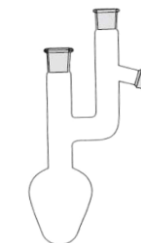
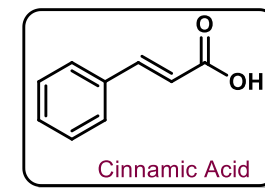
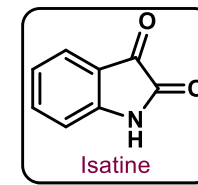


Rainer Ludwig Claisen



- Born in Cologne, Germany (1851)
- Army service as nurse (1870-1871)
- Scientific career:
 - 1874: PhD at the University of Bonn in Kekulé's laboratory
 - 1878: Habilitation at the University of Bonn
 - 1882: Worked with H. Roscoe and Carl Schorlemmer at Owens College (Manchester)
 - 1885: Worked with A. von Baeyer at LMU Munich
 - 1887: Habilitation as PD at LMU Munich
 - 1890: Full Professor of Organic Chemistry at TH Aachen
 - 1897: Full Professor of Chemistry at the University of Kiel
 - 1904: Honorary Professor at the University of Berlin, collaboration with E. Fischer
 - 1907: Emeritus, starts his own private laboratory in Godesberg am Rhein
- Scientific contributions:
 - 1879: Claisen Isatin Synthesis
 - 1881: Claisen-Schmidt condensation
 - 1887: Claisen Condensation/Claisen reaction
 - 1890: Synthesis of Cinnamates by Claisen Condensation
 - 1912: Claisen Rearrangement
- Design of the Claisen flask
- Died in Bonn, Germany (1930)

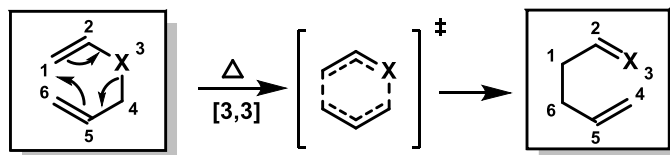


Claisen flask

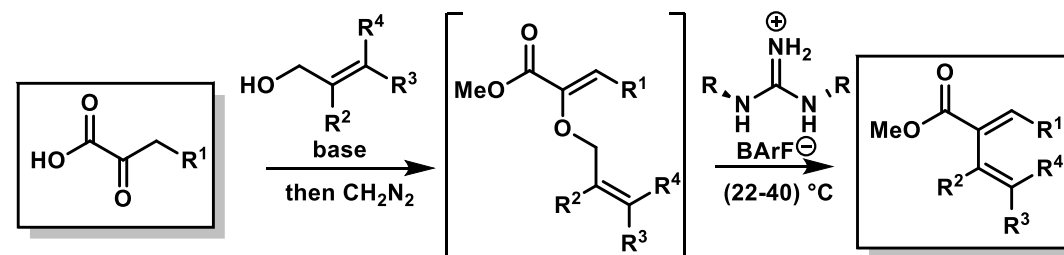
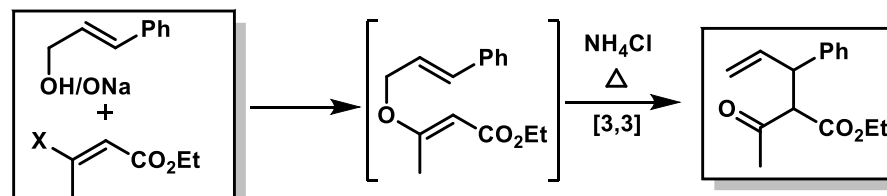
W Pötsch. Lexikon bedeutender Chemiker (VEB bibliographic institute Leipzig, 1989)

(Aliphatic) Claisen Rearrangement and several Preparation Methods for Allyl Vinyl Ethers (1912)

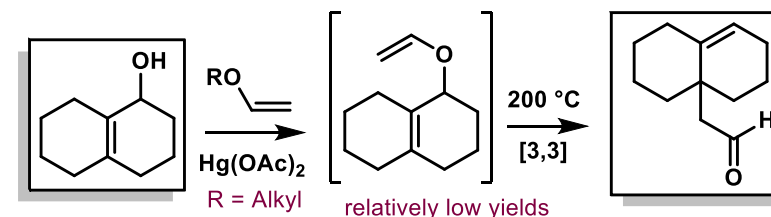
- [3,3]-sigmatropic rearrangement of allyl vinyl ethers
- preparation of unsaturated carbonyl compounds



X = O, N, S (also see Aza-Claisen and Thio-Claisen RA)

L. Claisen, *Ber. Dtsch. Chem. Ges.* **1912**, 45(3), 3157-3166.C. Uyeda, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, 130, 9228-9229.

R = OEt, Cl

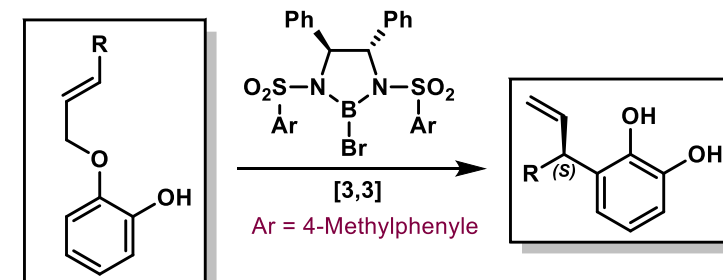
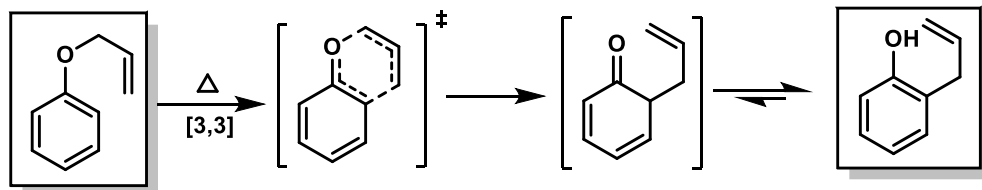
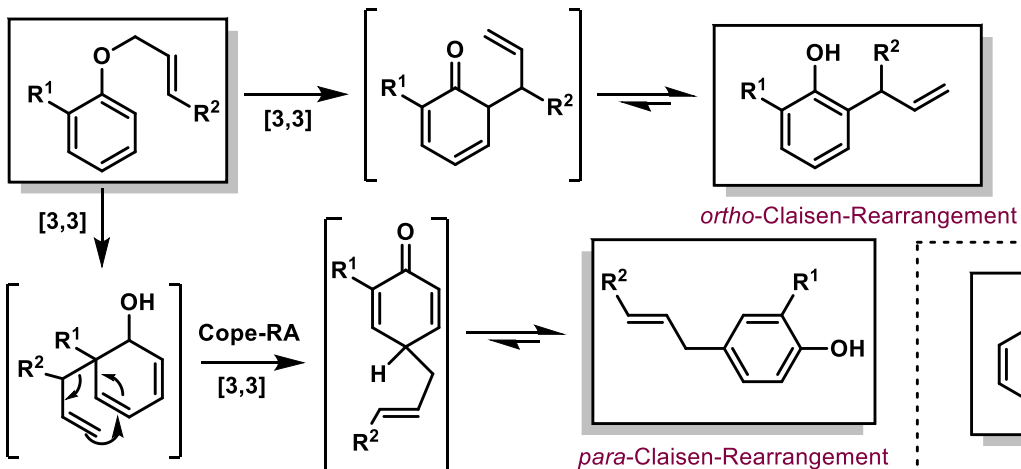
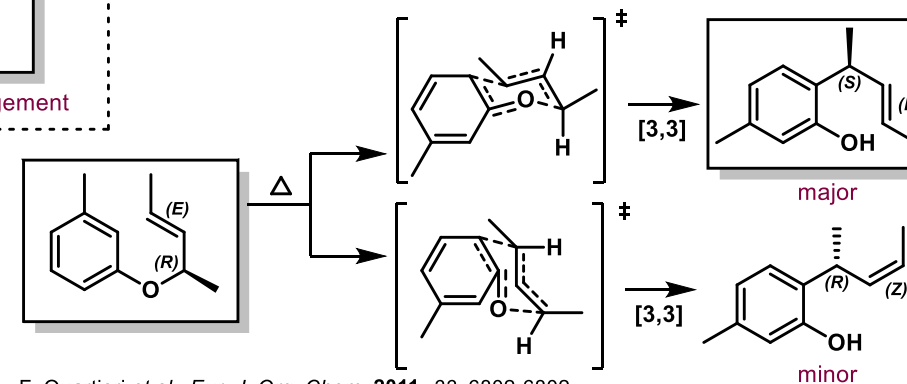
E. Bergmann, H. Corte, *J. Chem. Soc.* **1935**, 1363.W. M. Lauer, E. I. Kilburn, *J. Am. Chem. Soc.* **1937**, 59, 2586.

R = Alkyl

relatively low yields

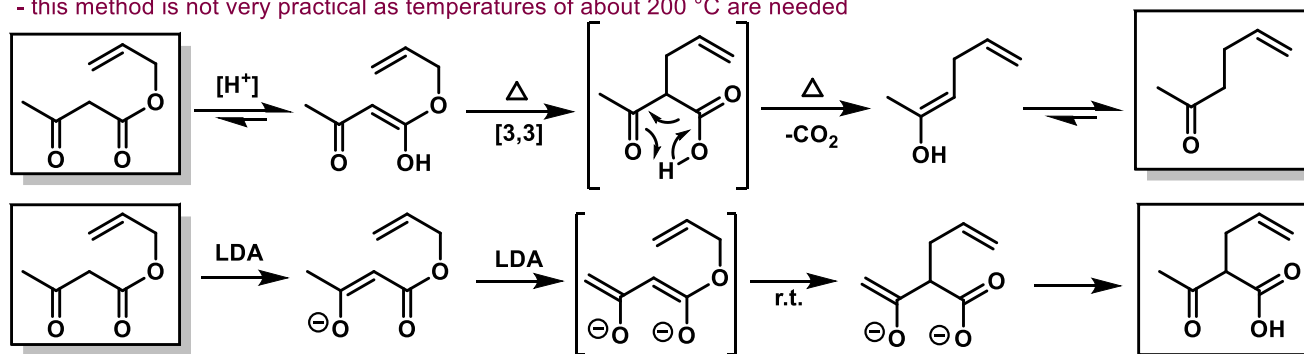
A. W. Burgstahler, I. C. Nordin, *J. Am. Chem. Soc.* **1961**, 83, 198.

Aromatic Claisen Rearrangements

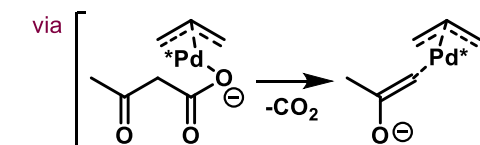
H. Ito, A. Sato, T. Taguchi, *Tetrahedron Lett.* **1997**, 38(27), 4815-4818.P. Wipf, S. Rodriguez, *Adv. Synth. Catal.* **2002**, 344(3+4), 434-440.F. Quartieri et al., *Eur. J. Org. Chem.* **2011**, 33, 6802-6802.

Caroll Rearrangement (Decarboxylative Allylation, 1940)

- thermal rearrangement of allyl ketoesters followed by decarboxylation
- this method is not very practical as temperatures of about 200 °C are needed

M. F. Carroll, *J. Chem. Soc.* **1940**, 704. M. F. Carroll, *J. Chem. Soc.* **1940**, 1266. M. F. Carroll, *J. Chem. Soc.* **1941**, 507.

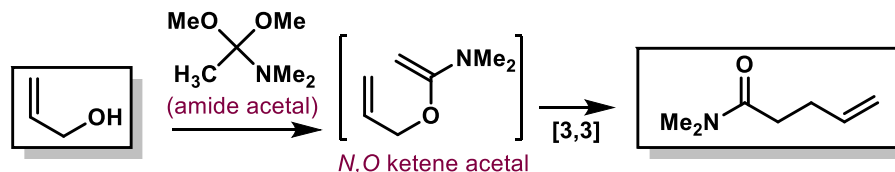
The reaction can also proceed under milder conditions with a Pd(0) catalyst



Finally, the Caroll rearrangement can also proceed enantioselectively by usage of chiral ligands (e.g. Trost ligand)

I. Shimizu, R. Yamada, J. Tsuji, *Tetrahedron Lett.* **1980**, 33, 3199-3202.
 B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, 127(49), 17180-17181.

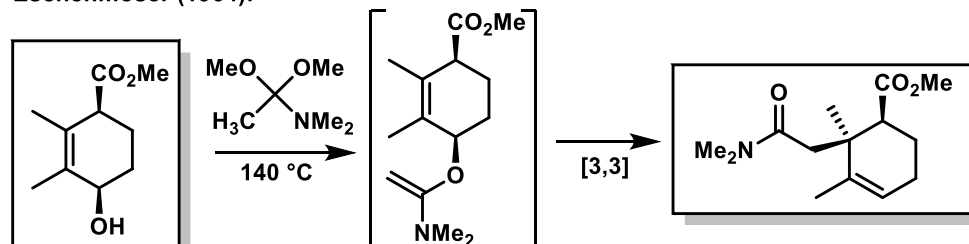
Eschenmoser-Claisen Rearrangement (1964)



- allows the formation of a C-C bond in the beta position of a Nitrogen atom
- importance in Natural Product Synthesis (especially Alkaloids)
- N,O ketene acetal formation sometimes problematic, because elevated temperature is needed, which sometimes results in decomposition of the resulting amides
- very high synthetic relevance because of mild reaction conditions

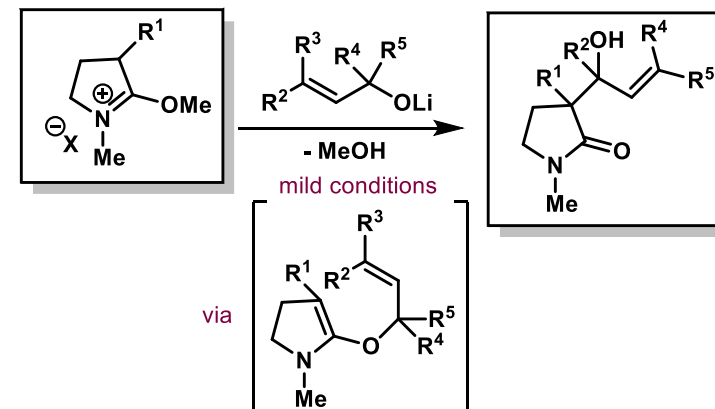
A. E. F. Wick, D. Felix, K. Steen, A. Eschenmoser, *Helv. Chim. Acta* **1964**, 47, 2425.

Eschenmoser (1964):



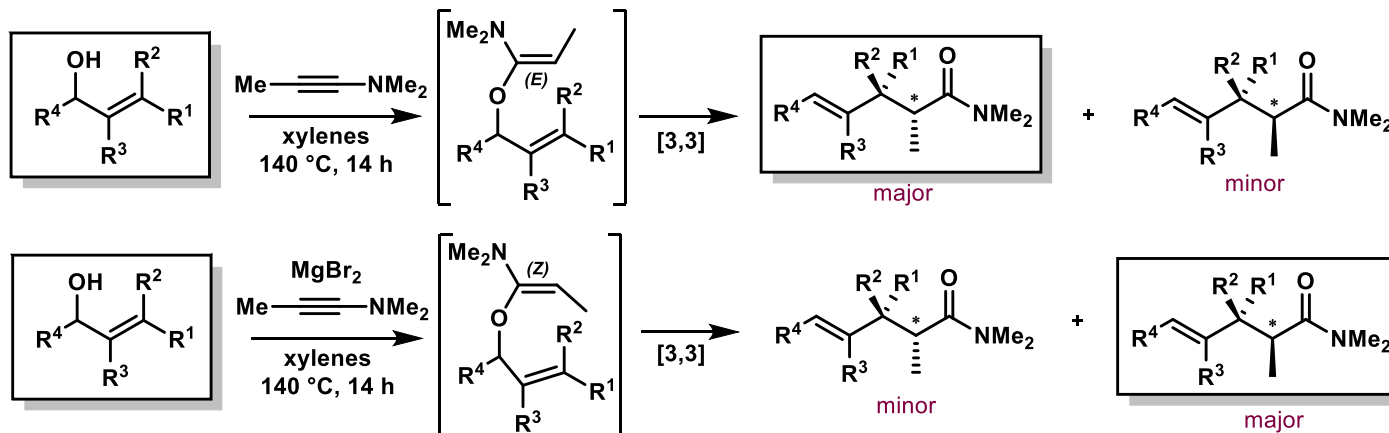
- elevated temperature only required for the alcohol exchange reaction
- the actual rearrangement proceeds under mild conditions, which increases the synthetic value of the Eschenmoser-Claisen rearrangement

A. E. F. Wick, D. Felix, K. Steen, A. Eschenmoser, *Helv. Chim. Acta* **1964**, 47, 2425.



B. Coates, D. Montgomery, P. J. Stevenson, *Tetrahedron Lett.* **1991**, 32, 4199.

Ficini-Claisen Rearrangement (Ynamine Claisen Rearrangement):

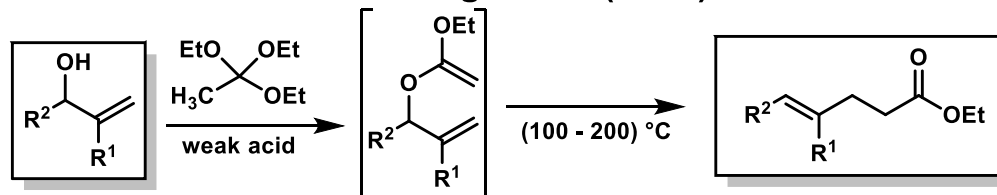


Heating of the reaction mixture forms the kinetically favoured (E)-isomer resulting high yields of the major product

Lewis acids (like MgBr₂) change the equilibrium towards the thermodynamically favoured (Z)-isomer changing the diastereoselectivity of the product

J. Ficini, C. Barbara, *Tetrahedron Lett.* **1966**, 6425. J. Ficini, *Tetrahedron* **1976**, 32, 1449. P. A. Bartlett, W. F. Hahne, *J. Org. Chem.* **1979**, 44, 882.

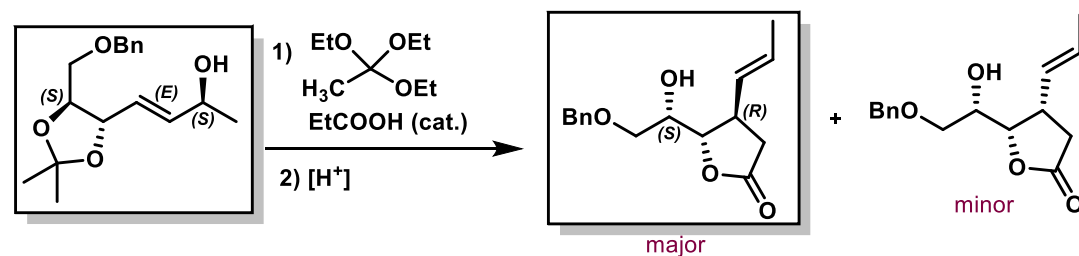
Johnson-Claisen Rearrangement (1970)



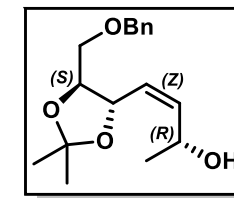
- affords *trans*-trisubstituted alkenes
- excess of ethyl orthoacetate is needed
- catalytic trace amount of a weak acid is needed (like propanoic acid)

W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brockson, T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *44*, 882.

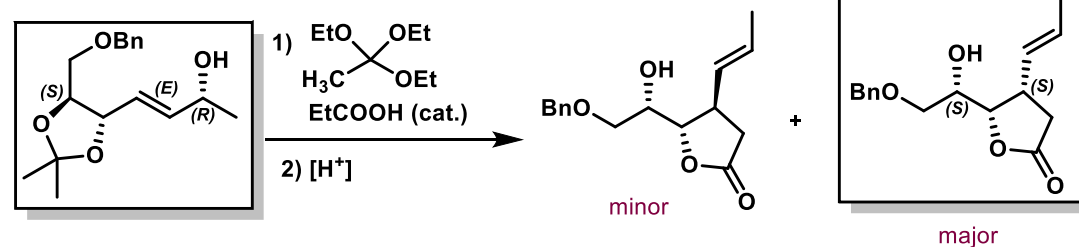
Diastereoselective Johnson-Claisen Rearrangement with subsequent lactonization:



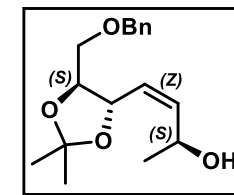
similar results with



as reactant



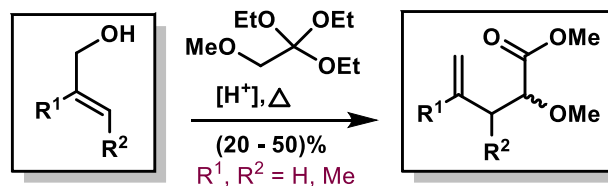
similar results with



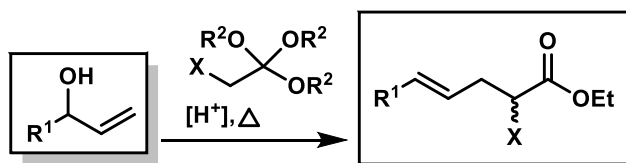
as reactant

The Claisen Rearrangements (Eds.: M. Hiersemann, U. Nubbemeyer), Wiley-VCH, Weinheim, Germany, **2007**.

Johnson-Claisen Rearrangement with a heteroatomic substituent



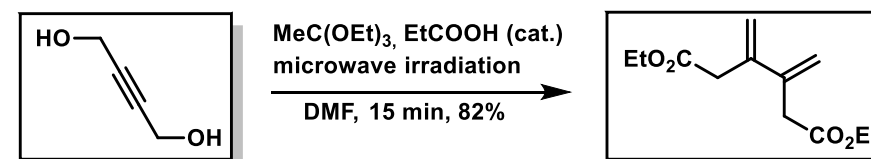
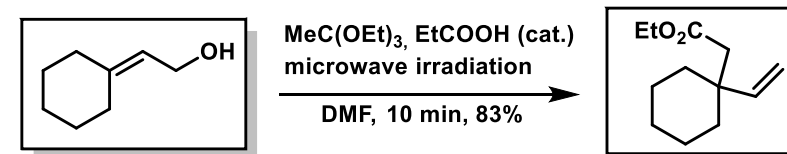
G. W. Daub, D. H. Teramura, K. E. Bryant, M. T. J. Burch, *J. Org. Chem.* **1981**, *46*, 1485.



X = Cl, SMe, F; R¹ = Alkyl; R² = Et, nPr

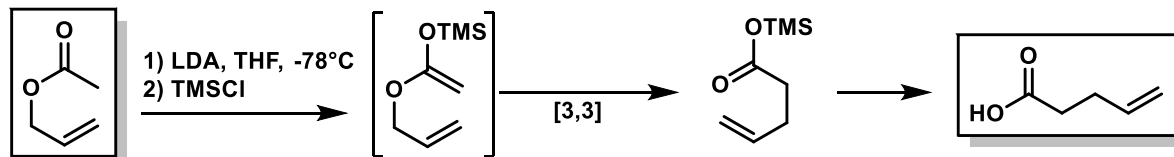
R. T. Elworthy *et al.*, *Tetrahedron Lett.* **1994**, *35*(28), 4951-4954.

Johnson-Claisen Rearrangement under microwave conditions



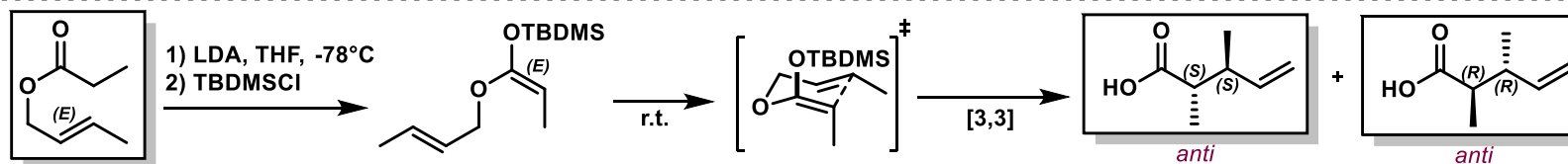
A. Srikrishna, S. Nagaraju, P. Kondaiah, *Tetrahedron* **1995**, *51*(6), 1809-1816.

Ireland-Claisen Rearrangement (1972)

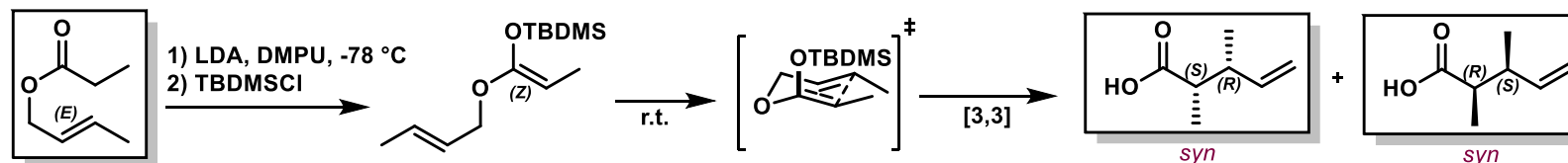


- reaction proceeds under mild neutral or basic conditions
- allows the preparation of polyfunctionalized structures
- easy to prepare the allylic ester reactants
- ease of controlling stereochemistry at C2- and C3-position
- chirality transfer between the allylic stereocenter of the allyl ketene acetal
- high level of alkene stereocontrol

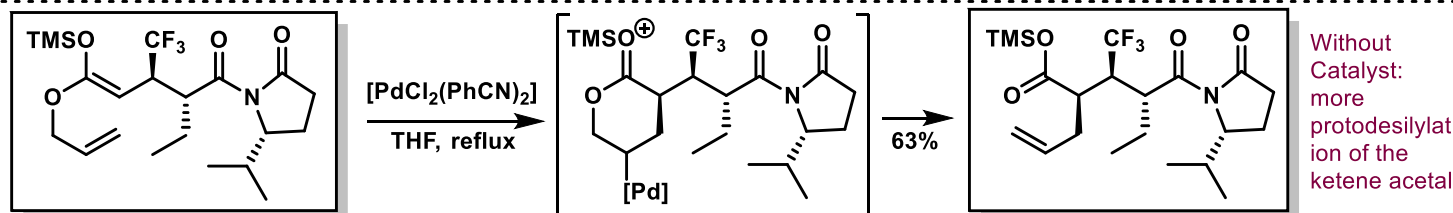
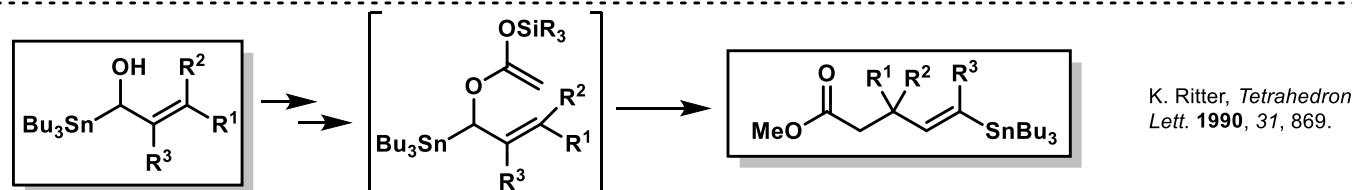
R. E. Ireland, R. H. Mueller, *J. Am. Chem. Soc.* **1972**, *94*, 5897. R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868.



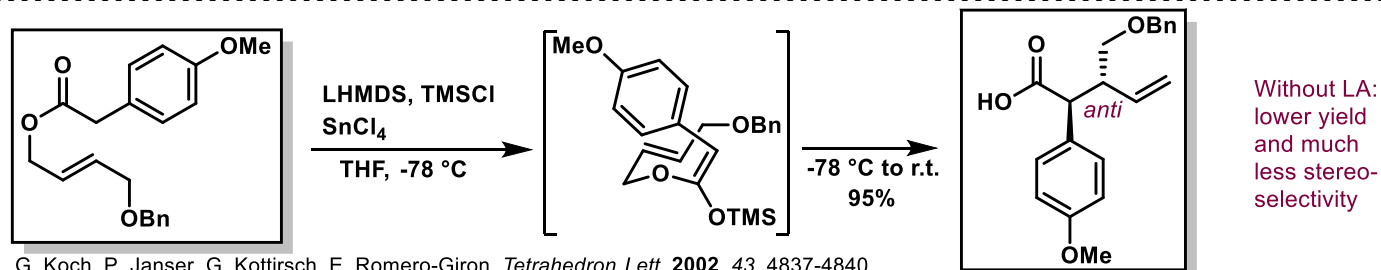
E. Enders, *Tetrahedron: Asymmetry* **1996**, *7*, 1847-1882.



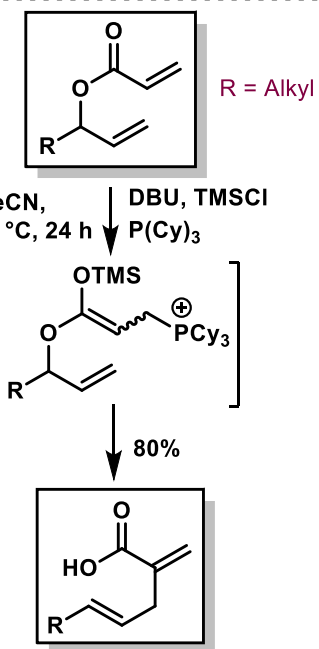
Y. Chai, *Tetrahedron* **2002**, *58*, 2905-2928.



T. Yamazaki, N. Shinohara, T. Kitazume, S. Sato, *J. Org. Chem.* **1995**, *60*, 8140-8141.

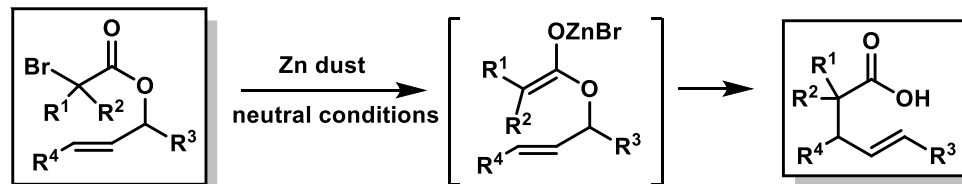


G. Koch, P. Janser, G. Kottirsch, E. Romero-Giron, *Tetrahedron Lett.* **2002**, *43*, 4837-4840.



T. Hanamoto, Y. Baba, J. Inanaga, *J. Org. Chem.* **1993**, *58*, 299-300.

Reformatsky-Claisen Rearrangement (1973)

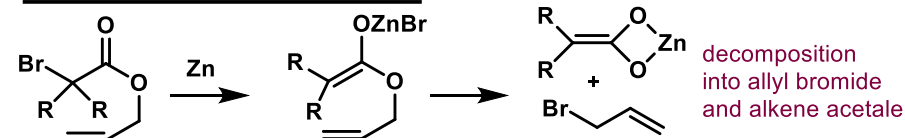


J. E. Baldwin, J. A. Walker, *J. Chem. Soc., Chem. Commun.* **1973**, 4, 117.

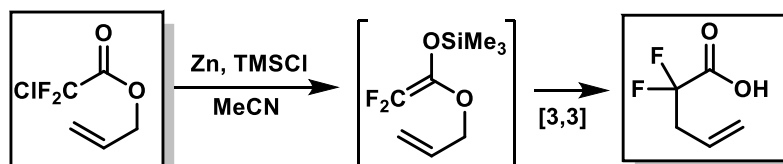
	R ¹	R ²	R ³	R ⁴	Yield
1	Me	Me	H	H	100%
2	Me	H	H	Me	96%
3	H	H	H	H	<15%
4	Me	H	Ph	Me	16%

Low yields for the simple allylic ester (3) and the secondary ester (4) because of side reactions:

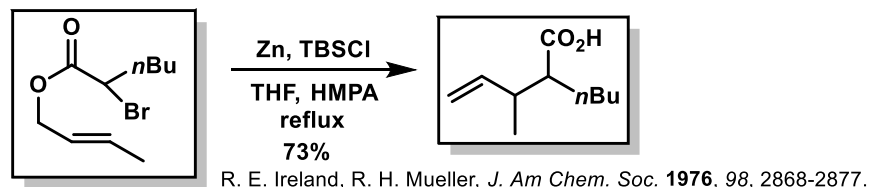
- intermolecular Claisen condensation
- decomposition of the Zn enolate



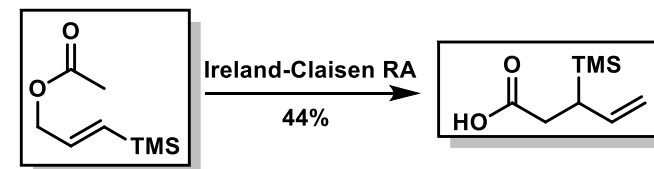
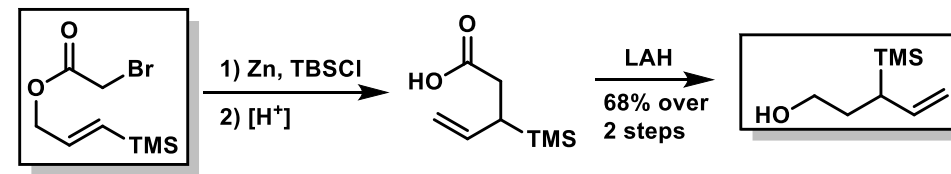
Reformatsky-Claisen Rearrangement in presence of a silylating agent:



H. Greuter, R. W. Lang, A. J. Romann, *Tetrahedron Lett.* **1988**, 29, 3291.



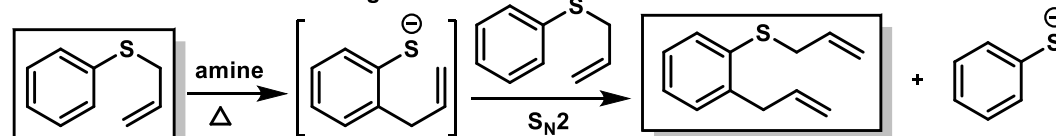
R. E. Ireland, R. H. Mueller, *J. Am. Chem. Soc.* **1976**, 98, 2868-2877.



M. Wada, T. Shigehisa, K. Akiba, *Tetrahedron Lett.* **1985**, 26, 5191-5194.

Thio-Claisen Rearrangement (1912)

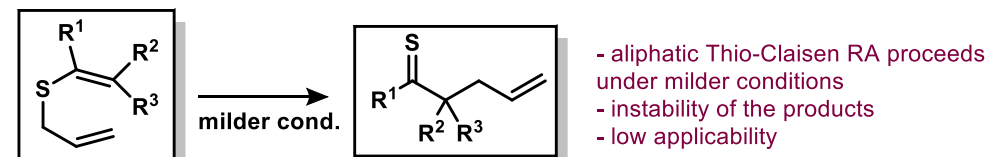
Aromatic Thio-Claisen Rearrangement



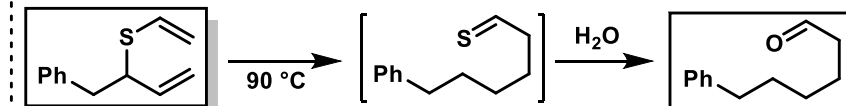
H. Kwart, J. L. Schwartz, *J. Org. Chem.* **1974**, 39, 1575. H. Kwart, C. M. *J. Am. Chem. Soc.* **1962**, 84, 1754.

- requires higher energy than normal Claisen rearrangement
- S_N2 displacement by the thiolate intermediate
- very low applicability

Aliphatic Thio-Claisen RA



H. Takahashi, K. Oshima, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **1973**, 95, 5803.



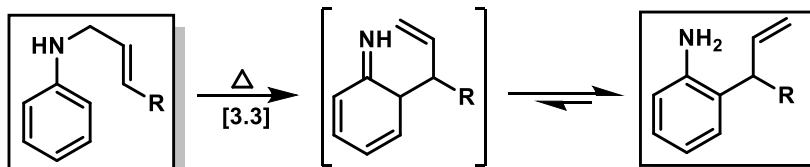
K. Oshima, H. Takahashi, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **1973**, 95, 2693.

Aza-Claisen Rearrangement (1912)

- requires extremely harsh conditions (200-350) °C
- undesired byproducts (lower yield)

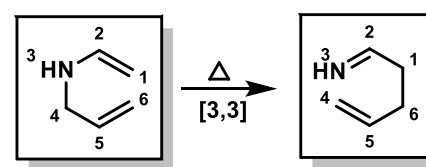
also see: Aza-Claisen Rearrangement in the Cyclization Reactions of Nitrogen-Containing Enynes via Ruthenium Vinylidene Complexes (P.-Y. Chiang, Y.-C. Lin, Y. Wang, Y.-H. Liu, *Organometallics* **2010**, 29(22), 5776-5782.)

Aromatic Aza-Claisen Rearrangement



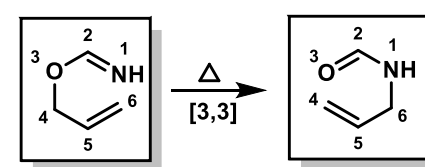
S. Jolidon, H.-J. Hansen, *Helv. Chim. Acta* **1977**, 60, 978.

Aliphatic Aza-Claisen Rearrangement

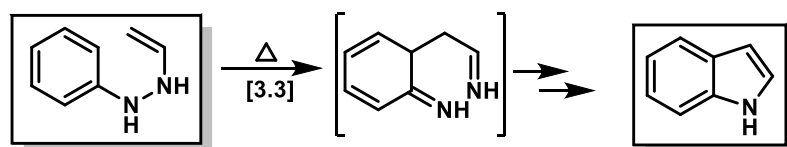


G. B. Bennett, *Synthesis* **1977**, 589.

Aliphatic 1-Aza-Claisen Rearrangement

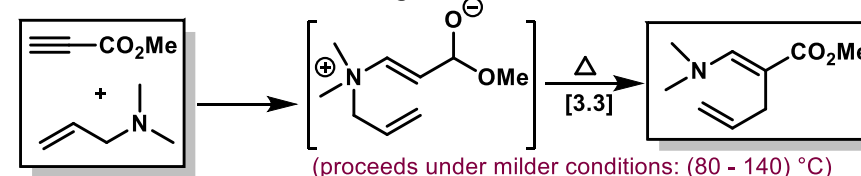


Fischer Indole Synthesis (3,4-Diaza-Claisen RA/Cope RA)

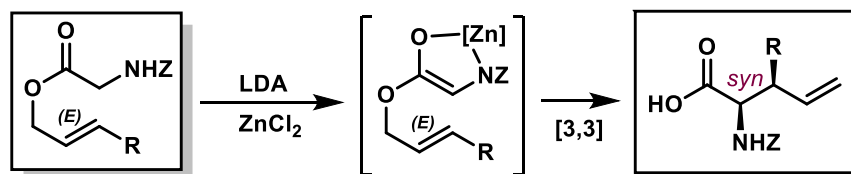


U. Nubbemeyer, Recent Advances in Charge-Accelerated Aza-Claisen Rearrangements. In: Mulzer J. (eds) *Natural Products Synthesis II. Topics in Current Chemistry*, 244. Springer, Berlin, Heidelberg.

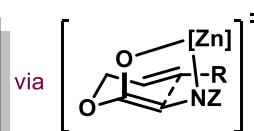
Zwitterionic Aza-Claisen Rearrangement



Chelate-Claisen Rearrangement (1994)

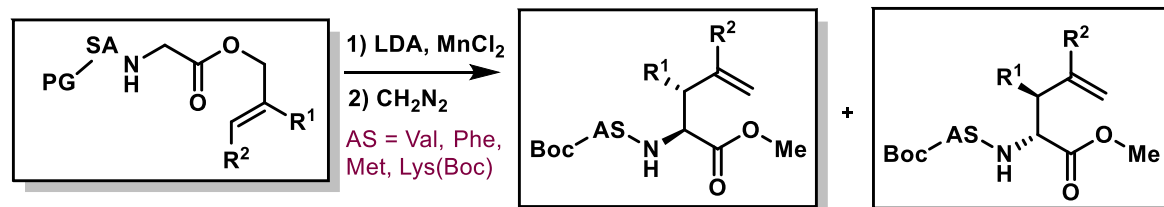


Z = Bz (Benzoyl-) U. Kazmaier, *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 998.



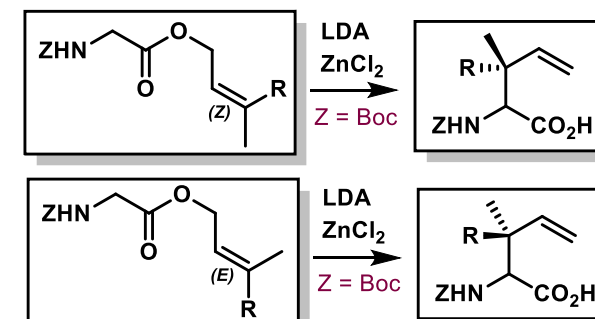
- chelation increases the thermal stability with no negative influence on the reactivity of those enolates
- very high diastereoselectivity because of rigid geometry of the transition state
- Synthesis of amino acids
- driving force: transformation of the high-energy ester enolate into a chelate-bridged, stabilized carboxylate

Modification of Dipeptides



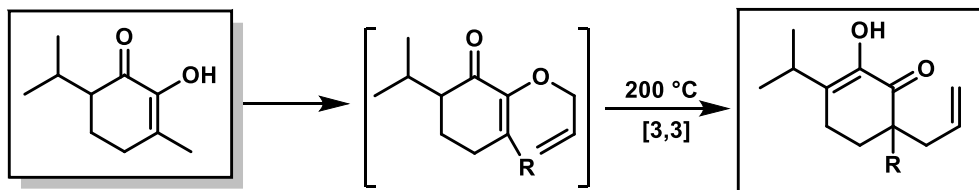
U. Kazmaier, S. Maier, *Chem. Commun.* **1998**, 2535-2536.

Synthesis of quarternary AS



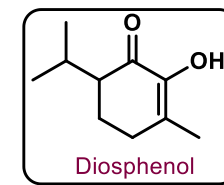
U. Kazmaier, *Synlett* **1995**, 11, 1138-1140.

Diosphenol-Claisen Rearrangement (1980)



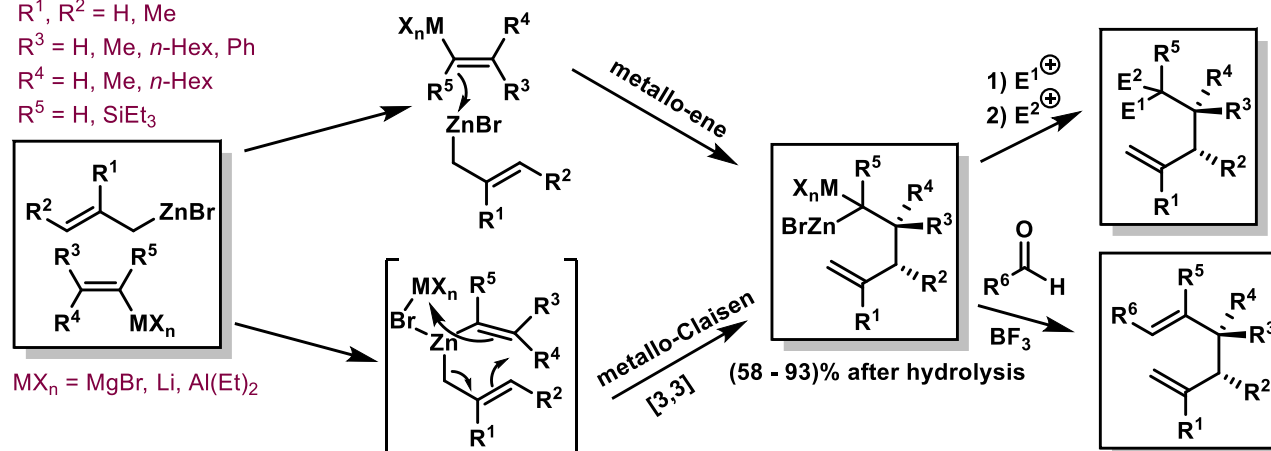
A. A. Ponaras, *Tetrahedron Lett.* **1980**, 21, 4803.

- allyl ethers derived from diosphenol, with an endocyclic vinyl double bond, give rise to a bond between a functionalized carbon moiety and a sterically hindered carbon which is part of a cyclic structure
- the resulting bisketone usually tautomerizes into the ketoenol derivative.



Metallo-Claisen Rearrangement (1986)

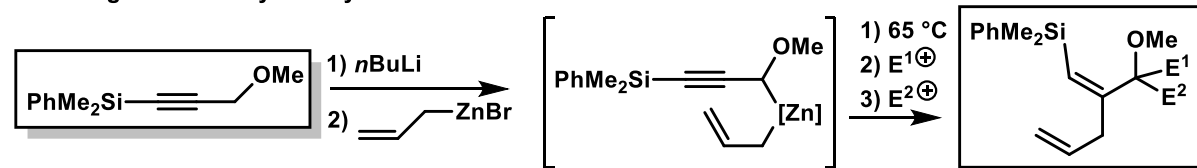
$R^1, R^2 = \text{H, Me}$
 $R^3 = \text{H, Me, } n\text{-Hex, Ph}$
 $R^4 = \text{H, Me, } n\text{-Hex}$
 $R^5 = \text{H, SiEt}_3$



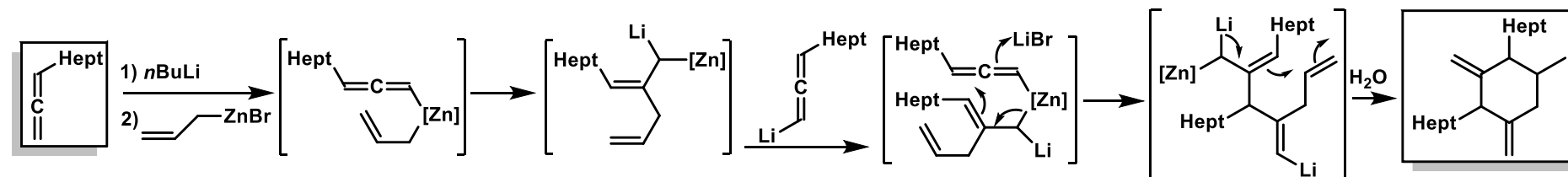
$\text{MX}_n = \text{MgBr, Li, Al(Et)}_2$

- carbometallation of an alkenyl organometallic derivative of magnesium, lithium, or aluminium by an allylic zinc bromide to provide *gem*-dimetallic compounds
- two mechanistic rationales: metallo-Claisen rearrangement and metallo-ene reaction
- high diastereoselectivity because of short length of the C-C formed bond in the late transition state of the metallo-Claisen process
- the *gem*-dimetallic compounds can react with two different electrophiles to obtain *gem*-difunctionalized structures

Rearrangement of Allyl Allenyl Derivatives

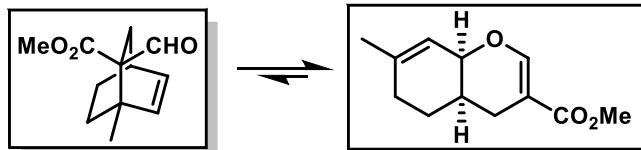


P. Knochel, J. F. Normant, *Tetrahedron Lett.* **1986**, 27, 1039. P. Knochel, J. F. Normant, *Tetrahedron Lett.* **1986**, 27, 1043. P. Knochel, J. F. Normant, *Tetrahedron Lett.* **1986**, 27, 4427. P. Knochel, J. F. Normant, *Tetrahedron Lett.* **1986**, 27, 4431. J. F. Normant, J. C. Quirion, A. Alexakis, Y. Masuda, *Tetrahedron Lett.* **1989**, 30, 3955. J. F. Normant, J. C. Quirion, *Tetrahedron Lett.* **1989**, 30, 3959. A. Hiral, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2000**, 122, 11791.

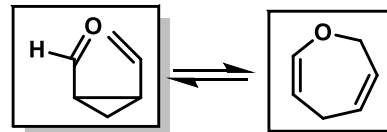


Retro-Claisen Rearrangement

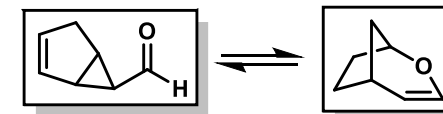
- Retro-Claisen disfavored because of the higher thermodynamic stability of the unsaturated carbonyl compounds (thermodynamic control, irreversible)
- some structural motifs however undergo Retro-Claisen RA
- driving force: relief of torsional strain in presence of a catalytic amount of lewis acid (e.g. BF_3)



R. K. Beckman, Jr., C. J. Flann, K. M. Poss, *J. Am. Chem. Soc.* **1985**, *107*, 4359.

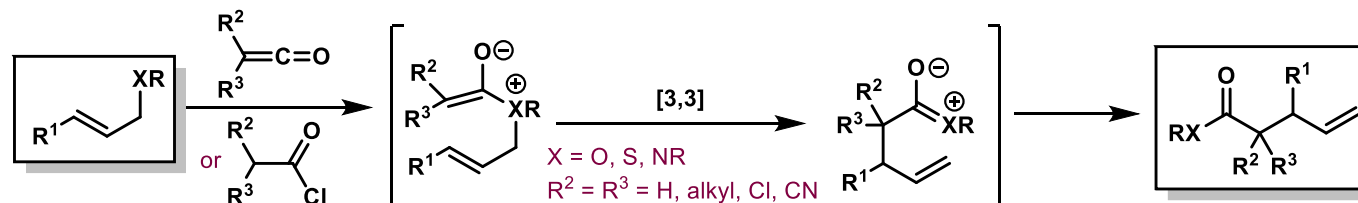


S. J. Rhoads, R. D. Cockroft, *J. Am. Chem. Soc.* **1969**, *91*, 2815.



M. Rey, A. S. Dreiding, *Helv. Chim. Acta* **1965**, *48*, 1985.

Bellus-Claisen Rearrangement (1979)

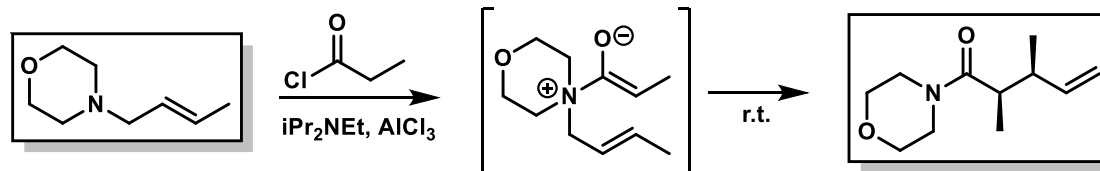


(also see Acyl Claisen RA)

J. Gonda, *Angew. Chem. Int. Ed.* **2004**, *43*(27), 3516-3524.

Synthesis of unsaturated esters via zwitterionic intermediates generated *in situ* from allylic ethers and ketenes or acyl halides (with lewis acid catalysis)

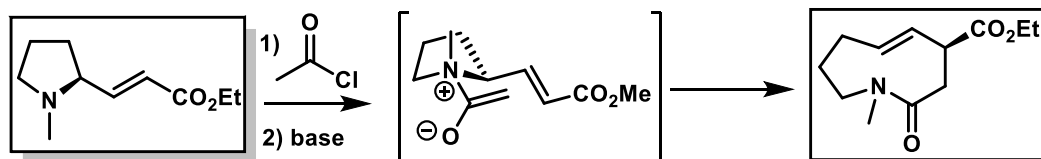
Acyl Claisen Rearrangement



T. P. Yoon, V. M. Dong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **1999**, *121*, 9726.

- Acyl-Claisen highly *syn*-selective (99:1) and proceeds under room temperature
- Eschenmoser-Claisen *anti*-selective (5:1) and proceeds under elevated temperatures
- Aza-Claisen highly *syn*-selective (99.5:0.5) and proceeds under elevated temperatures
- Synthesis of Tetrahydrofuranes, Pyrroles, Furanes, or Thiophenes

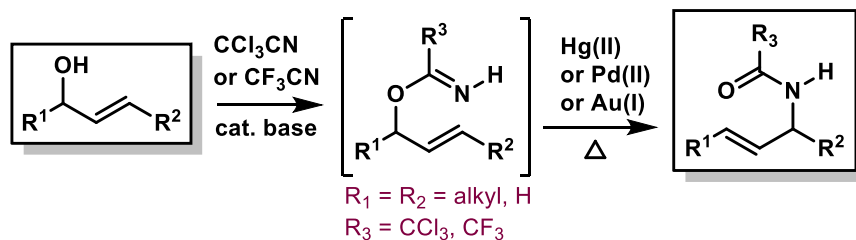
Ring Enlargement Acyl-Claisen Rearrangement



M. Diedrich, U. Nubbemeyer, *Angew. Chem. Int. Ed.* **1995**, *34*(9), 1026-1028.

- ketenes don't react with the allyl amines, since ketenes are not electrophilic enough
- Lewis acids increase the acidity of the alpha-protons by interacting with the carbonyl group of the acyl ammonium salt and stabilization of the zwitterionic intermediate and thus suppressing the elimination of ketene

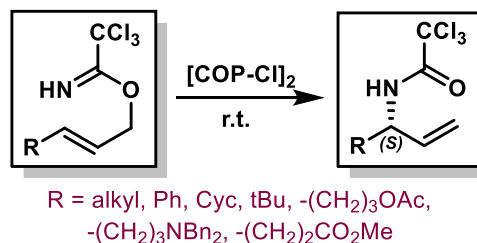
Overman Rearrangement (1974)



- rearrangement from allylic trichloroacetimidate/allylic trifluoroacetimidate ester to an allylic trichloroacetamide/allylic trifluoroacetamide
- milder reaction conditions are achieved by the use of $\text{Hg}(\text{OTf})_2$, or PdCl_2 , or AuCl as catalysts
- Overman Rearrangement is applied in many natural product synthesis

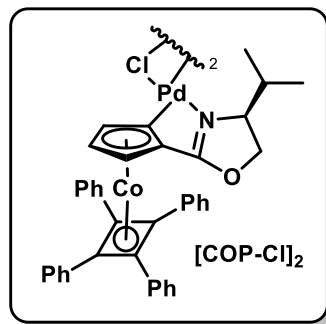
R. A. Fernandes, A. K. Chowdhury, P. Kattanguru, *Eur. J. Org. Chem.* **2013**, 2014(14), 1-40.

Enantioselective Overman Rearrangement

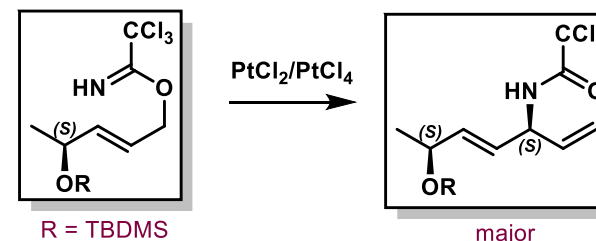


The (Z)-allylic trichloroacetimidates were found to be less reactive compared to (E)-isomers under similar reaction conditions

C. E. Anderson, L. E. Overman, *J. Am. Chem. Soc.* **2003**, 125, 12412-12413.

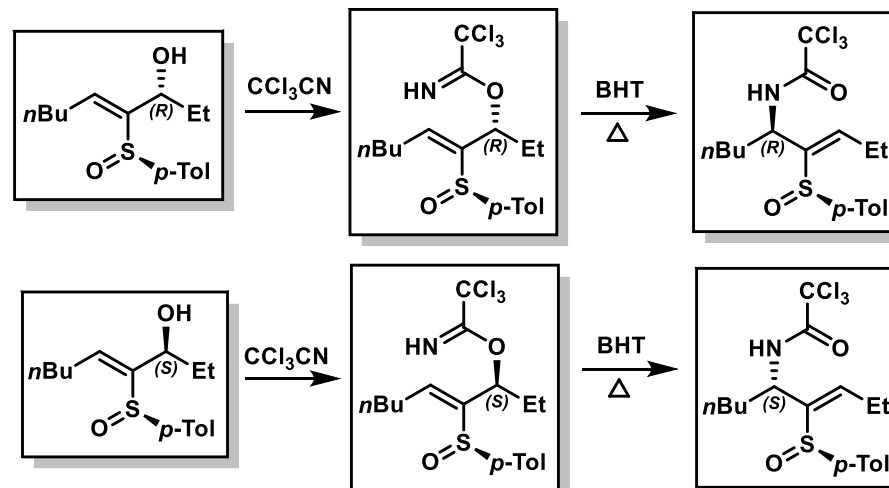


Ether directed diastereoselective metal-catalyzed Overman Rearrangement



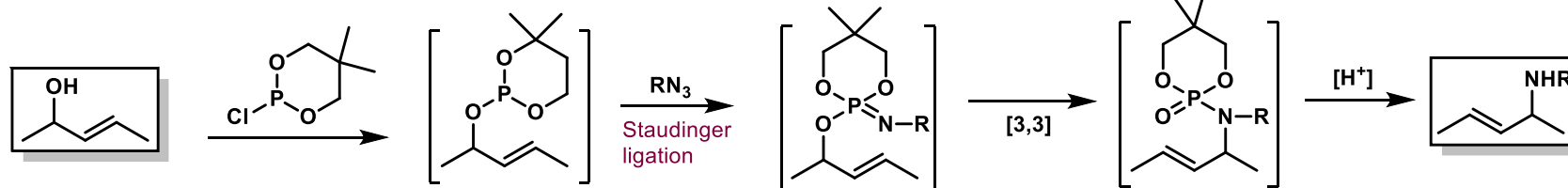
I. Jaunzeme, A. Jirgensons, *Tetrahedron* **2008**, 64(24), 5794-5799.

Overman Rearrangement of allylic sulfonyl imidates



I. Colomer *et al.*, *J. Org. Chem.* **2016**, 81(10), 4081-4097.

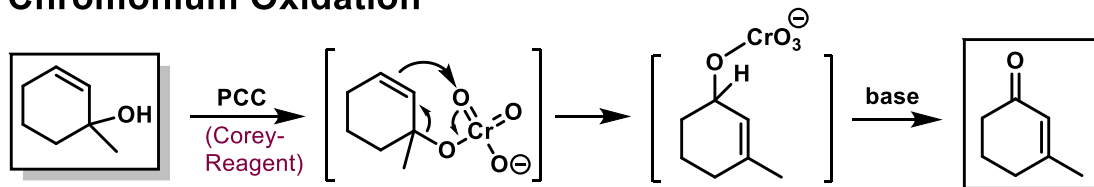
Chen-Mapp Reaction/Staudinger-Claisen Reaction (2005)



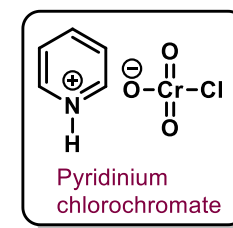
B. Chen, A. K. Mapp, *J. Am. Chem. Soc.* **2005**, 127(18), 6712-6718.

Rearrangement proceeds via allylic Phosphorimidates

Chromonium Oxidation

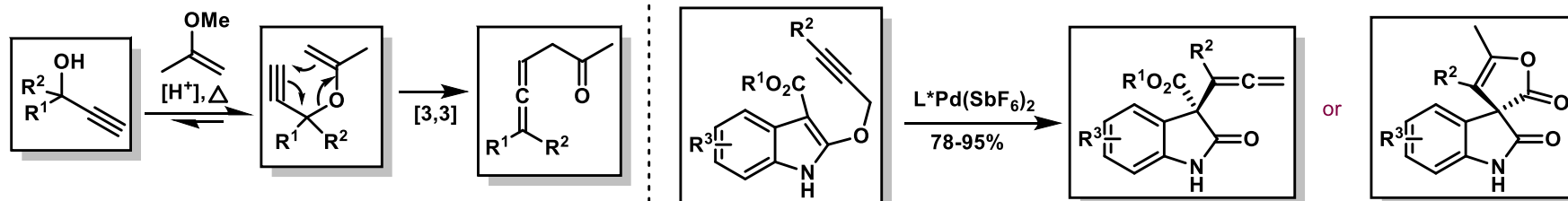


W. G. Dauben, D. M. Michno, *J. Org. Chem.* **1977**, 42(4), 682-685.
N. C. Wilde *et al.*, *J. Am. Chem. Soc.* **2014**, 136(13), 4909-4912.



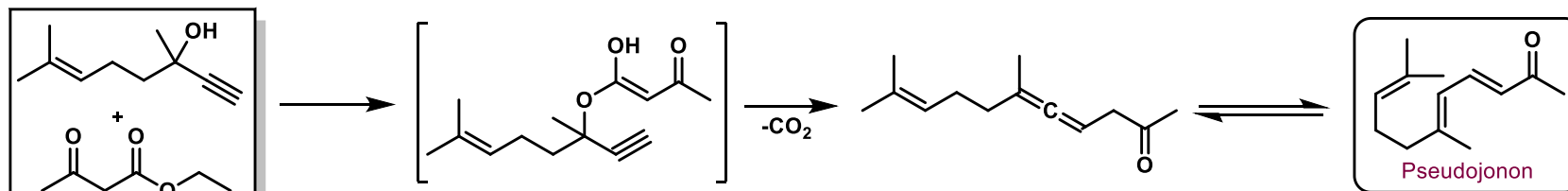
PCC can oxidize tertiary allylic alcohols to the corresponding transposed unsaturated carbonyl compounds in good to excellent yields

Saucy-Marbet Reaction/Propargyl Claisen Rearrangement (1965)



G. Saucy, R. Marbet, *Helv. Chim. Acta* **1967**, 50(4), 1158-1167.

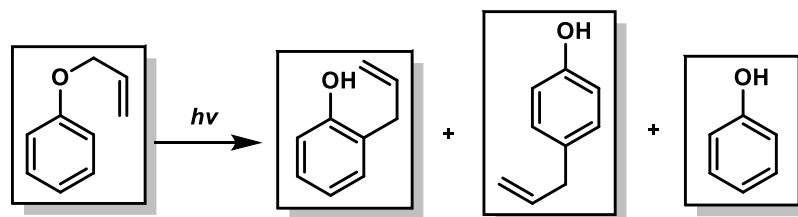
T. Cao, J. Deitch, E. C. Linton, M. C. Kozlowski, *Angew. Chem. Int. Ed.* **2012**, 51(10), 2448-2451.



Screening Information Dataset (SIDS) Initial Assessment Report (SIAR) for Pseudojonone:
link: <http://www.inchem.org/documents/sids/sids/141106.pdf> (retrieved 29.07.2018, 20:00)

Industrial Application

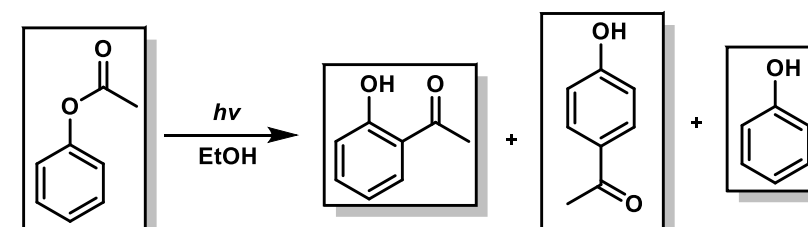
Photo-Claisen Rearrangement (1952)



The Photo-Claisen Rearrangement probably proceeds via a radicalic mechanism leading to a homolytic cleavage of the C-O bond resulting in several recombination reactions.

F. Galindo, *J. Photochem. Photobiol. C* **2005**, 6(2-3), 123-138.

Photo-Fries Rearrangement (1960)



The Photo-Fries Rearrangement also proceeds via a radical mechanism, which is solvent-dependant.

C. E. Kalmus, D. M. Hercules, *J. Am. Chem. Soc.* **1974**, 96(2), 449-456.