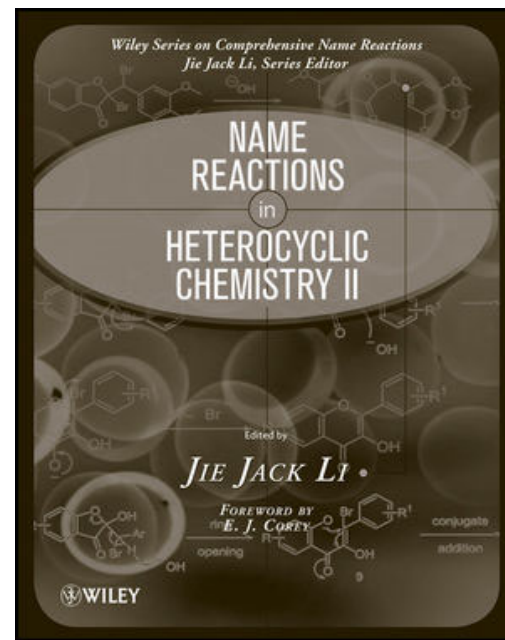
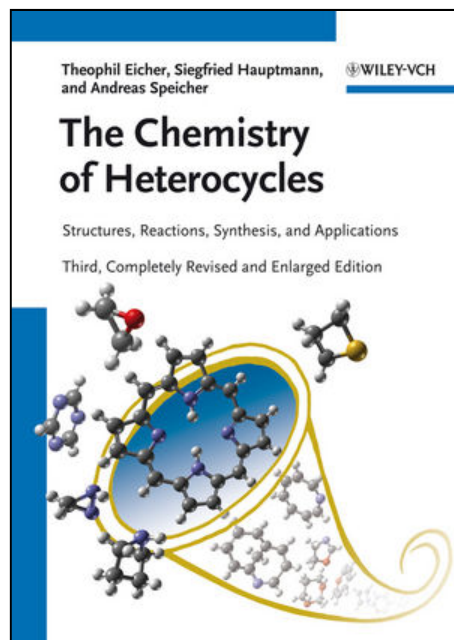
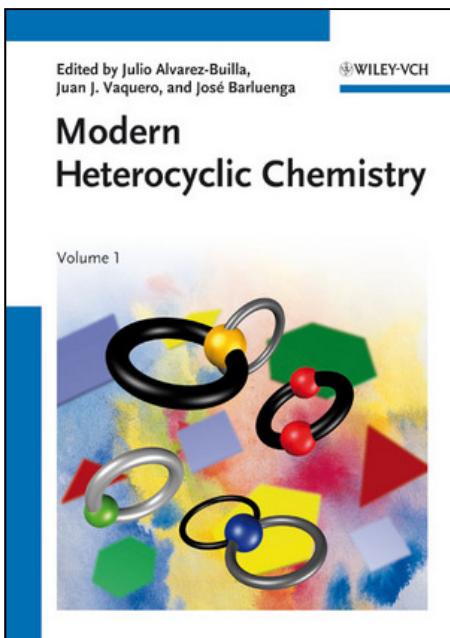


Heterozyklenchemie

Inhalt

- A. Nomenklatur
- B. Dreigliedrige Ringe
- C. Viergliedrige Ringe
- D. Fünfring-Aromaten
- E. Sechsring-Aromaten
- F. Siebengliedrige Ringe



**Heterozyklus (IUPAC):
Zyklische Verbindung mit mindestens zwei verschiedenen
Ringatomen**

"The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic [...].

Nevertheless, it is still, in the 21st century, possible to graduate from an American university with a Ph.D. in organic chemistry with but a desultory knowledge of heterocyclic chemistry (and even in extreme cases to be proud of it!).

For many recruits to positions in the pharmaceutical industry, a fast introduction to heterocyclic chemistry is a must."

(Alan J. Katritzky, *Chem. Rev.* **2004**, 2125)

Heterozyklenchemie

Nobelpreis für Chemie 2022 an Carolyn R. Bertozzi, Morten Meldal, K. Barry Sharpless

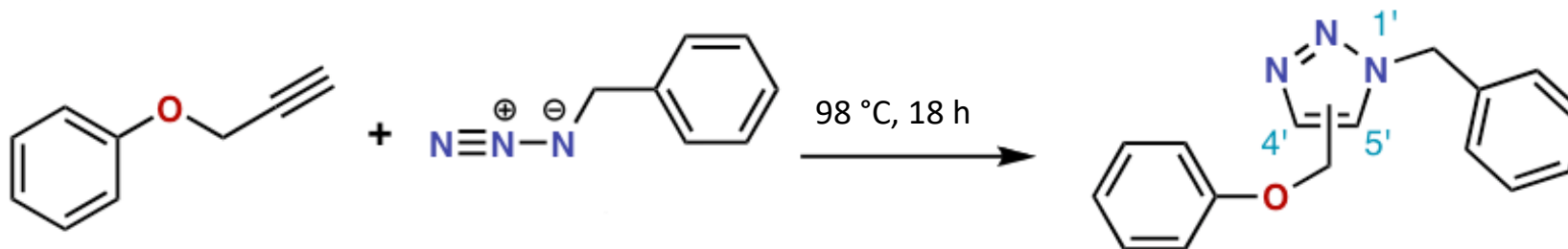
"It just says click – and the molecules are coupled together"



Rolf Huisgen
(1920-2020)

<https://cen.acs.org>

Huisgen-Reaktion

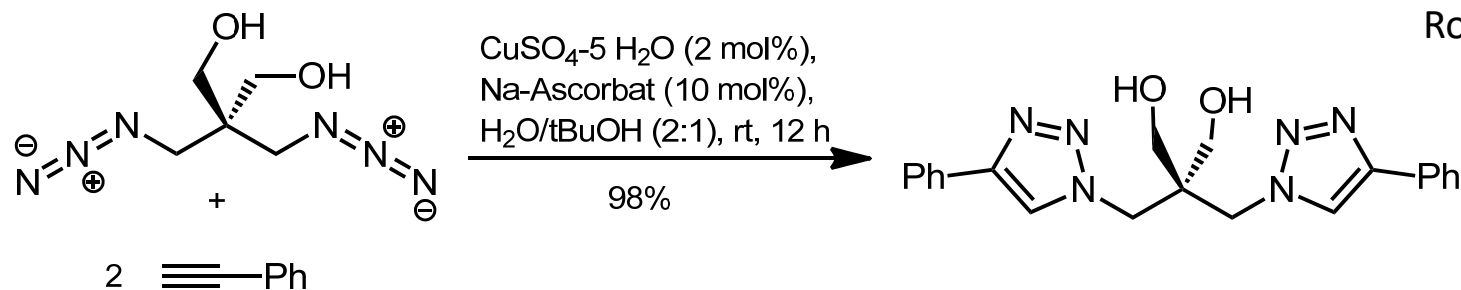


Cu(I)-Katalyse (Meldal, Sharpless, 2002):
schneller, regioselektiv zum 1,4-disubst. Triazol,
bioorthogonale "Click-Chemie"

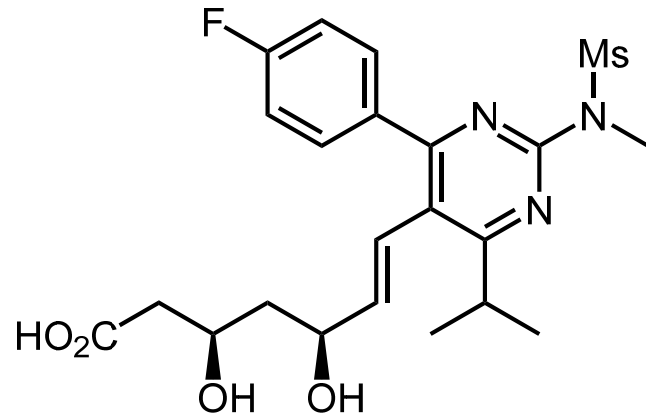
Cu(I) in situ aus Cu(II) und Ascorbat



Rolf Huisgen (1920-2020)



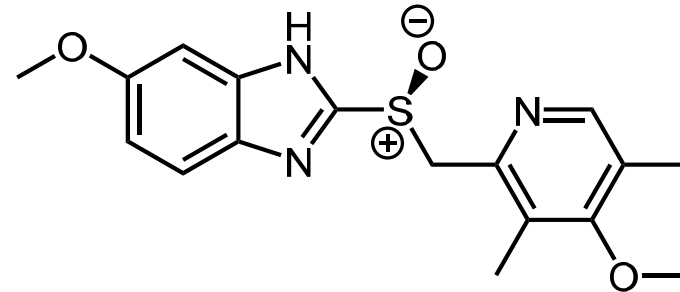
Ca. 45% der Pharmawirkstoffe sind Heterozyklen, darunter besonders umsatzstark (04/2014 - 03/2015):



Rosuvastatin

"Crestor", Astra-Zeneca/Shionogi, 21 Mrd. \$/a

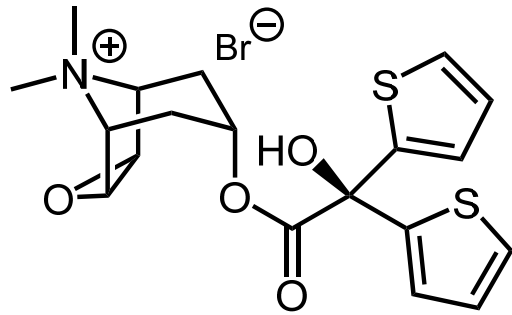
Inhibition der Reduktion des 3-Hydroxy-3-methylglutaryl-Coenzym A (HMG-CoA) zu Mevalonat, und damit der Synthese von Cholesterin



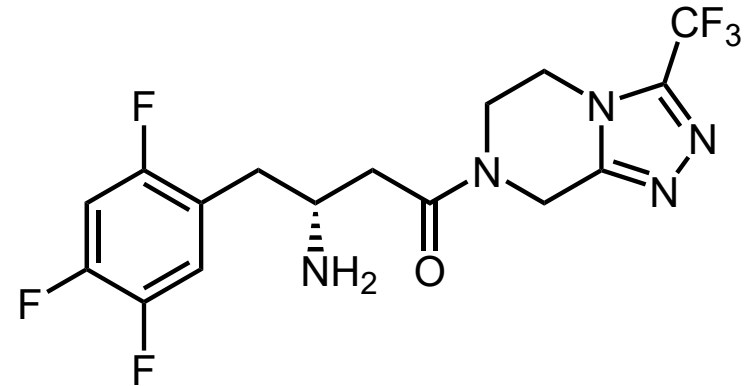
Esomeprazol (S-Enantiomer des Racemats Omeprazol)

"Nexium", Magengeschwüre, Reflux-Krankheit, Astra-Zeneca, 21 Mrd. \$/a)

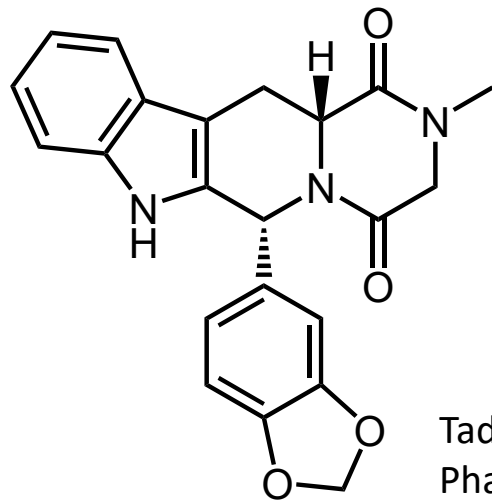
Hemmung der H⁺/K⁺-ATPase ("Protonenpumpenhemmer") in den Belegzellen des Magens



Thiotropiumbromid ("Spiriva", Boehringer Ingelheim/Pfizer, 10 Mrd. \$/a, Anticholinergikum, bei chronischer obstruktiver Lungenkrankheit)

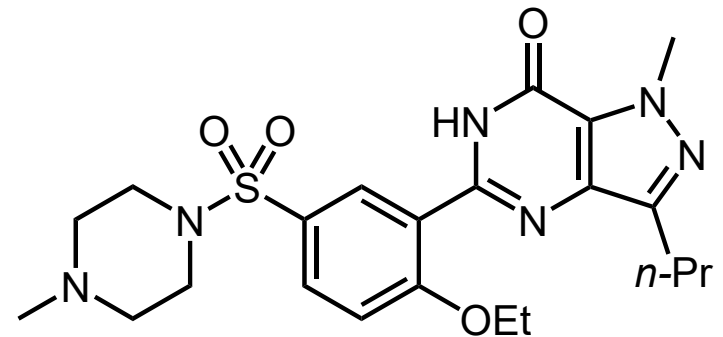


Sitagliptin ("Januvia", Merck&Co, 9 Mrd. \$/a, Hemmer der Dipeptidylpeptidase 4, Senkung des Blutzuckerspiegels, bei Diabetes Typ 2)



Gefäßerweiterung durch Hemmung der Phosphodiesterase 5

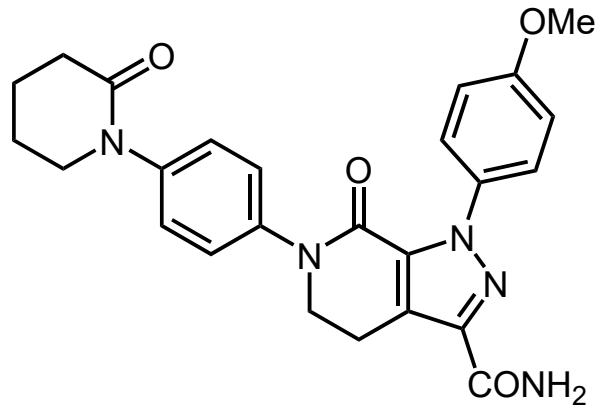
Tadalafil ("Cialis", Lilly Pharma, 7 Mrd \$/a)



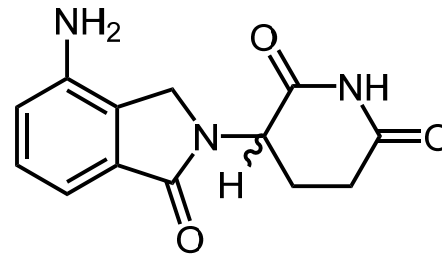
Sildenafil ("Viagra", Pfizer, 7 Mrd \$/a)

Heterozyklenchemie

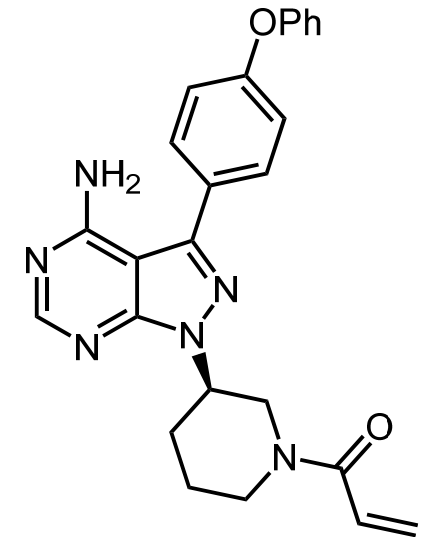
2021: Umsatzstärkste Heterozyklen (<https://www.drugdiscoverytrends.com>)



Apixaban ("Eliquis", 16 Mrd \$, Antikoagulans, Pfizer/BMS)



Lenalidomid ("Revlimid", 13 G\$, multiples Myelom, BMS)

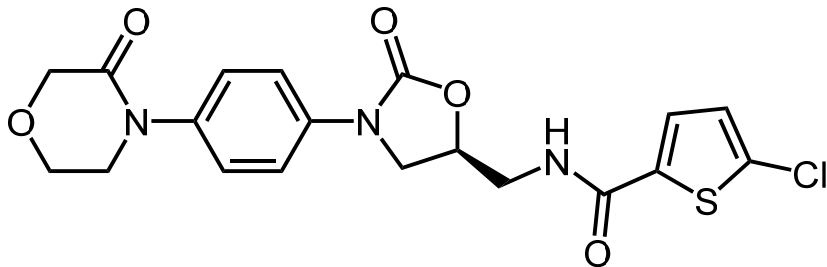


Ibrutinib ("Imbruvica", 10 G\$, Leukämie, Abbvie/Janssen)

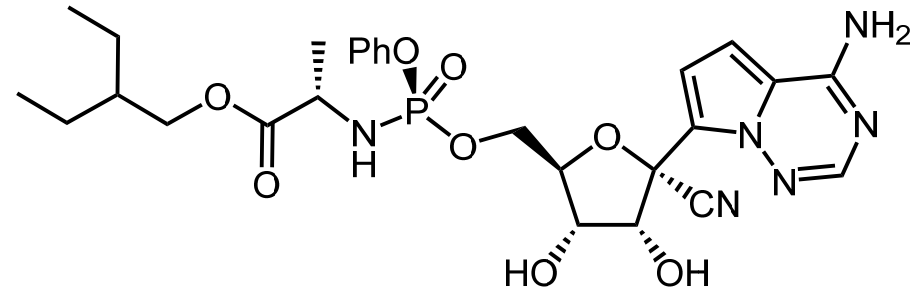


Heterozyklenchemie

2021: Umsatzstärkste Heterozyklen (<https://www.drugdiscoverytrends.com>)



Rivaroxaban ("Xarelto", 8 G\$, Antikoagulans, Bayer)

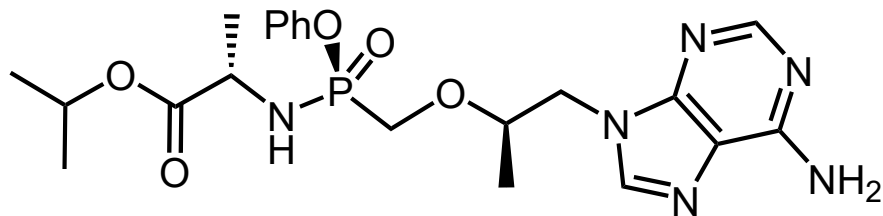
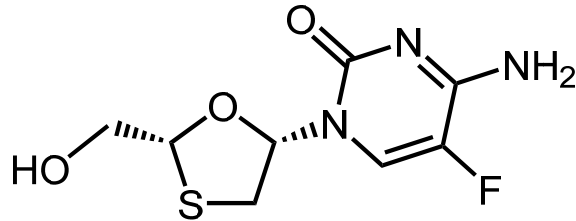
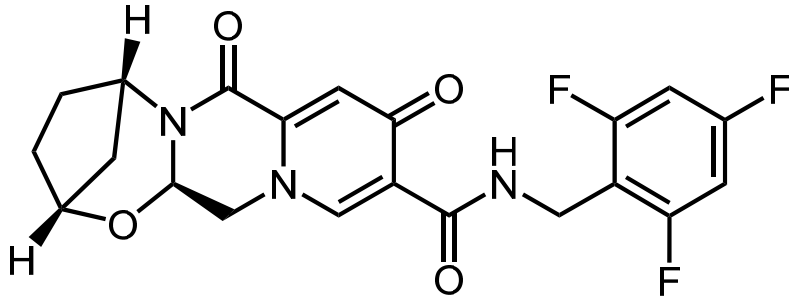


Remdesivir ("Veklury", 6 G\$, Covid-19, Gilead)



Heterozyklenchemie

2021: Umsatzstärkste Heterozyklen (<https://www.drugdiscoverytrends.com>)



Bictegravir, Emtricitabine, Tenofoviralfenamid (-> "Biktarvy", 9 G\$, AIDS, Gilead)

2021: Umsatzstärkste Heterozyklen (<https://www.drugdiscoverytrends.com>)

```
GAGAAΨAAAC ΨAGΨAΨΨCΨΨ CΨGGΨCCCCA CAGACΨCAGA GAGAACCCGC 50
CACCAΨGΨΨC GΨGΨΨCCΨGG ΨGCΨGCΨGCC ΨCΨGGΨGΨCC AGCCAGΨGΨG 100
ΨGAACCCΨC cap 5'-UTR sig S protein_mut 3'-UTR poly(A) ΨΨ 150
ACCAGAGC 200
CΨCΨACCCAG GACCΨGΨΨCC ΨGCCΨΨΨCΨΨ CAGCAACGΨG ACCΨGGΨΨCC 250
ACGCCAΨCCA CGΨGΨCCGGC ACCAAΨGGCA CCAAGAGAΨΨ CGACAACCCC 300
GΨGCΨGCCCY ΨCAACGACGG GGΨGΨACΨΨΨ GCCAGCACCG AGAAGΨCCAA 350
CAΨCAΨCAGA GGCΨGGAΨCΨ ΨCGGCACCAC ACΨGGACAGC AAGACCCACA 400
GCCΨGCΨGAΨ CGΨGAACAAC GCCACCAACG ΨG
ΨΨCCAGΨΨCΨ GCAACGACCC CΨΨCCΨGGGC GΨ
CAAGAGCΨGG AΨGGAAAGCG AGΨΨCCGGGΨ GΨ
GCACCΨΨCGA GΨACGΨGΨCC CAGCCΨΨΨCC ΨG
CAGGGCAACΨ ΨCAAGAACCΨ GCGCGAGΨΨC GΨ
CΨACΨΨCAAG AΨCΨACAGCA AGCACACCCC ΨA
ΨGCCΨCAGGG CΨΨCΨCΨGCΨ CΨGGAACCCC ΨG
AΨCAACAΨCA CCCGGΨΨΨCA GACACΨGCΨG GC
GACACCΨGGC GAΨAGCAGCA GCGGAΨGGAC AG
AΨGΨGGGCΨA CCΨGCAGCCΨ AGAACCCΨΨC ΨG
GGCACCAΨCA CCGACGCCGΨ GGAΨΨGΨGCΨ CΨ
AAAGΨGCACC CΨGAAGΨCCΨ ΨCACCGΨGGA AA
...
```



Ugur Sahin, Özlem Türeci
The New York Times, 20.11.2020

aus: WHO,
International nonproprietary names
programme 11889

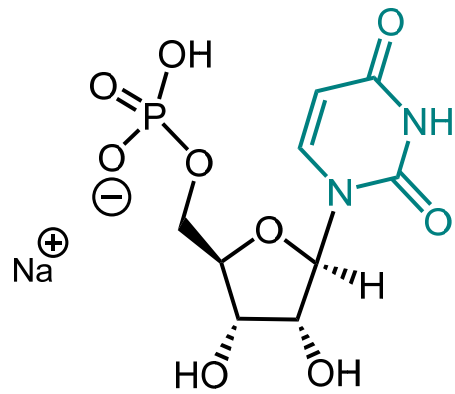
Ψ (hier) = 1-Methyl-3'-
pseudouridyl
(m¹Ψ)

Cominarty (60 G\$,
Biontech/Pfizer)

"The meteoric rise of the
COVID-19 vaccine from
Pfizer and BioNTech has
little precedent in the
pharmaceutical industry."

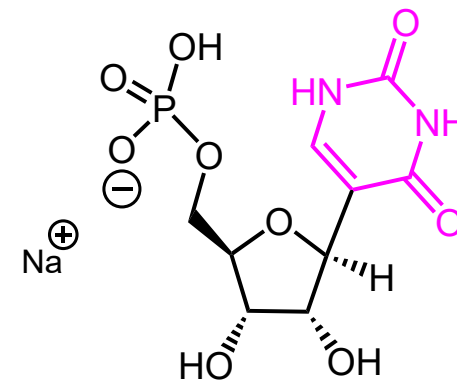
<https://www.nytimes.com/2020/11/10/business/biontech-covid-vaccine.html>

What is Ψ ? Ok, it's a Greek letter.



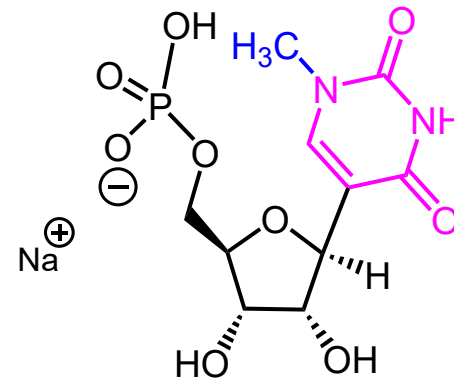
Uridinmonophosphat

Umwandlung von Uridin in Pseudouridin ist die häufigste Modifikation zellulärer RNA.

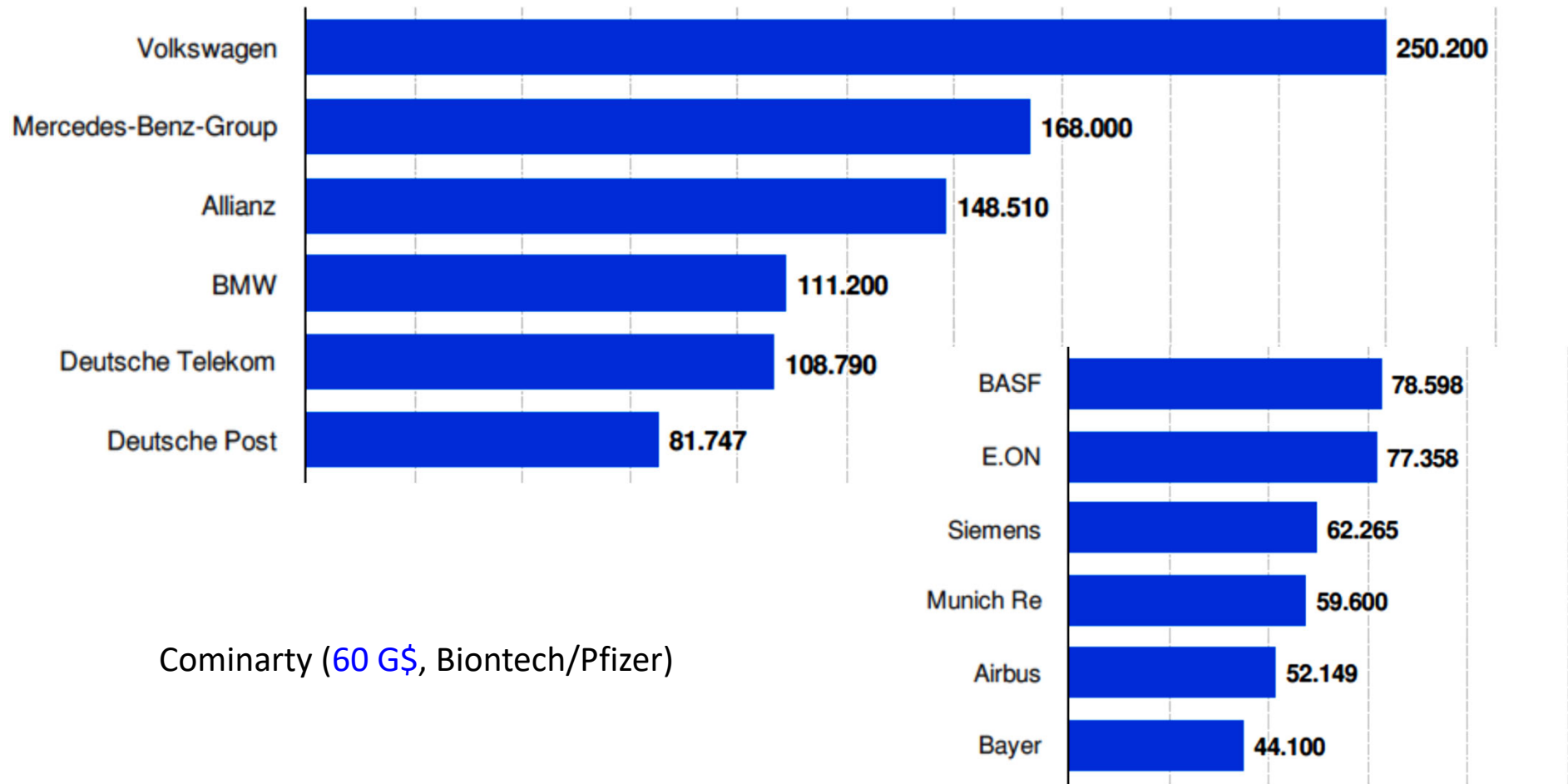


Pseudouridinmonophosphat

mRNA mit *N*-Methylpseudouridinmonophosphat-Bausteinen wird vom Immunsystem nicht erkannt.

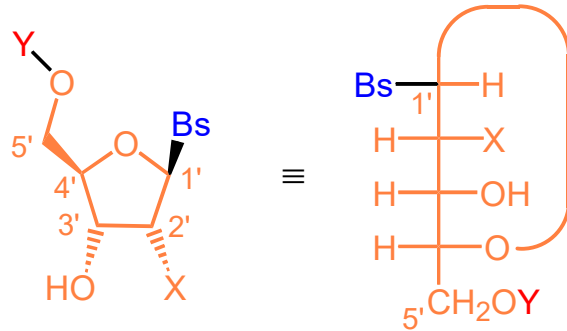


Zum Vergleich: Umsätze ausgewählter DAX-Konzerne 2021 (<https://de.statista.com>):



Heterozyklenchemie

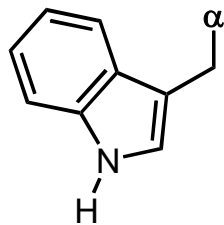
z. B. Bausteine der Nukleinsäuren



Bs = H, Y = H, X = OH: D-Ribose
 X = H: D-2'-Desoxyribose

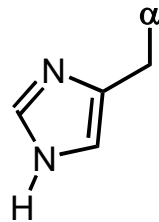
Tetrahydrofuran

z. B. proteinogene Aminosäuren



Tryptophan (Trp, W)

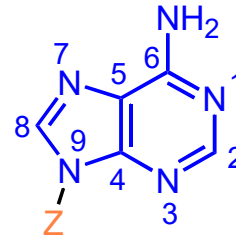
Indol



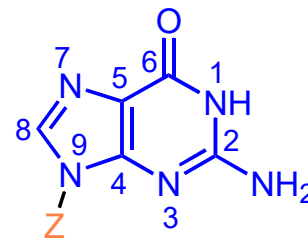
Histidin (His, H)

Imidazol

Bs:

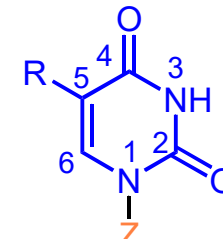


Adenin

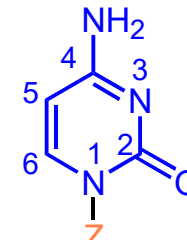


Guanin

Purin

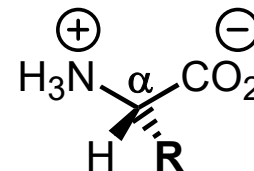


Uracil (R=H) in RNA
 Thymin (R=Me) in DNA



Cytosin

Pyrimidin



(allgemeiner Aufbau)

A. Nomenklatur - A.1 Stammsysteme

Hantzsch-Widman-System (1887/8; IUPAC seit 1957)

Ringgröße	N-haltig		nicht N-haltig	
	unges.	voll gesättigt	unges.	voll gesättigt
3	-irin	-iridin	-iren	-iran
4	-et	-etidin	-et	-etan
5	-ol	-olidin	-ol	-olan
6	-in	Perhydro-	-in	-an
7	-epin	Perhydro-	-epin	-epan
8	-ocin	Perhydro-	-ocin	-ocan
9	-onin	Perhydro-	-onin	-onan
10	-ecin	Perhydro-	-ecin	-ecan
> 10	Ersetzungs-Nomenklatur			

**Priorisierung u.
Präfixes ausgew.
Heteroatome**

Ox(a) > Thi(a) >
Selen(a) > Az(a) >
Phosph(a) > Sil(a) >
Bor(a)

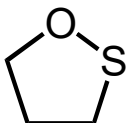
unvollst. ungesättigt:
Präfixes "Dihydro-",
"Tetrahydro-" usw.

A. Nomenklatur - A.1 Stammsysteme

Beispiele systematisch bezeichneter Stammsysteme:



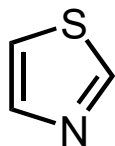
Oxiran



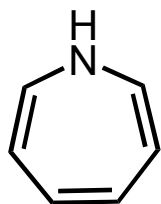
1,2-Oxathiolan



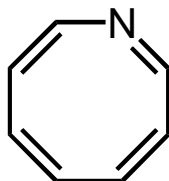
Aziridin



1,3-Thiazol

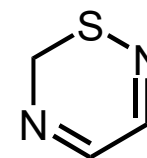


1H-Azepin



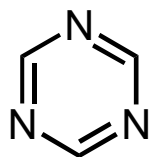
Azocin

Lindel, TU BS

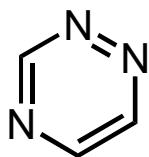


6H-1,2,5-Thiadiazin

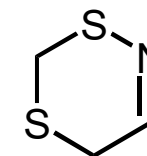
Multiplizität ident. Heteroatome:
Präfixes Di-, Tri-, Tetra- usw.



1,3,5-Triazin



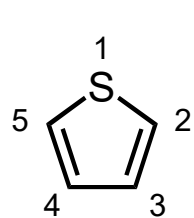
1,2,4- (nicht 1,3,4-)
Triazin



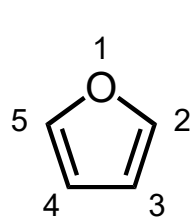
4H,6H-1,5,2-Dithiazin
nicht -1,3,4-, -1,3,6-, -1,5,4-

Unter den höchst priorisierten Heteroatomen (z. B. Thi(a) > Az(a)) erhält dasjenige die Position 1, ausgehend von dem ein minimales geordnetes Tupel aller Heteroatom-Positionen abzählbar ist.

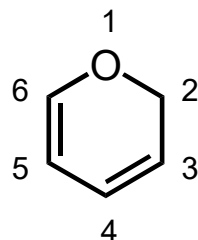
Spezielle Stammsysteme, beginnend mit der niedrigsten Priorität (in Klammern):



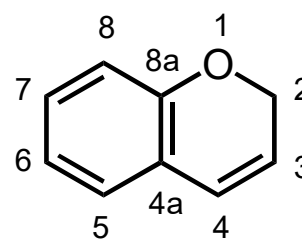
Thiophen (Nr. 1)



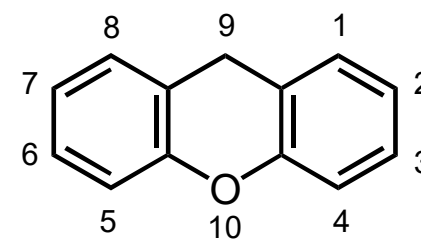
Furan (5)



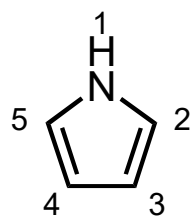
2H-Pyran (6)



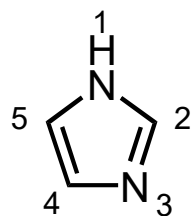
2H-Chromen (8)



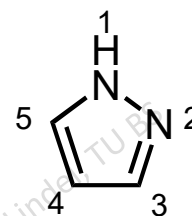
9H-Xanthen (9)



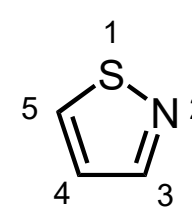
1H-Pyrrol (12)



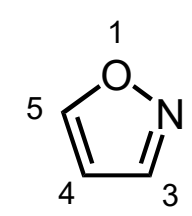
1H-Imidazol (13)



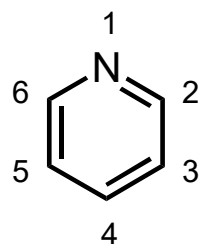
1H-Pyrazol (14)



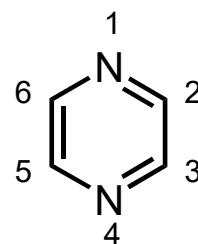
Isothiazol (14a)



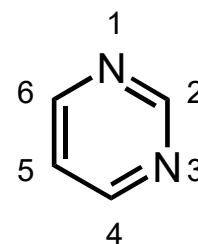
Isoxazol (14b)



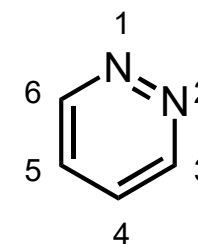
Pyridin (15)



Pyrazin (16)



Pyrimidin (17)

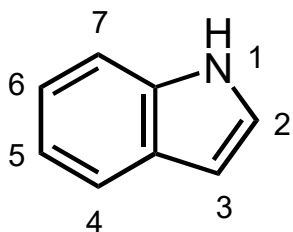


Pyridazin (18)

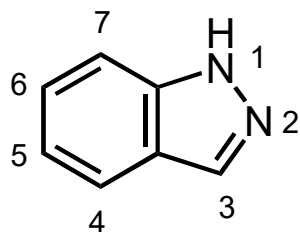
A. Nomenklatur - A.1 Stammsysteme

B.2 Stammsysteme mit Trivial-Bezeichnungen,

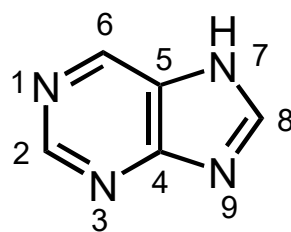
Fortsetzung:



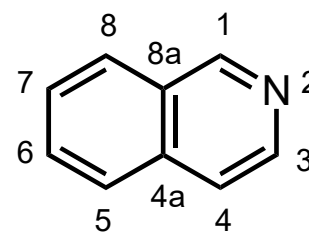
1H-Indol (22)



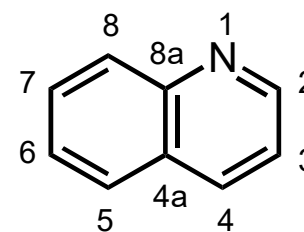
1H-Indazol (23)



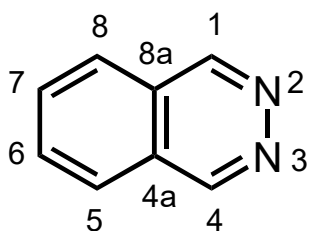
7H-Purin (24)



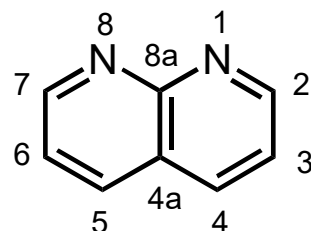
Isochinolin (26)



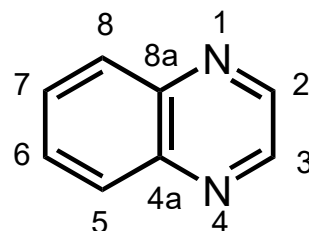
Chinolin (27)



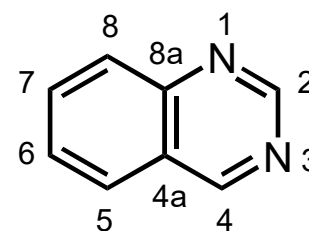
Phthalazin (28)



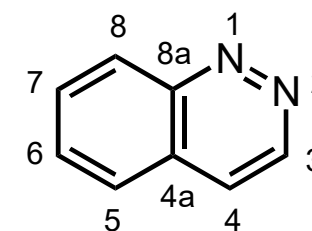
1,8-Naphthyridin (29)



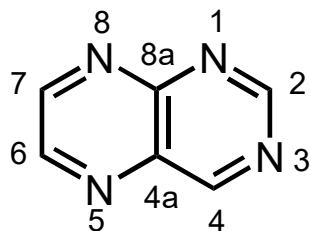
Chinoxalin (30)



Chinazolin (31)



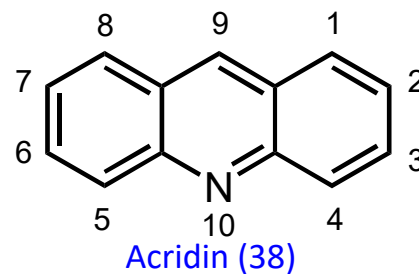
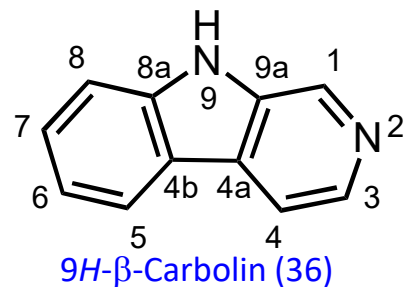
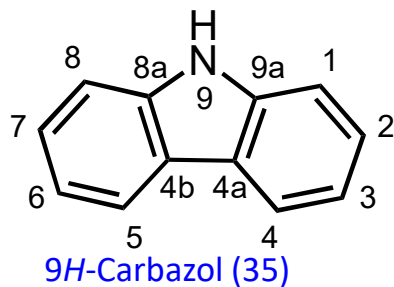
Cinnolin (32)



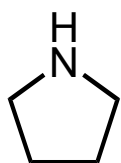
Pteridin (33)

dt. "chin..." = engl. "quin..."

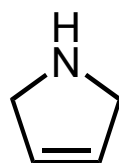
A. Nomenklatur - A.1 Stammsysteme



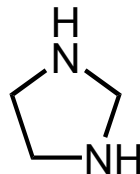
weitere gebräuchliche Trivialnamen,
deren Verwendung in systematischen Namen von der IUPAC nicht empfohlen wird:



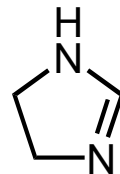
Pyrrolidin



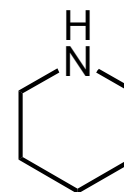
3-Pyrrolin



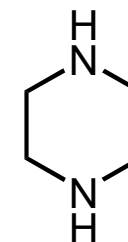
Imidazolidin



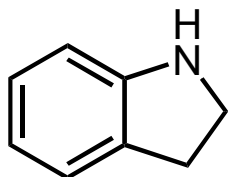
2-Imidazolin



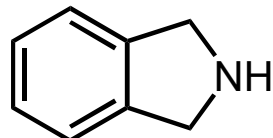
Piperidin



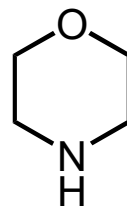
Piperazin



Indolin



Isoindolin



Morpholin

A. Nomenklatur - A.2 Anellierte Systeme

2 Ebenen:

Komponentensysteme (**Stammsystem** / anellierte Ringe) und **Gesamtsystem**

1) Orientierung des Gesamtsystems:

- (a) Zahl der Ringe in horizontaler Anordnung maximal,
- (b) maximale Zahl von Ringen im rechten oberen Quadranten.

und minimale Nummerierung

- (c) der Gesamtheit der Heteroatome,
- (d) höher priorisierter Heteroatome,
- (e) zwei Ringen gemeinsamer C-Atome,
- (f) hydrierter Atome.

(fallende Priorität der Regeln (a)-(f))

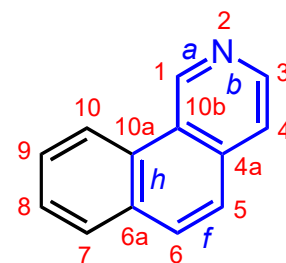
2) Benennung (Regeln nach fallender Priorität):

- (a): Stammsystem N-haltig und von möglichst hoher Priorität (s. Liste).

Nummerierung des Gesamtsystems:

Im Uhrzeigersinn; beginnend mit dem Atom in der am weitesten links befindlichen Position des rechten oberen Rings (kein Brückenkopfatom!).

Positionsziffern des anellierten Systems entsprechen nicht denen der Teilsysteme!



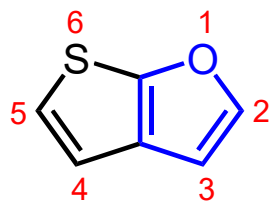
Benz[*h*]isochinolin
(nicht:
Pyrido[3,4-*a*]naphthalin)

[:

Kleinbuchstabe: ermittelt aus der Positionsziffernnumerierung d. **Stammsystems** ("*a*": zw. Atomen 1 und 2, usw.). Ziffern: beteiligte Bindung des anellierten Systems, beginnend mit der an die niedriger nummerierte Position des Stammsystems geknüpften Position.

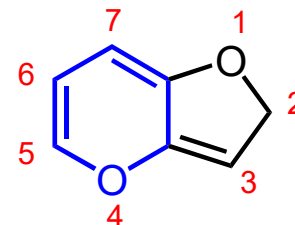
A. Nomenklatur - A.2 Anellierte Systeme

(b) Stammsystem bei Abwesenheit von Stickstoff nach Priorität der Heteroatome ("O>S>P>B")



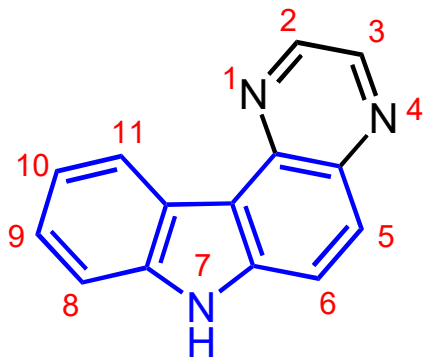
Thieno[2,3-*b*]furan
nicht: Furo[2,3-*b*]thiophen

(d) Stammsystem mit größtem Ring



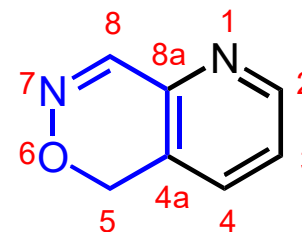
2*H*-Furo[3,2-*b*]pyran
nicht: 2*H*-Pyrano[3,2-*b*]furan

(c) Stammsystem mit der größten Zahl von Ringen



7*H*-Pyrazino[2,3-*c*]carbazol
nicht: 7*H*-Indolo[3,2-*f*]chinoxalin

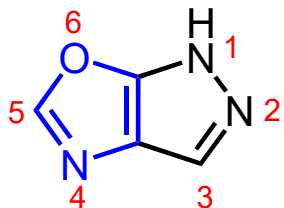
(e) Stammsystem mit der größten Zahl von Heteroatomen



5*H*-Pyrido[2,3-*d*]-*o*-oxazin
nicht: *o*-Oxazino[4,5-*b*]pyridin

A. Nomenklatur - A.2 Anellierte Systeme

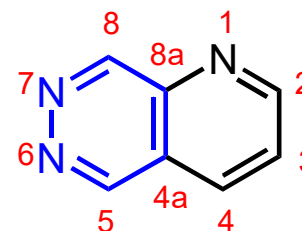
(f) Stammsystem mit der größten Vielfalt von Heteroatomen



Oxazol nicht in Liste definierter Stammsysteme (Trivialnamen) verzeichnet
=> systematische Benennung ("O>S>Se>N>P>Si>B")

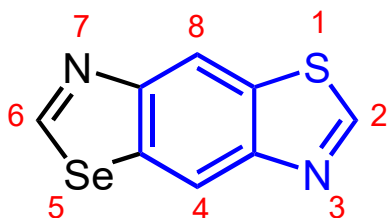
1*H*-Pyrazolo[4,3-*d*]oxazol
nicht: 1*H*-Oxazolo[5,4-*c*]pyrazol

(h) sonst: Stammsystem mit der kleinsten Zahl von Heteroatomen in der Nähe der Ringverknüpfungen



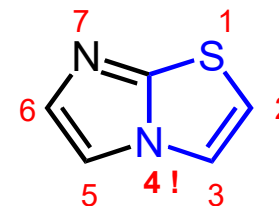
Pyrazino[2,3-*d*]pyridazin

(g) bei gleicher Vielfalt Stammsystem mit dem höchst priorisierten Heteroatom



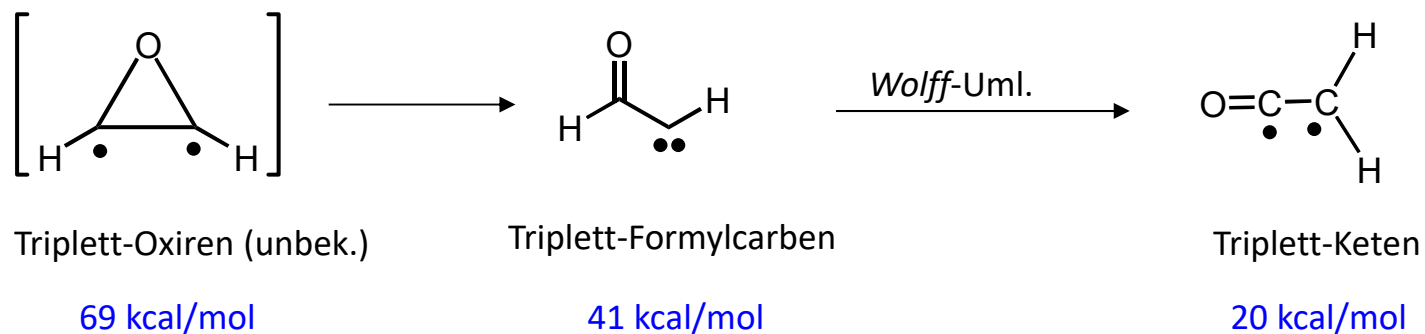
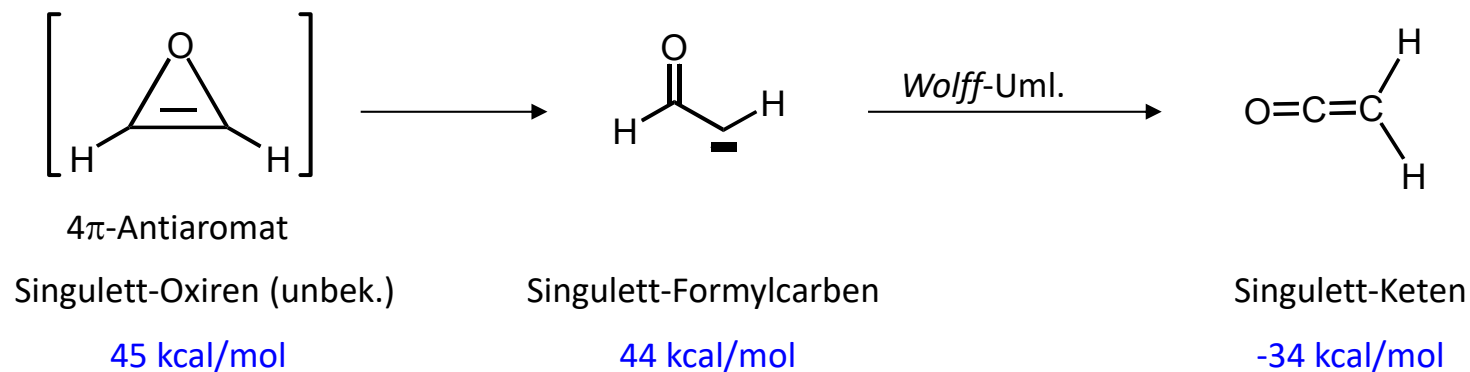
Selenazolo[5,4-*f*]benzothiazol
nicht: Thiazolo[5,4-*f*]benzoselenazol

Allgemein zählen Brückenkopf-Heteroatome zu beiden Ringsystemen und erhalten eine eigene Nummer:



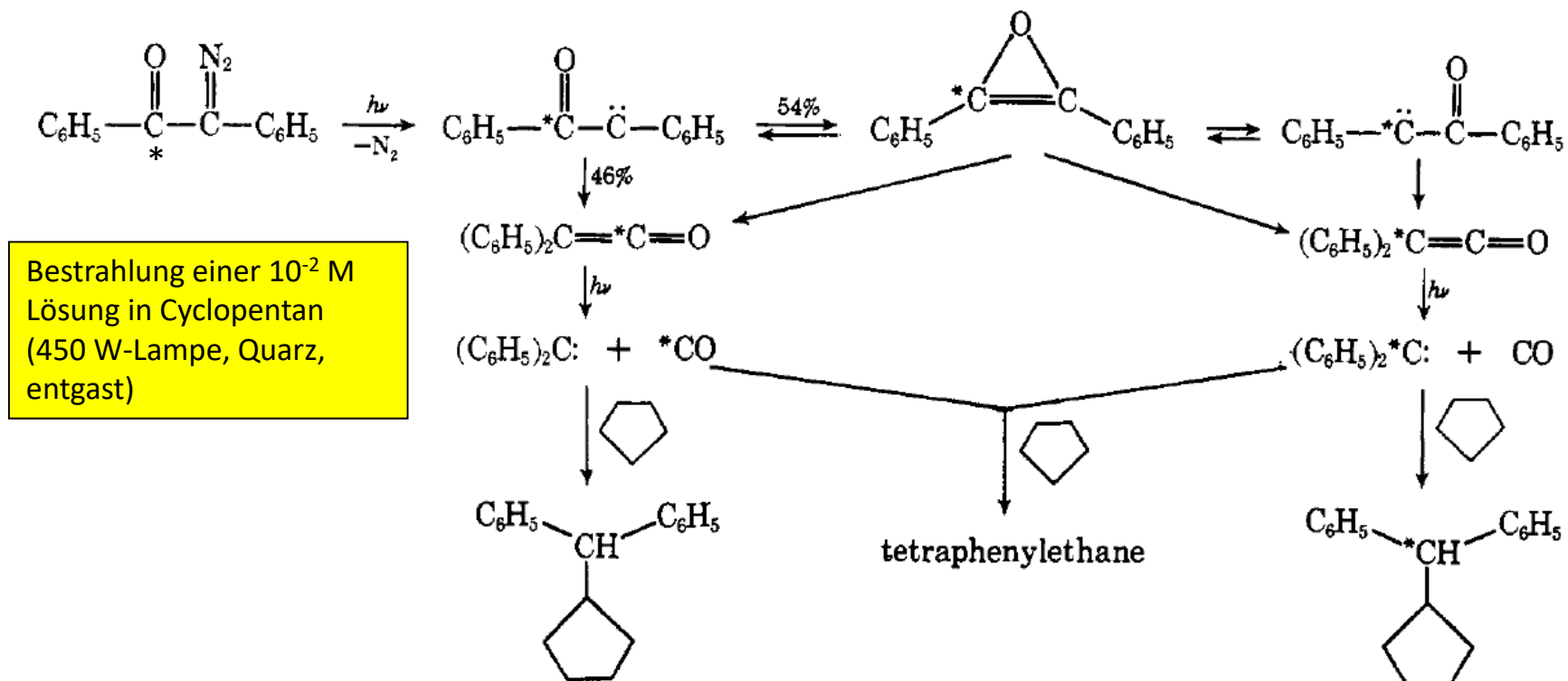
Imidazo[2,1-*b*]thiazol

Oxiren



B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.1 Oxiren

Oxiren als Intermediat zwischen zwei Formylcarbenen:

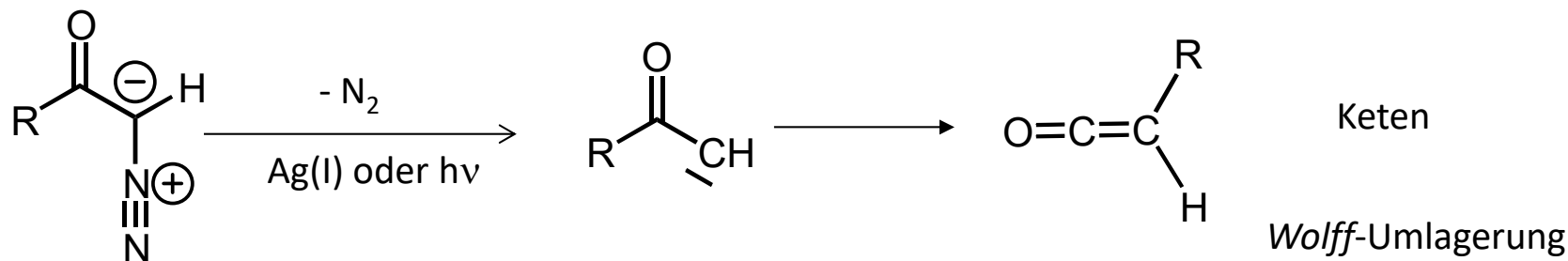


^{13}C -Isotopenmarkierung findet sich in beiden Keten-Positionen, nachgewiesen durch Analyse der Markierung in den Endprodukten \Rightarrow Oxiren ist Intermediat.

aus: Strausz et al., *JACS* **1970**, 6654

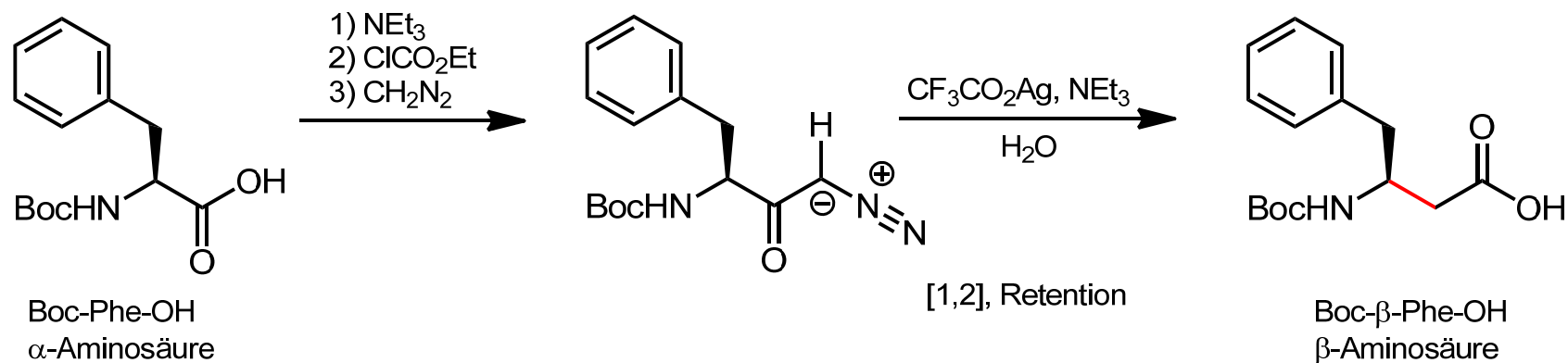
B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.1 Oxiren

Wolff-Umlagerung: α -Diazocarbonylverbindung zum Keten



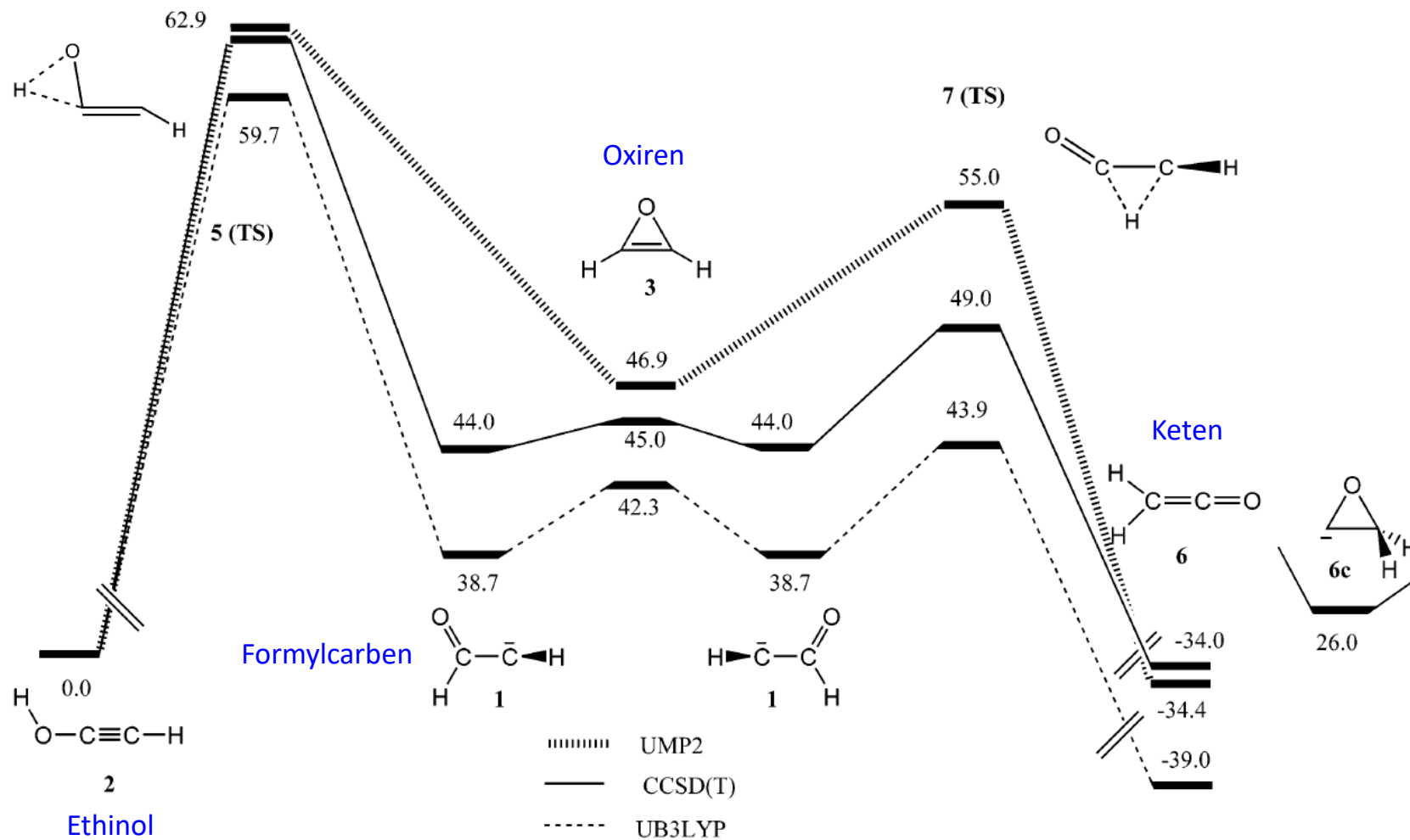
α -Diazoketon synthetisierbar z. B. aus dem Säureanhydrid mit TMSCHN_2 oder aus dem Keton, z. B. durch i) Base, ii) TosN_3 unter Bildung von TosNH_2 .

Schlüsselschritt der *Arndt-Eistert*-Homologisierung von Carbonsäuren, z. B.:



B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.1 Oxiren

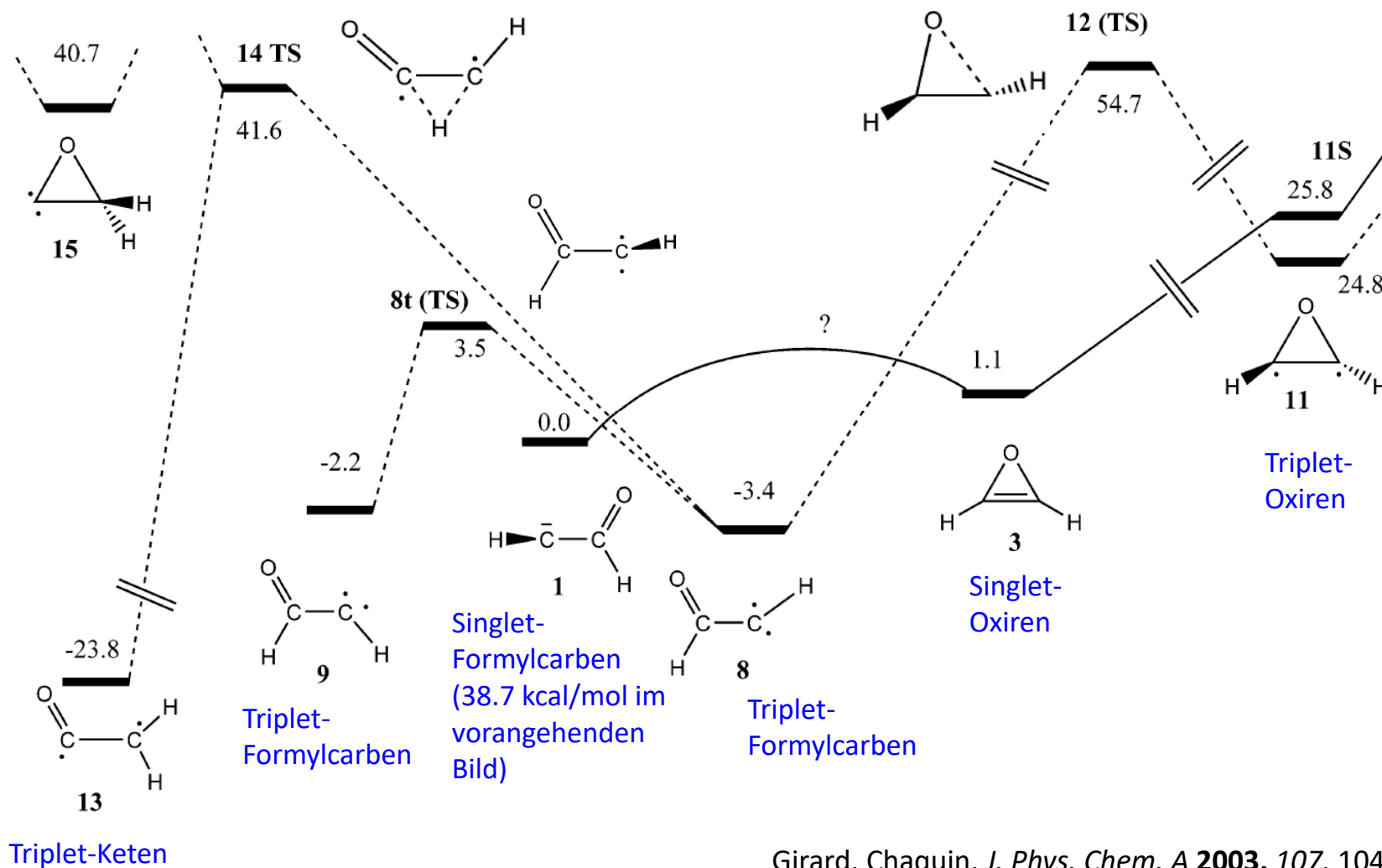
Energieprofil der Singulett-Zustände der C₂H₂O-Isomere (3 Rechenmethoden)



Girard, Chaquin, *J. Phys. Chem. A* **2003**, *107*, 10462-10470

B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.1 Oxiren

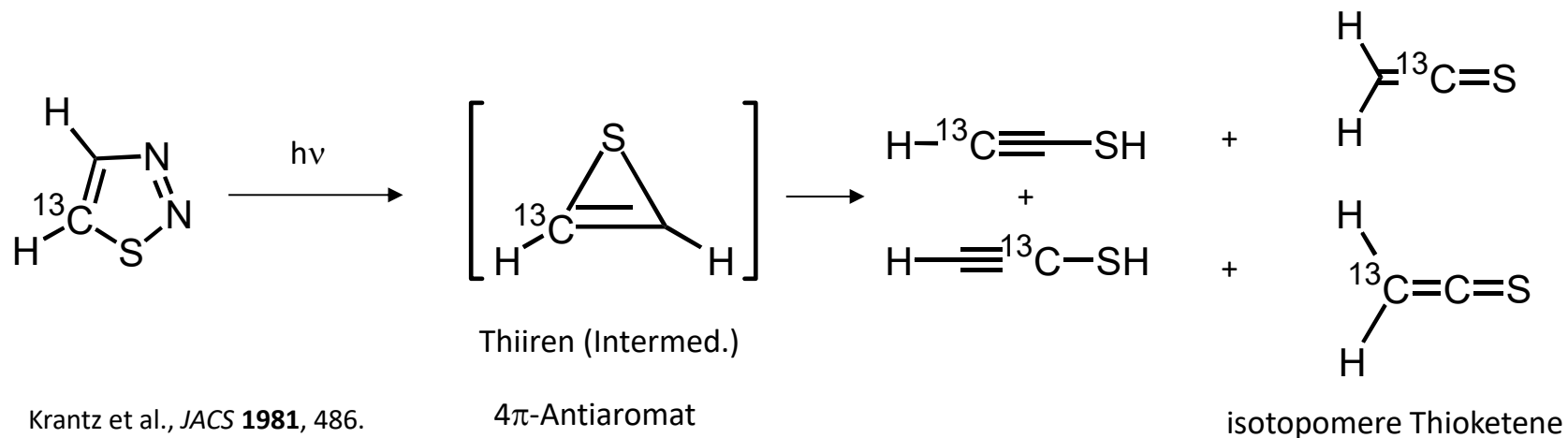
Energieprofil der Singulett-Zustände der C₂H₂O-Isomere (CCSD-(T)/cc-PVTZ-Niveau)



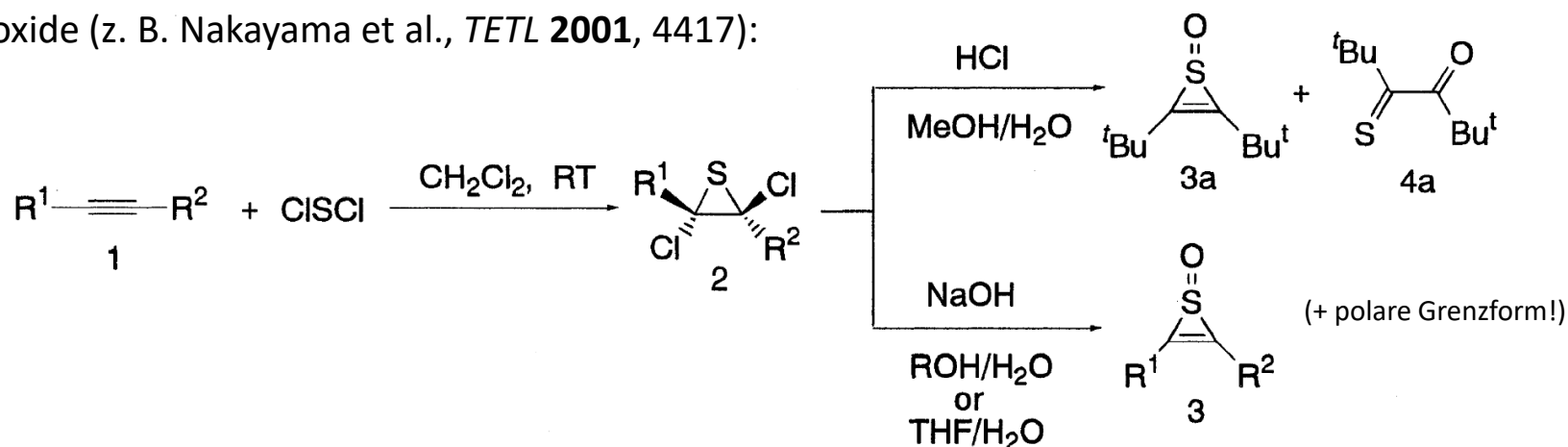
Girard, Chaquin, *J. Phys. Chem. A* **2003**, *107*, 10462-10470

B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.2 Thiiren

Thiiren: durch Isotopenmarkierung als Intermediat nachgewiesen



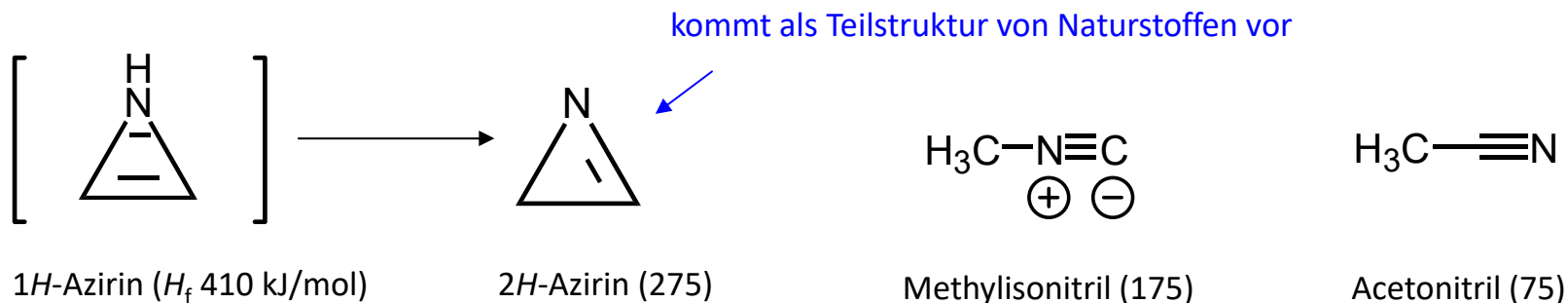
Thiiren-1-oxide (z. B. Nakayama et al., *TETL* **2001**, 4417):



a: $\text{R}^1, \text{R}^2 = t\text{-butyl}$; b: $\text{R}^1 = \text{R}^2 = 1\text{-adamantyl}$; c: $\text{R}^1 = 1\text{-adamantyl}, \text{R}^2 = t\text{-butyl}$

B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.3 Azirin

Azirin

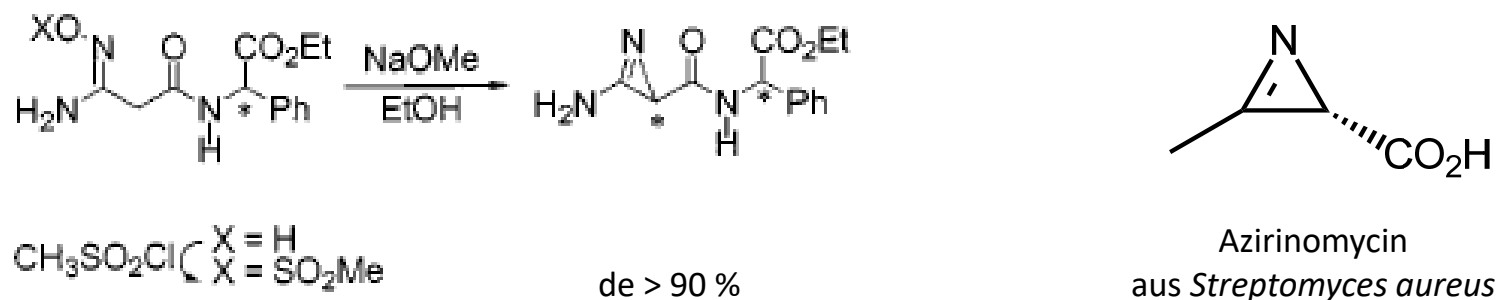


4π -antiaromatisches System kann ohne Ringöffnung durch Tautomerisierung vermieden werden.

J. Phys. Chem. A **1998**, 102, 7074

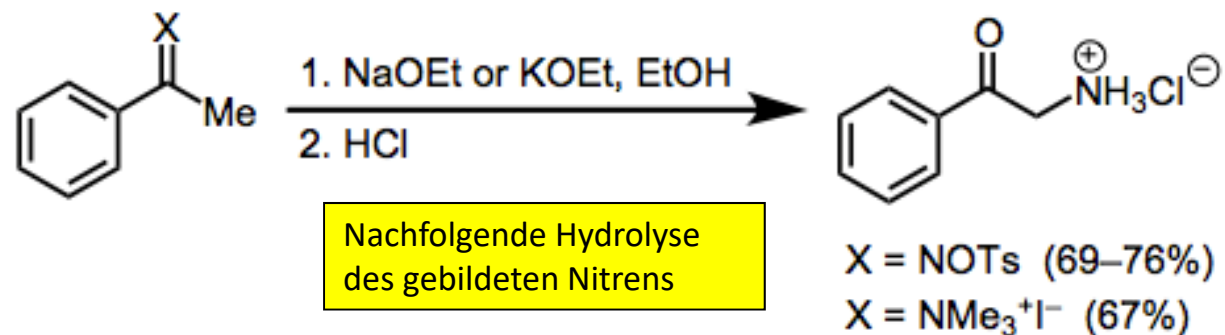
Spannungsenthalpie von 2H-Azirin ca. 190 kJ/mol (< als bei Cyclopropen: ca. 230 kJ/mol).

Synthese: a) modif. *Neber*-Reaktion (1926)

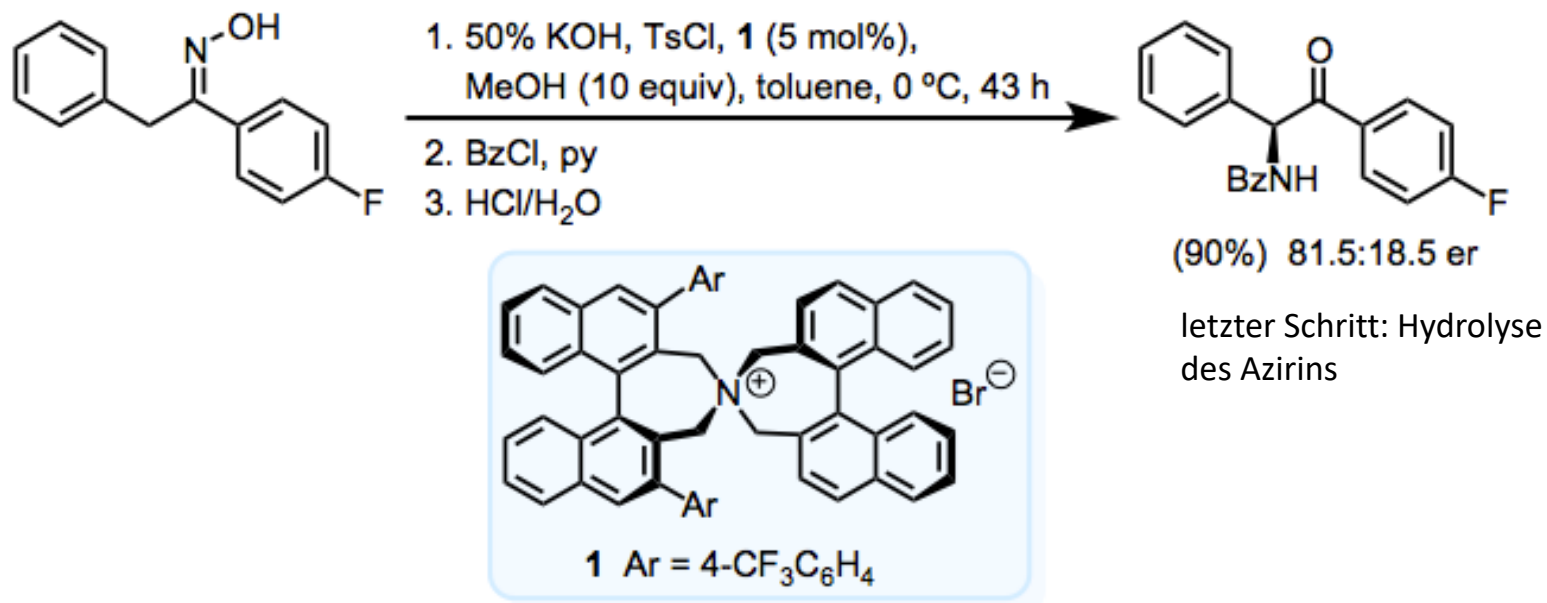


B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.3 Azirin

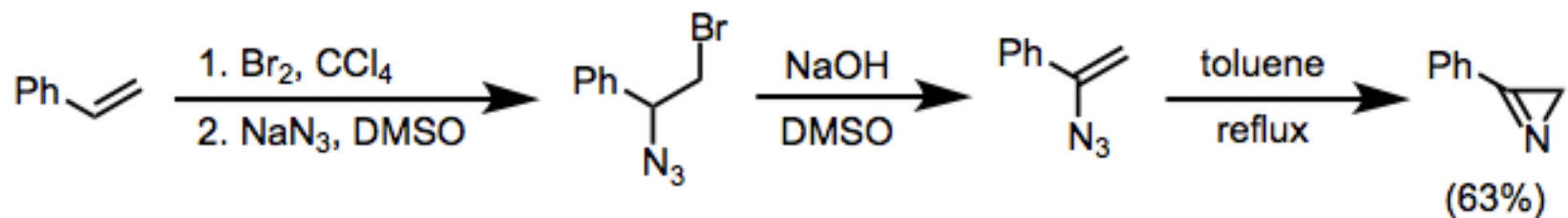
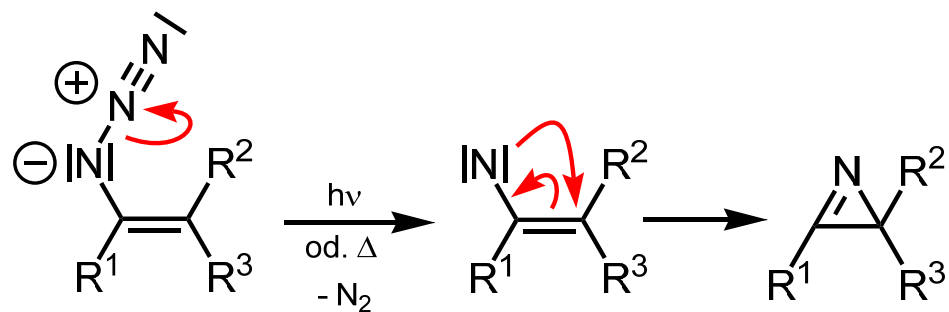
Neber, P. W.; Huh, G. *Liebigs Ann. Chem.* **1935**, 515, 283



enantioselektiv: *JACS* **2002**, 7640



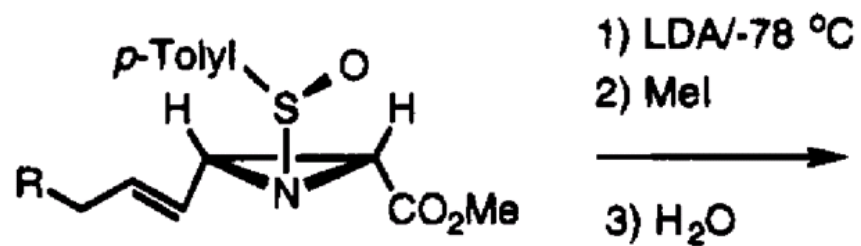
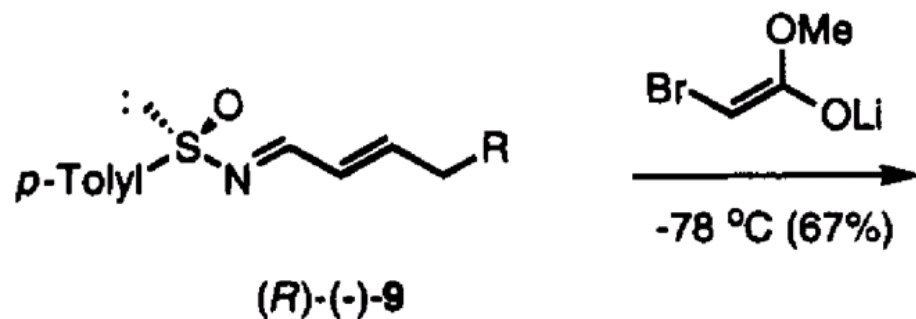
b) Thermo- od. Photolyse v. Alkenylaziden über das Nitren:



Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 2077

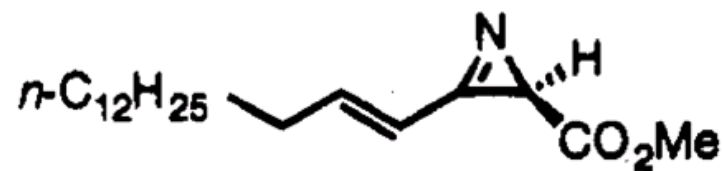
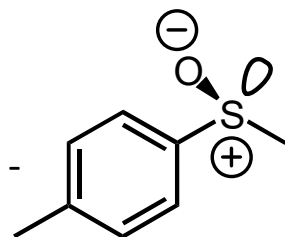
B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.3 Azirin

c) durch Eliminierung aus Aziridin:



(2R,3R)-(-)-10

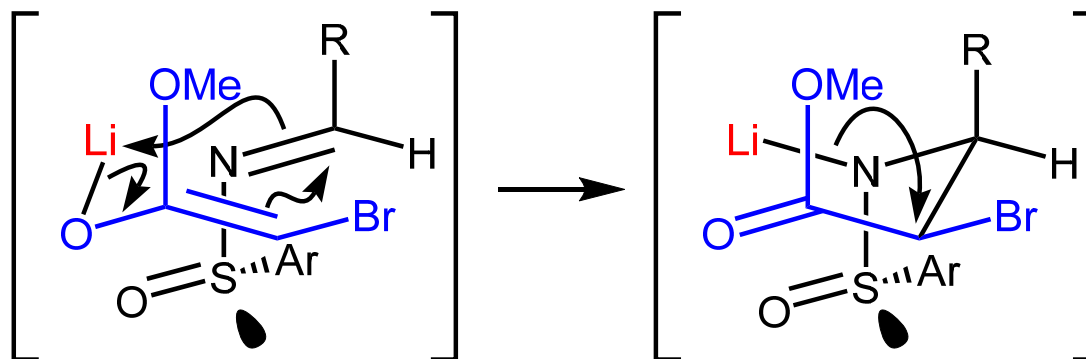
R = $n\text{-C}_{12}\text{H}_{25}$



R-(-)-Dysidazirin aus dem Meeresschwamm *Dysidea fragilis*

Davis et al., *JACS* 1995, 3651

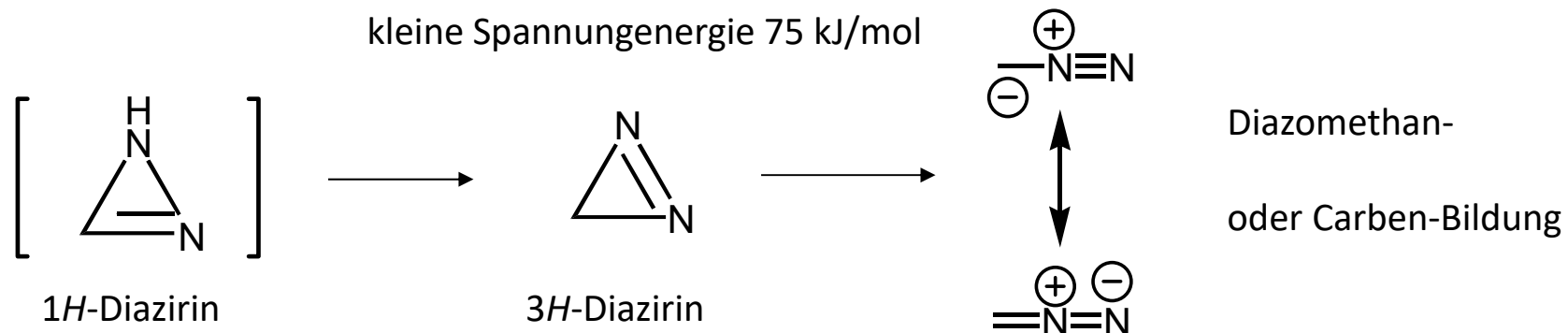
Mechanismus des 1. Schritts:



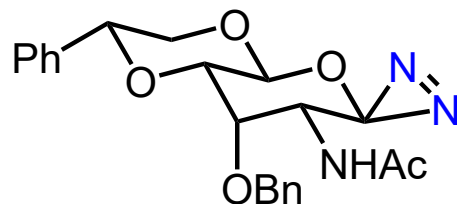
Davis et al., *JACS* **1995**, 3651

B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.4 Diazirin

Diazirin



3H-Diazirine sind bei Raumtemp. normalerweise stabil:



Bindungslänge:

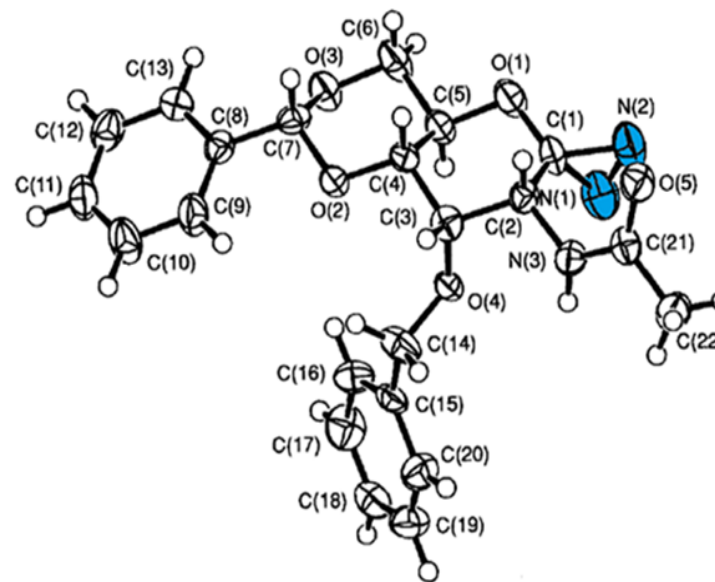
N=N = 126 pm

C-N = 147 pm

Winkel:

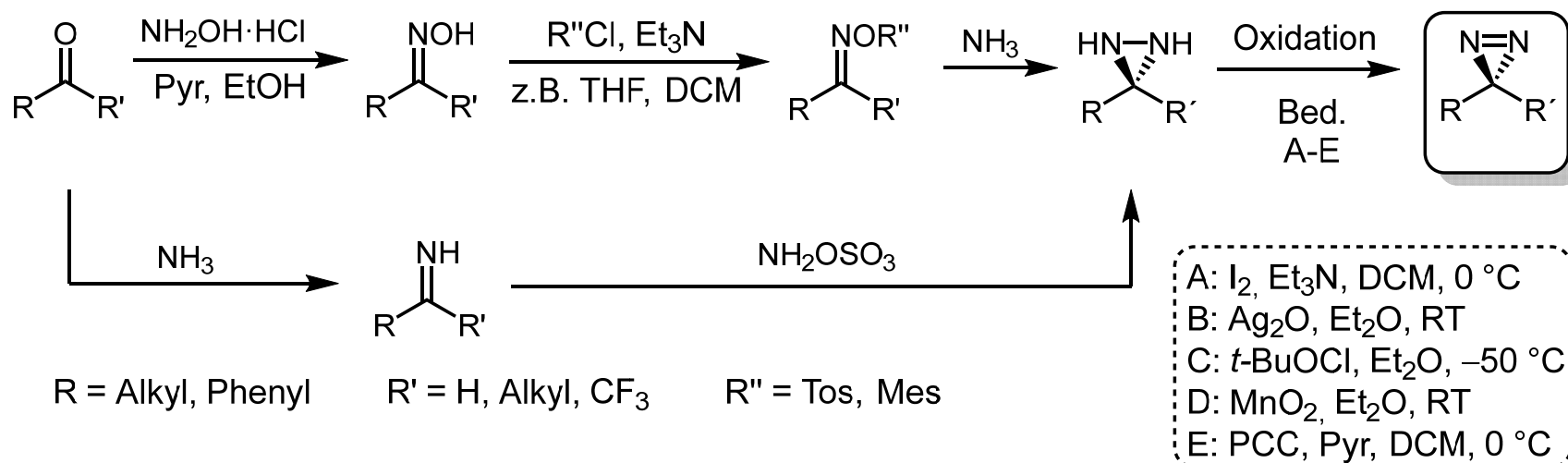
N-C-N = 50.8°

O-C(N₂)-C = 116.0°

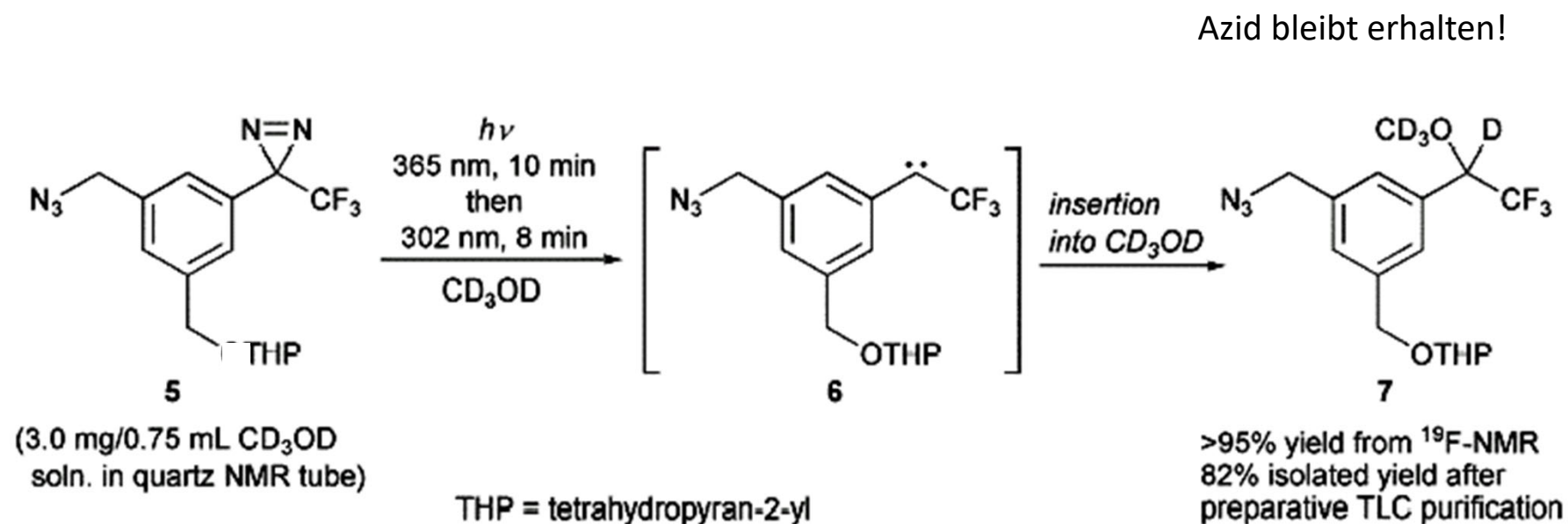


Helv. Chim. Acta **1992**, 75, 1572-1577.

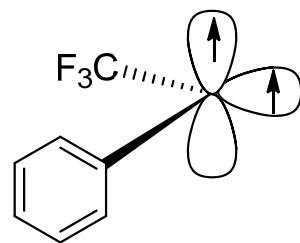
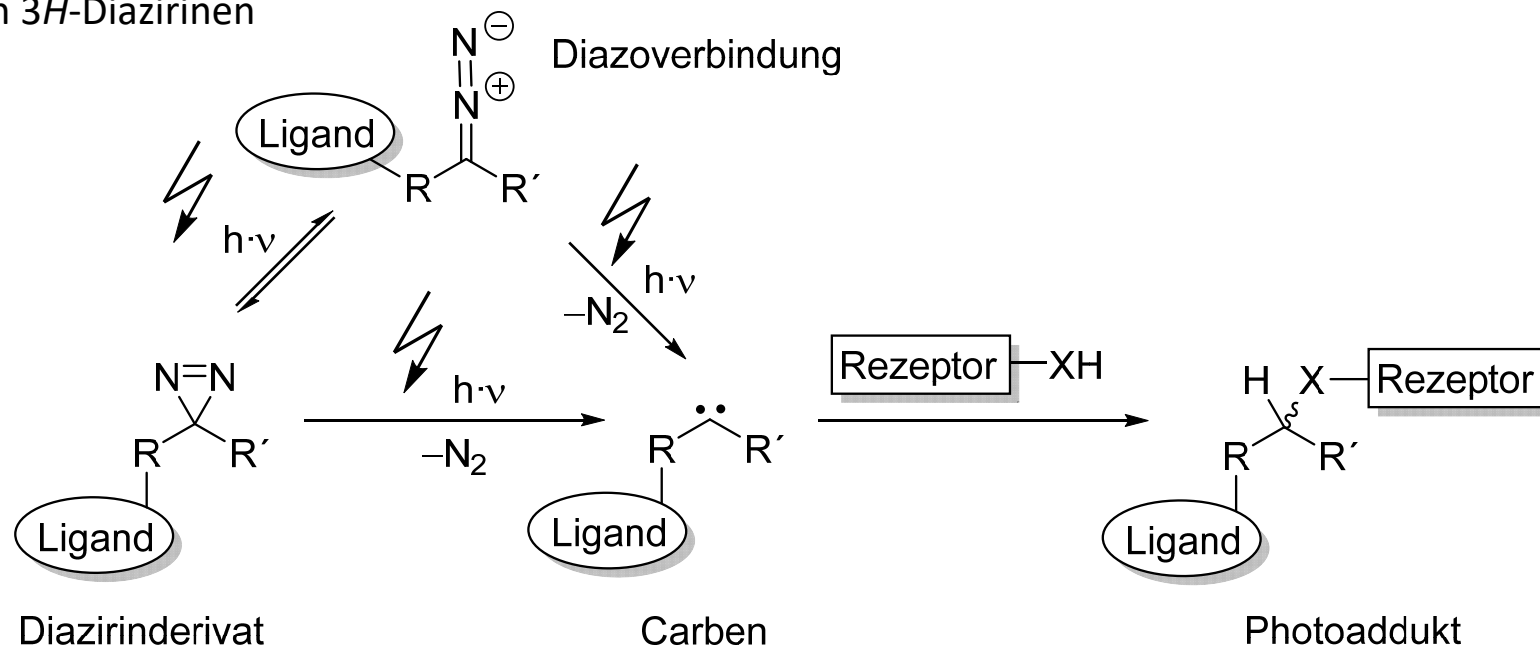
Synthese von 3H-Diazirinen



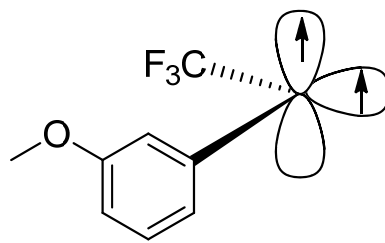
3H-Diazirine sind Carben-Quellen:



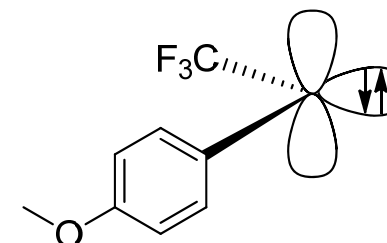
Photoreaktivität von 3H-Diazirinen



Tripletcarben



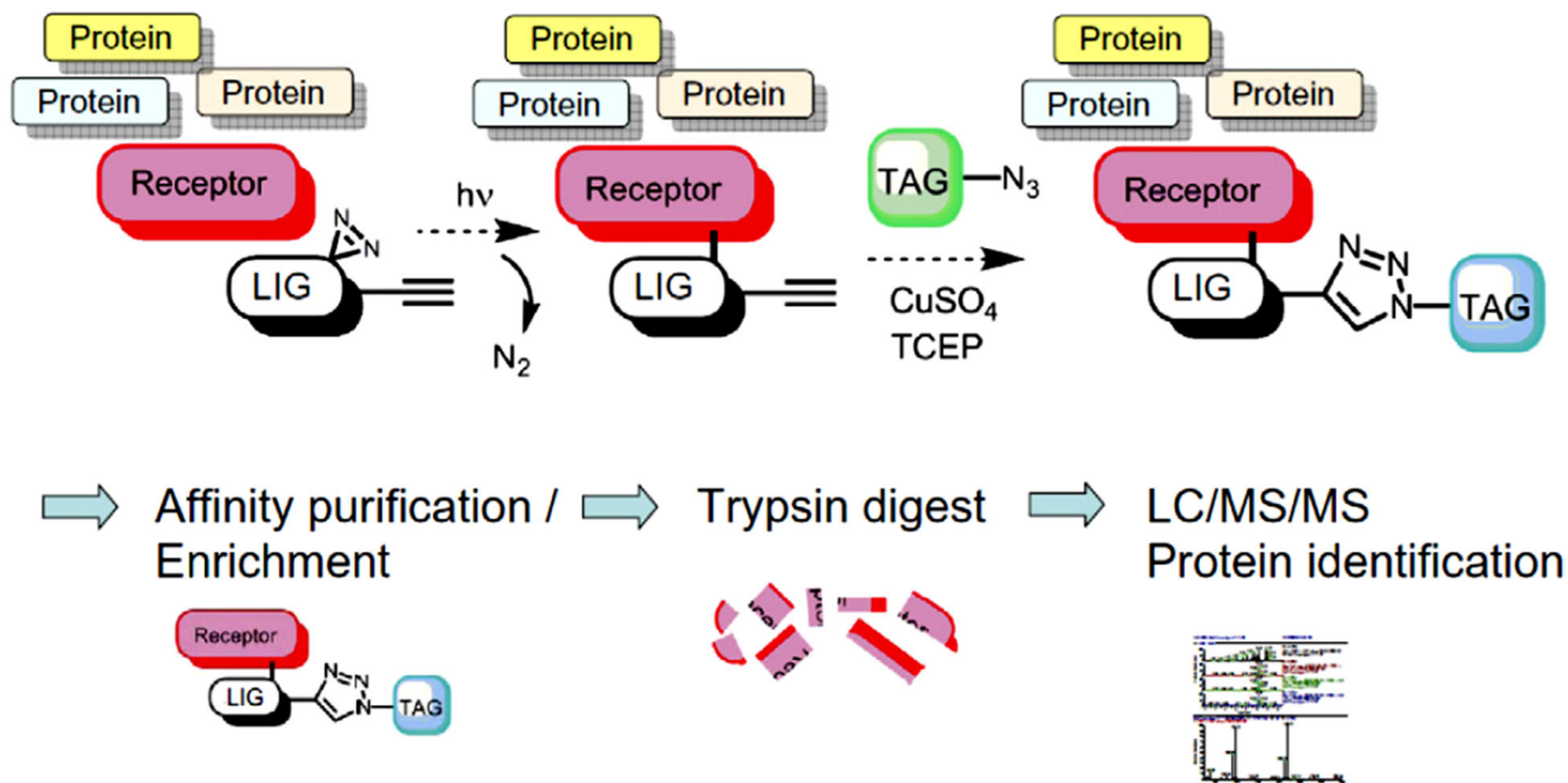
Tripletcarben



Singulettcarben

B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.4 Diazirin

Photoreaktion eines potentiellen Liganden (z. B. eines funktionalisierten Naturstoffs) mit z. B. einem Proteingemisch, gefolgt von Identifizierung und Isolierung kovalenter Addukte und deren massenspektrometrischer Analyse; Identifizierung häufig mit Hilfe von "Click-Chemie".

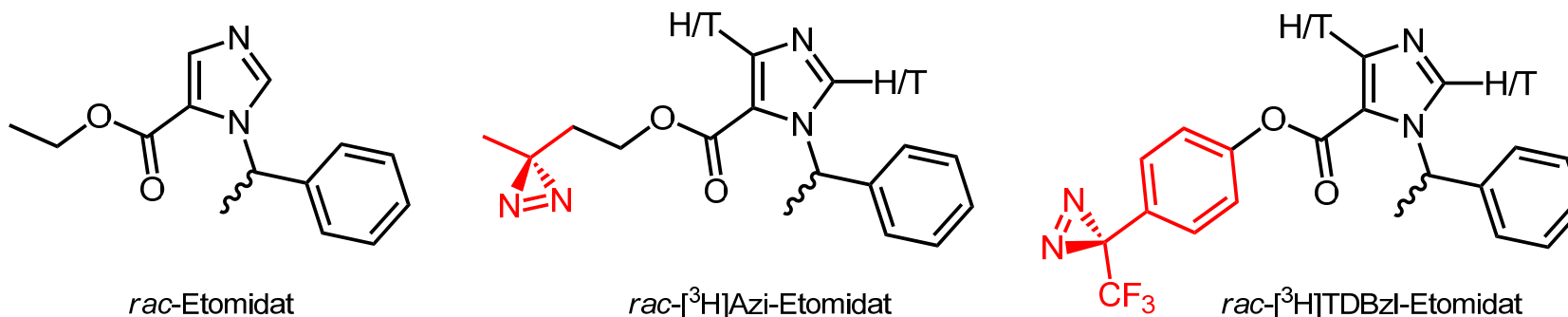


from: Meijler et al., *Bioorg. Med. Chem.* **2012**, *20*, 554

B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.4 Diazirin

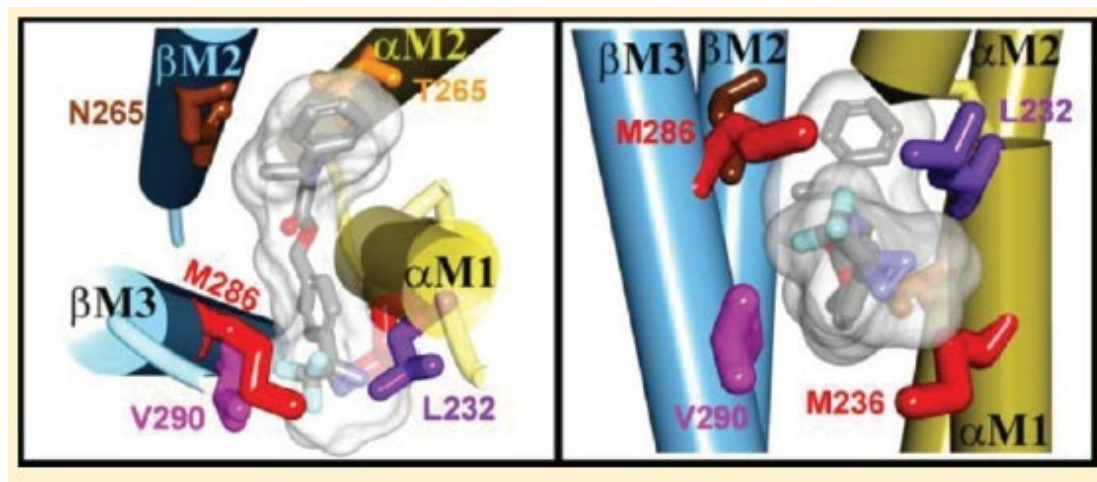
Anästhetikum Etomidat: (*R*)-Enantiomer 10-fach stärker wirksam als (*S*)-Enantiomer

Bindung an den γ -Aminobuttersäure-Rezeptor Typ A (GABA_ARs)



Links: Photomarkierung durch [³H]TDBzl-Etomidat: β 3Val-290 in der β 3M3-Transmembran-Helix
Rechts: Photomarkierung durch [³H]Azietomidat: α 1Met-236 in α 1M1

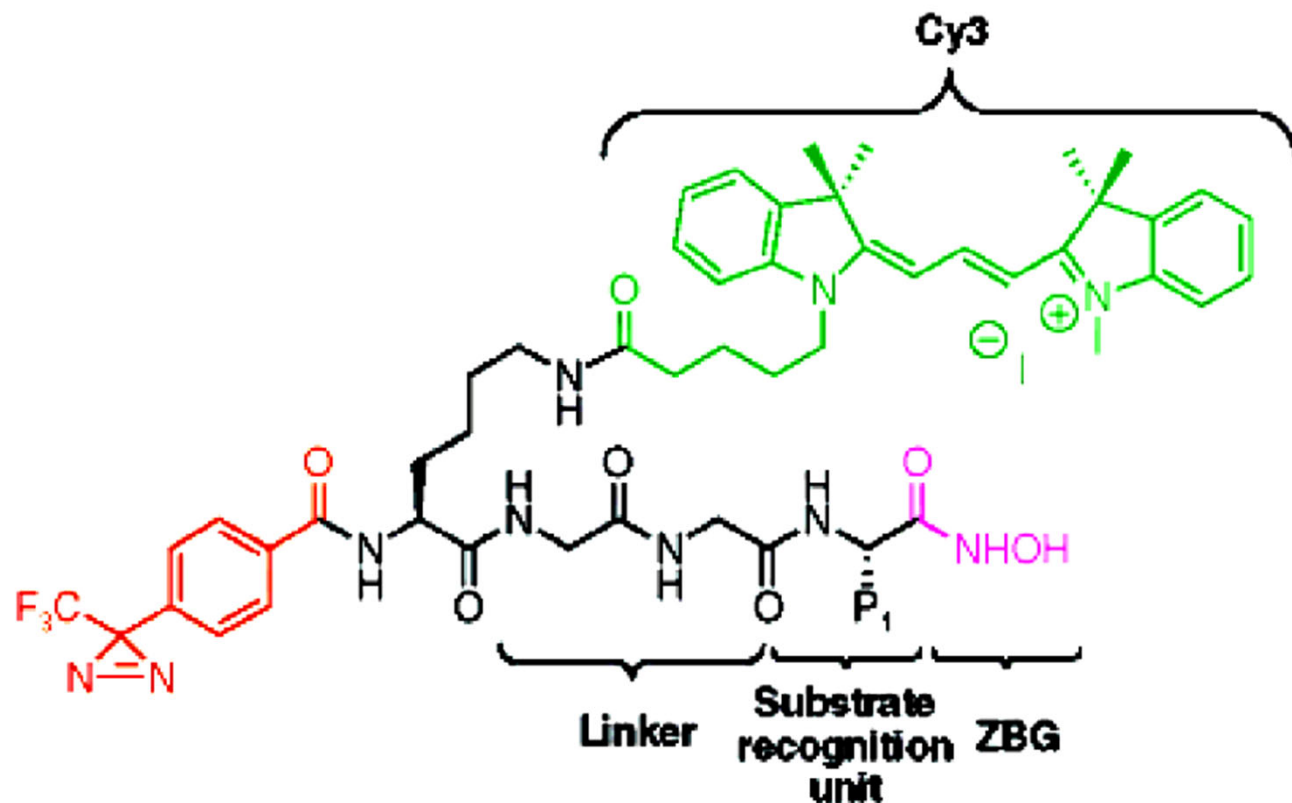
In den α M2- und β M2-Helices wurde keine Aminosäure photomarkiert.



Cohen et al., *Biochemistry* 2012, 51, 836

B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.4 Diazirin

Photoaffinitätsmarkierung von Proteinen (hier selektive Hydroxamat-Sonde für Metalloproteasen mit Zn^{2+} im aktiven Zentrum) mit Diazirinen:

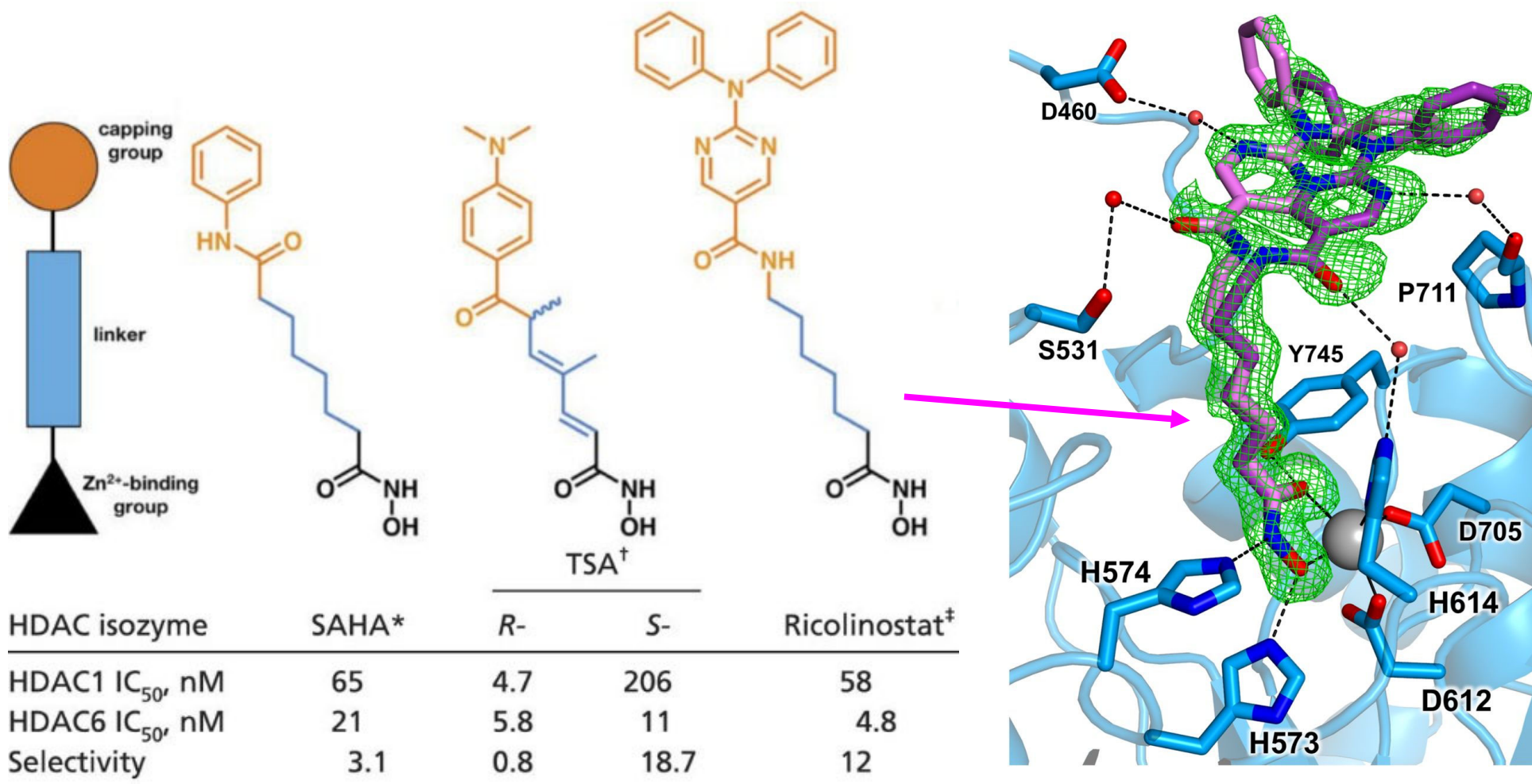


Kovalente Verknüpfung des Fluorophors an das Protein => leichte Identifizierung im Gel.

JACS **2004**, 14435.

B. Dreigliedrige Ringe – B.1 Oxiren, Thiiren, Azirin, Diazirin – B.1.4 Diazirin

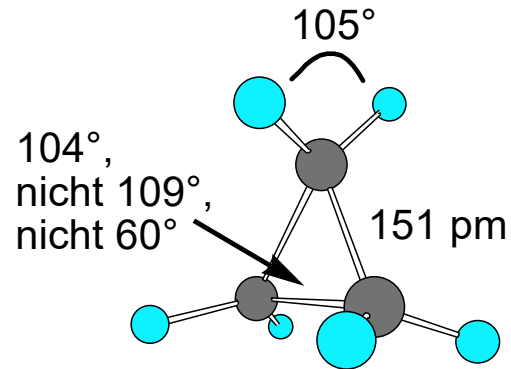
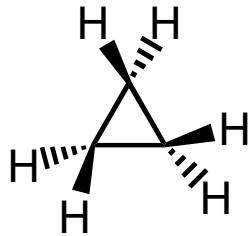
Hydroxamate binden an Zn^{2+} im aktiven Zentrum von Enzymen, hier der Histon-Deacetylase 6 (HDAC-6)



PNAS 2017, 114, 13459.

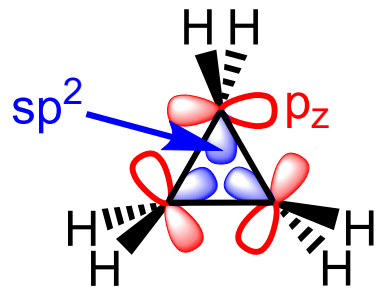
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

Monocyclische Alkane: C_nH_{2n}



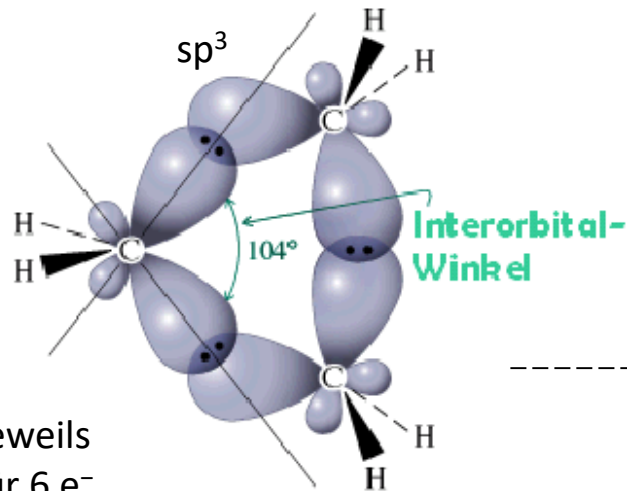
Cyclopropan unterliegt Ringspannung (*Baeyer-Spannung*).

Wie bestimmt man eine Ringspannung?



Walsh-Modell

Konstruktion von jeweils 6 MOs aus 6 AOs für 6 e⁻

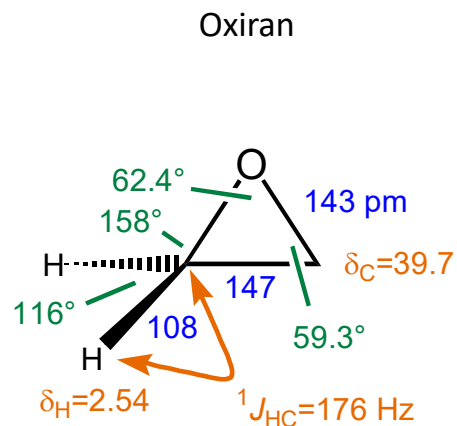


Förster-Coulson-Modell

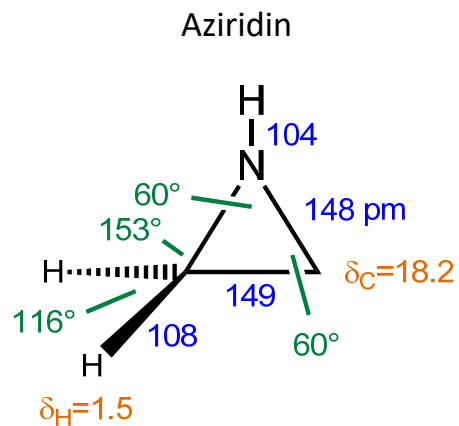


"Bananenbindungen"

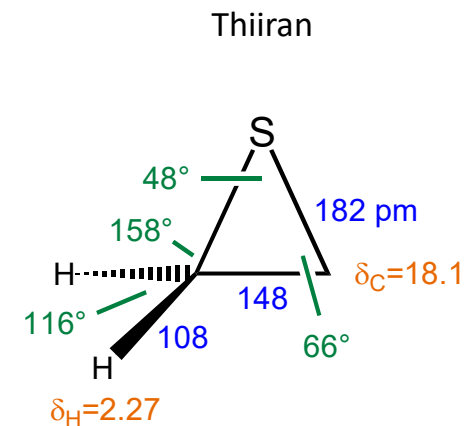
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran



Spannungsenthalpie 114 kJ/mol
Sdp. 11 °C; 7 Mio. t/a Produktion



113 kJ/mol
Sdp. 57 °C



83 kJ/mol
Sdp. 55 °C

	3	4	5	6
CH2	115	111	26	0
O	110	103	23	0
N	112	105	24	0

Adam, Bargon, *Chem. Rev.* **2004**, 251.

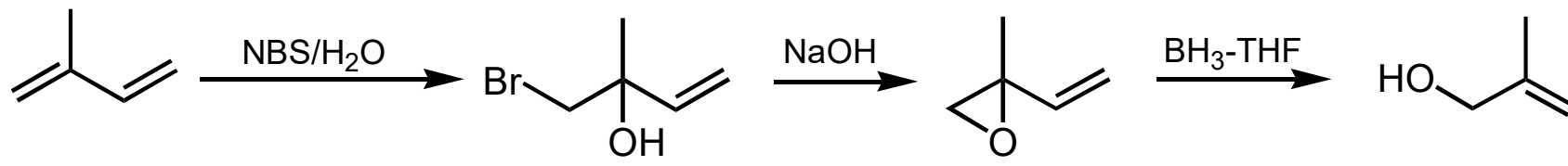
JOC **2002**, 3488

in kJ/mol; 3- und 4-Ringe etwa gleich gespannt; Heteroatome verursachen kaum Veränderung.

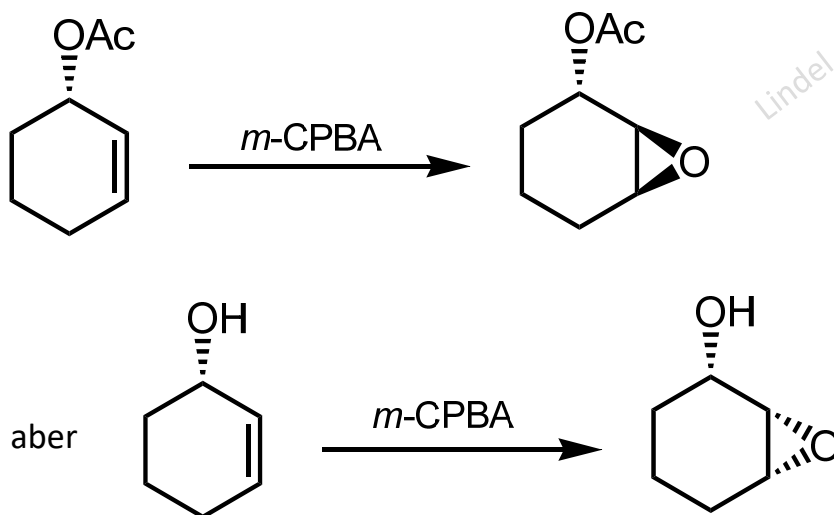
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

Oxiran-Synthesen

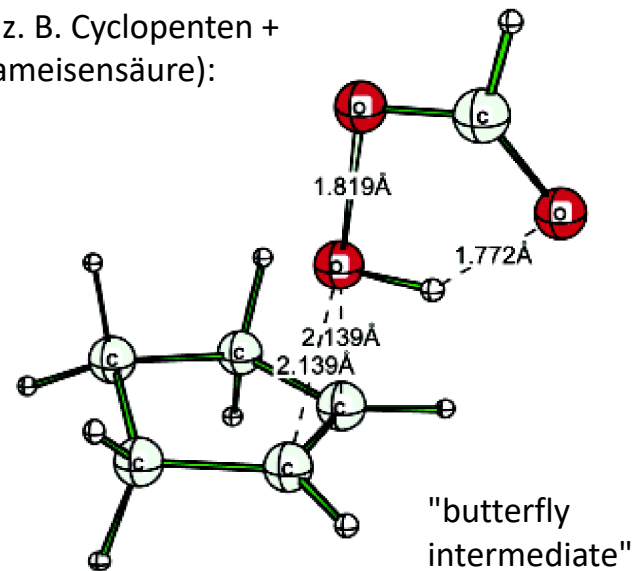
a) aus Halohydrinen mit Basen, z. B.



b) aus Alkenen mit Persäuren, z. B.



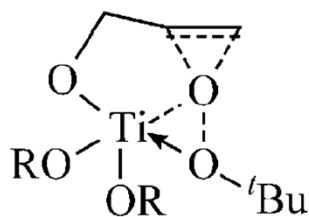
ÜZ (z. B. Cyclopenten + Perameisensäure):



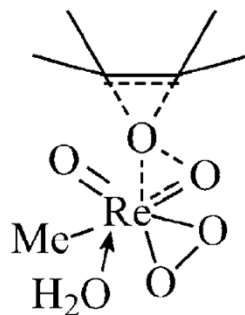
JACS 2003, 924.

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

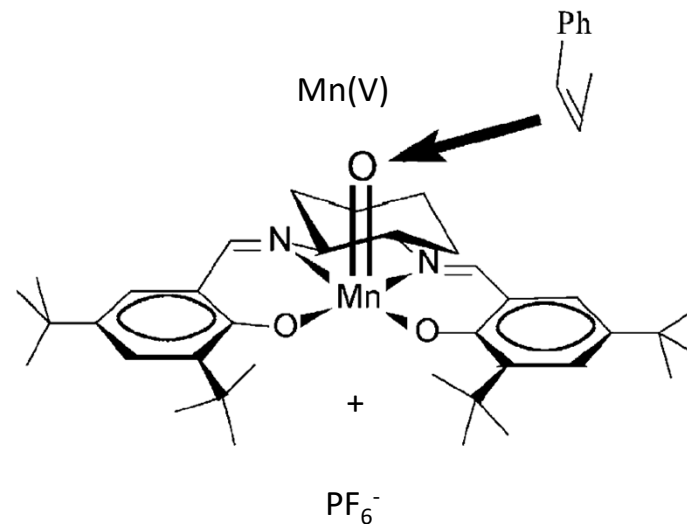
c) Übergangsmetall-katalysiert



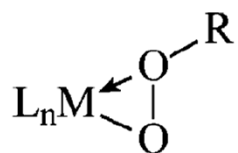
Peroxy-
Sharpless-



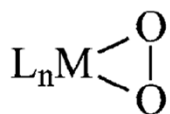
Peroxo-
Herrmann-



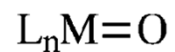
Oxo-Variante
Jacobsen-Epoxidierung



Peroxy
M = Ti, V



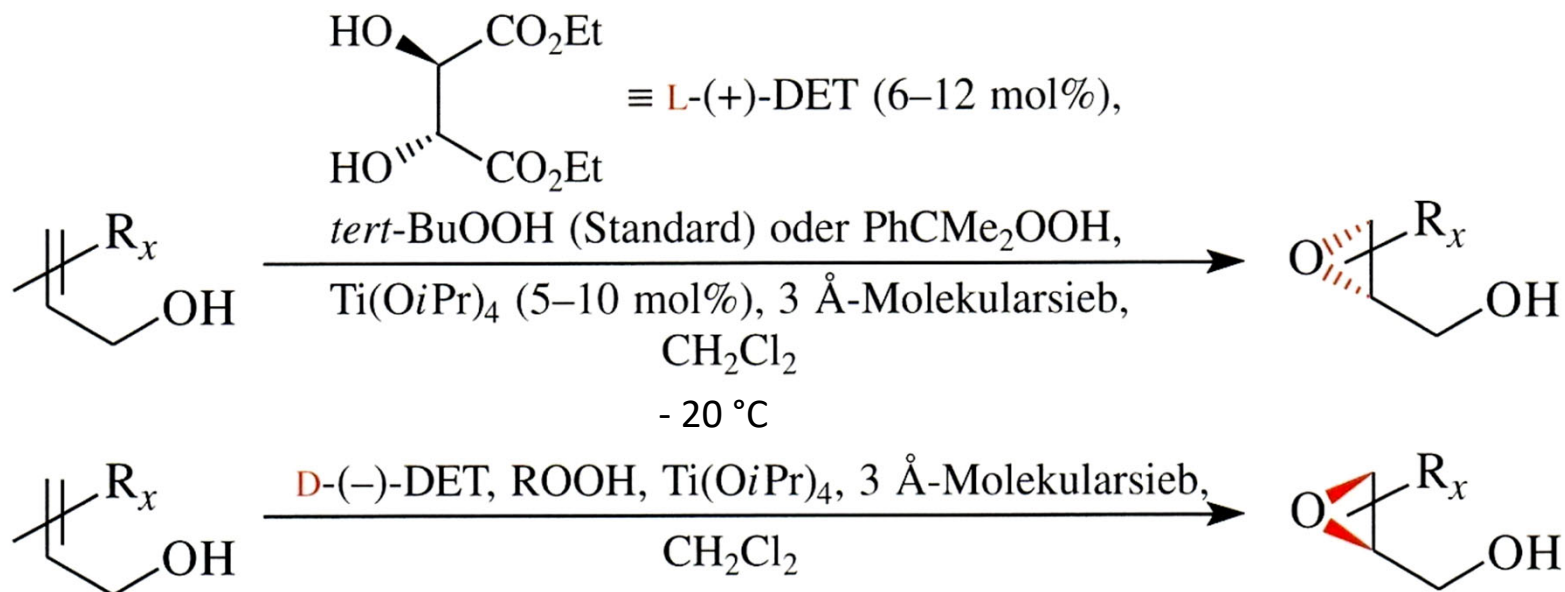
Peroxo
M = Re



Oxo
M = Mn, Cr

aus: W. Adam et al.,
J. Organomet. Chem. **2002**, 661, 3.

Sharpless-Epoxidierung



prochiraler
Allylkohol

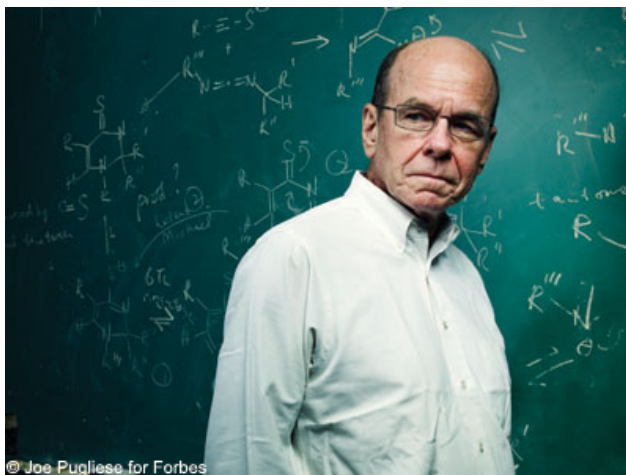
L(+)-DET => S an C2 (meist)

Ein prochirales Molekül ist in einem einzigen Schritt zu einem chiralen Molekül desymmetrisierbar. Deskriptoren der Seiten eines trigonalen Systems: *Re* und *Si*.

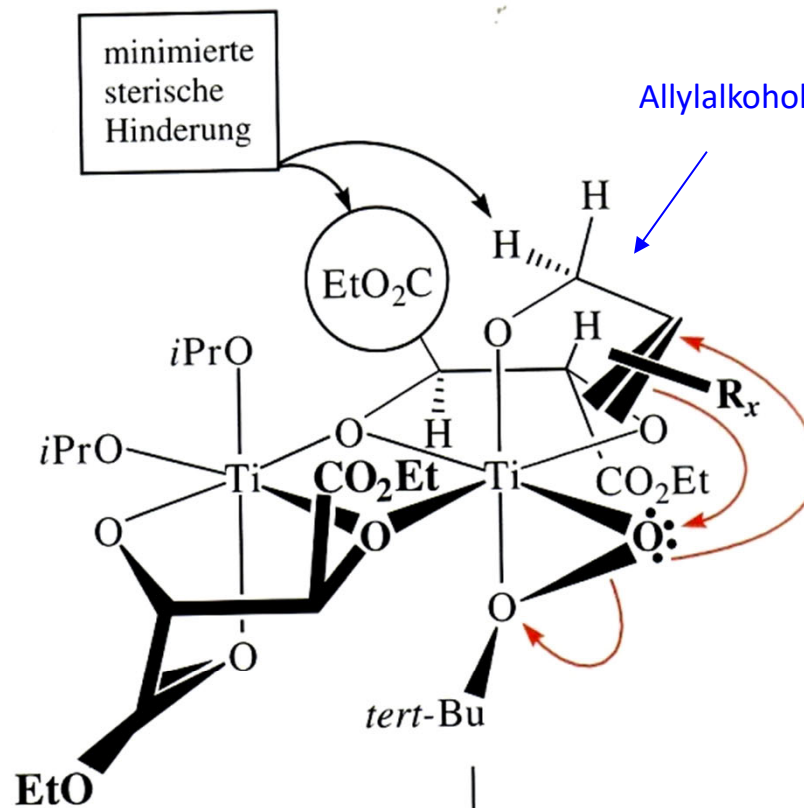
aus: Brückner, *Reaktionsmechanismen*

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

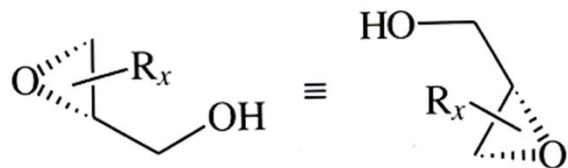
Sharpless-Epoxidierung verläuft über zweikernigen Komplex:



K. Barry Sharpless (Nobelpreis 2001)



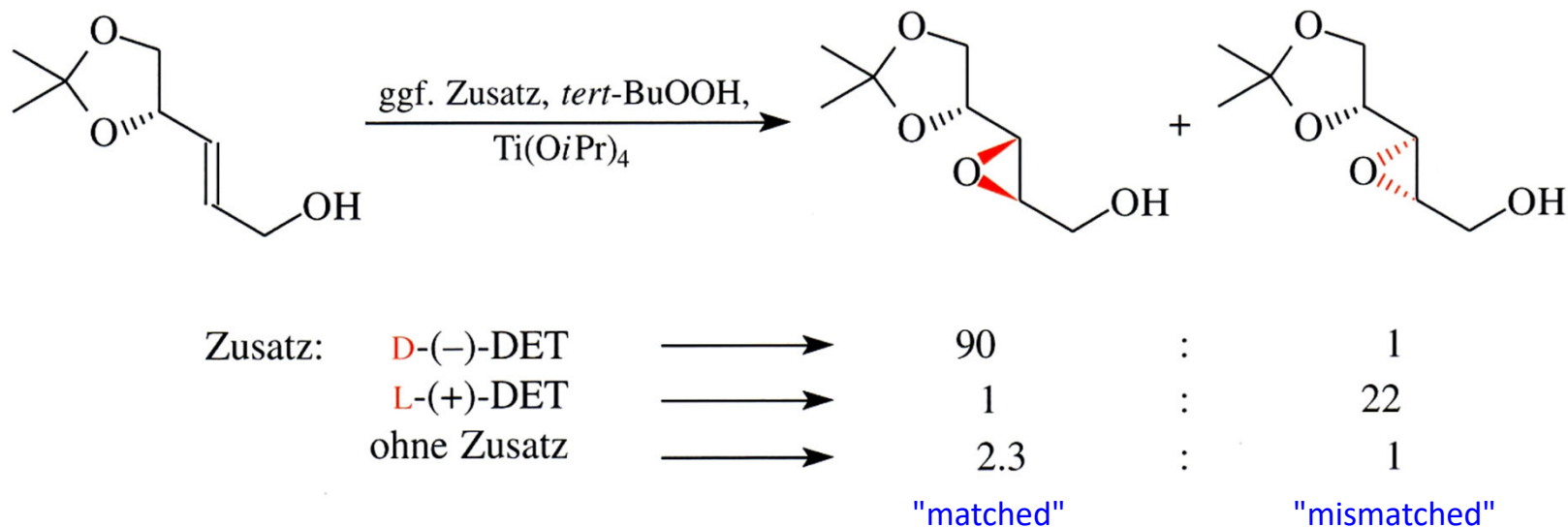
L(+)-DET => S an C2 (meist)



aus: Brückner, Reaktionsmechanismen

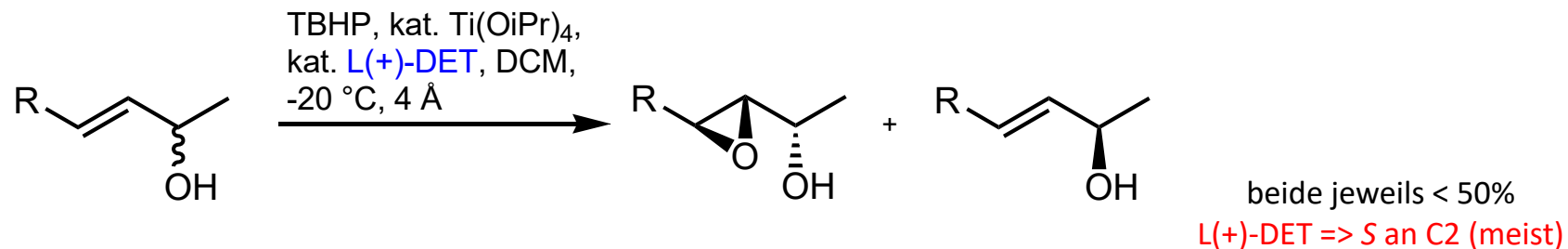
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

Sharpless-Epoxidierung sekundärer Allylalkohole: "matched" und "mismatched"



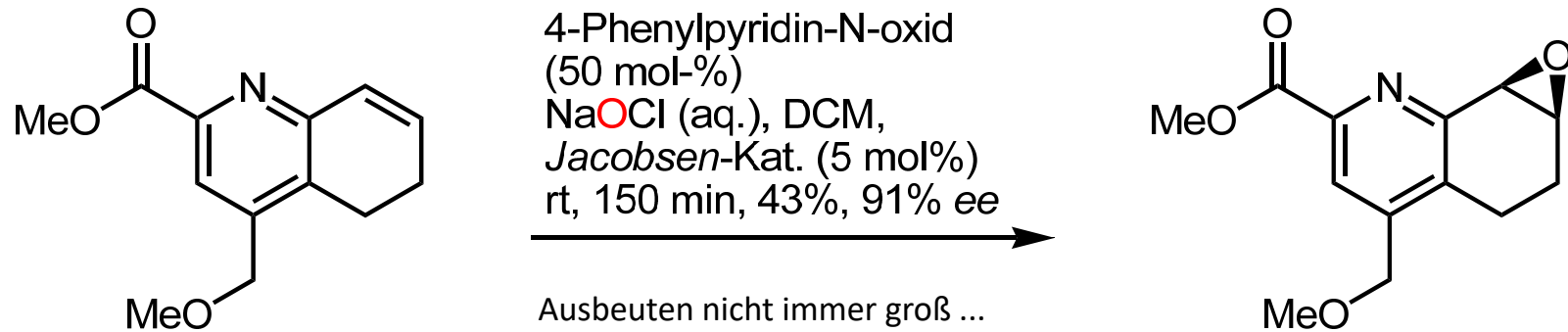
Reagenz-kontrolliert: stereochemische Information des Substrats wird nahezu "überschrieben".

Kinetische Trennung enantiomerer sekundärer Allylalkohole ("Sharpless kinetic resolution")

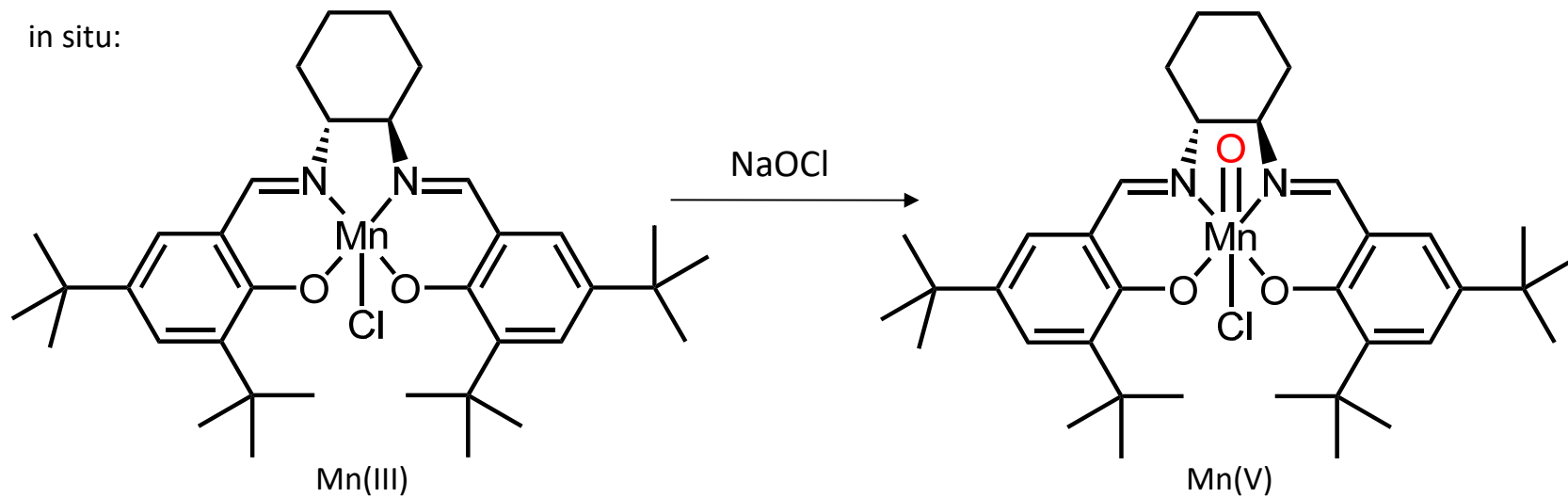


B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

Jacobsen-Katsuki-Epoxidierung

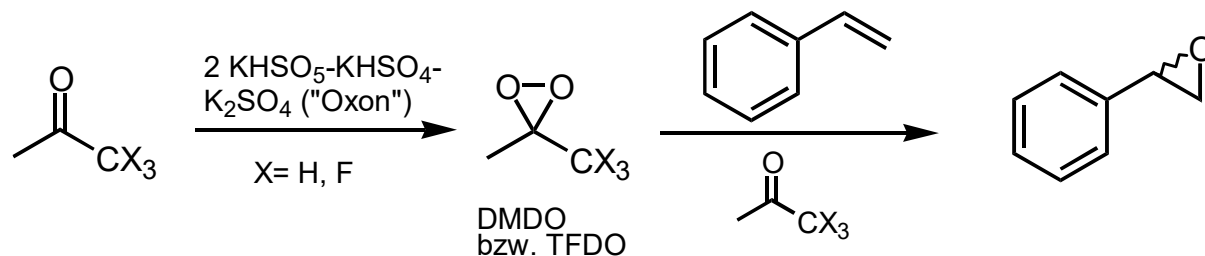


in situ:



B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

d) Epoxidierung von Alkenen mit Dioxiranen



Dimethyldioxiran: Murray et al., *JACS* **1984**, 2462, *JOC* **1985**, 2847. Adam et al., *JOC* **1987**, 2800. Trifluordimethyldioxiran: Curci et al., *JOC* **1988**, 3890.

Reaktivität gegenüber Alkenen:

TFDO (100000, -I-Effekt) > DMDO (100) > PhCO₃H (1)

Spannungsenthalpien:

DMDO: ca. 75 kJ/mol

Dioxiran: ca. 105 kJ/mol

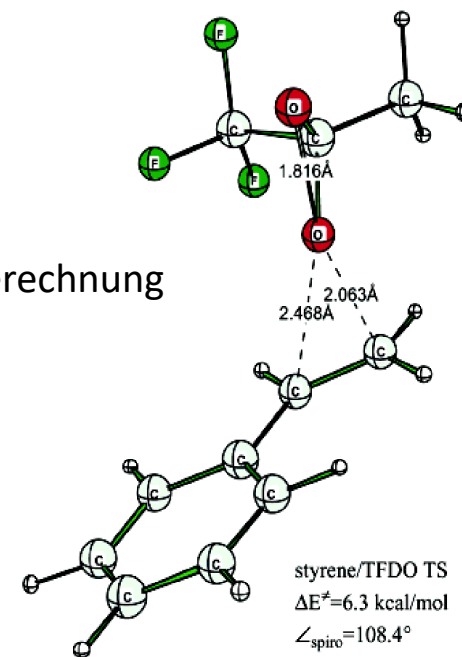
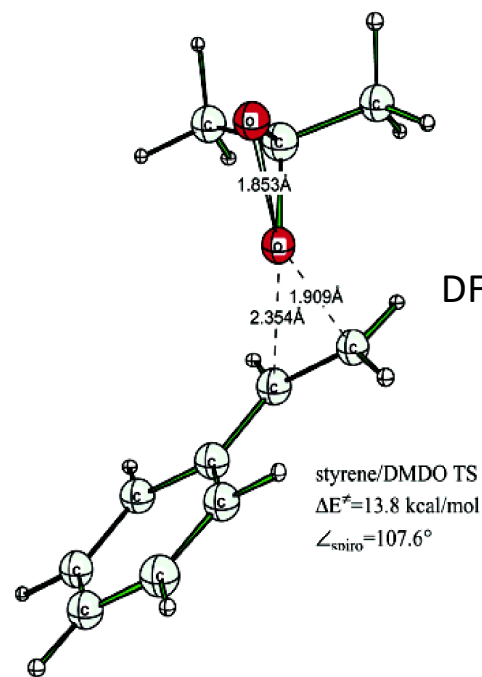
TFDO: ca. 110 kJ/mol

Oxiran: ca. 115 kJ/mol

- **Triebkraft: Bruch der O-O-Bindung.**

- O-Elektrophilie entscheidend für Reaktionsgeschwindigkeit

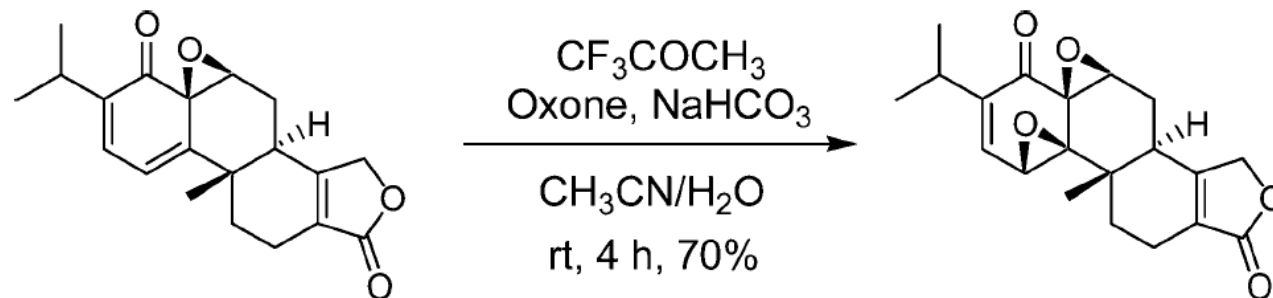
- Ringspannung spielt keine Rolle



JACS **2003**, 924.

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

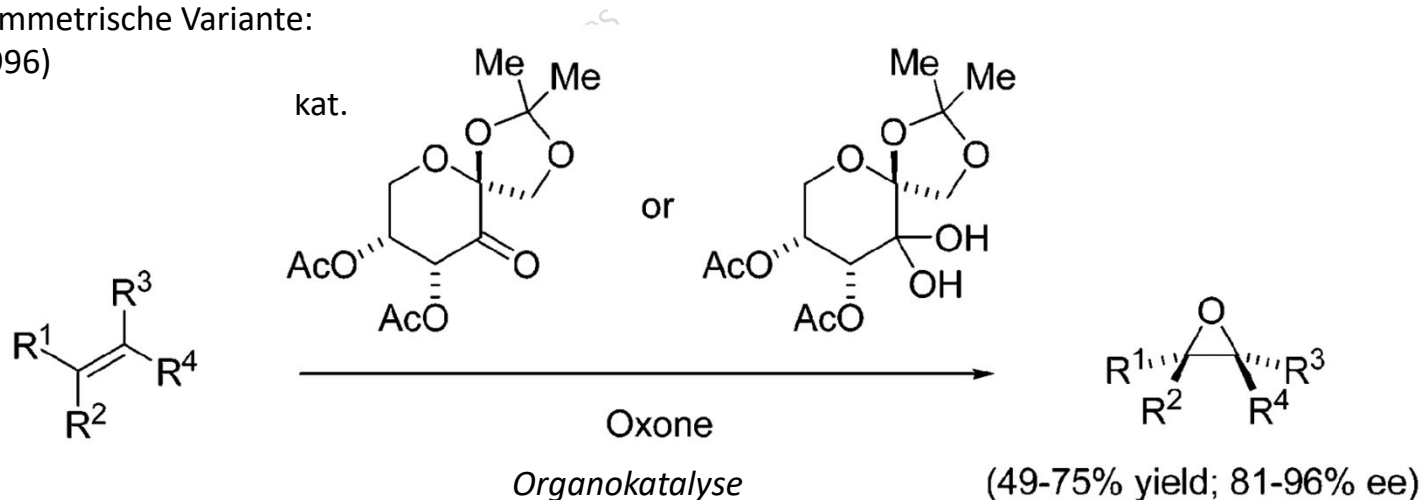
Synthese empfindlicher
Epoxide möglich:



- elektronenreichste DB reagiert.
- Diepoxid isolierbar.

Acc. Chem. Res. **2004**, 497.

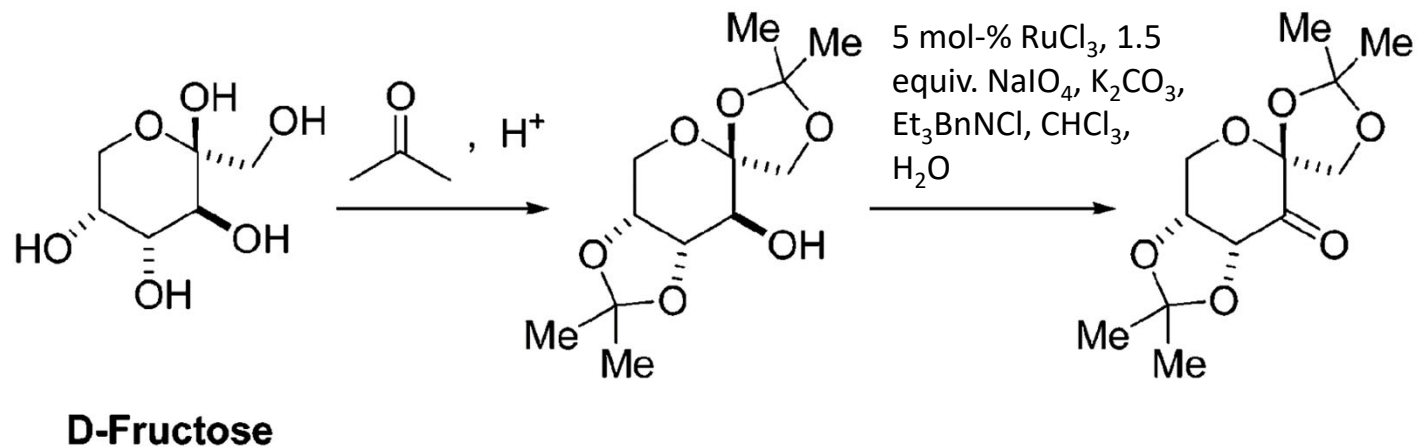
Stöchiometrisch-asymmetrische Variante:
Shi-Epoxidierung (1996)



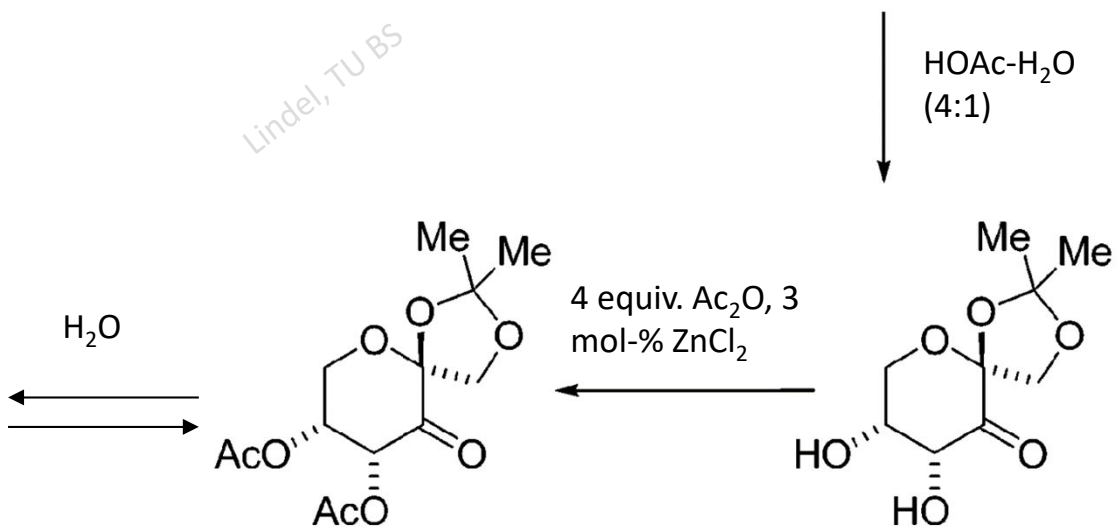
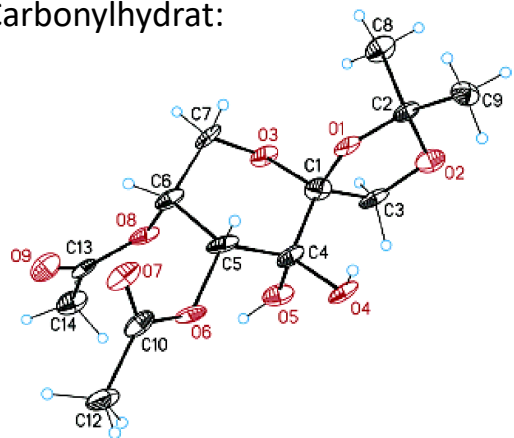
z. B. Umwandlung von (*E*)-Stilben zum *R,R*-Epoxid ($R^1=R^4=H$, $R^2=R^3=Ph$).

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

Synthese des *Shi*-
Reagenzes:

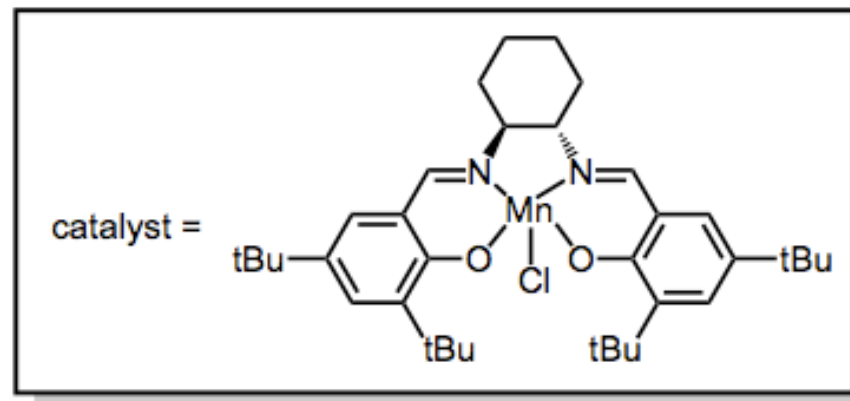
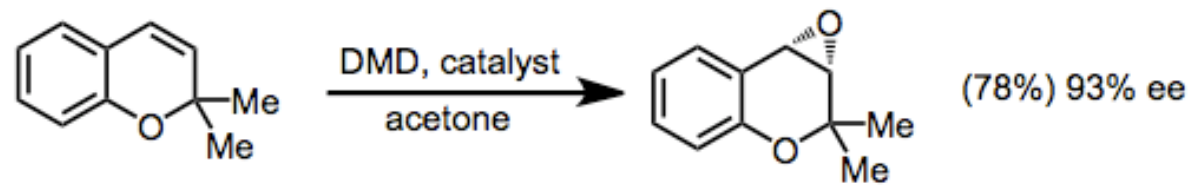


Carbonylhydrat:



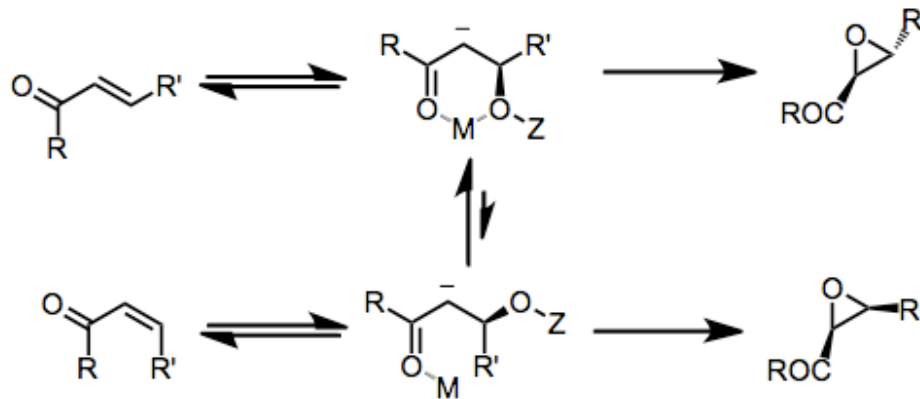
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

Enantioselective Oxidation mit DMDO in Gegenwart eines chiralen Salen-Katalysators (Lévai, A.; Adam, W.; Fell, R. T.; Gessner, R.; Patonay, T.; Simon, A.; Tóth, G. *Tetrahedron* **1998**, *54*, 13105)

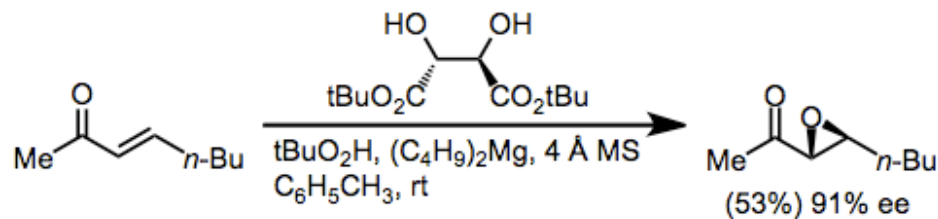


B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

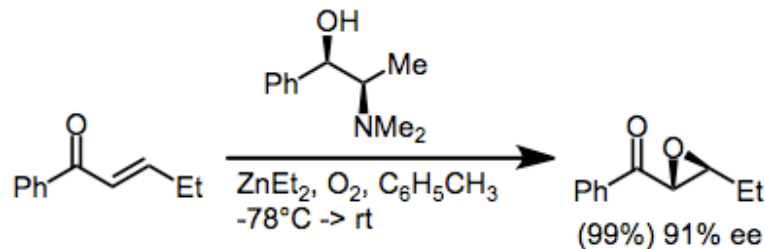
Asymmetrische nukleophile Epoxidierung von α,β -Doppelbindungen



klassisch: Weitz-Scheffer-Epoxidierung mit H_2O_2 /Base



Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725.

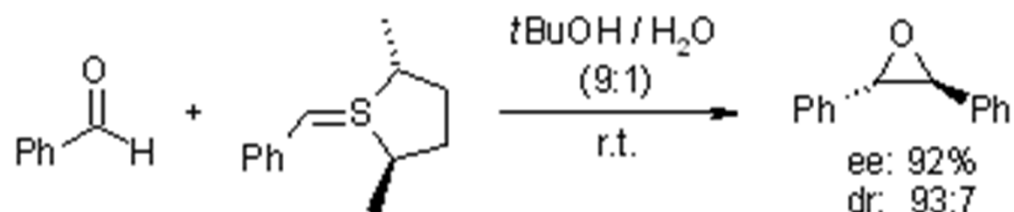


Enders, D.; et al.. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1725.

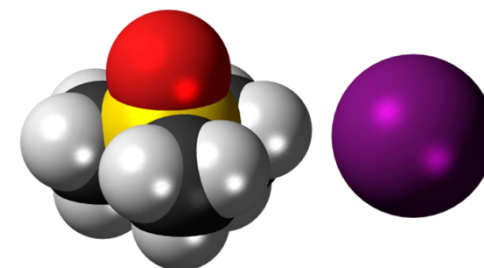
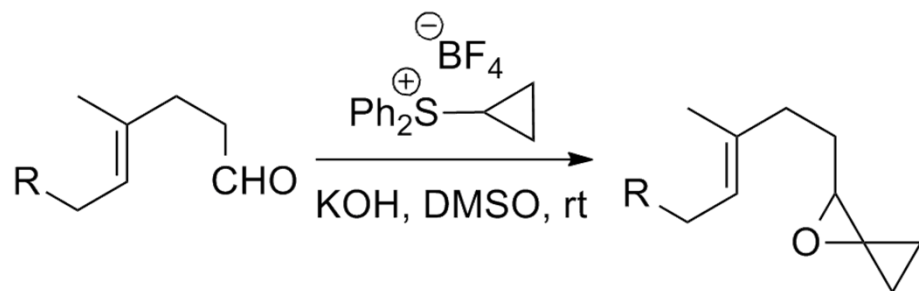
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.1 Oxiran

Epoxide aus Carbonylverbindungen und Schwefel-Yliden

Cyclopropanierung von Ketonen zu Oxiranen

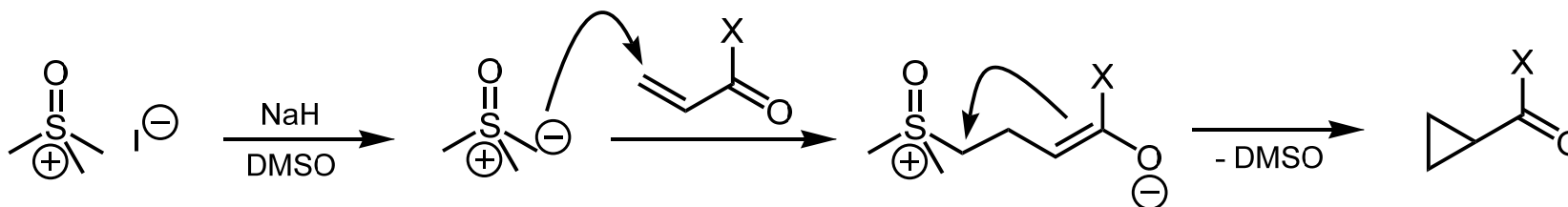


Sulfonium-Ylid geht keine Wittig-analoge Reaktion ein!

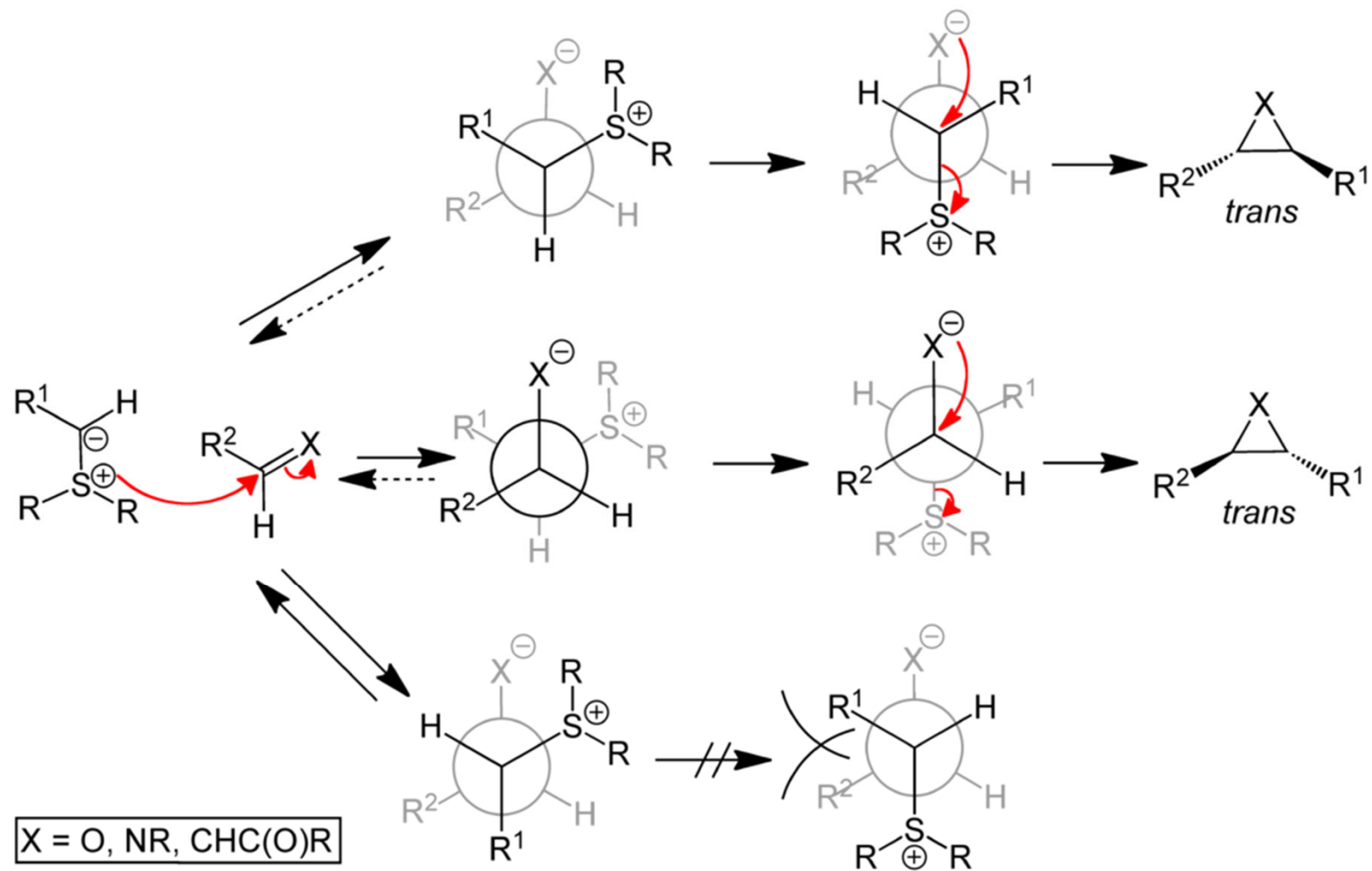


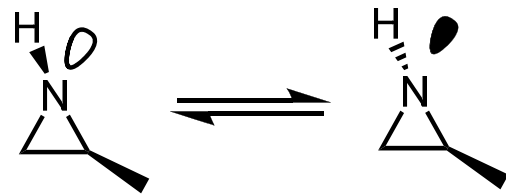
Dimethyloxosulfoniummethylid
(Corey-Chaykovsky-Reagenz)

Bei α,β -ungesättigten Carbonylverbindungen: α,β -Cyclopropanierung

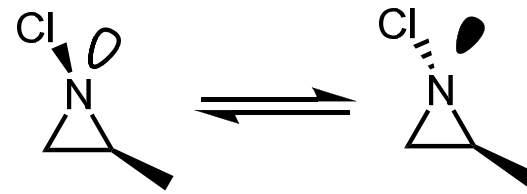


Johnson-Corey-Chaykovsky-Reaktion: Mechanismus

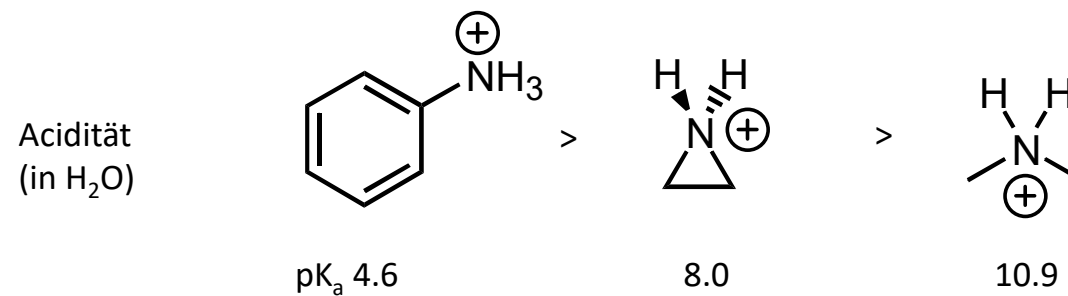




Diastereomere, nicht trennbar

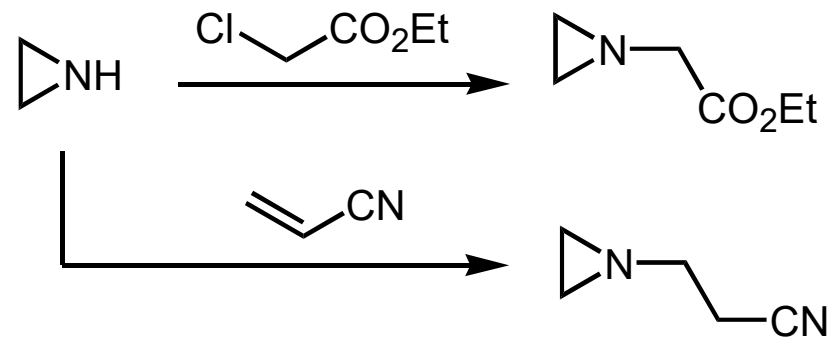


Diastereomere, trennbar

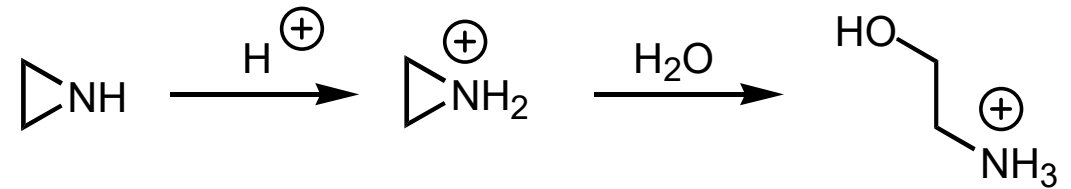


Reaktivität

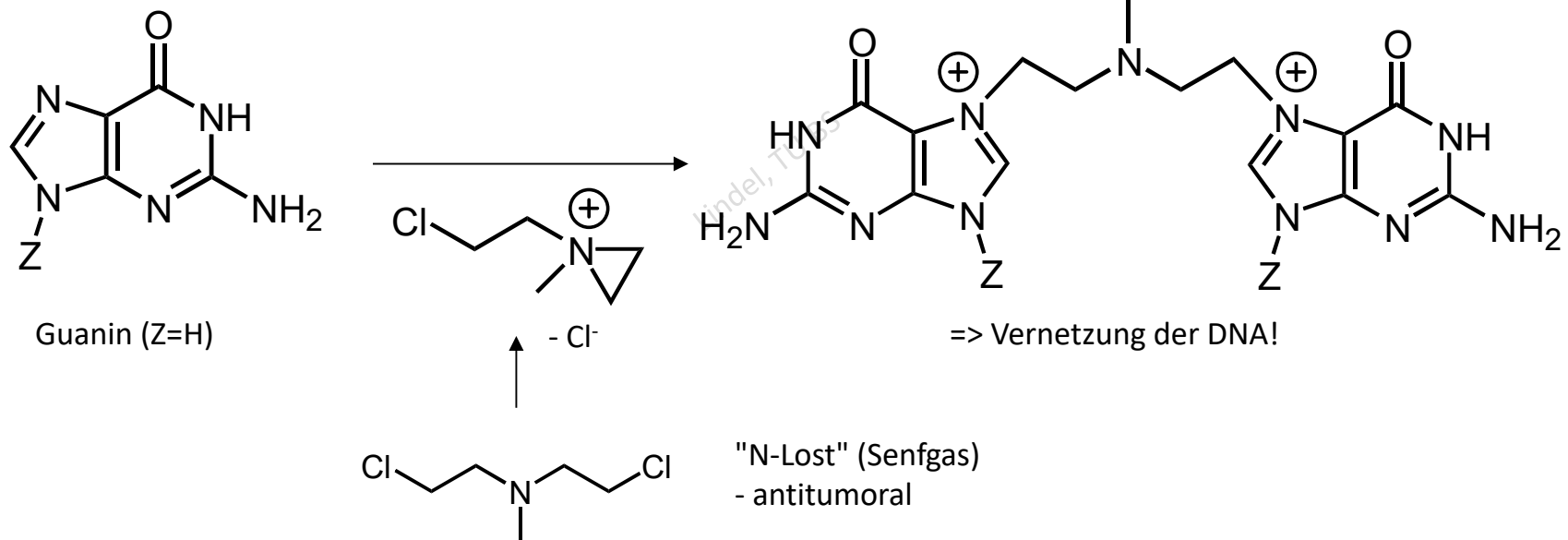
a) gegenüber Elektrophilen:



b) gegenüber Nukleophilen

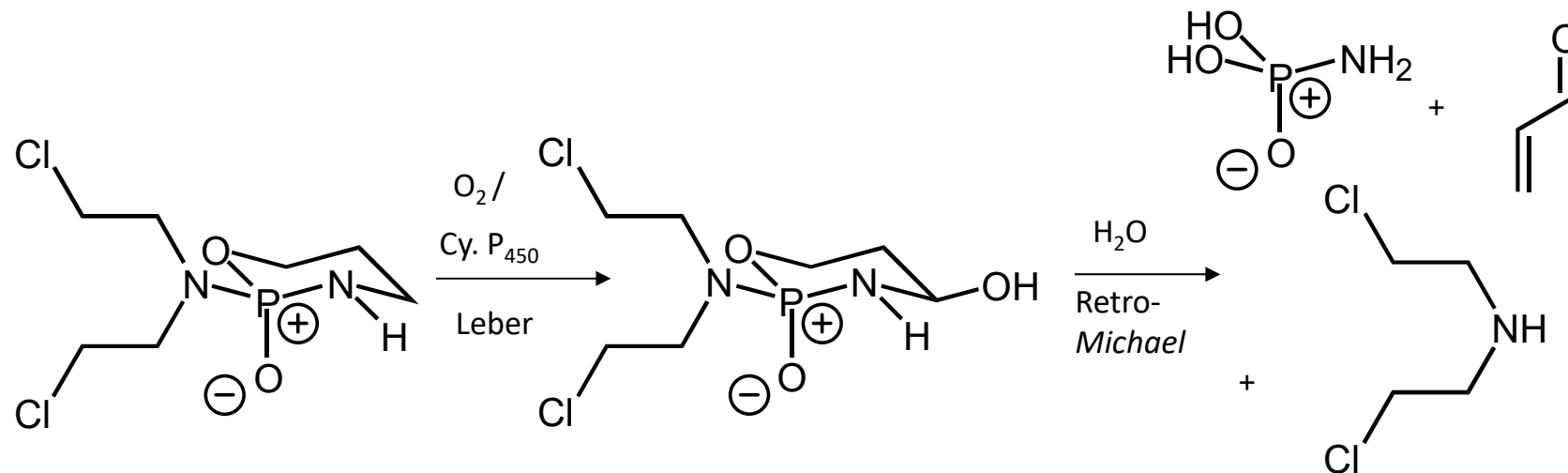


z. B. Schädigung von DNA:



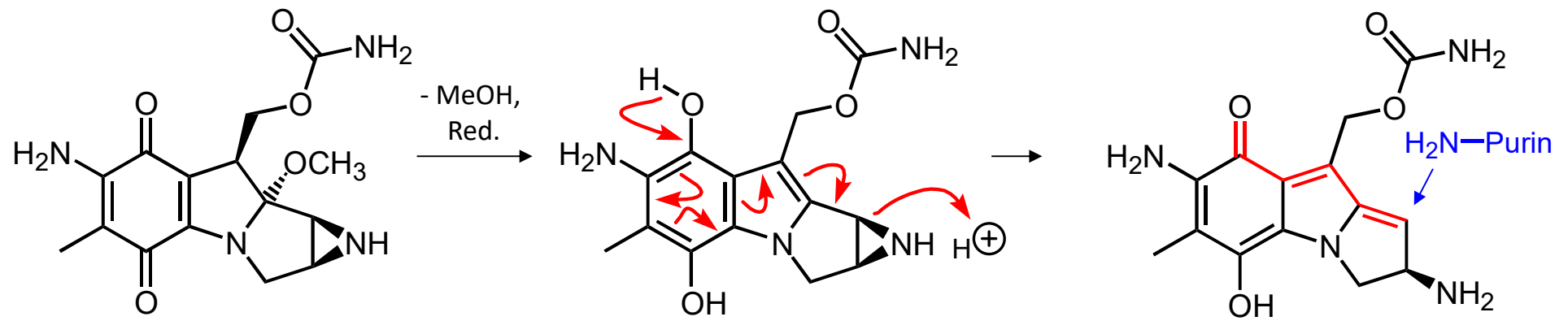
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

Krebstherapeutikum Cyclophosphamid (Asta Medica, 1956): maskierter N-Lost



B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

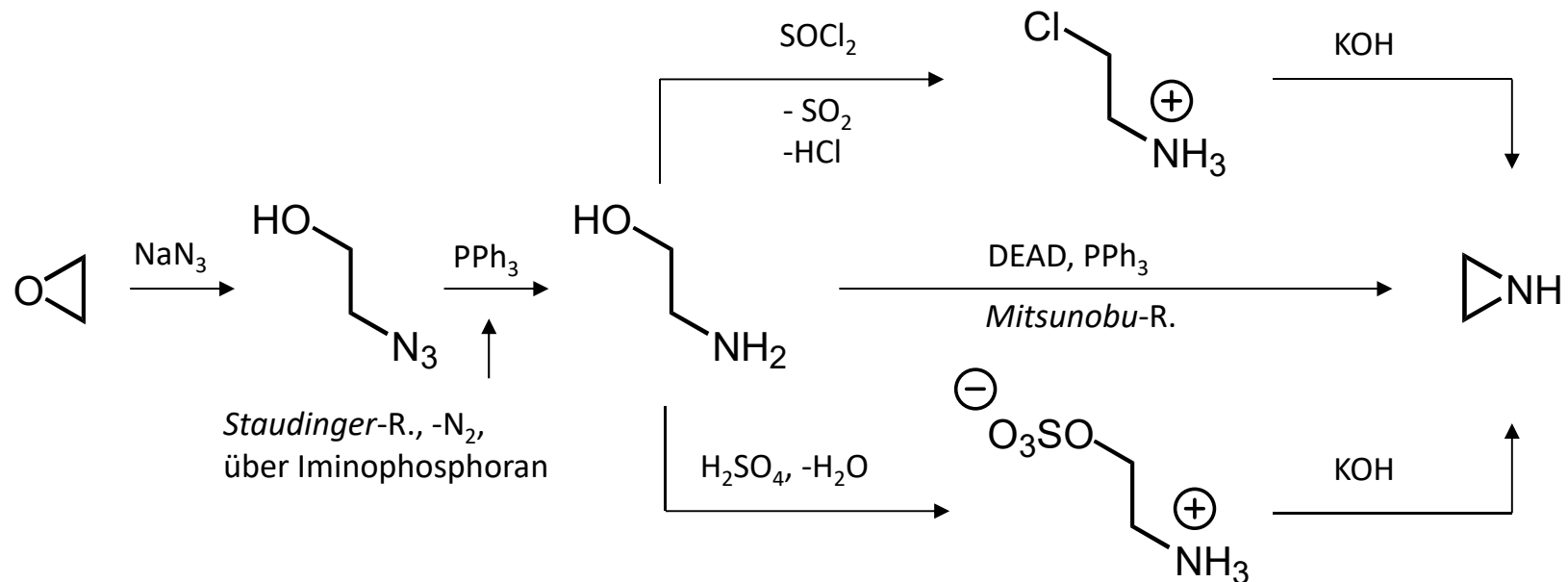
Krebstherapeutikum Mitomycin C aus Streptomyceten (*Streptomyces caespitosus*, 1956):



Review Mitomycine: Williams et al., *Chem. Rev.* **2013**, 6816

Synthese von Aziridin

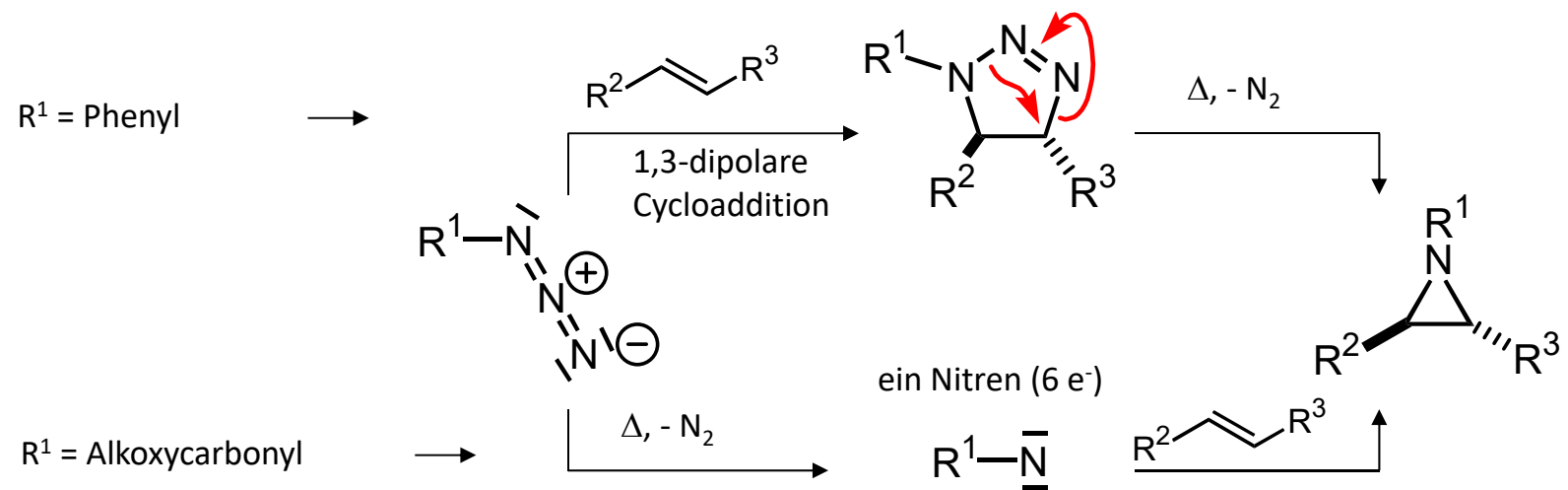
a) Cyclisierung β -subst. Amine



B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

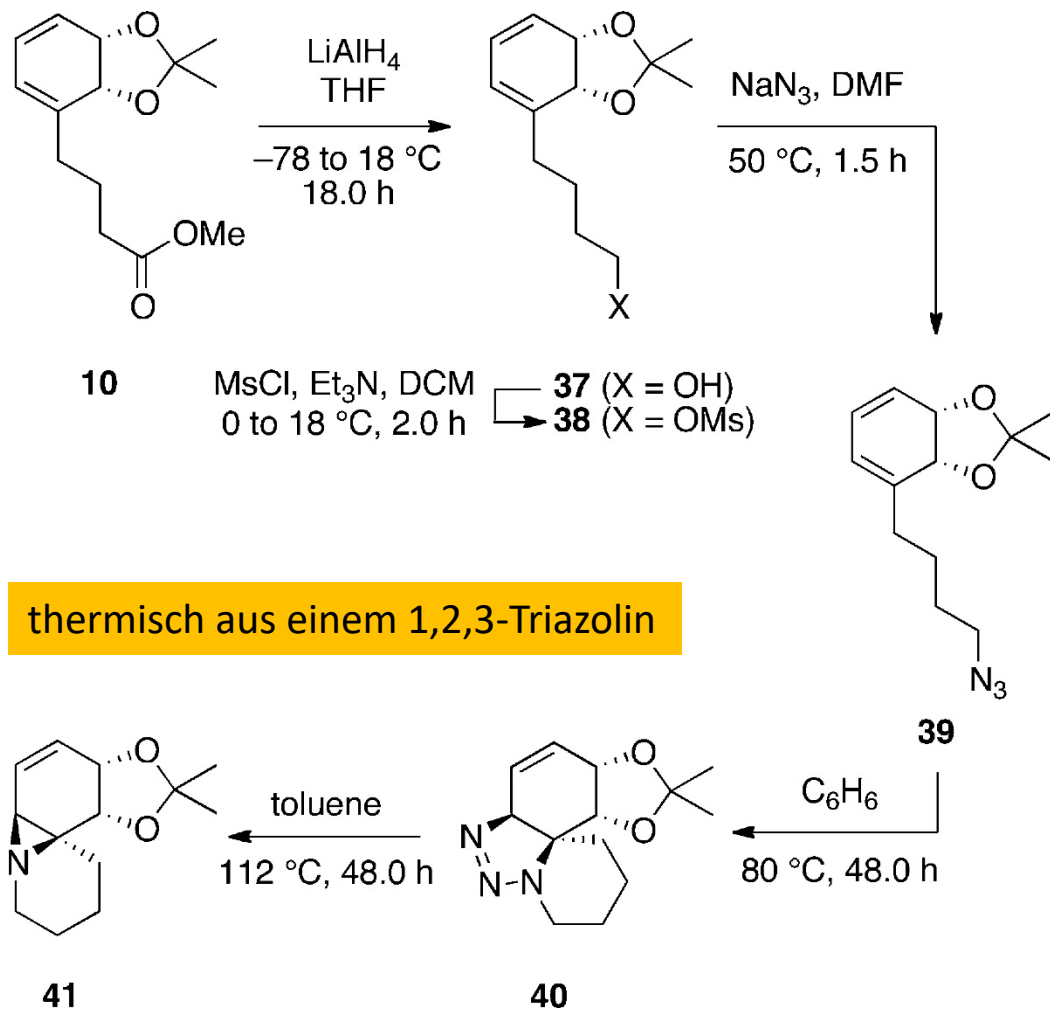
Synthese von Aziridin

b) Stickstoff-Abspaltung aus Aziden



B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

Banwell et al., *JOC* **2013**, 7100; <https://doi.org/10.1021/jo400952u>

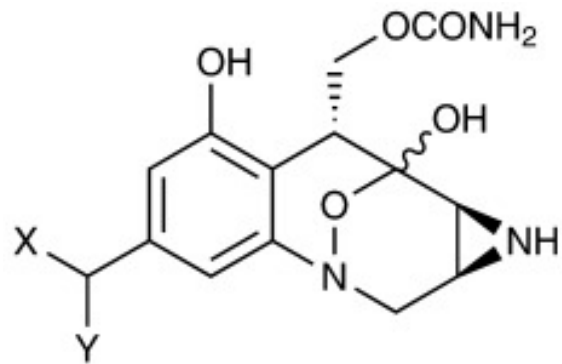


thermisch aus einem 1,2,3-Triazolin

"Upon simply heating azide **39** in refluxing benzene, the anticipated cycloaddition reaction took place producing the crystalline triazoline **40** in 90% yield. The structure of the latter compound was confirmed by single-crystal X-ray analysis establishing that, once again, the intramolecular addition process involved delivery of the azido group to the more accessible β -face of the *cis*-1,2-dihydrocatechol residue. Heating the triazoline **40** in refluxing toluene resulted in the extrusion of dinitrogen and the consequent formation of the annulated aziridine **41** (85%). A more direct route to the latter compound involved heating azide **39** in refluxing toluene for 72 h."

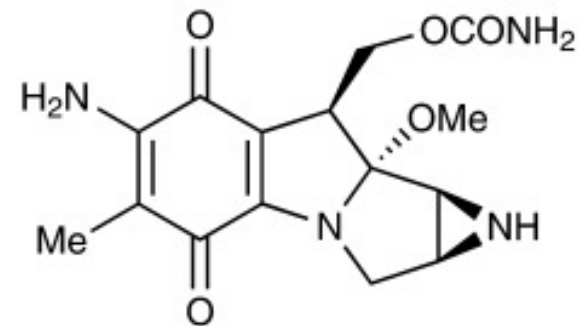
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

Total Synthesis of (±)-FR66979 (Ducray, Ciufolini, *Angew. Chem.* **2002**, 4688)



FR66979 **1a**: X = H; Y = OH

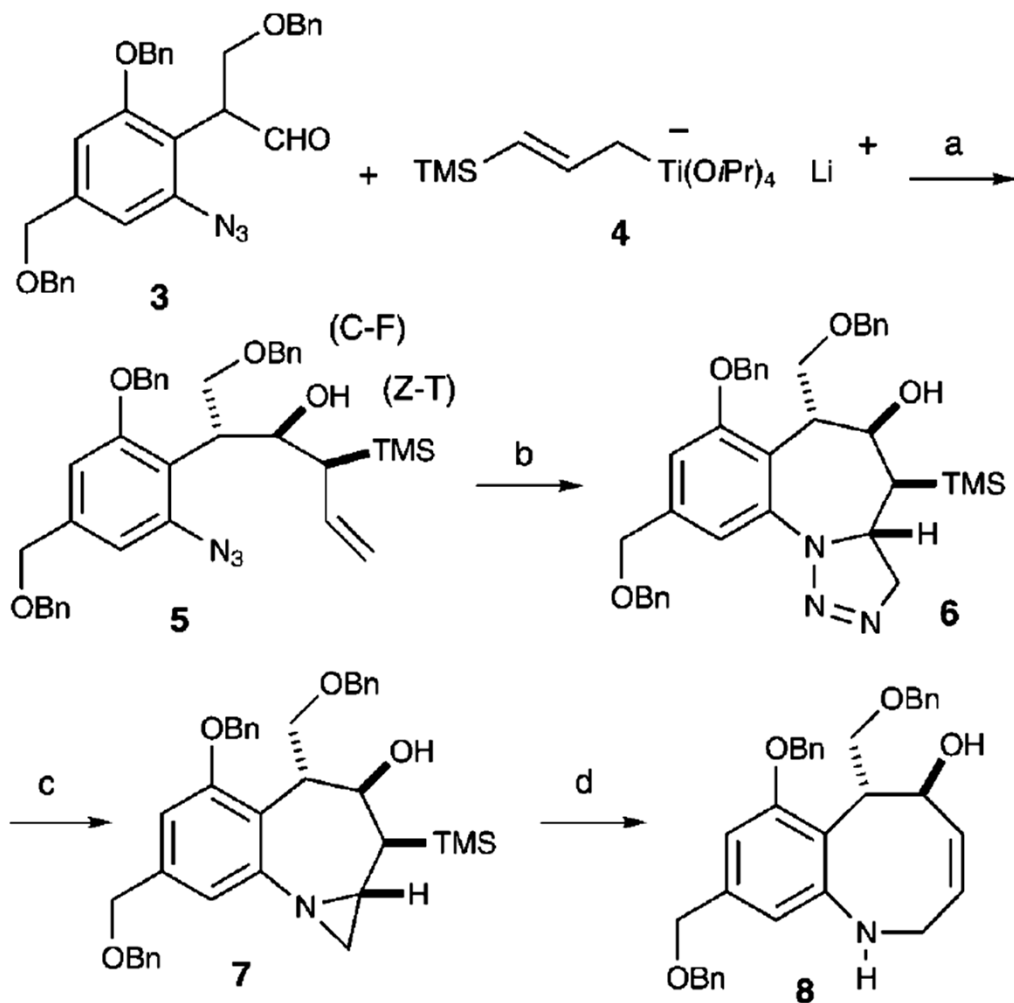
FR900482 **1b**: X, Y = O



mitomycin C **2**

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

Total Synthesis of (±)-FR66979 (Ducray, Ciufolini, *Angew. Chem.* **2002**, 4688)

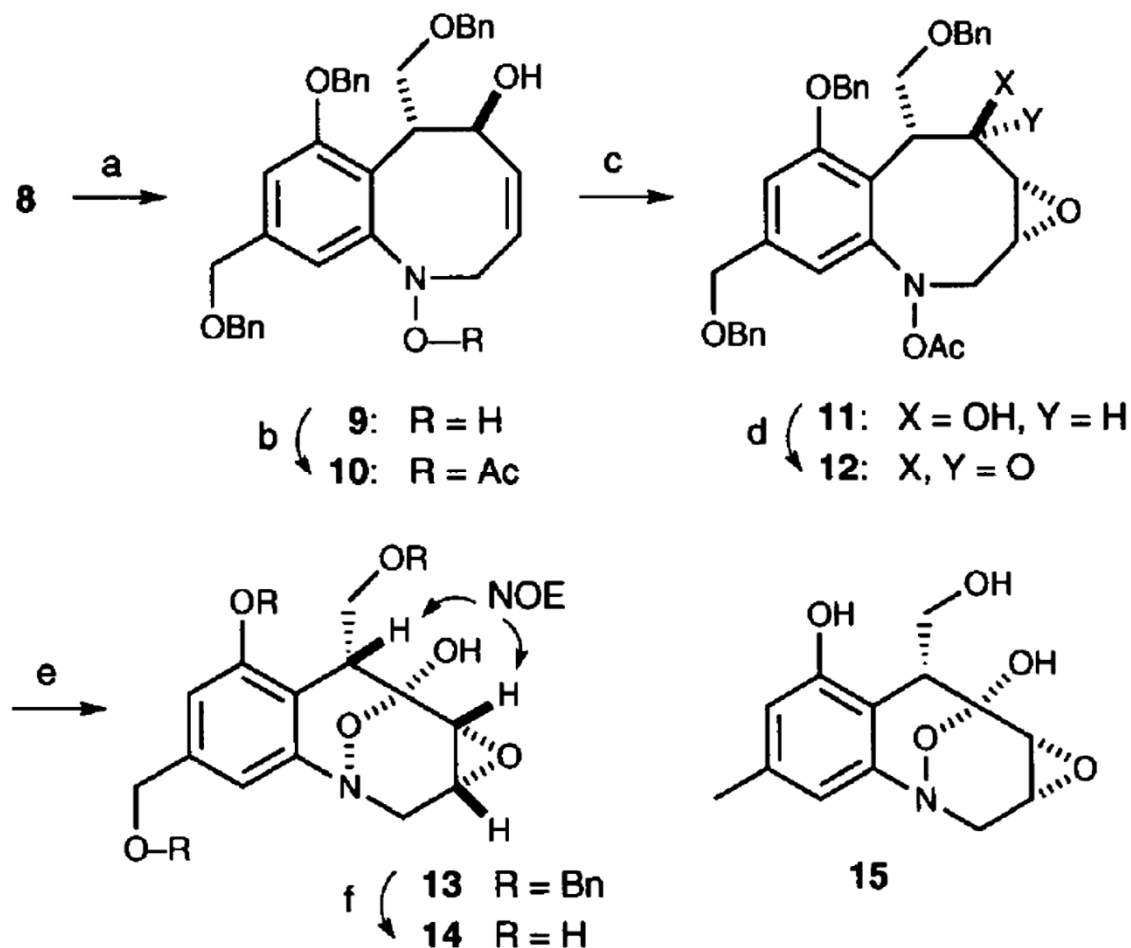


a) THF, -78 °C; b) toluene, 100 °C, 80 % over two steps; c) *hν*, THF, 77%; d) nBu₄NOH, DMF, -20 °C, 49%. DMF = *N,N*-dimethylformamide.

Aziridin photochemisch aus einem 1,2,3-Triazolin

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

Total Synthesis of (±)-FR66979 (Ducray, Ciufolini, *Angew. Chem.* **2002**, 4688)

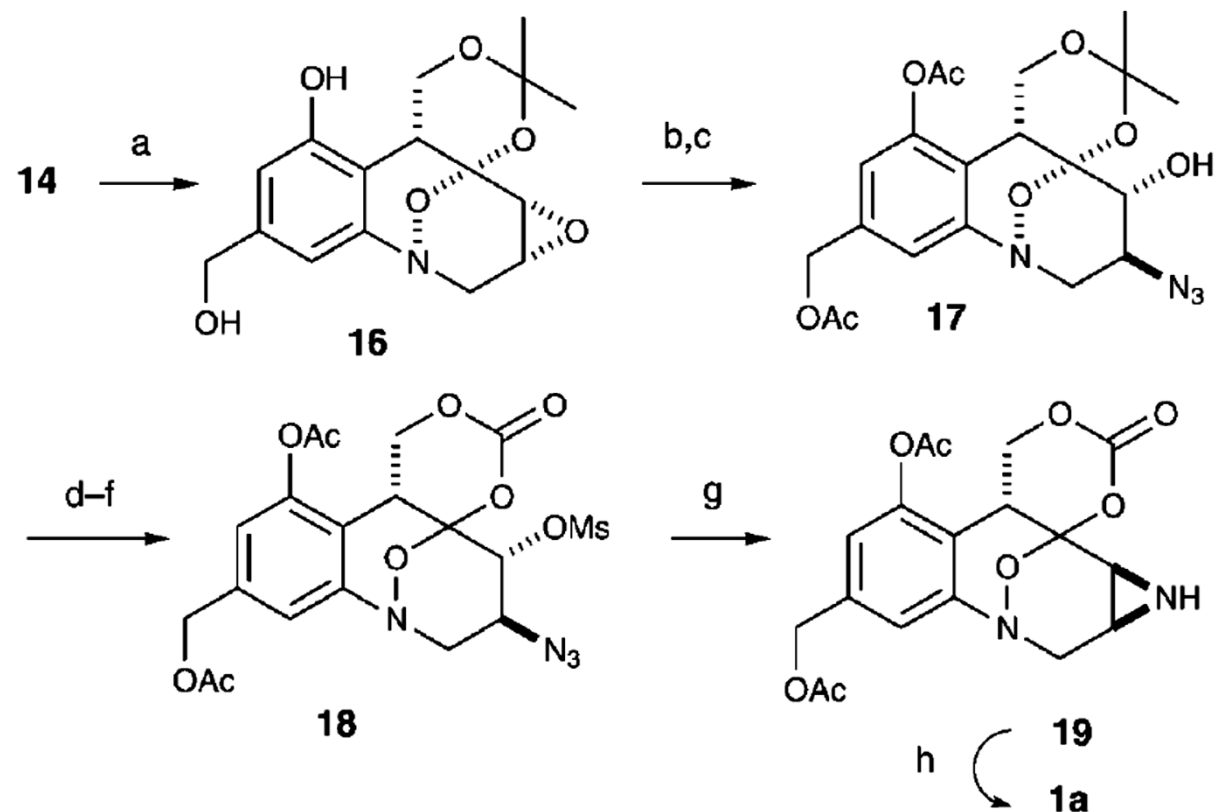


a) MCPBA, CH₂Cl₂, 0 °C; b) neat Ac₂O, room temperature, 87 % over two steps; c) MCPBA, CH₂Cl₂, NaHCO₃, room temperature, 70 %; d) cat. TPAP, NMO, CH₂Cl₂, molecular sieves (4 Å), room temperature, 83 %; e) N₂H₄·H₂O, MeOH, CH₂Cl₂, 100 %; f) H₂ (1 atm), Pd/C, EtOAc, 97 % crude. MCPBA = *m*-chloroperoxybenzoic acid, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide.

Name the heterocycles!

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

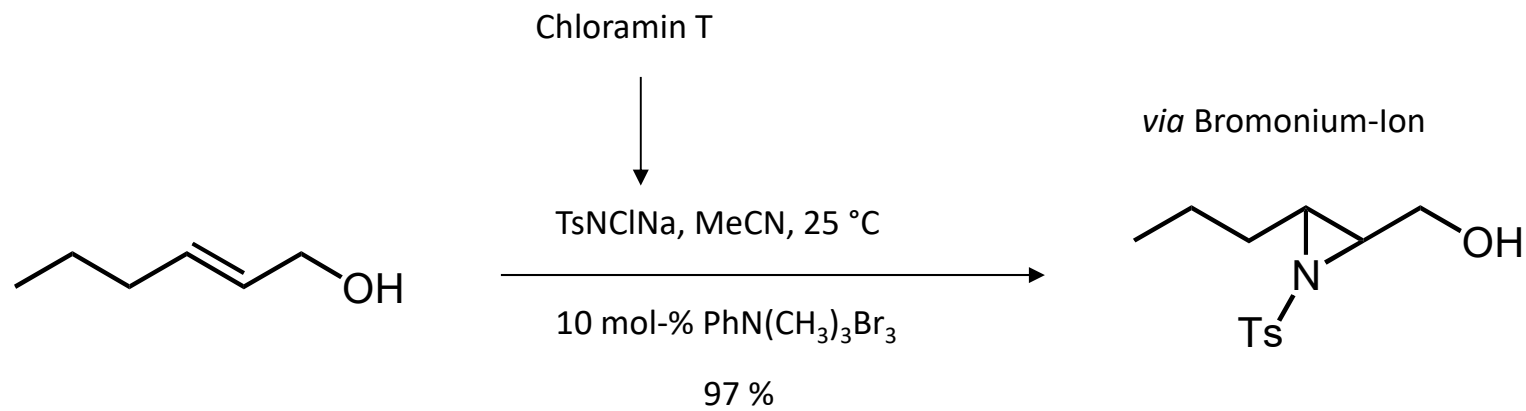
Total Synthesis of (±)-FR66979 (Ducray, Ciufolini, *Angew. Chem.* **2002**, 4688)



a) 2-Methoxypropene, PPTS, DMF, room temperature, 83%; b) LiN_3 , DMF, 100 °C, 67%; c) Ac_2O , K_2CO_3 , THF, room temperature, 81%; d) MsCl , Et_3N , CH_2Cl_2 , room temperature, 71%; e) TFA, CH_2Cl_2 , room temperature; f) COCl_2 , CH_2Cl_2 , Et_3N , 0 °C, 28%; g) Ph_3P , $i\text{Pr}_2\text{NEt}$, aqueous THF (90%), 60 °C, 78%; h) NH_3 , MeOH, room temperature, 40%. PPTS = pyridinium *p*-toluenesulfonate, Ms = methanesulfonyl, TFA = trifluoroacetic acid.

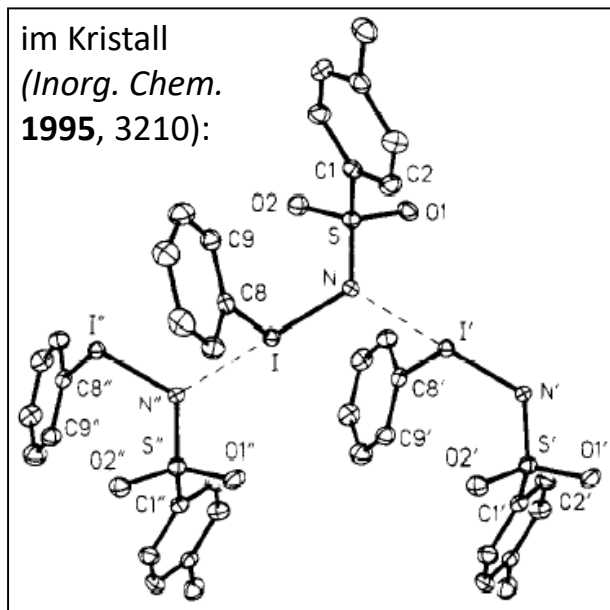
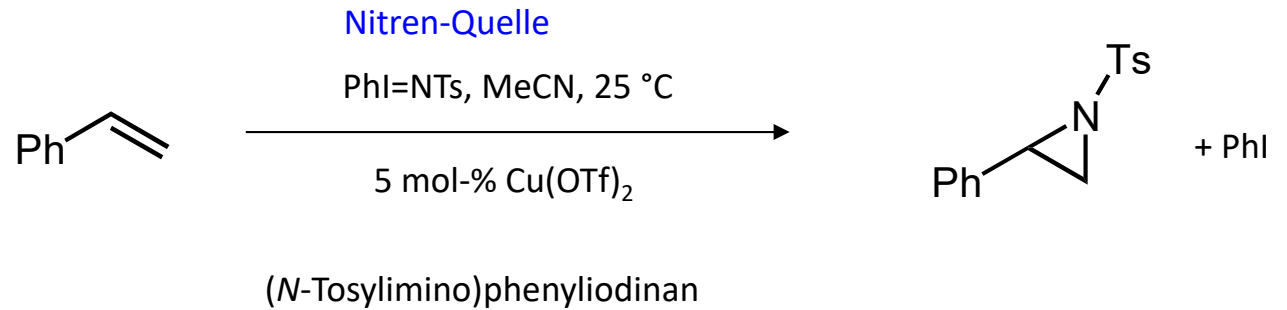
Aziridin durch
intramolekulare nukleophile
Substitution

c) Alken + Iminoiodinan



B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

c) Alken + Iminoiodinan

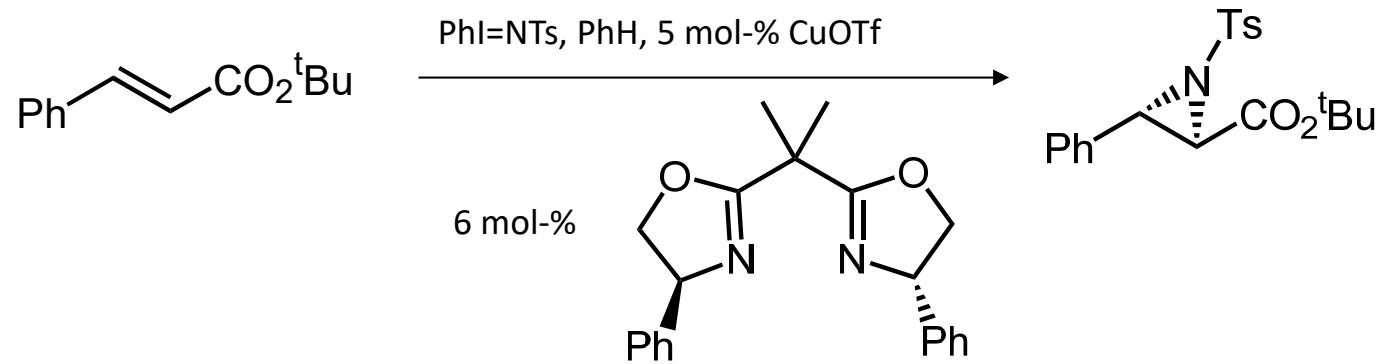


Evans et al., *JOC* **1991**, 6744; *JACS* **1994**, 2742;
Dodd et al., *Synlett* **2003**, 1571.

Fe(III)-, Mn(III)-katalysiert: Mansuy et al. *JCSCC* **1984**, 1161.

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

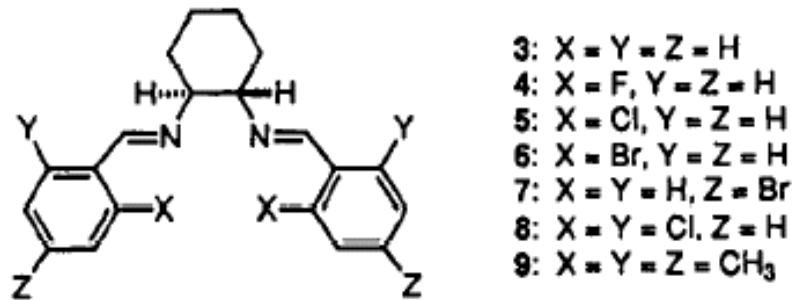
Enantioselektive Evans-Aziridinierung: besonders geeignet für *trans*-Aziridine



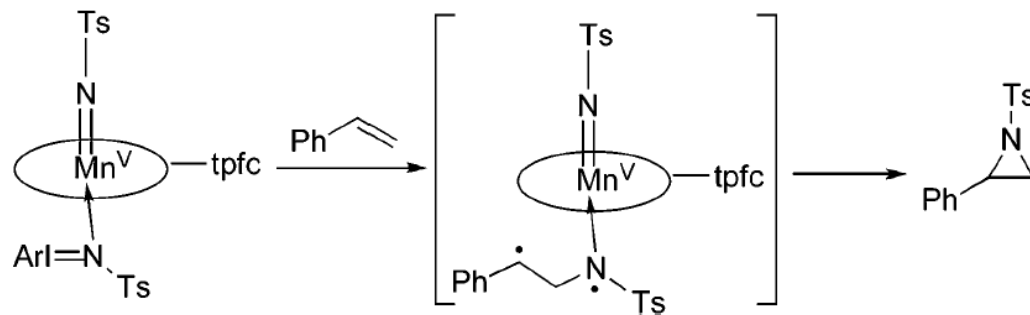
Bisoxazolin-Cu-Komplexe: Evans et al., *JACS* **1993**, 5328.

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

Enantioselektive Jacobsen-Aziridinerung : besonders geeignet für *cis*-Aziridine

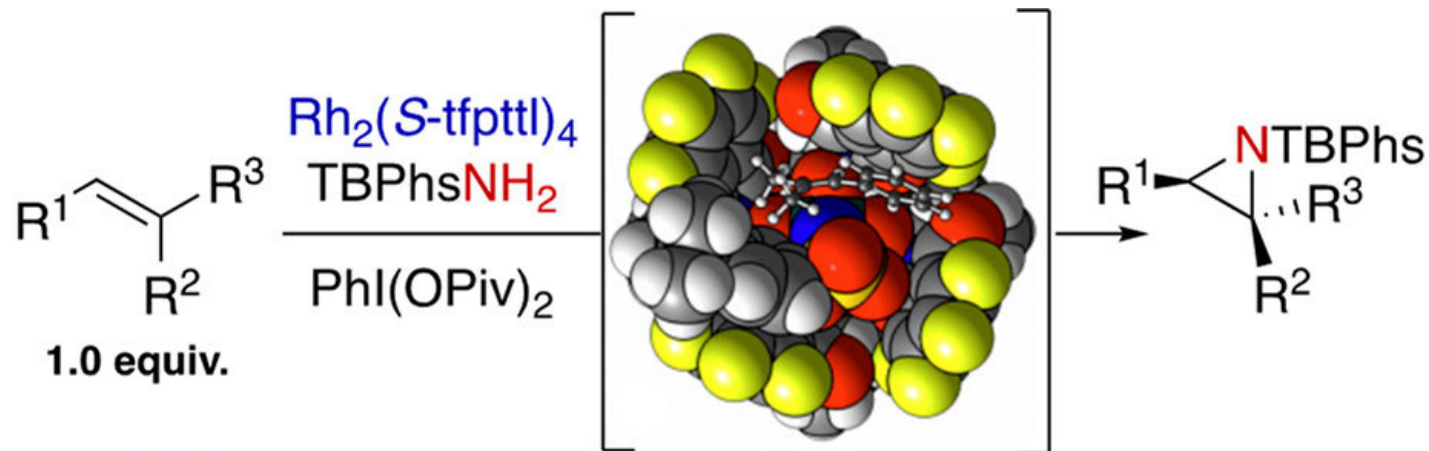


Salen-Cu-Komplexe: Jacobsen et al., *JACS* **1993**, 5326.



ee nicht immer gut, da radikalische Intermediate beteiligt.

Enantioselektive Aziridinerung: Rh(II)-Katalyse (something recent)



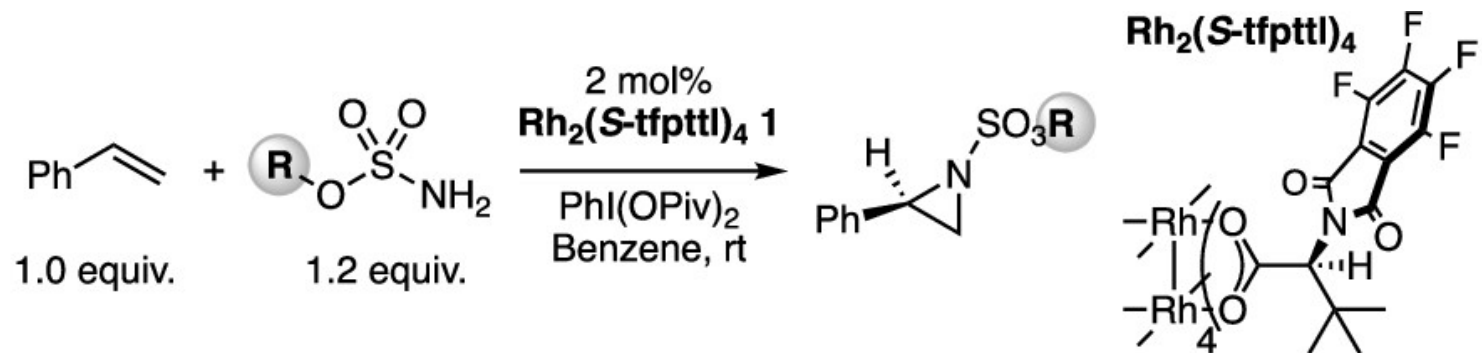
$TBPhsNH_2$: *p*-*t*Bu-phenylsulfamate

- *Low catalyst loading: 0.1 to 1 mol%*
- *Large scope (>35 examples): mono-, di-, or tri-substituted aziridines*
- *Excellent yields up to 95% and e.r. up to 99.5:0.5*
- *Two-spin state mechanism*
- *Stereochemical model rationalizing the enantiocontrol*

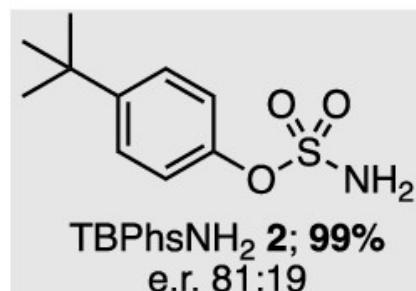
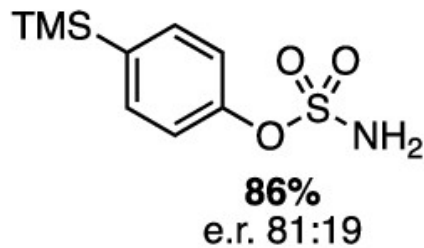
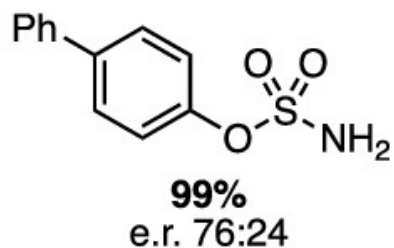
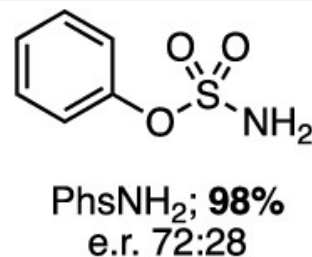
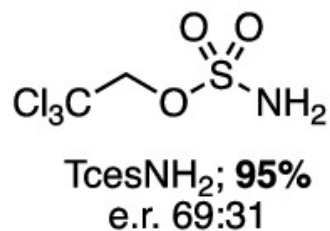
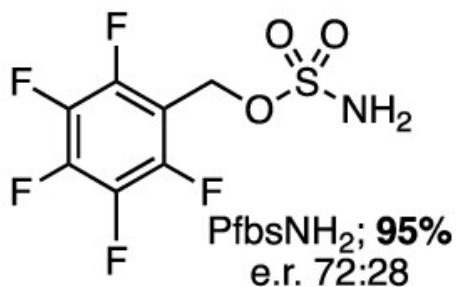
aus: Dauban et al., *JACS* **2022**, 17156

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

Enantioselektive Aziridinierung: Rh(II)-Katalyse (something recent)



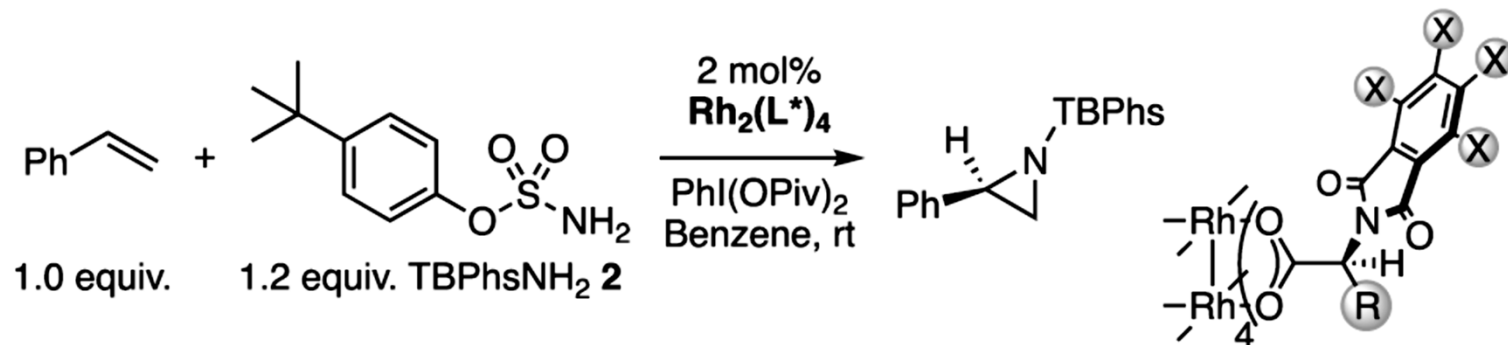
Suche nach der besten Stickstoffquelle



aus: Dauban et al., *JACS* **2022**, 17156

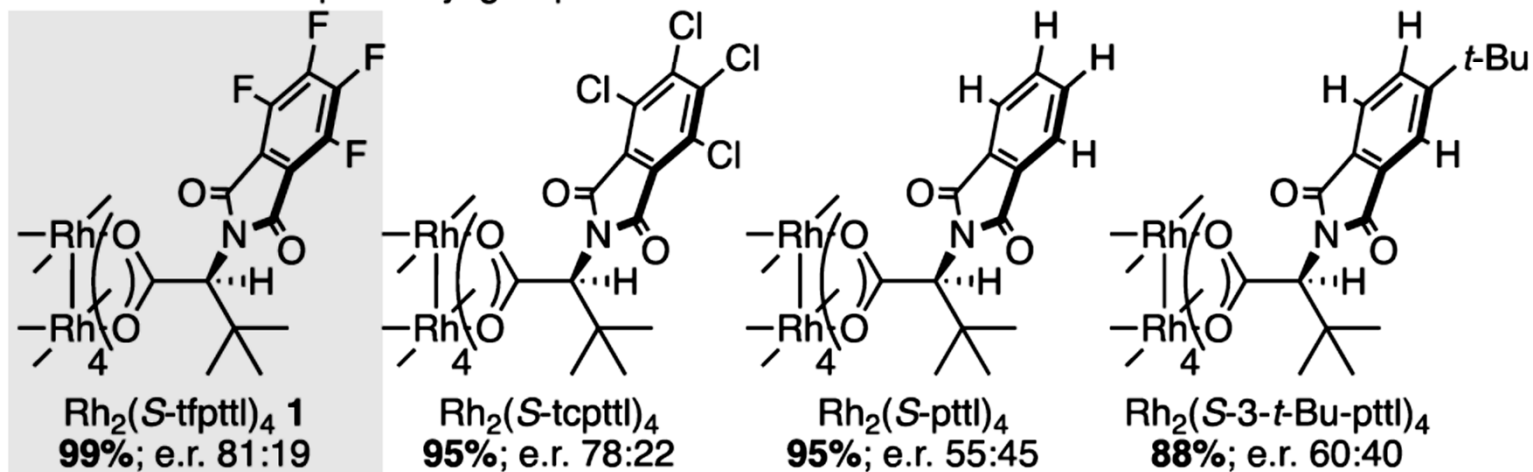
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

Enantioselektive Aziridinierung: Rh(II)-Katalyse (something recent)



Suche nach dem besten Liganden

Substitution of the phthaloyl group

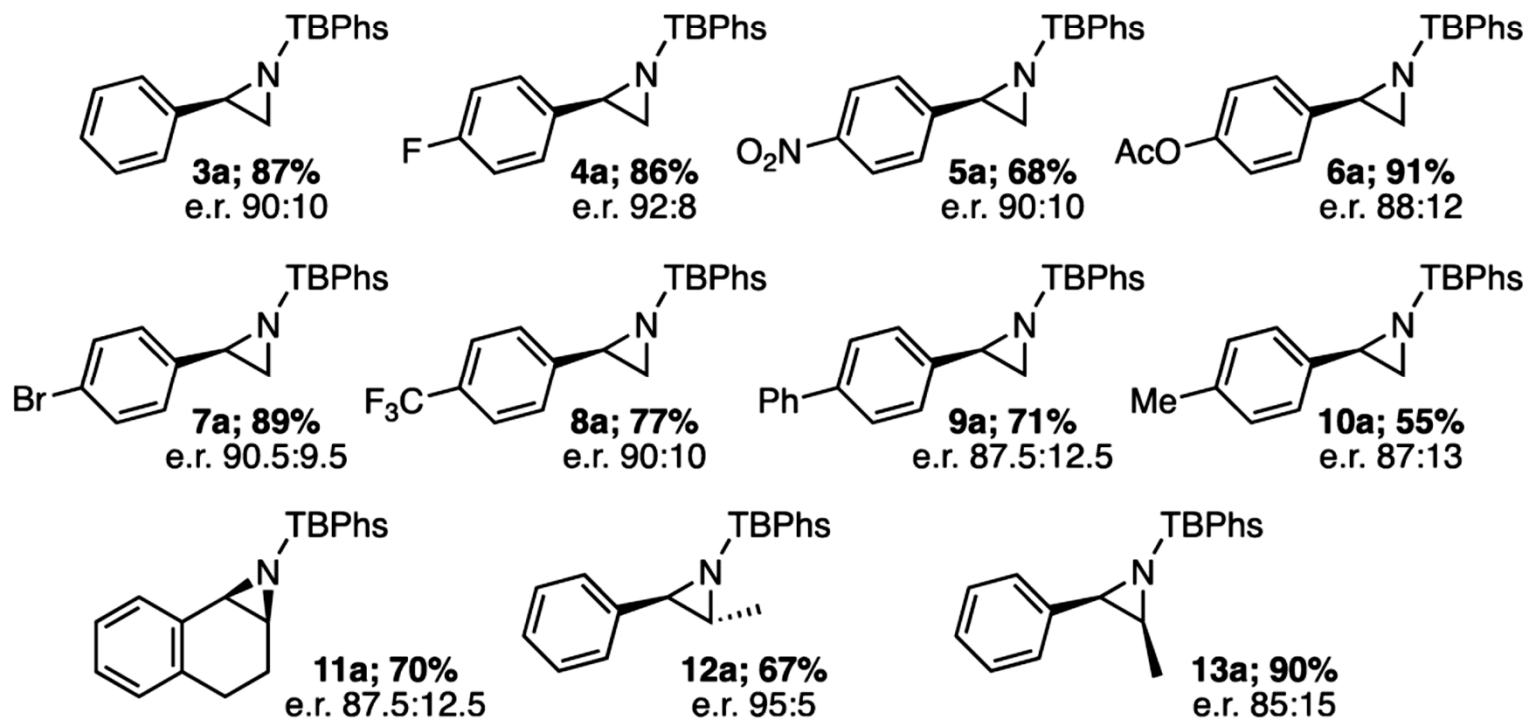
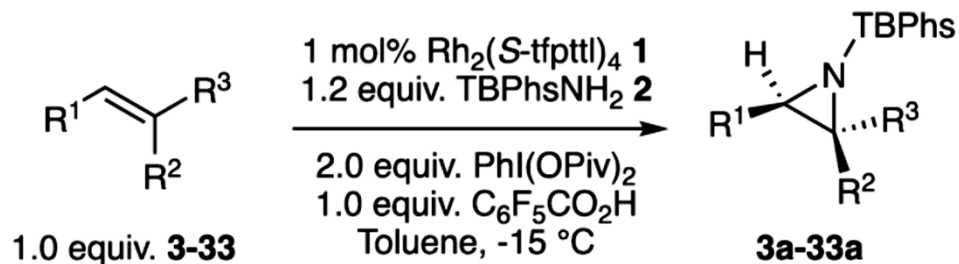


Amino acid side chain

aus: Dauban et al., *JACS* **2022**, 17156

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

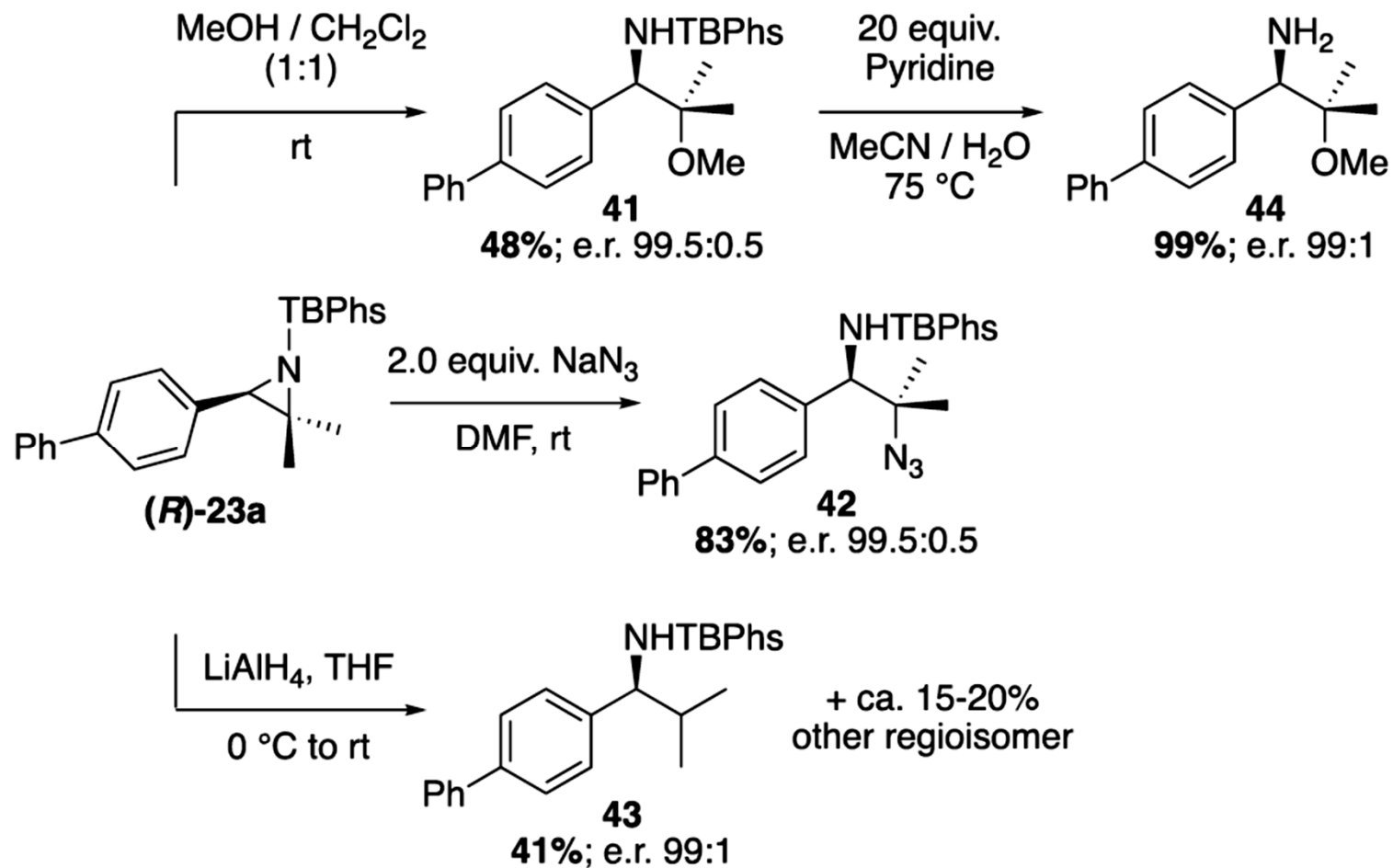
Enantioselective Aziridiniierung: Rh(II)-Katalyse (something recent)



Anwendung auf einfache Edukte

aus: Dauban et al., *JACS* **2022**, 17156

Enantioselektive Aziridinierung: Rh(II)-Katalyse (something recent)



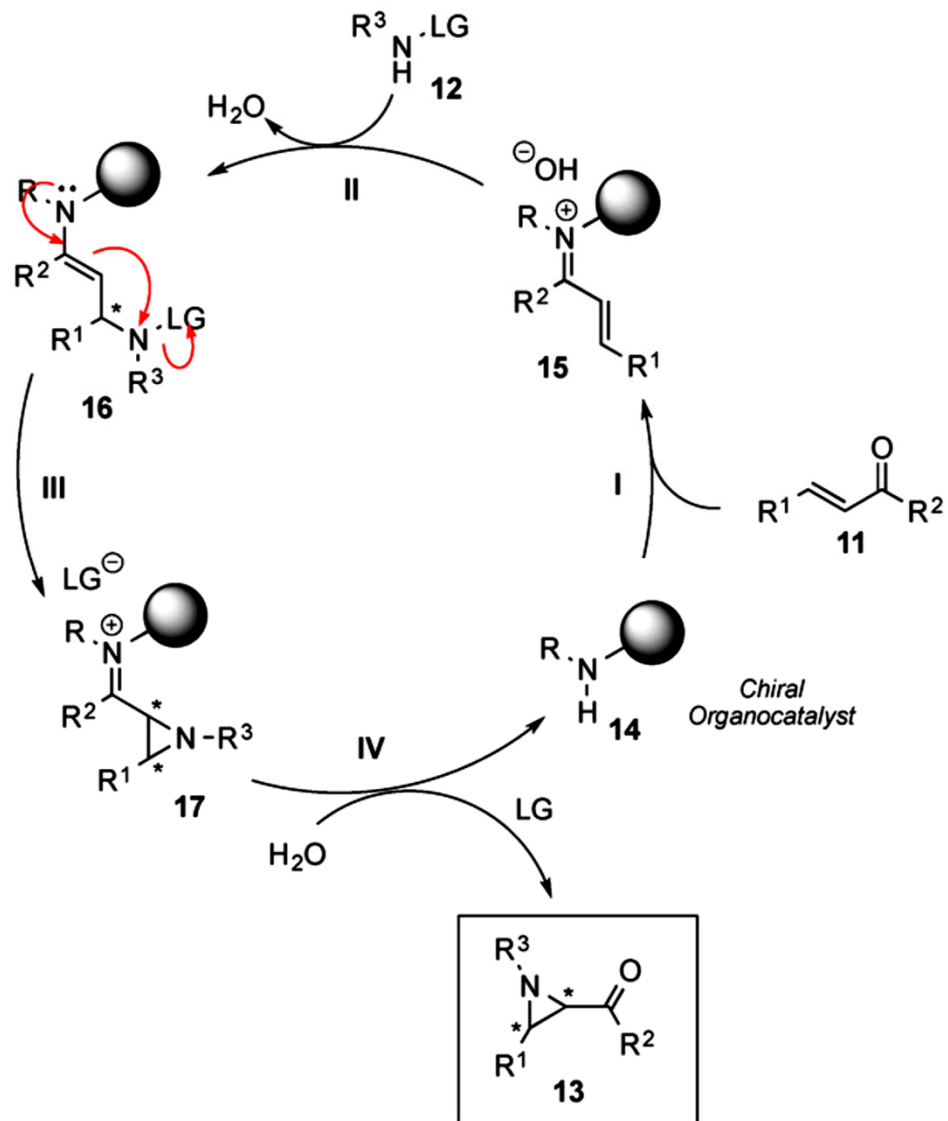
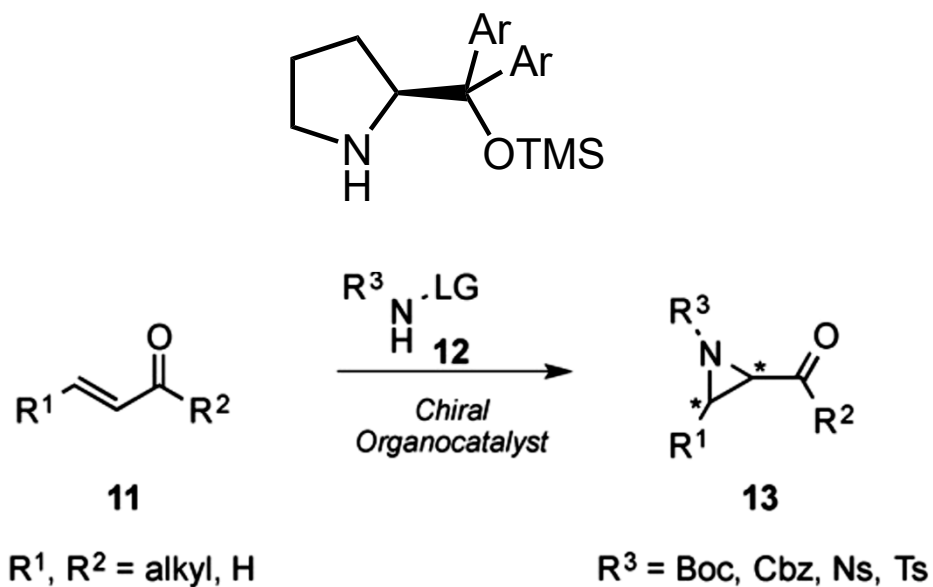
Folgechemie;
hier auch:
Entschützung!

aus: Dauban et al., *JACS* **2022**, 17156

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

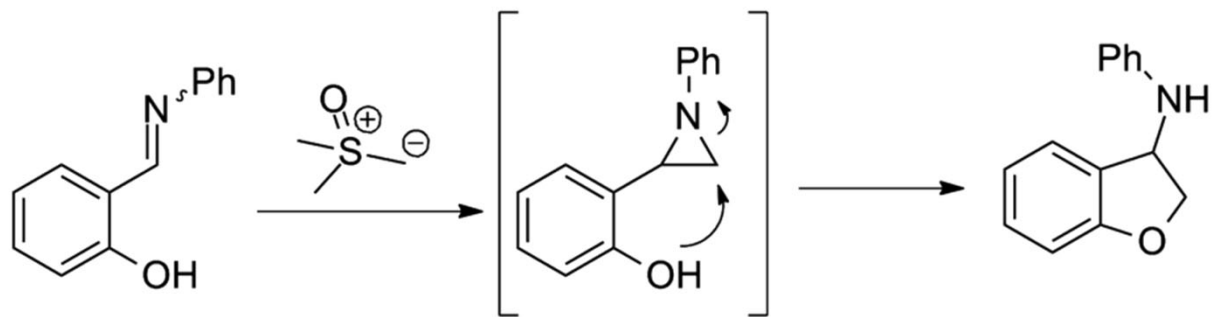
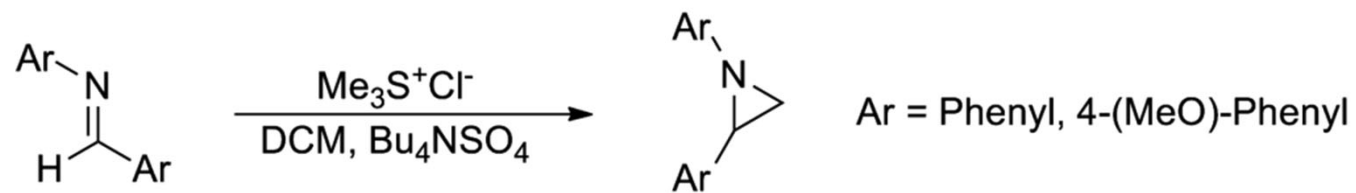
Pendant zur enantiosele. Weitz-Scheffer-Epoxidierung:
Enantioselektive Aziridinierung durch Organokatalyse

Review: Gasperi et al., *Asian J. Org. Chem.* **2018**, 2357



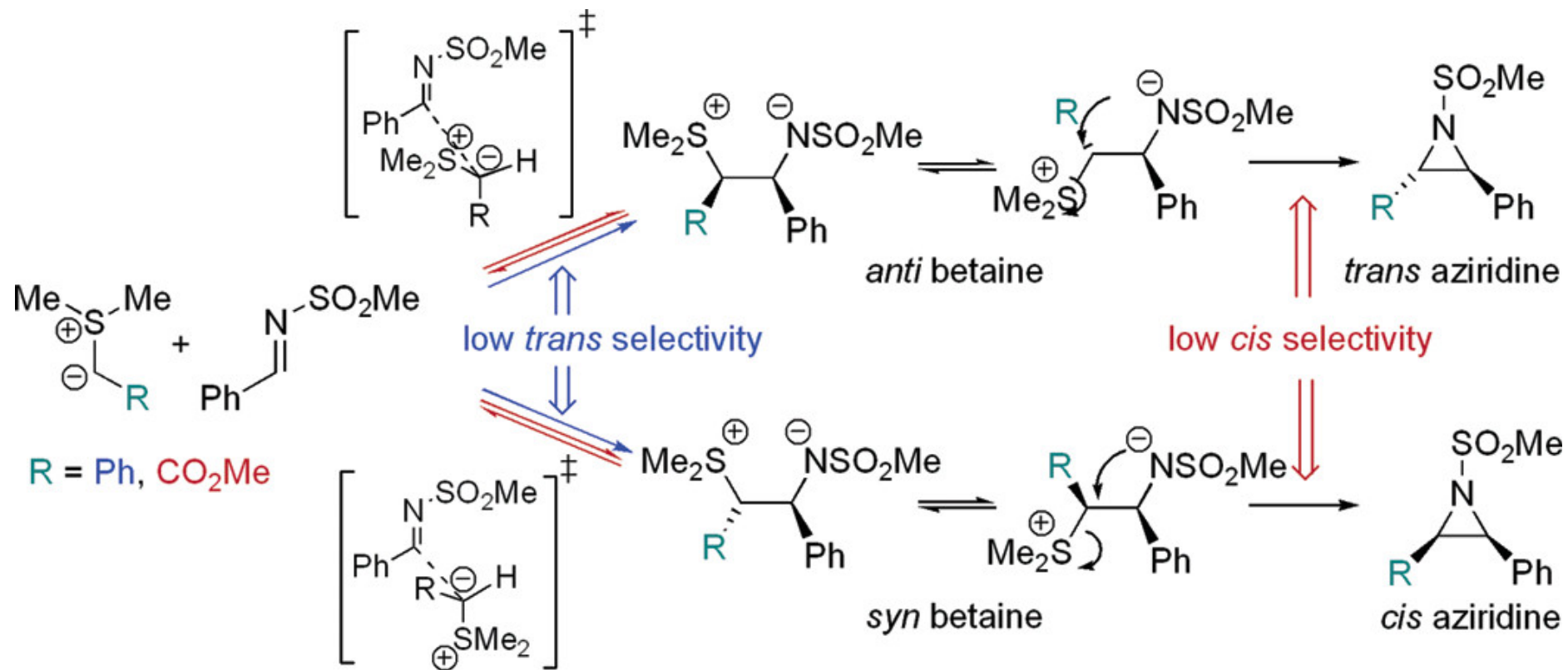
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

Aziridine durch Johnson-Corey-Chaykovsky-Reaktion von Schwefelyliden mit Iminen



B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.2 Aziridin

Aziridine durch Johnson-Corey-Chaykovsky-Reaktion von Schwefelyliden mit Iminen

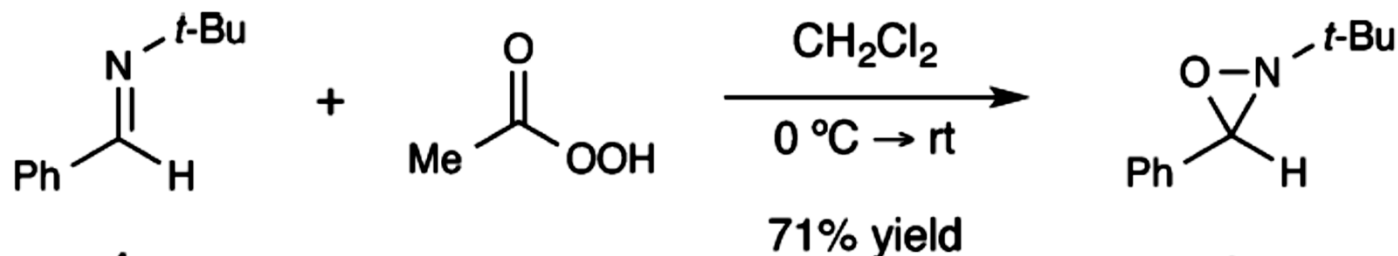


aus: JOC 2006, 2726

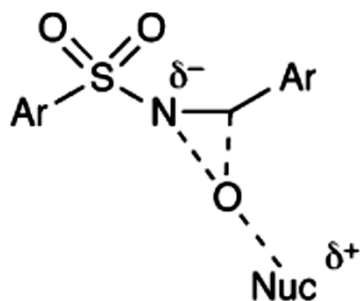
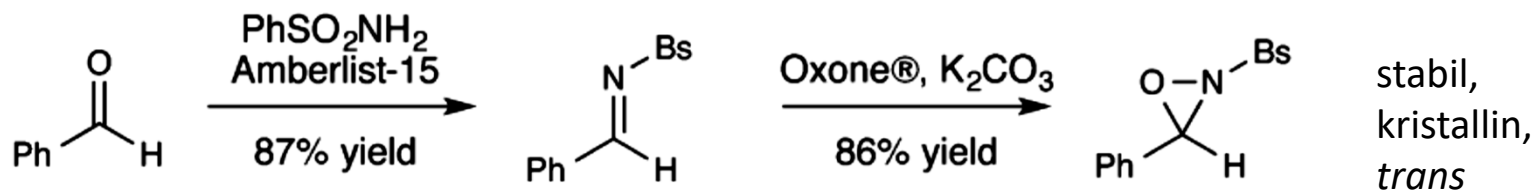
B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.3 Oxaziridin

Erstes Oxaziridin: Emmons 1957

konfigurationsstabil (*trans*)
(Energiebarriere 100-130 kJ/mol)



N-Sulfonyloxaziridines (Davis)

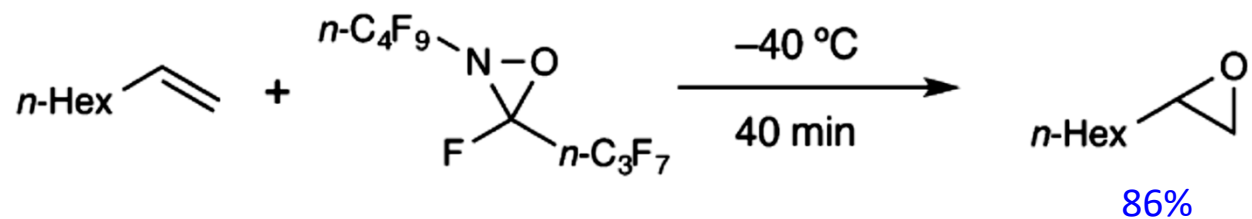
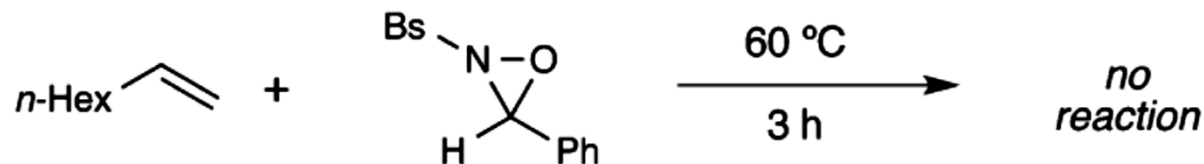


- konzertierter O-Transfer
- signifikante Ladungstrennung
- N-O-Bindungsspaltung bevorzugt

elektrophile
Epoxidierung

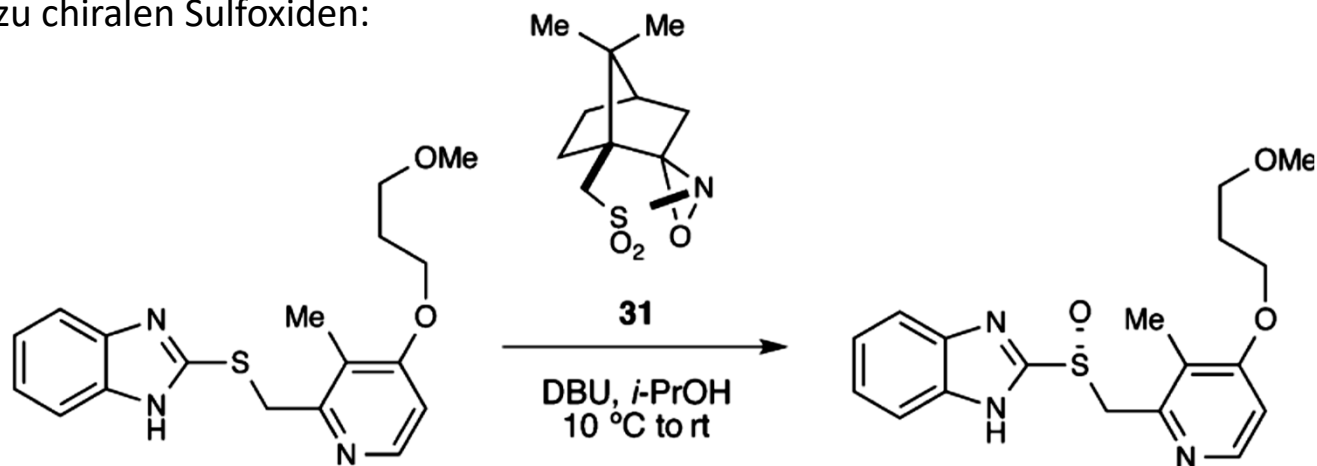
aus: *Chem. Rev.* **2014**, 8016

B. Dreigliedrige Ringe – B.2 Gesättigte Dreigliedrige Ringe – B.2.3 Oxaziridin



Fluorierte Seitenkette erhöht Elektrophilie.

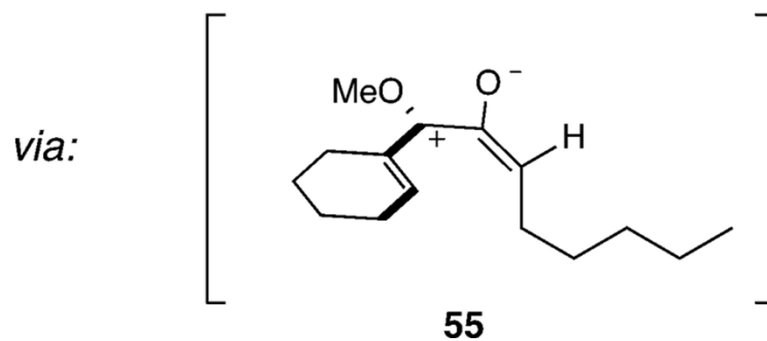
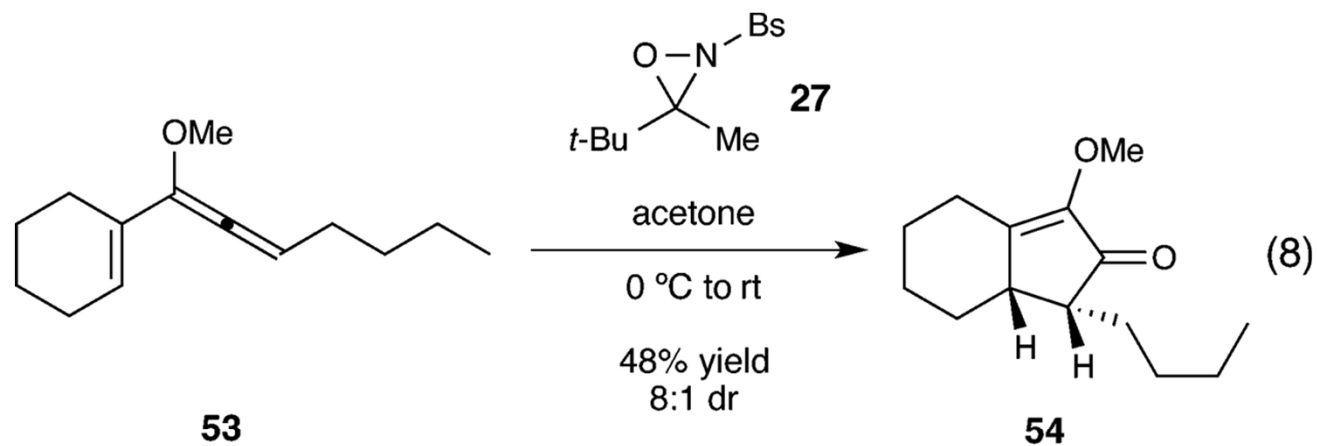
zu chiralen Sulfoxiden:



70%, ee 76%

aus: *Chem. Rev.* **2014**, 8016

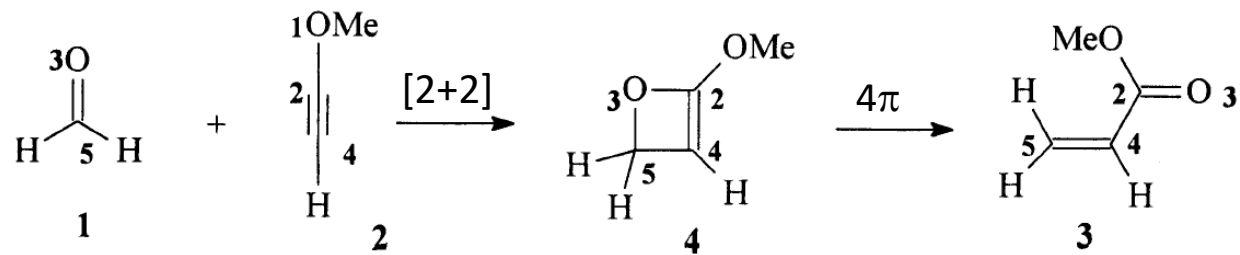
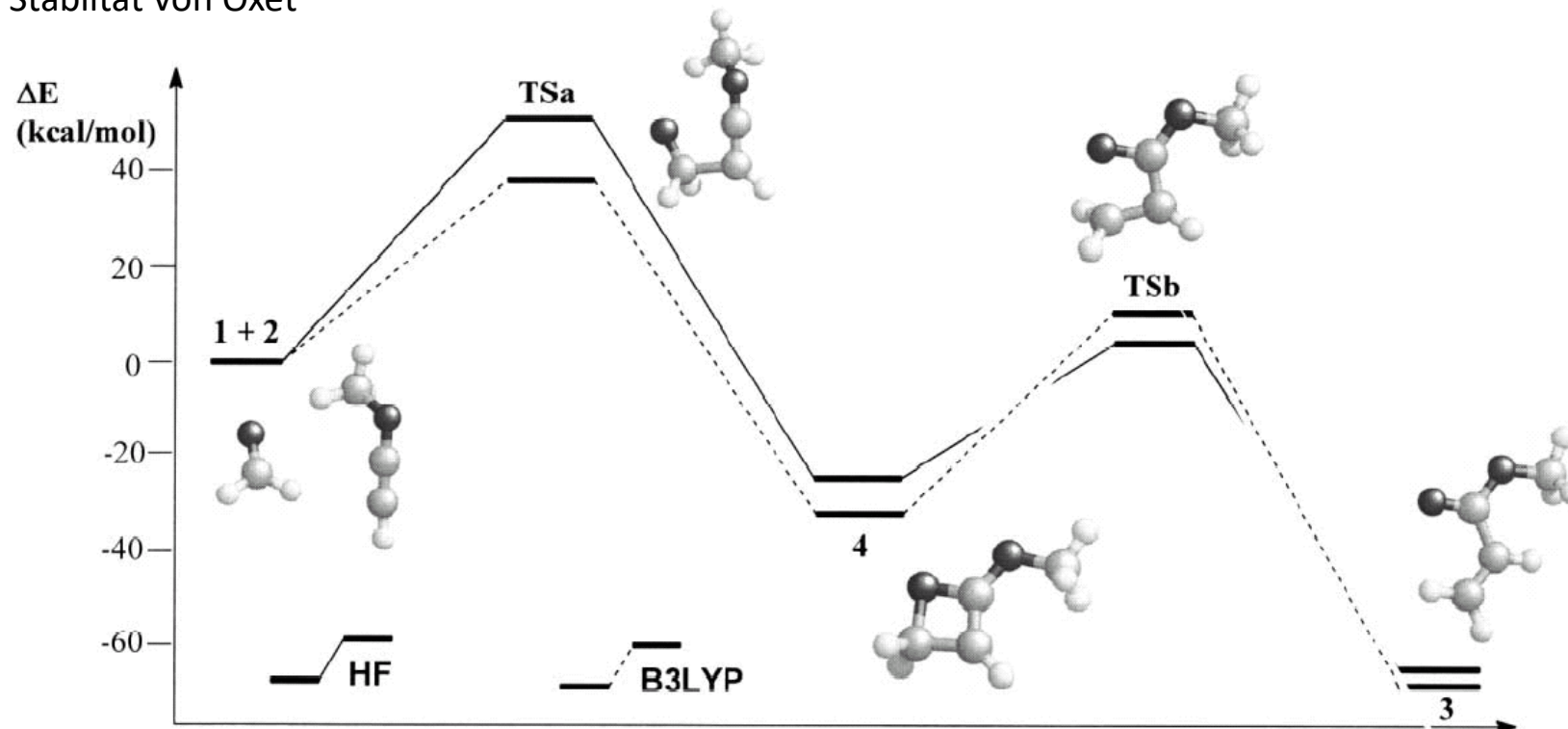
Oxaziridine: Sauerstoff-Transfer mit 4π -elektrozyklischer (Nazarov-) Reaktion



aus: *Chem. Rev.* **2014**, 8016

C. Viergliedrige Ringe – C.1 Ungesättigte viergliedrige Heterozyklen – C.1.1 Oxet

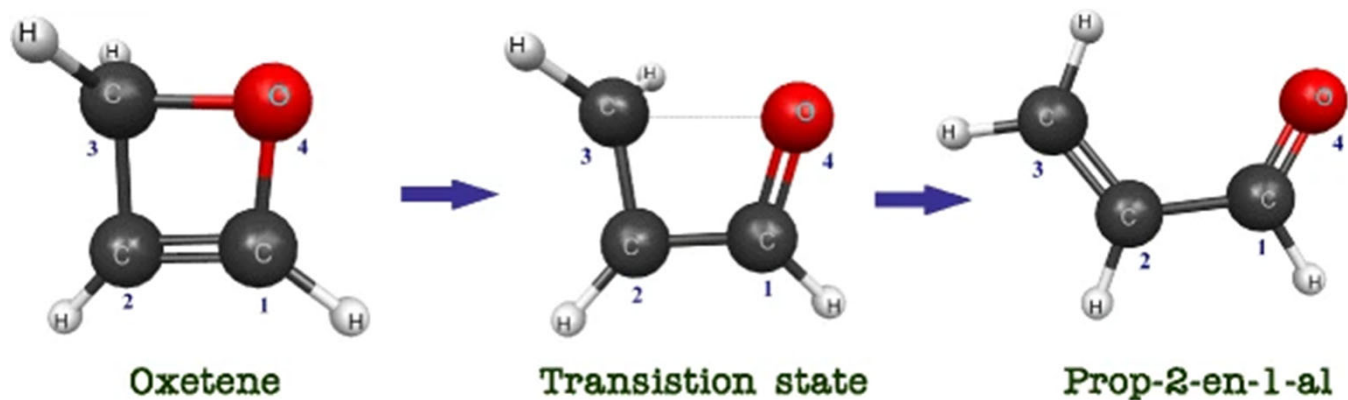
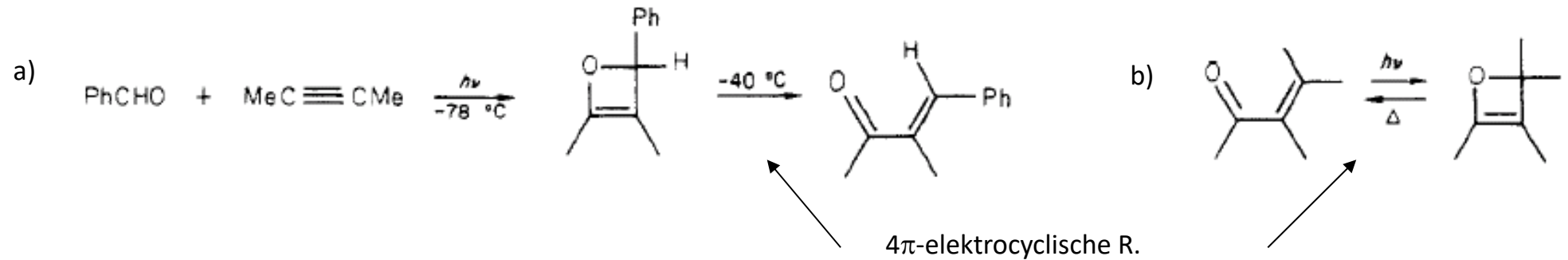
Stabilität von Oxet



aus: Pons et al., *Tetrahedron* **2001**, 3099.

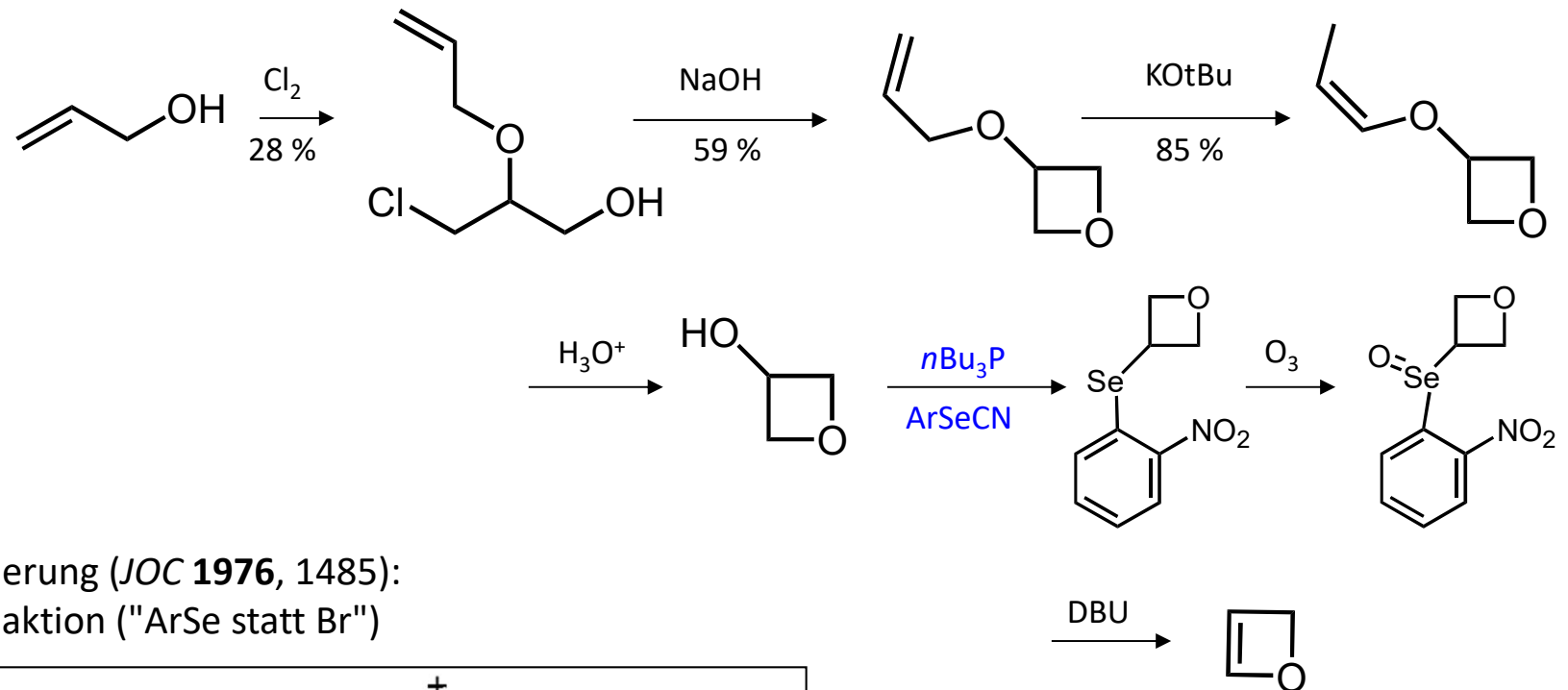
C. Viergliedrige Ringe – C.1 Ungesättigte viergliedrige Heterozyklen – C.1.1 Oxet

Photochemische Oxet-Synthesen durch [2+2]-Cycloaddition und 4 π -elektrozyklische Reaktion:

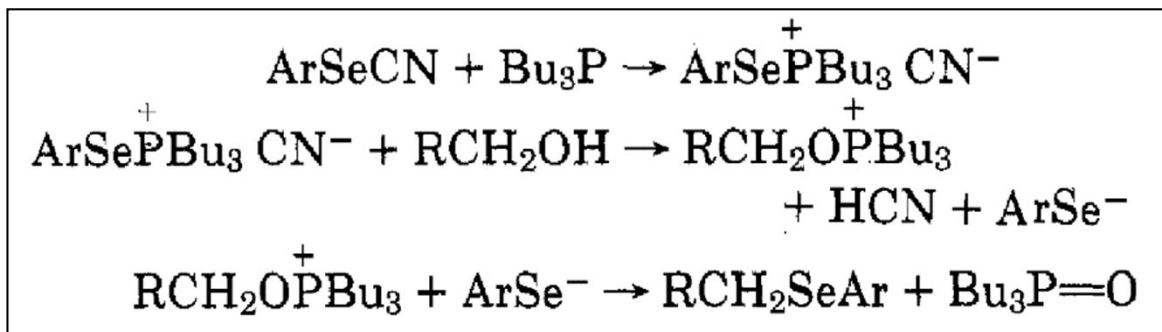


C. Viergliedrige Ringe – C.1 Ungesättigte viergliedrige Heterozyklen – C.1.1 Oxet

Synthese der Stammverbindung Oxet:



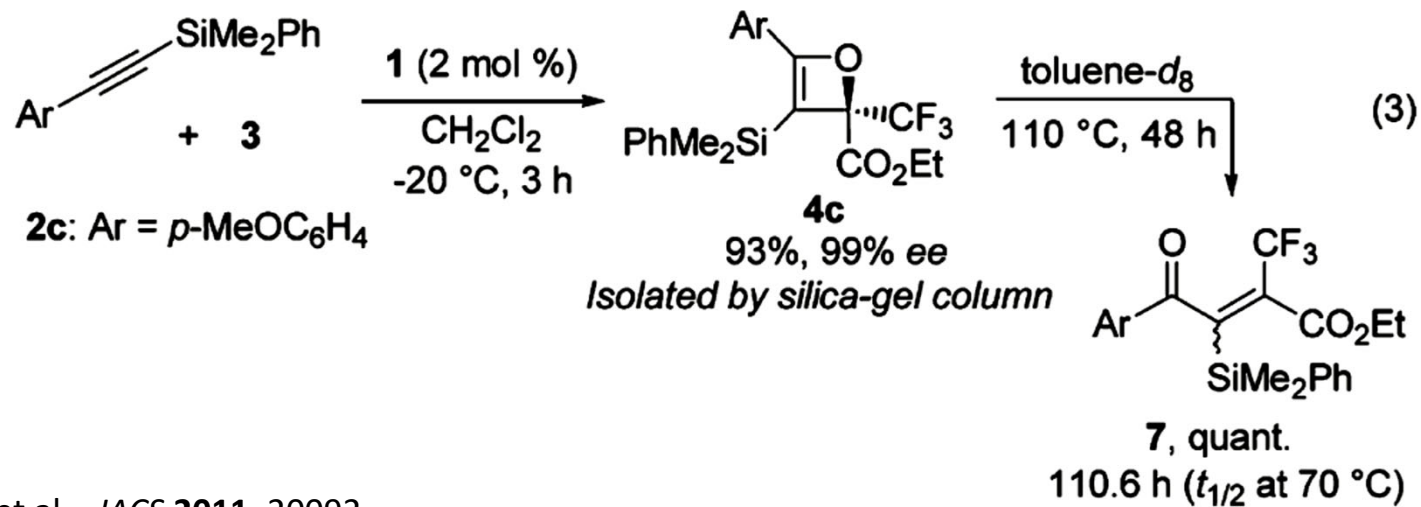
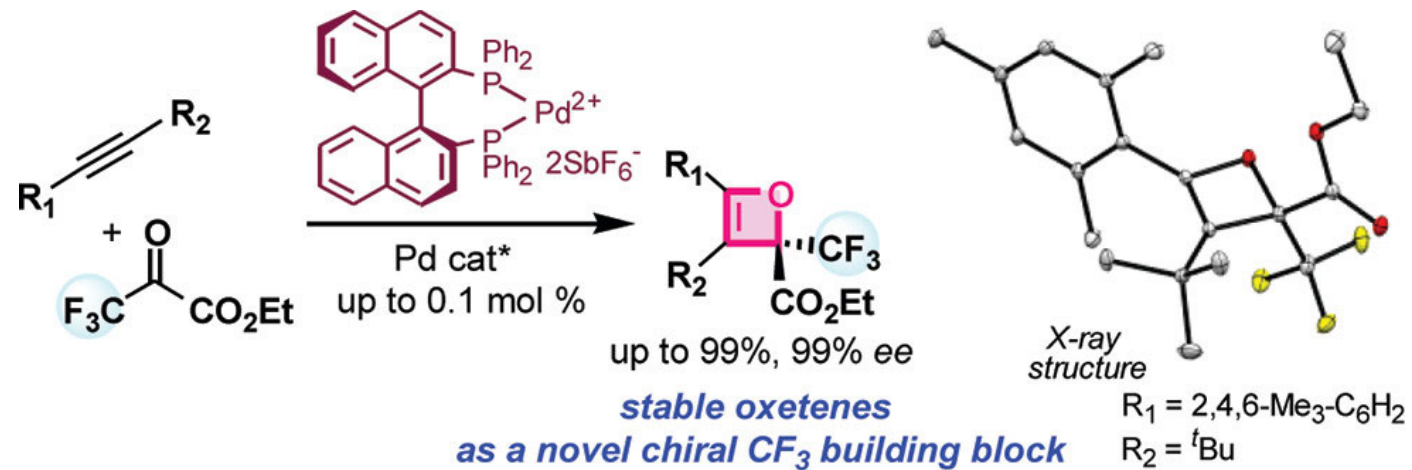
Grieco-Dehydratisierung (*JOC* **1976**, 1485):
 ähnl. der Appel-Reaktion ("ArSe statt Br")



Friedrich, Lam, *JOC* **1981**, 306

C. Viergliedrige Ringe – C.1 Ungesättigte viergliedrige Heterozyklen – C.1.1 Oxet

Enantioselective Synthese eines stabilen Oxets (= Oxetens):



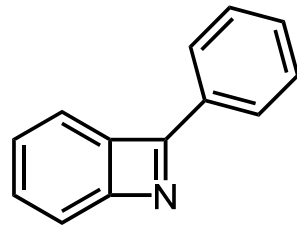
aus: Mikami et al., *JACS* **2011**, 20092

C. Viergliedrige Ringe – C.1 Ungesättigte viergliedrige Heterozyklen – C.1.2 Azet, Diazet, Dithiet

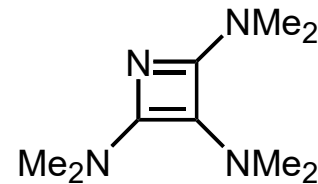
Azet



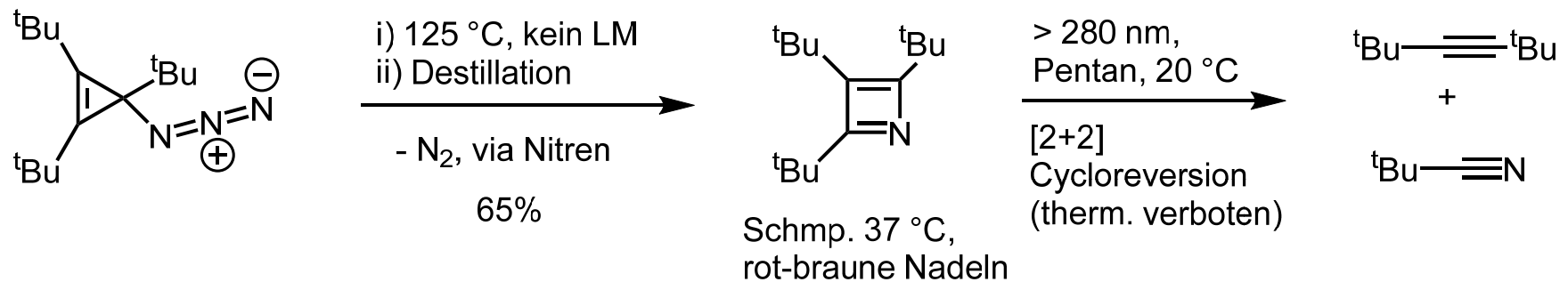
isoelektronisch zu Cyclobutadien, Stammverbindung unbekannt.



Rees et al., *JCSCC* **1973**, 19

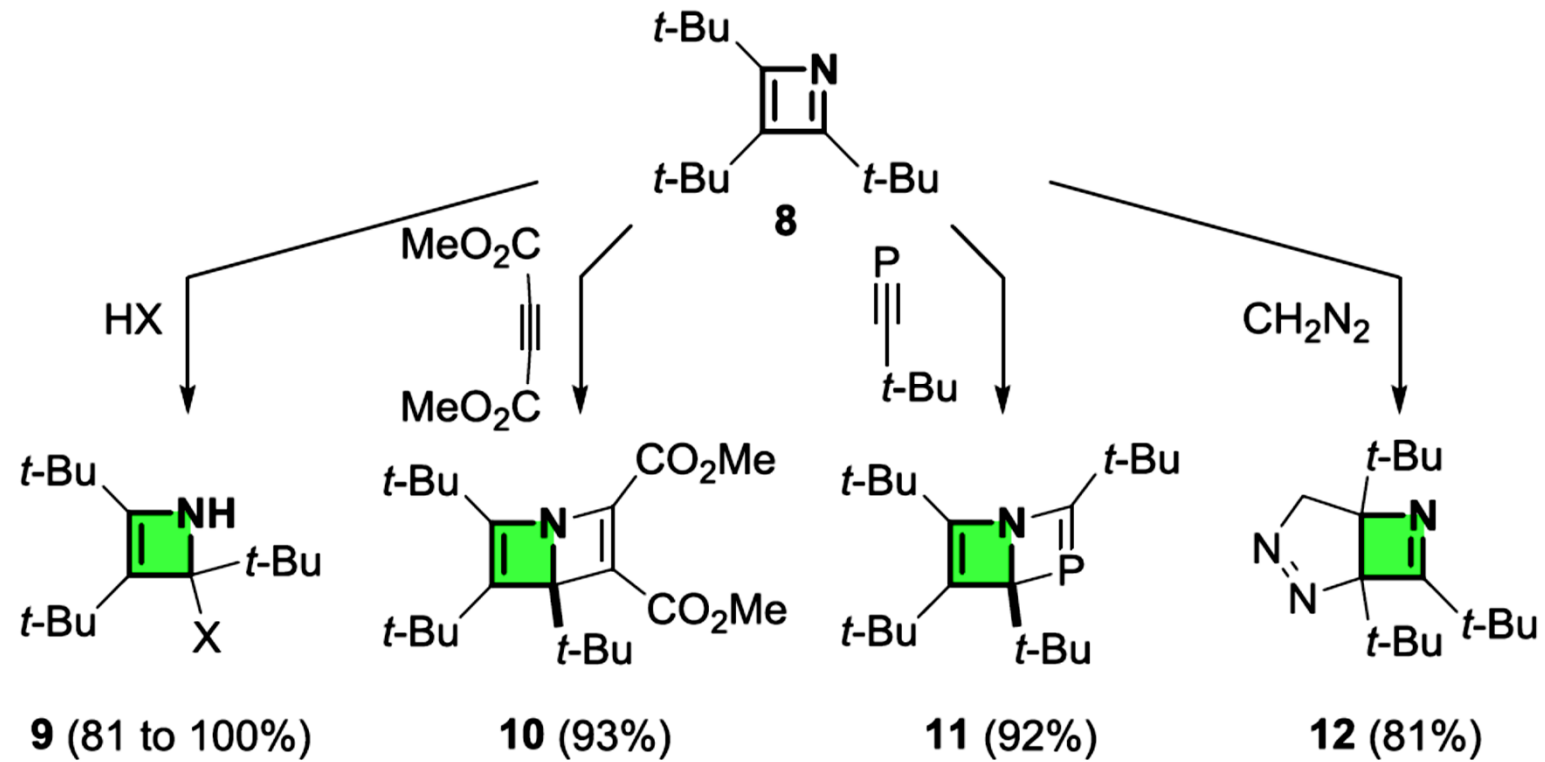


Gompper et al., *ACIE* **1973**, 847



Regitz et al., *ACIE* **1986**, 842

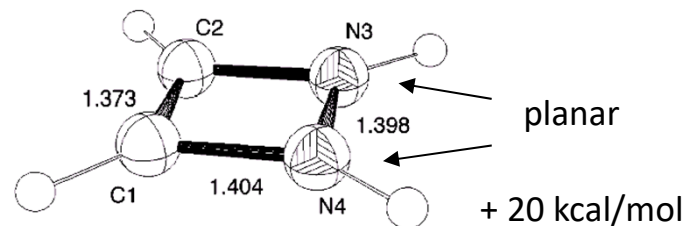
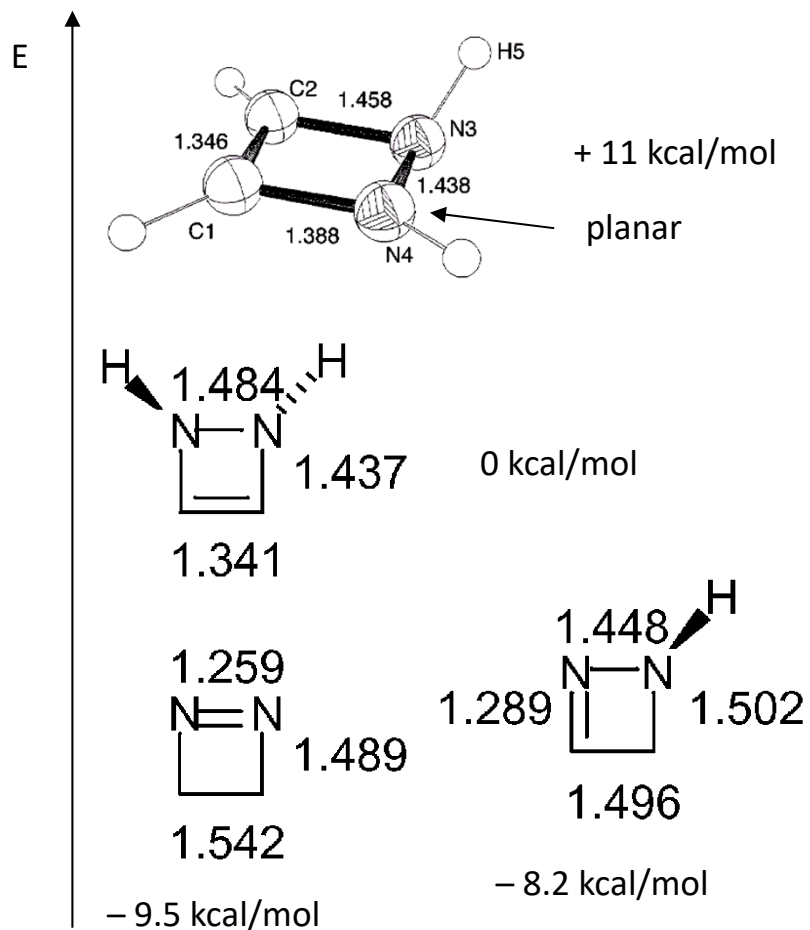
Azet



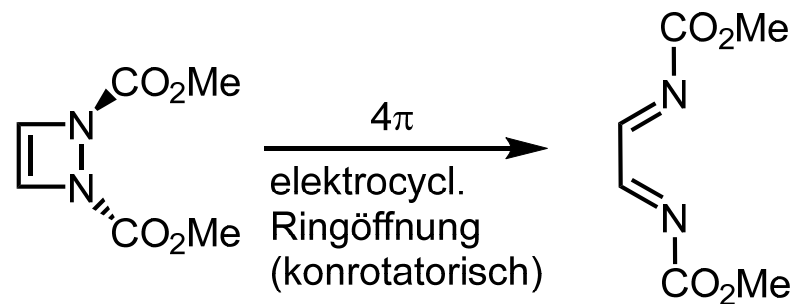
aus: Didier et al., *TETL* **2018**, 3975

C. Viergliedrige Ringe – C.1 Ungesättigte viergliedrige Heterozyklen – C.1.2 Azet, Diazet, Dithiet

Aromatizität von 6π -viergliedrigen Ringen (s. Breton, *JOC* **2002**, 6699; Budzelaar, *JACS* **1987**, 6290)



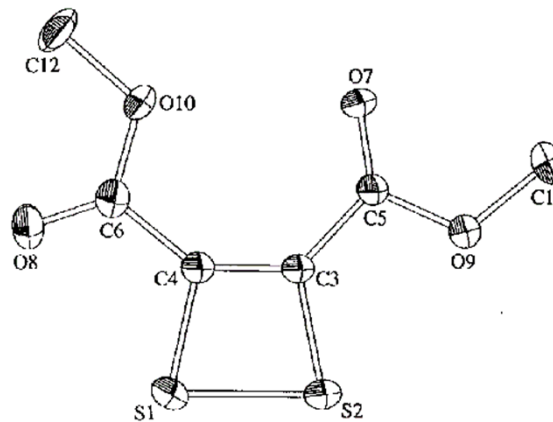
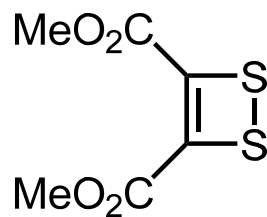
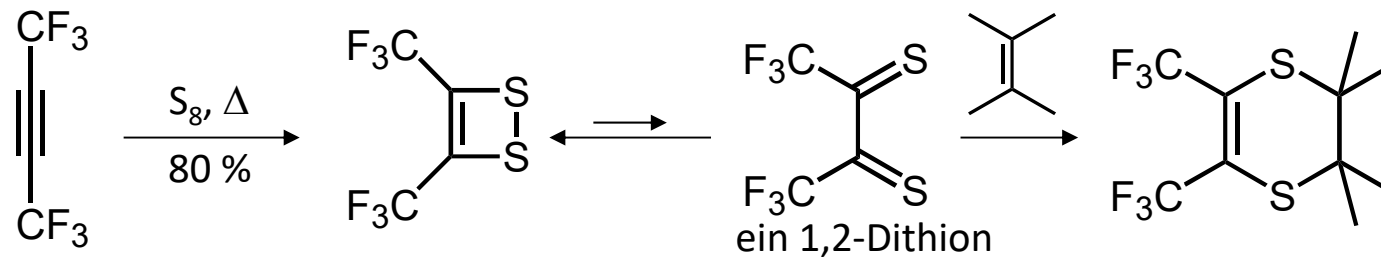
=> **1,2-Dihydro-1,2-diazet** nicht aromatisch.
Optimierte Geometrien (RB3LYP/6-311+G(2d,p))



Warrener, *Chem. Commun.* **1972**, 818.

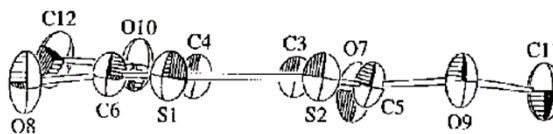
1,2-Dithiet

isoelektronisch zu Benzol (6π -Aromat), Stammverbindung trotzdem unbekannt.



planar im Kristall, z. B.:

(Kamigata, *JOC* **1998**, 6192)



(Side View)

C. Viergliedrige Ringe - C.2 Oxetan, Dioxetan, Azetidin

Ringspannung



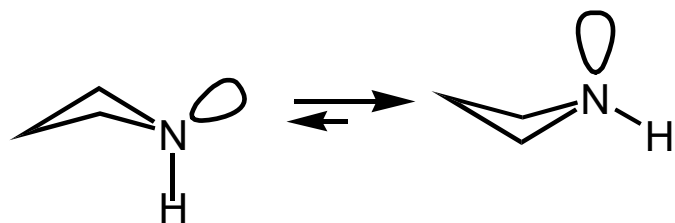
Oxetan (Sdp. 48 °C)

Inversionsbarriere 0.18 kJ/mol =>
geringer als die Schwingungsenergie => schnelle Inversion



Thietan (Sdp. 94 °C)

Inversionsbarriere 3.28 kJ/mol =>
oberhalb der niedrigsten 4 Schwingungsniveaus
=> langsame Inversion
=> Ring nicht als planar zu betrachten



Azetidin (Sdp. 62 °C)

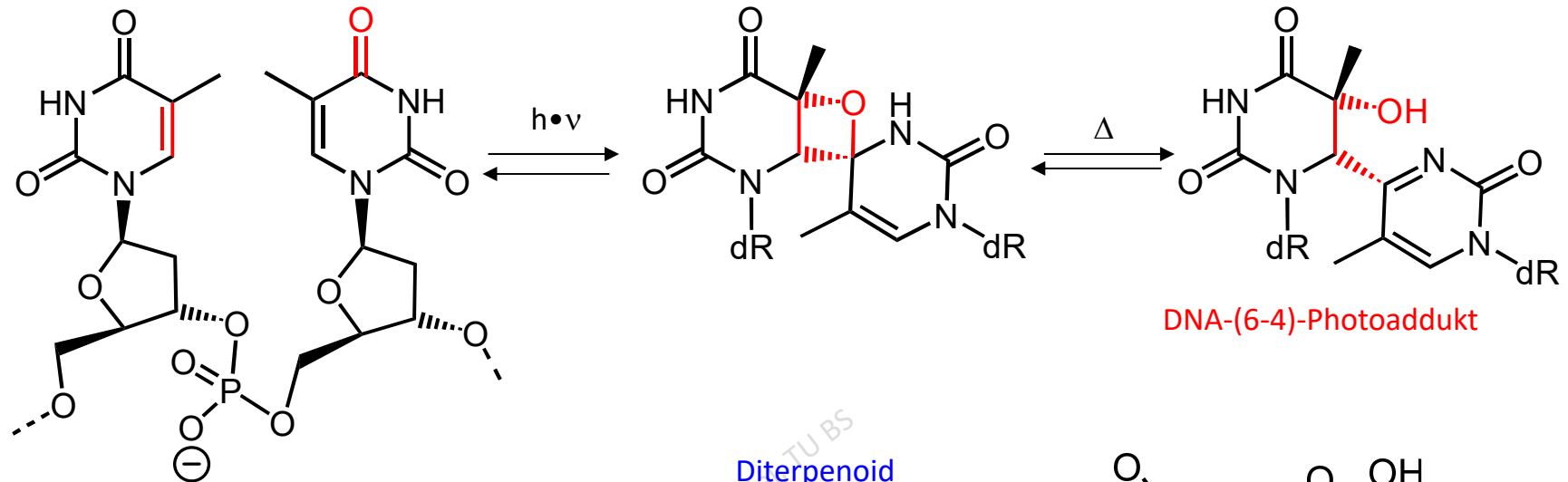
Inversionsbarriere 5.5 kJ/mol
(vgl. Cyclobutan 6.2 kJ/mol)

Verringerung der *Pitzer-Spannung* durch Faltung ("puckering").
Spannungsenthalpie nur 3-7 kJ/mol geringer als die der Dreigliedrige Ringe.

- gesättigte Viergliedrige Ringe durch Cyclisierung der 3-Haloverb. zugänglich.

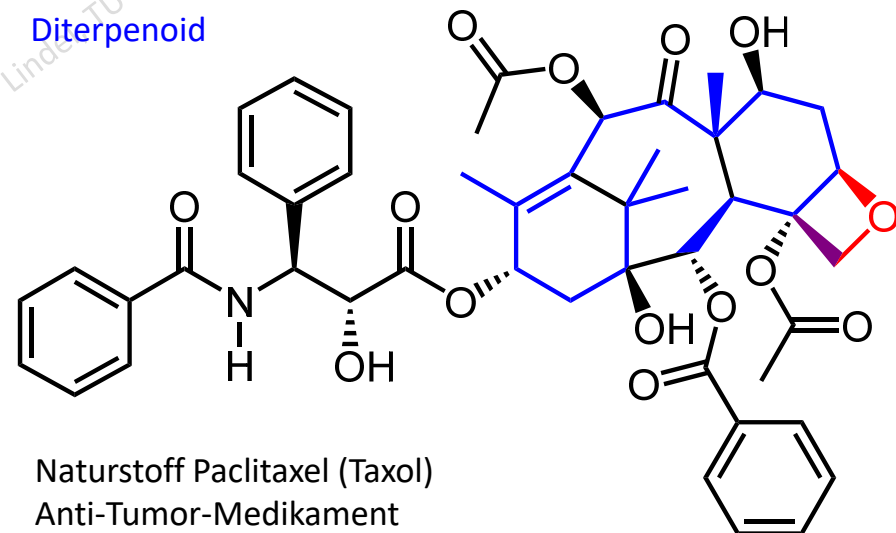
C. Viergliedrige Ringe - C.2 Oxetan, Dioxetan, Azetidin

Oxetane in der Natur



Pazifische Eibe *Taxus brevifolia*

Diterpenoid

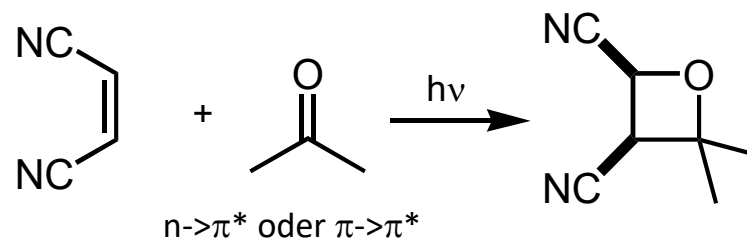


C. Viergliedrige Ringe - C.2 Oxetan, Dioxetan, Azetidin

Oxetan-Synthesen

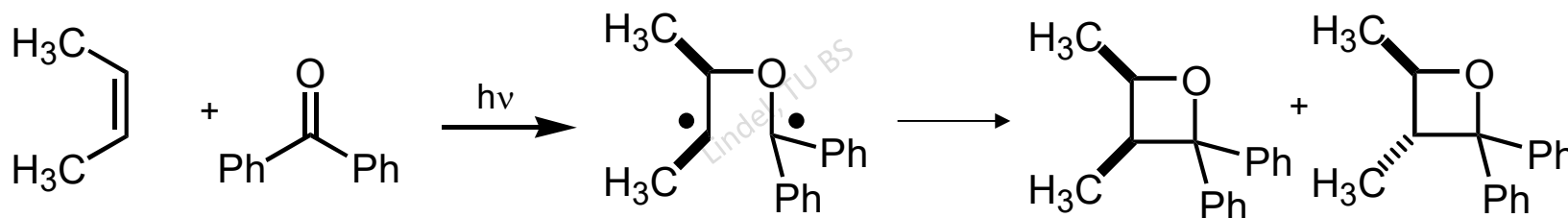
a) Zyklisierung γ -subst. Alkohole (nicht gezeigt)

b) [2+2]-*Paterno-Büchi*-Reaktion

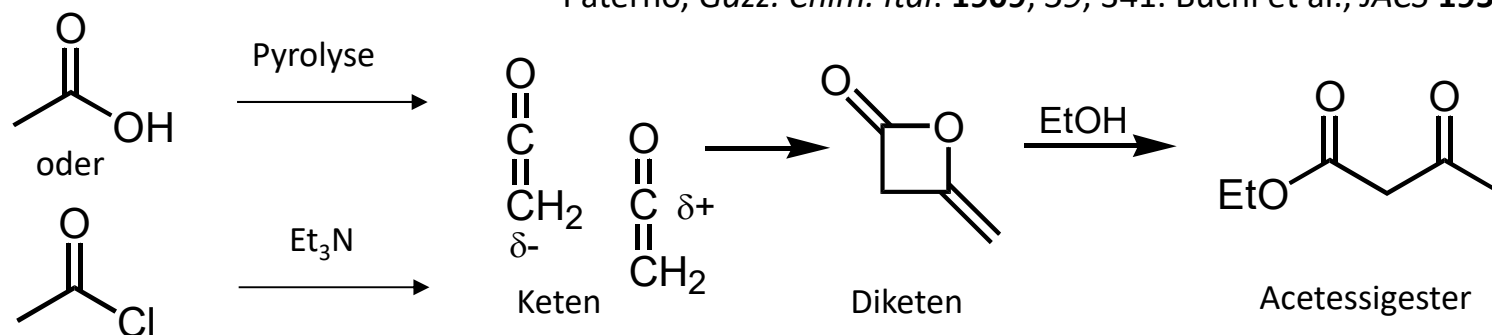


aliphatische Ketone: nahezu stereospezifisch

aromatische Ketone: diastereomere Produkte über 1,4-Diradikal-Intermediate, deren relative Stabilität auch die Regioselektivität bestimmt.



Dioxetanon:



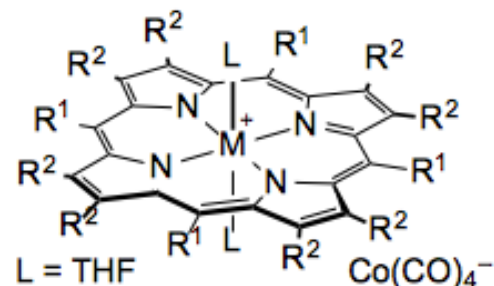
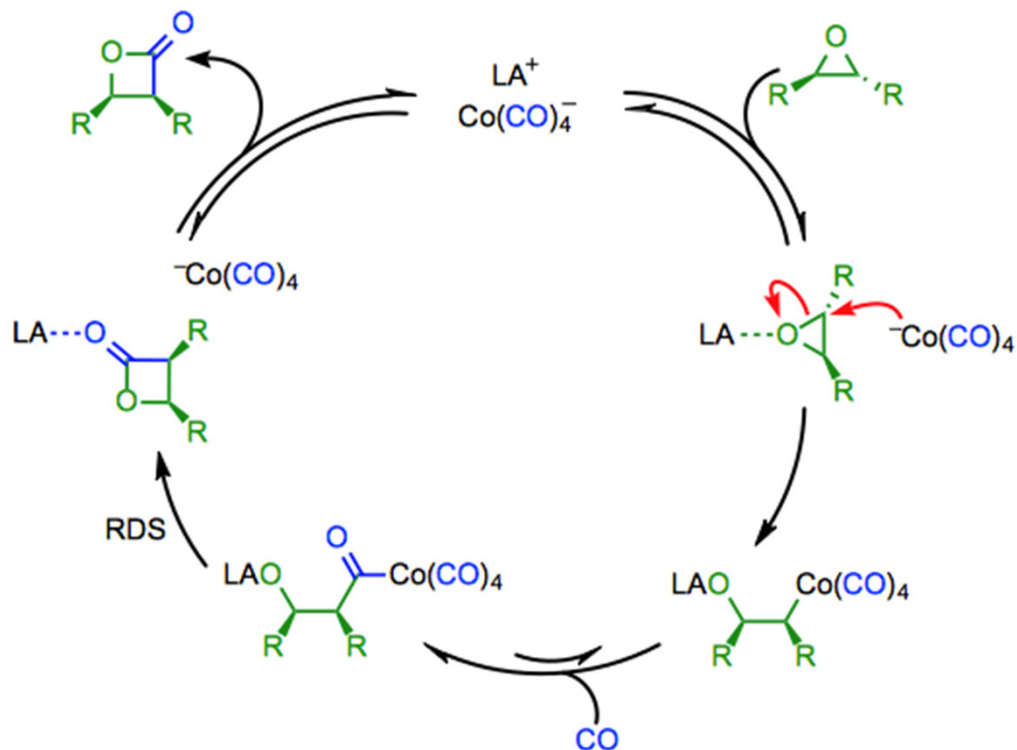
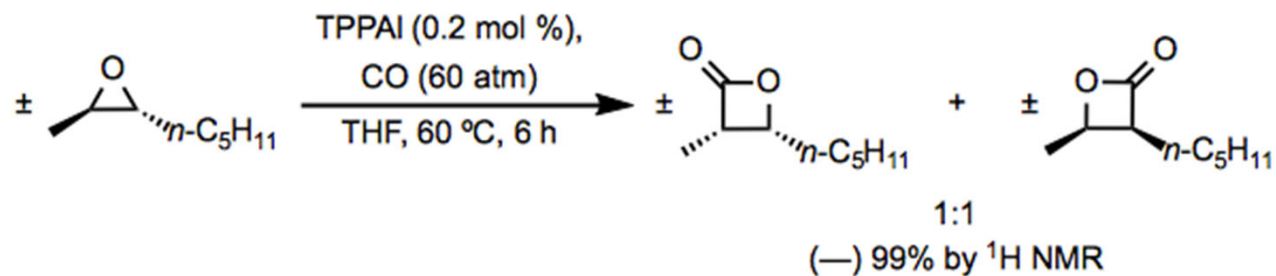
Paterno, *Gazz. Chim. Ital.* **1909**, 39, 341. Büchi et al., *JACS* **1954**, 4327.

C. Viergliedrige Ringe - C.2 Oxetan, Dioxetan, Azetidin

Oxetan-Synthesen

Carbonylierung von Epoxiden zu Oxetanonen

(z. B. Kramer, J. W.; Lobkovsky, E. B.; Coates, G. W. *Org. Lett.* **2006**, *8*, 3709)



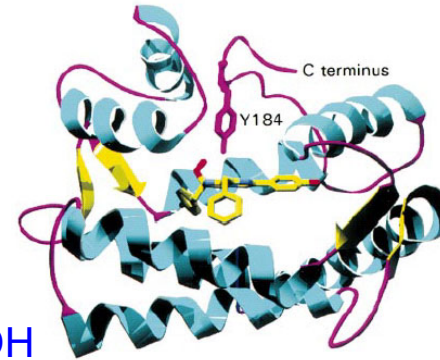
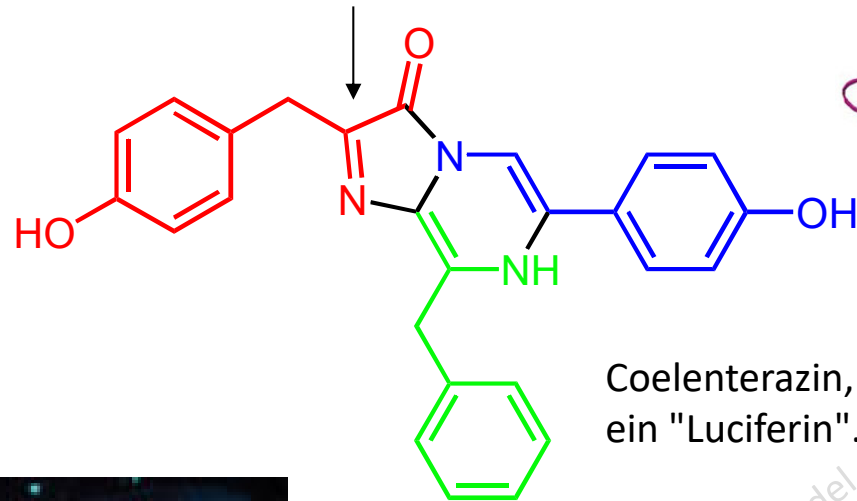
TPPAI: M = Al, R¹ = 4-ClC₆H₄, R² = H

TPPCr: M = Cr, R¹ = Ph, R² = H

OEPCr: M = Cr, R¹ = H, R² = Et

C. Viergliedrige Ringe - C.2 Oxetan, Dioxetan, Azetidin

1,2-Dioxetane in der Natur



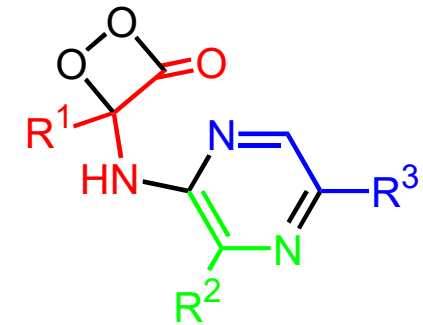
Shimomura et al.,
Nature **2000**, 405, 372.

1) Ca^{2+}

2) Luciferase

O_2

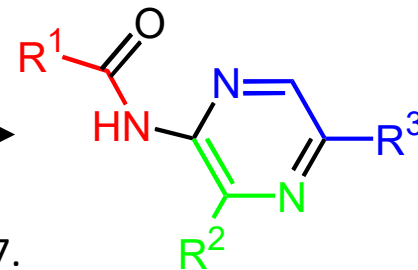
via Hydroperoxid



Imidazolopyrazin Coelenterazin
in der Qualle *Aequorea* sp.

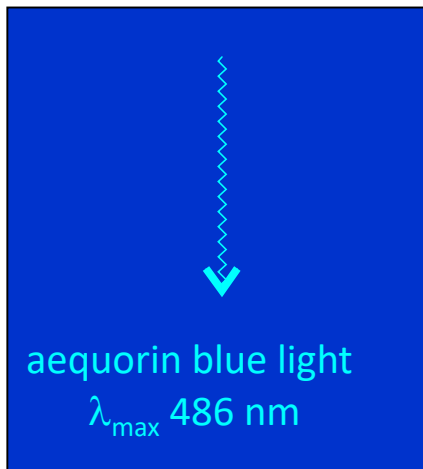
$-\text{CO}_2$

mögl. Mech.
s. *JACS* **2005**, 8667.



Coelenteramid*

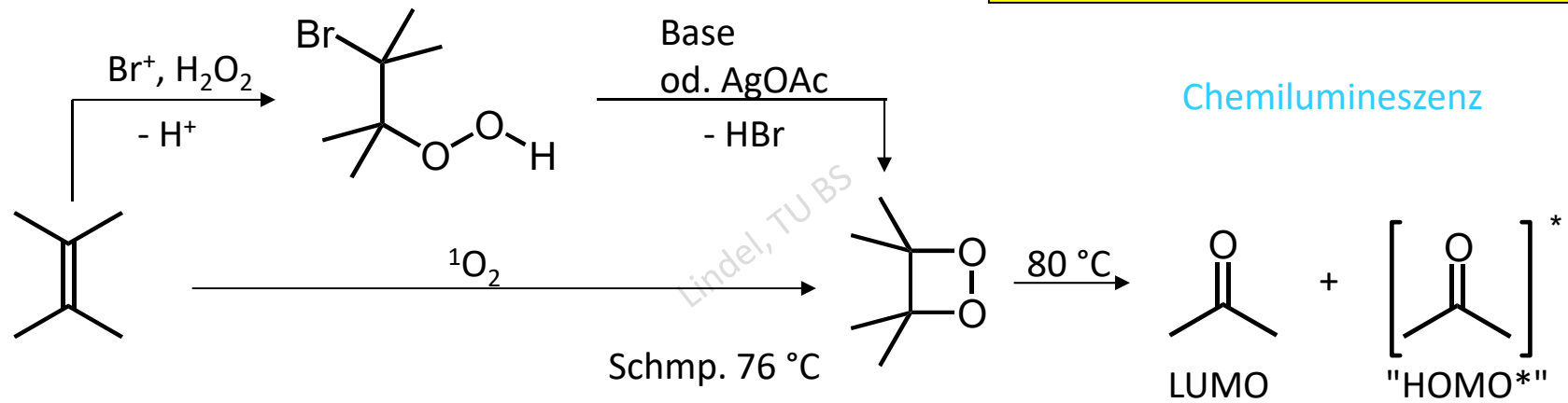
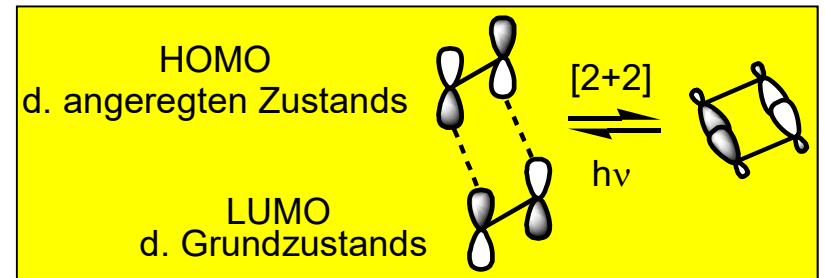
γ^*



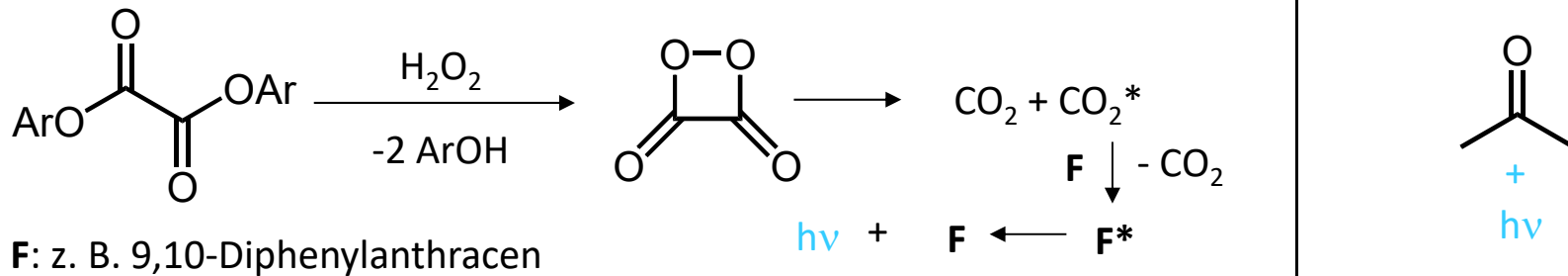
C. Viergliedrige Ringe - C.2 Oxetan, Dioxetan, Azetidin

Dioxetan-Synthesen

- a) Dehydrohal. von β -Halohydroperoxiden
- b) Photooxygenierung von Alkenen



Versuch für die Experimentalvorlesung

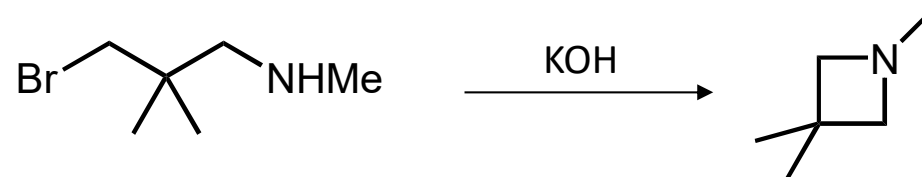


F: z. B. 9,10-Diphenylanthracen

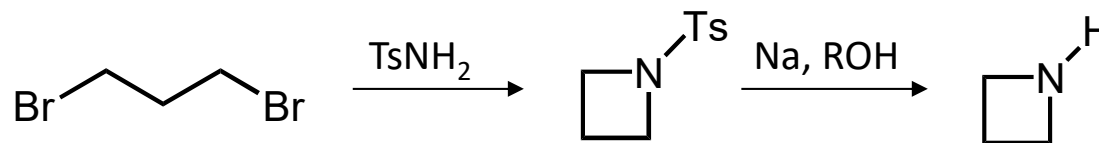
C. Viergliedrige Ringe - C.2 Oxetan, Dioxetan, Azetidin

Azetidin-Synthesen

a) Cyclisierung γ -subst. Amine

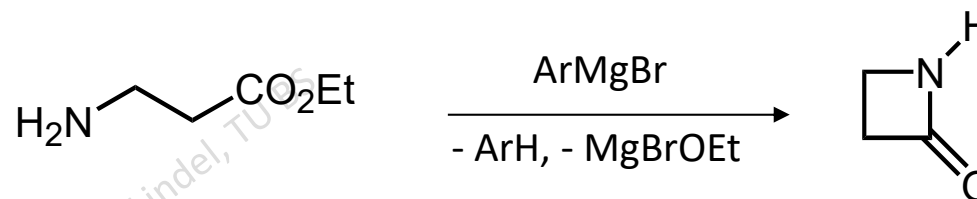


ebenso

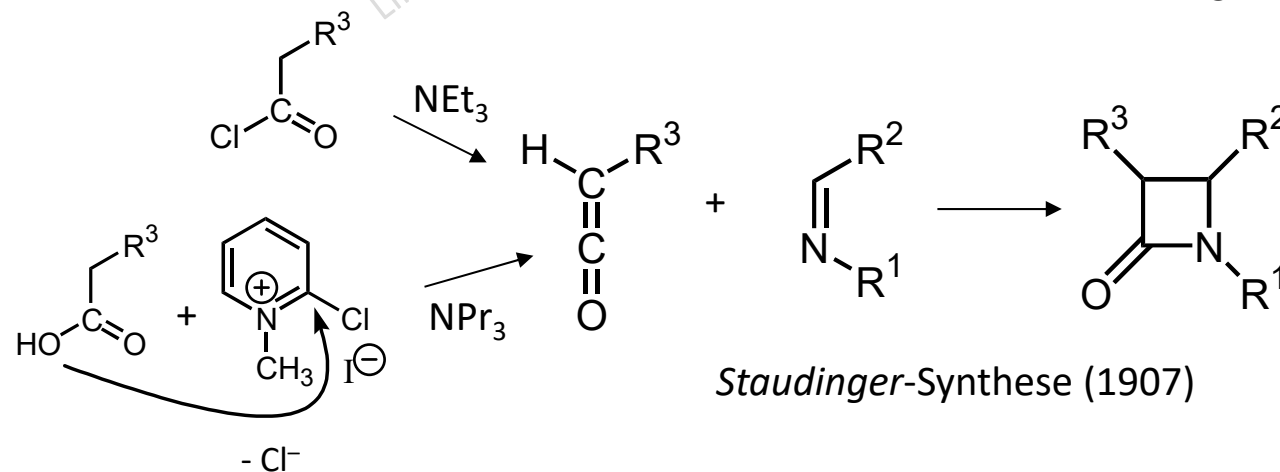


Azetidinone (β -Lactame)

b) Cyclodehydratisierung
von β -Aminosäureestern



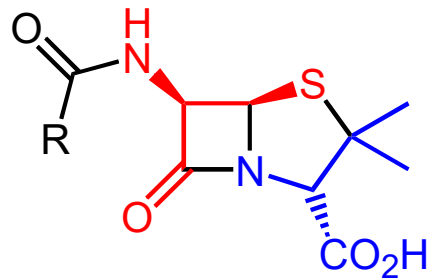
c) [2+2]Cycloadditionen



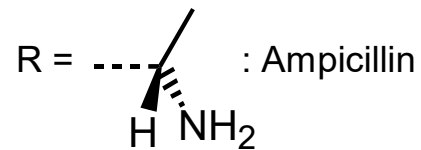
Mukaiyama (1977):
(2-Pyridon-Bildung)

Staudinger-Synthese (1907)

Azetidinone: β -Lactam-Antibiotika



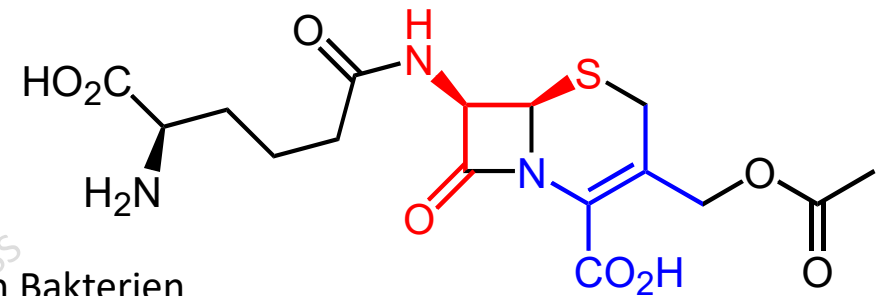
R = Bn: Penicillin G



Biosynthese
aus Cys und Val.

Wachstumshemmung von Bakterien
durch den Schimmelpilz
Penicillium notatum: Fleming 1929

Reinigung: 1941
Strukturaufklärung: 1945



Cephalosporin C aus
Cephalosporium acremonium
(Isol. 1955, Strukturaufkl. 1961)

D. Fünfring-Aromaten

Übersicht Kap. D

D.1 Furan

D.2 Pyrrol

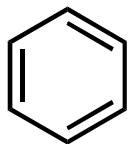
D.3 Indol

D.4 Oxazol

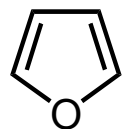
D.5 Thiazol

D.6 Imidazol

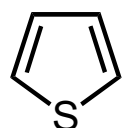
6 π -Überschuß-
Aromaten



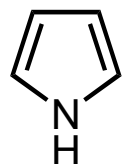
150 /
100



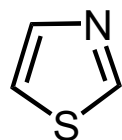
113 /
53



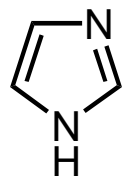
180 /
82



146 /
85



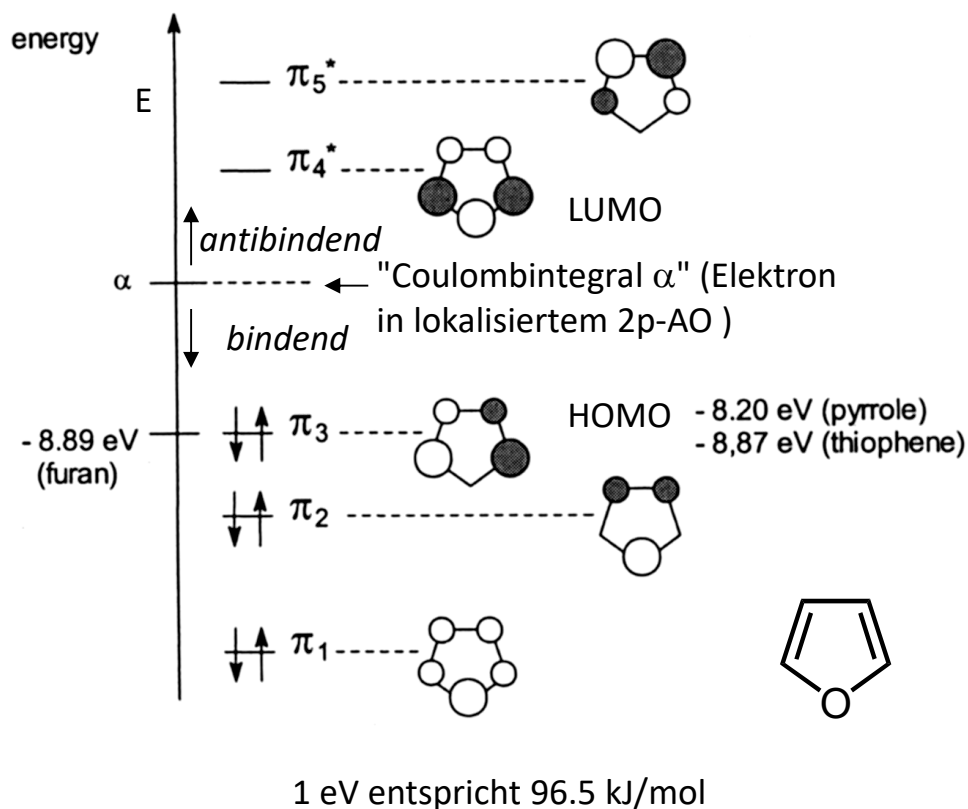
176 /
79



167 /
79

Resonanzstab. [kJ/mol] /
Bindungsl.-ausgleich [%]

π -MO-Energieniveauschema von Furan (geringere
Symmetrie als bei Stammverb. Cyclopentadienid)



zur Aromatizität: *Chem. Rev.* **2005**, 3773

Bird, *TETH* **1996**, 9945; **1997**, 13111.

A Mnemonic Device for Molecular Orbital Energies

ARTHUR A. FROST AND BORIS MUSULIN

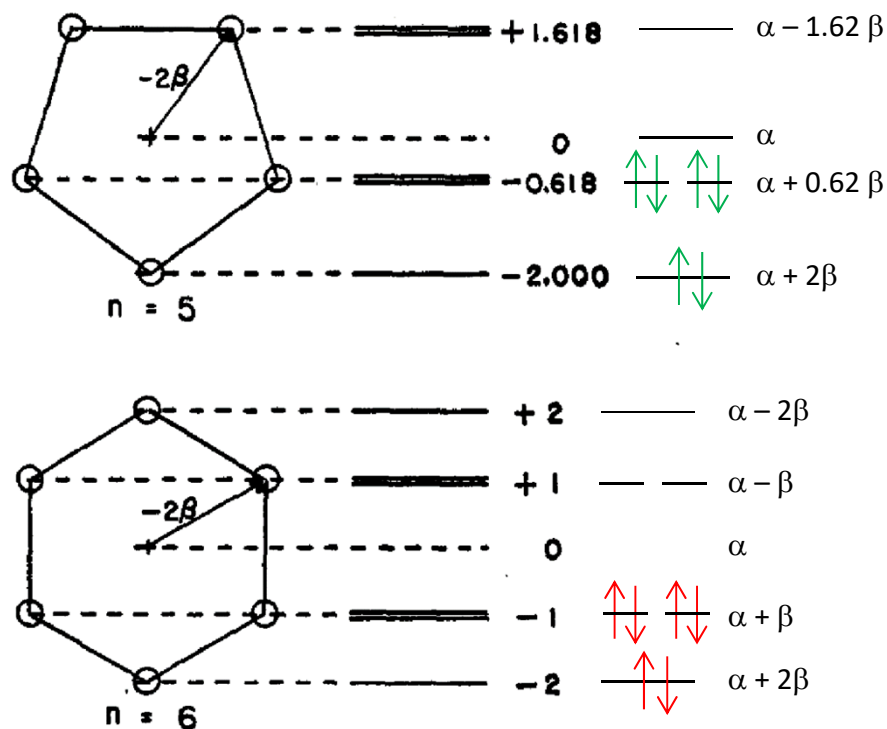


FIG. 1. Projection scheme for construction of energy level diagram of ring compounds. Resonance energies, unit: $-\beta$.

J. Chem. Phys. 1953, 572.

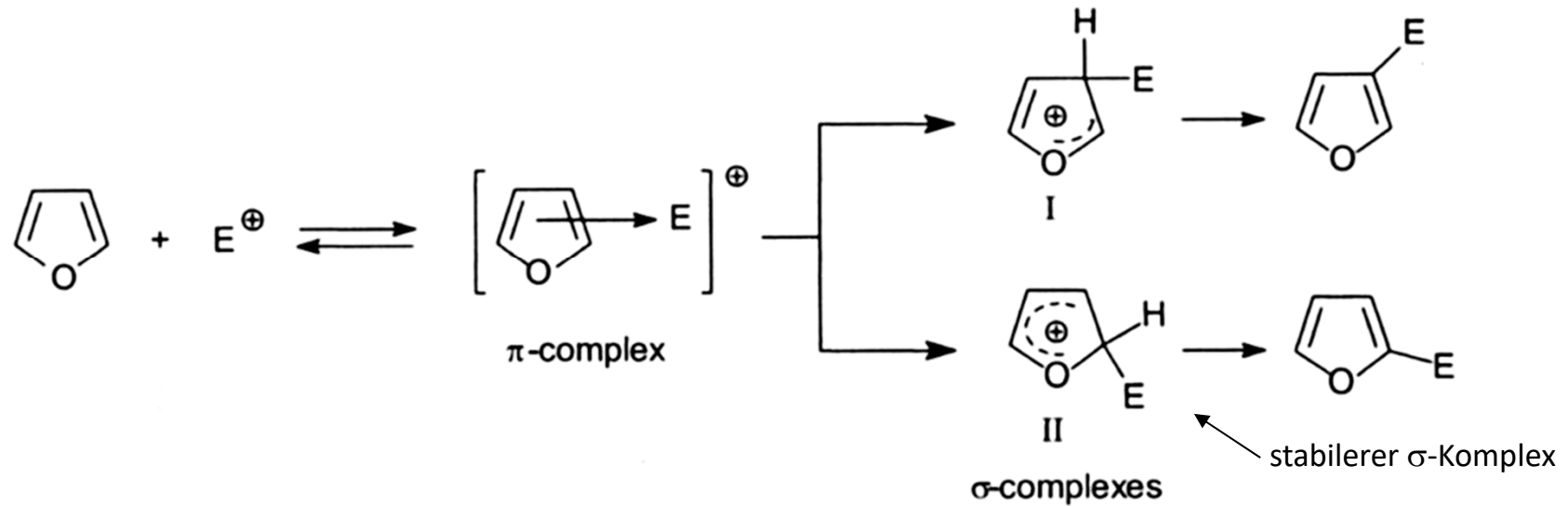
Frost-Musulin-Diagramm:

Abschätzung der aromatischen Stabilisierungsenergie aus dem Coulombintegral α und dem Überlappungsintegral β

Ring wird auf die Spitze gestellt.

MOs unterhalb der Nulllinie sind bindend, auf der Linie nicht bindend, oberhalb antibindend.

Wenn nach der Besetzung der MOs eine Gesamtstabilisierungsenergie < 0 resultiert, ist das System aromatisch stabilisiert.

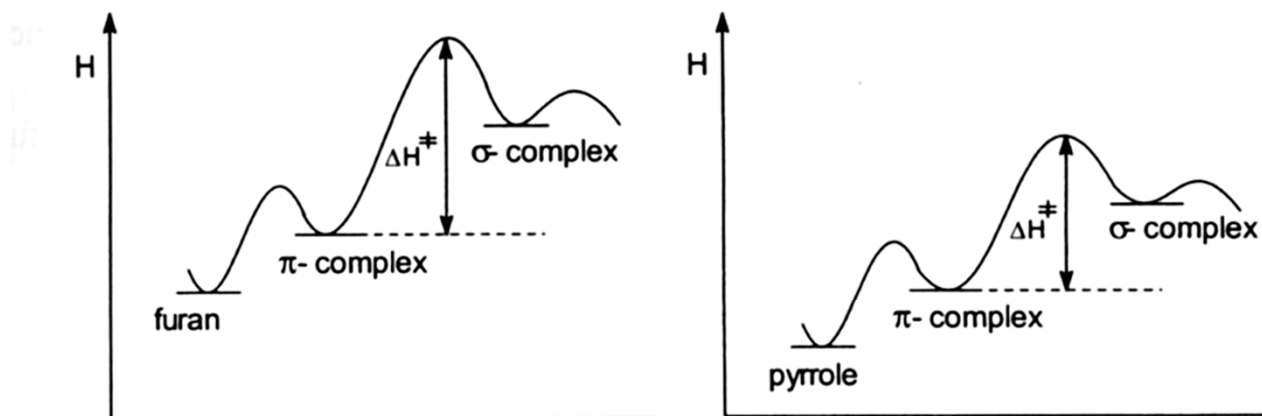


Regioselektivität d. S_EAr zugunsten der 2-Position, da

- a) HOMO-Koeffizient größer als in der 3-Position;
- b) σ -Komplex stabiler.

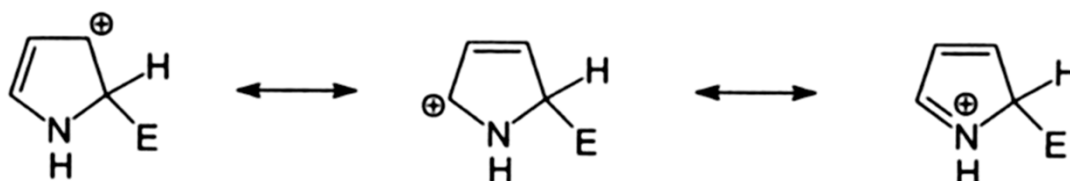
Pyrrrol: ebenso 2-Position > 3-Position

Elektrophile aromatische Substitution an Furan und Pyrrol



Furan reagiert 10^{11} -mal schneller als Benzol,

Energy profile of the formation of the π - and σ -complex in the electrophilic substitution of furan and pyrrole



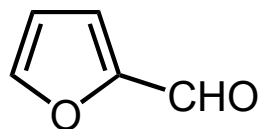
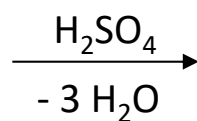
Pyrrol 10^5 -mal schneller als Furan (obwohl aromatischer). Grund: Carbenium-Iminium-Mesomerie bei Pyrrol; ΔH^\ddagger kleiner als bei Furan.

D. Fünfring-Aromaten - D.1 Furan

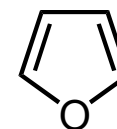
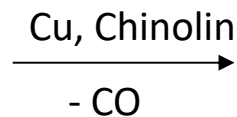
Vorkommen

- Furan-2-carbonsäure aus C₆-Zucker-Disäuren (z. B. Galaktarsäure);
- 5-(Hydroxymethyl)-2-furaldehyd aus Saccharose (Molisch-Probe).

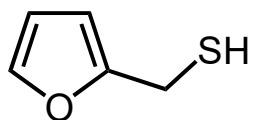
Pentosen
(z. B. aus Kleie, lat. "furfur")



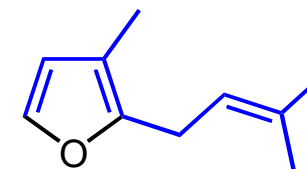
Furfural



Sdp. 162 °C, "nachwachsender Rohstoff"



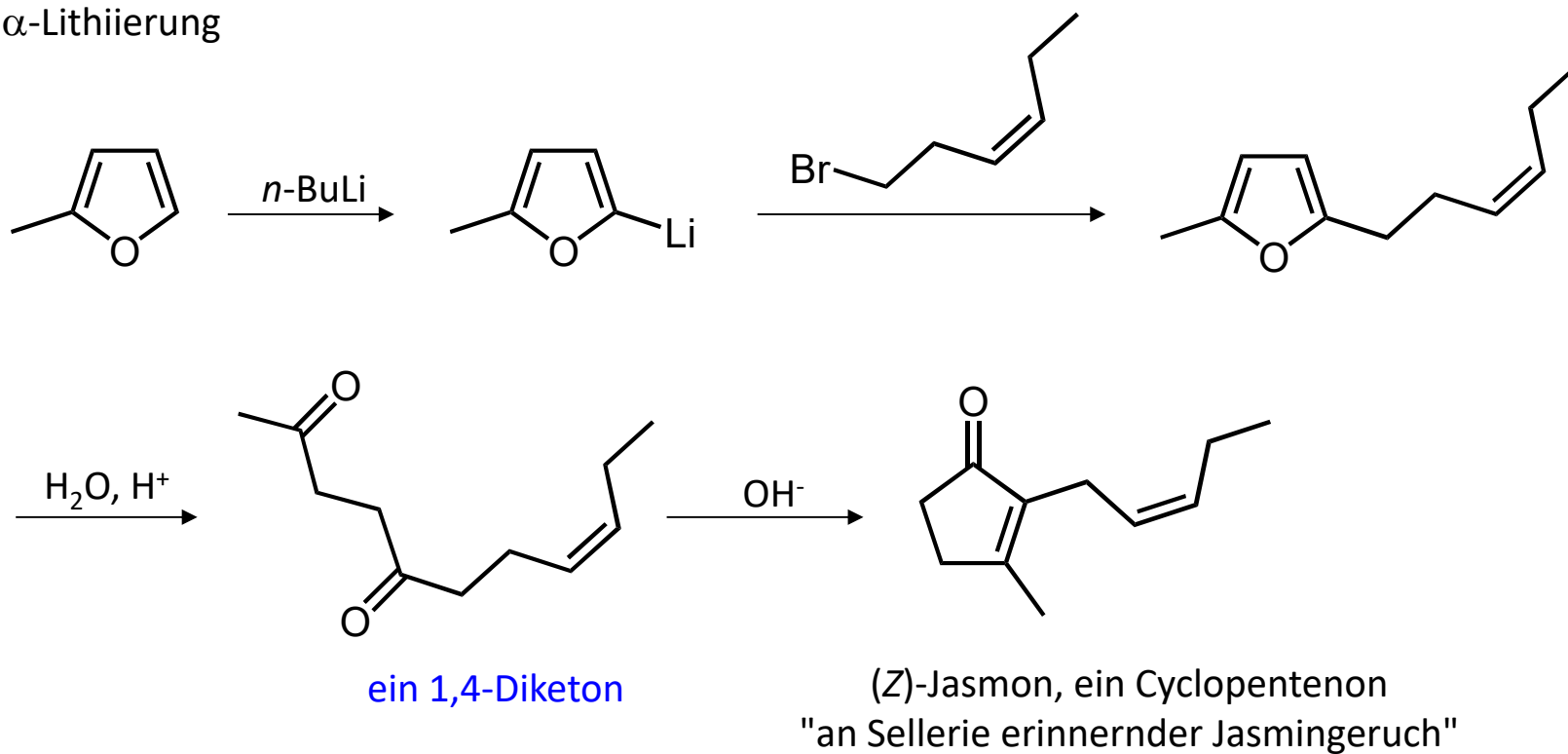
2-Furylmethanethiol
(im Kaffee-Aroma (neben anderen Furanen), Geruchsschwelle 5 ppb)



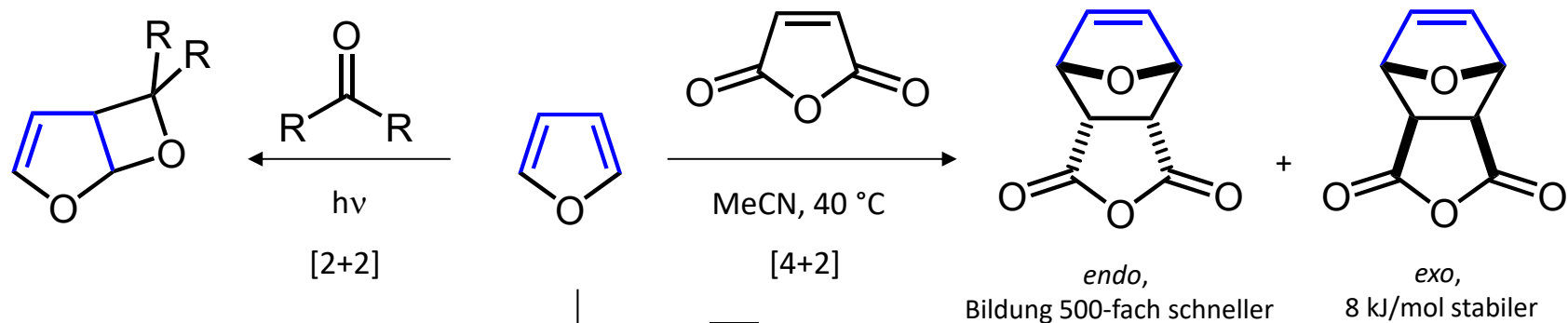
Rosenfuran
(Duftstoffkomponente
des Rosenöls),
monoterpenoid

Reaktivität (Auswahl):

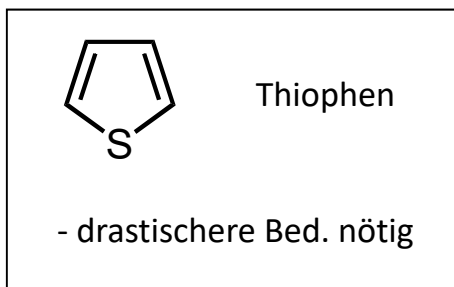
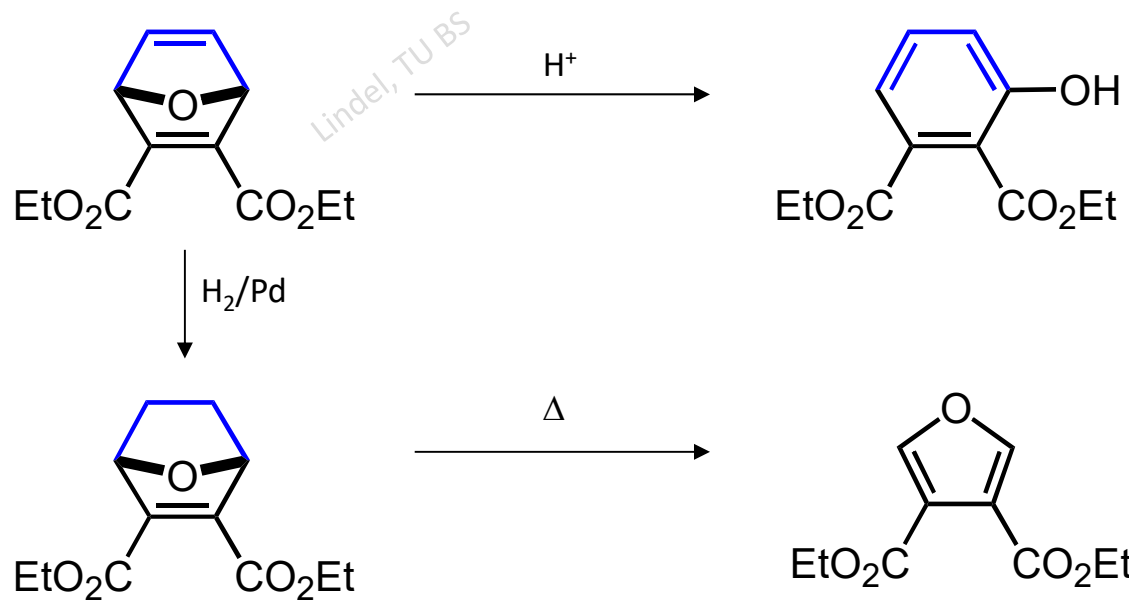
a) α -Lithiierung



b) Cycloadditionen

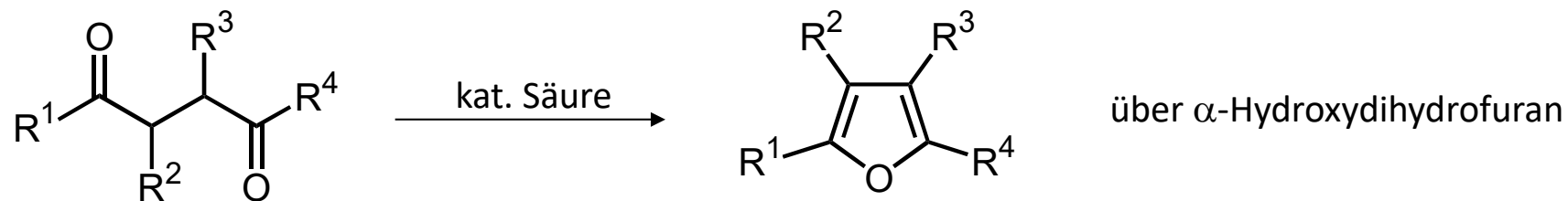


Diels-Alder-Reaktionen von Furan: *TETH* **1997**, 14179.



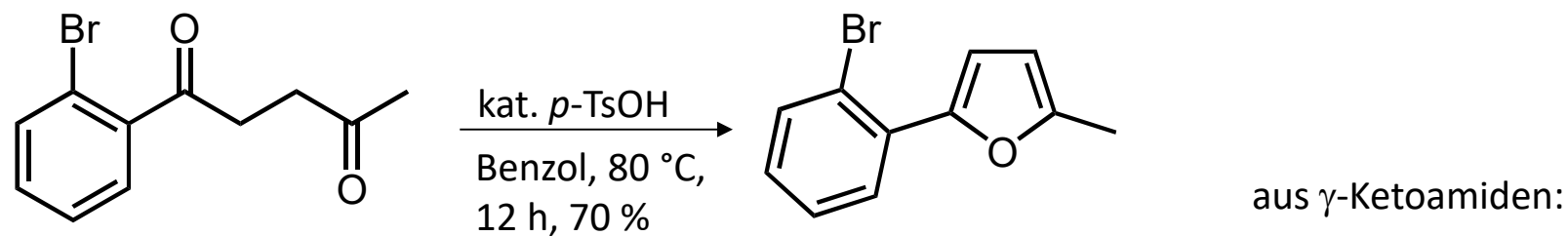
Synthese

a) Paal-Knorr-Synthese

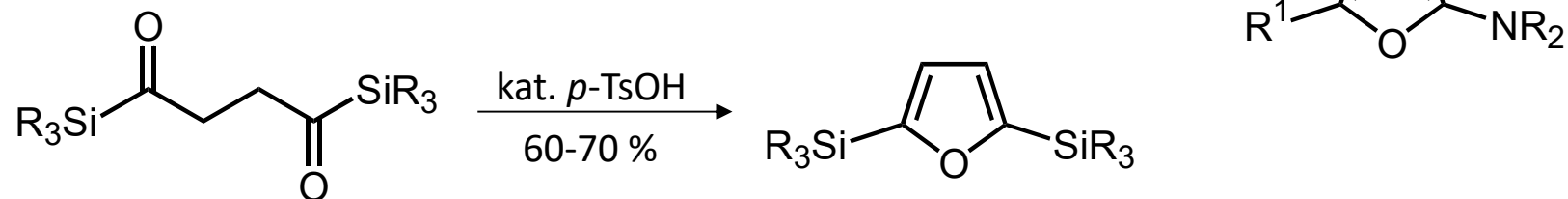


1,4-Diketon

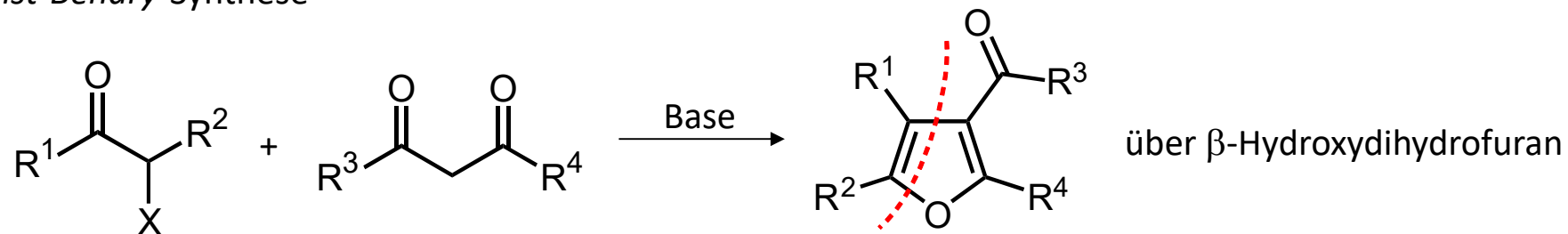
z. B.



ebenso:

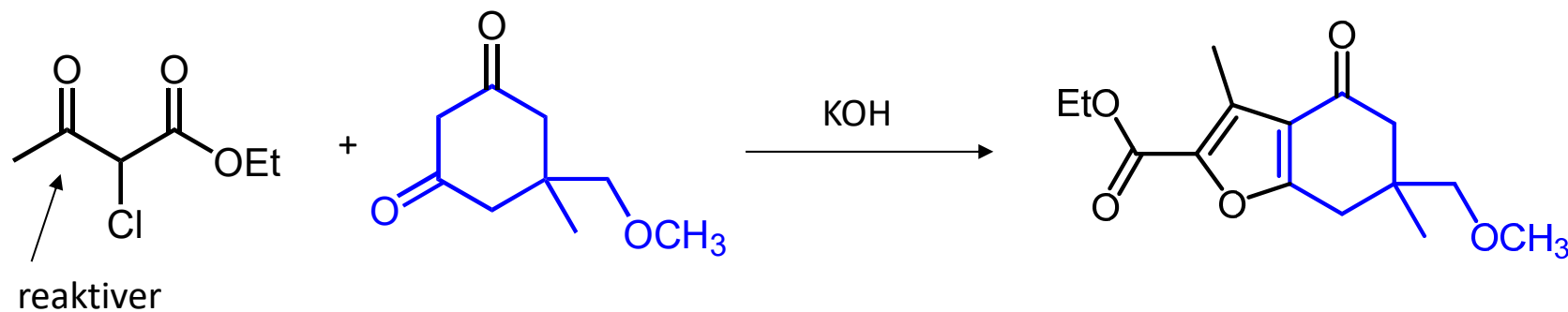
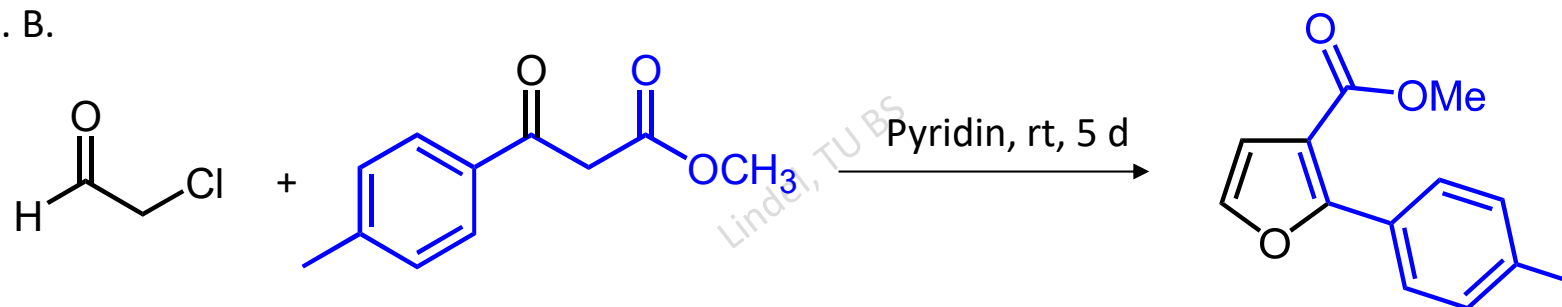


b) Feist-Bénary-Synthese

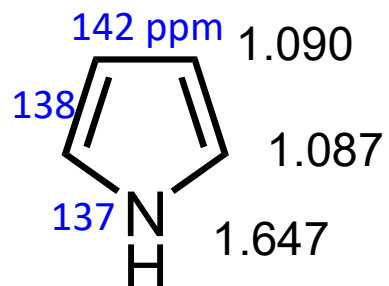


α -Halocarbonylverb. β -Ketoester

z. B.

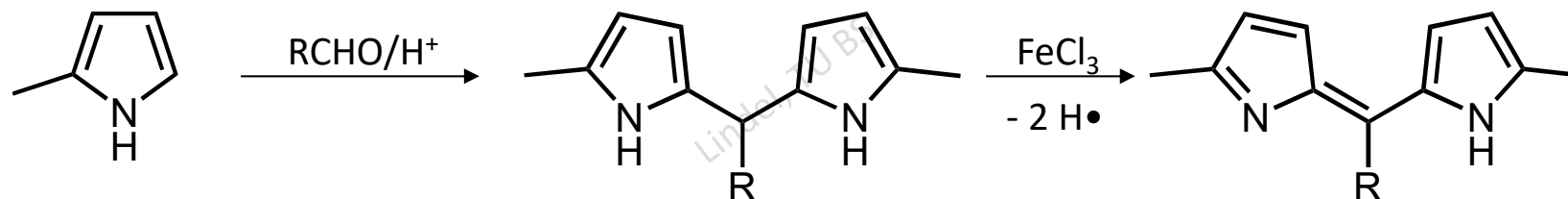


Vorkommen

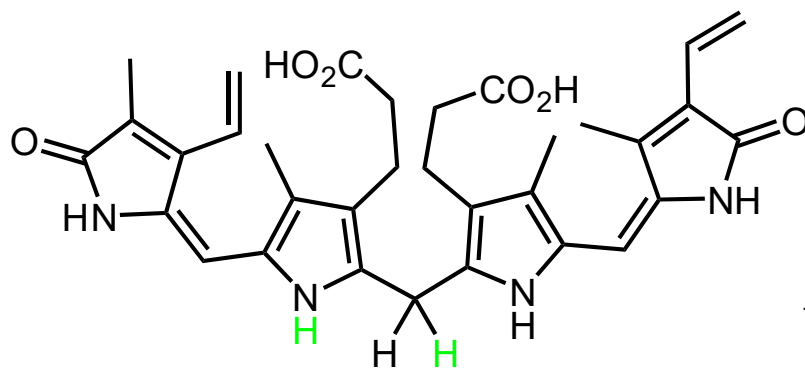


pK_a 17.5 (in Wasser)

Elektronendichte



ein Pyrrolyl(pyrryl-2-ylidene)methan
orange für R=Me

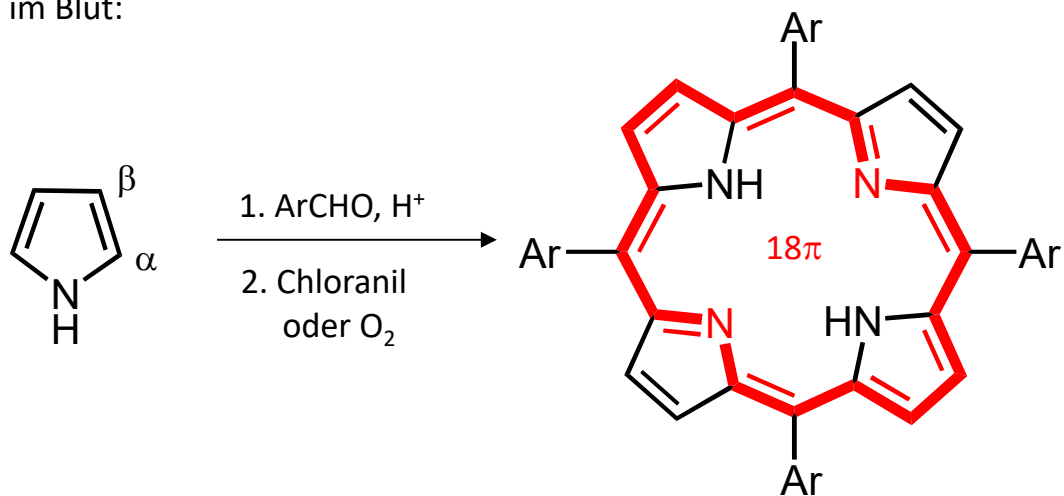


Bilirubin:
Abbauprodukt des Blutfarbstoffs in der Galle
(lat. "bilis" Galle; "ruber" rot)

Biliverdin (ital./span. "verde" grün)

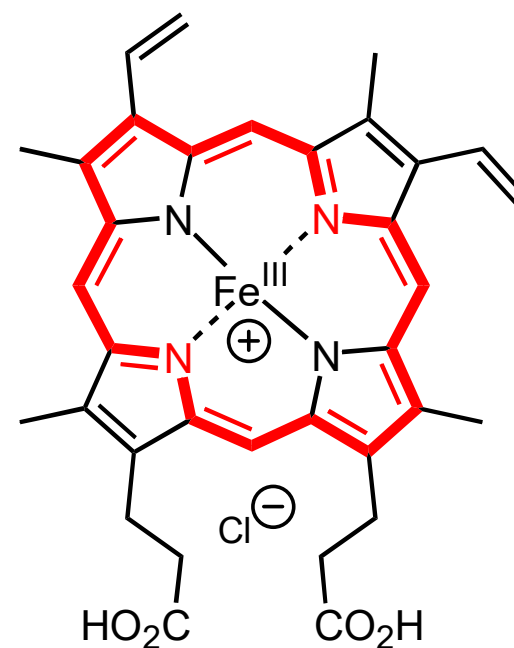
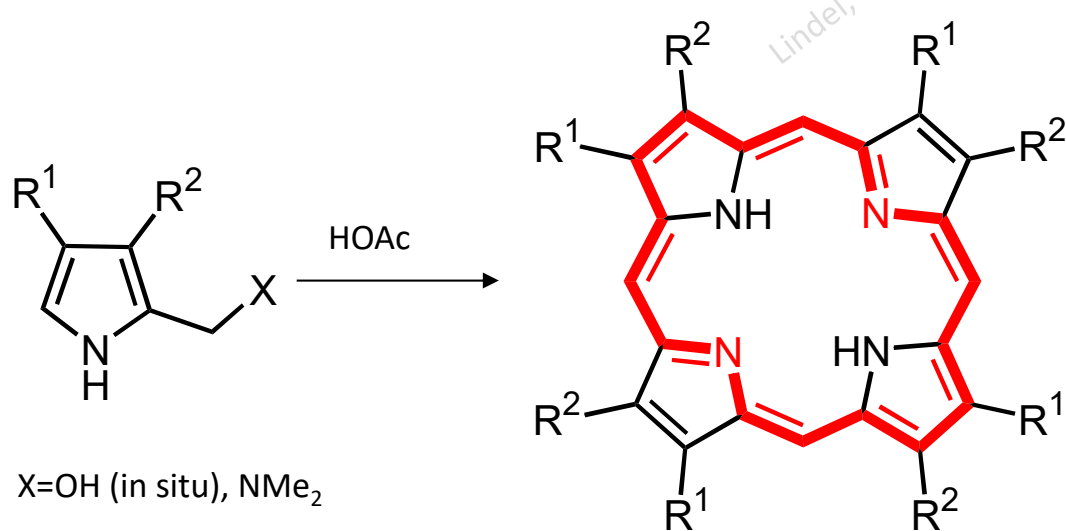
D. Fünfring-Aromaten - D.2 Pyrrol

im Blut:

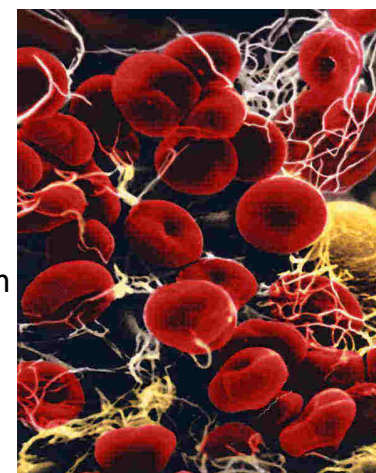


cycl. Tetrapyrrole

Wenn H statt Ar: *Porphin*

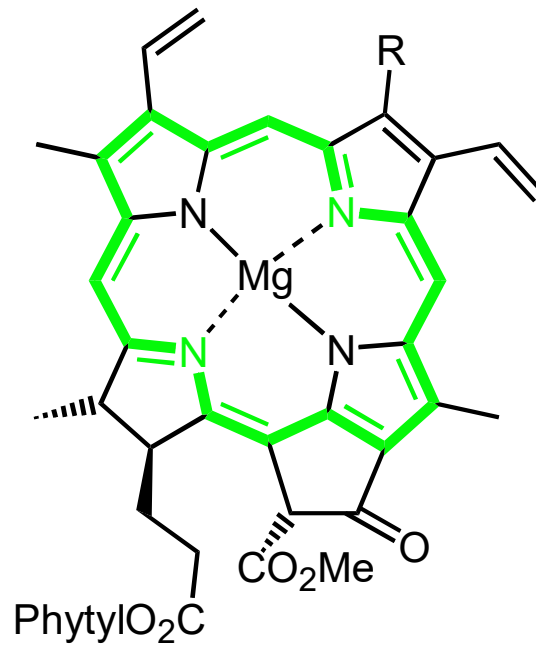


Hämin aus Hämoglobin, erhalten durch Abspaltung vom Proteinteil und Fällung mit NaCl.

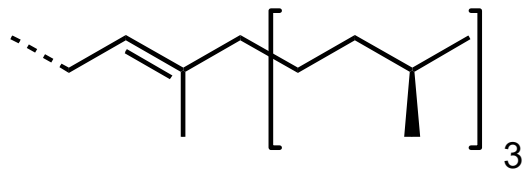


D. Fünfring-Aromaten - D.2 Pyrrol

im Blatt:

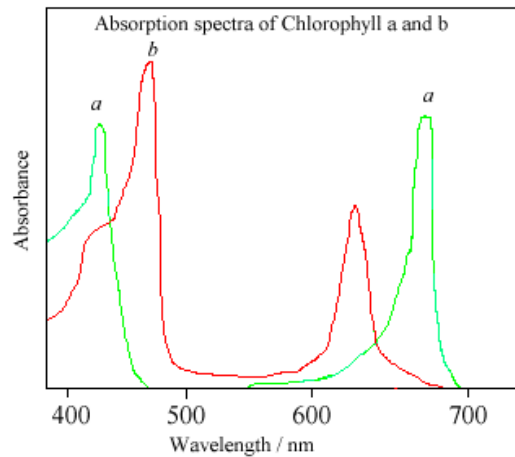


Phytyl =



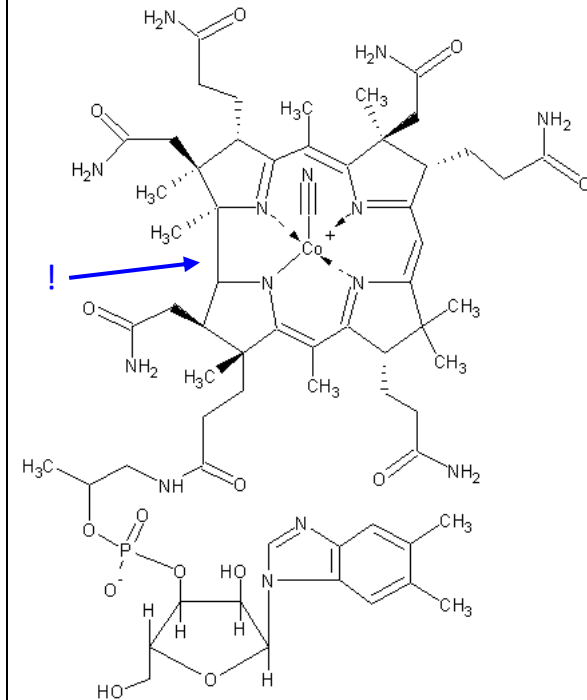
zykl. Tetrapyrrole

R=CH₃: Chlorophyll a
R=CHO: Chlorophyll b



Herbst: Chlorophylle werden als Stickstoffquelle abgebaut, Carotinoide/Anthocyan-Farbstoffe (Flavylum) werden sichtbar.

Coenzym zur Methylierung:



Cyanocobalamin: Corrin-Ringgerüst



Katalysator v. Alkylierungen und Isomerisierungen

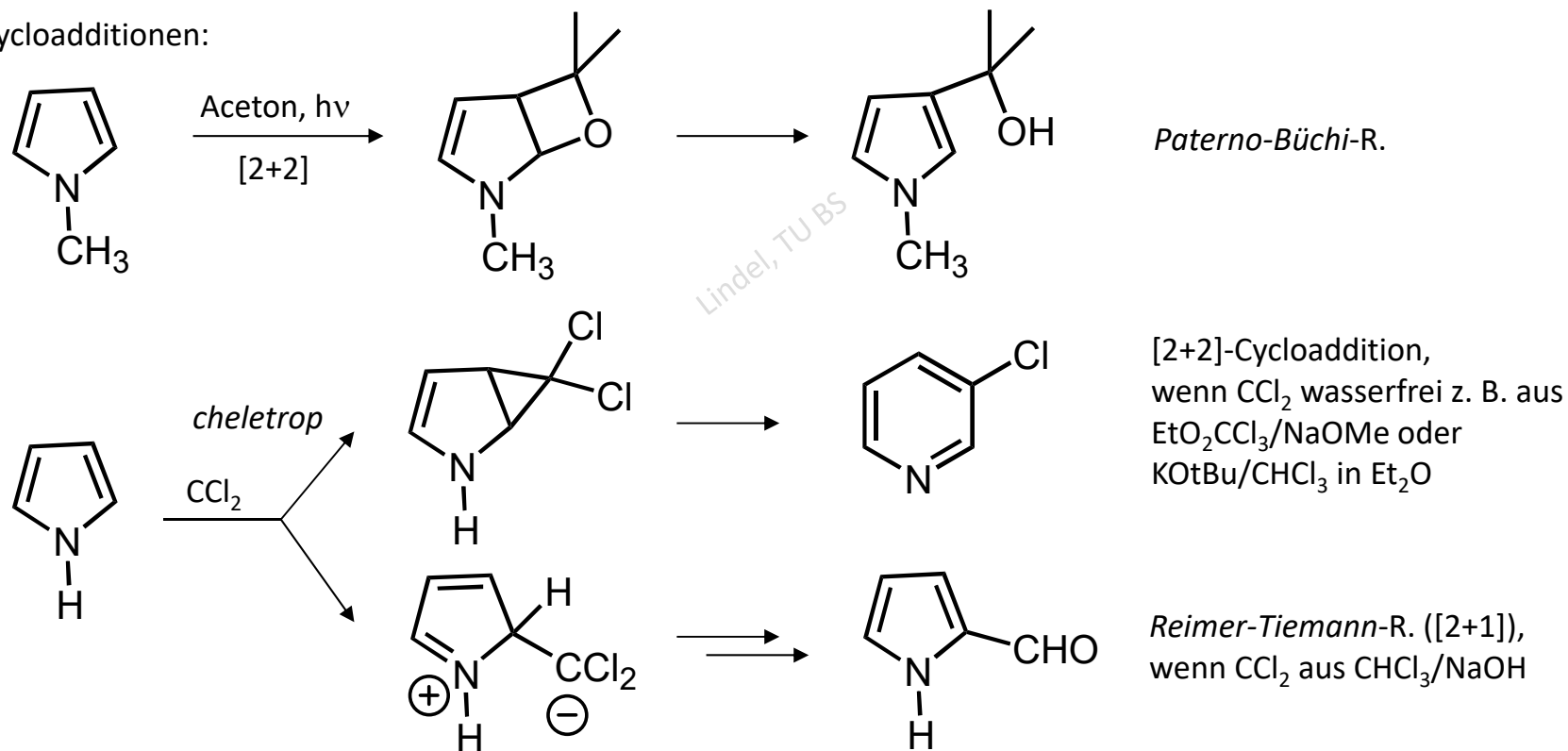
D. Fünfring-Aromaten - D.2 Pyrrol

Reaktivität

Reaktion der 2-Position:

2-Halopyrrol durch Reaktion m. NCS bzw. NBS; 2,3,4,5-Tetrahalopyrrol d. R. m. SO_2Cl_2 , NaOCl bzw. Br_2 ;
2-Nitropyrrol d. R. m. $\text{HNO}_3/\text{Ac}_2\text{O}$ bei -10°C . ebenso b. Diazotierung, Formylierung, Acylierung, Michael-R..
Acylierung der 3-Position: vorher *N*-sulfonylieren (1. NaH, 2. PhSO_2Cl , 3. $\text{RCOCl}/(\text{AlCl}_3)$, 4. NaOH).
Lithiierung der 2-Position: vorher *N*-methylieren (1. NaH, 2. MeI, 3. BuLi, 4. z. B. CO_2 zum Li-Salz).

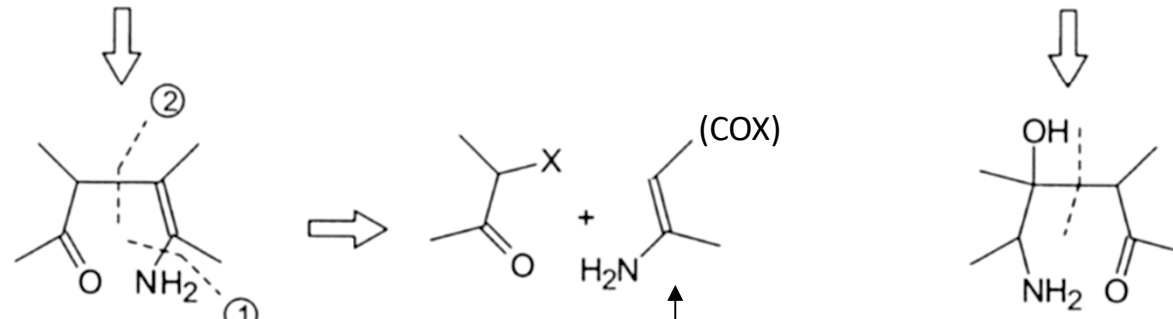
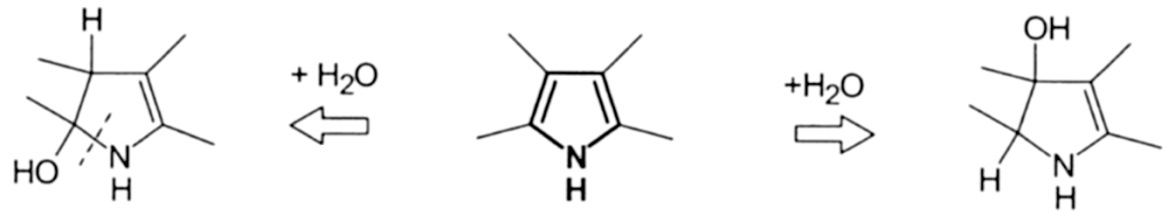
Cycloadditionen:



D. Fünfring-Aromaten - D.2 Pyrrol

Synthese

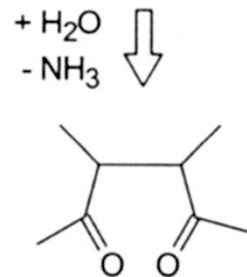
Retrosynthese



Hantzsch
3 Komponenten

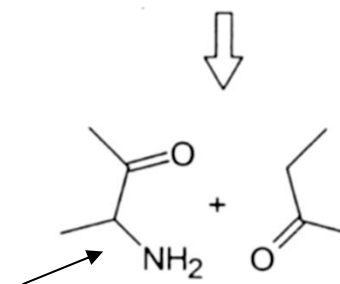
aus β -Keto-Verb.
und Amin
(β -Aminoacrylsäureester)

Paal-Knorr
2 Komponenten



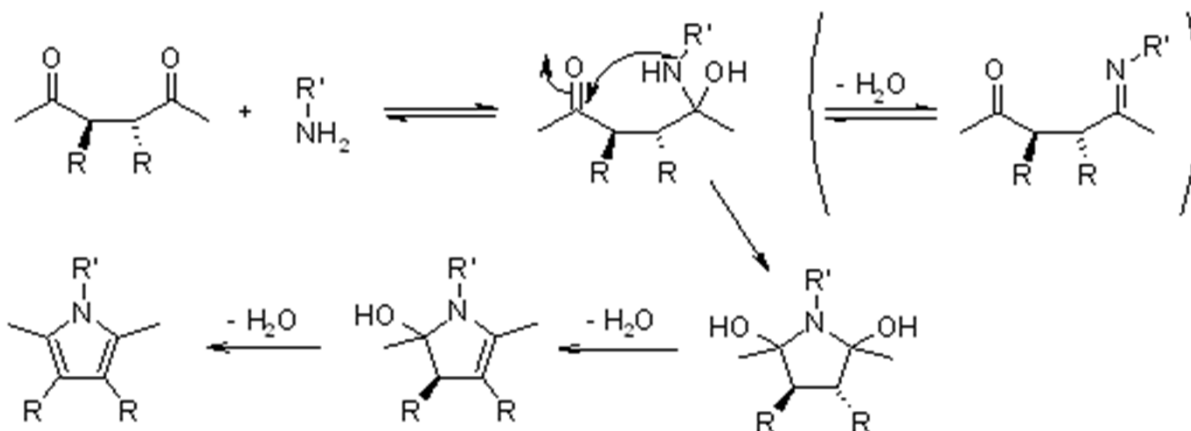
erzeugt aus Keton: 1) RONO, 2) H₂

Knorr
2 Komponenten

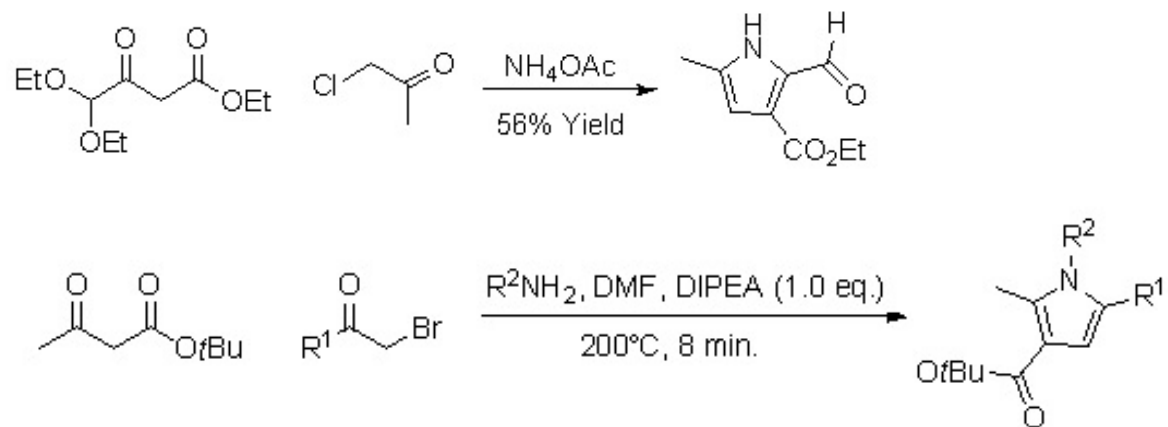


D. Fünfring-Aromaten - D.2 Pyrrol

a) *Paal-Knorr-Synthese*: 1,4-Diketon + (RNH₂ oder NH₃), analog zur *Paal-Knorr-Furan-Synthese*

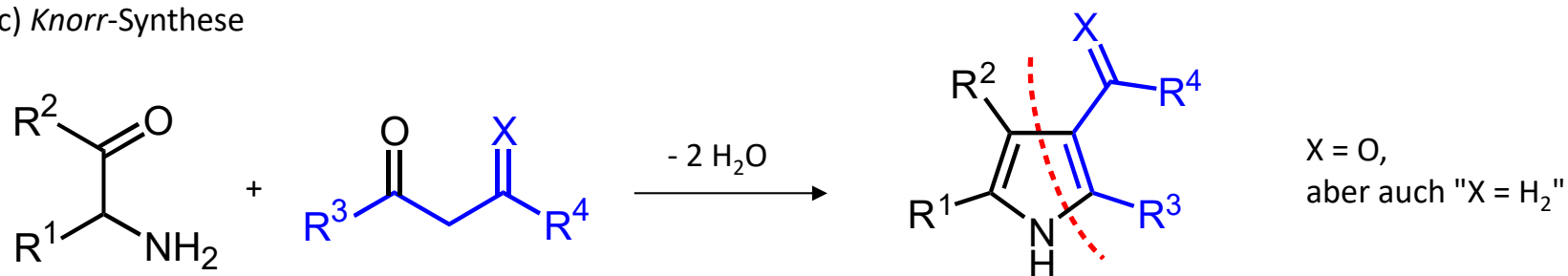


b) *Hantzsch-Synthese*: α -Halocarbonylverb. + β -Dicarbonylverb. + (RNH₂ oder NH₃), analog zur *Feist-Bénary-Furan-S.*, z. B.:

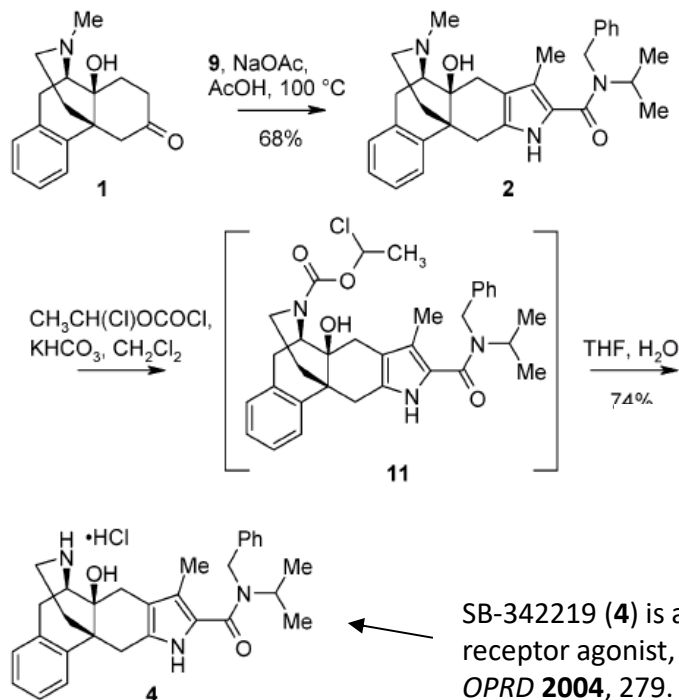


D. Fünfring-Aromaten - D.2 Pyrrol

c) Knorr-Synthese

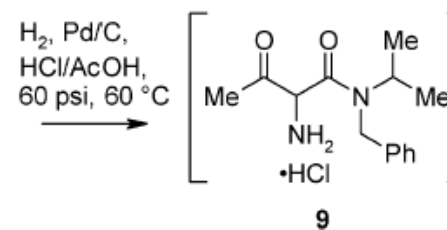
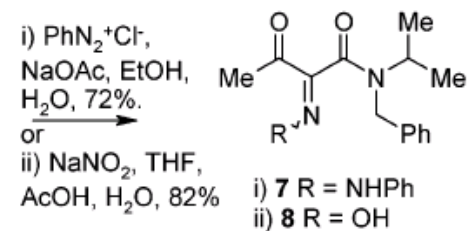
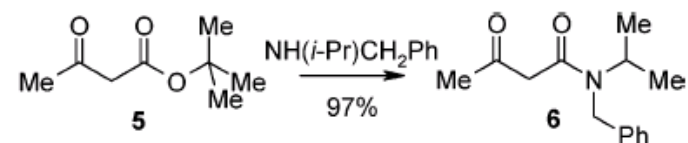


z. B.



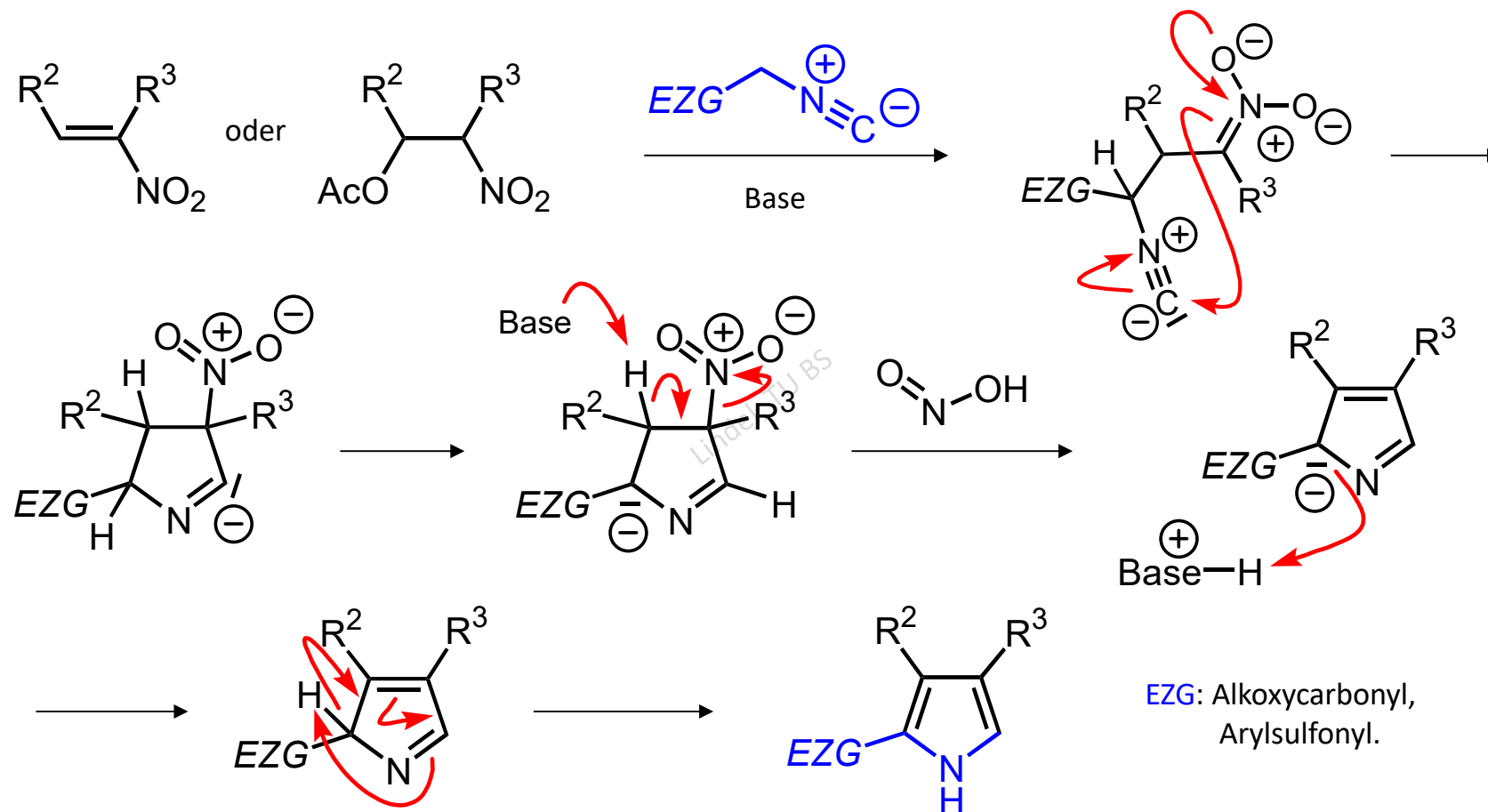
SB-342219 (**4**) is a selective δ -opioid receptor agonist, Glaxo-Smith-Kline, *OPRD* **2004**, 279.

Edukt:



D. Fünfring-Aromaten - D.2 Pyrrol

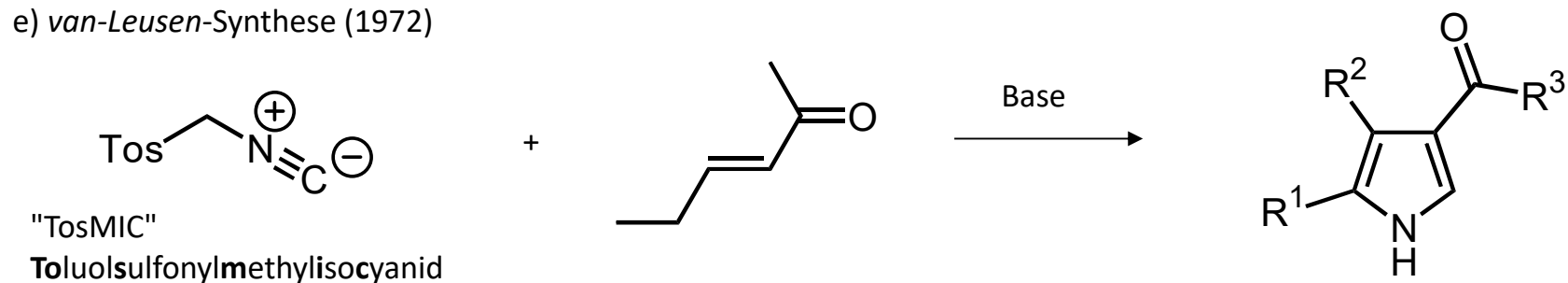
d) Barton-Zard-Synthese von α -Akzeptor-substituierten Pyrrolen (TETH 1990, 7587):



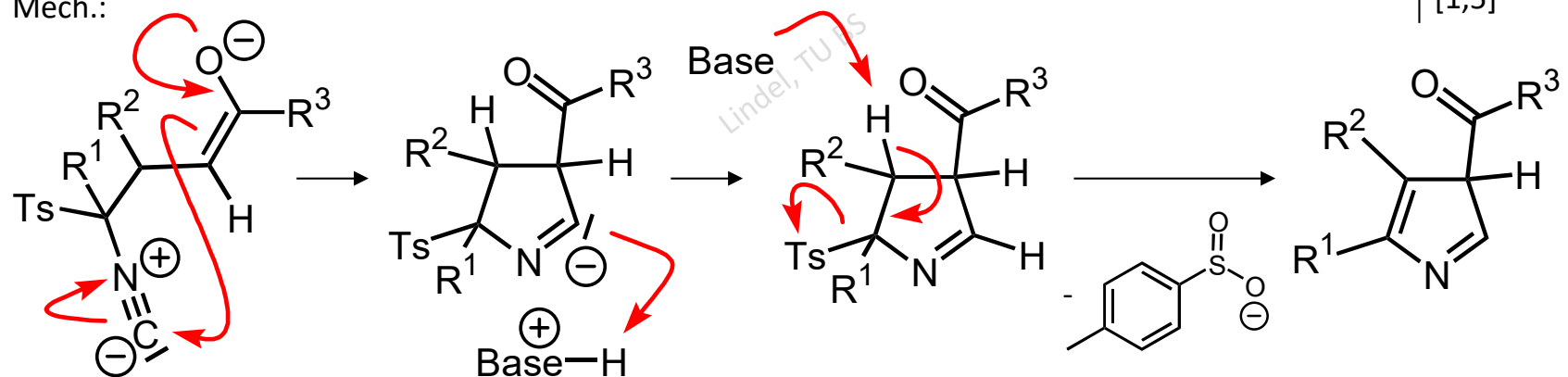
- im Unterschied zur van-Leusen-Synthese hier Eliminierung von HNO_2 (statt v. HTos dort)

D. Fünfring-Aromaten - D.2 Pyrrol

e) *van-Leusen-Synthese* (1972)

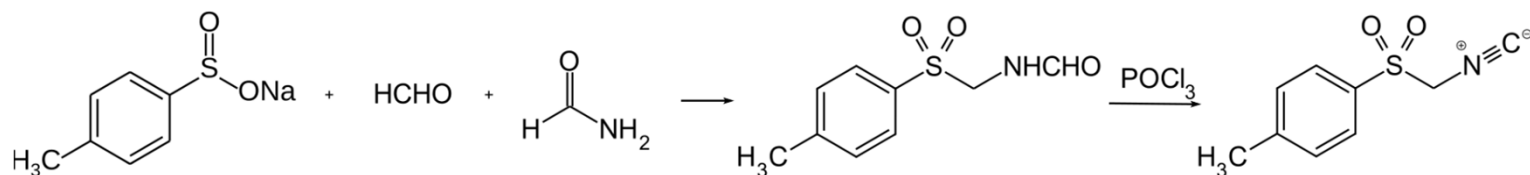


Mech.:



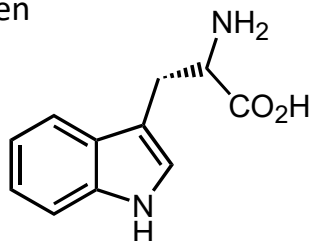
- im Unterschied zur Barton-Zard-Synthese hier Eliminierung von HTos (statt v. HNO_2 dort)

- TosMIC:

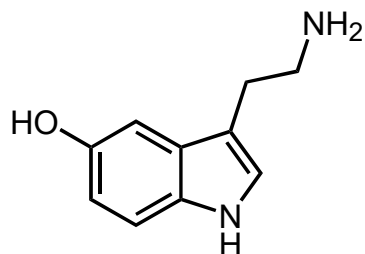


D. Fünfring-Aromaten - D.3 Indol

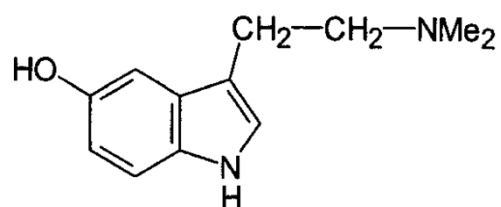
Vorkommen



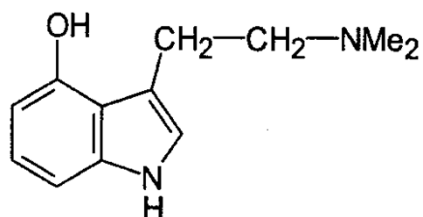
proteinogene Aminosäure
L-Tryptophan (Trp, W)



Neurotransmitter Serotonin



Bufotenin



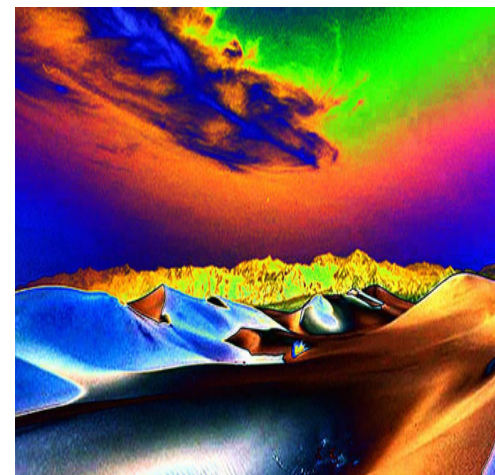
Psilocin

Phosphors.-ester: Psilocybin

Psilocybin, Psilocin: Indol-Alkaloide aus dem mexikan. Rauschpilz "Teonanácatl" ("Gottesfleisch"), halluzinogen; die orale Aufnahme ruft Farbvisionen, ein Gefühl der Bewußtseinerweiterung, auch der Persönlichkeitsspaltung und eine stark erhöhte Lichtempfindlichkeit hervor. Ca. 1 % der Wirkung von LSD. Mechanismus: 5-Hydroxytryptamin(=Serotonin)-Rezeptor-Agonisten (Drug and Alcohol Dependence **1998**, 189).



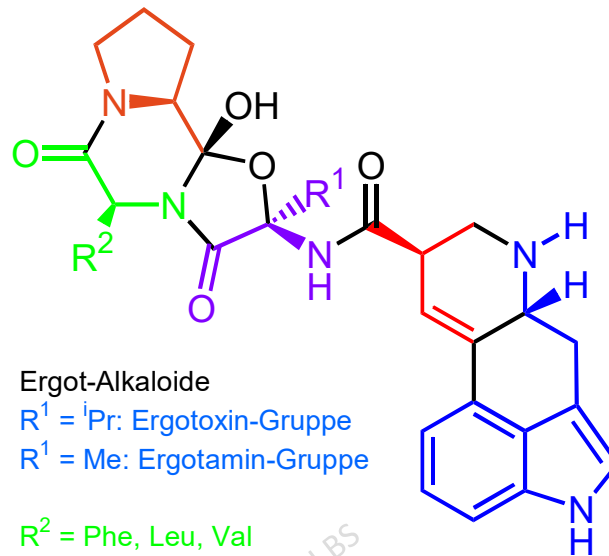
Psilocybe mexicana



D. Fünfring-Aromaten - D.3 Indol

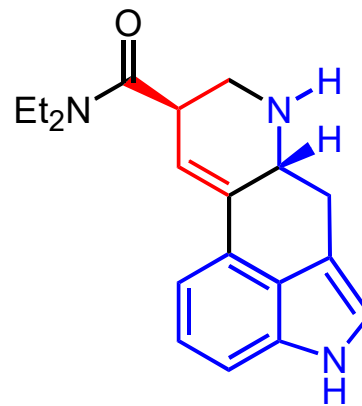


PLATE XXXVII.—*Claviceps purpurea* (Rye ergot). (From Jackson: *Experimental Pharmacology and Materia Medica*.)



Ergot-Alkaloide
 $R^1 = iPr$: Ergotoxin-Gruppe
 $R^1 = Me$: Ergotamin-Gruppe
 $R^2 = Phe, Leu, Val$

Mutterkorn-Alkaloide aus *Claviceps purpurea*

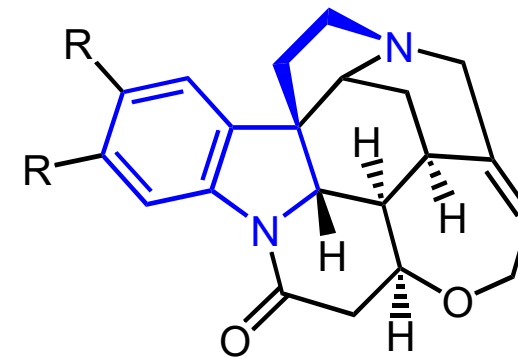


Lysergsäurediethylamid



PLATE XII.—*Strychnos nux-vomica* (Nux Vomica). (From Jackson: *Experimental Pharmacology and Materia Medica*.)

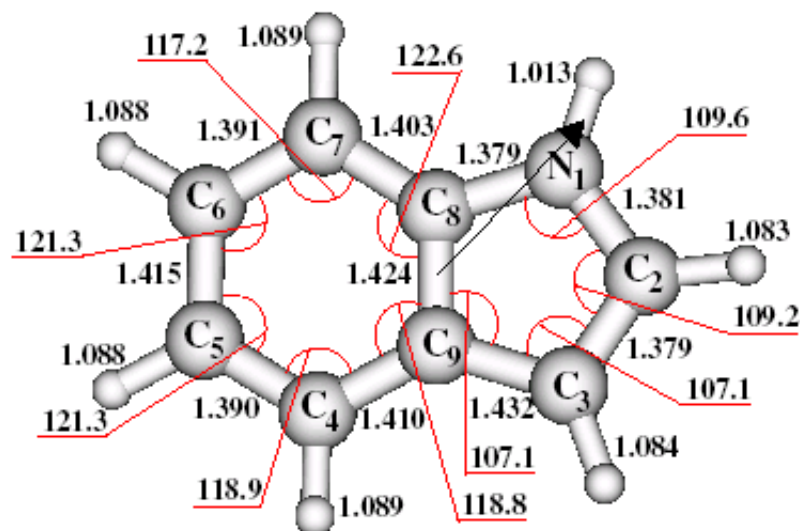
Krähenaugenbaum
Strychnos nux-vomica
 mit Brechnuß



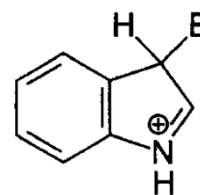
$R=H$: Strychnin; $R=OCH_3$: Brucin

D. Fünfring-Aromaten - D.3 Indol

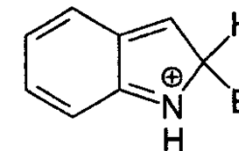
Reaktivität



S_EAr : σ -Komplexe



aromatisch
=> günstig



ortho-chinoid
=> höhere Energie

=> S_EAr an der 3-Position bevorzugt.
Wenn 3-Pos. blockiert: 2-Pos. > 6-Pos.

1H -NMR (acetone- d_6)
 δ (ppm)

H-1: 10.12	H-5: 7.00
H-2: 7.27	H-6: 7.08
H-3: 6.45	H-7: 7.40
H-4: 7.55	

^{13}C -NMR (CDCl $_3$)
 δ (ppm)

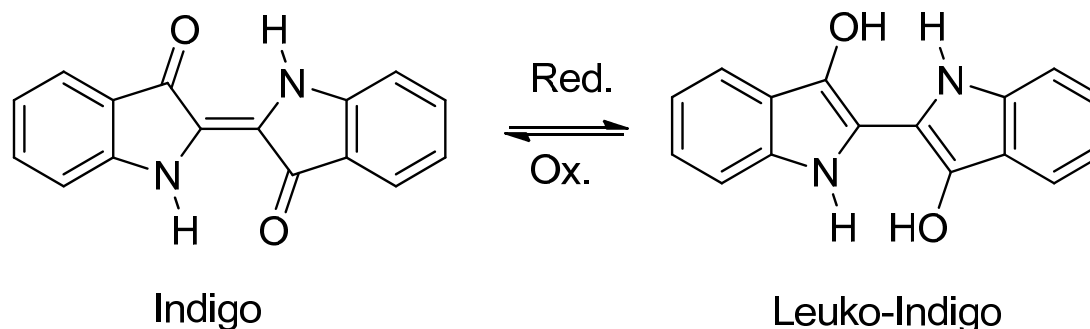
C-2: 123.7	C-6: 119.0
C-3: 101.8	C-7: 110.4
C-4: 119.9	C-3a: 127.0
C-5: 121.1	C-7a: 134.8

3-Chlorierung mit SOCl $_2$ od. aq. NaOCl,
3-Bromierung mit NBS,
3-Sulfonierung mit Pyridin-SO $_3$,
3-Formylierung nach Vilsmeier-Haack,
3-Acetylierung m. Ac $_2$ O,
Gramin-Synthese mit H $_2$ CO/HNMe $_2$ /H $^+$;

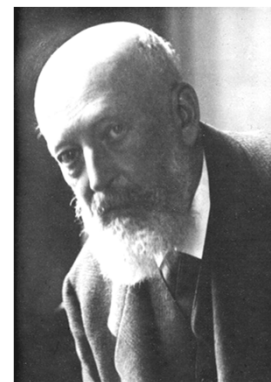
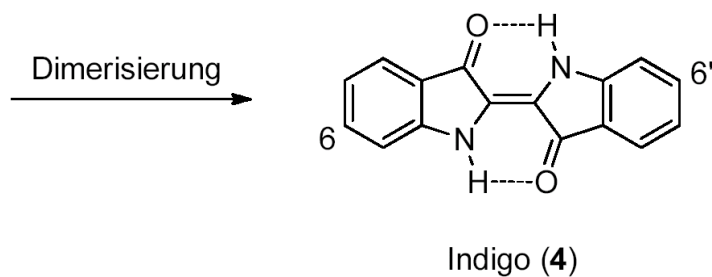
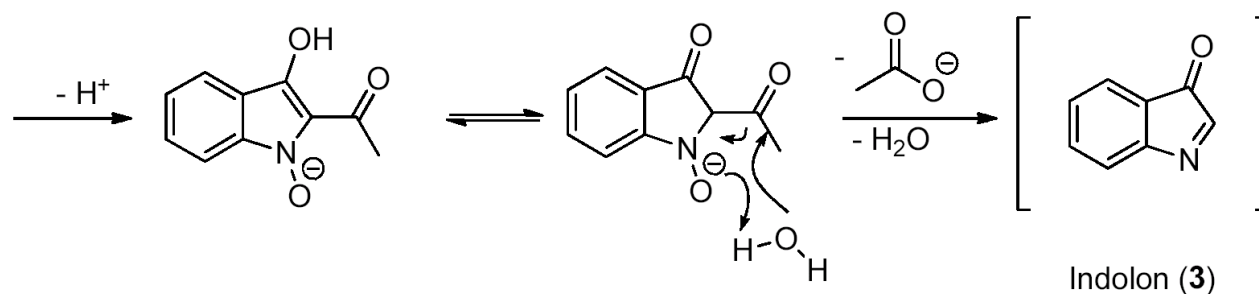
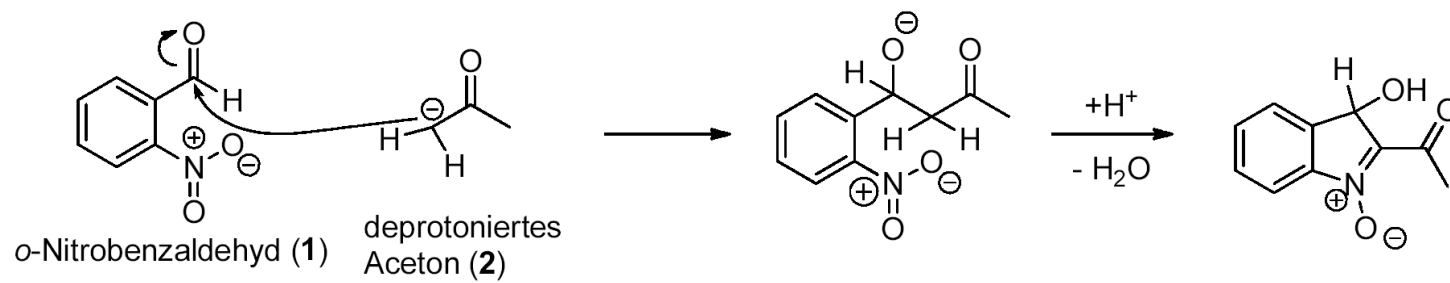
N-Alkylierung nach Deprotonierung m. NaH.

aus dem Schnupperstudium Chemie: Synthese des Farbstoffs Indigo (A. v. Baeyer)

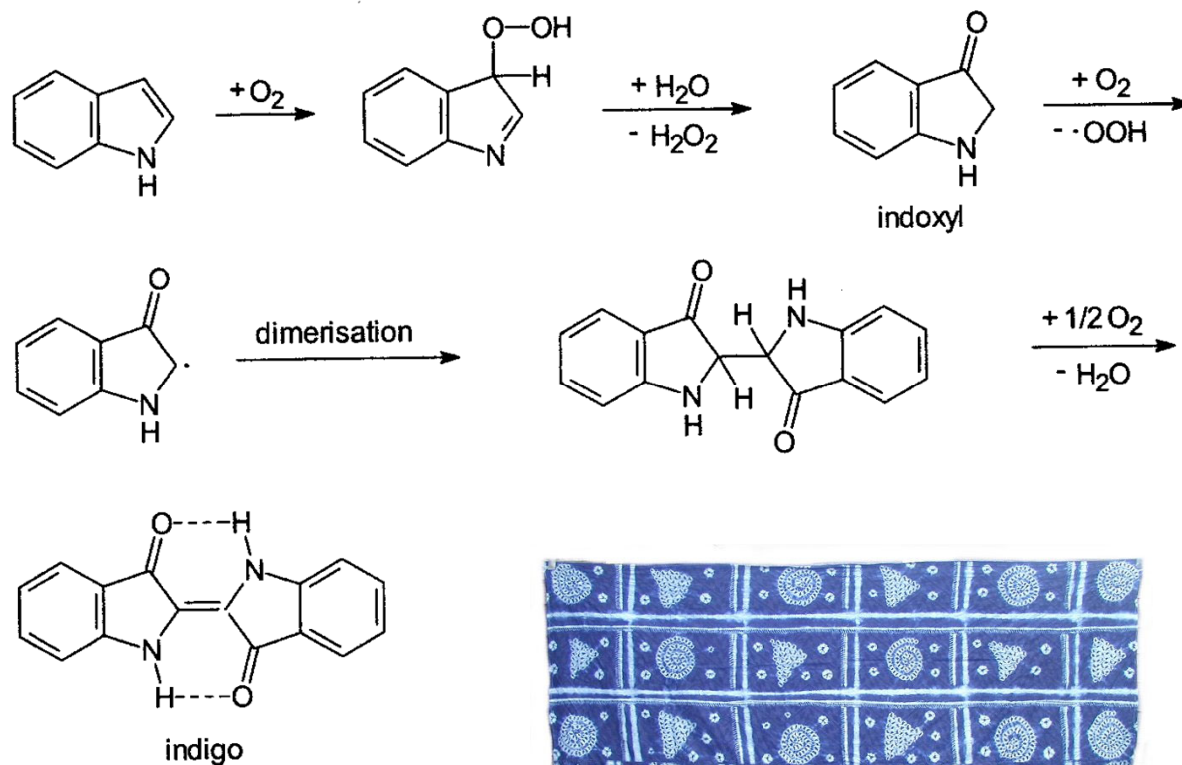
Synthese: In einem Rundkolben (100 mL) wird zu einem Gemisch aus Aceton (10 mL) und Wasser (10 mL) *o*-Nitrobenzaldehyd (1 g) gegeben. Nach vollständiger Auflösung tropft man Natronlauge (2 M, 10 mL) zu. Die Mischung wird 10 min gerührt und dann im Eisbad gekühlt. Der Niederschlag wird durch einen Büchner-Trichter abgesaugt und mit Wasser (20 mL) und Ethanol (20 mL) gewaschen. Das Produkt (Indigo) wird in eine Porzellanschale übergeführt und 30 min im Trockenschrank bei 120 °C getrocknet.



aus dem Schnupperstudium Chemie: Synthese des Farbstoffs Indigo



Adolf von-Baeyer
(1835-1917, NP 1905
"für die Entwicklung der
organischen Chemie
und der chemischen
Industrie durch seine
Arbeiten über die
organischen Farbstoffe
und die
hydroaromatischen
Verbindungen")




Indigo-gefärbtes Tuch aus Westafrika

Aus der Purpurschnecke
Hexaplex trunculus

c1ccc2c(c1)c(=O)[nH]2C(=C)c3ccc2c3Br + c1ccc2c(c1)c(=O)[nH]2C(=C)c3ccc2c3Br >> c1ccc2c(c1)c(=O)[nH]2C(=C)c3ccc2c3Br

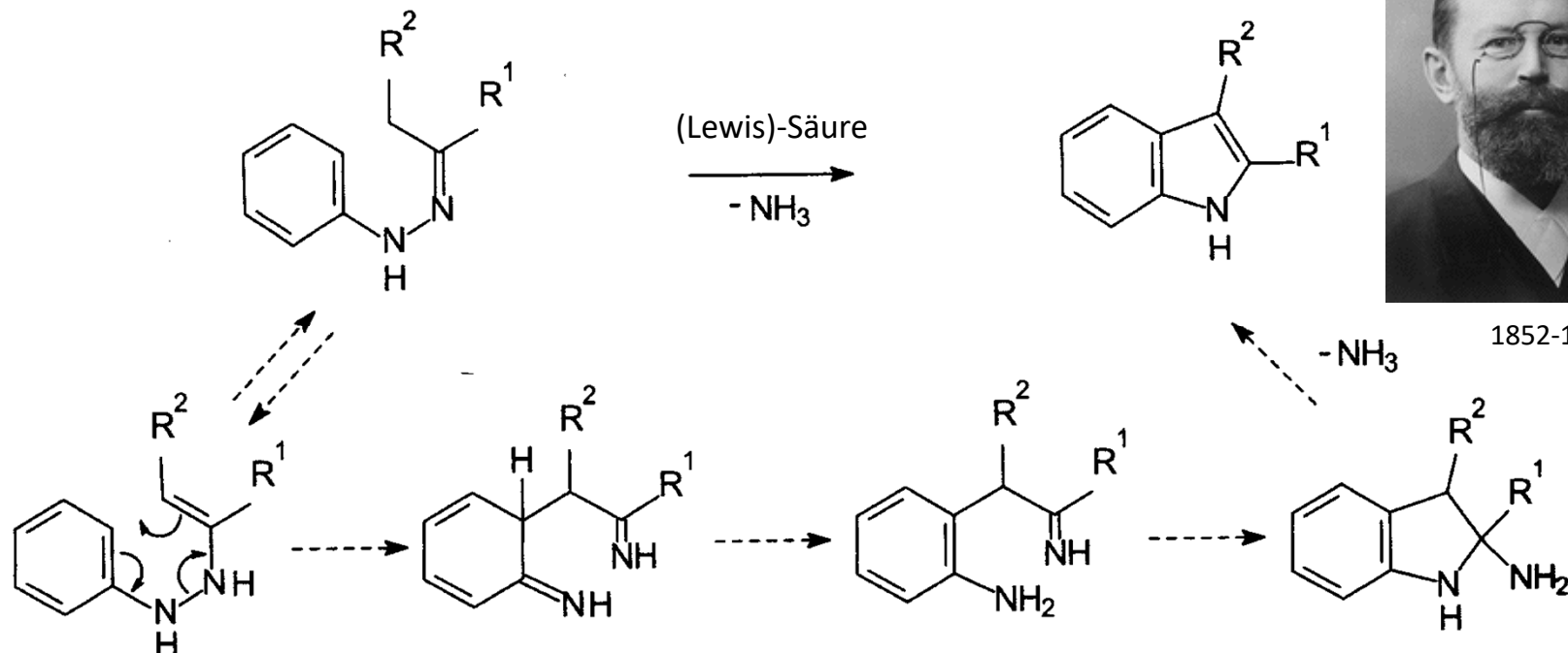
6,6'-Dibromindigo


c1ccc2c(c1)c(=O)[nH]2C(=C)c3ccc2c3Br + O=O >> c1ccc2c(c1)c(O=N)[nH]2C(=C)c3ccc2c3Br + O

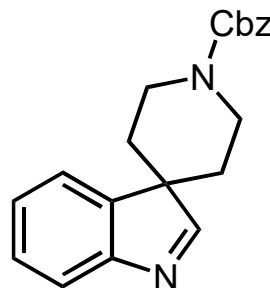
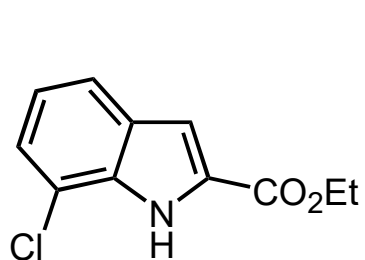
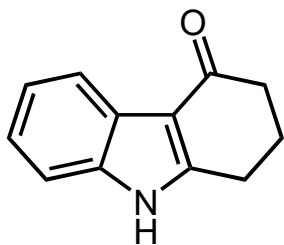
6-Bromindirubin-3'-oxim
(zur Konservierung von Stammzellen)

D. Fünfring-Aromaten - D.3 Indol

a) Fischer-Synthese (Emil Fischer, 1883/4)

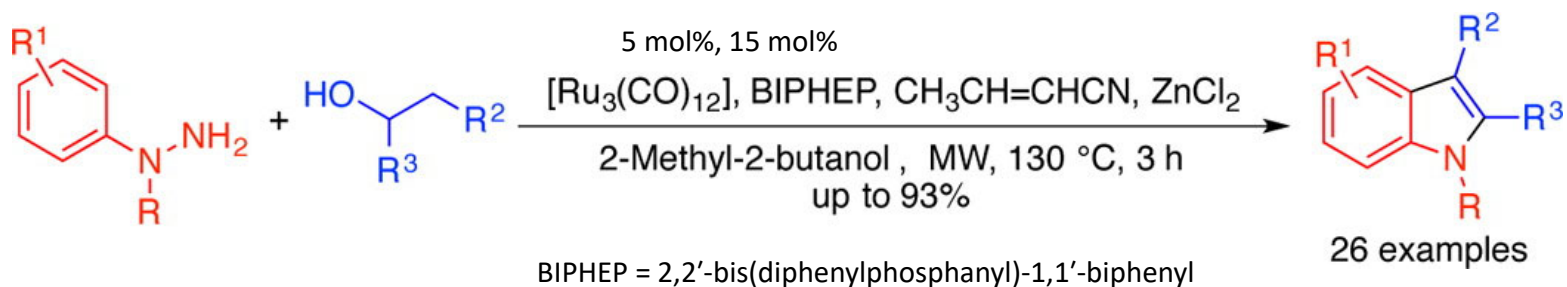


Übungsbeispiele:

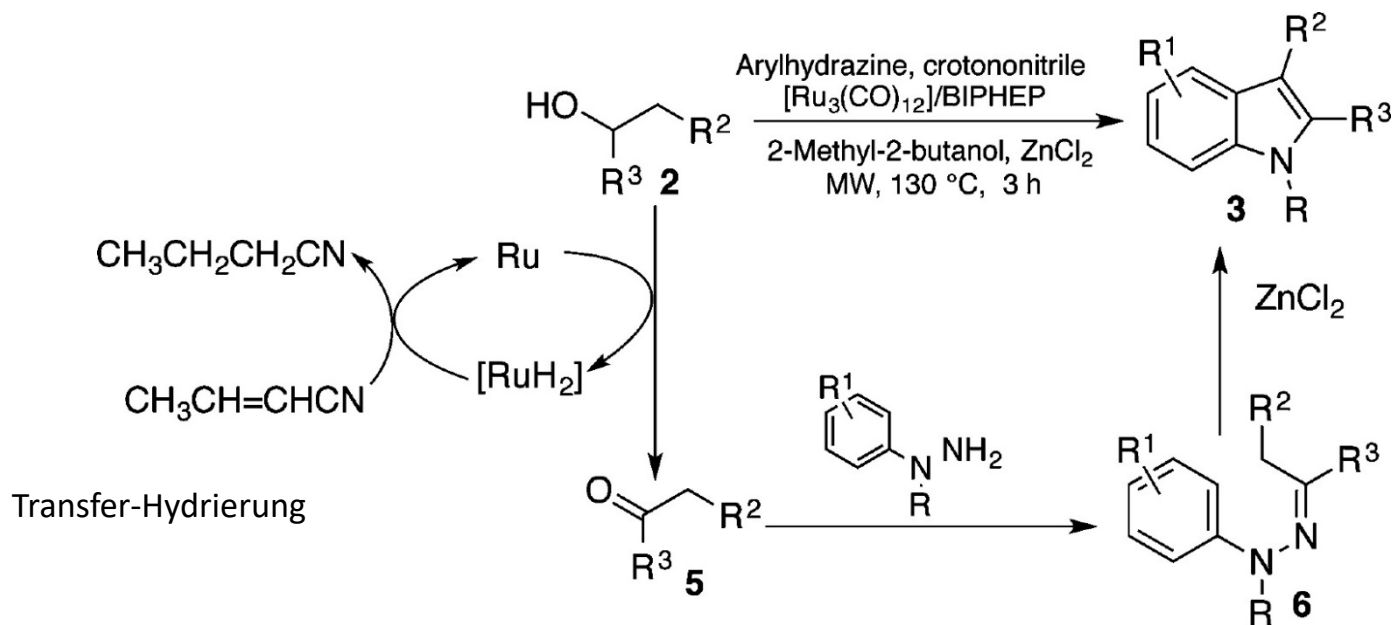


D. Fünfring-Aromaten - D.3 Indol

Fischer-Synthese mit vorangehender Transferdehydrierung



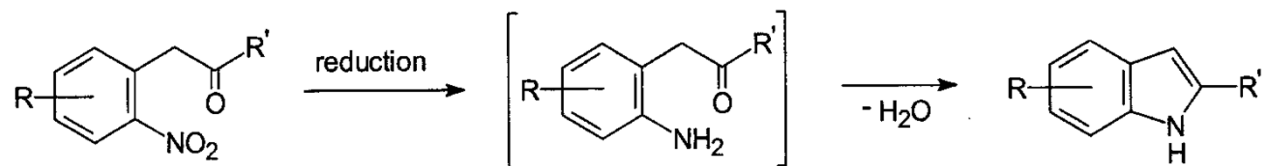
Mechanismus (*Org. Lett.* **2012**, 6112):



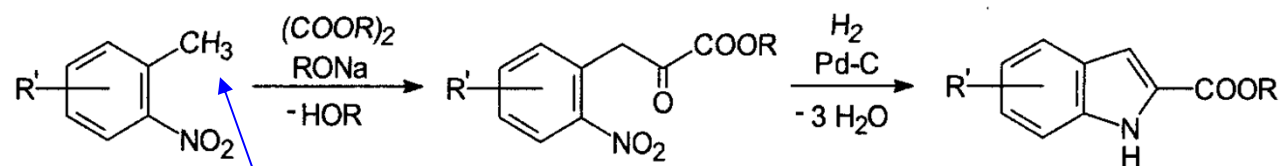
D. Fünfring-Aromaten - D.3 Indol

Indolsynthese ausgehend von Nitrotoluol-Derivaten:

b) *Reisert-Synthese*

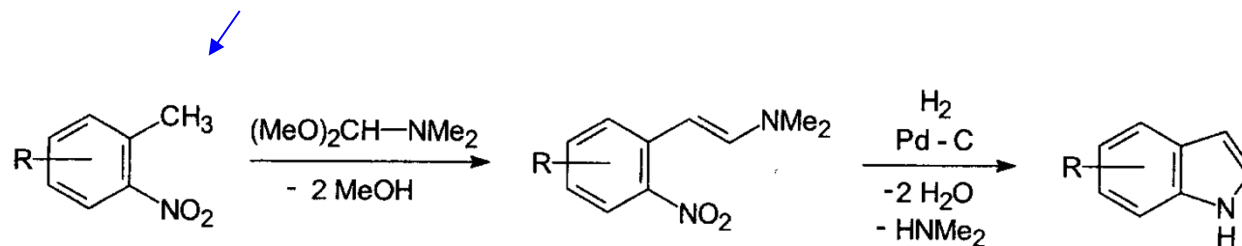


oder:



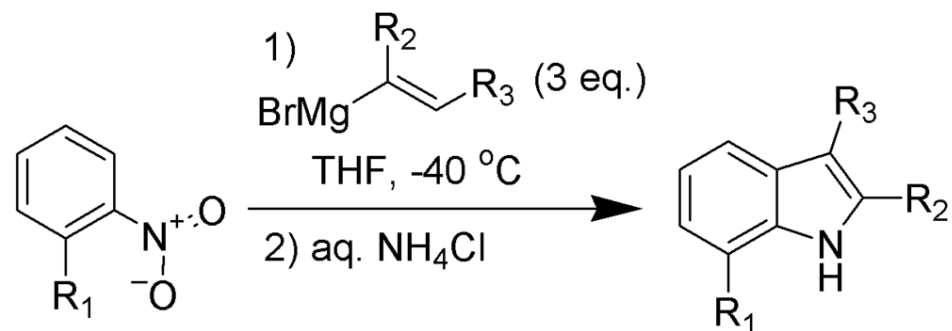
c) *Batcho-Leimgruber-Synthese*

CH-azide

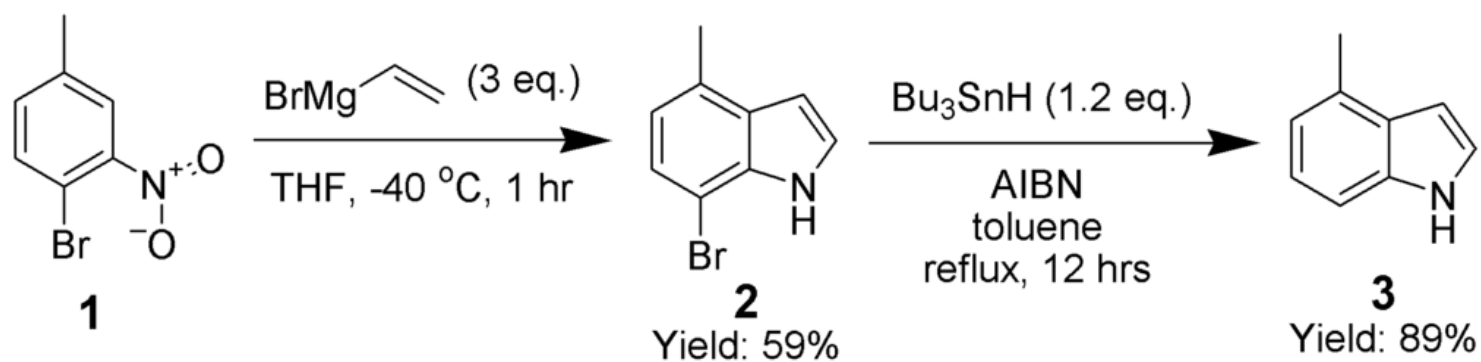


D. Fünfring-Aromaten - D.3 Indol

d) Bartoli-Indolsynthese: Methode der Wahl für 7-substituierte Indole (*TETL* **1989**, 2129)

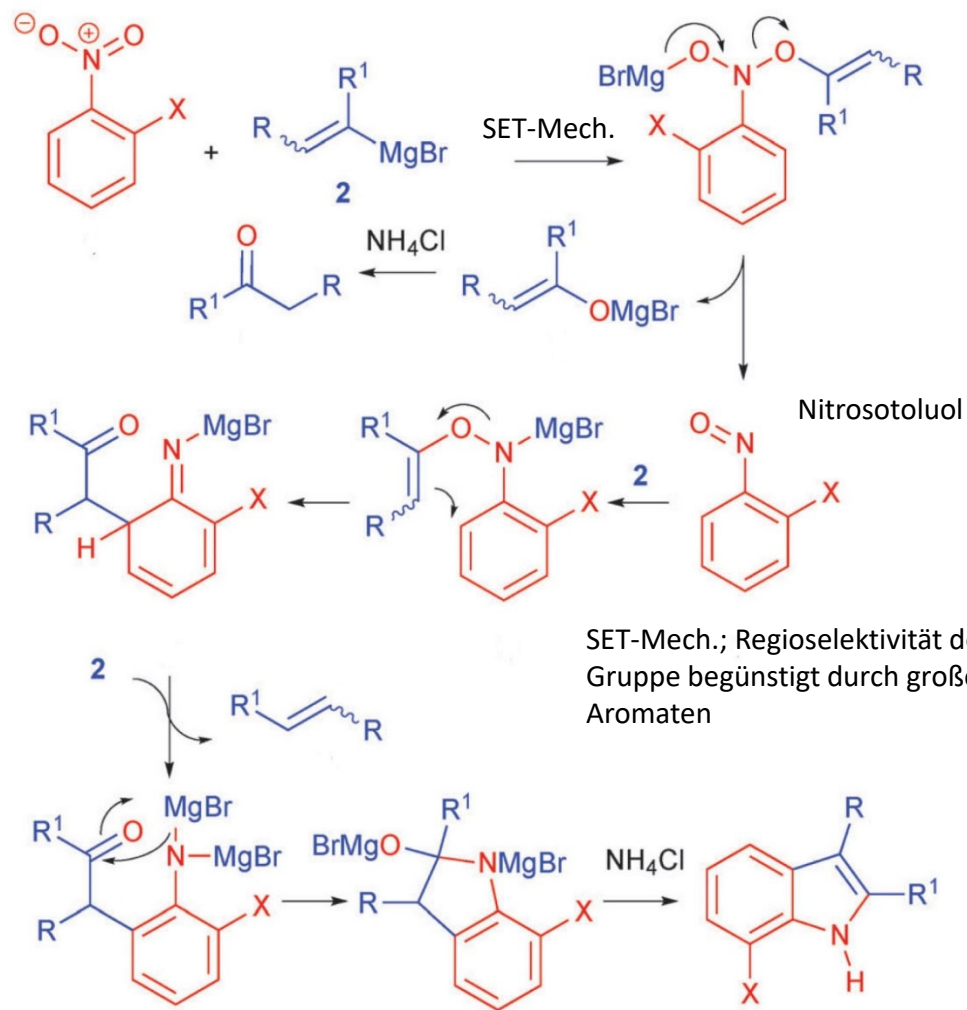


Dobbs-Variante der Bartoli-Indolsynthese: 7-Brom-Substituent steigert Ausbeute (*JOC* **2001**, 66, 638)



D. Fünfring-Aromaten - D.3 Indol

Bartoli-Indolsynthese: Mechanismus, nur eins der 3 Äquivalente Alkenylmagnesiumbromid wird eingebaut.

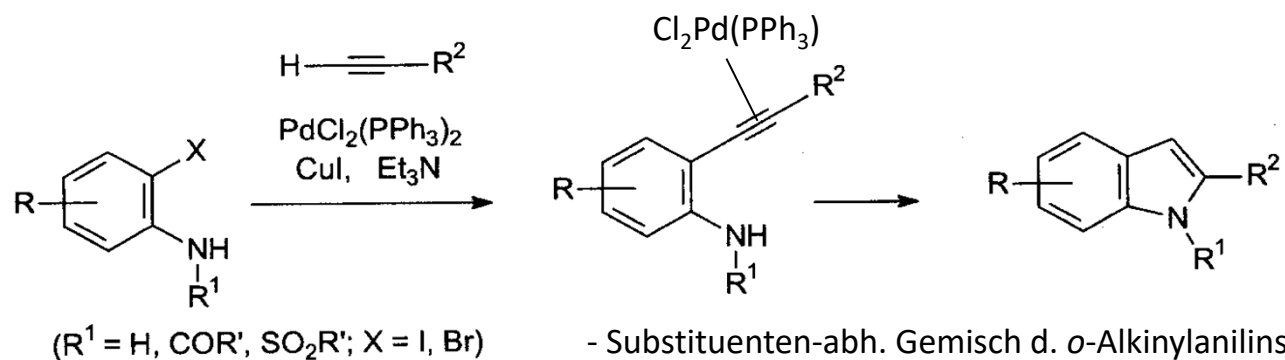


Bartoli et al.,
Chem. Soc. Rev. **2014**, 4728

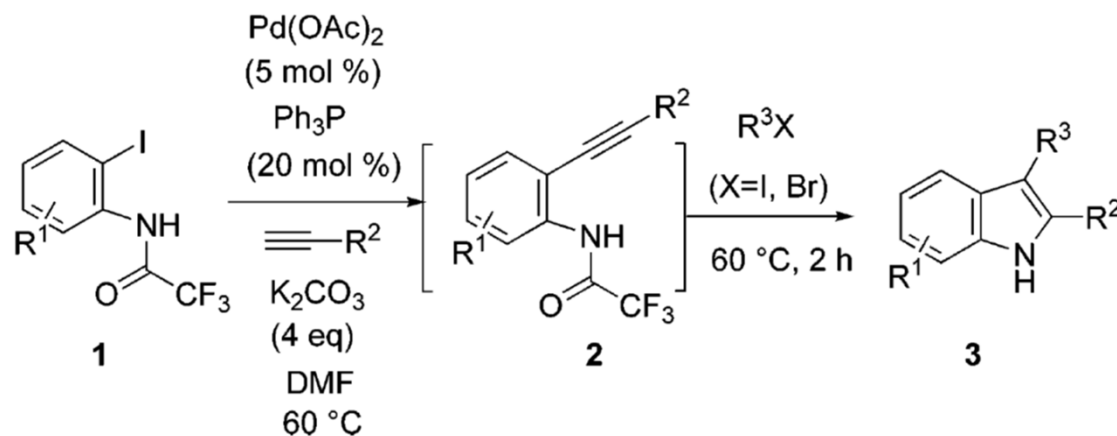
D. Fünfring-Aromaten - D.3 Indol

e) Metall-katalysierte Hydroaminierungen

Kombination aus *Sonogashira*-Kreuzkupplung (1975) und *Castro*-Indolsynthese (1966):



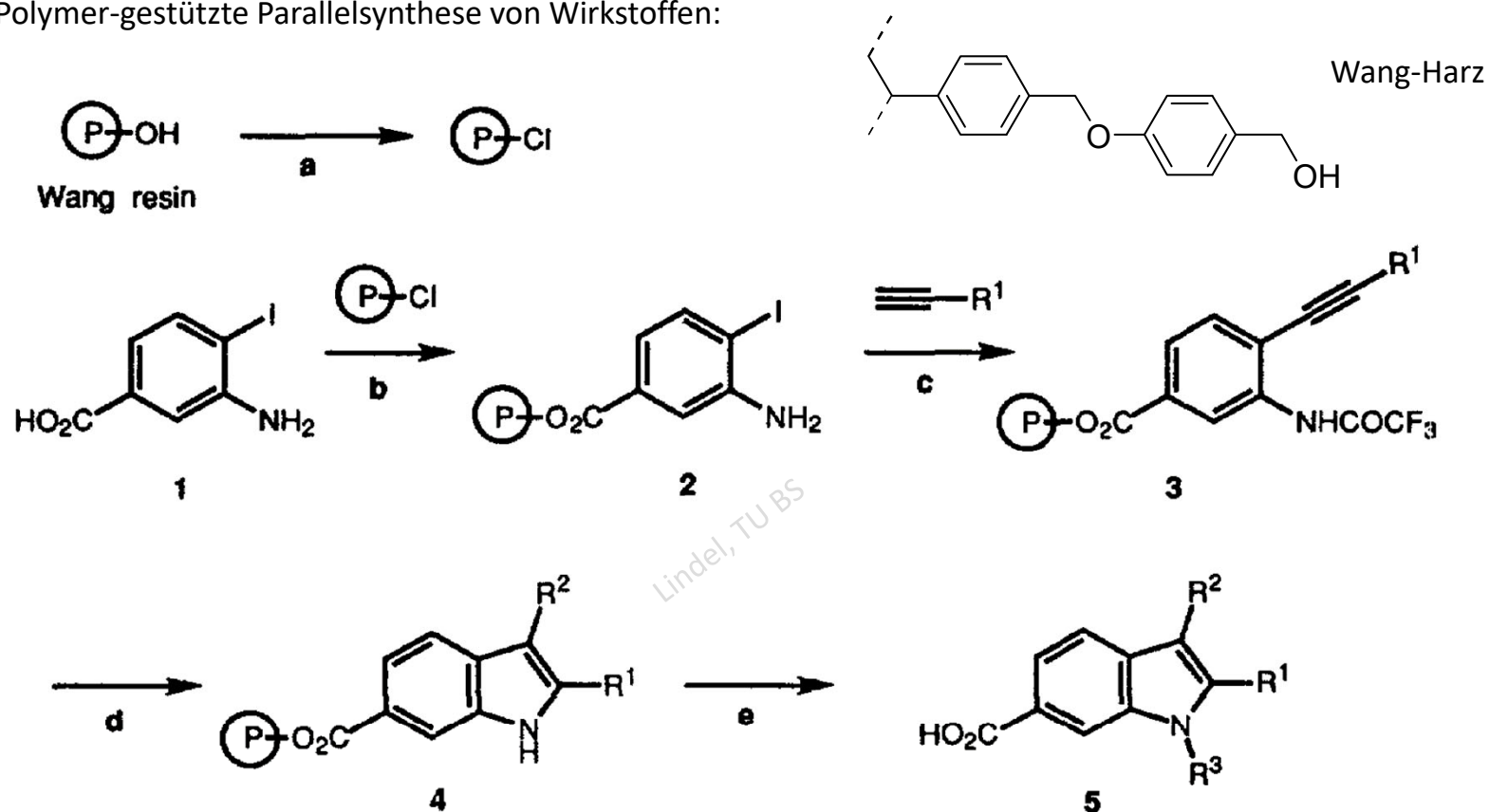
- Substituenten-abh. Gemisch d. *o*-Alkinylanilins und d. Indols,
- Zyklisierung zum Indol auch in alleiniger Anwesenheit v. Pd oder Cu.



Org. Lett. 2006, 3271

D. Fünfring-Aromaten - D.3 Indol

z. B. Polymer-gestützte Parallelsynthese von Wirkstoffen:

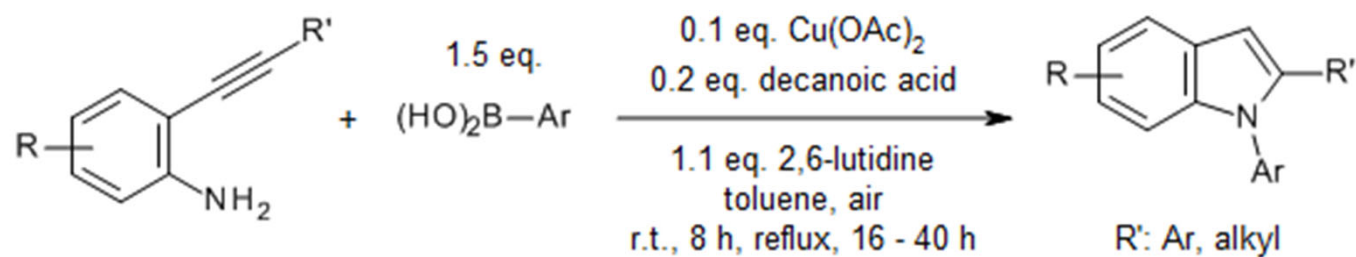
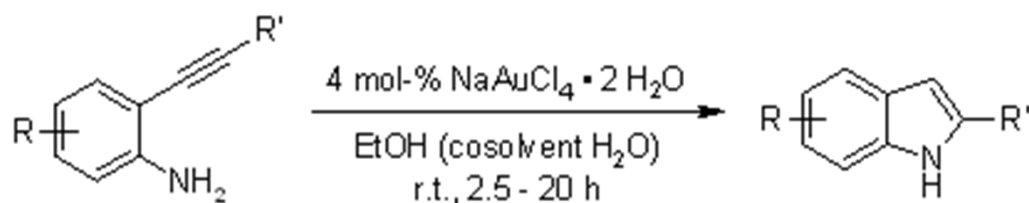
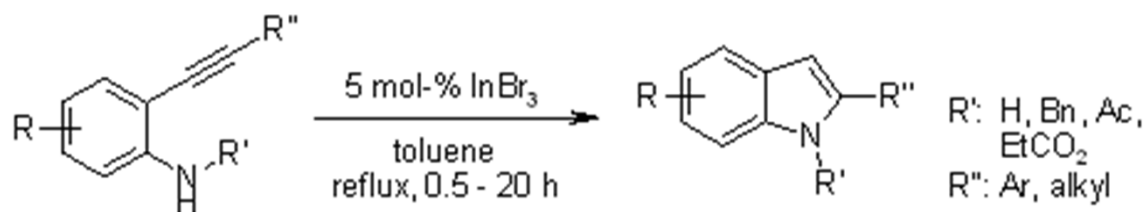
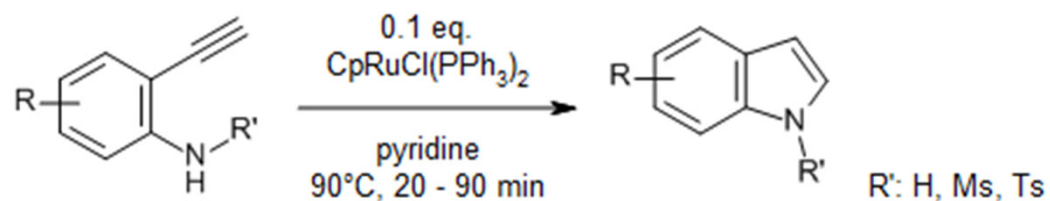


a: MsCl, LiCl, collidine, DMF, 18 h; **b:** Cs₂CO₃, DMF, 50° C, 24 h; **c:** i) PdCl₂(PPh₃)₂, CuI, Et₂NH, DMF, 2 h; ii) (CF₃CO)₂O, pyridine, CH₂Cl₂, 2 h; **d:** R²OTf, Pd(PPh₃)₄, K₂CO₃, DMF, 24 h; **e:** i) R³X, NaH, DMF, 4 h; ii) TFA, CH₂Cl₂, 2 h.

TETL 1997, 7963.

D. Fünfring-Aromaten - D.3 Indol

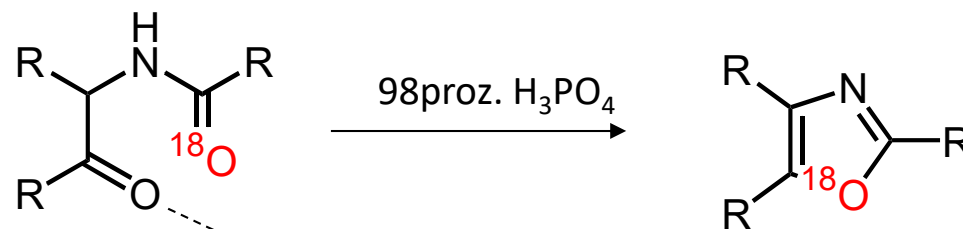
Effizientere, katalytische Varianten



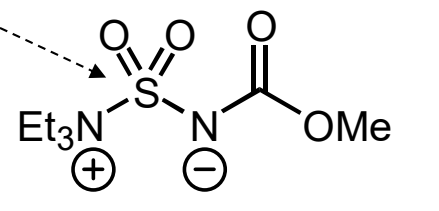
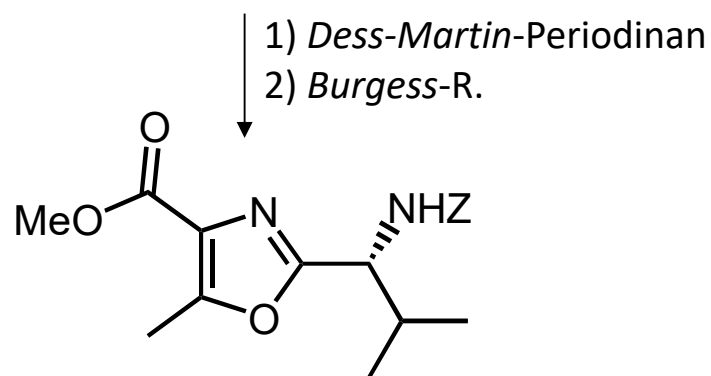
D. Fünfring-Aromaten - D.4 Oxazol

Aufbauende Synthesen

a) *Robinson-Gabriel-Synthese*

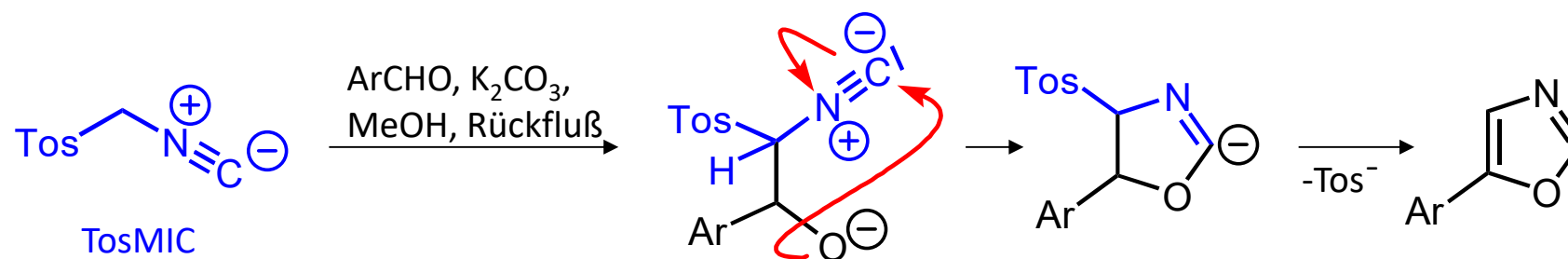


z. B. ZHN-Val-Thr-OMe



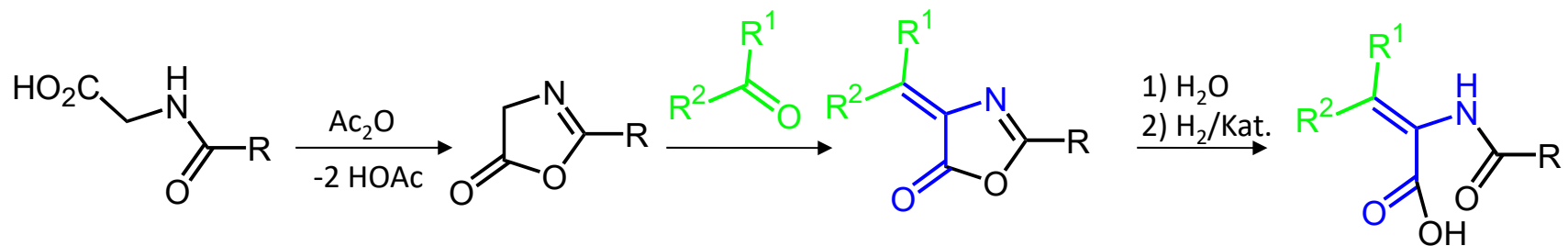
Burgess-Reagenz (1973)
- NEt_3H^+ , - $\text{MeO}_2\text{CNHSO}_3^-$

b) *van Leusen-Synthese* (1972):



D. Fünfring-Aromaten - D.4 Oxazol

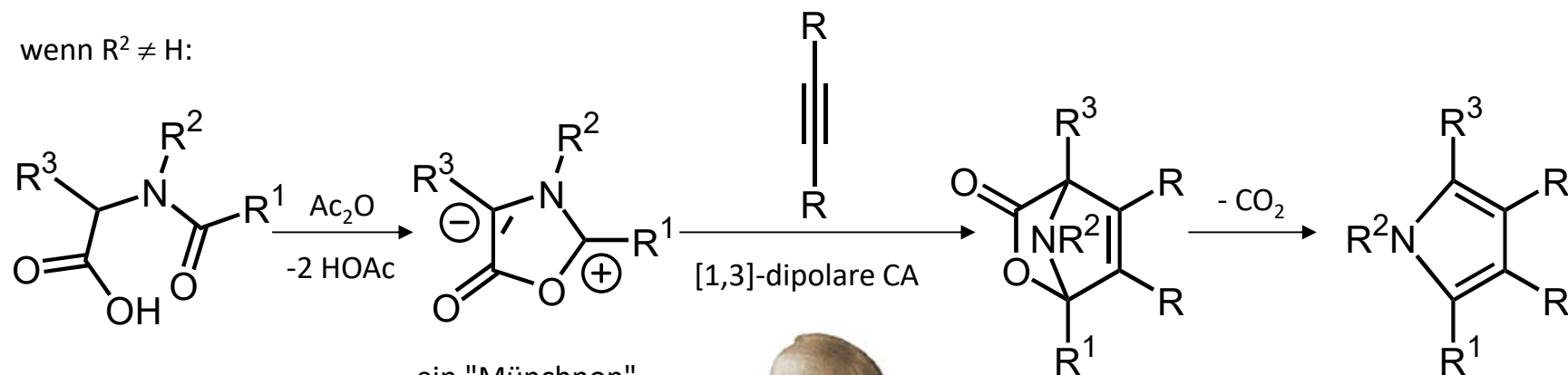
c) Erlenmeyer-Azlacton-Synthese von Oxazolonen: guter Zugang zu Aminosäuren



ein Acylglycin (R=Ph: Hippursäure)

ein Azlacton (=5-Oxazol)

wenn $\text{R}^2 \neq \text{H}$:



ein "Münchnon"
(Rolf Huisgen)

mesomeres Zwitterion

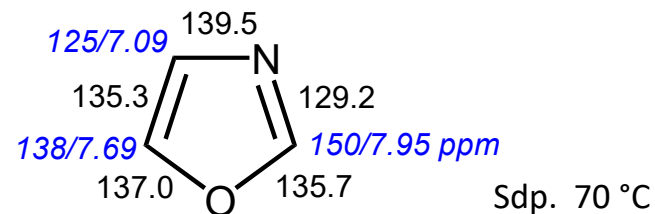


ein Pyrrol

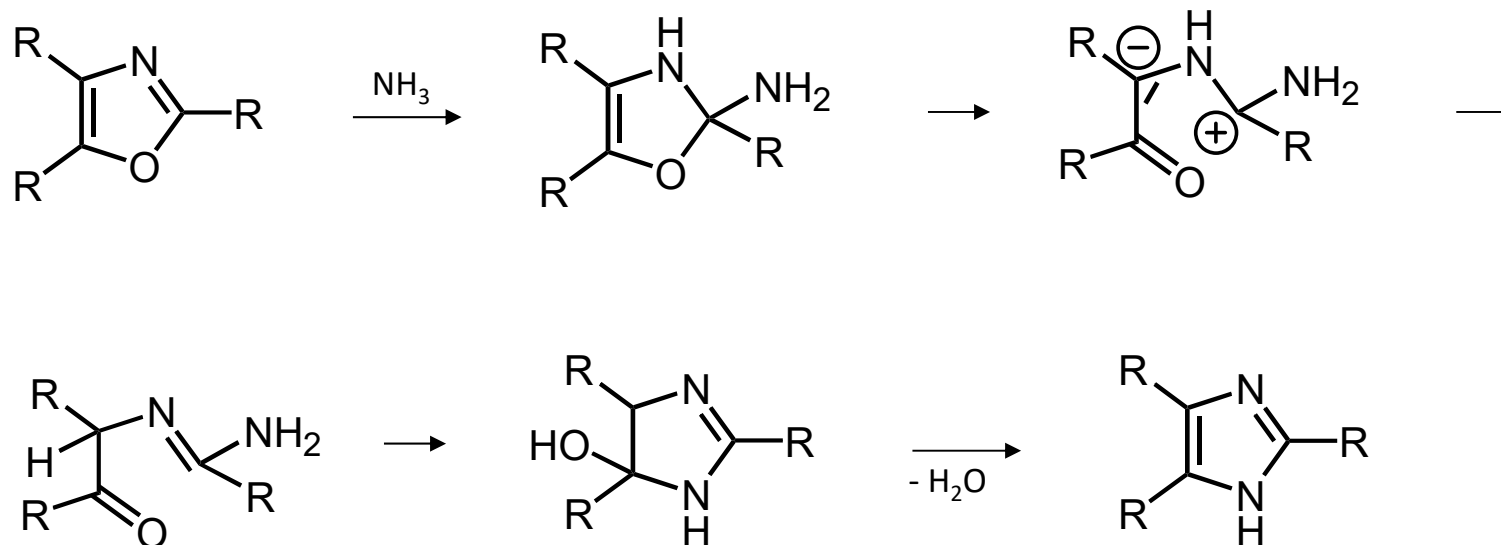
D. Fünfring-Aromaten - D.4 Oxazol

Reaktivität

- vergleichbar mit Furan; elektronenärmste Position C2.
- Lithiierung an C2 (+ DMF -> 2-Formylierung).
- Quaternisierung mit Haloalkanen am N.
- Synthese-Intermediat auf dem Weg zu anderen Heterozyklen



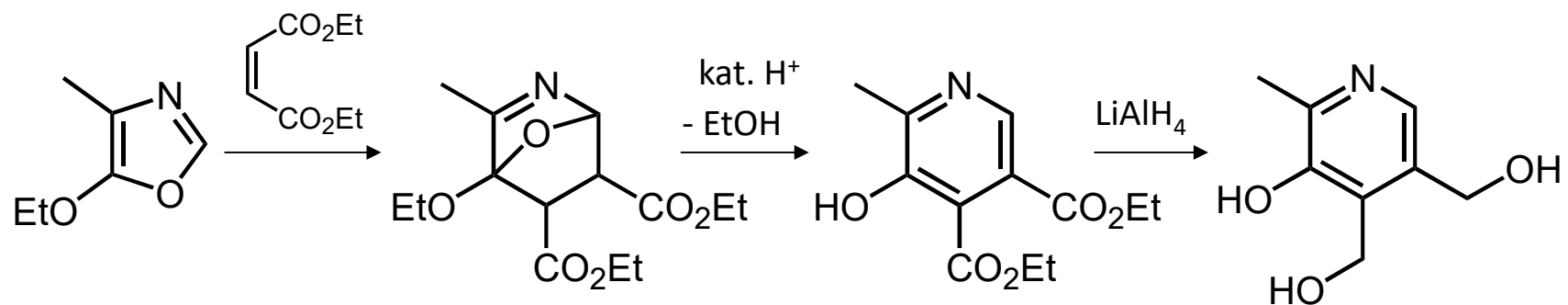
a) nukleophiler Angriff an C2: Umwandlung in Imidazol



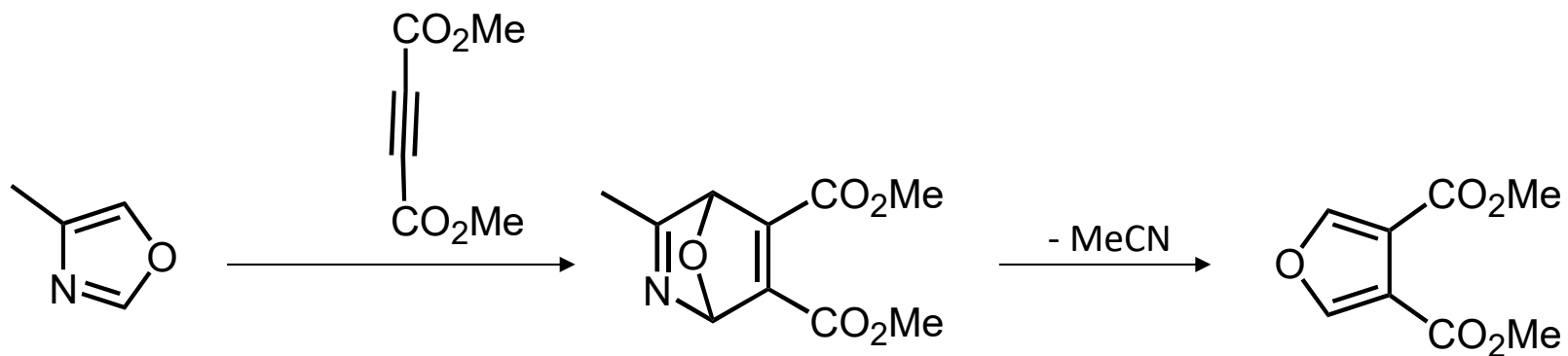
D. Fünfring-Aromaten - D.4 Oxazol

b) *Diels-Alder*-Reaktionen

Umwandlung in Pyridin:

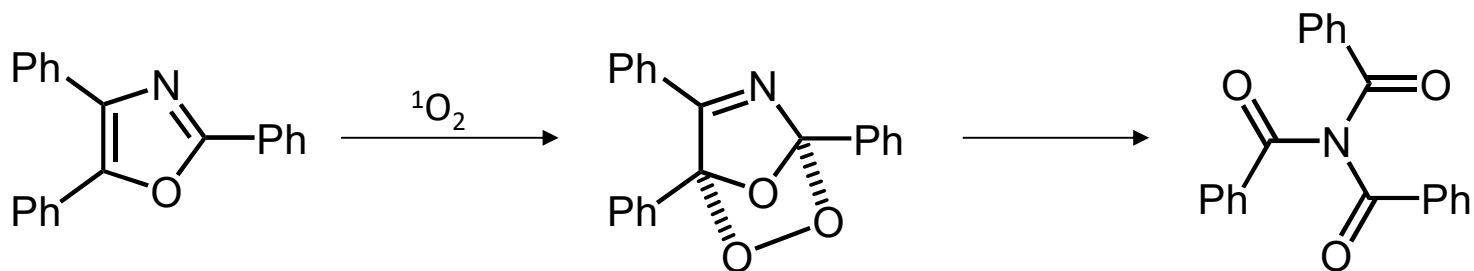


Umwandlung in Furan:

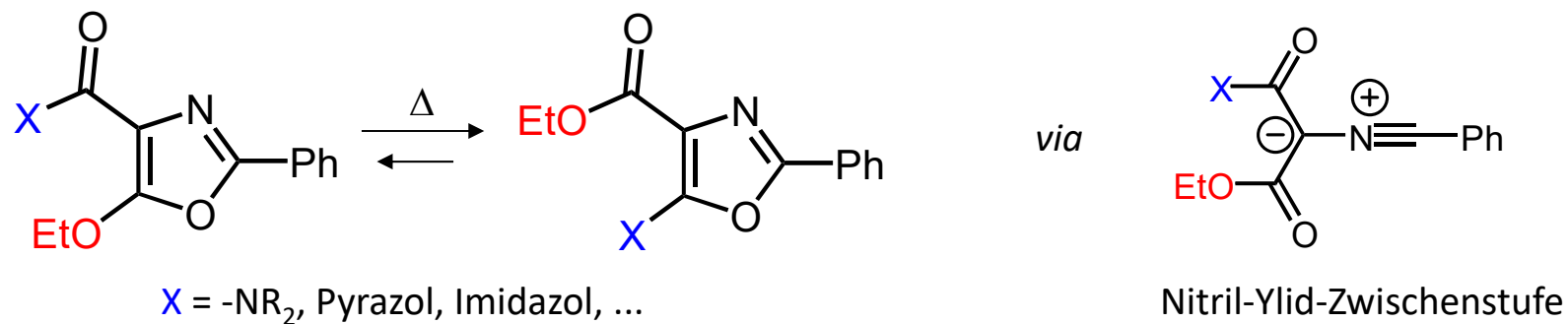


D. Fünfring-Aromaten - D.4 Oxazol

Reaktion mit Singulett-Sauerstoff:



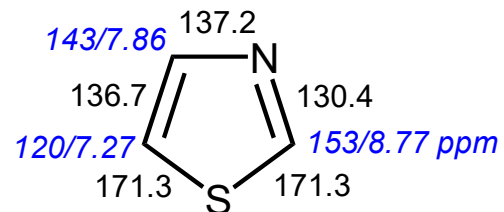
c) Cornforth-Umlagerung



D. Fünfring-Aromaten - D.5 Thiazol

Reaktivität

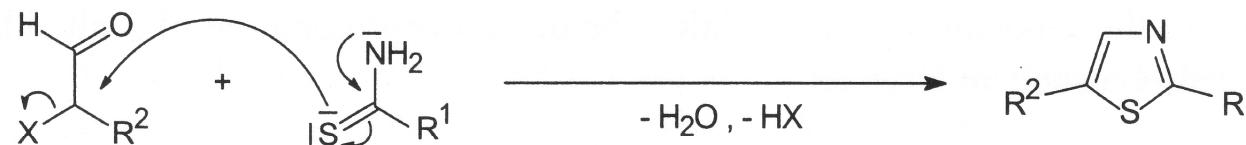
- elektronenärmste Position C2.
- Lithiierung an C2 (+ DMF -> 2-Formylierung).
- Quaternisierung mit Haloalkanen am N.
- keine Diels-Alder-Reaktionen



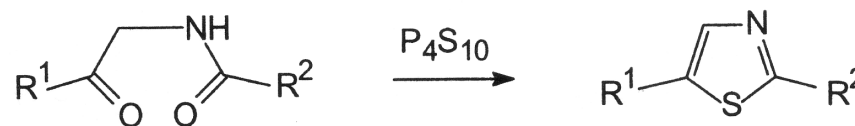
Sdp. 118 °C

D.42 Aufbauende Synth.

a) Hantzsch-Synthese:



b) Gabriel-Synthese

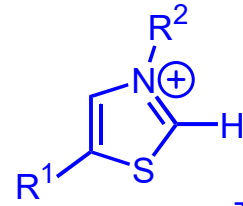
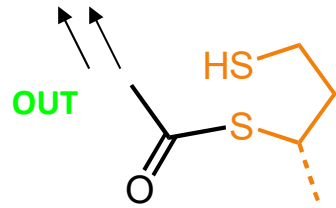


D. Fünfring-Aromaten - D.5 Thiazol

Biologische Bedeutung

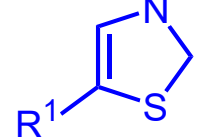
Oxidative Decarboxylierung von Pyruvat

Acetyl-CoA



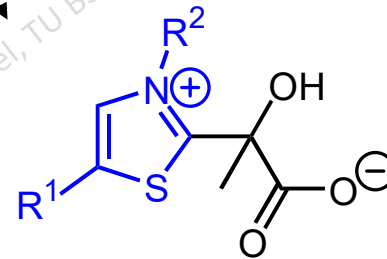
RNH₂
(Base)

Thiazol-Singulettcarben



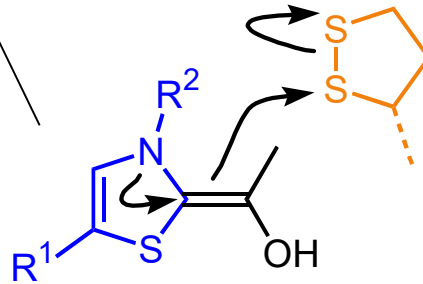
Brenztraubensäure
(Salz: Pyruvat)

IN

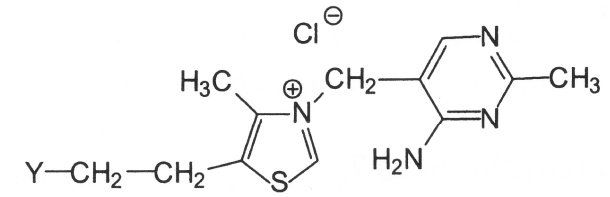


- CO₂

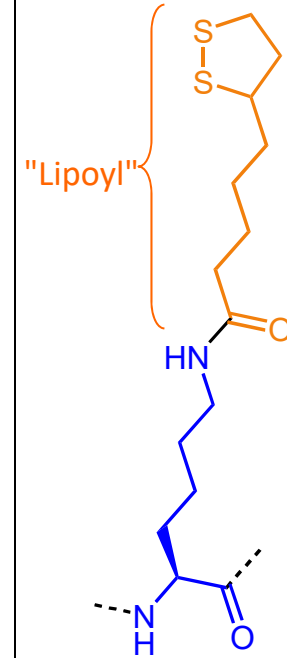
Breslow 1958



Organokatalyse



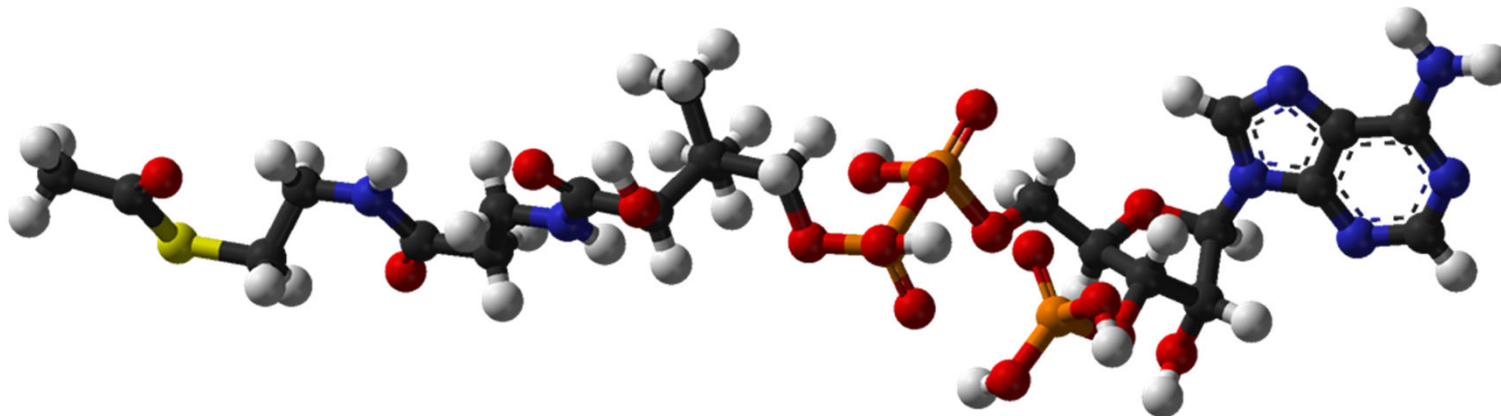
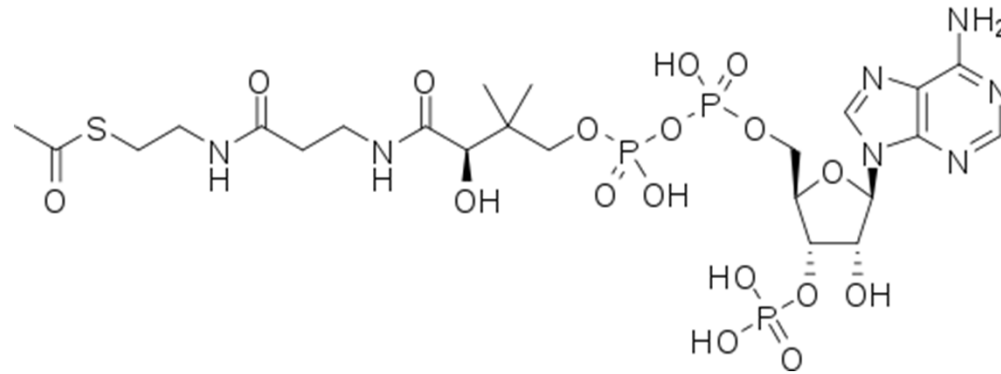
Y=PP: Thiaminpyrophosphat (Vit. B₁)



Lys der Dihydrolipoyl-Transacetylase

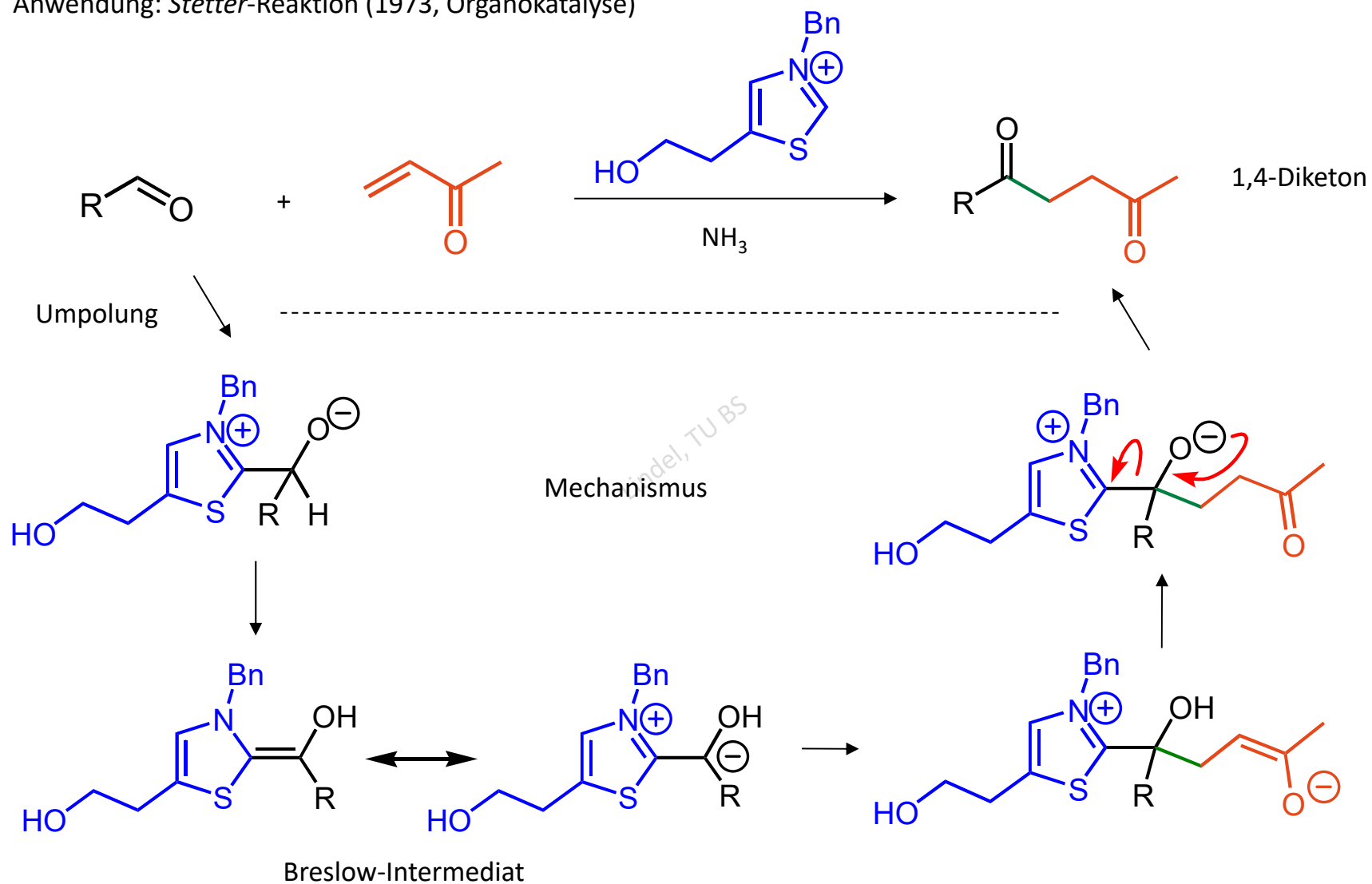
D. Fünfring-Aromaten - D.5 Thiazol

Acetyl-CoA



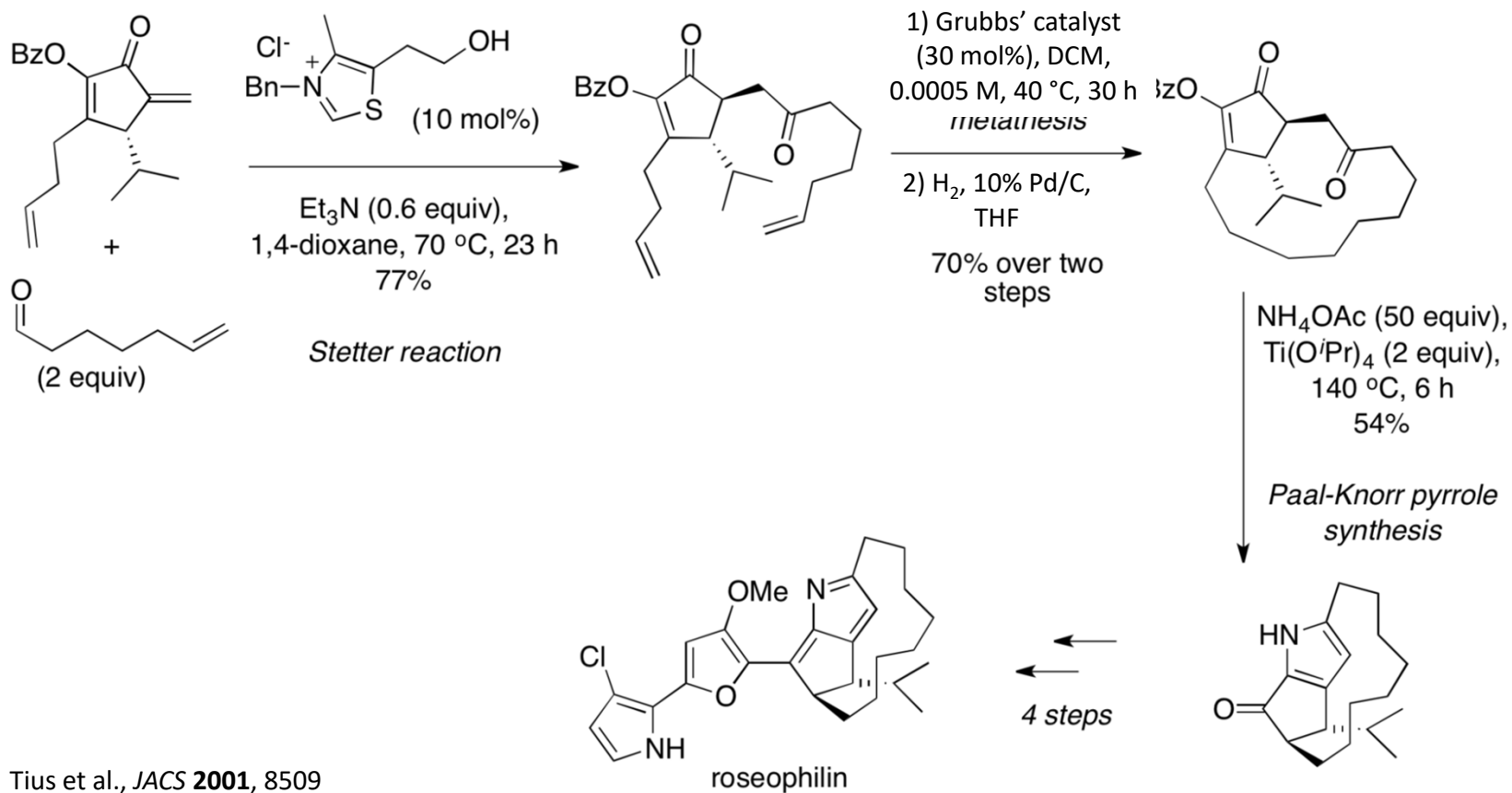
D. Fünfring-Aromaten - D.5 Thiazol

Anwendung: *Stetter-Reaktion* (1973, Organokatalyse)



D. Fünfring-Aromaten - D.5 Thiazol

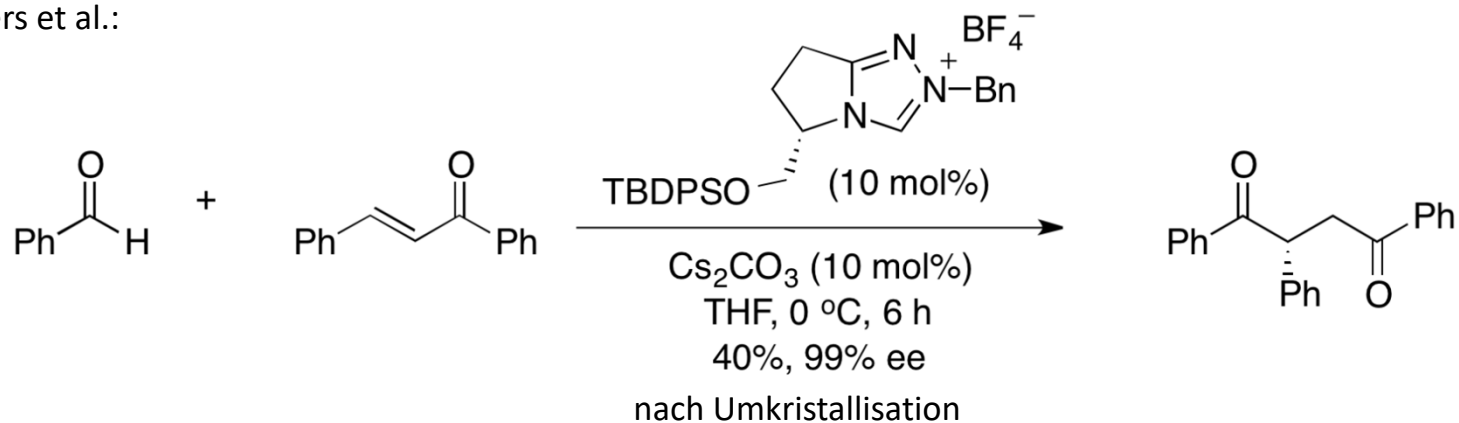
Stetter-Reaktion liefert Paal-Knorr-Vorstufen.



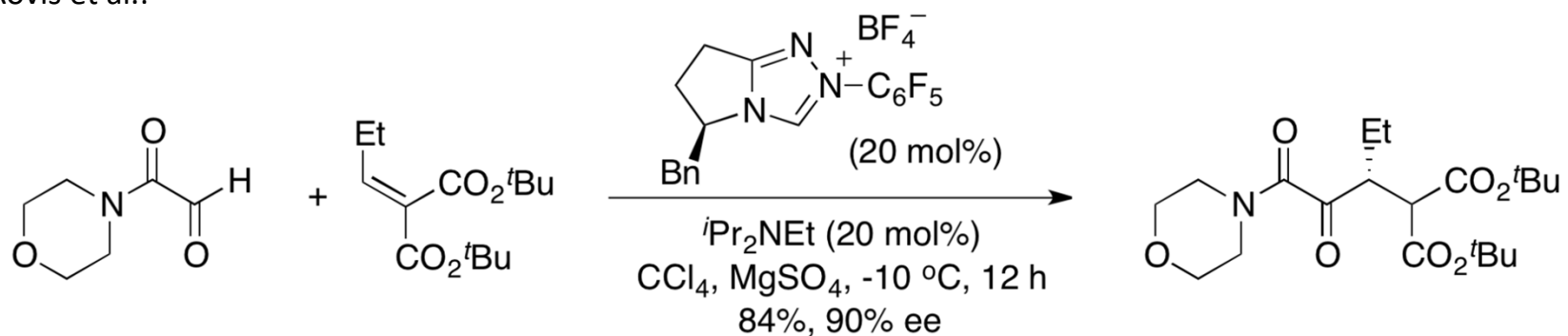
D. Fünfring-Aromaten - D.5 Thiazol

Asymmetrische *Stetter*-Reaktion durch chiralen Organokatalysator

Enders et al.:

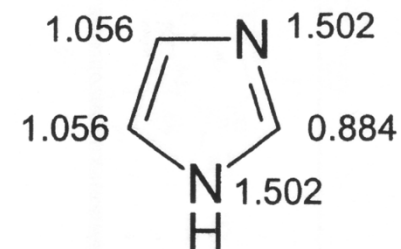
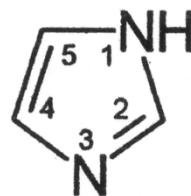
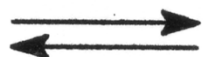
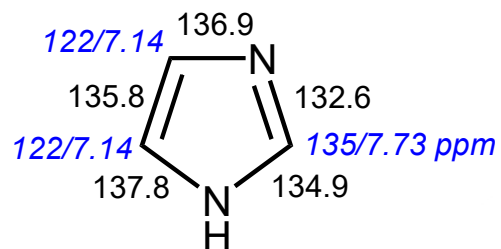


Rovis et al.:



D. Fünfring-Aromaten - D.6 Imidazol

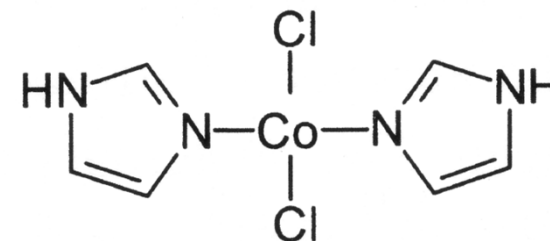
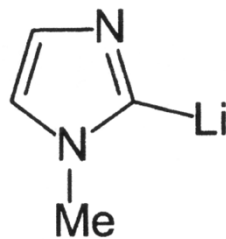
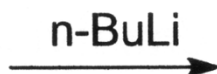
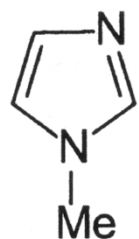
Reaktivität



Festsubstanz (m. p. 90 °C (intermol. H-Brücken), extrem stabil bis 500 °C)

Elektronendichte-Vert.

- pK_a (ImH₂⁺): 7.00, pK_a (ImH): 14.52 (N-Deprotonierung mit NaOEt).
- annulare Tautomerie(!): 4-Nitroimidazol, 5-Methoxyimidazol.



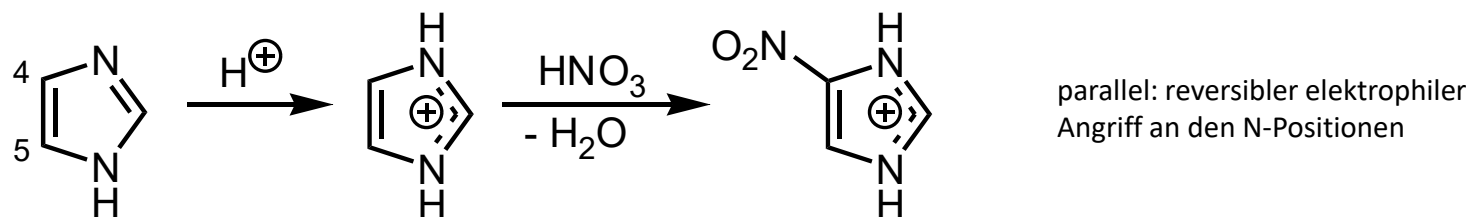
- Lithiierung an C2 (bei 1-subst. Imidazolen).
- Lithiierung an C5 (bei 1,2-disubst. Imidazolen).

- Metallkomplexe über "Pyridin-N" (z. B. Häm (Fe), Vit. B₁₂ (Co))

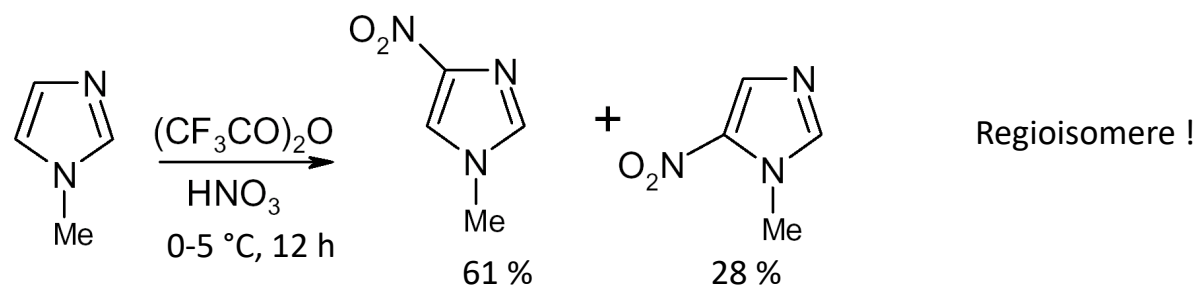
D. Fünfring-Aromaten - D.6 Imidazol

S_EAr : N-Elektrophile

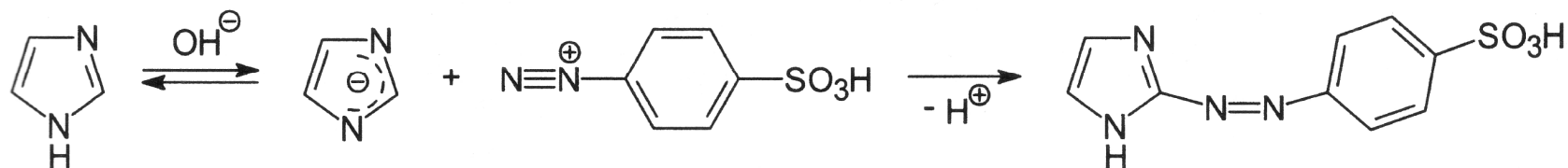
Nitrierung der 4- und 5-Position (**saure Bed.**, langsam, ebenso wie 4-Sulfonierung):



größte C-Elektronendichte beim Imidazolium-Ion ImH_2^+ in Pos. 4, 5.



aber: leichte Diazotierung der 2-Position (**schwach alkal. Bed.**):

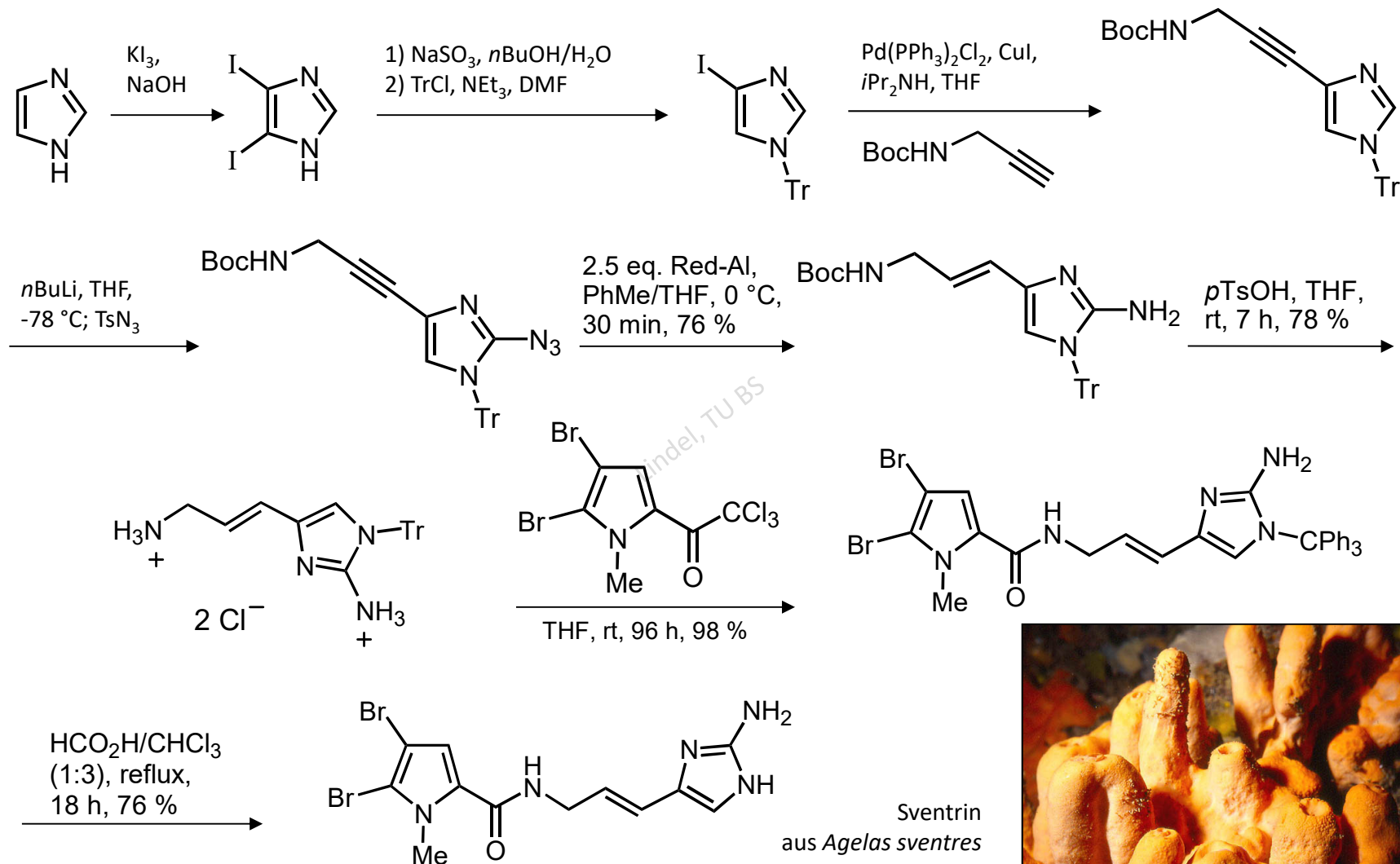


größte C-Elektronendichte in Pos. 2 des Imidazolats Im^- .

J. Chem. Soc., Perkin Trans. 2 **1989**, 2055.

D. Fünfring-Aromaten - D.6 Imidazol

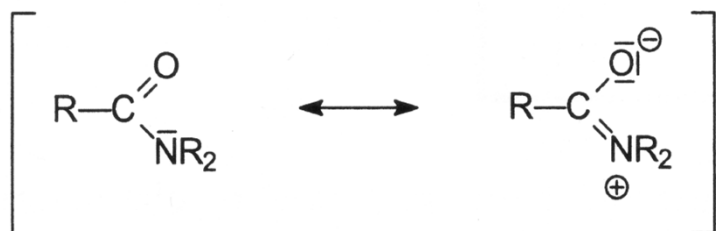
S_EAr : Halogenierung



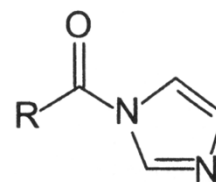
D. Fünfring-Aromaten - D.6 Imidazol

Imidazol-Reagenzien

a) Imidazol als Acylgruppen-Überträger



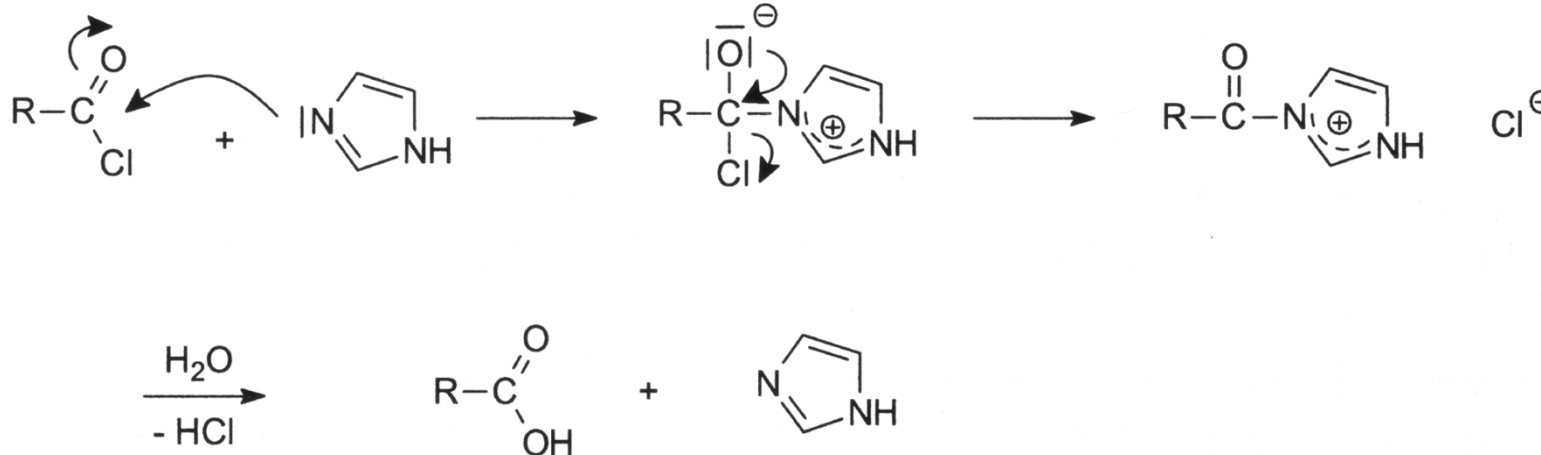
Mesomerie-Stabilisierung bei "normalen" Amiden



z. B. Carbonyldiimidazol
("Staabs Reagenz")

keine Mesomerie-Stabilisierung wg. 6 π -System!

Nukleophile Katalyse:



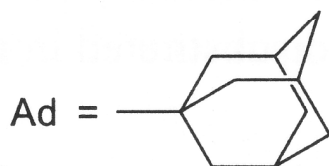
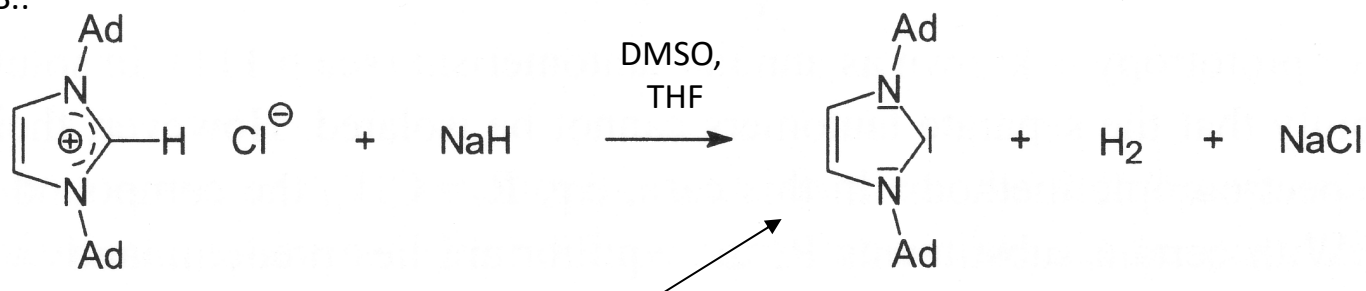
oder z. B. sterisch gehinderte Alkohole

D. Fünfring-Aromaten - D.6 Imidazol

b) Imidazol-Carbene

- 2-Deprotonierung von N,N'-Dialkyl-(bzw. -aryl)imidazolium-Ionen: stabile Carbene!

z. B.:

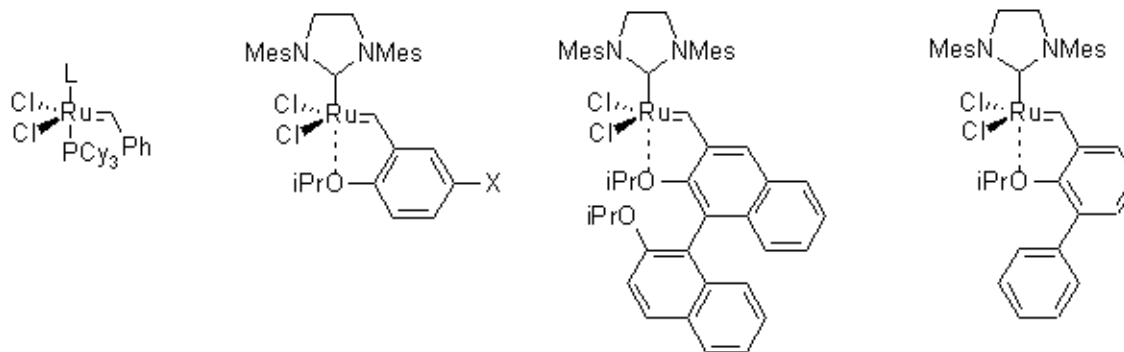


Singulett-Carben (formal leeres p_π-Orbital, doppelt bes. sp²-Orbital), stabilisiert durch Delokalisierung der zwei benachbarten p-Elektronenpaare.

A. J. Arduengo III et al., *JACS* **1991**, 361; *Acc. Chem. Res.* **1999**, 913.

"Grubbs-Katalysatoren"
zur Alken- und Enin-Metathese
(s. Vorl. "Metallorg. Chemie")
[Nobelpreis für Chemie 2005](#)

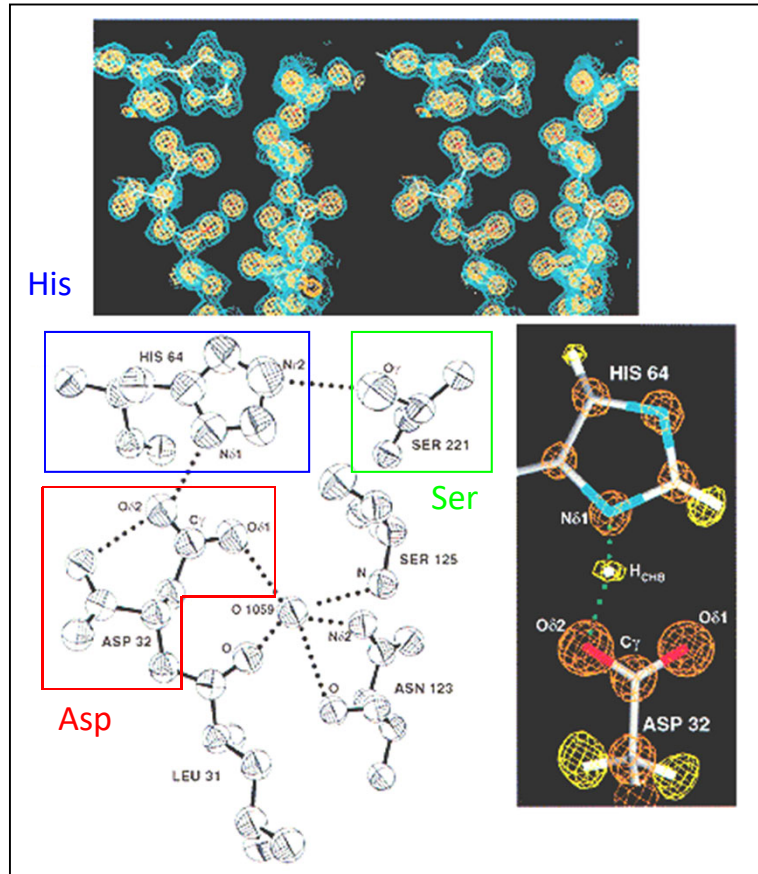
s. *Angew. Chem.* **2002**, 4210.



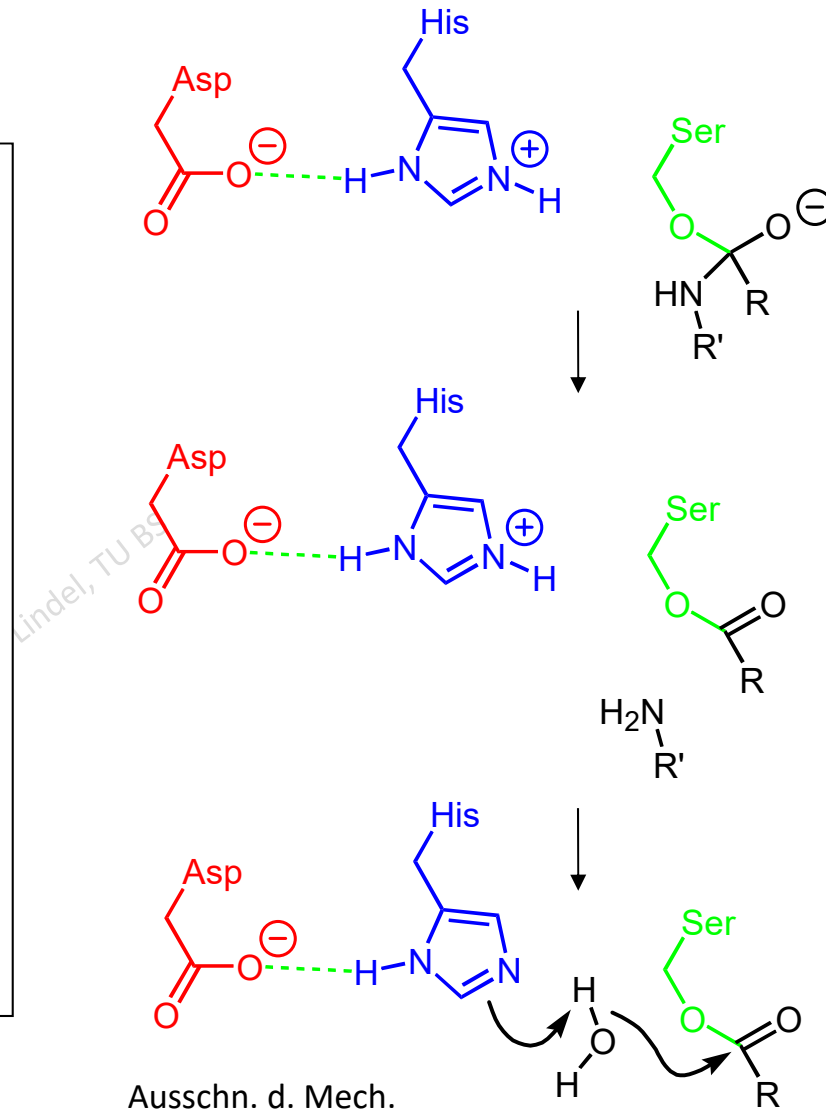
D. Fünfring-Aromaten - D.6 Imidazol

c) Imidazol in Enzymen

Serin-Proteasen: katalytische Triade



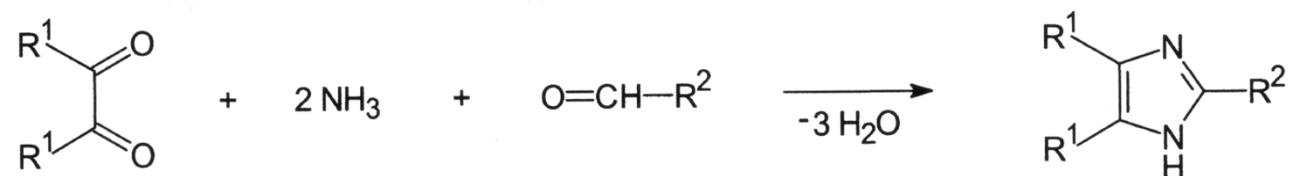
Subtilisin, 78 pm Auflösung,
Bott et al., *Biochemistry* **1998**, 13446.



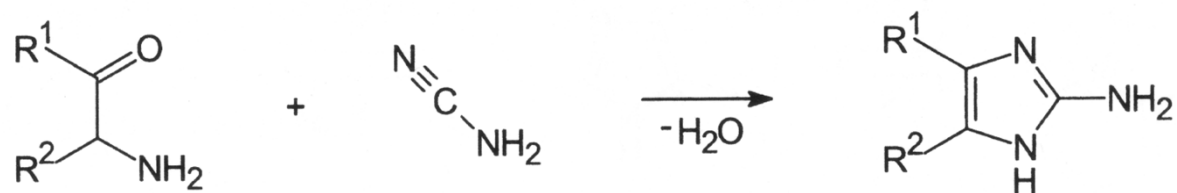
D. Fünfring-Aromaten - D.6 Imidazol

Synthesen

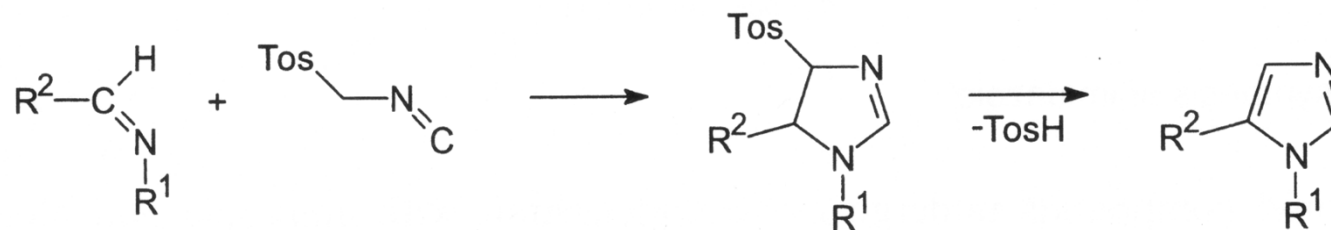
a) "Ur-Variante", Synthese unsubst. Imidazols ("Glyoxalin") ausgehend v. Glyoxal:



b) Marckwald-Synthese v. 2-Aminoimidazolen



c) van-Leusen-Synthese



E. Sechsring-Aromaten

Übersicht Kap. E

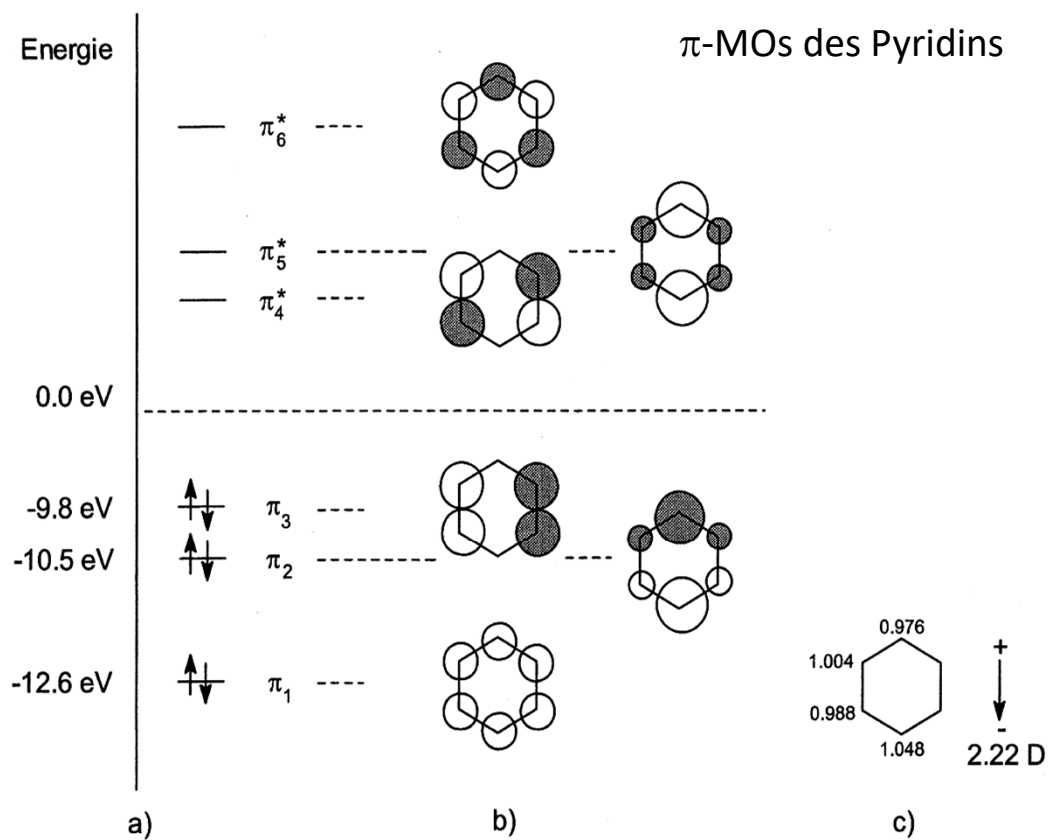
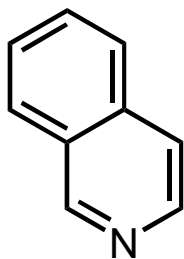
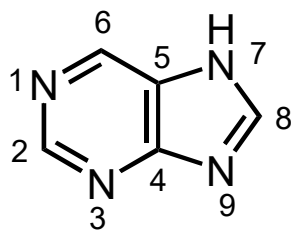
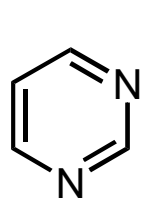
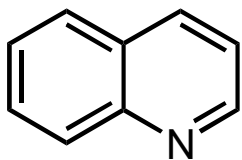
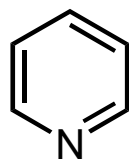
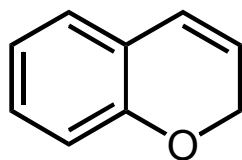
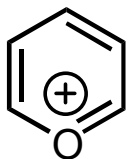
E.1 Pyrylium und Chromen

E.2 Pyridin

E.3 Chinolin

E.4 Isochinolin

E.5 Purin und Pyrimidin



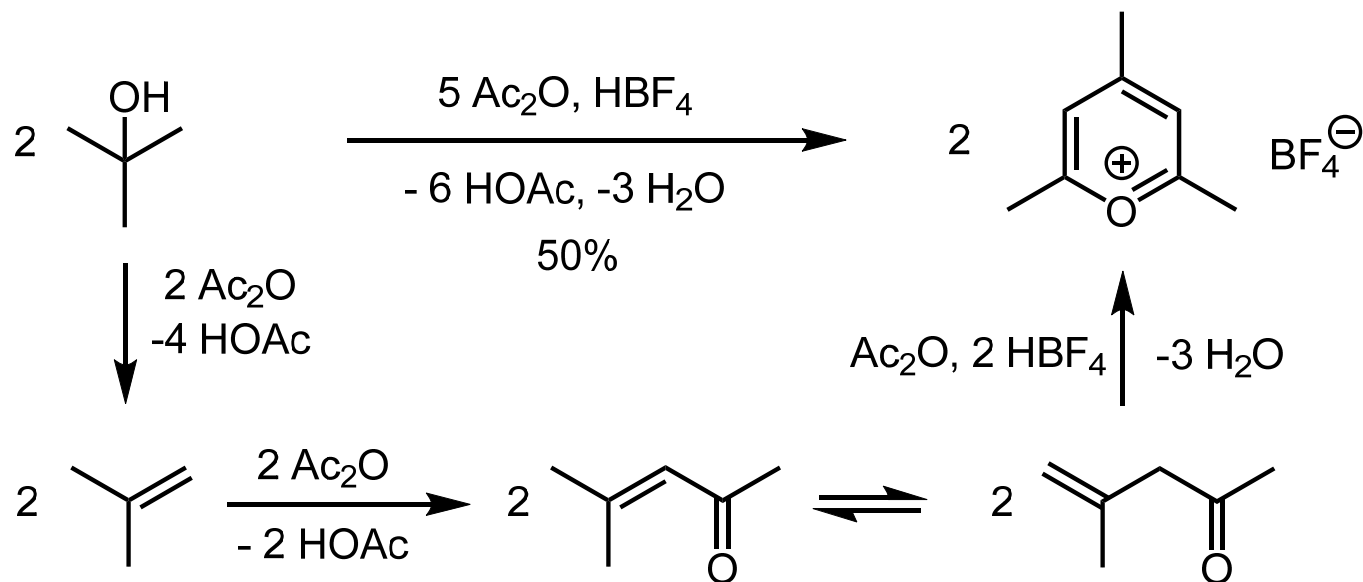
Electronic structure of pyridine

(a) energy level scheme of the π -MOs and electronic occupation

(b) π -MO (the N-atom occupies the lowest corner of the hexagon)

(c) π -electron densities calculated by *ab initio* MO methods [46] and dipole moment

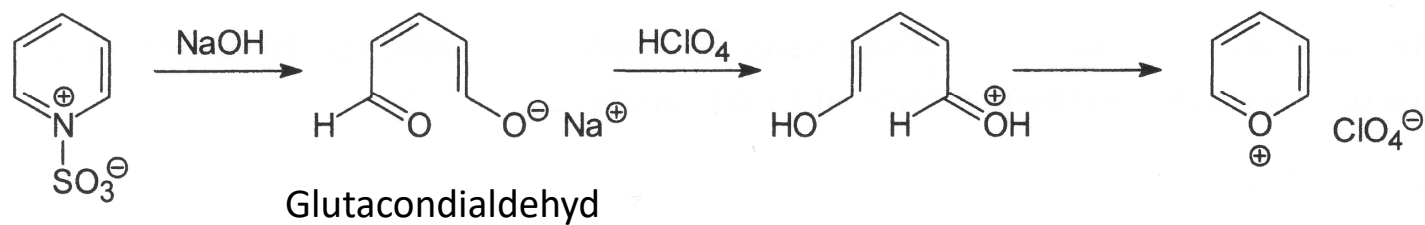
Synthese von 2,4,6-Trimethylpyryliumsalzen



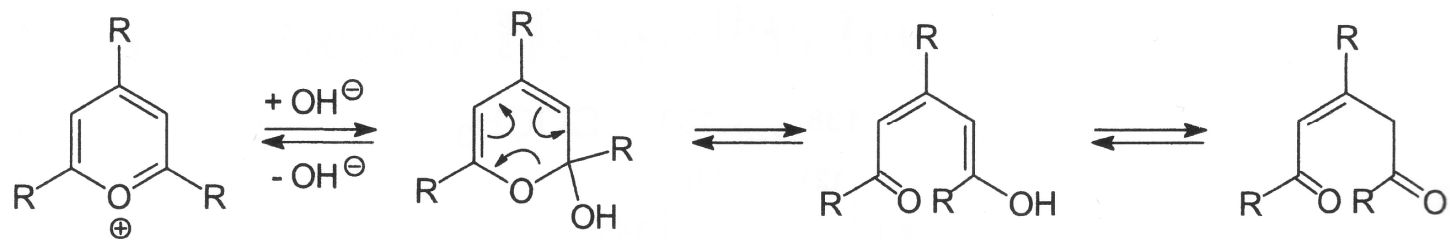
oder: Triflat

Perchlorate (früher verwendet) generell: Explosionsgefahr

Von Pyridinium zu Pyrylium:

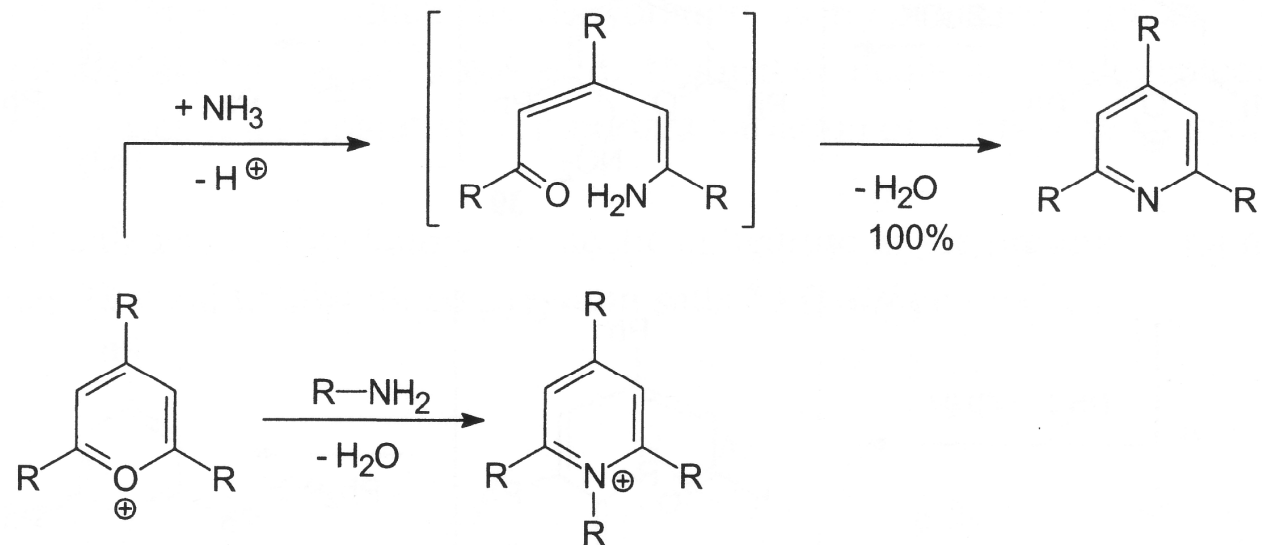


Reversible Hydrolyse:

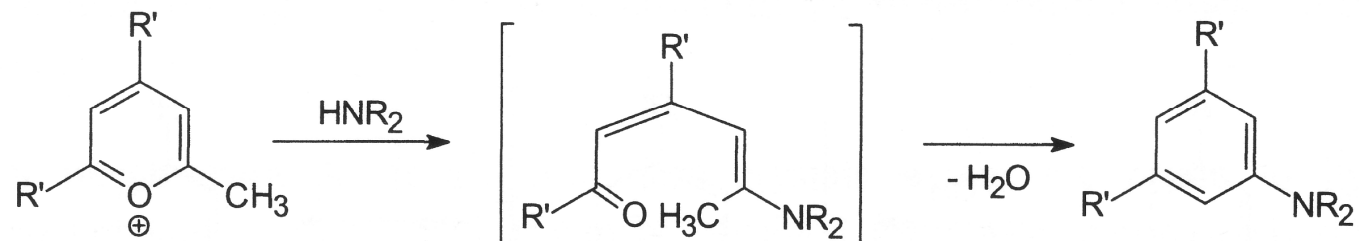


E. Sechsring-Aromaten - E.1 Pirylium und Chromen

Von Pirylium zu Pyridin: mit Ammoniak oder *primären* Aminen

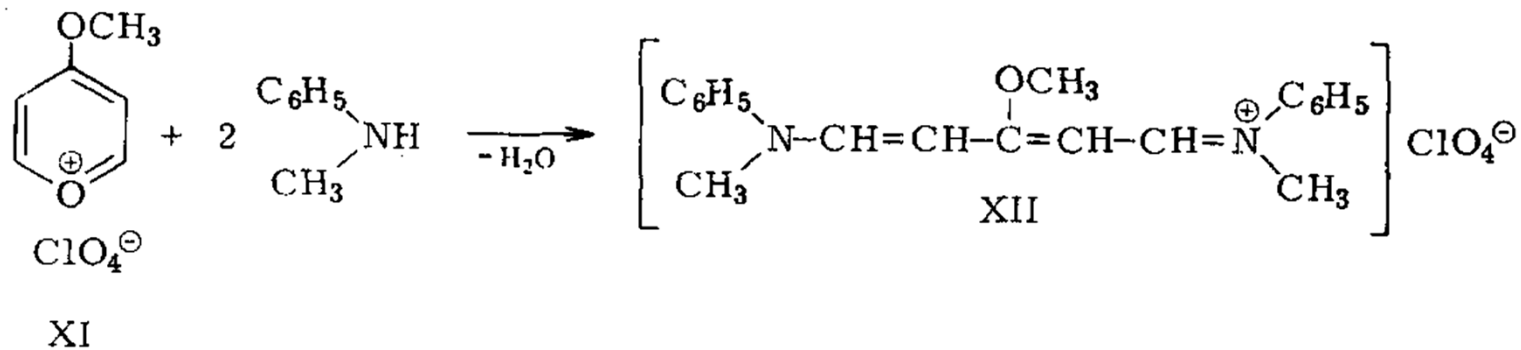


Von Pirylium zu Anilinen: mit *sekundären* Aminen

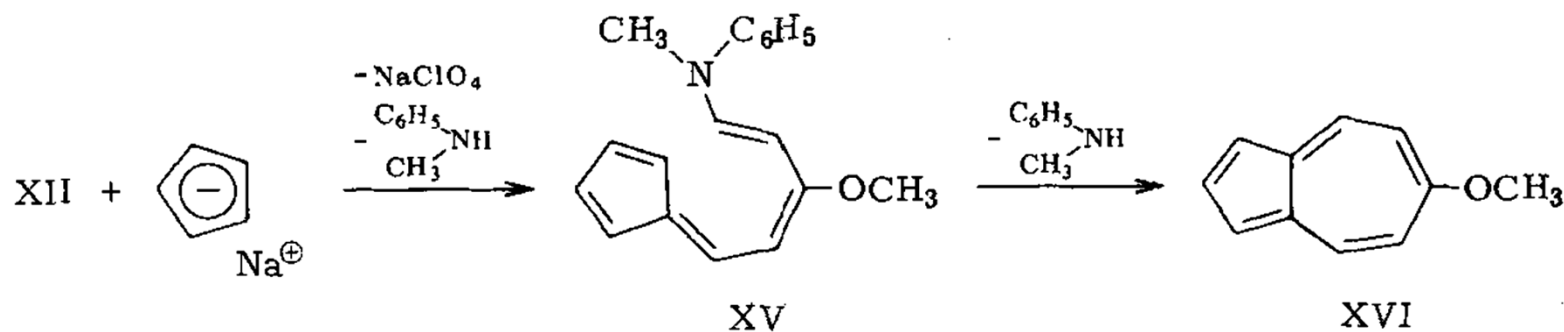


E. Sechsring-Aromaten - E.1 Pirylium und Chromen

Von Pirylium zu Azulen:



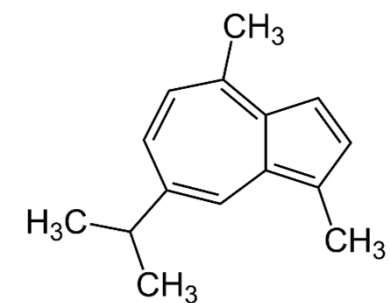
Klaus Hafner (1927-2021)



Variante der Ziegler-Hafner-Synthese, ausgehend von Pyridin, 2,4-Dinitrochlorbenzol und Dimethylamin (1955)

Hafner, Asmus, *Justus Liebigs Ann. Chem.* **1964**, 671

Guiaiazulen aus *Entoloma hochstetteri*

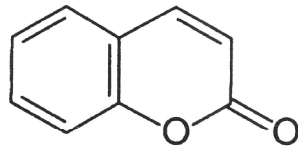
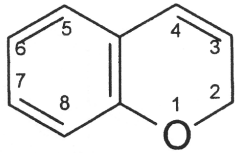


10 π

intramolekularer
charge transfer

E. Sechsring-Aromaten - E.1 Pyrylium und Chromen

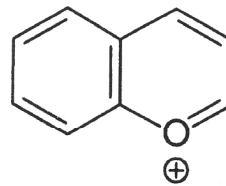
Chromen



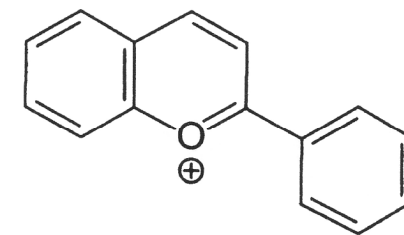
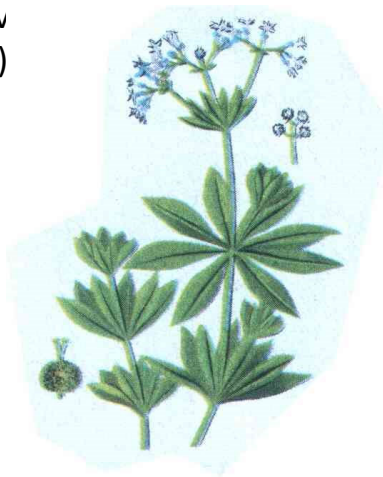
Cumarin (engl. Coumarin),
Lacton der (Z)-2-Hydroxyzimtsäure,
Riechstoff des Waldmeisters,
gerinnungshemmend (Verhinderung der Bildung v
Prothrombin u. a. Gerinnungsfaktoren, Rattengift)



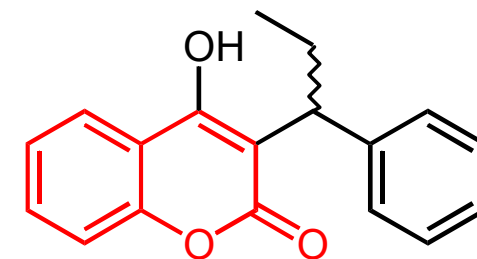
Galium odoratum (L.) (= *Asperula odorata*)



Benzo[*b*]pyrylium
(Chromenylium)



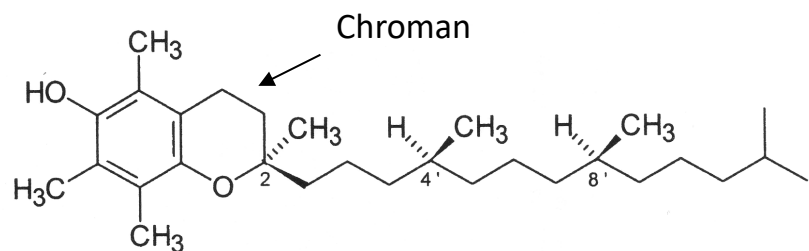
Flavylum



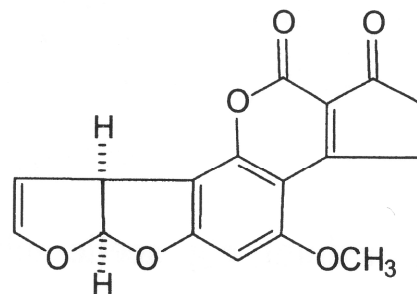
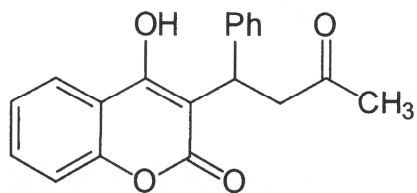
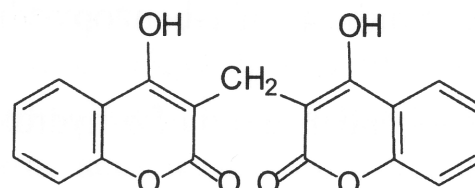
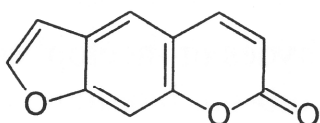
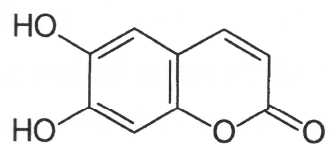
Phenprocoumon ("Marcumar"),
nach Herzinfarkten, Vitamin K-Antagonist

E. Sechsring-Aromaten - E.1 Pyrylium und Chromen

Naturstoffe mit Cumarin-Teilstruktur

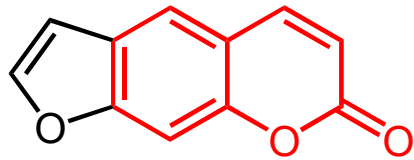


Vitamin E (Radikalfänger)

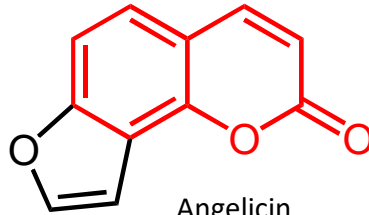


Cancerogenes Mycotoxin
Aflatoxin B₁ aus *Aspergillus flavus*
("Fluch der Pharaonen",
Schimmelpilz b. Nüssen, Mais, Mehl)

E. Sechsring-Aromaten - E.1 Porylium und Chromen

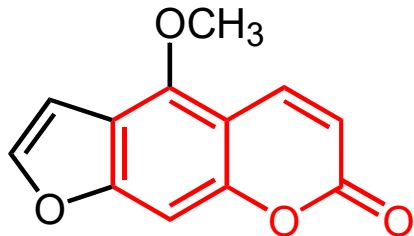


Psoralen

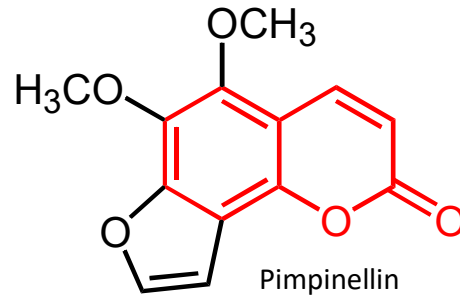


Angelicin

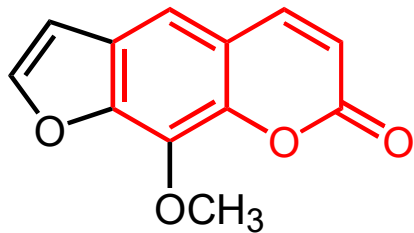
Im UV-Licht Anregung in $Ps(S_1)$, von dort entweder [2+2]Cycloaddukt an DNA, oder ISC zu $Ps(T_1)$ und von dort aus Bildung von Singulett-Sauerstoff oder des Radikalanions.
Verwendung v. Psoralen z. B. zur Photochemotherapie gegen Psoriasis.



Bergapten



Pimpinellin



Xanthotoxin



Riesenbärenklau (*Heracleum mantegazzianum*, > 3 m)

giftig durch: Bergapten, Xanthotoxin, Pimpinellin
Dermatitis nach Bestrahlung benetzter Haut mit Sonnenlicht

Mech. der Phototoxizität: s. Eriksson et al., *J. Photochem. Photobiol.* **2003**, 154. 235.

Wechselwirkung von Psoralen mit DNA:
Photo-[2+2]-Cycloaddition

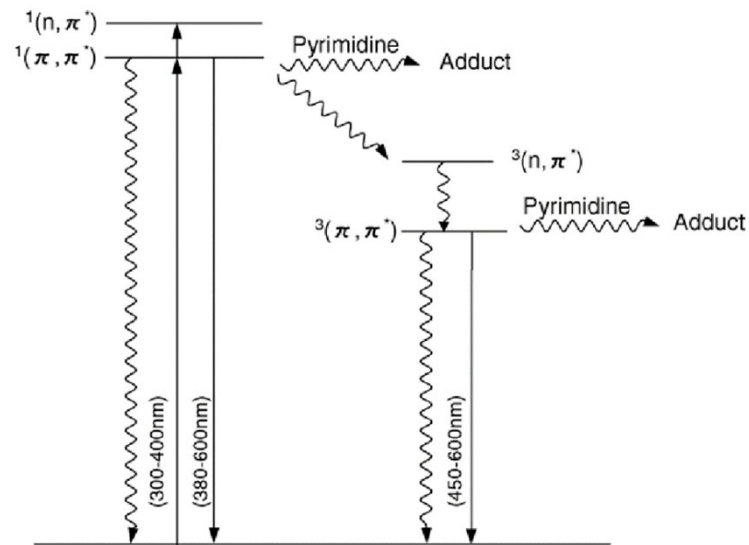
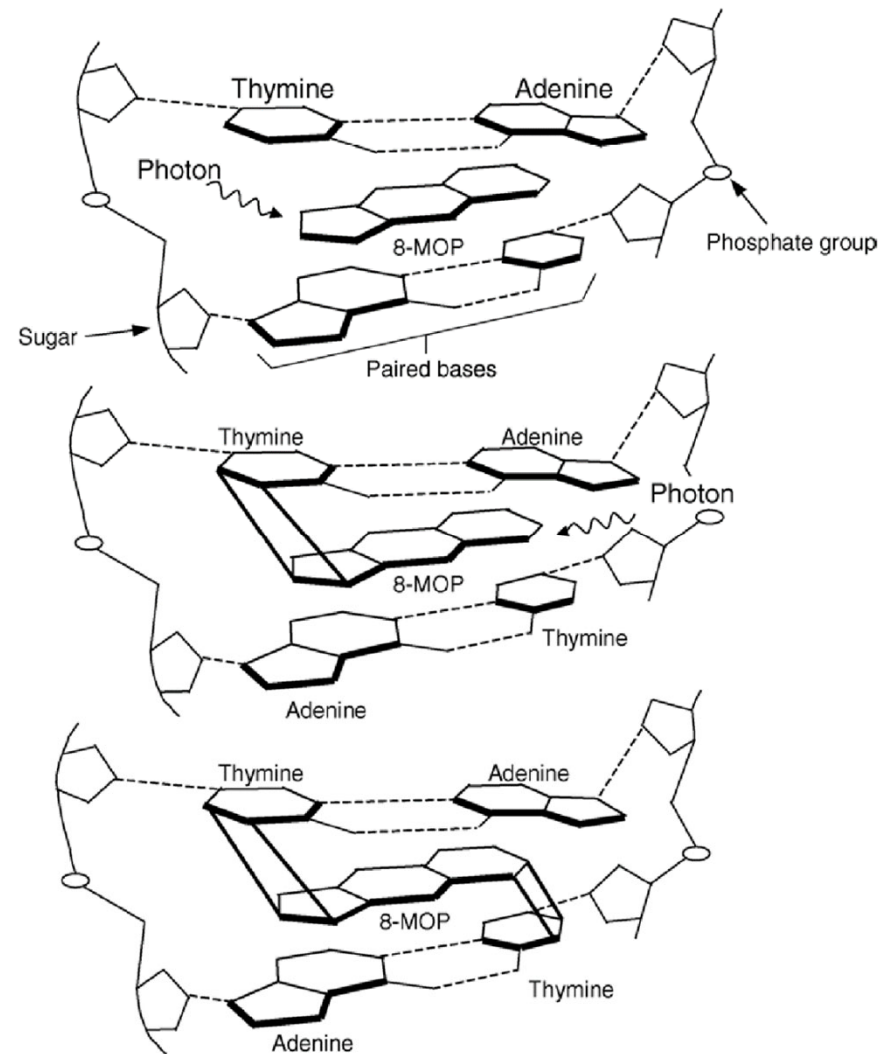


Fig. 3. Schematic representation of the energy levels of psoralen in the excited state.

aus:

N. Kitamura et al., *J. Photochem. Photobiol. C* **2005**, 169, 168.



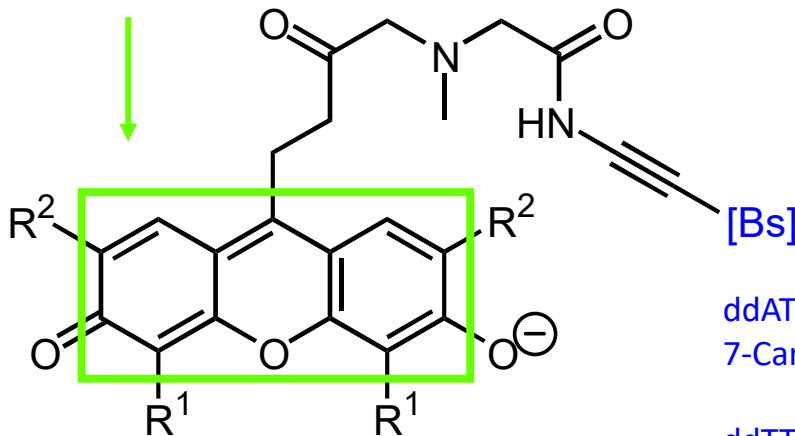
E. Sechsring-Aromaten - E.1 Pyrylium und Chromen

z. B. Farbstoffe in der Biochemie

Didesoxynucleotid-Methode

parallele DNA-Sequenzierung:
Farbstoff-codierte ddNTPe !

Xanthen-Gerüst



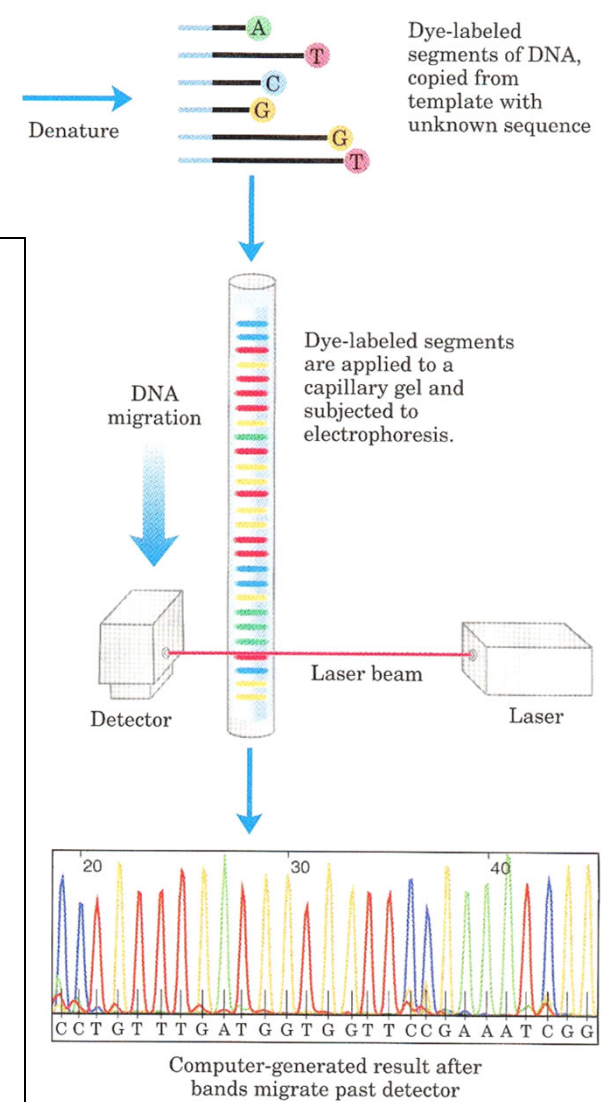
unbekannte DNA,
(5'->3')-Primer,
DNA-Polymerase,
4 dNTPe, 4 ddNTPe

ddATP, ddGTP:
7-Carbapurin-7-Pos.

ddTTP, ddCTP:
Pyrimidin-5-Pos.

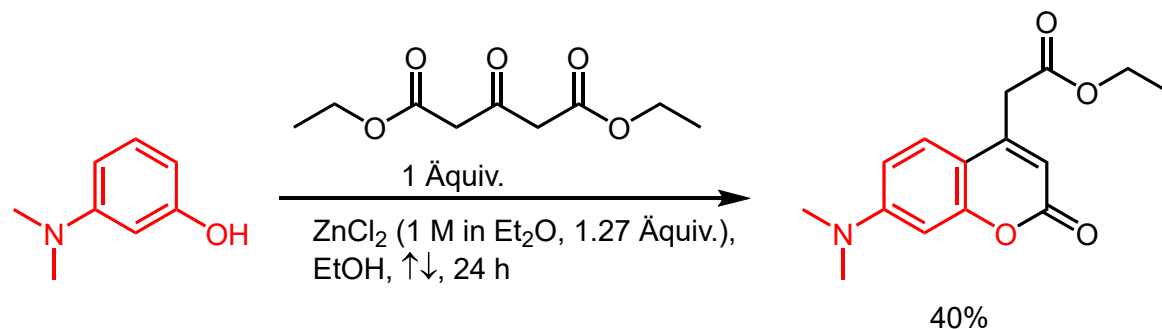
	R ¹	R ²
A-512	H	CH ₃
G-505	H	H
T-526	CH ₃	CH ₃
C-519	CH ₃	H

λ_{\max} {

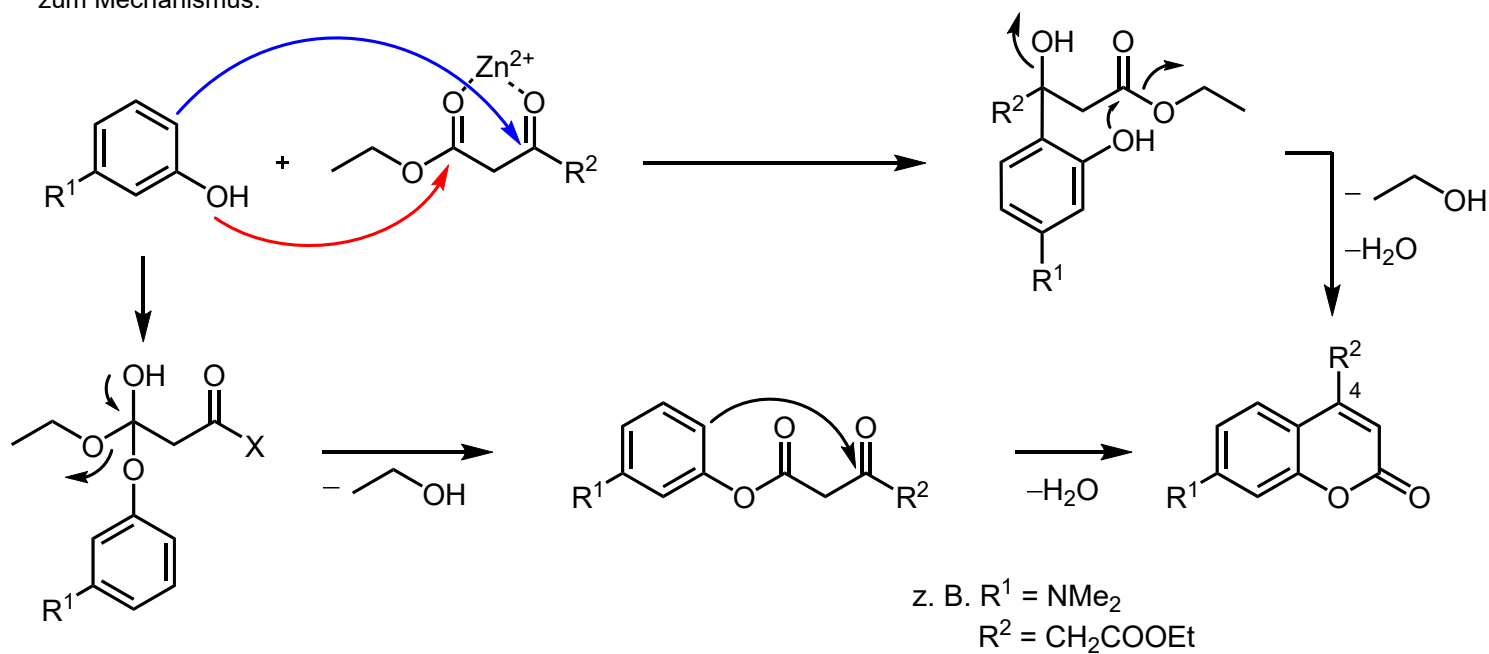


E. Sechsring-Aromaten - E.1 Pyrylium und Chromen

Pechmann-Synthese von Cumarinen:

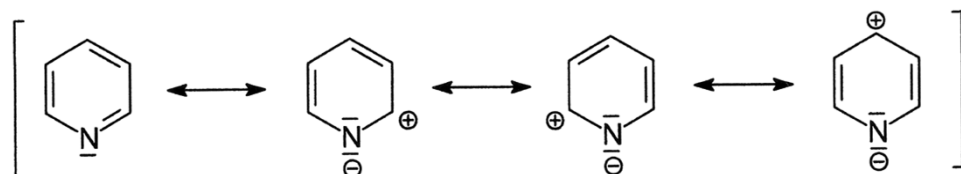


zum Mechanismus:



E. Sechsring-Aromaten - E.2 Pyridin

Reaktivität

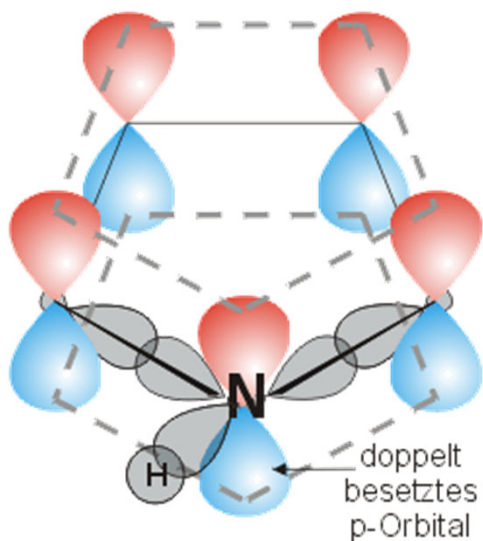


Bindungslängenausgleich 86 %

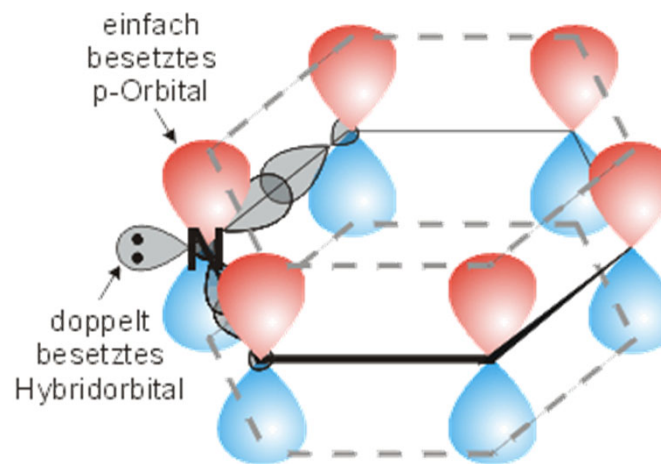
Resonanzstab.-energie 137 kJ/mol
(Benzol: 150 kJ/mol).

höchste Elektronendichte am N,
gefolgt von C-3/5.

S_EAr bevorzugt an C-3/5 (schwierig),
 S_NAr bevorzugt an C-2/6.



"elektronenreicher" 6π -Aromat Pyrrol

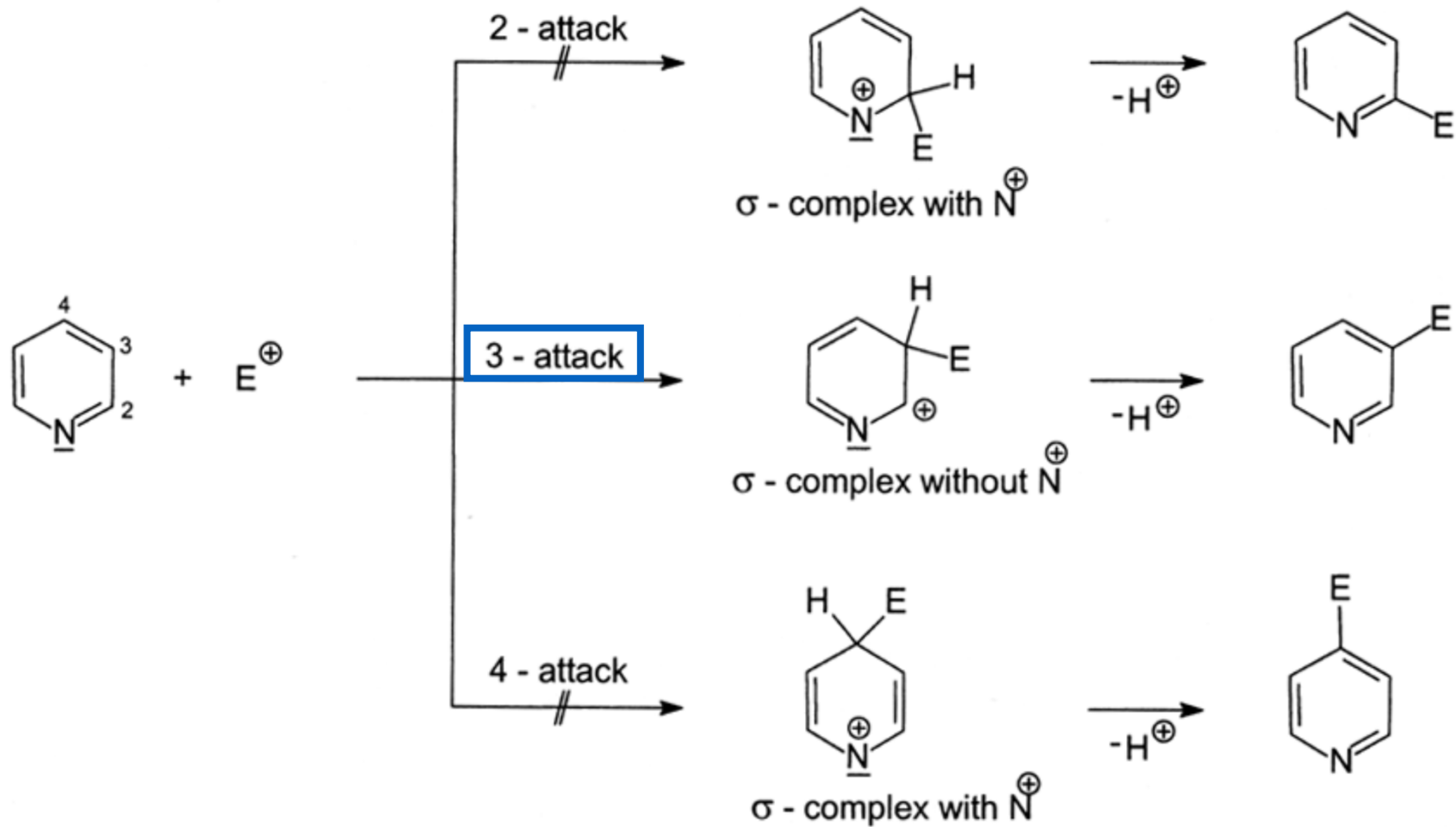


"elektronenarmer" 6π -Aromat Pyridin

E. Sechsring-Aromaten - E.2 Pyridin

S_EAr schwierig;

regioselektiv i. d. 3/5-Position; nur dann weist keine mesomere Grenzformel des kationischen σ -Komplexes eine Nitrenium-Teilstruktur auf.

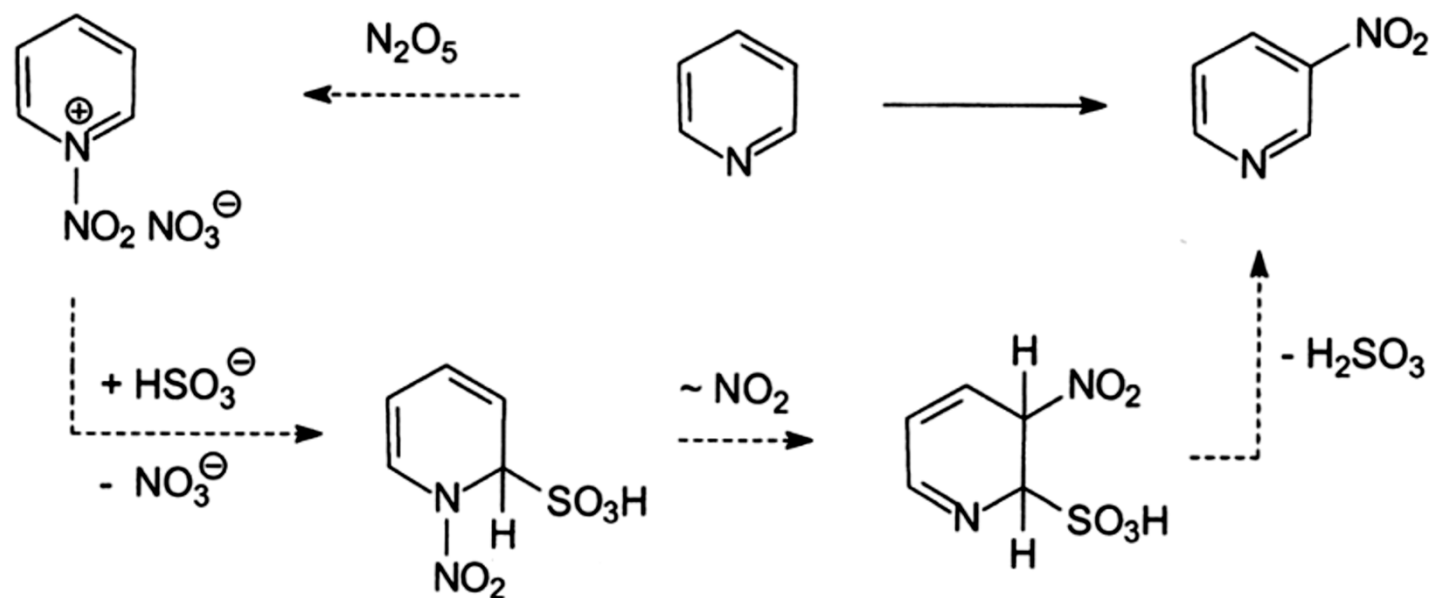


Drastische Bedingungen (S_{EAr}):

Nitrierung in HNO_3/H_2SO_4 bei $300\text{ }^\circ\text{C}$ mit 15 % Ausb. an 3-Nitropyridin; 70 % mit N_2O_5 in SO_2 .

3-Sulfonierung in Oleum/kat. $Hg(II)$ bei $250\text{ }^\circ\text{C}$ (70 %).

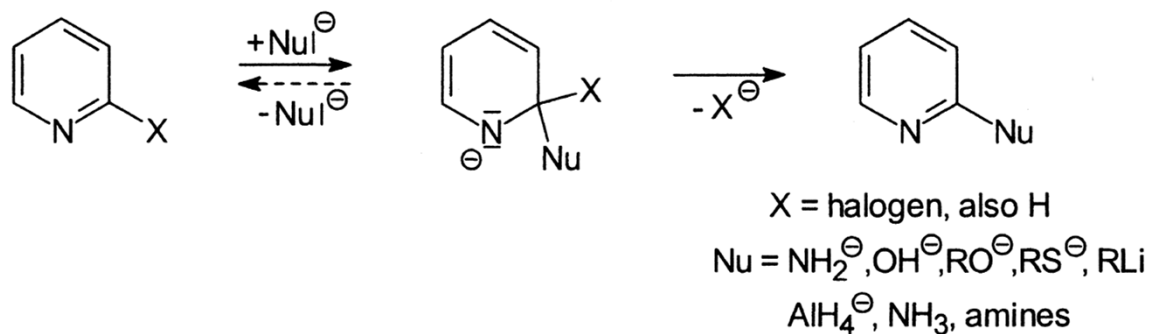
3- Halogenierung mit Cl_2 oder Br_2 ab $200\text{ }^\circ\text{C}$.



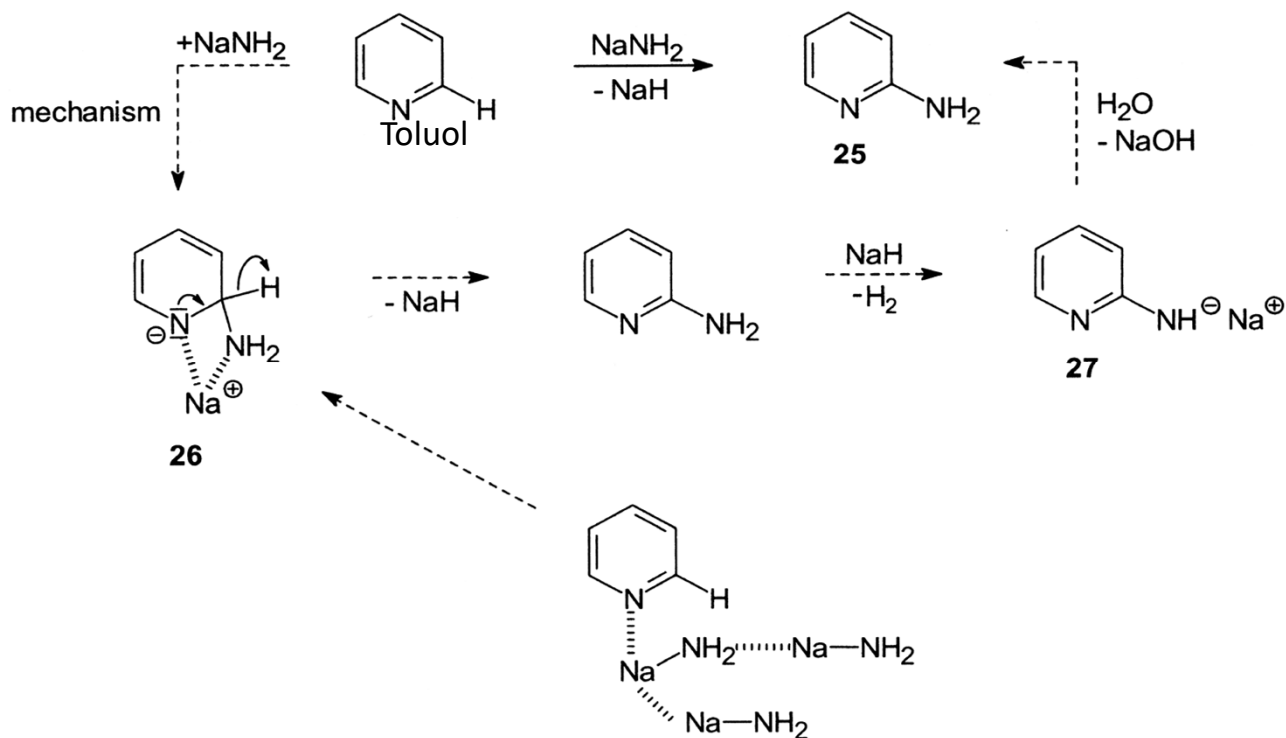
E. Sechsring-Aromaten - E.2 Pyridin

S_NAr : bevorzugt i. d. 2/4-Position.

Additions/Eliminierungs-Mech.
bei unsubst. Pyridinen:



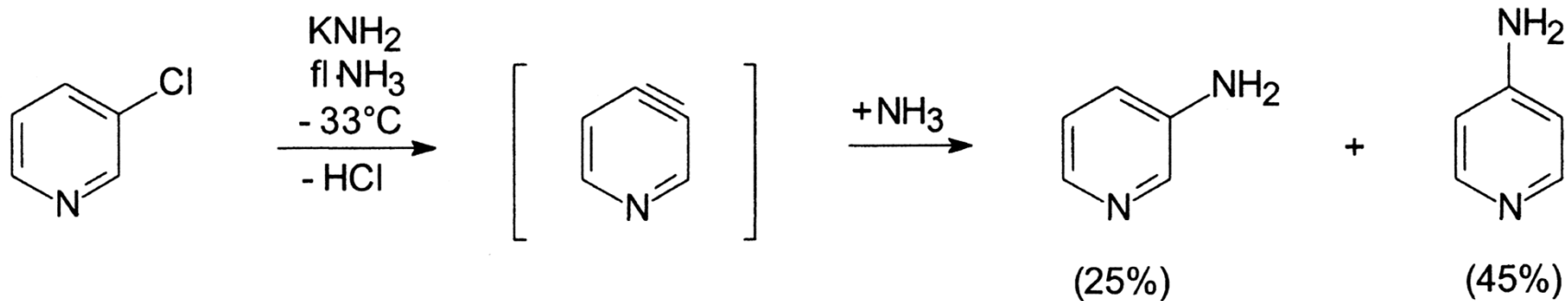
Tschitschibabin-Reaktion



E. Sechsring-Aromaten - E.2 Pyridin

S_NAr : bevorzugt i. d. 2/4-Position.

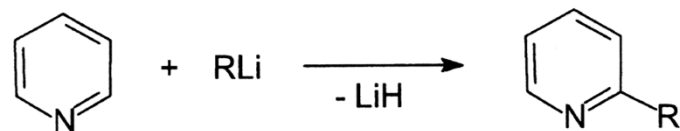
Eliminierungs/Additions-Mech. bei 3-Chlorpyridinen:



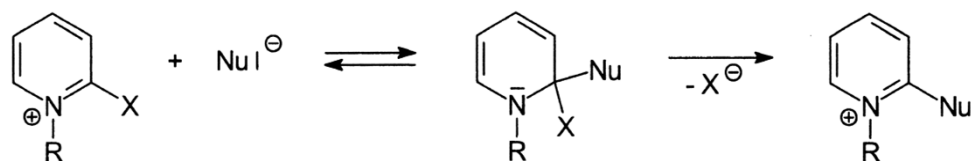
E. Sechsring-Aromaten - E.2 Pyridin

Ziegler-Reaktion

RMgX führt zu Gemisch aus 2- und 4-Produkt.

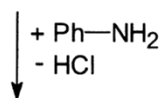
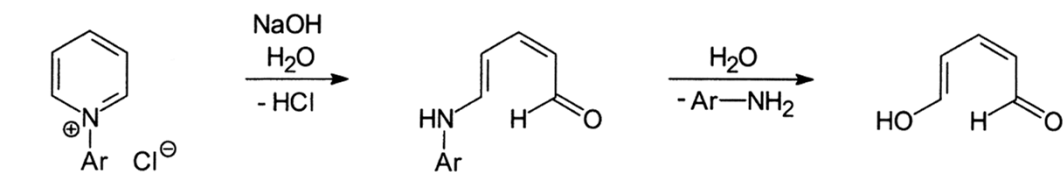


S_NAr ca. 10^6 -fach schneller bei **Pyridinium-Salzen**:

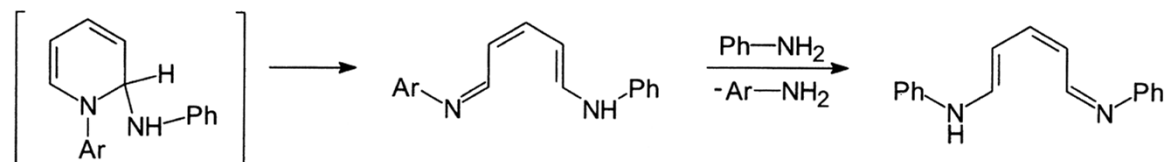


z. B.:
Reduktion von *N*-Alkylpyridiniumsalzen zu *N*-Alkyldihydro- und tetrahydropyridinen mit NaBH_4 .

Hydrolyse von Pyridinium-Ionen:



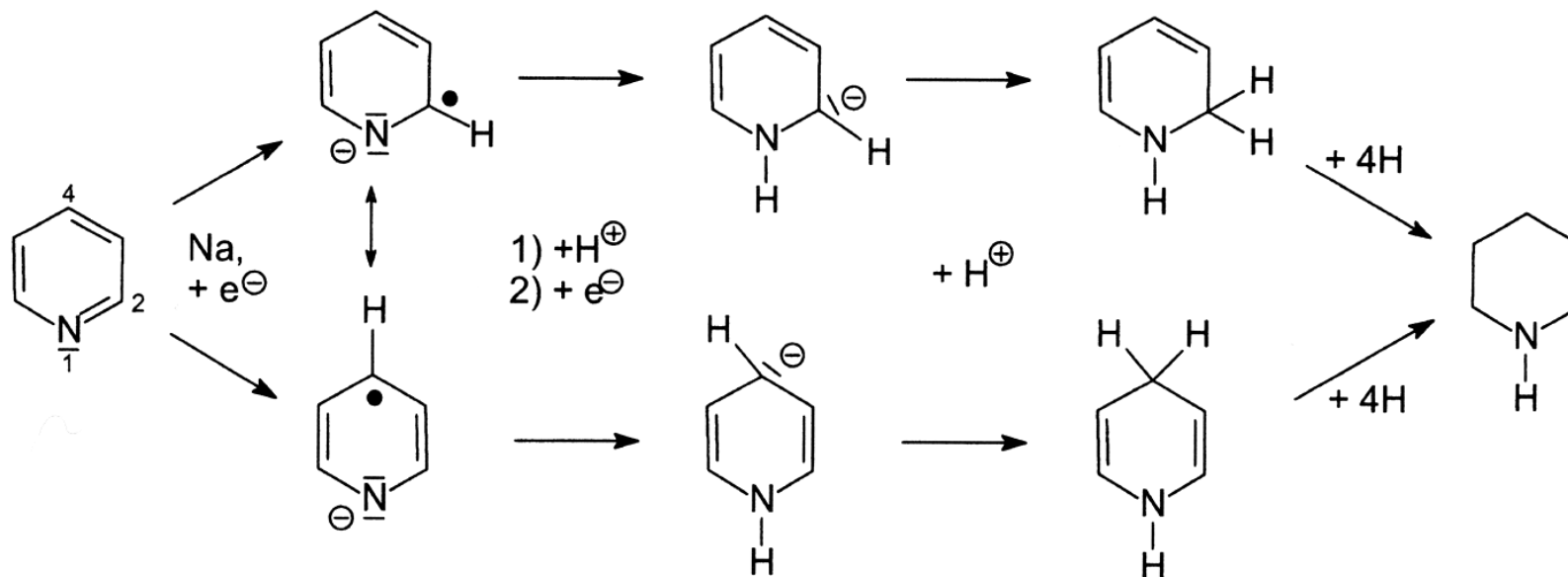
Ar = 2,4-dinitrophenyl



E. Sechsring-Aromaten - E.2 Pyridin

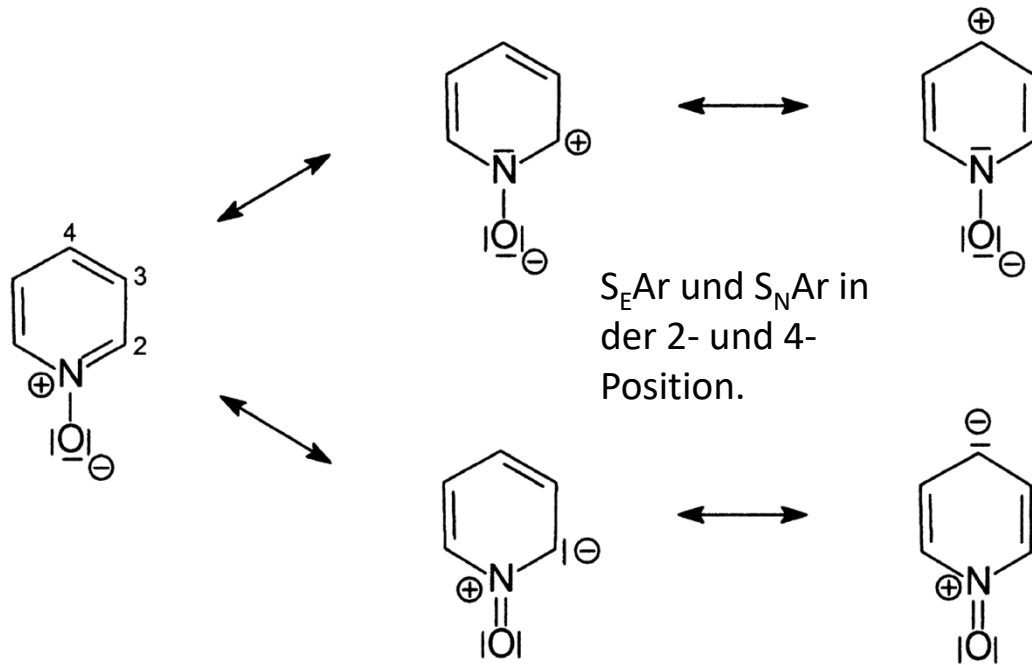
Birch-Reduktion von Pyridin mit Na in protischem Medium:

Einzel-Elektronen-Transfer über das Radikal-Anion, gefolgt von 1,2- oder 1,4-Addition eines Protons und folgend eines Elektrons.



E. Sechsring-Aromaten - E.2 Pyridin

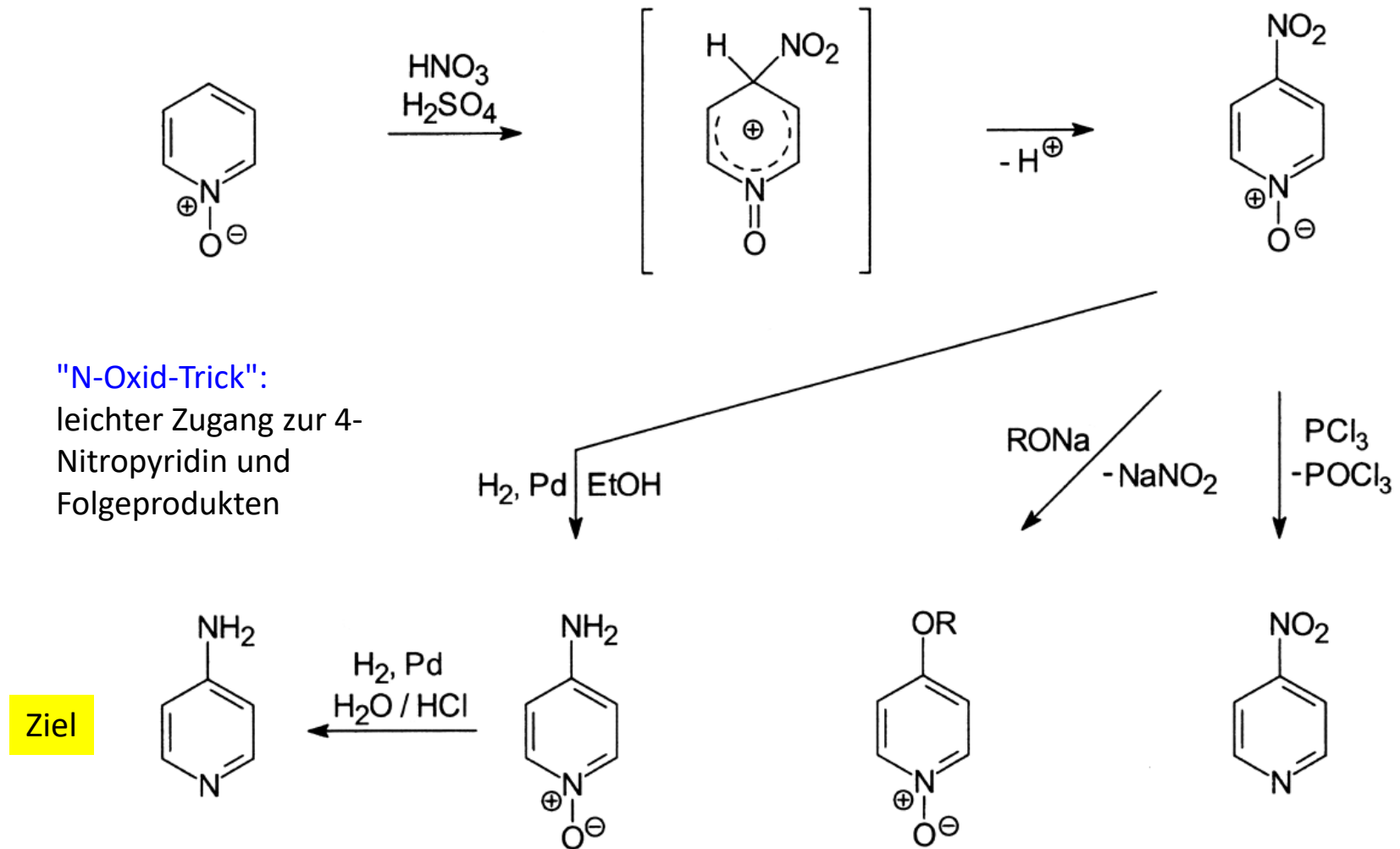
Pyridin-N-Oxid: andere Reaktivität



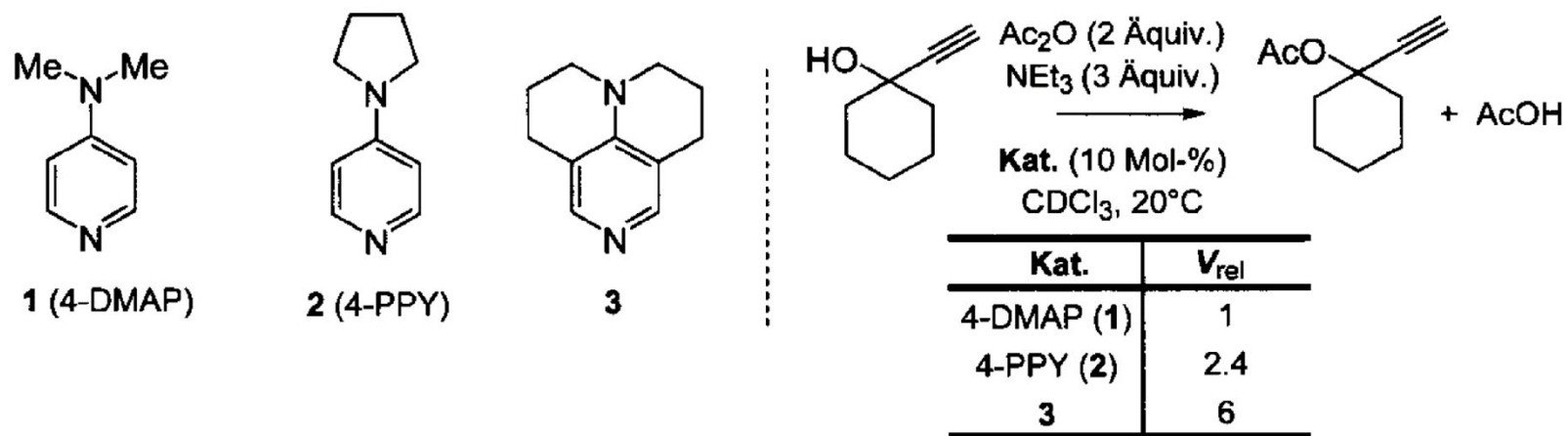
Zugang durch Oxidation von Pyridin mit Persäuren, Deoxygenierung mit Phosphanen.

E. Sechsring-Aromaten - E.2 Pyridin

Pyridin-N-Oxid: andere Reaktivität

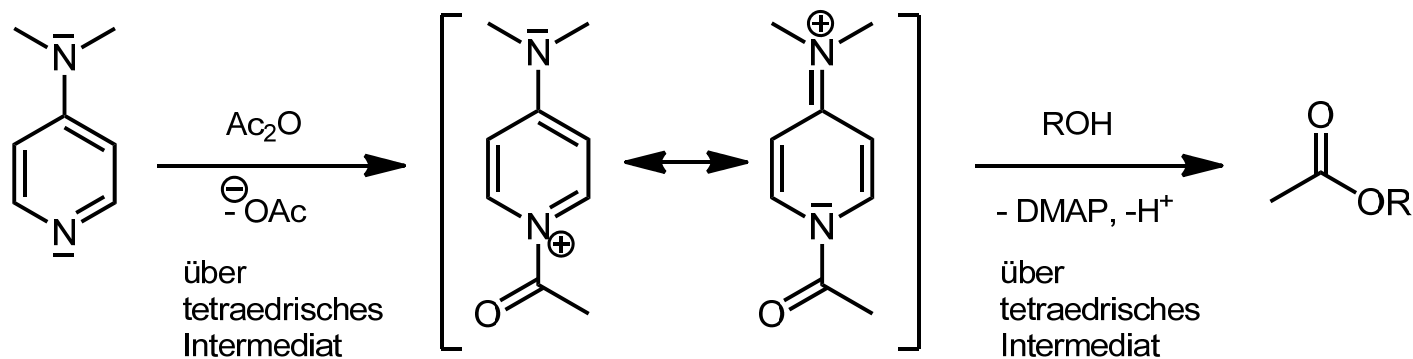


Nukleophiler Katalysator 4-Dimethylaminopyridin (*Steglichs* Reagenz)



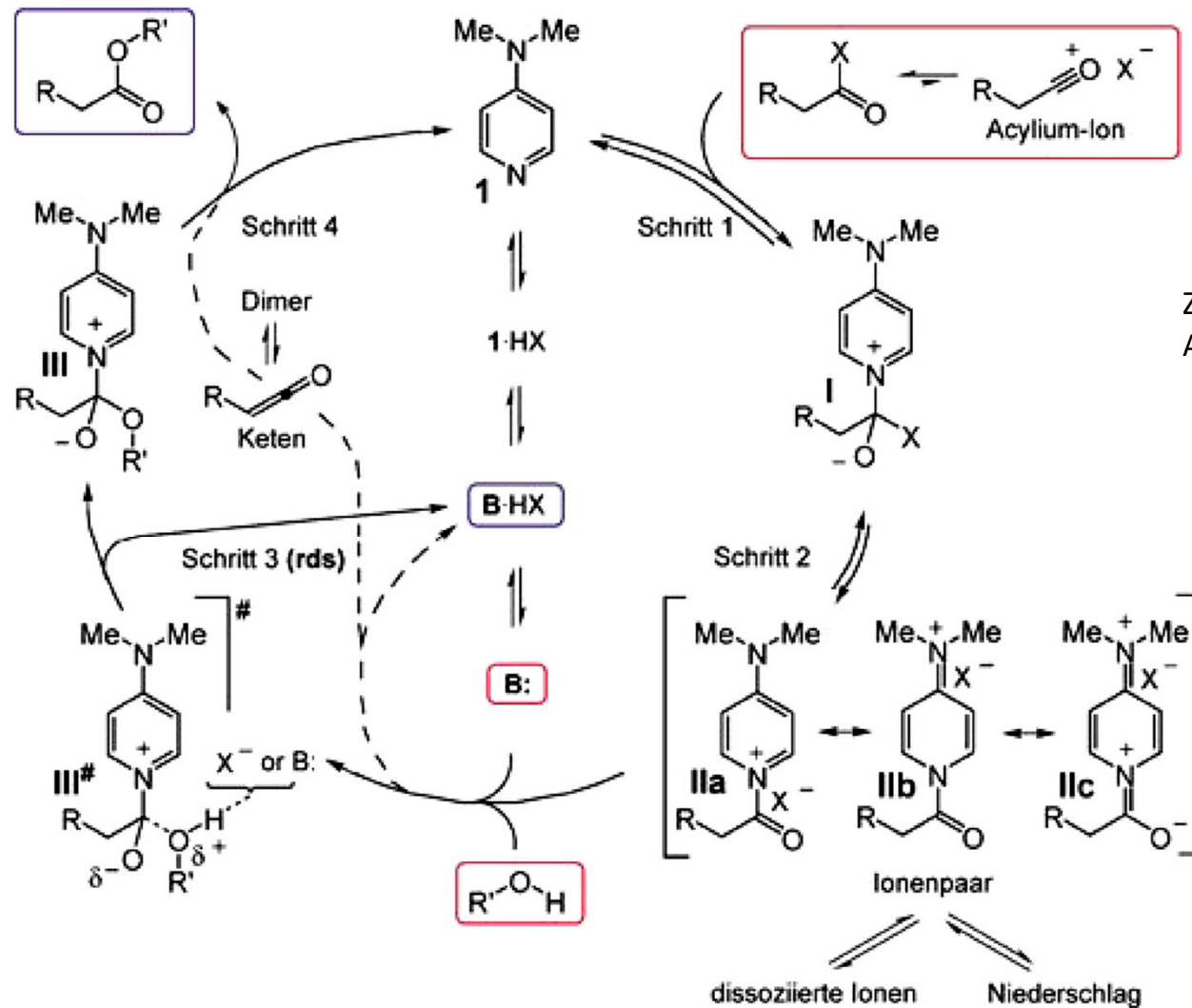
DMAP: W. Steglich, G. Höfle, *Angew. Chem.* **1969**, 1001.

Verbindung **3**: M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich, H. Zipse, *Angew. Chem.* **2003**, 4975.



Formulieren Sie dies als Katalysezyklus!

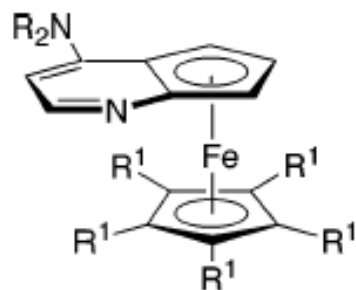
E. Sechsring-Aromaten - E.2 Pyridin



Zyklus der DMAP-katalysierten Alkohol-Veresterung

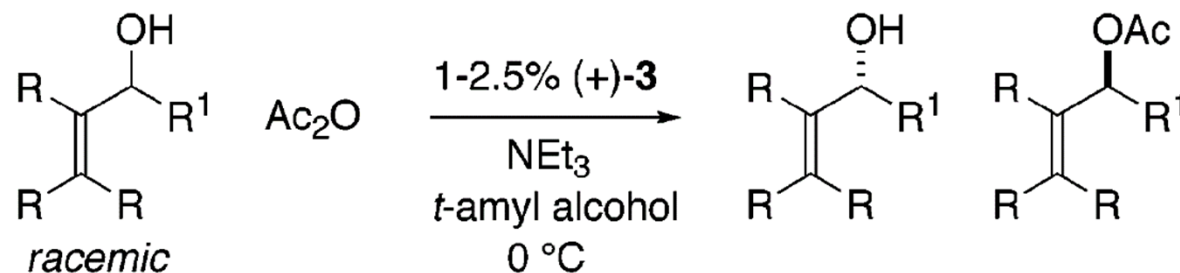
aus:
Angew. Chem. **2004**, 5552.

Nukleophiler Katalysator 4-Dimethylaminopyridin (chirale Version)



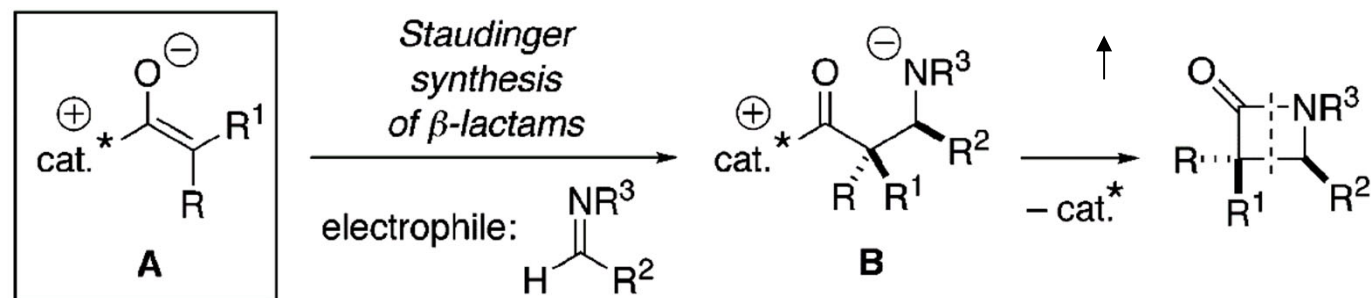
NR₂ = dimethylamino R¹ = Me (-)-1
 pyrrolidino Me (-)-2
 dimethylamino Ph (-)-3
 pyrrolidino Ph (-)-4

planar-chiral



z. B. 29
 99% ee @ 59% conv.

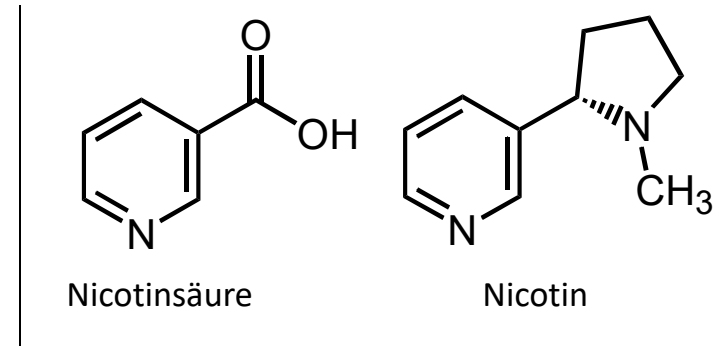
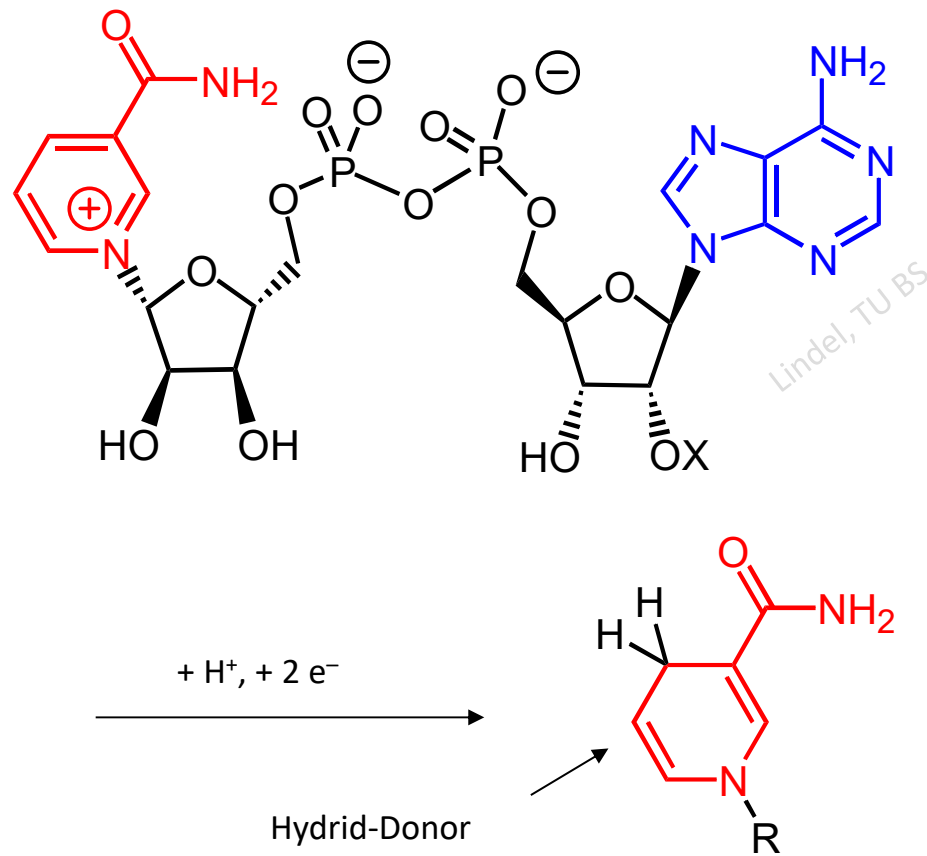
aus: G. Fu,
 Acc. Chem. Res. 2004, 542.



trans-Anordnung d. größten Subst.

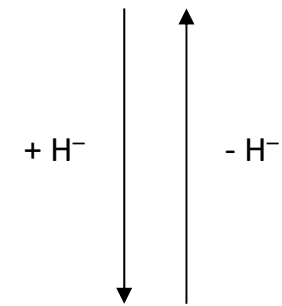
E. Sechsring-Aromaten - E.2 Pyridin

Oxidation mit "NAD⁺" (bzw. Reduktion mit "NADH/H⁺")



X = H:
Nicotinamid-Adenin-Dinucleotid ("NAD⁺")

X = OPO₃H⁻: ("NADP⁺")

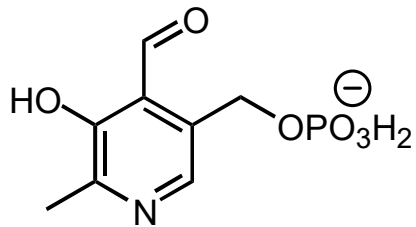


"NADH" bzw. "NADPH"

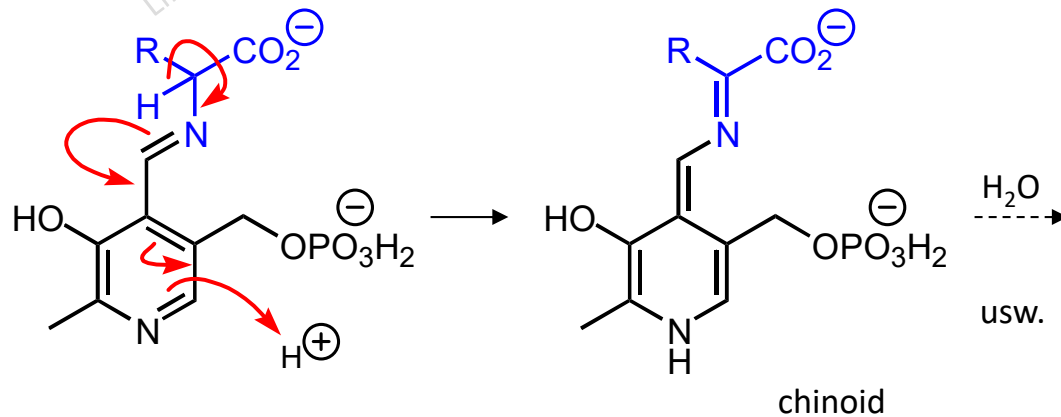
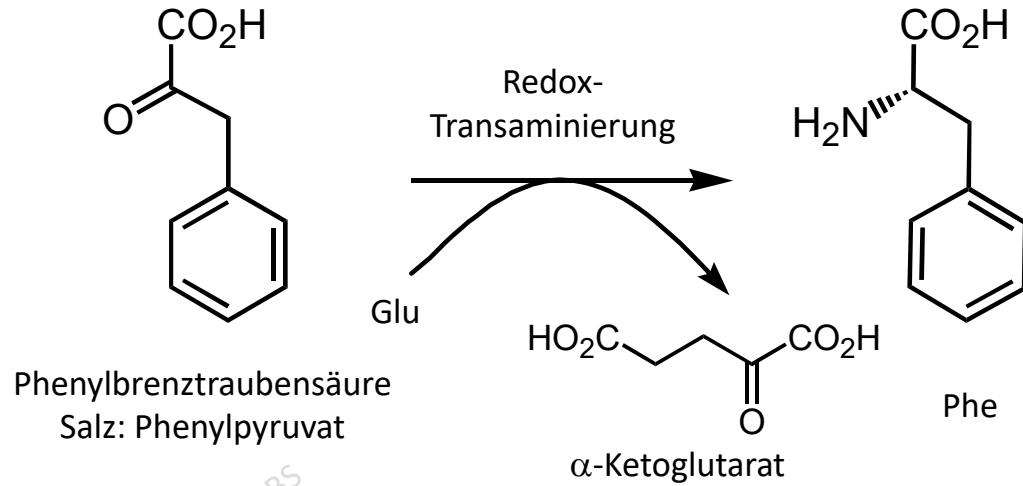
E. Sechsring-Aromaten - E.2 Pyridin

Vitamin B₆

Transaminierung via
Coenzym



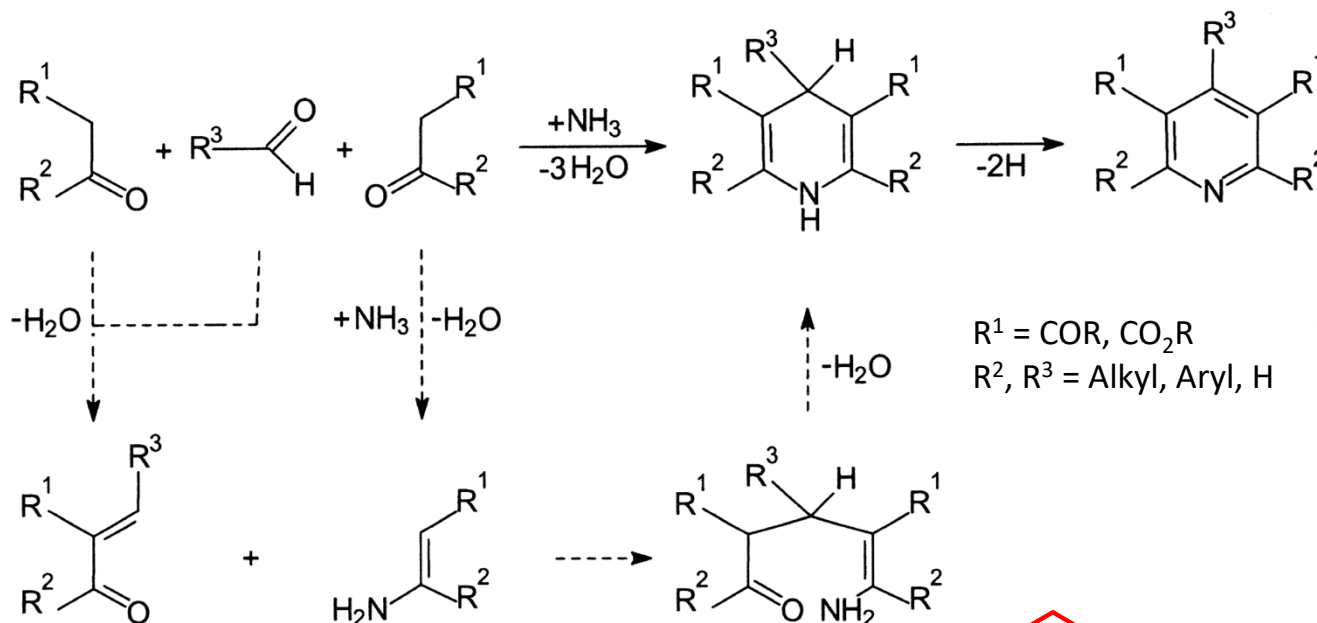
Pyridoxalphosphat (Vit. B₆)



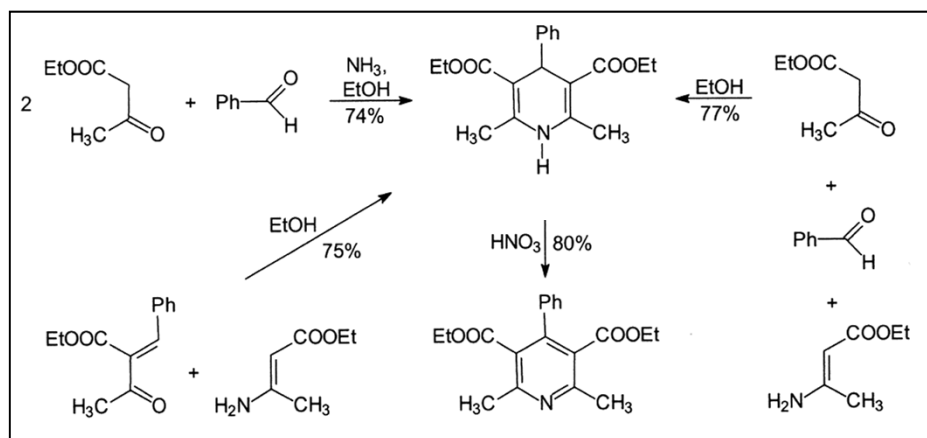
E. Sechsring-Aromaten - E.2 Pyridin

Pyridin-Synthesen

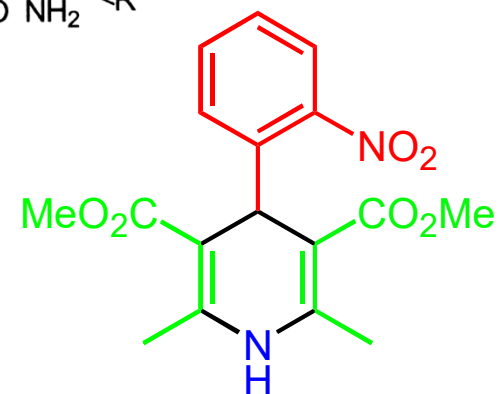
a) Hantzschsche Pyridin-Synthese (1882)



4-Komponenten-Reaktion über 1,4-Dihydropyridine



mehrere Synthesewege möglich!

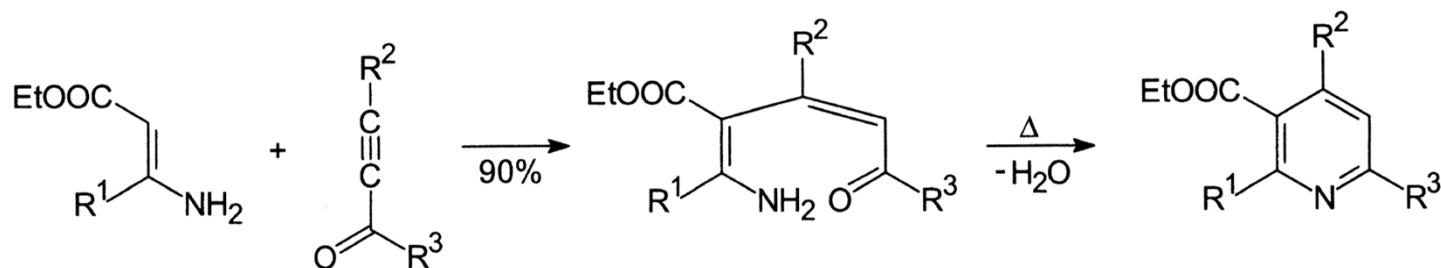


Nifedipin: Ca²⁺-Kanal-Antagonist
(gegen Bluthochdruck, Bayer AG)

E. Sechsring-Aromaten - E.2 Pyridin

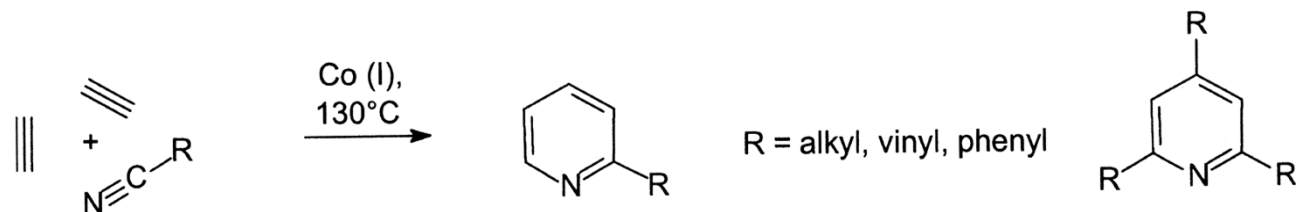
b) Bohlmann-Rahtz-Synthese (1957)

Michael-Addition v. Enaminen an acetylenische Ketone.



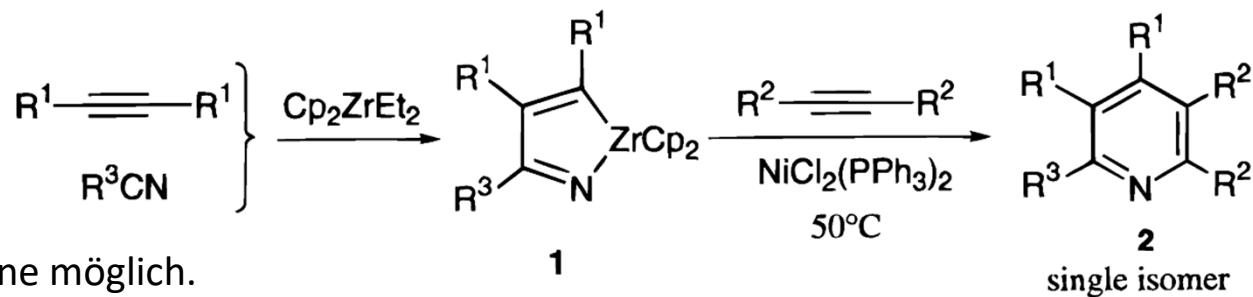
c) durch Cycloaddition:

Bönnemann-Synthese (1978)



Cyclotrimerisierung des Alkyls kann durch Überschuß an Nitril unterdrückt werden.

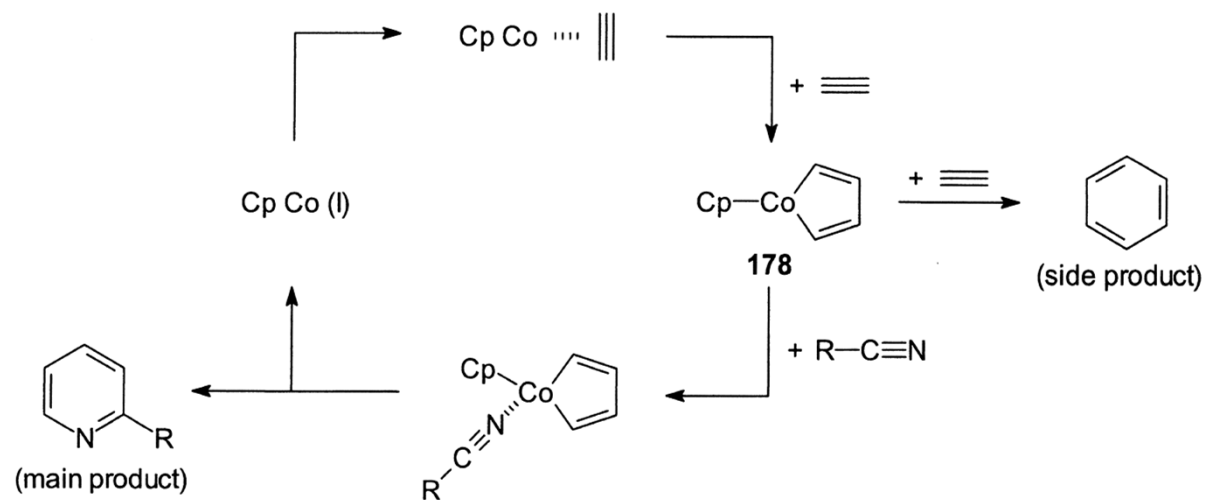
Takahashi et al.,
JACS **2000**, 4994.



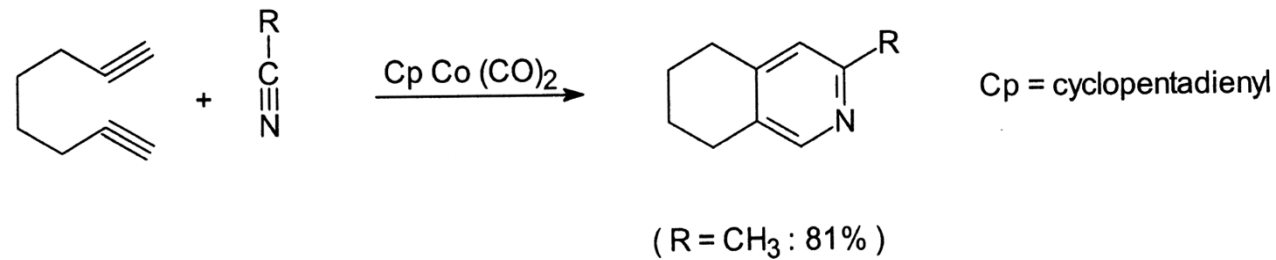
Verwendung zweier verschiedener Alkine möglich.

E. Sechsring-Aromaten - E.2 Pyridin

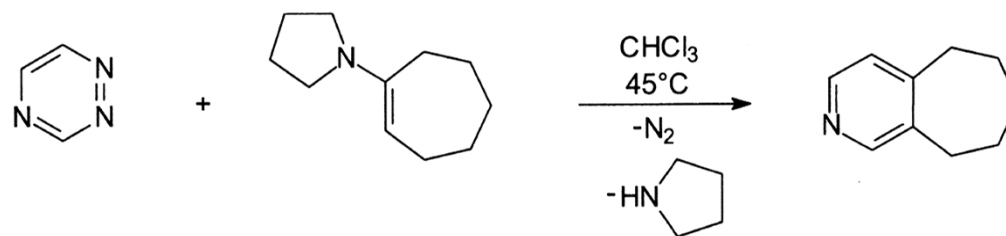
Mech. d. *Bönnemann*-Synth.:



Bsp.:

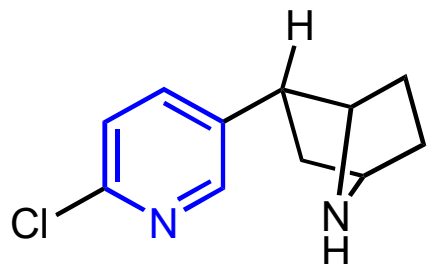


Neunhöffer-Boger-Synth.:



E. Sechsring-Aromaten - E.2 Pyridin

Pyridin-Alkaloide

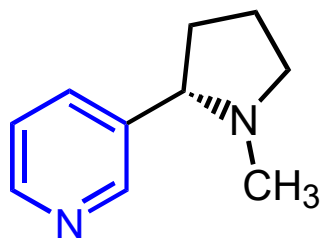


wird von südamerikanischen Pfeilgiftfröschen mit der Nahrung aufgenommen. 200-fach analgetische Wirkung von Morphin, allerdings als Acetylcholin-Agonist auf die Nicotin-Rezeptoren. Isolierung 1992 durch Daly et al., Synthese z. B. durch Corey et al. (1993).



Epipedobates tricolor

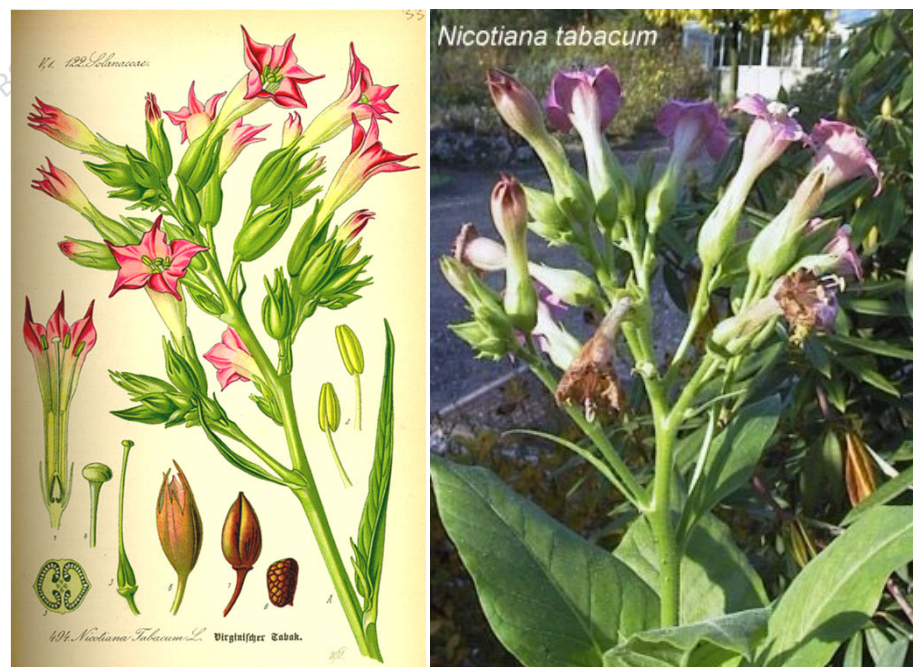
Epibatidin



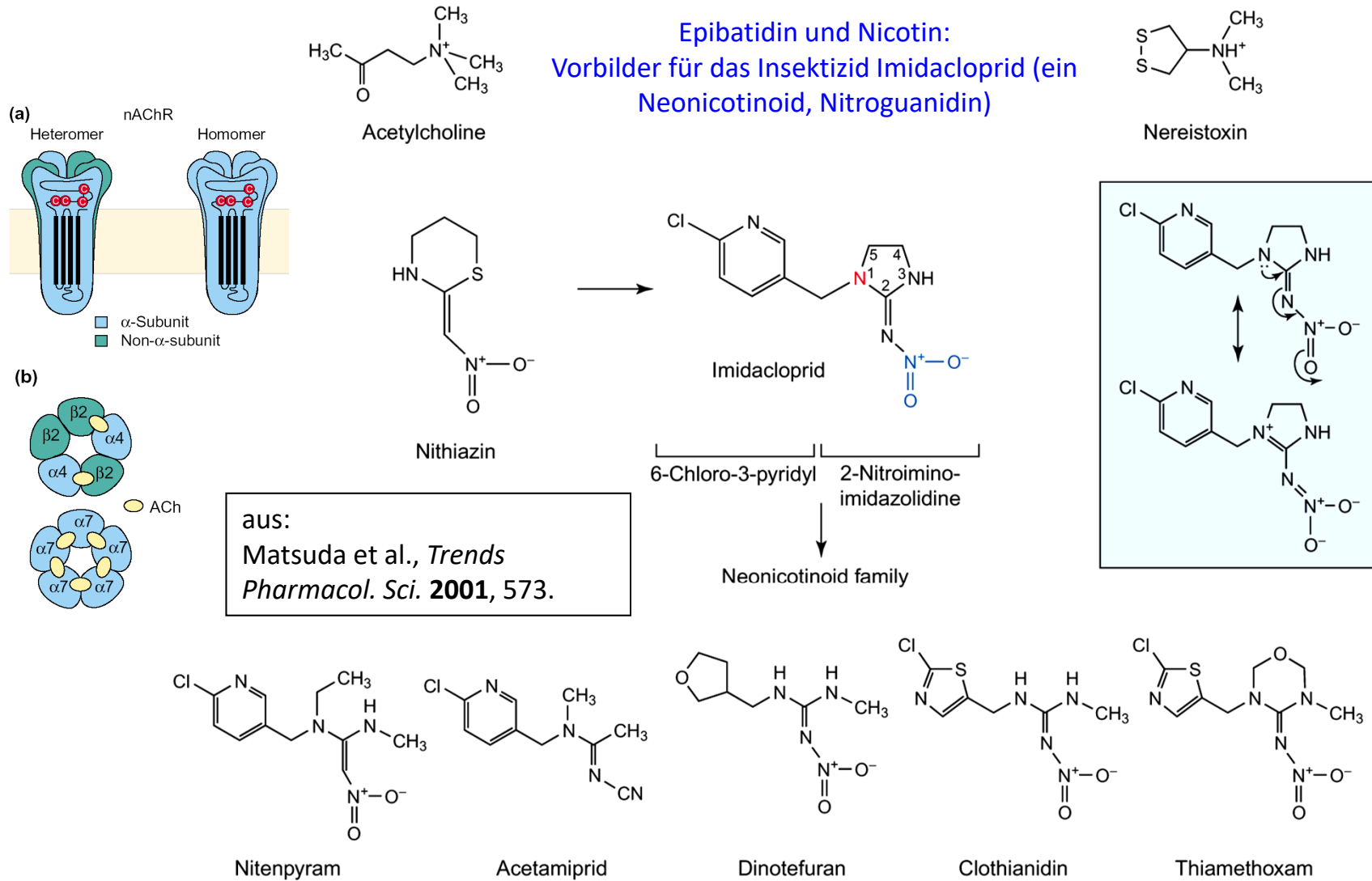
Nicotin

Hauptalkaloid der Tabakpflanze *Nicotiana tabacum*

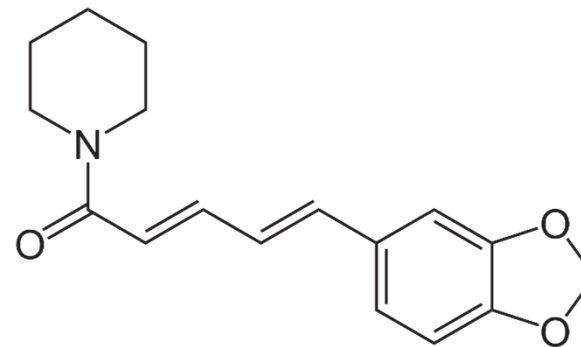
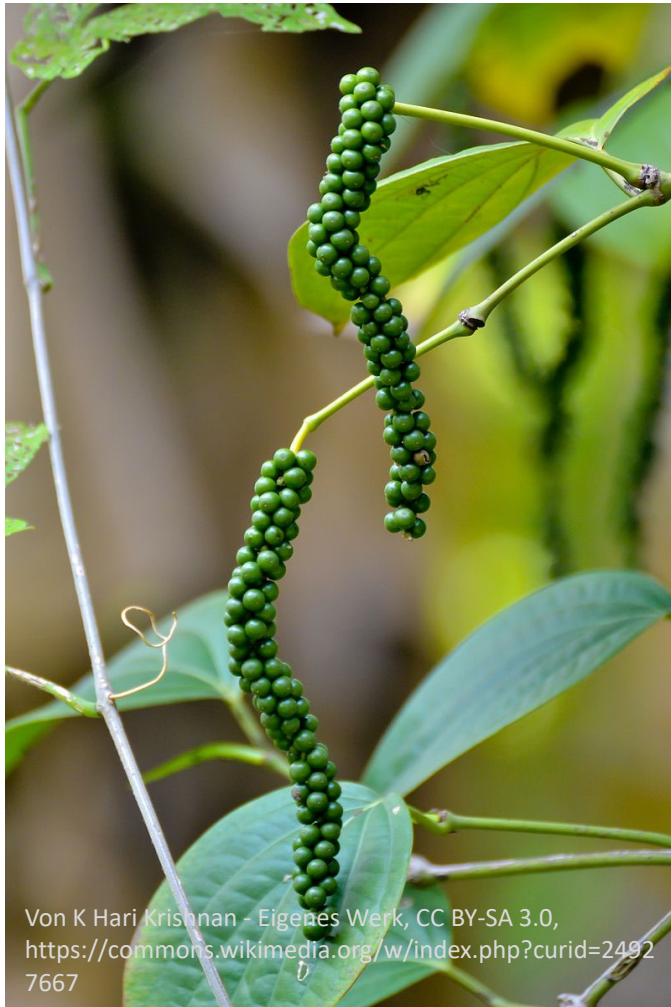
wirkt als Acetylcholin-Agonist, also als Neurotransmitter, auf die Nicotin-Rezeptoren. Tödliche Dosis: 100 mg für den Menschen.



E. Sechsring-Aromaten - E.2 Pyridin

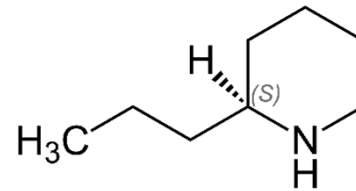


Piperidin



Piperin aus schwarzem Pfeffer
(*Piper nigrum*)

Piperidin

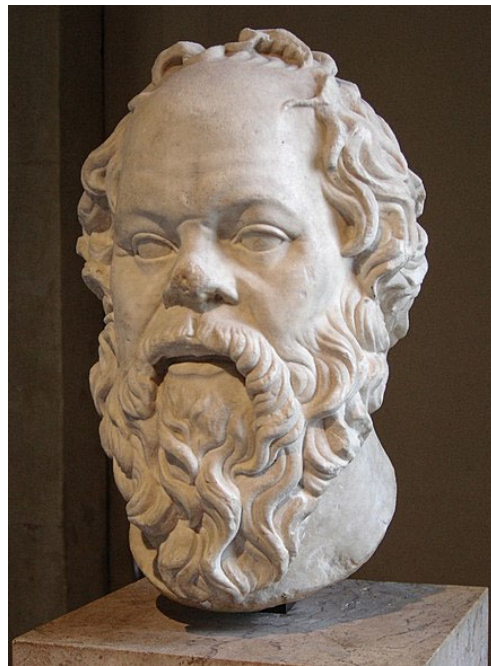


Coniin aus dem gefleckten Schierling
Conium maculatum L.

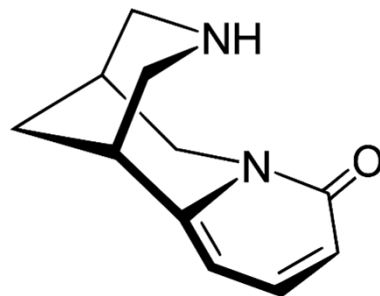
Sokrates

Coniin blockiert reversibel nikotinerge
Acetylcholin-Rezeptoren.

Lähmung, Tod durch Ersticken.

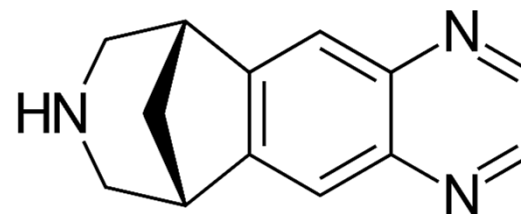


Piperidin

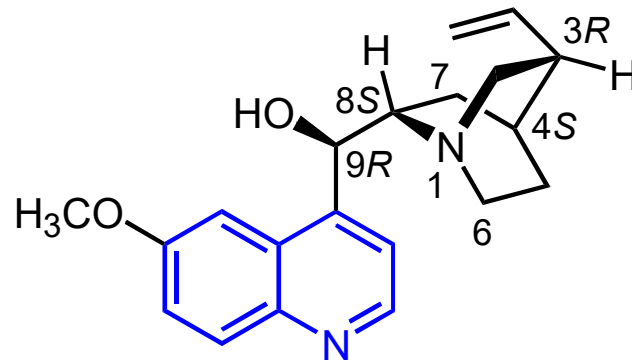


Nikotinergeres Cytisin aus dem Goldregen *Laburnum*

Varenicilin zur Raucherentwöhnung



Biol. Bedeutung



(-)-Chinin (engl. quinine; Analogon ohne Methoxygruppe: (-)-Cinchonidin)

aus der Rinde subtropischer Bäume der Gattungen *Cinchona* und *Remija*, isoliert 1820 von Pelletier und Caventou, eingesetzt als Chemotherapeutikum gegen Malaria, Konstitutionsbeweis durch Totalsynthese (Woodward, Doering 1944).

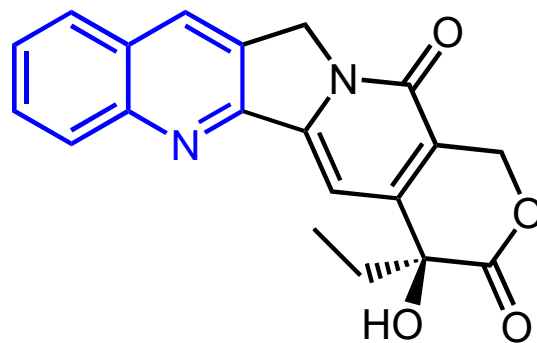
Hemmung des Wachstums der ungeschlechtlichen Formen des Malaria-Erregers *Plasmodium falciparum*.

(+)-Chinidin: 8R,9S-Diastereomer von Chinin (Analogon ohne Methoxygruppe: (+)-Cinchonin).



E. Sechsring-Aromaten - E.3 Chinolin

Biol. Bedeutung

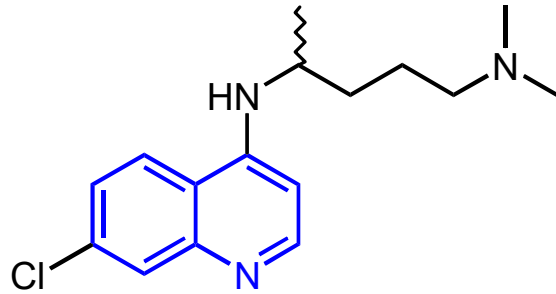


Camptothecin
aus *Camptotheca acuminata*

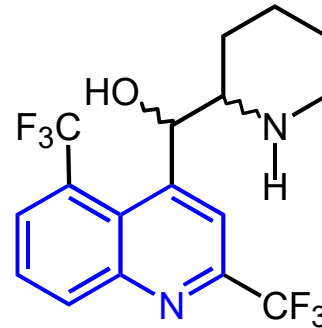
DNA-Topoisomerase I-Inhibitor,
seit 1996 zugelassen zur Therapie
versch. Krebsarten

E. Sechsring-Aromaten - E.3 Chinolin

Wichtige Pharmaka auf Chinolin-Basis:

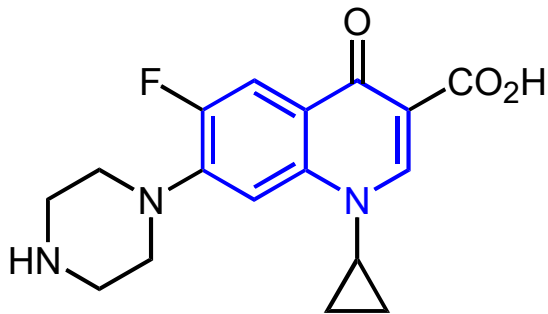


Chloroquin ("Resochin")



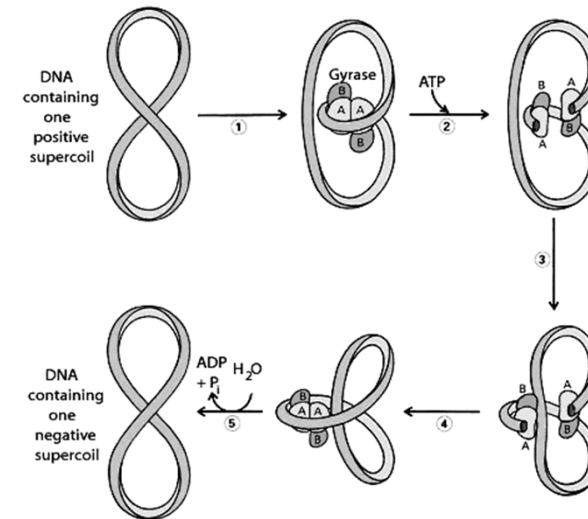
Mefloquin ("Lariam")

Chinin-Mimetika, wirksam gegen Schizonten des Malaria-Erregers *Plasmodium* sp.



Ciprofloxacin ("Ciprobay")
antibakterieller Gyrase-Hemmstoff.

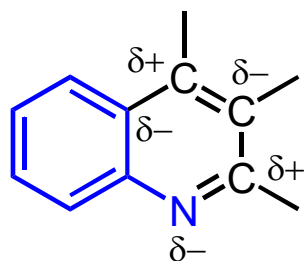
Gyrase: eine DNA-Topoisomerase II, verantwortl. für das negative "Supercoiling" der DNA und die Packung der DNA während der Replikation.



<http://138.192.68.68/bio/Courses/biochem2/DNA/DNAStructure.html>

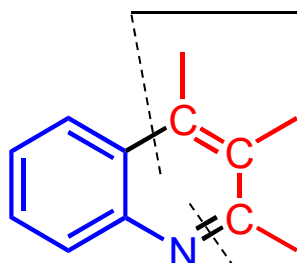
E. Sechsring-Aromaten - E.3 Chinolin

Synthesen



(ehemalige) Polarisierung der zu Chinolin führenden Synthesebausteine.
Fast immer Anilin als Edukt.

"Anilin + C₃-Baustein"
(sortiert nach 1. Retroschnitt):



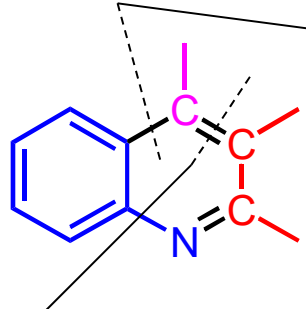
ausgehend v. Zimtsäureaniliden,
v. **β-Diketonen** od. **β-Ketoaldehyden** (Combes),
v. **β-Ketoestern** (Knorr, Konrad-Limpach),
v. **Alkoxyethylenmalonestern** (Gould-Jacobs).

Sonderweg über Dimere:
v. **Glycerin/Acroleinen** (Skraup/Doebner-Miller)

ausgehend v. o-Aminocinnamoylverb.,
v. (o-Aminophenyl)**inonen** (Marinelli)

"Anilin + C₁- + C₂-Baustein":

Fall 1:

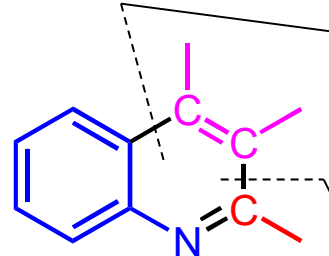


v. **N-Acylanilin** und
DMF/POCl₃ (Meth-Cohn)

offen:
v. **o-Acylanilin** und
Keton (Friedländer)

v. Isatin und **Keton** (Pfitzinger)

Fall 2:



v. **Aldehyd** und
α-Ketocarbonsäure (Doebner),
v. **Phenylimin** und **Alkin/Alken**
(Makioka).

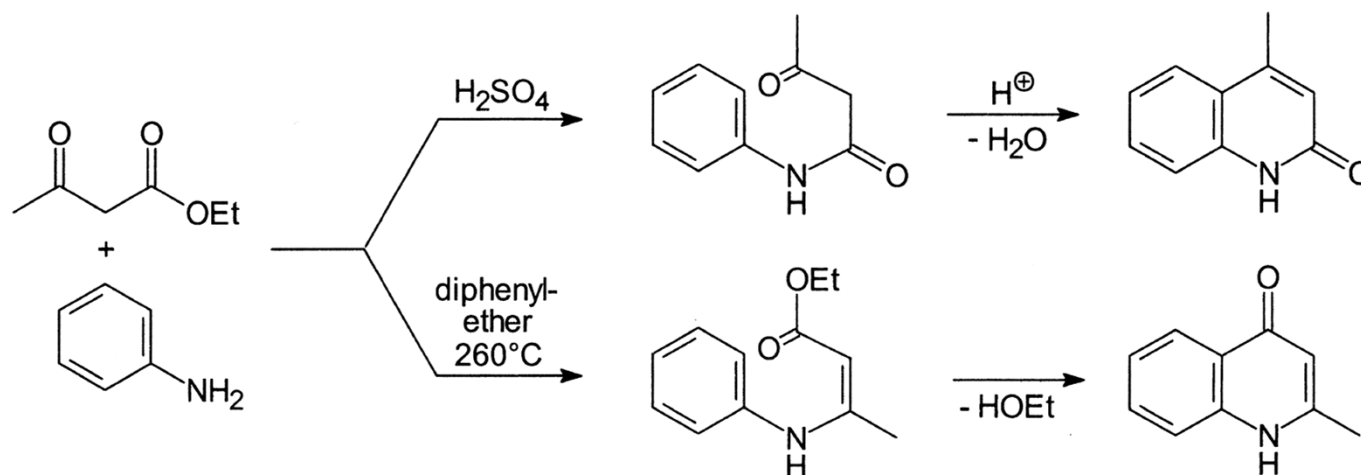
v. **o-Alkenylphenylimin** (Quiang)

beide mögl.: ausg. v. **o-Acyl-N-acylanilin** (Camps)

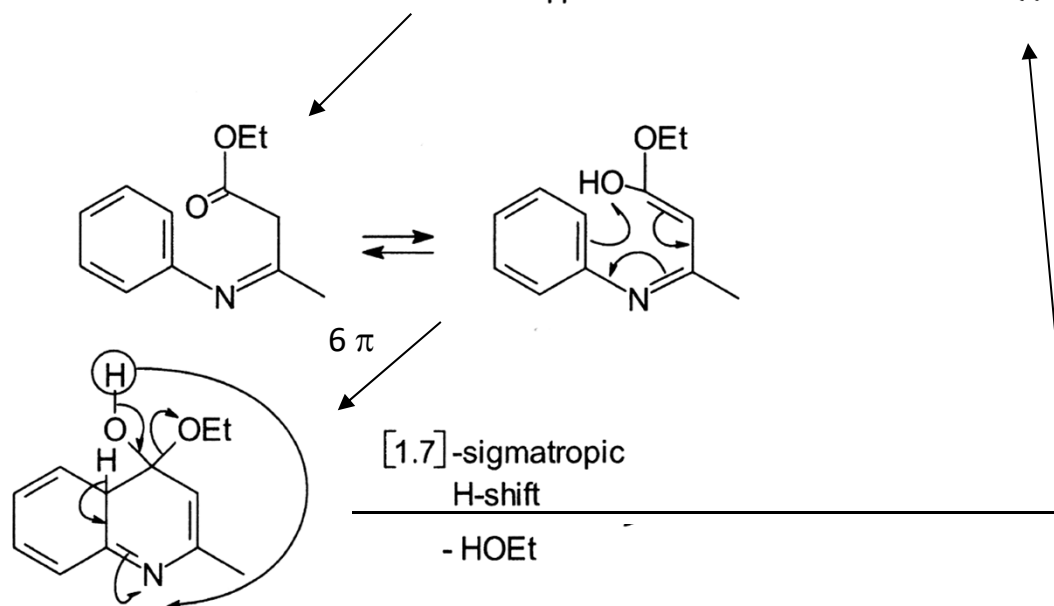
E. Sechsring-Aromaten - E.3 Chinolin

Knorr-S.
(-> Chinoline),

Konrad-Limpach-S.
(-> 4-Chinolone)

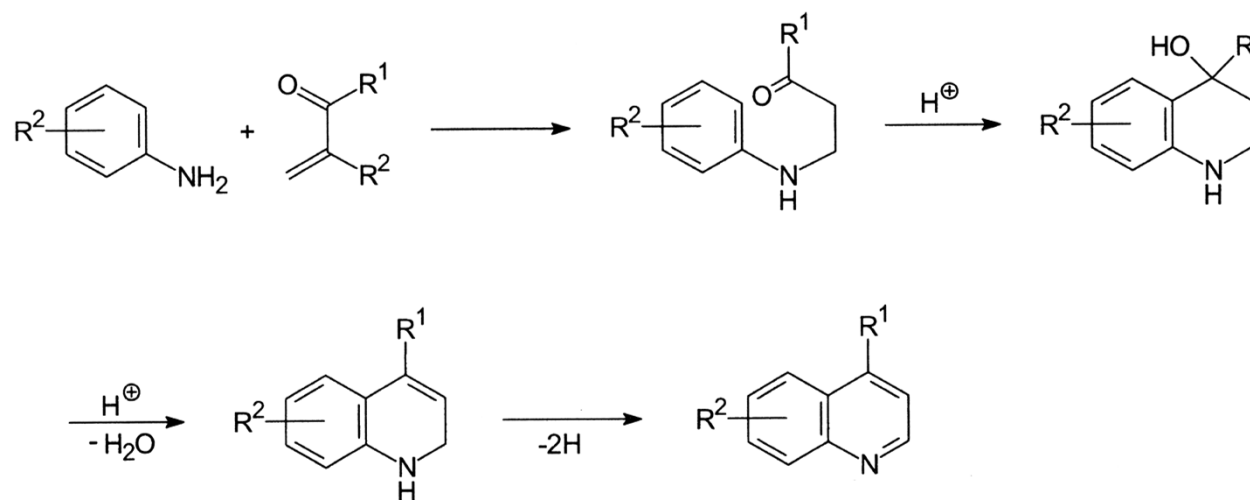


Verbesserung der *Knorr-Synthese*:
z. B. Verwendung von Thioestern.

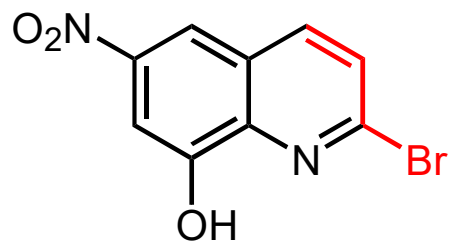


E. Sechsring-Aromaten - E.3 Chinolin

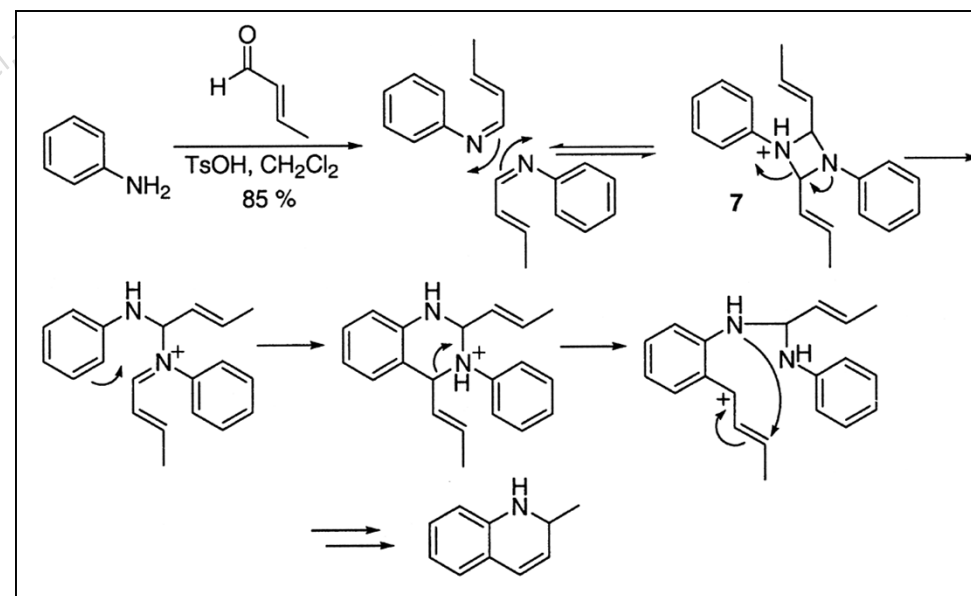
Skraup-Synthese
(urspr. ausg. v. Glycerin),
Doebner-Miller-Synthese:



z. B. von



alternativer Mech. (Eisch, *JOC* **1989**, 1269):



E. Sechsring-Aromaten - E.4 Isochinolin

Biologische Bedeutung

20.000 Mohnkapseln liefern 1 kg Opium.

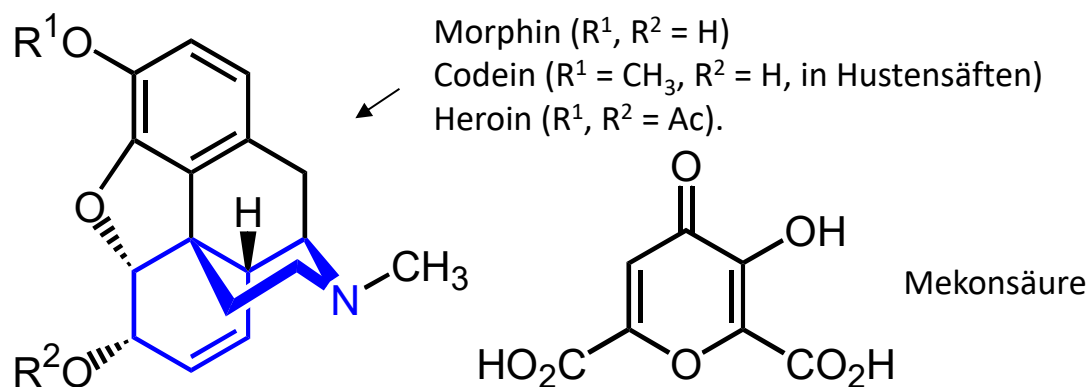
Rohopium: zu 20-30 % bestehend aus ca. 40 (50) verschiedenen, überwiegend als Salze der Mekonsäure sowie der Milchsäure, Fumarsäure und Schwefelsäure vorliegenden Alkaloiden vom Morphinan- und Benzylisochinolin-Typ; vom Morphinan-Typ insbesondere Morphin (3-23 %), Codein (0.2-3.5 %) und Thebain (0.2-1.0 %), vom Benzylisochinolin-Typ Papaverin (0.5-3.0 %), Noscapin (= Narcotin, 2-12 %) und Narcein (0.1-0.7 %).

Morphinwirkungen, u. a.:

zentral wirksames Analgetikum durch Angriff an Opioid-Rezeptoren (analgetisch wirksame Dosis 10 mg, sedativ-hypnotische Wirkung bei einer Dosierung von 10 mg, narkotische Wirkung bei Dosierung von 50-100 mg.

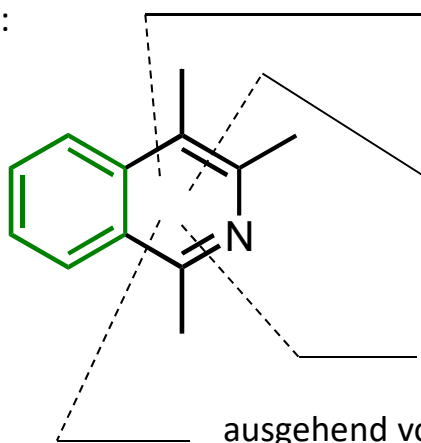


PLATE XIII.—*Papaver somniferum* (Opium Poppy). (From Jackson: *Experimental Pharmacology and Materia Medica*.)



Synthesen

1. Retroschnitt:



ausgehend v.
Benzaldehyden und Aminosäureacetalen
(Pomeranz-Fritsch)

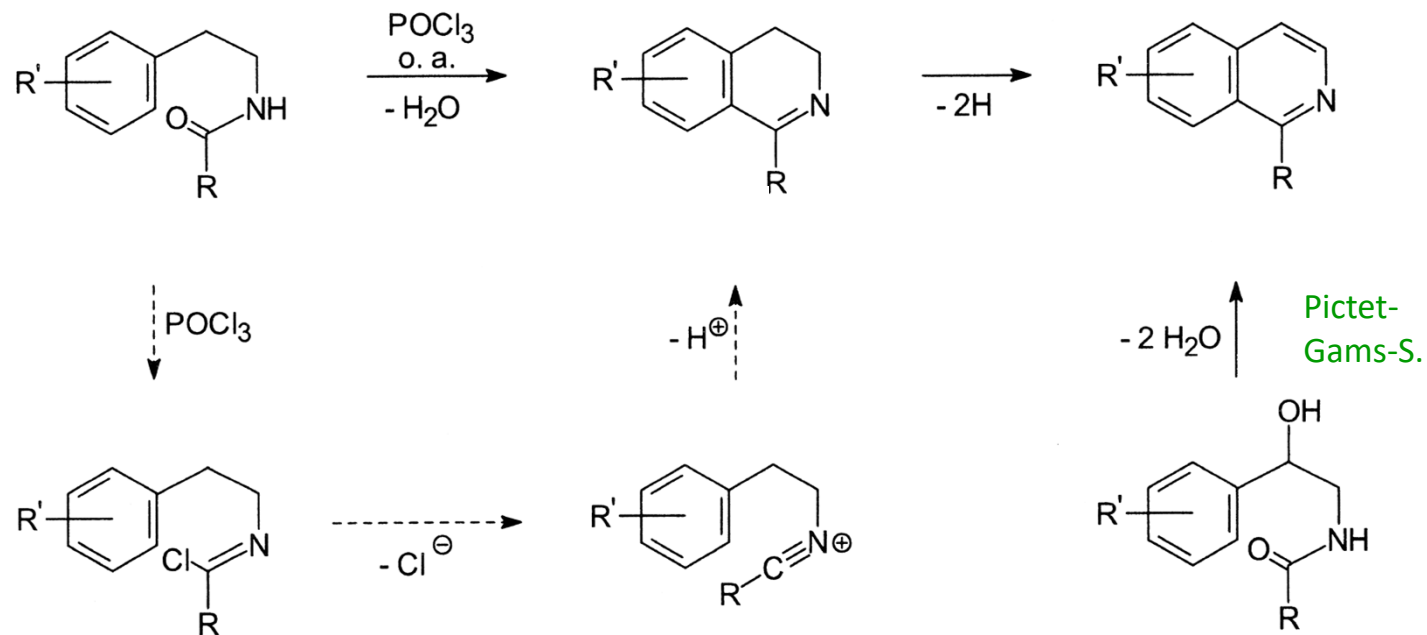
ringerweiternde Umlagerung von
Phthalimiden (Gabriel-Colman)
außerdem: (2-Formylphenyl)ethanale
+ prim. Amine (und Analoga)

ausg. v. o-Carbonyl-azidozimtsäureester
(Aza-Wittig-Weg)

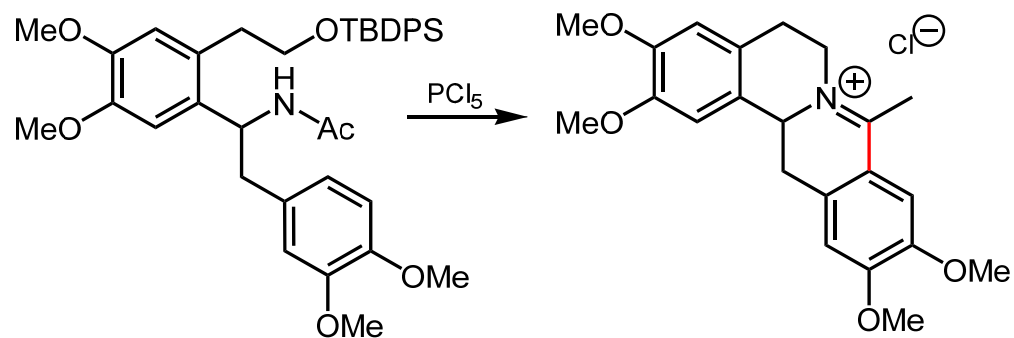
ausgehend von
N-Acyltyramin (Bischler-Napieralski, Pictet-Gams, Pictet-Huber),
v. Tyramin und Aldehyden (Pictet-Spengler)

E. Sechsring-Aromaten - E.4 Isochinolin

a) Bischler-Napieralski-S.



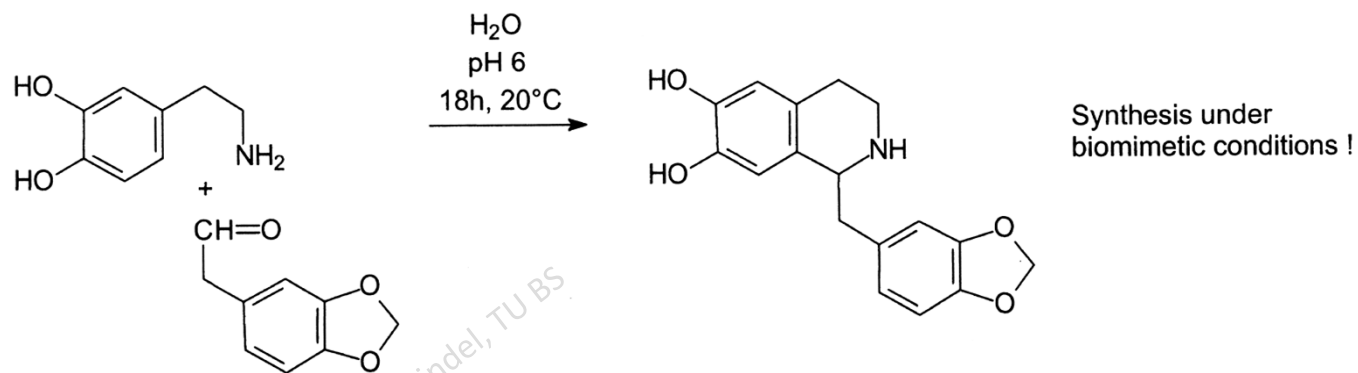
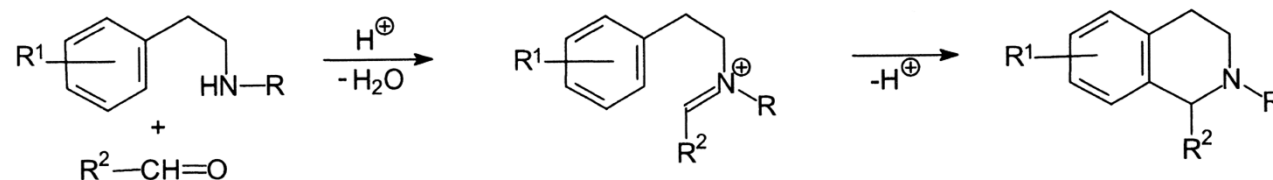
z. B.:



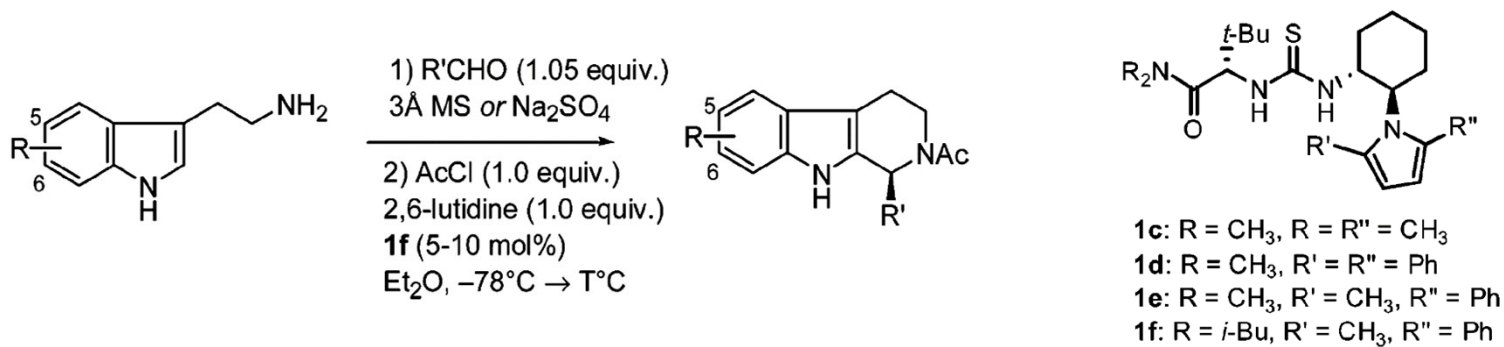
JOC 1996, 4062.

E. Sechsring-Aromaten - E.4 Isochinolin

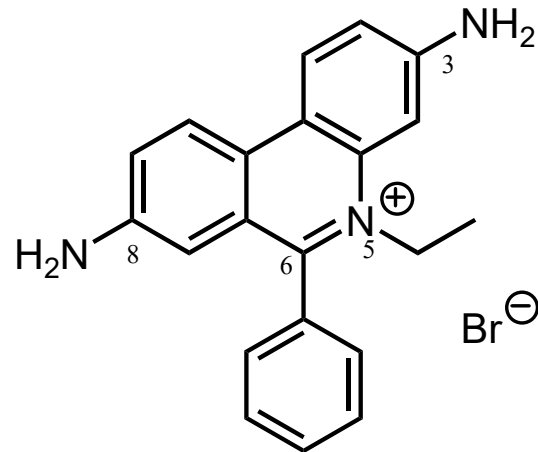
b) *Pictet-Spengler-S.*



enantioselektiv katalysierte *Pictet-Spengler S.* (Jacobsen et al., *JACS* **2004**, 10558):



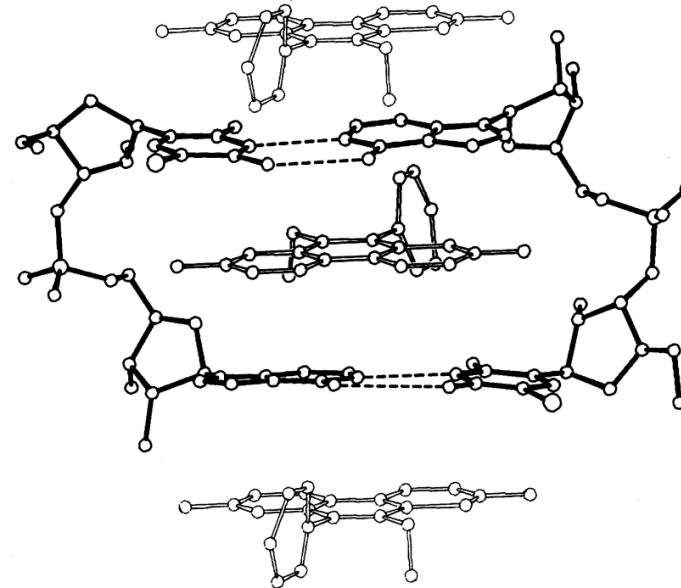
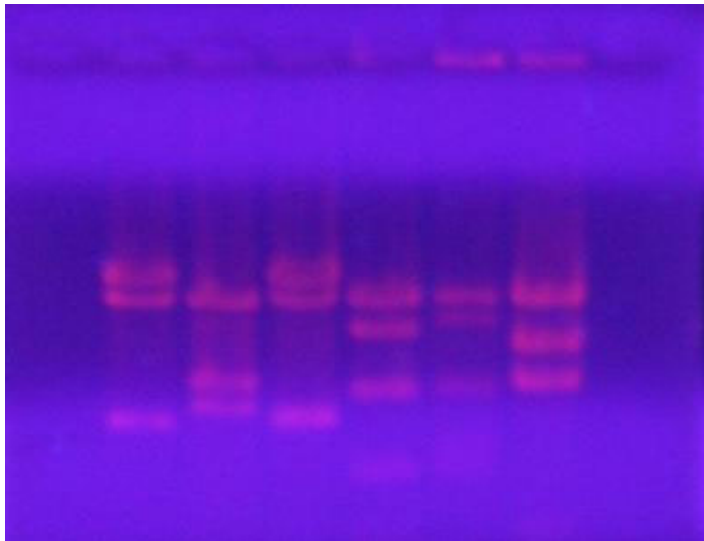
E. Sechsring-Aromaten - E.4 Isochinolin



Ethidiumbromid

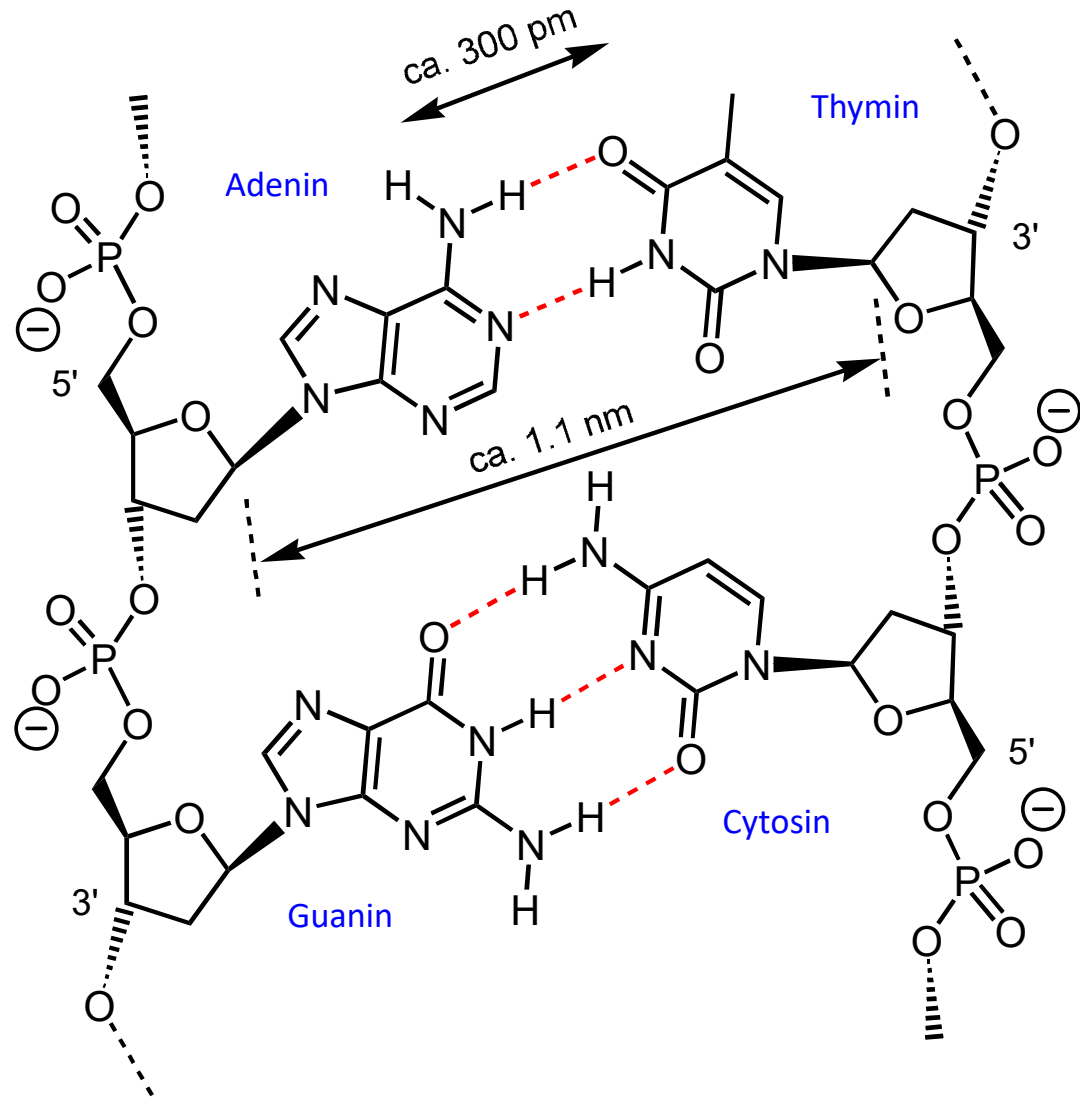
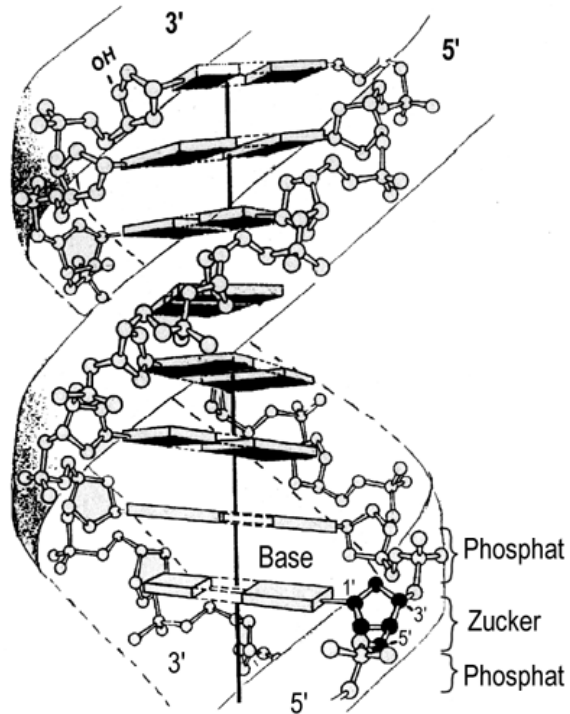
(IUPAC: 3,8-Diamino-5-ethyl-6-phenyl-phenanthridiniumbromid)

Quantifizierung von DNA und RNA nach der Gelelektrophorese (bis zu 3 Moleküle je 10 Basen) auf Basis der Erhöhung der Fluoreszenz der Verbindung nach Interkalation (erstmals 1973).



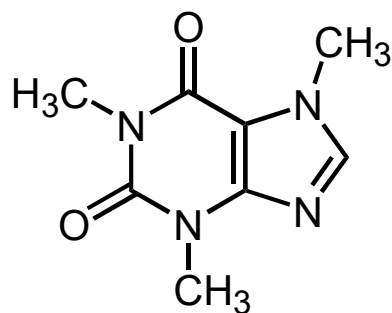
Struktur des Ethidium-(5-Ioduridylyl(3'-5')-Adenosin)-Komplexes im Kristall (Sobell et al., *PNAS* **1975**, 72, 628).

Watson-Crick-Basenpaarung



+ 2'-Desoxynucleoside: Adenosin, Guanosin, Cytidin, Thymidin

E. Sechsring-Aromaten - E.5 Purin und Pyrimidin



Koffein (= 1,3,7-Trimethylxanthin)

Isolierung: *Runge*, 1820.

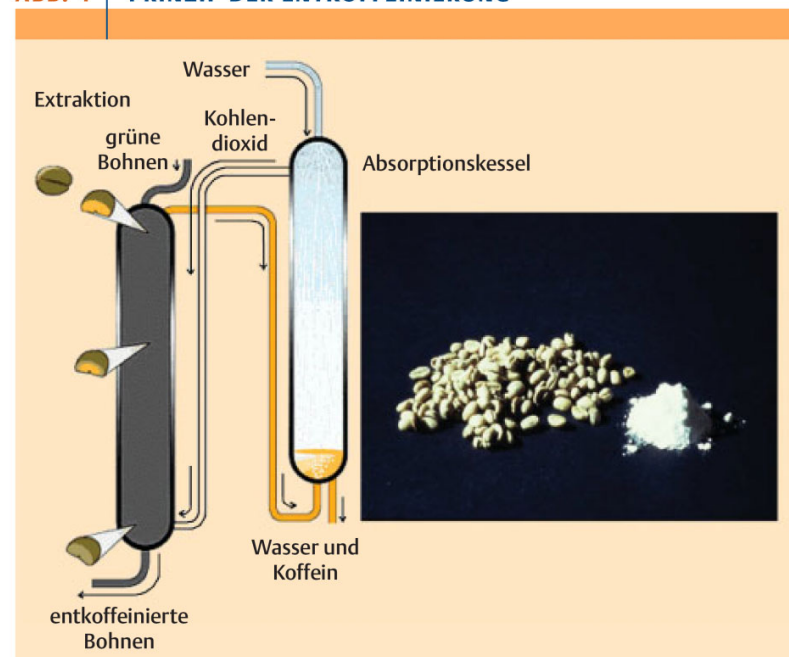
Coffein hemmt die Phosphodiesterase, die cyclisches AMP (Adenosinmonophosphat) in AMP umwandelt, besitzt somit eine erregende Wirkung auf das ZNS.



Nicht verarbeitete Kaffeebohnen.

Leitner, CHIUZ 2003, 32.

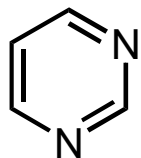
ABB. 4 | PRINZIP DER ENTKOFFEINERUNG



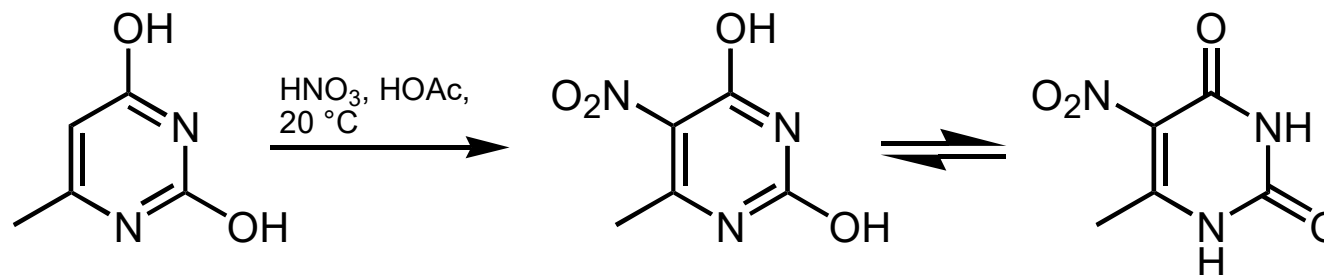
Prinzip der Entkoffeinierung von grünen Kaffeebohnen mit $scCO_2$. Die abgebildeten Proben stammen aus den Pionierarbeiten von Dr. Kurt Zosel am Max-Planck-Institut für Kohlenforschung.

E. Sechsring-Aromaten - E.5 Purin und Pyrimidin

Reaktivität

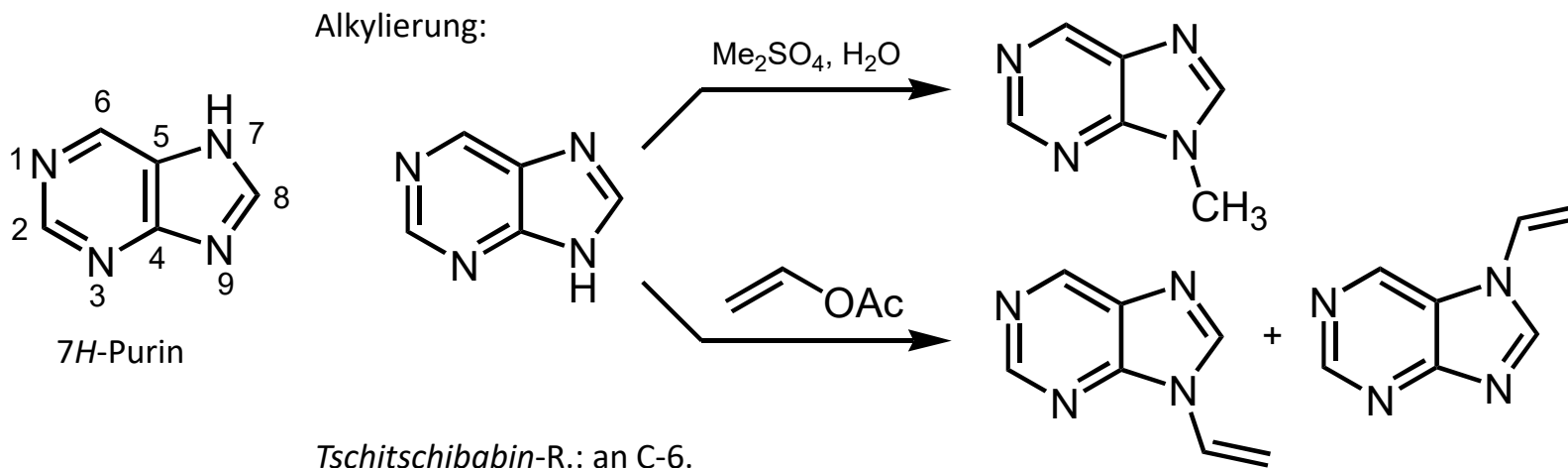


S_E Ar: geringe Reaktivität (ähnlich 1,3-Dinitrobenzol, 3-Nitropyridin) steigerbar durch elektronenspendende Substituenten, z. B:



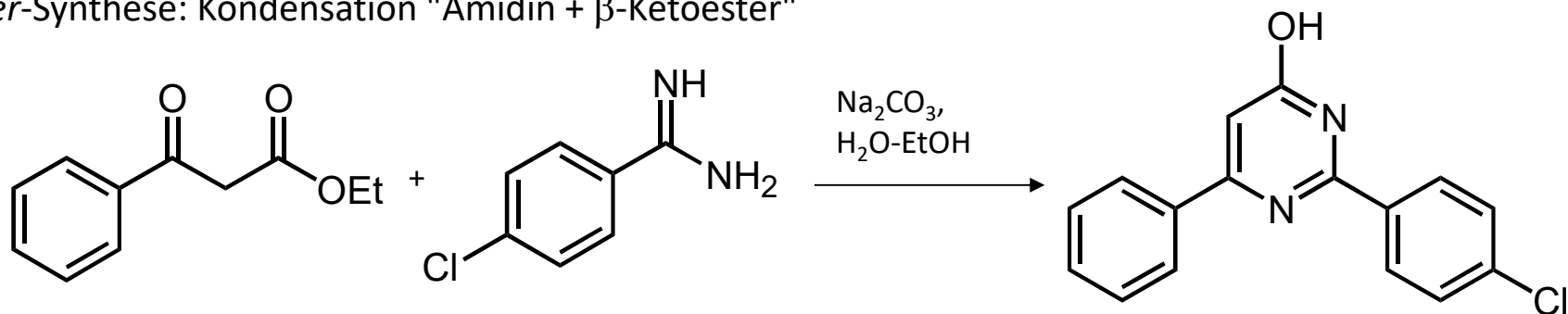
Reaktivität wie Benzol

S_N Ar: bevorzugt an C4 und C6 (z. B. Organometallverb.)

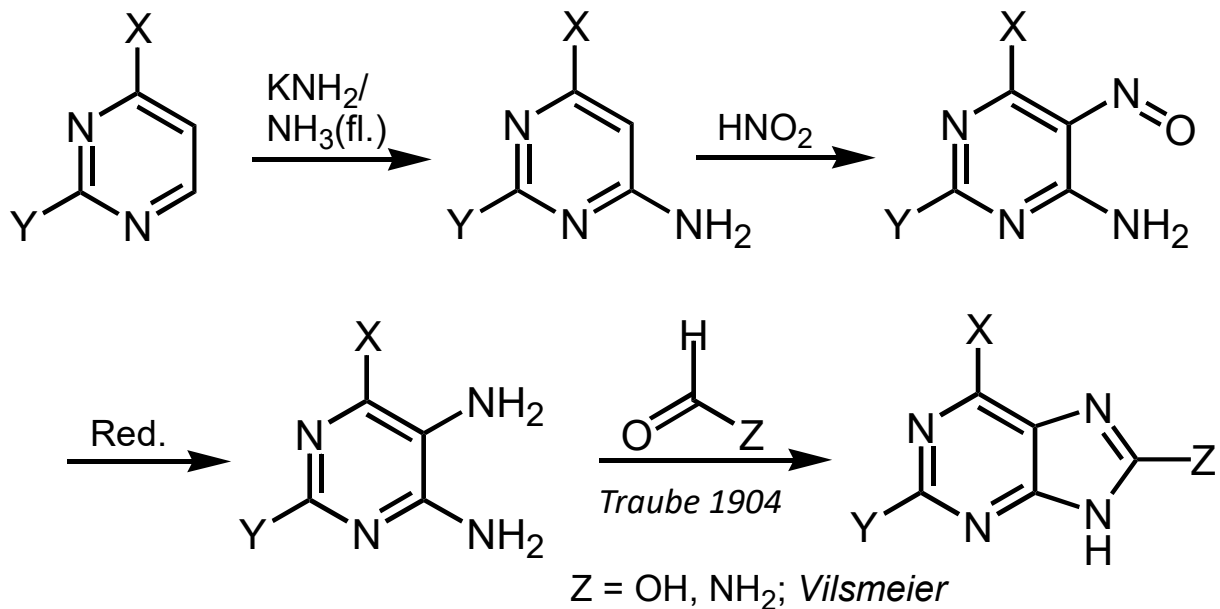


Pyrimidin-Synthesen

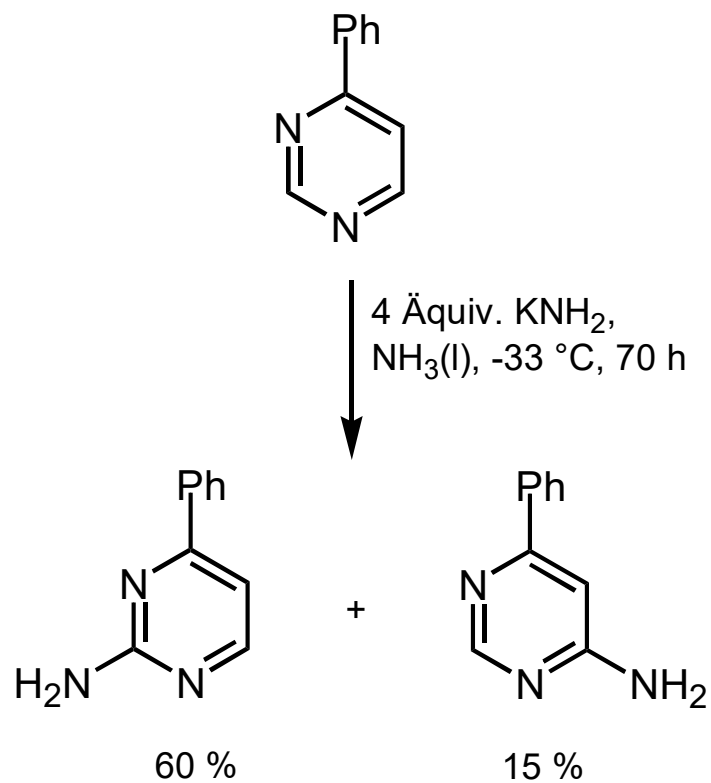
a) *Pinner-Synthese*: Kondensation "Amidin + β -Ketoester"



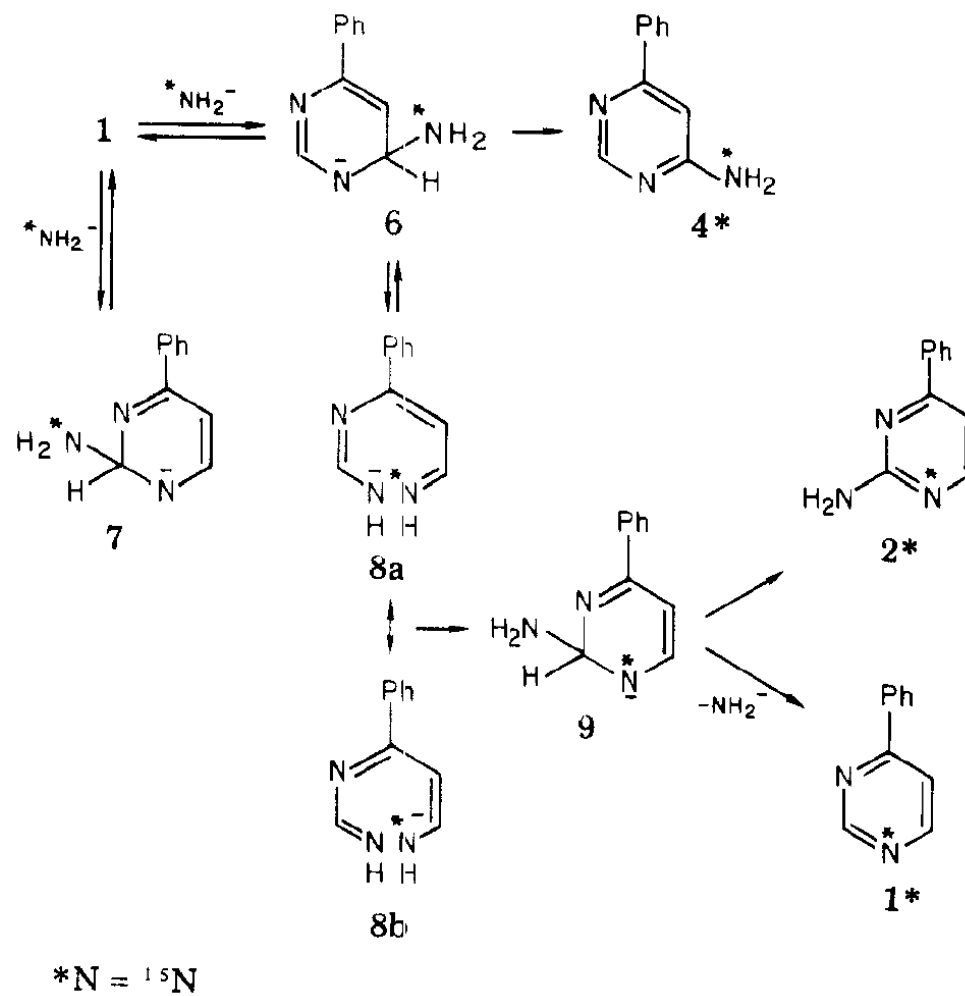
b) *Traube-Synthese*: Kondensation "4,5-Diaminopyrimidin + X-CHO"



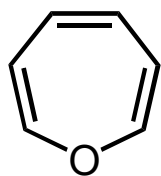
Tschitschibabin-Reaktion von Pyrimidin



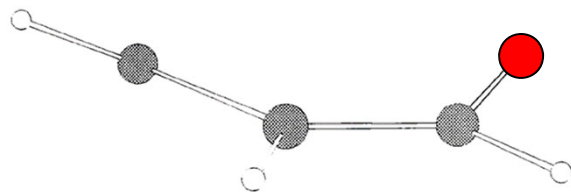
Mech.:



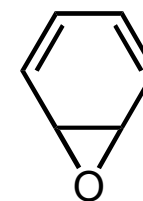
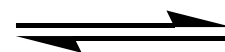
F. Siebengliedrige Ringe - F.1 Oxepin



Oxepin



6 π -elektrozykl. R.,
disrotatorisch, thermisch erlaubt

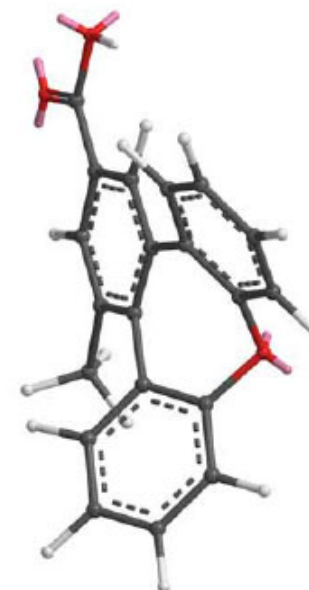
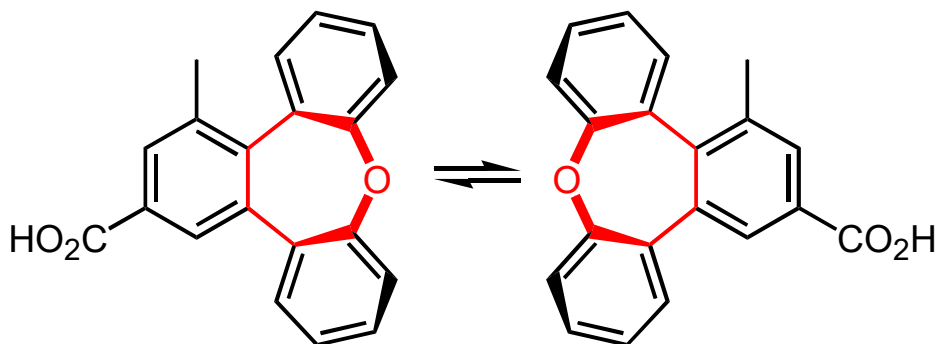


Benzoloxid

Toyota et al., *J. Phys. Chem. A* **2003**, *107*, 2749.

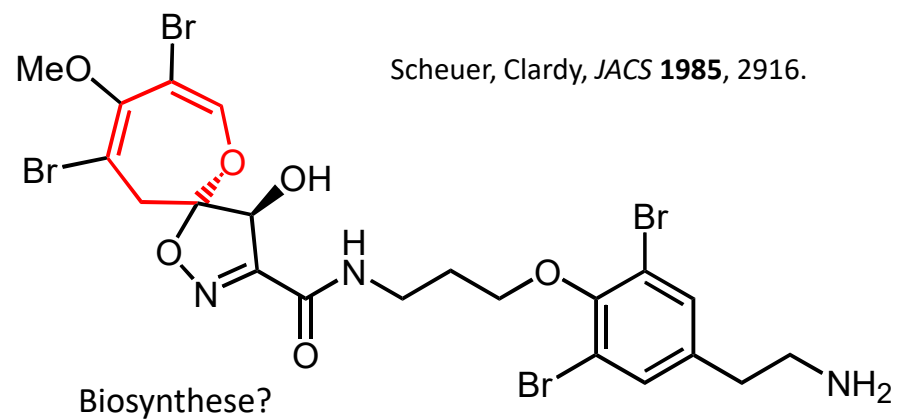
8 π , lokalisierte C=C-Bindungen (Bindungslängenalternanz), gewinkelt (Boat-C_s-Geometrie)
=> Nicht-Aromat

Racemisierung ($\Delta G^\ddagger = 87$ kJ/mol):



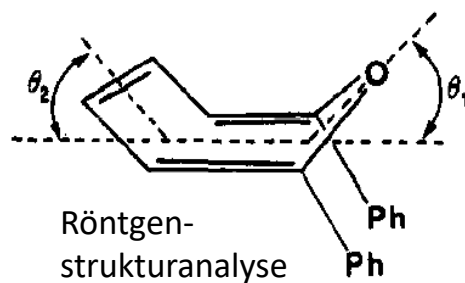
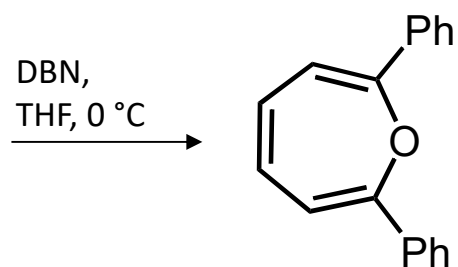
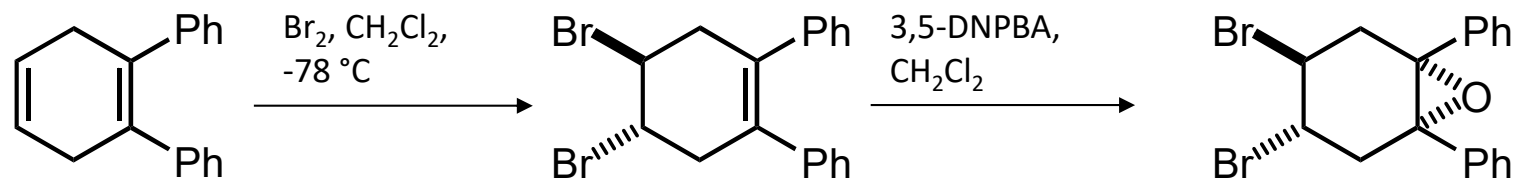
Naturstoff Psammaplysin A aus dem Meeresschwamm
Psammaplysilla purpurea

Scheuer, Clardy, *JACS* **1985**, 2916.



F. Siebengliedrige Ringe - F.1 Oxepin

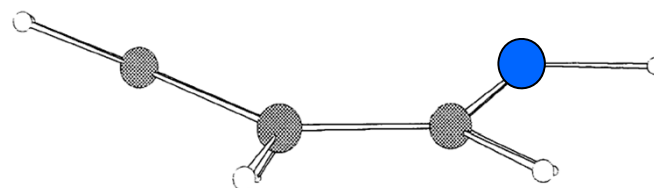
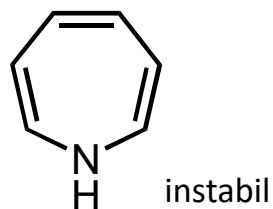
Synthese von 2,7-Diphenyloxepin:



Boyd et al., *JOC* **1986**, 2784.
3,5-DNPBA: 3,5-Dinitroperbenzoesäure
DBN: 1,5-Diazabicyclo[4.3.0]non-5-en

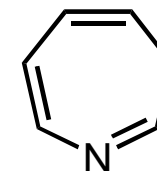
F. Siebengliedrige Ringe - F.2 Azepin

F.2 Azepin



Toyota et al., *J. Phys. Chem. A* **2003**, 107, 2749.

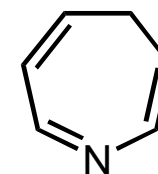
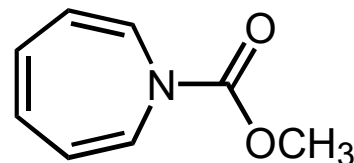
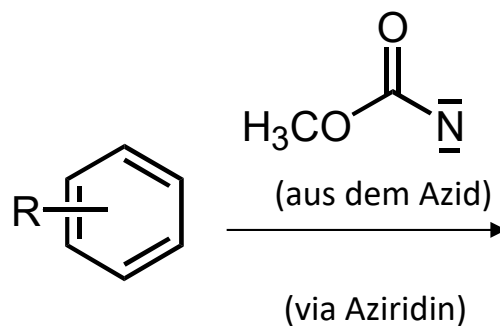
Säure od. Base



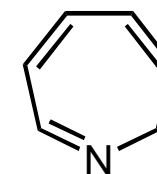
3H-Azepin

8π , lokalisierte C=C-Bindungen (Bindungslängenalternanz), gewinkelt (Boot- C_s -Geometrie)
=> Nicht-Aromat

stabiler: *N*-subst. 1H-Azepine:



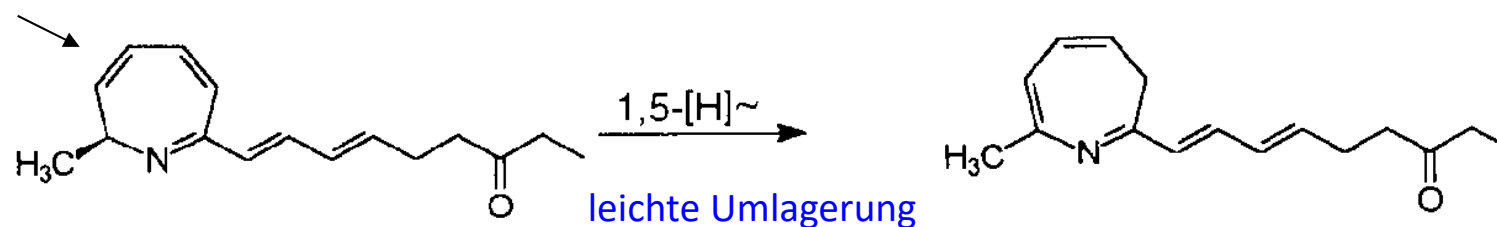
4H-Azepin



2H-Azepin

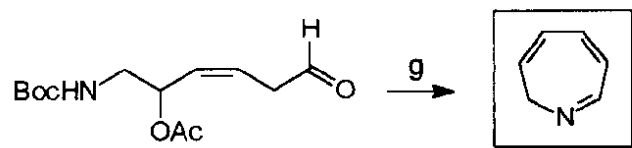
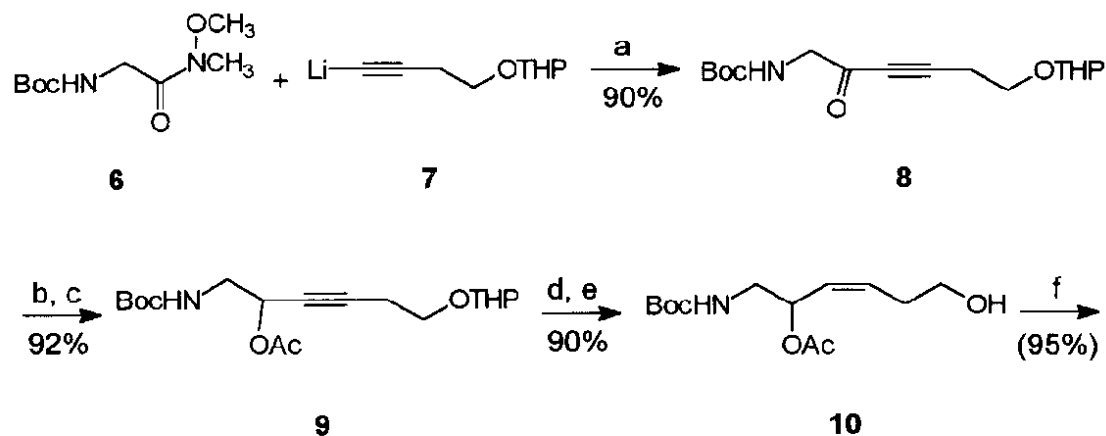
F. Siebengliedrige Ringe - F.2 Azepin

2H-Azepin als Teilstruktur des Naturstoffs Chalciporon aus dem Pfefferröhrling *Chalciporus piperatus*:



Synthese von 2H-Azepin:

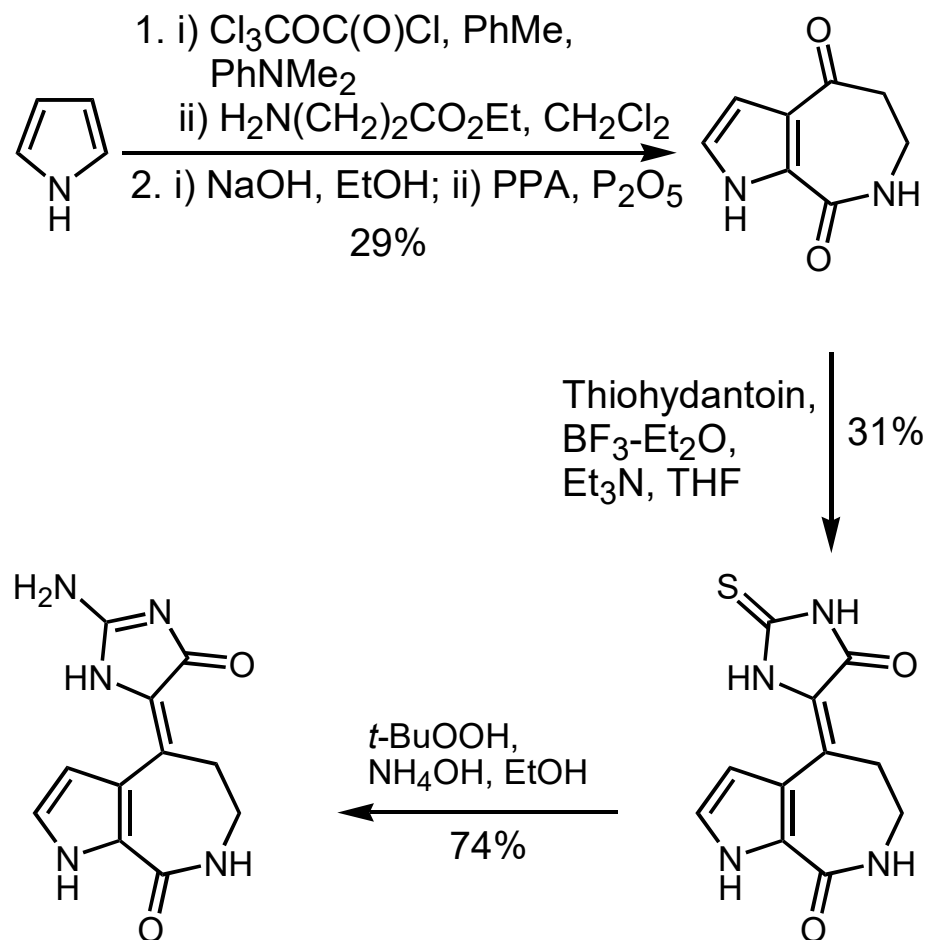
Steglich et al., *ACIE* **1995**, 1469.



a) THF, -78 \rightarrow -50 $^{\circ}$ C, verd. HOAc b) NaBH₄, MeOH, 0 $^{\circ}$ C. c) Ac₂O, Pyridin, cat. DMAP, DCM: d) DME, kat. PPTS, 70 $^{\circ}$ C. e) H₂ (1 bar), Lindlar. f) DMP, DCM. g) TFA, DCM, -10 $^{\circ}$ C; dann DMAP or DABCO.

F. Siebengliedrige Ringe - F.2 Azepin

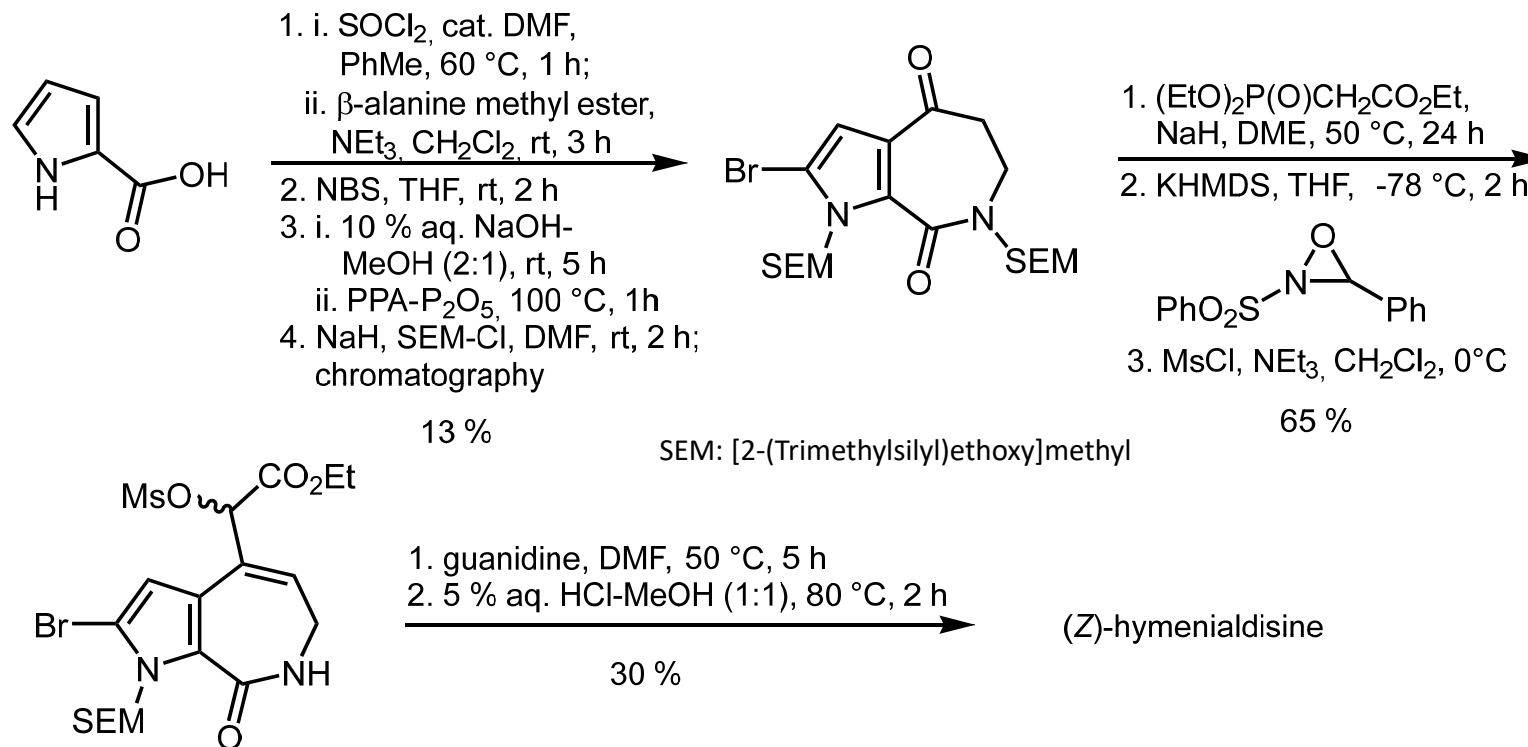
Ein Azepinon: Mariner Naturstoff
Debromhymenialdisin aus dem
Schwamm *Hymeniacidon* sp.



De Nanteuil, G. et al. *TETL* **2003**, 9263

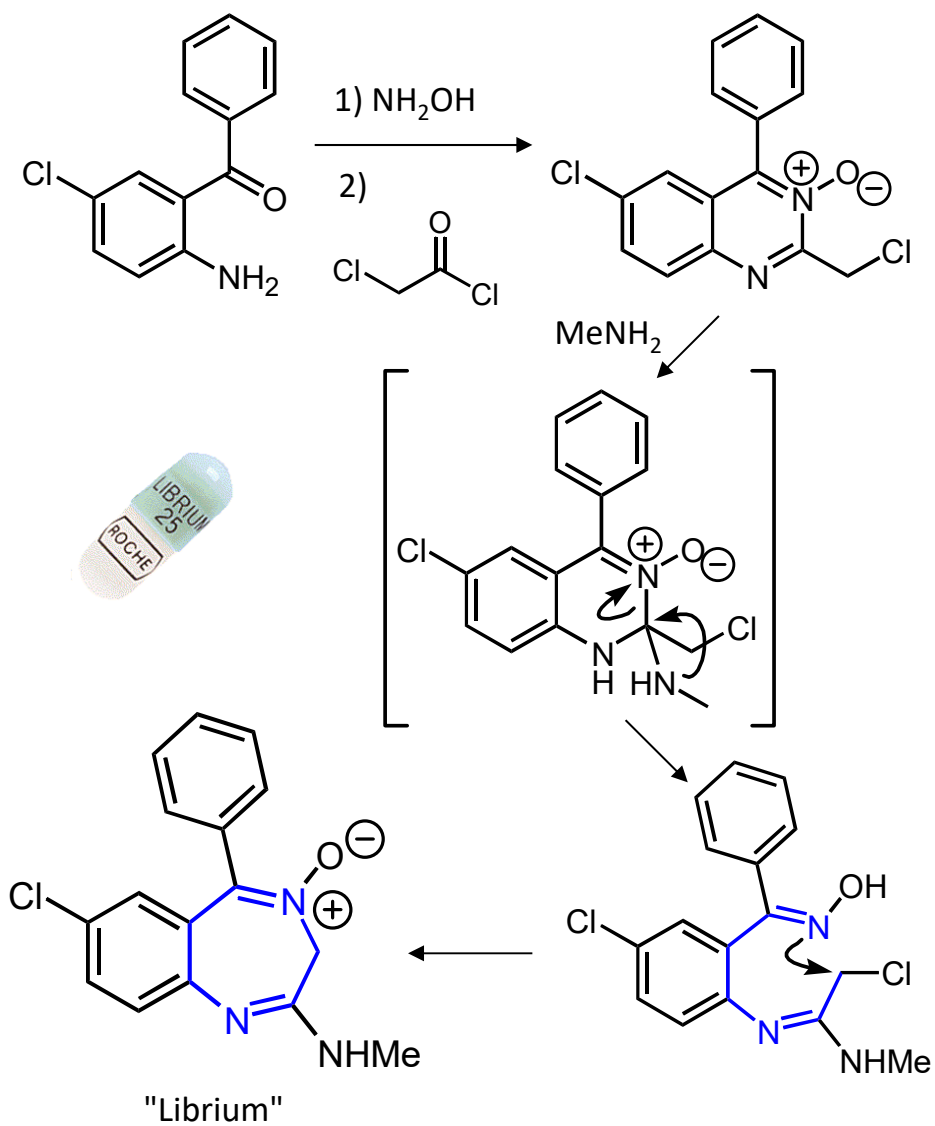
F. Siebengliedrige Ringe - F.2 Azepin

Synthesen des Marinen Naturstoffs Hymenialdisin, eines Kinase-Inhibitors

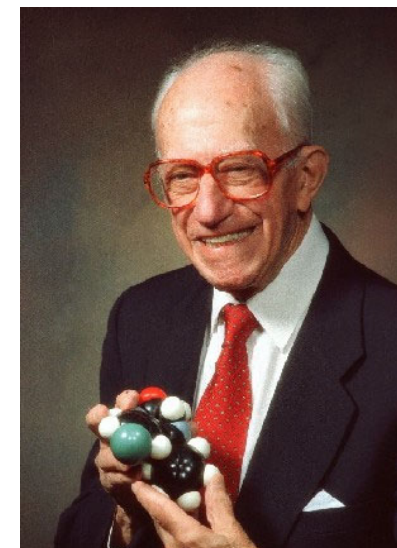


Annoura, H.; Tatsuoka, T. *TETL* **1995**, 413

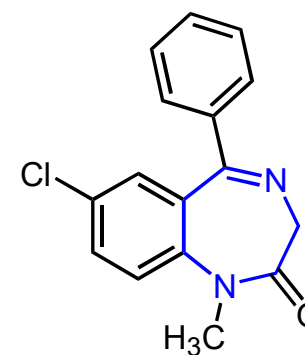
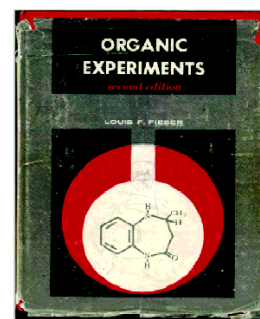
F. Siebengliedrige Ringe - F.3 Diazepine



1955 gab man das Projekt auf. 1957 entdeckte man bei Aufräumarbeiten ein Gefäß, welches ein Chinazolinoxid enthalten sollte und dessen Inhalt sich in einem letzten Test als Tranquillans herausstellte. Weitere Untersuchungen revidierten die Struktur.

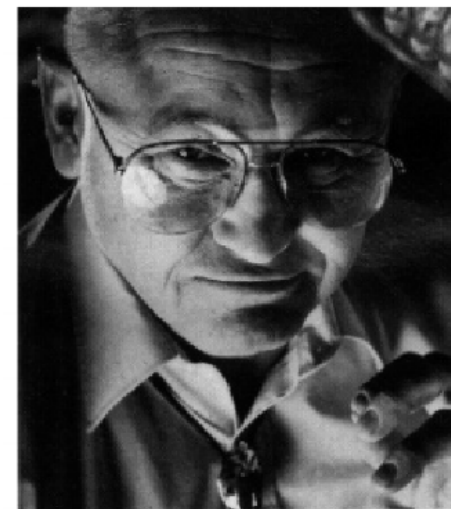
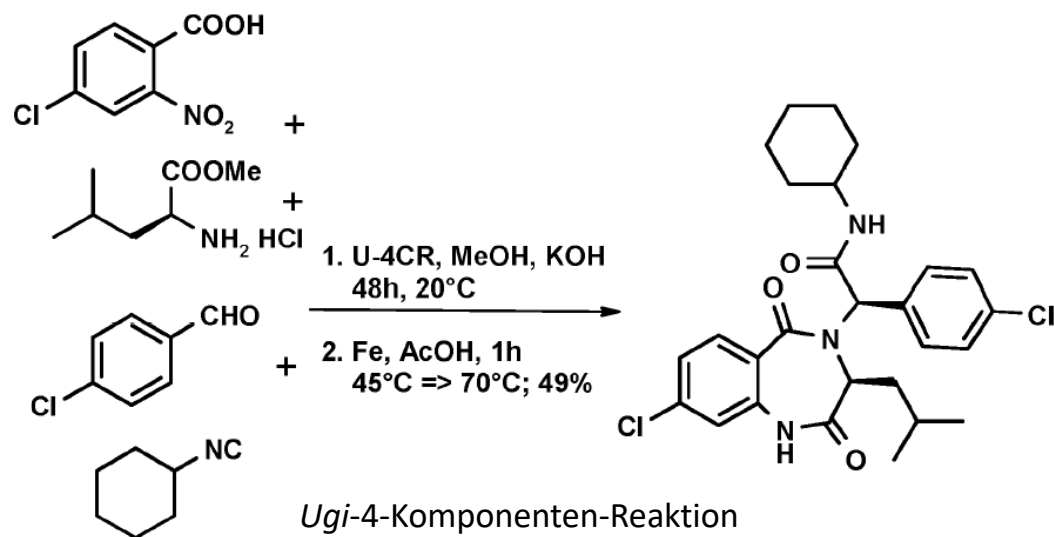


Leo Sternbach

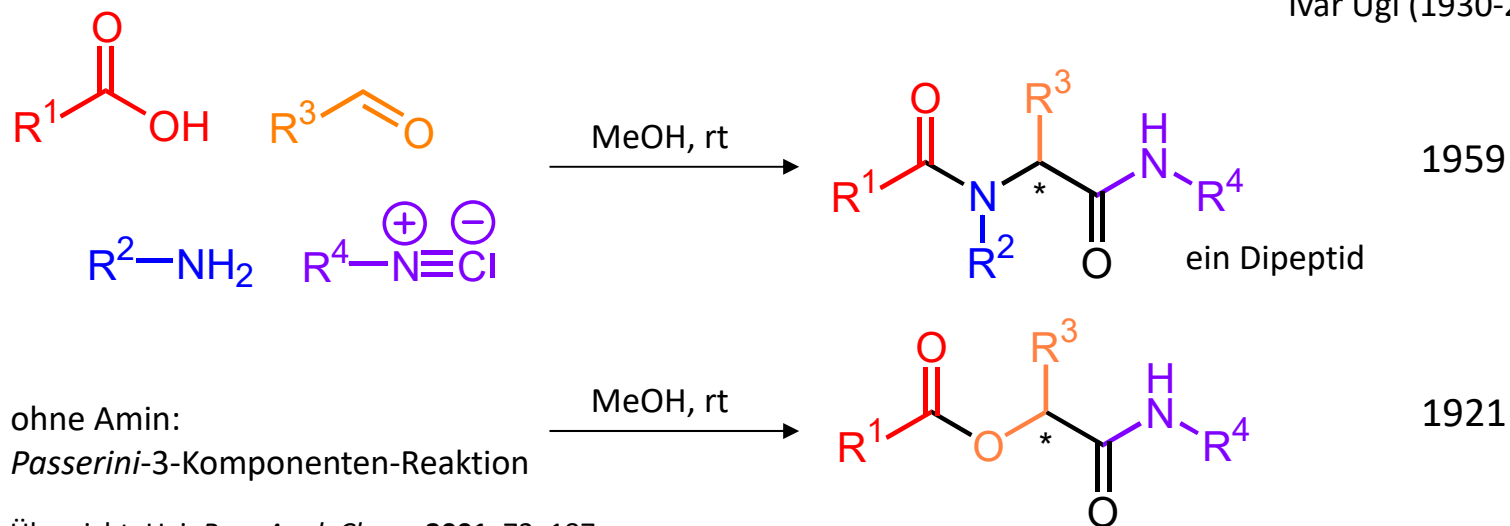


Diazepam, ("Valium", 10x aktiver)

F. Siebengliedrige Ringe - F.3 Diazepine



Ivar Ugi (1930-2005)

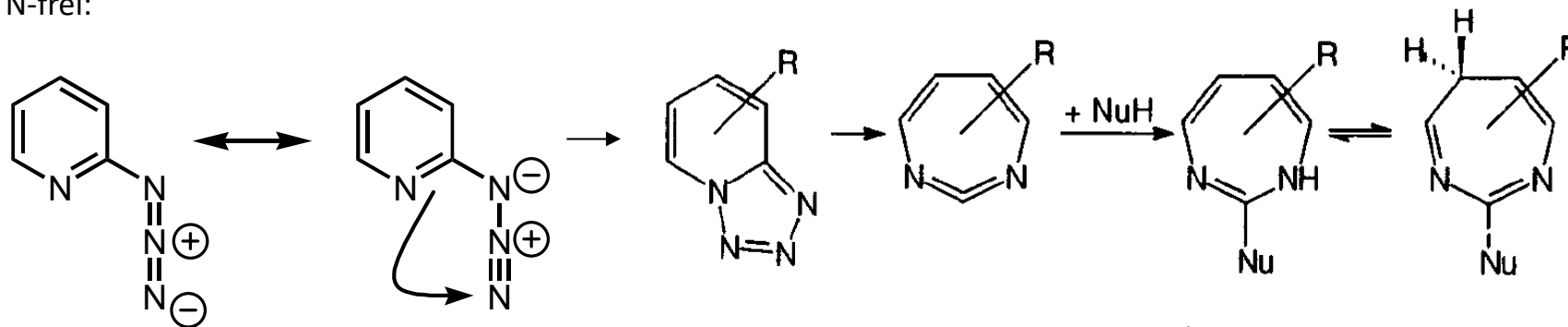


Übersicht: Ugi, *Pure Appl. Chem.* **2001**, 73, 187.

F. Siebengliedrige Ringe - F.3 Diazepine

1,3-Diazepine

N-frei:



Wentrup et al., *Perkin Trans. 2*, **1997**, 1851.