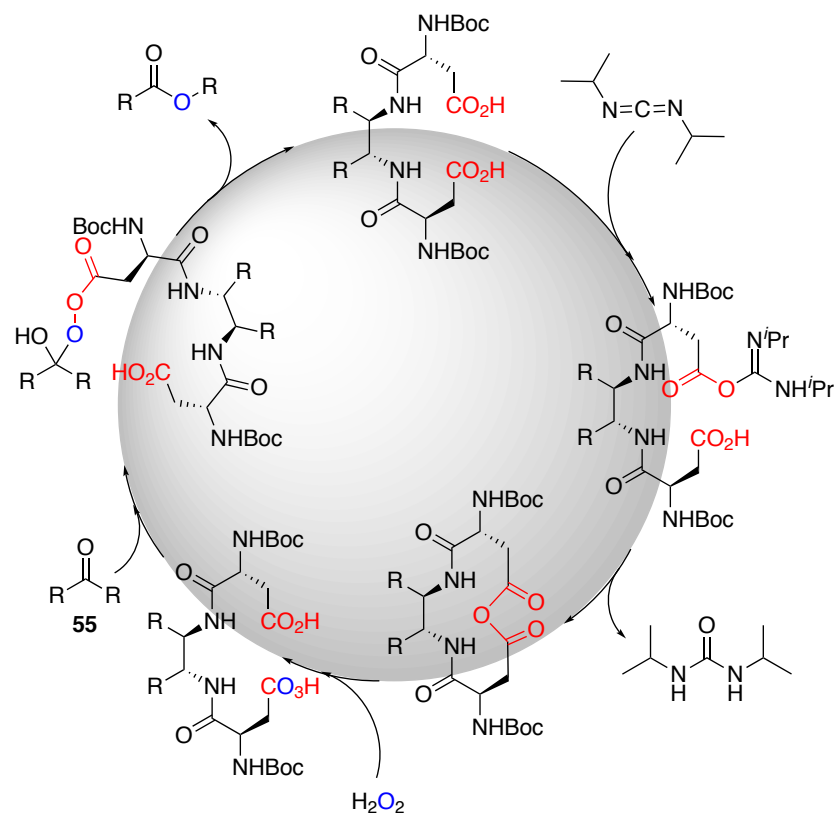


Organokatalytische Lactonsynthese

31.10.14

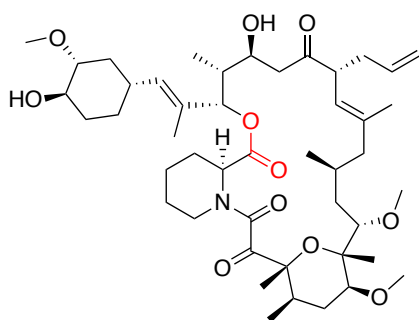
Dominik Niedek

*Institut für Organische Chemie
Justus-Liebig-Universität
35392 Gießen, Germany*

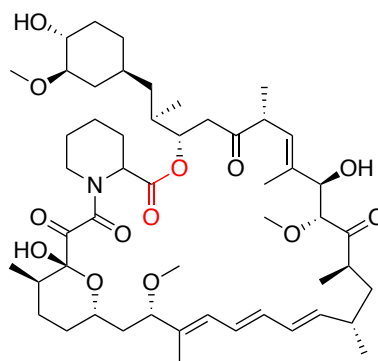




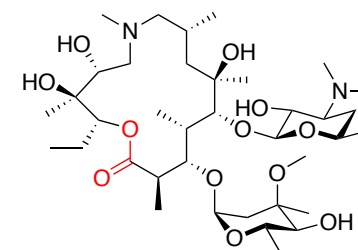
- Pharmaindustrie



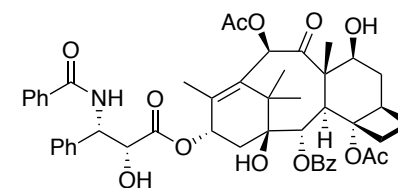
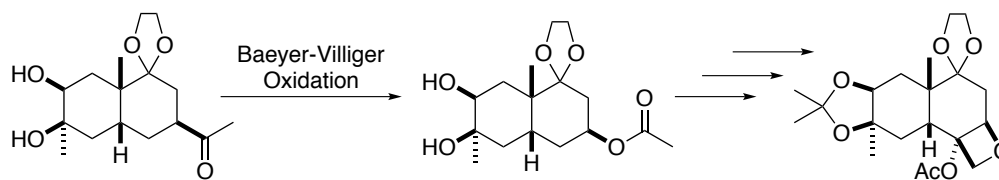
FK-506 (Tacrolimus)



Rapamycin



Azithromycin

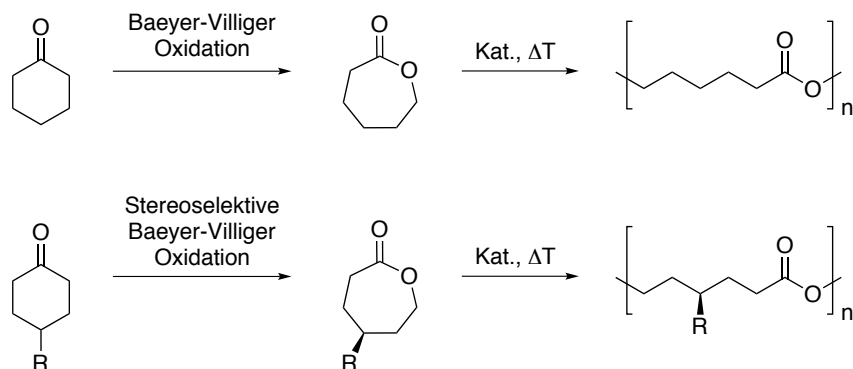


Taxol

R. E. Marker, *J. Am. Chem. Soc.* **1940**, 62, 2621–2625; T. Kino, H. Hatanaka, M. Hashimoto, M. Nishiyama, T. Goto, M. Okuhara, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1987**, 40, 1249–1255; T. K. M. Shing, C. M. Lee, H. Y. Lo, *Tetrahedron Lett.* **2001**, 42, 8361–8363.



- Chemische Industrie (z.B. Polymerchemie)



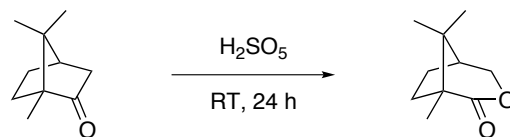
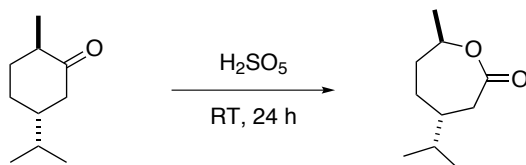
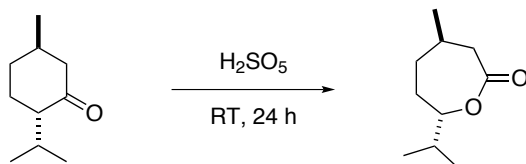
„Intelligente Kunststoffe“

- Kunststoffe mit neuen Eigenschaften
- Homogene, optisch aktive Thermoplaste

Anwendung: Oberflächenbeschichtungen, stationäre Phasen in der Chromatographie etc.

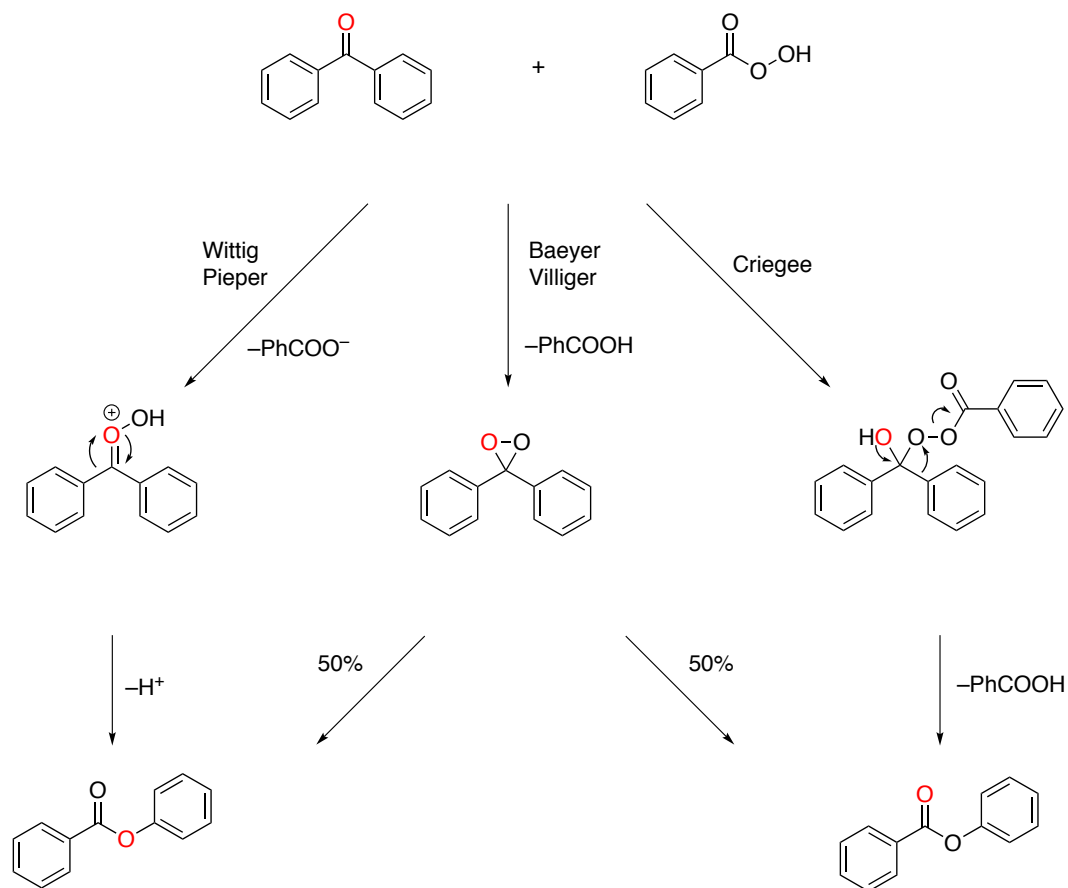


- 1899 von Adolf von Baeyer und Victor Villiger entdeckt
- Oxidation von Ketonen zu Estern bzw. Lactonen





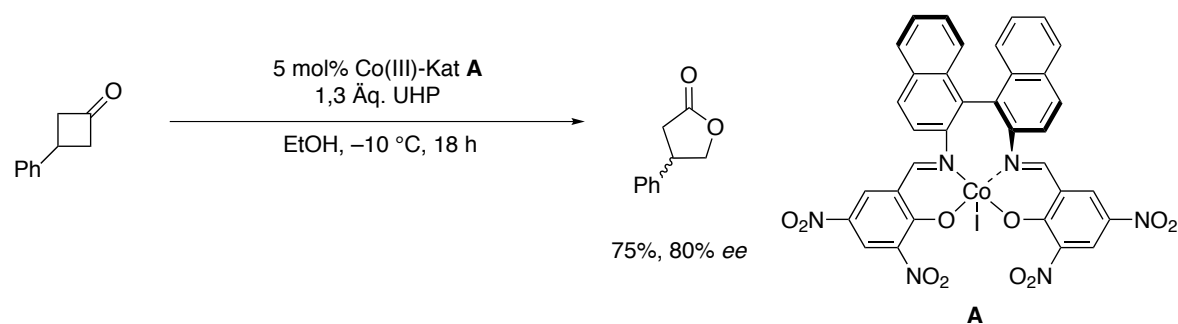
- Toleranz gegenüber funktioneller Gruppen
- Regioselektivität abhängig von Wanderungstendenz:
tert. Alkyl > Cy > *sec.* Alkyl > Bn > Ph > *prim.* Alkyl > Me
- Retention der Konfiguration
- Oxidationsmittel: CF_3COOOH > *m*CPBA > CH_3COOOH >> H_2O_2 > *t*BuOOH
- Kein universelles Protokoll verfügbar
- Epimerisierungsgefahr
- Stöchiometrische Verwendung org. Persäuren: hohe Reaktivität, aber teuer, instabil, schwer zugänglich, ein Äquivalent der entsprechenden Säure als Abfallprodukt
- Wasserstoffperoxid als stöchiometrisches Oxidationsmittel (geringe Reaktivität, Löslichkeit etc.)



=> Mechanismus nach Criegee *et al.* experimentell bestätigt

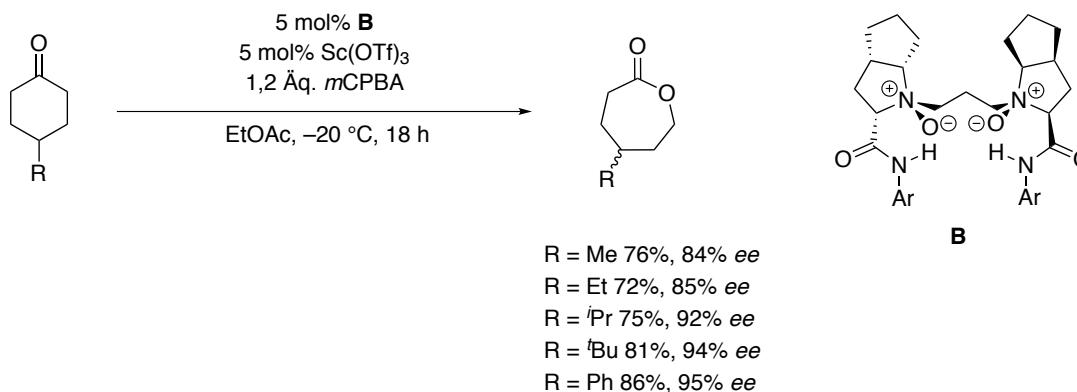


- Aktivierung einer Komponente:
Carbonylgruppe, Oxidationsmittel, Criegee Intermediat
- Zahlreiche Katalysatorsysteme auf Basis von Übergangsmetallen
z.B. Cobalt, Scandium
- Enantioselektive Varianten mit hoher Selektivität, Reaktivität und
einem großen Substratpool dennoch selten

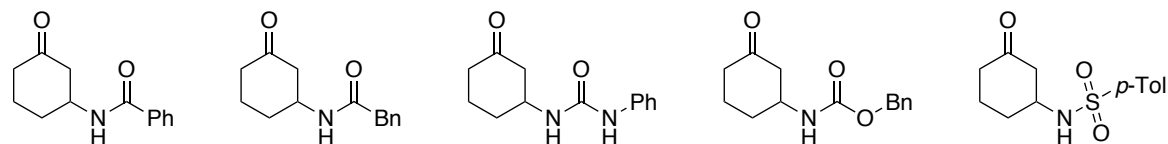
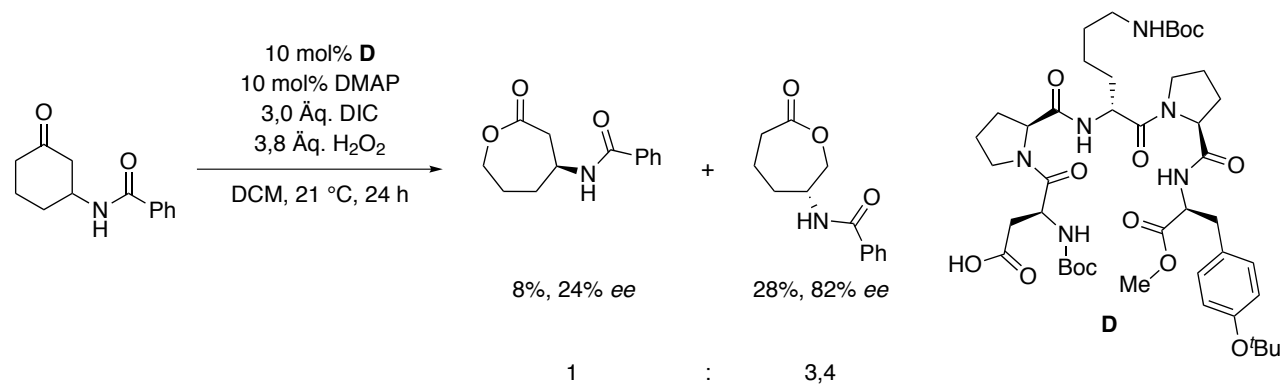
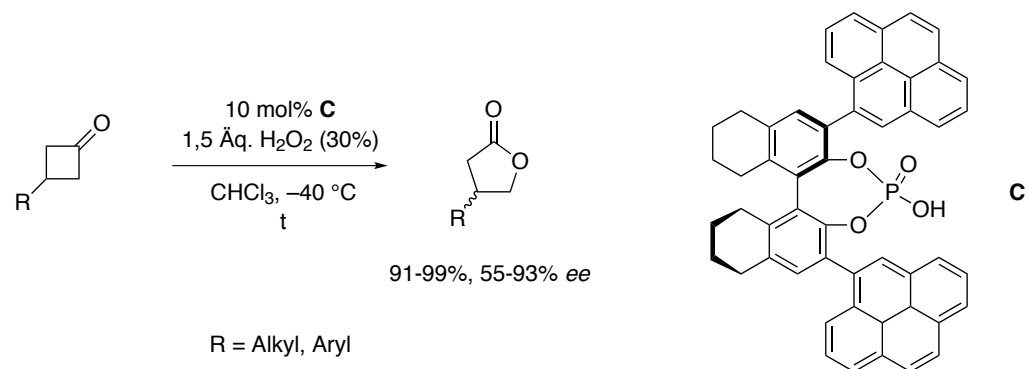




- Aktivierung einer Komponente:
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- Zahlreiche Katalysatorsysteme auf Basis von Übergangsmetallen
z.B. Cobalt, Scandium
- Enantioselektive Varianten mit hoher Selektivität, Reaktivität und
einem großen Substratpool dennoch selten



Baeyer-Villiger Oxidationen - Asymmetrische Organokatalytische Variante

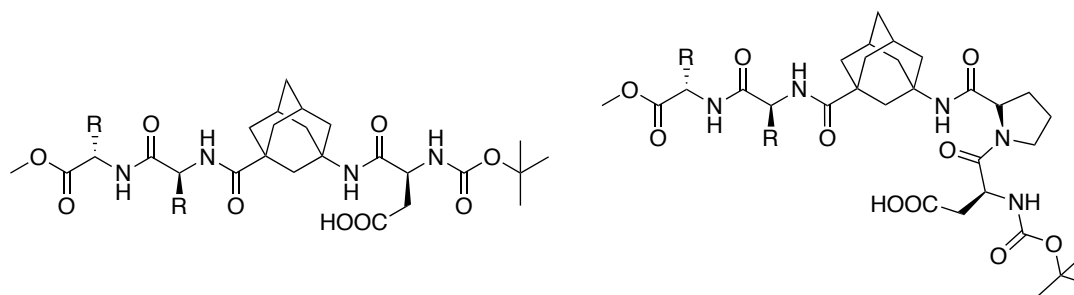


S. Xu, Z. Wang, X. Zhang, X. Zhang, K. Ding, *Angew. Chem. Int. Ed.* **2008**, 47, 2840-2843; S. Xu, Z. Wang, X. Zhang, K. Ding, *Eur. J. Org. Chem.* **2011**, 110-116; G. Peris, S. J. Miller, *Org. Lett.* **2008**, 10, 3049-3052; D. K. Romney, S. M. Colvin, S. J. Miller, *J. Am. Chem. Soc.* **2014**, 136, 14019-14022.

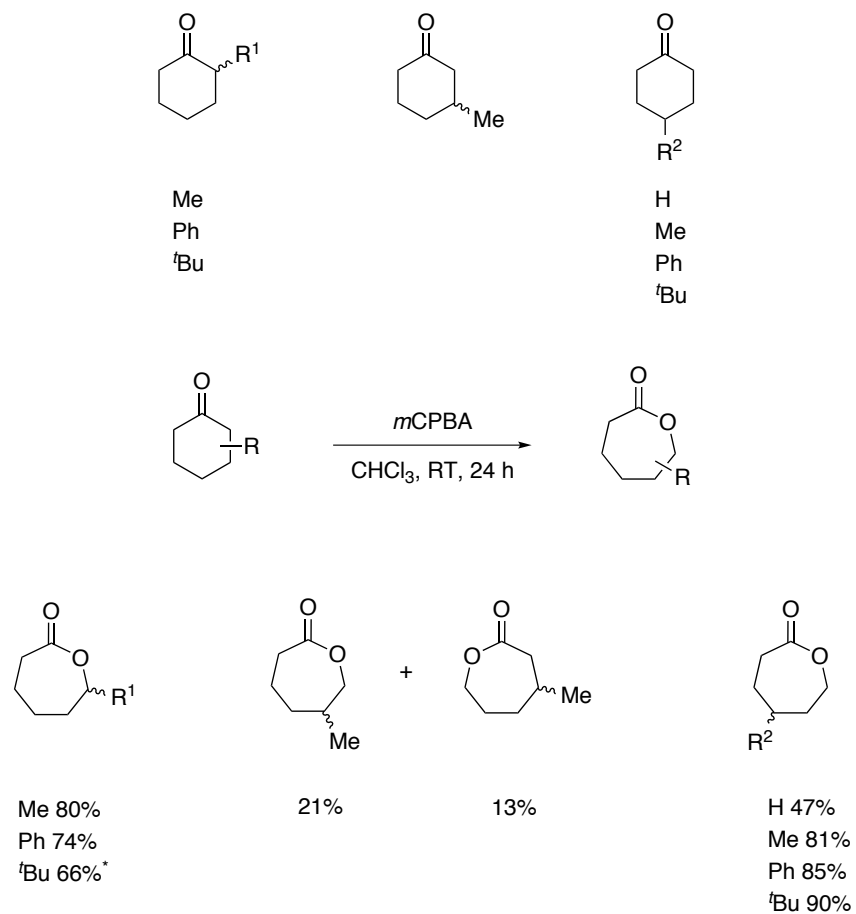


Stereoselektive peptidkatalysierte Baeyer-Villiger Oxidation

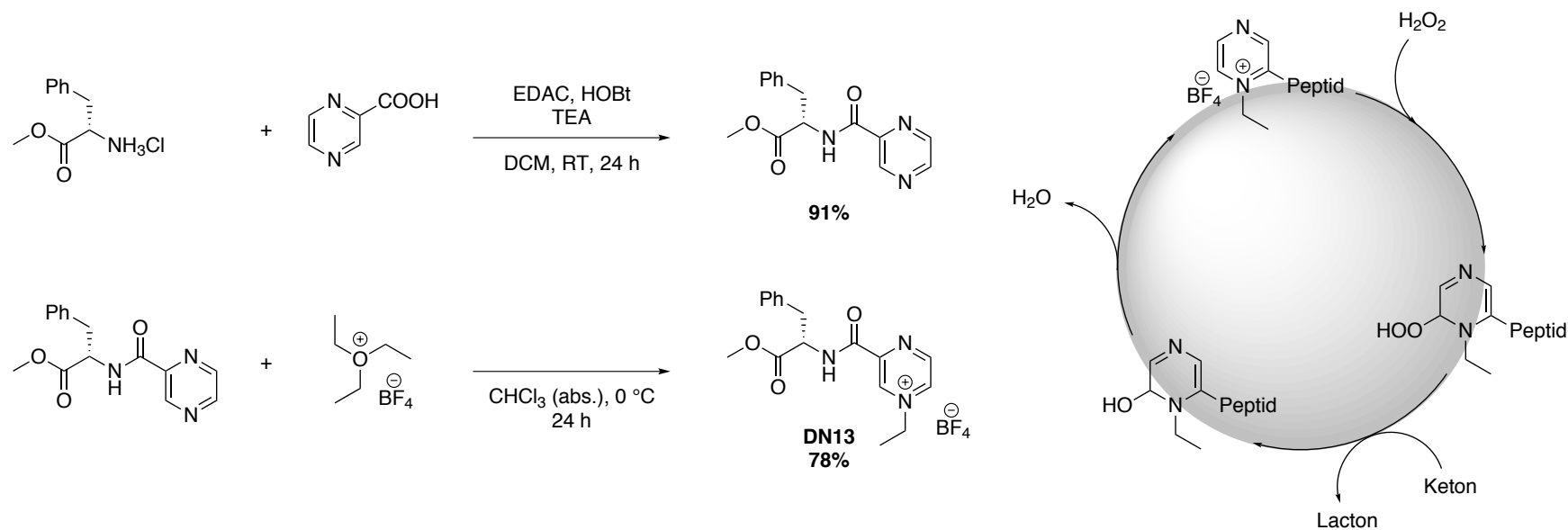
- Erstellen einer Substratbibliothek
- Erarbeiten eines optimierten Katalyseprotokolls
- Bereits vorhandene Katalysatoren für BVO testen
- Darstellen weiterer Peptidkatalysatoren



- Zugang zu enantiomerenangereicherten Lactonen



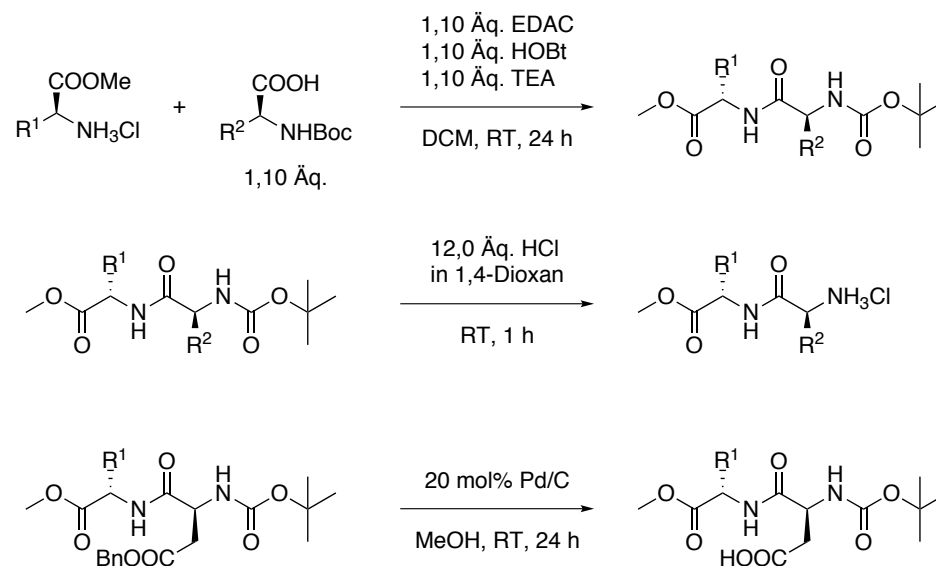
*2,4 Äq. *m*CPBA, 96 h

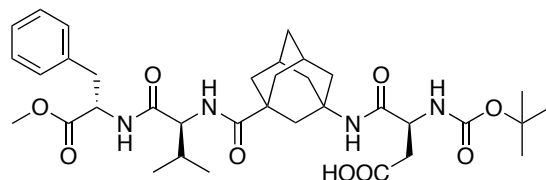


- ⇒ Zugang zu neuem katalytischen Motiv
- ⇒ Reaktivität für Cyclohexanon-derivate zu gering
- ⇒ Test an reaktiveren Substraten

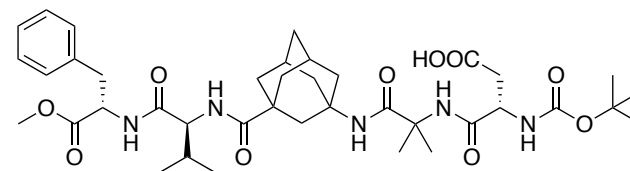


- Boc-Strategie in Lösung via EDAC/HOBt Vermittler
- Orthogonale Schutzgruppenstrategie für Amine und Säurefunktion in der Seitenkette der Asparaginsäure (Boc- und Benzylschutzgruppe)
- Allgemeines Syntheschema:

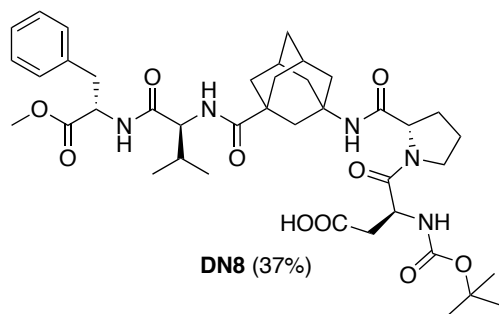




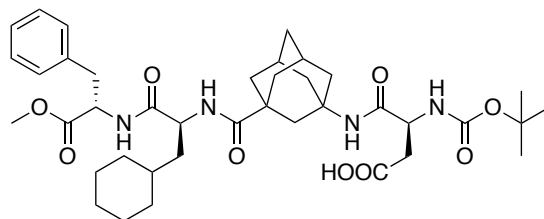
DN6 (46%)



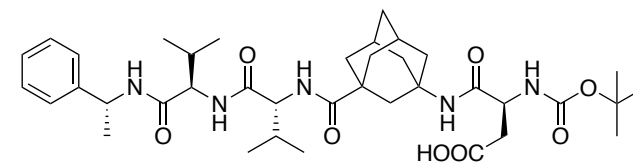
DN7 (15%)



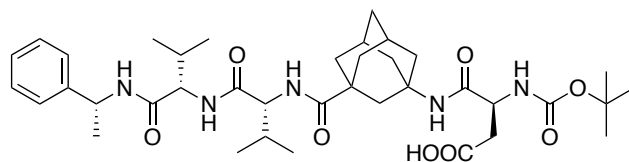
DN8 (37%)



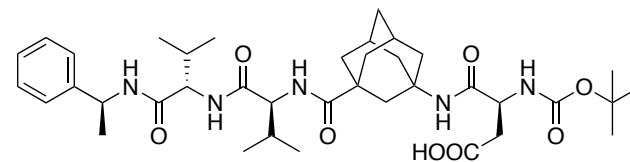
DN9 (32%)



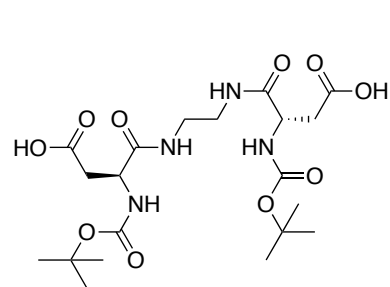
DN10 (21%)



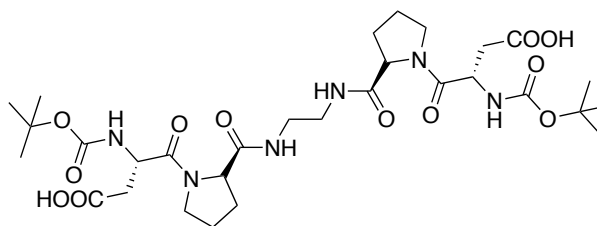
DN11 (22%)



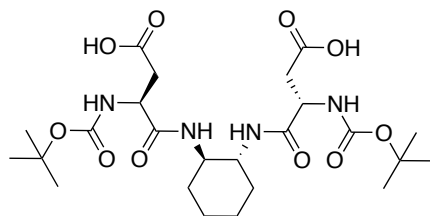
DN12 (22%)



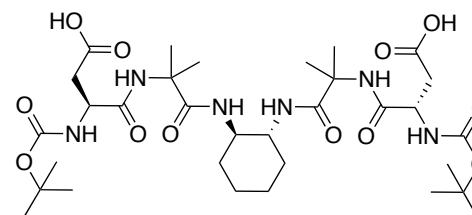
DN1 (15%)



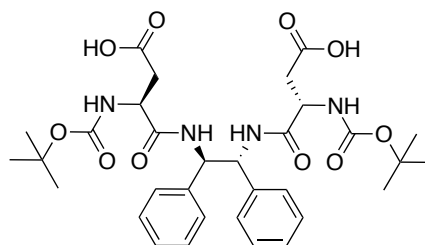
DN2 (49%)



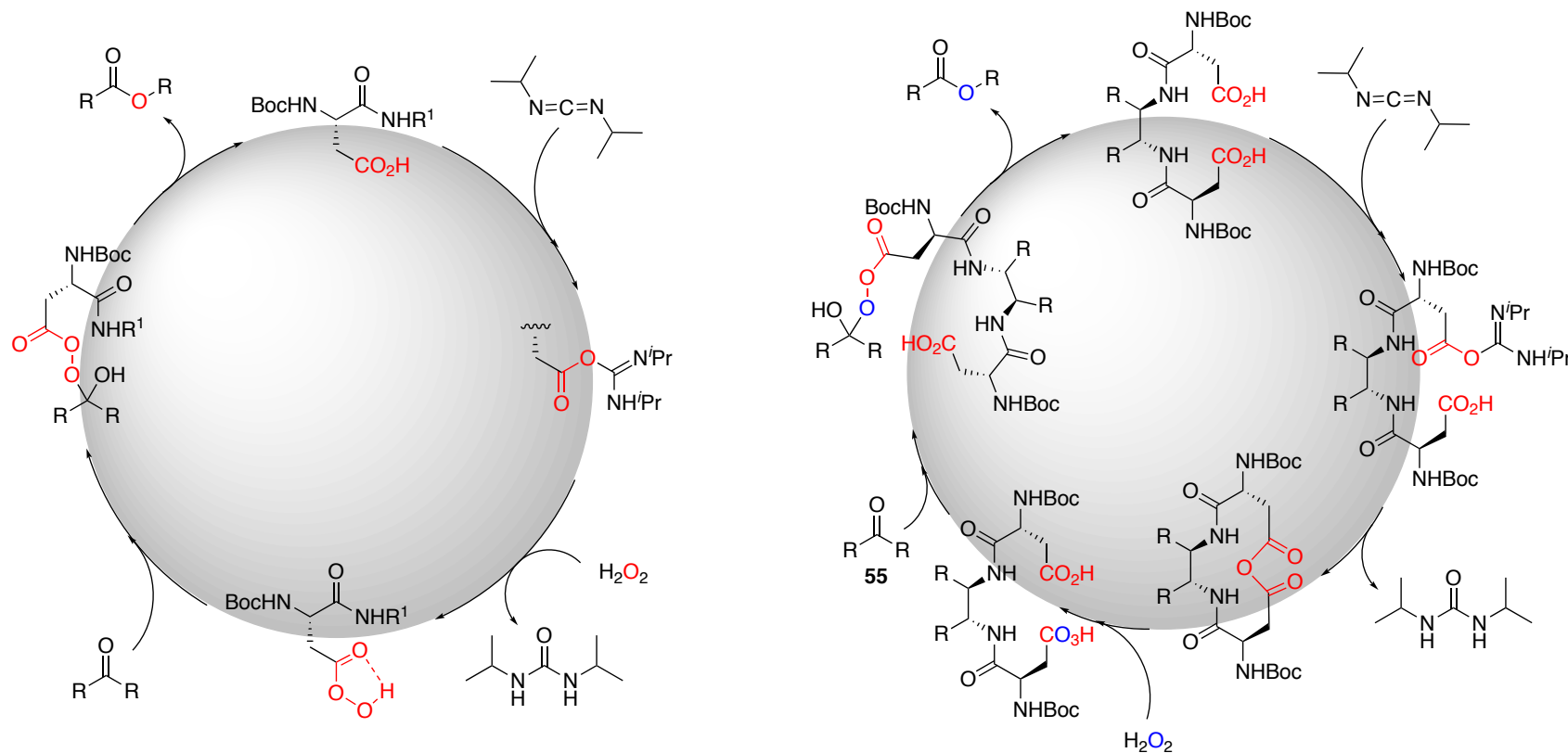
DN3 (76%)



DN5 (39%)

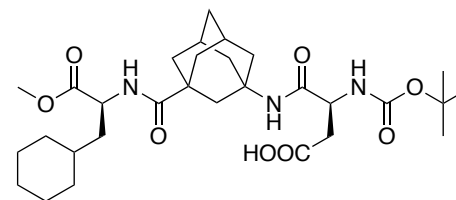


DN4 (82%)

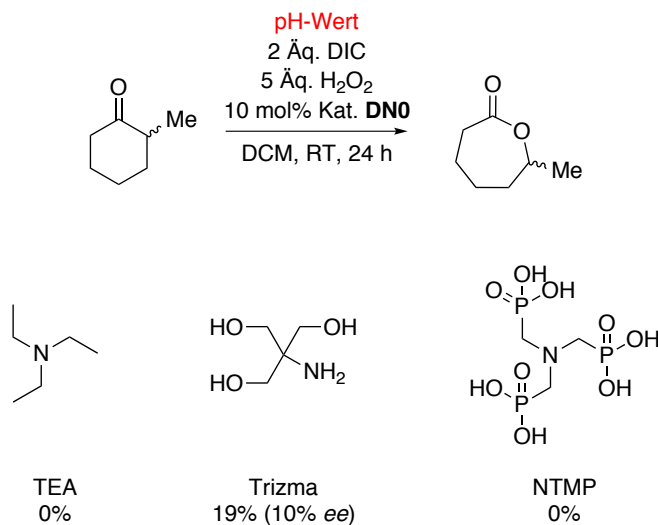




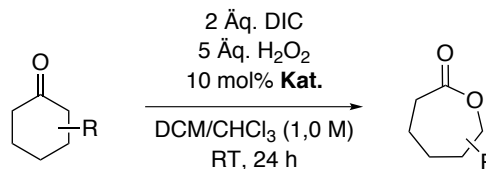
- Optimierung der Reaktionsbedingungen anhand folgender Parameter:
 - Katalysatorbeladung
 - Zugabe von DMAP
 - Zugabe von Thioharnstoff
 - Carbodiimid
 - Konzentration
 - Lösungsmittel
 - Oxidationsmittel
 - Temperatur
 - Reaktionsdauer
 - pH-Wert



DNO



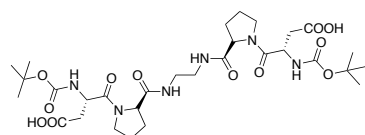
- Zu saure bzw. basische Reaktionsführung liefert kein BVO Produkt
- Trizma[®] verlangsamt die Reaktion, aber liefert Selektivität ($pK_s = 8,2$)



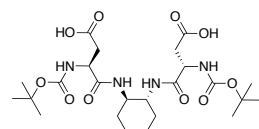
Erkenntnisse:

- Unerwartet starker Einfluss des pH-Werts
- DMAP wird nicht benötigt
- Hintergrundreaktion bei Konzentrationen $> 1,0 \text{ M}$ nicht vernachlässigbar
- Breites Spektrum an Lösungsmitteln einsetzbar
- Portionsweise Zugabe weder für Carbodiimid noch für Oxidationsmittel erforderlich
- Tiefere Temperaturen verlangsamen die Reaktion

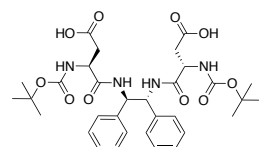
Katalysetestreaktionen



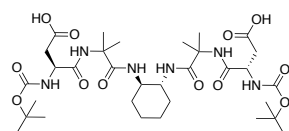
DN2 (49%)



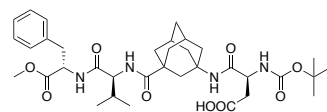
DN3 (76%)



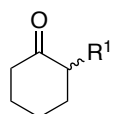
DN4 (82%)



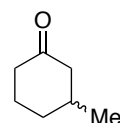
DN5 (39%)



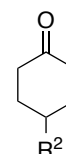
DN6 (46%)



Me
Ph
tBu

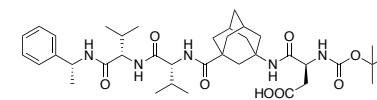
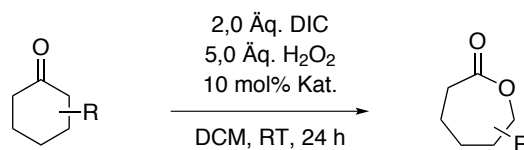


Me

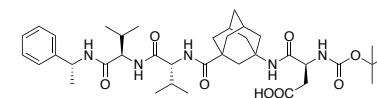


R²

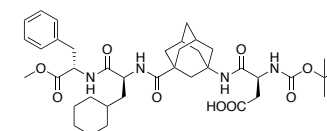
H
Me
Ph
tBu



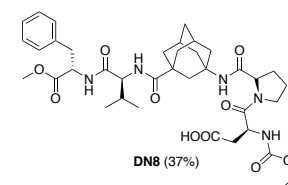
DN11 (22%)



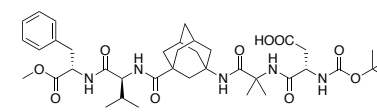
DN10 (21%)



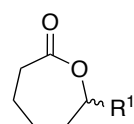
DN9 (32%)



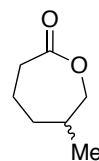
DN8 (37%)



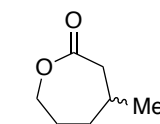
DN7 (15%)



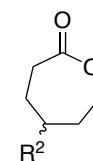
Me 2-82% (0-6% ee)
Ph 24-90% (0-6% ee)
tBu 0-1% (0-8% ee)



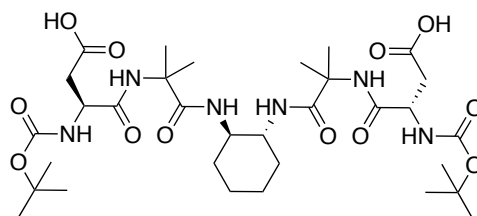
1-12% (0-8% ee)



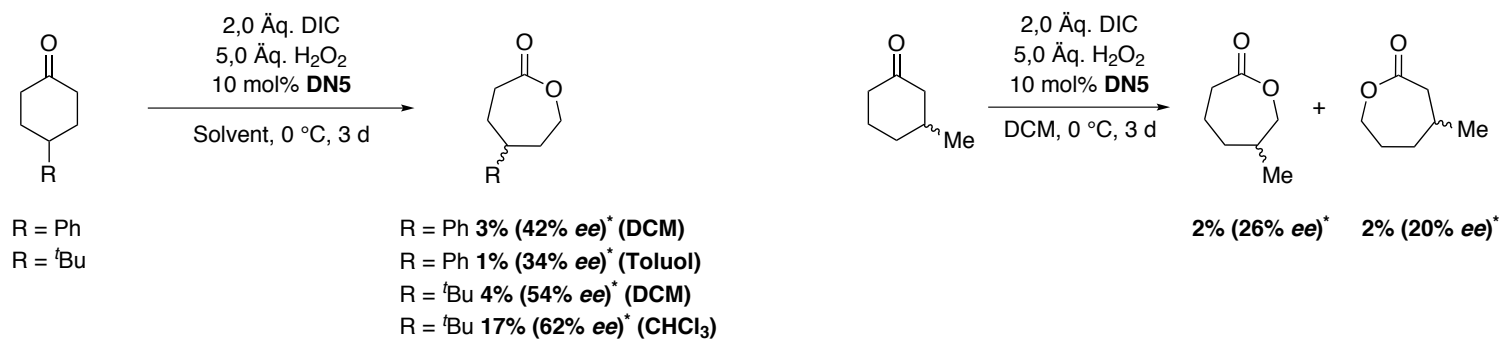
1-12% (0-10% ee)



Me 3-29% (0-8% ee)
Ph 1-28% (0-12% ee)
tBu 4-26% (0-12% ee)



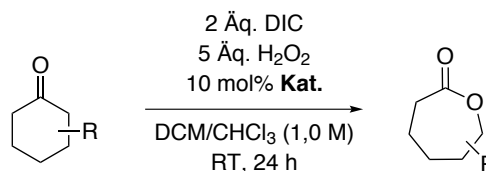
DN5 (39%)



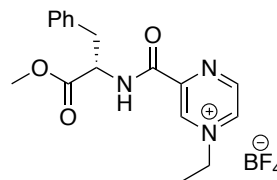
*bestimmt via chiraler Gaschromatographie



- Substratbibliothek erstellt
- Optimiertes Katalyseprotokoll erstellt

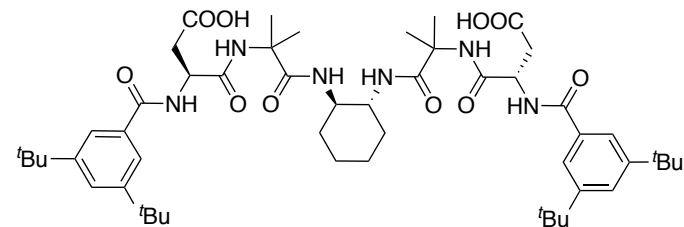
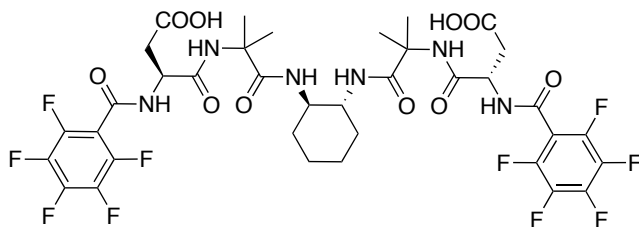
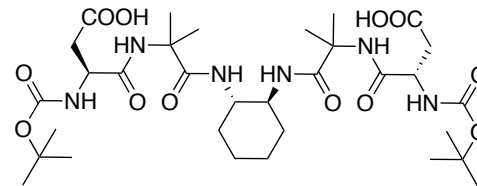
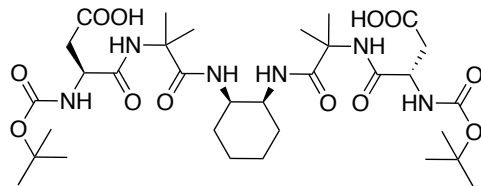
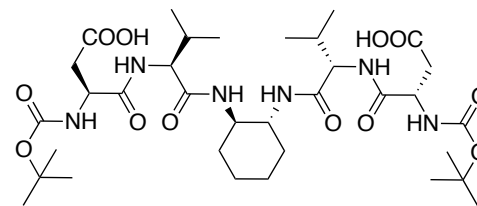
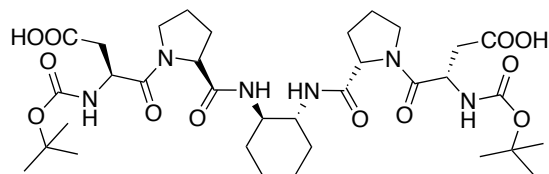


- Mono- und Disäurekatalysatoren auf Peptidbasis (Ausbeute bis zu 82%)
- Peptidbasierender Pyraziniumsalz Katalysator (Ausbeute 71%)



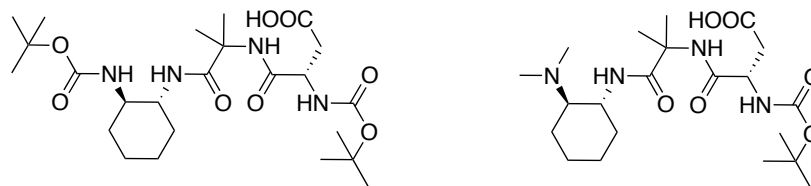


Synthese weiterer C_2 -symmetrischer Katalysatoren

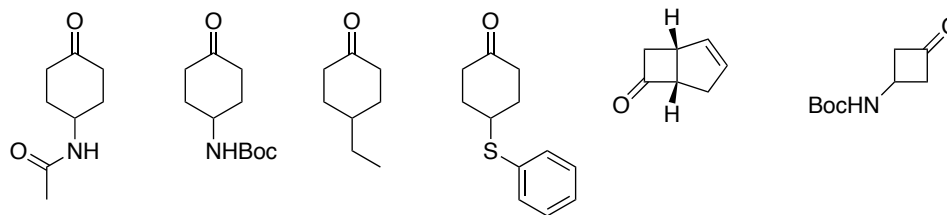




Synthese von Monosäurekatalysatoren auf Diaminbasis

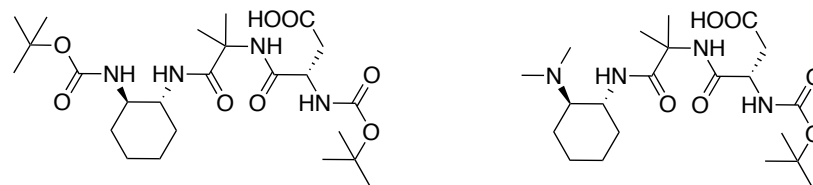


Erweiterung des Substratpools

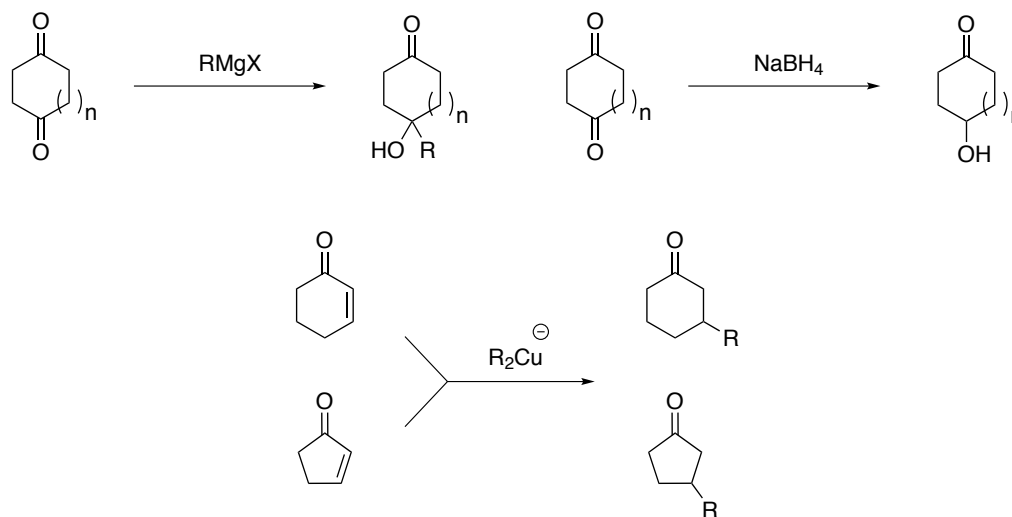




Synthese von Monosäurekatalysatoren auf Diaminbasis

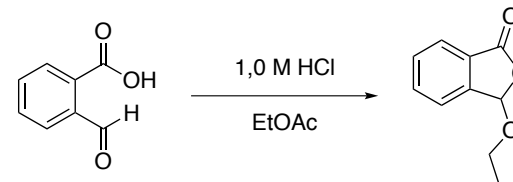


Erweiterung des Substratpools

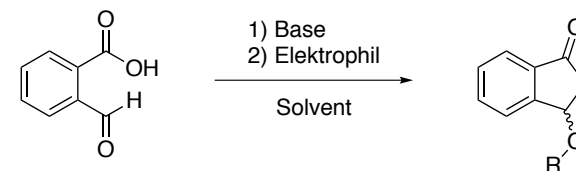




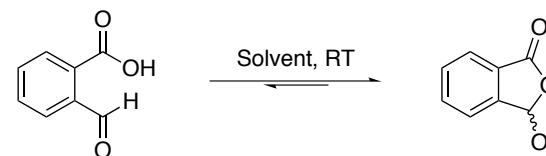
- Zufällige Beobachtung



- Grundidee: gezielte Darstellung



- Untersuchung der Stabilität von 2-Carboxybenzaldehyd

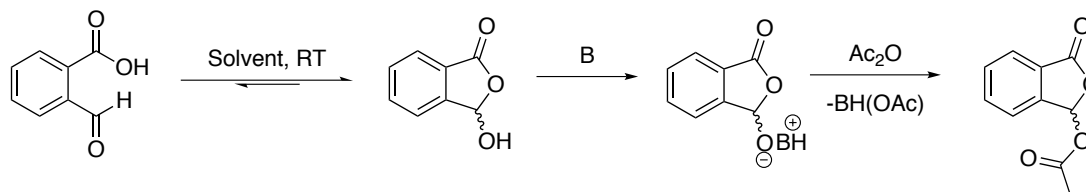


	KBr-Pressling	CHCl ₃ -Lösung
C=O (cm ⁻¹)	1741	1767
	1761	

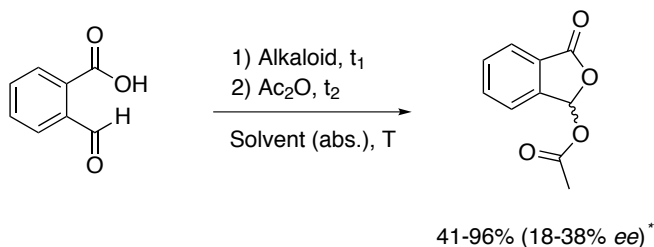
Solvent	¹ H	¹³ C	Verhältnis
DMSO-d ₆	6,68	98,3; 168,5	1:10
	10,48	167,6; 192,9	
CDCl ₃	6,66	98,0; 169,7	0:1



- Erweiterte Grundidee:



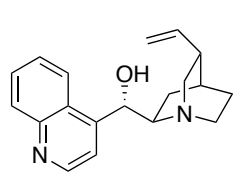
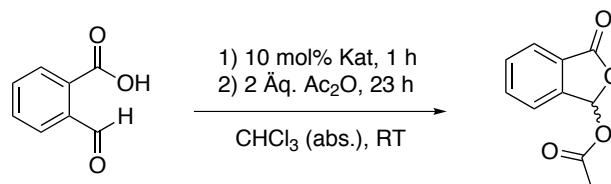
- Direkte Umsetzung: Cinchonaalkaloide als Base



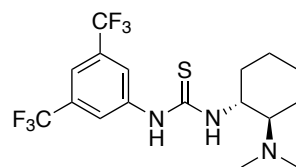
Optimierung der Reaktionsbedingungen

- Alkaloid (Art und Menge)
- Menge Ac_2O
- Lösungsmittel
- Temperatur
- Reaktionszeiten

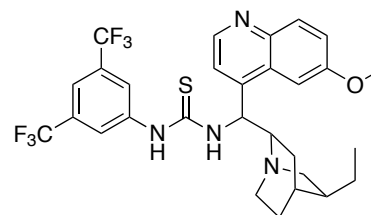
*bestimmt via chiraler Gaschromatographie



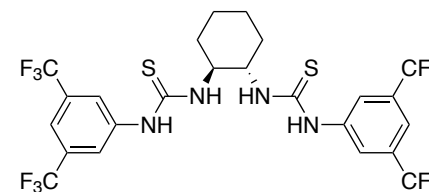
I



II



III



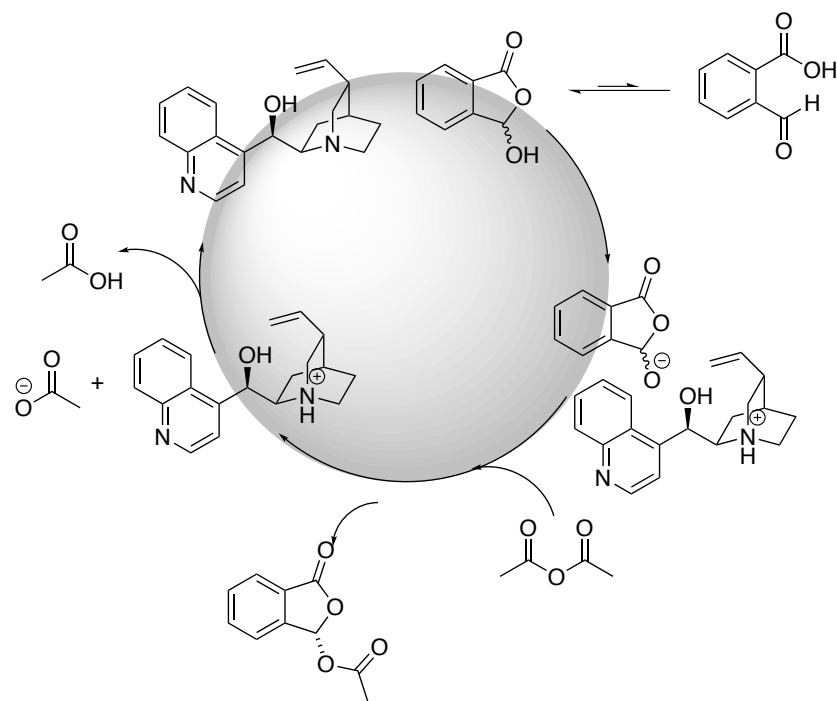
IV

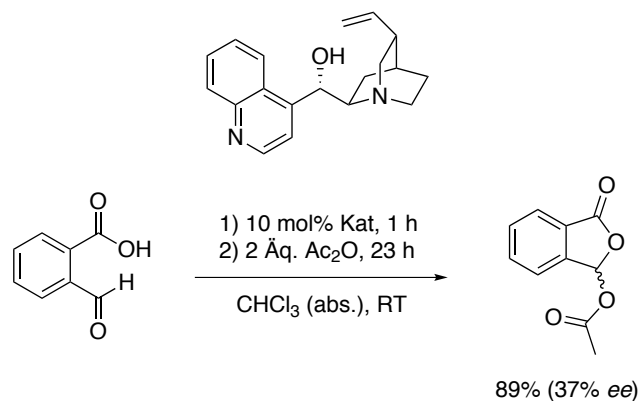
Eintrag	Katalysator	Ausbeute [%] ¹⁾	e.r. [%] ²⁾
1	I	89	68:32
2	II*	77	60:40
3	III*	74	38:62
4	IV**	96	51:49

¹⁾isolierte Ausbeute ²⁾bestimmt via chiraler Gaschromatographie

*Katalysatoren synthetisiert von Honman Yau, PhD

**Katalysator synthetisiert von Dr. Katharina Lippert

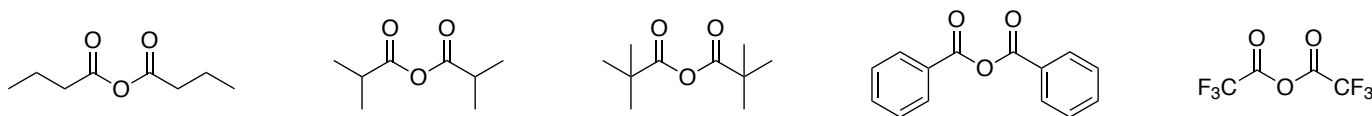




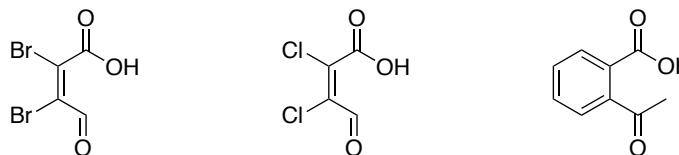
- Weiterer Zugang zu Lactonen durch Cyclisierung von 2-Carboxybenzaldehyd
 - Stöchiometrische Variante
 - Katalytische enantioselektive Variante
 - Möglicher Mechanismus



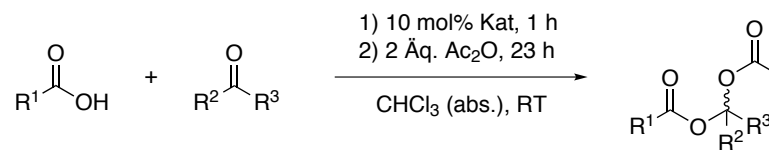
Verwendung weiterer Säureanhydride



Erweiterung des Substratpools



Erstellen eines Protokolls für eine intermolekulare Variante der Synthese von geminalen Diestern



$\text{R}^1, \text{R}^2, \text{R}^3 = \text{Alkyl, Aryl}$



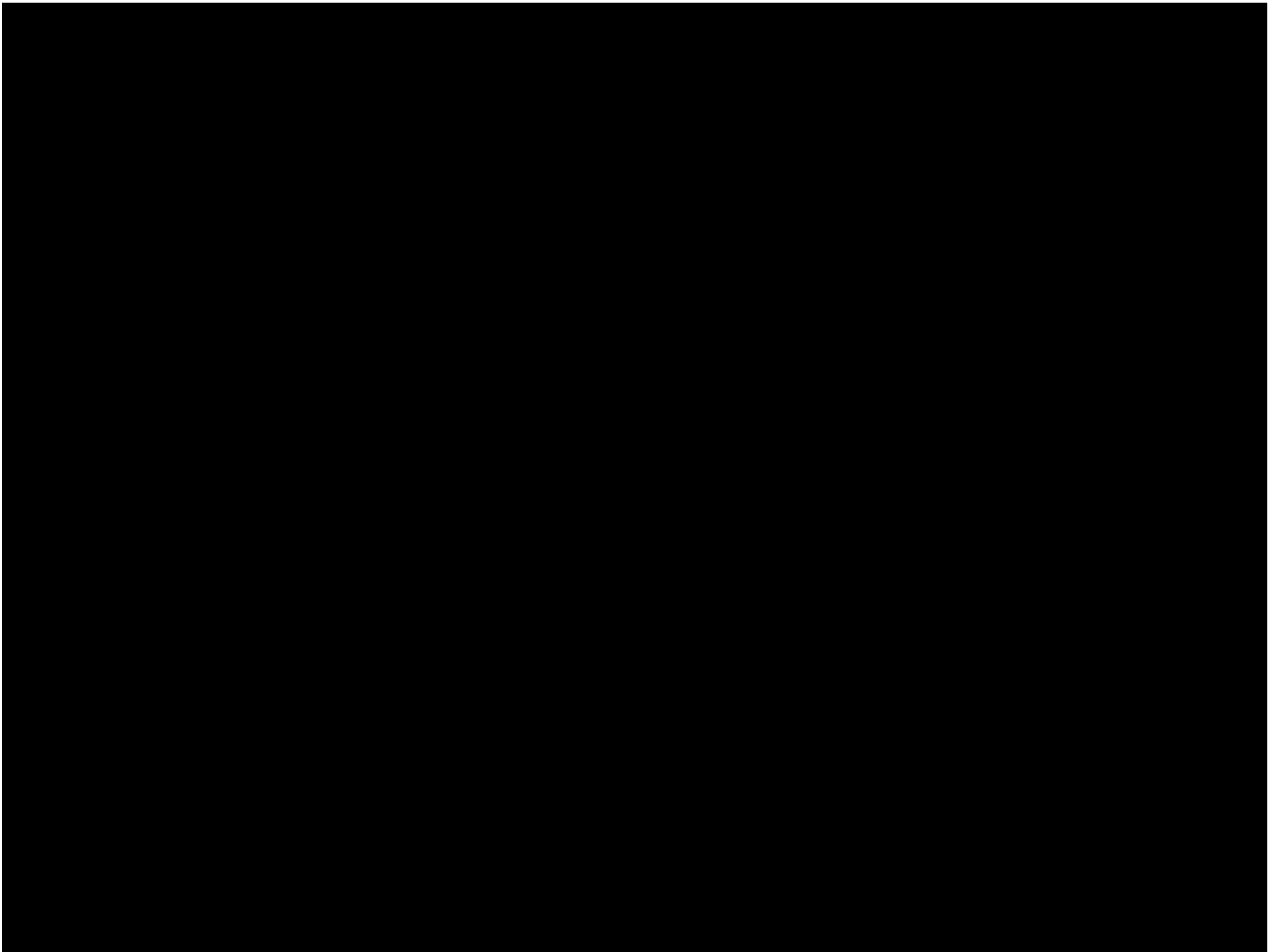
- Prof. Schreiner
- Dipl. Chem. S. Schuler
- R. Wende, M. Sc.
- C. Hofmann, M. Sc.
- Philipp, Michi, Alex und Jan
- Cesare Savarino
- Dr. Honman Yau und Dr. Katharina Lippert
- Dr. Dennis Gerbig
- AG Schreiner
- Team der OC-Analytik
- Rainer Schmidt



Vielen Dank für Ihre Aufmerksamkeit!

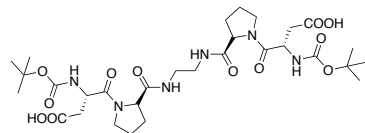
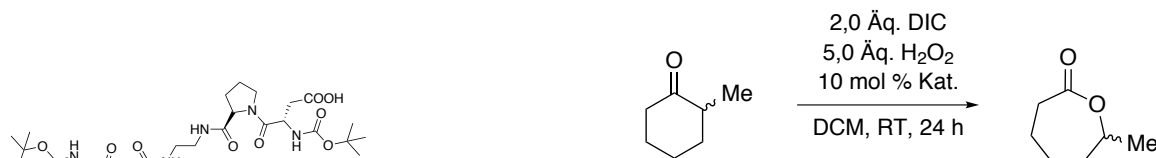


Fragen???

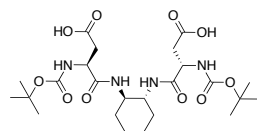




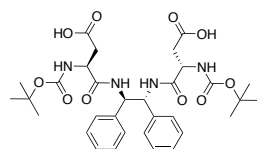
2-Methylcyclohexanon



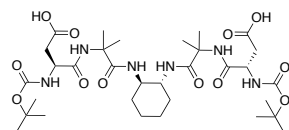
DN2 (49%)



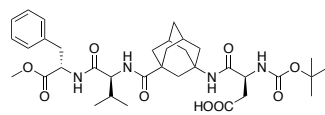
DN3 (76%)



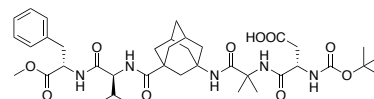
DN4 (82%)



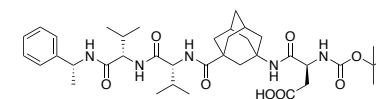
DN5 (39%)



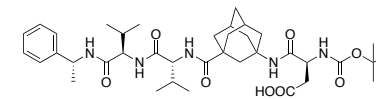
DN6 (46%)



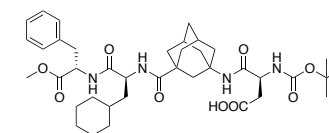
DN7 (15%)



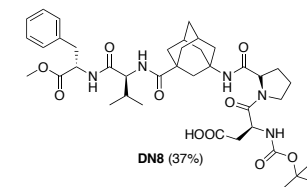
DN11 (22%)



DN10 (21%)



DN9 (32%)



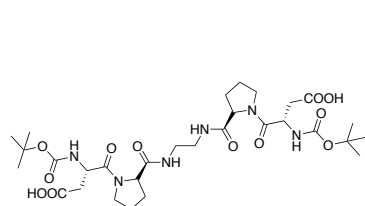
DN8 (37%)

Eintrag	Katalysator	C [%] [*]	e.r. (Edukt) [*]	e.r. (Produkt) [*]
1	DN2	36	50:50	50:50
2	DN3	17	51:49	52:48
3	DN4	20	51:49	52:48
4	DN5	43	50:50	49:51
5	DN6	2	50:50	47:53
6	DN7	82	50:50	50:50
7	DN8	43	50:50	51:49
8	DN9	44	50:50	50:50
9	DN10	57	50:50	50:50
10	DN11	38	50:50	50:50

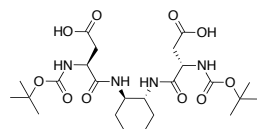
^{*}bestimmt via chiraler Gaschromatographie



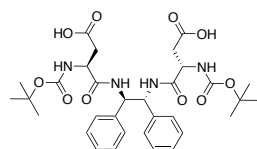
3-Methylcyclohexanon



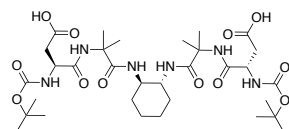
DN2 (49%)



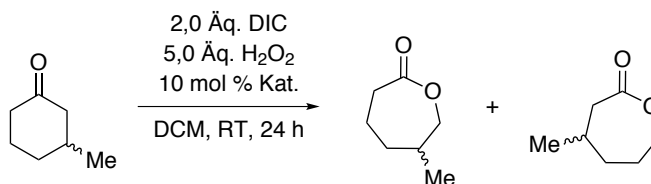
DN3 (76%)



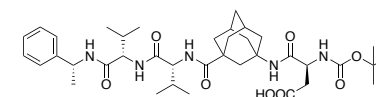
DN4 (82%)



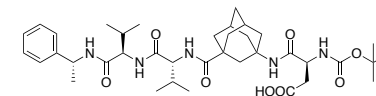
DN5 (39%)



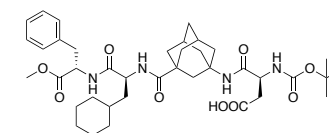
Eintrag	Katalysator	C [%] [*]	e.r. (77d ¹) [*]	e.r. (77d ²) [*]	Verhältnis [*]
1	DN2	19	50:50	50:50	96:100
2	DN3	10	50:50	50:50	88:100
3	DN4	6	50:50	50:50	98:100
4	DN5	23	53:47	47:53	97:100
5	DN6	2	46:54	45:55	92:100
6	DN8	13	50:50	50:50	97:100
7	DN9	15	50:50	50:50	95:100
8	DN10	14	50:50	50:50	95:100
9	DN11	9	50:50	50:50	95:100



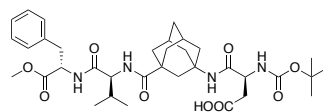
DN11 (22%)



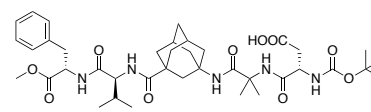
DN10 (21%)



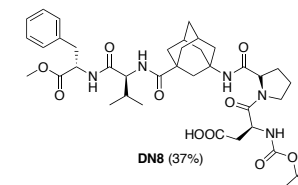
DN9 (32%)



DN6 (46%)



DN7 (15%)

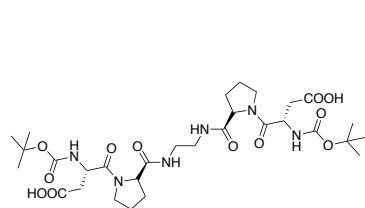


DN8 (37%)

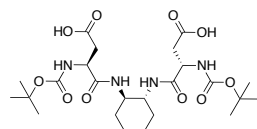
^{*}bestimmt via chiraler Gaschromatographie



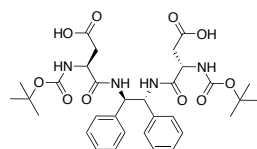
4-Methylcyclohexanon



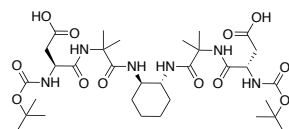
DN2 (49%)



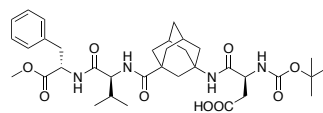
DN3 (76%)



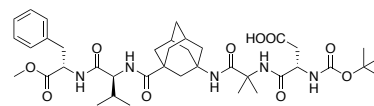
DN4 (82%)



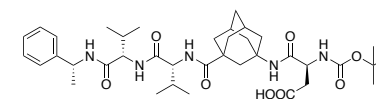
DN5 (39%)



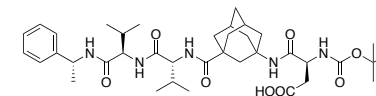
DN6 (46%)



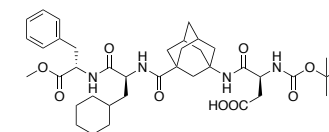
DN7 (15%)



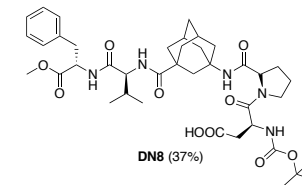
DN11 (22%)



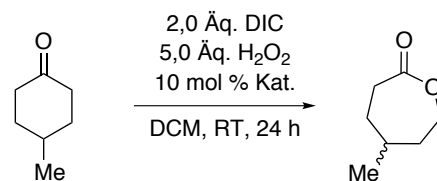
DN10 (21%)



DN9 (32%)



DN8 (37%)

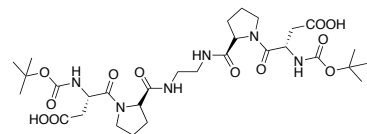


Eintrag	Katalysator	C [%] [*]	e.r. [*]
1	DN2	25	50:50
2	DN3	14	49:51
3	DN4	8	47:53
4	DN5	29	46:54
5	DN6	3	50:50
6	DN7	10	50:50
7	DN8	18	50:50
8	DN9	21	50:50
9	DN10	20	50:50
10	DN11	14	50:50

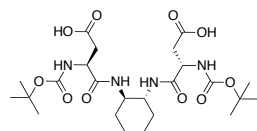
^{*}bestimmt via chiraler Gaschromatographie



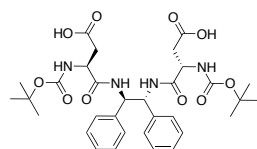
2-*tert.*-Butylcyclohexanon



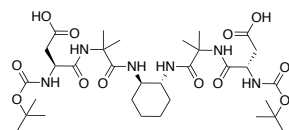
DN2 (49%)



DN3 (76%)

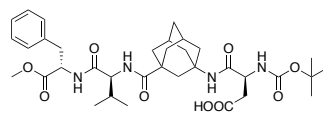


DN4 (82%)

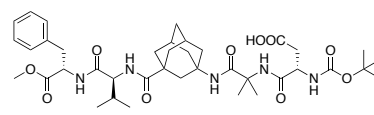


DN5 (39%)

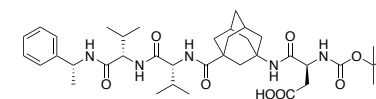
Eintrag	Katalysator	C [%] [*]	e.r. (Edukt) [*]	e.r. (Produkt) [*]
1	DN2	1	50:50	49:51
2	DN3	0	50:50	-
3	DN4	0	50:50	-
4	DN5	1	50:50	46:54
5	DN6	0	50:50	50:50
6	DN7	1	50:50	50:50
7	DN8	0	50:50	-
8	DN9	0	50:50	-
9	DN10	0	50:50	-
10	DN11	0	50:50	-



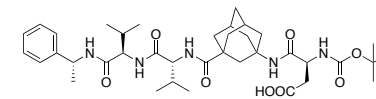
DN6 (46%)



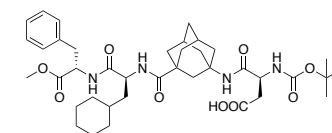
DN7 (15%)



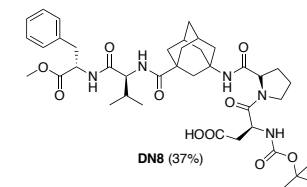
DN11 (22%)



DN10 (21%)



DN9 (32%)

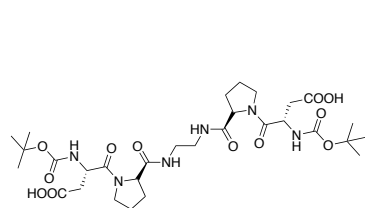


DN8 (37%)

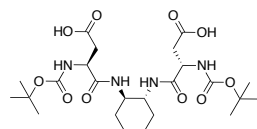
^{*}bestimmt via chiraler Gaschromatographie



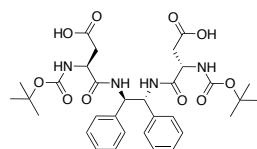
4-*tert*.-Butylcyclohexanon



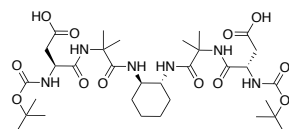
DN2 (49%)



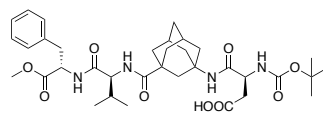
DN3 (76%)



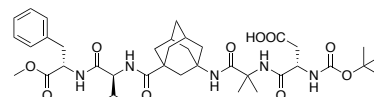
DN4 (82%)



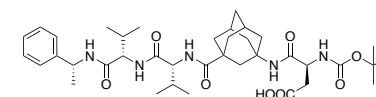
DN5 (39%)



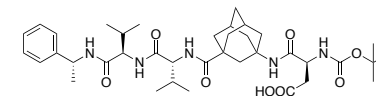
DN6 (46%)



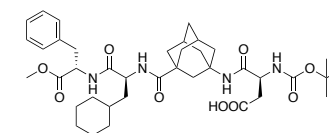
DN7 (15%)



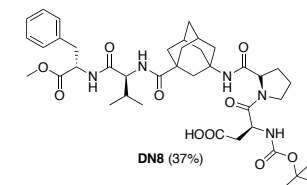
DN11 (22%)



DN10 (21%)

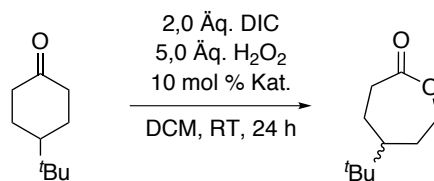


DN9 (32%)



DN8 (37%)

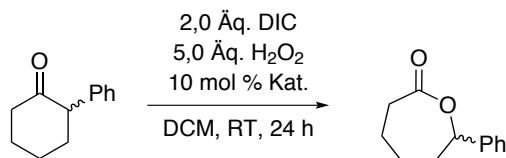
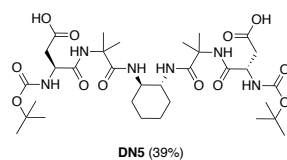
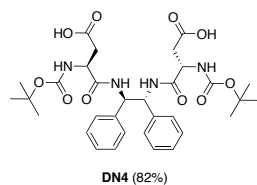
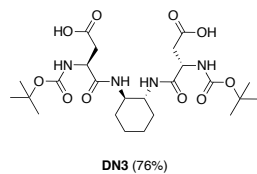
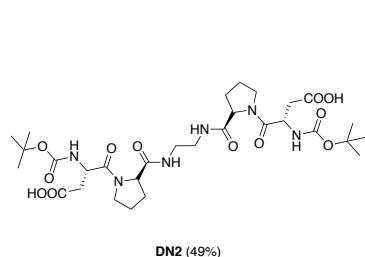
Eintrag	Katalysator	C [%] [*]	e.r. [*]
1	DN2	28	50:50
2	DN3	14	52:48
3	DN4	1	52:48
4	DN5	25	56:44
5	DN6	5	49:51
6	DN7	18	50:50
7	DN8	18	50:50
8	DN9	22	49:51
9	DN10	22	50:50
10	DN11	16	50:50



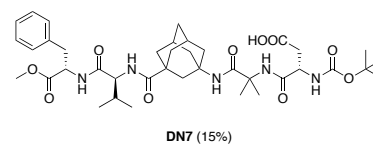
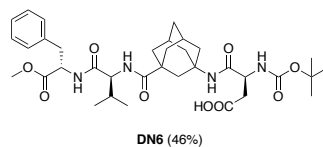
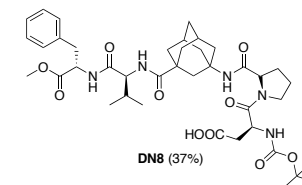
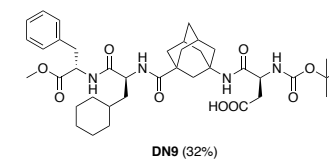
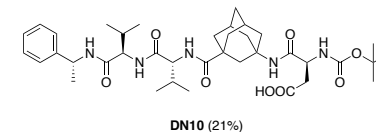
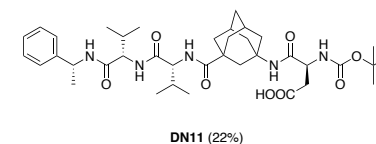
^{*}bestimmt via chiraler Gaschromatographie



2-Phenylcyclohexanon



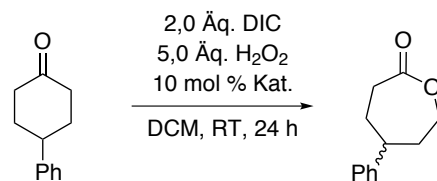
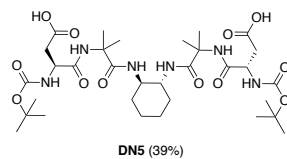
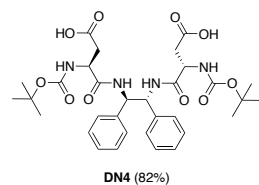
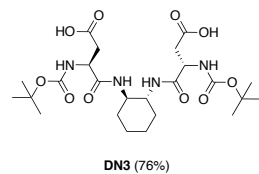
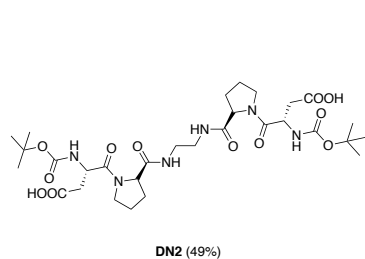
Eintrag	Katalysator	C [%] [*]	e.r. (Edukt) [*]	e.r. (Produkt) [*]
1	DN2	53	50:50	50:50
2	DN3	35	49:51	53:47
3	DN4	33	51:49	51:49
4	DN5	44	n.b.	49:51
5	DN6	24	50:50	50:50
6	DN7	90	n.b.	50:50
7	DN8	52	50:50	50:50
8	DN9	72	50:50	50:50
9	DN10	86	n.b.	50:50
10	DN11	64	50:50	50:50



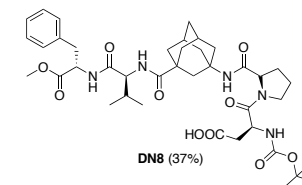
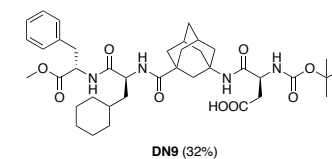
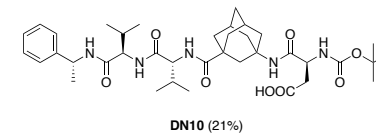
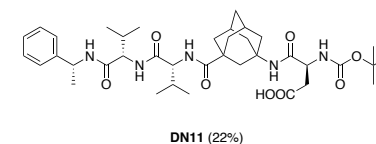
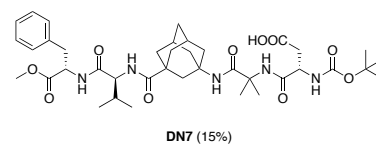
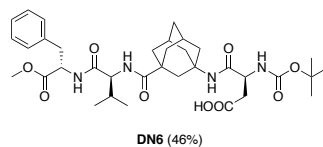
^{*}bestimmt via chiraler Gaschromatographie
n.b. = nicht bestimmt



4-Phenylcyclohexanon



Eintrag	Katalysator	C [%] [*]	e.r. [*]
1	DN2	21	50:50
2	DN3	10	52:48
3	DN4	6	53:47
4	DN5	26	56:44
5	DN6	4	51:49
6	DN7	10	50:50
7	DN8	12	50:50
8	DN9	11	50:50
9	DN10	14	51:49
10	DN11	4	51:49



*bestimmt via chiraler Gaschromatographie