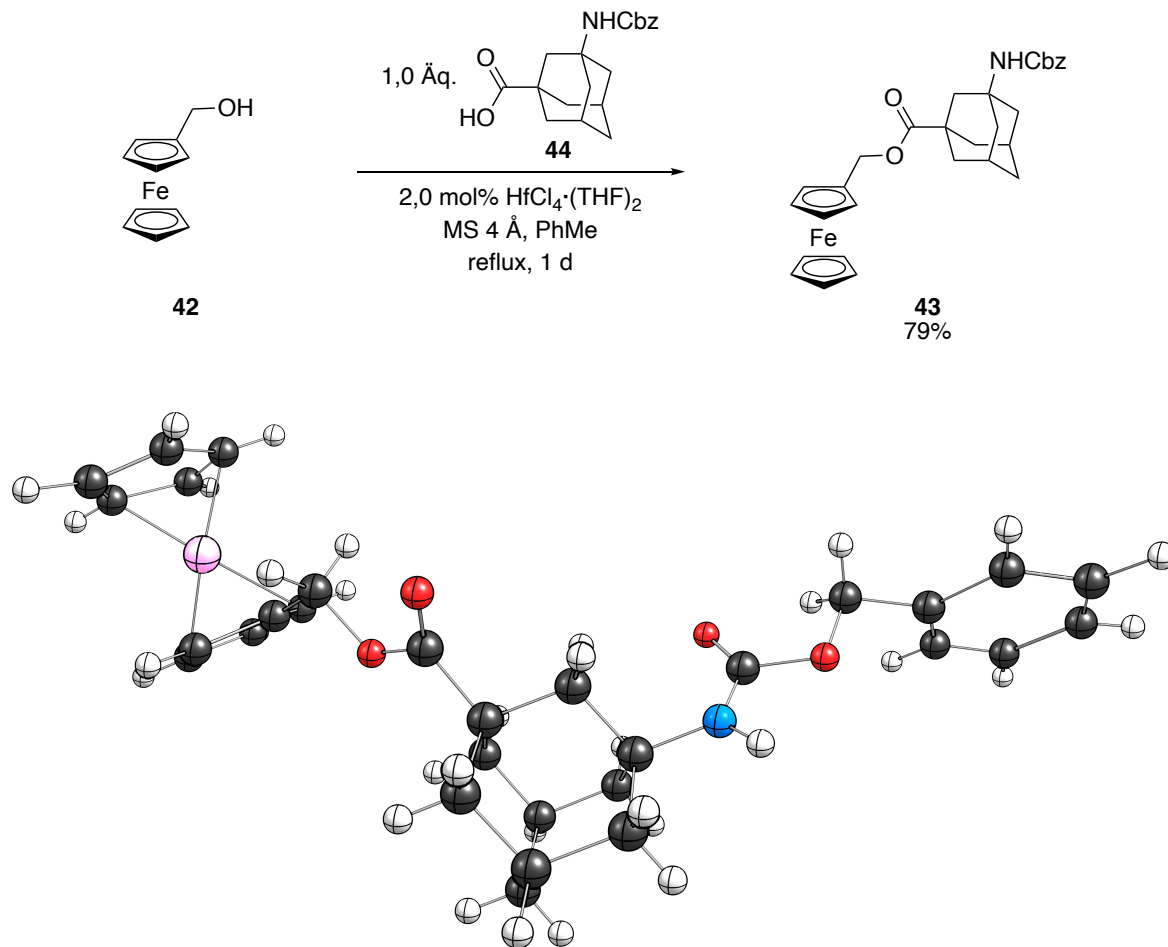
- Höhere Reaktivität
- HRMS: ✓
- Aufreinigung mittels Säulenchromatographie: ✗



Eintrag	X =	Reagenzien und Bedingungen	Umsatz/%
1	OH (44, 1,1 Äq.)	1,0 Äq. 42, 12 mol% DMAP, 3,0 Äq. EDAC·HCl, 5,7 Äq. Pyridin, DCE, reflux, 1 d	50
2	OH (44, 1,1 Äq.)	1,0 Äq. 42, 2,0 Äq. DiPEA, 2,0 Äq. HBTU, DMF, RT, 5 d	< 10
3	OH (44, 1,1 Äq.)	1,0 Äq. 42, 2,0 Äq. DiPEA, 2,0 Äq. COMU, DMF, 90 °C, 1 d	10
4	Cl (45, 1,0 Äq.)	1,1 Äq. 42, 2,6 Äq. TEA, DCM, RT, 1 d	< 5
5	Cl (45, 1,0 Äq.)	1,1 Äq. 42, 2,6 Äq. TEA, 1,0 Äq. DMAP, DCM, RT, 1 d	10
6	 (46, 1,0 Äq.)	1,2 Äq. 42, 25 mol% Sc(OTf) ₃ , 1,5 Äq. DMAP, DCM, RT, 3 d	< 10
7	OH (44, 1,1 Äq.)	1,0 Äq. 42, 1,5 Äq. 4-Nitrobenzoesäureanhydrid, 2 mol% Sc(OTf) ₃ , MeNO ₂ , MeCN, RT, 1 d	50
8	OH (44, 1,0 Äq.)	1,0 Äq. 42, 2,1 mol% HfCl ₄ , 4 Å MS, abs. Toluol, reflux, 1 d	90
9	OH (44, 1,0 Äq.)	1,0 Äq. 42, 2,0 mol% HfCl ₄ ·(THF) ₂ , 4 Å MS, abs. Toluol, reflux, 1 d	quant.

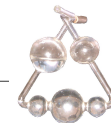


- Lewis-Säure katalysierte Veresterung:

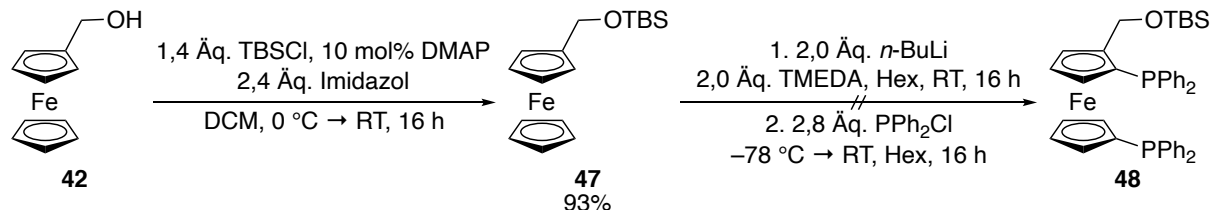


K. Ishihara, S. Ohara, H. Yamamoto, *Science* **2000**, 290, 1140–1142.

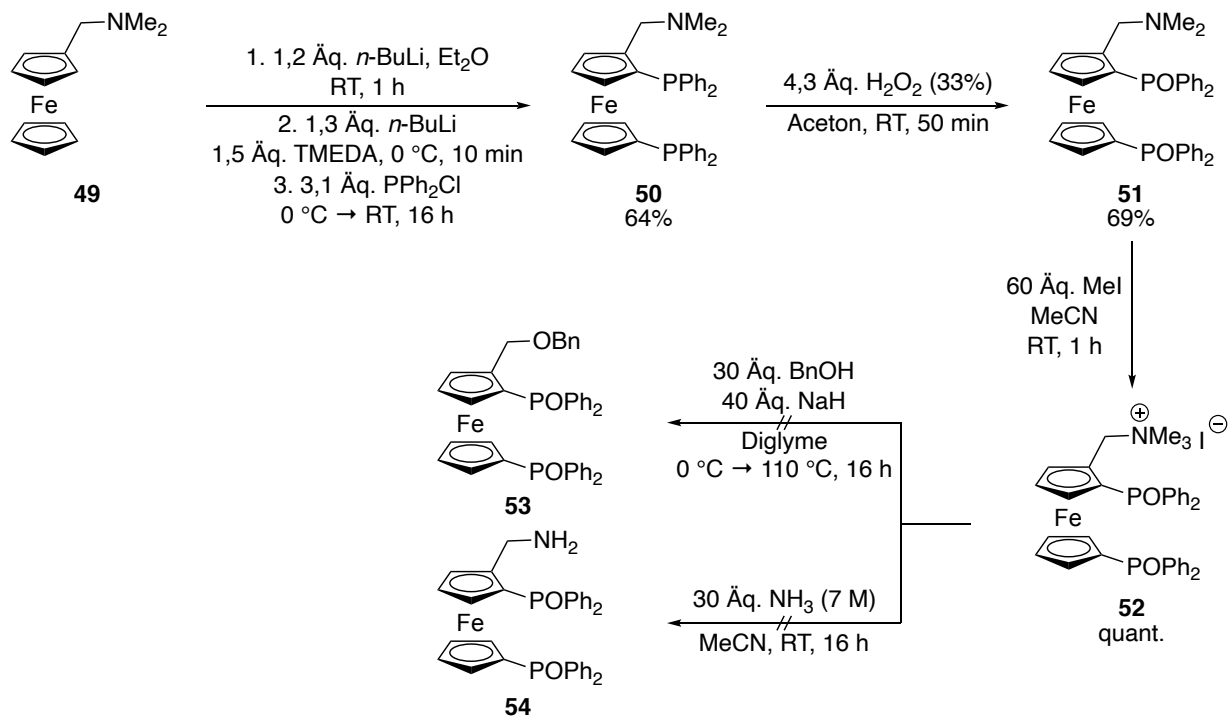
K. Ishihara, M. Nakayama, S. Ohara, H. Yamamoto, *Synlett* **2001**, 2001, 1117–1120.

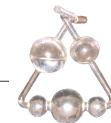


- Testreaktion der Phosphorylierung:

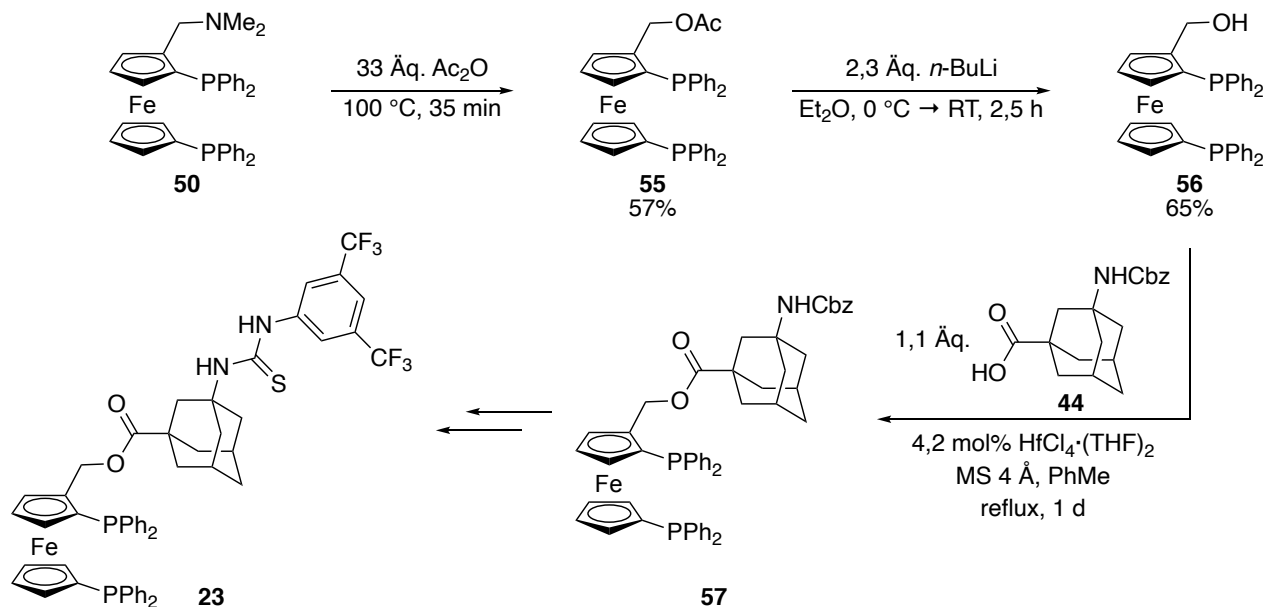


- Syntheseroute über Ferrocenylmethyl-Ammoniumsalz:





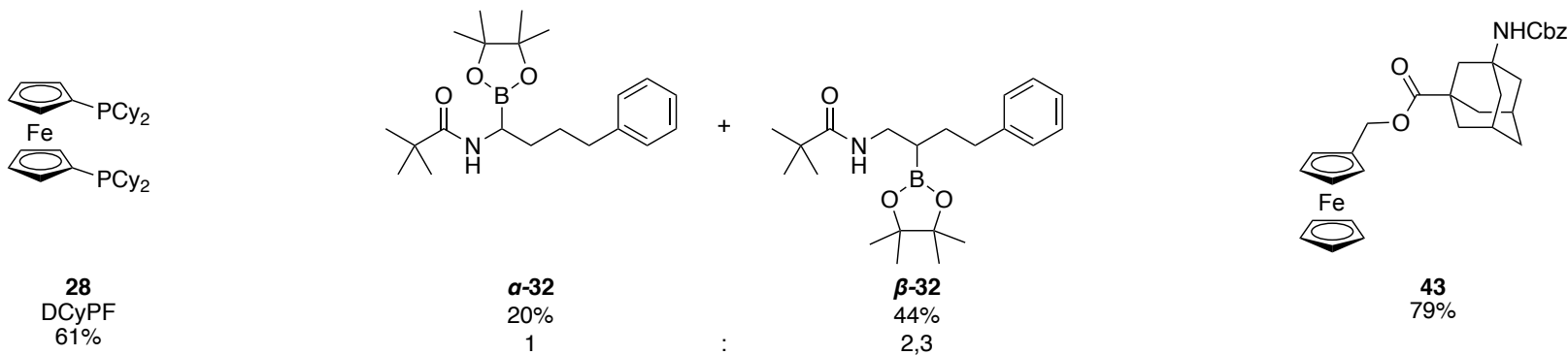
- Syntheseroute über das Ferrocenylmethyl-Acatat:



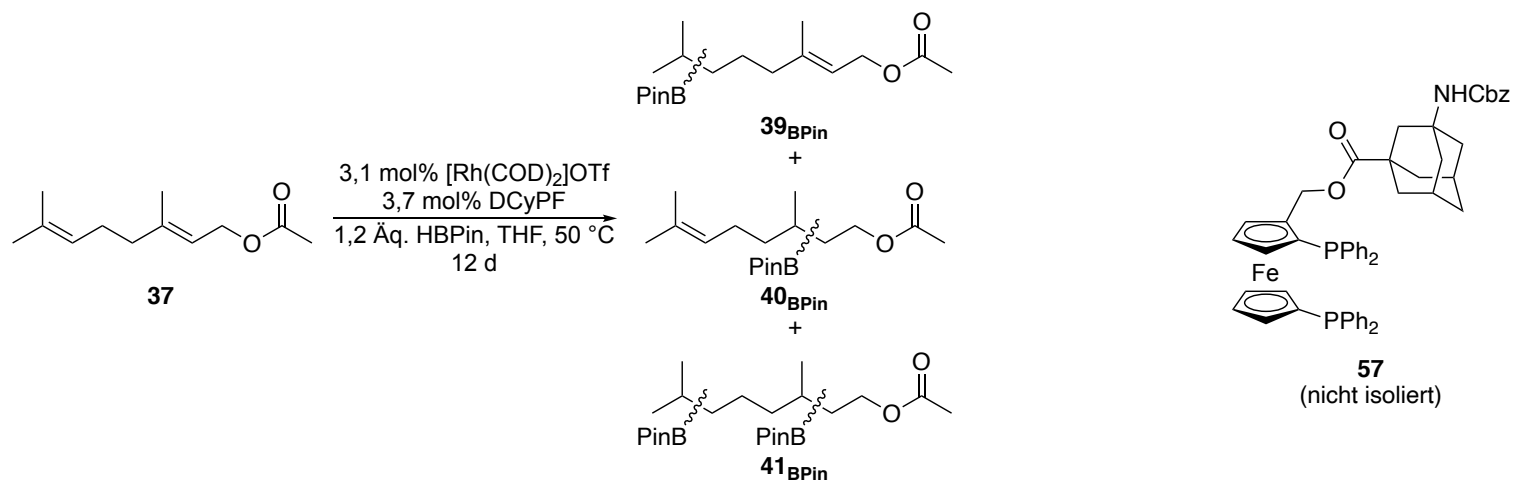
➤ Aufreinigung von **57**: ✗



- Synthese:

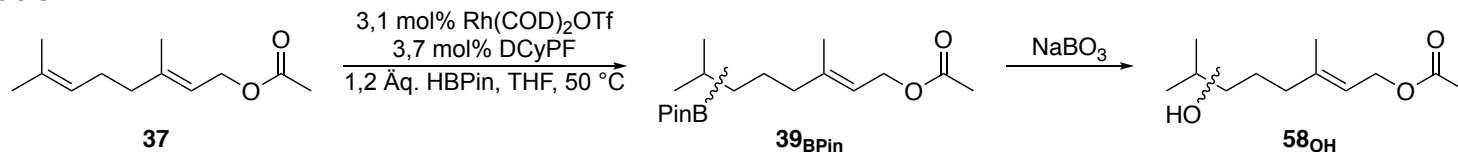


- Synthese Standards und Ligand:

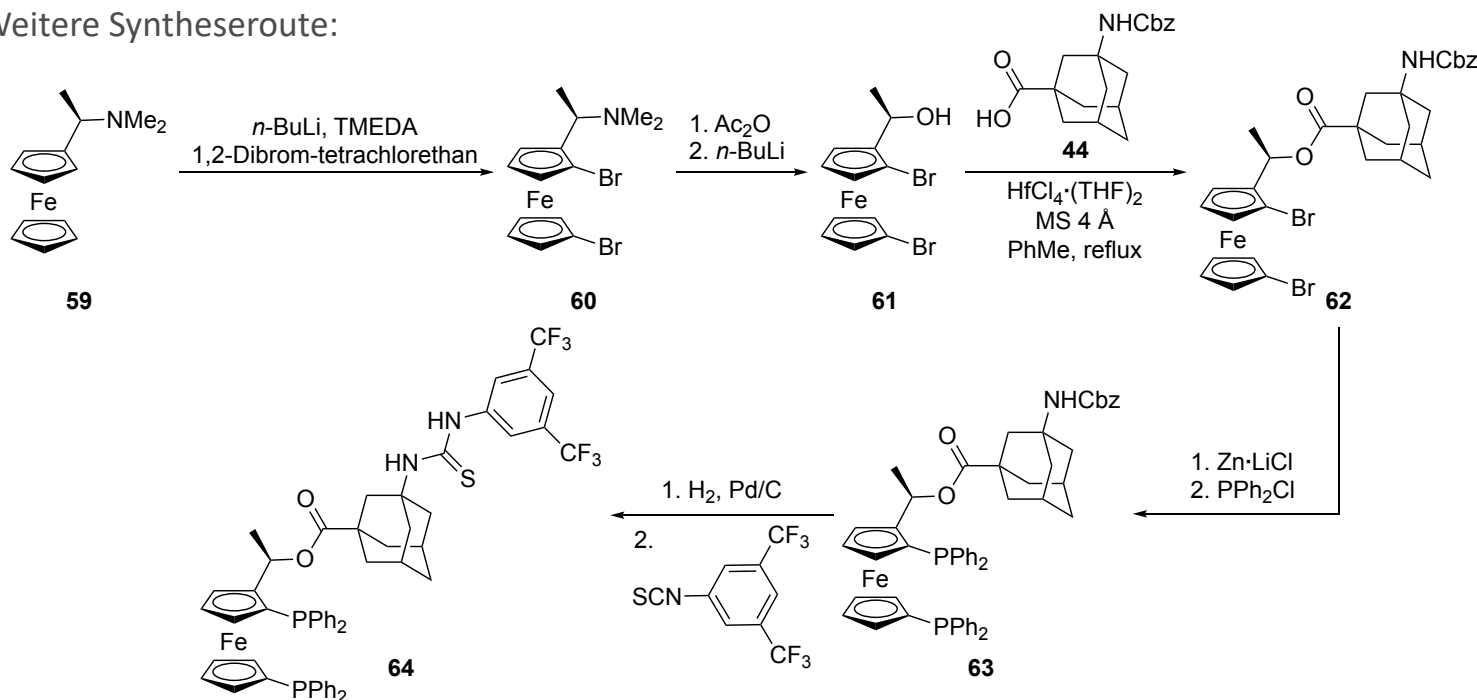




- Oxidation:



- Weitere Syntheseroute:



- Computergestützte Rechnungen von Katalysator-Substrat-Komplexen:

- Weitere Substrate
- Andere *Spacer* z.B. Diamantan, Naphthalin



Danke...

- Prof. Dr. P. Schreiner, PhD
- Friedemann “Friedhelm” Dreßler
- B201/B204/B205
- OC-Analytik und Jonathan Becker
- AG Schreiner

