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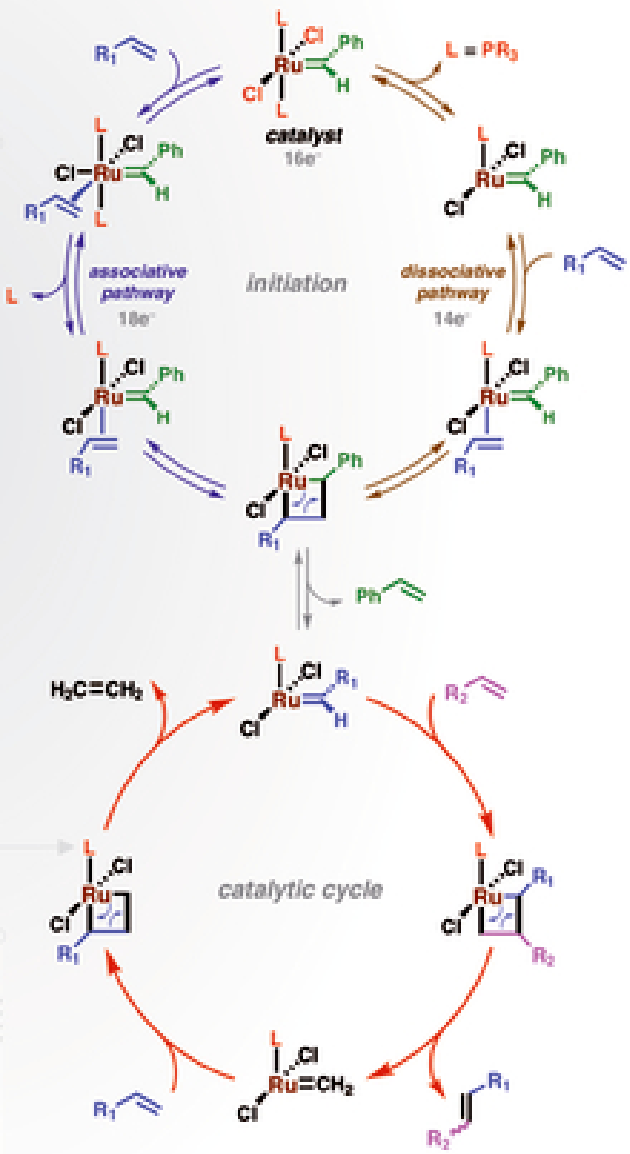

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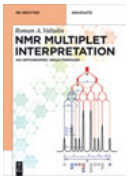

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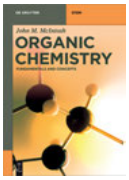

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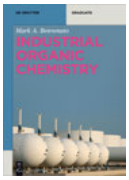

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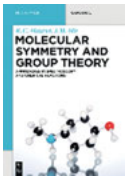

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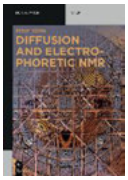

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Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.

— Marie Curie

Preface and Overview

Pedagogical Principles. At first, every body of knowledge that is new to us seems to have boundless complexity and creates the initial impression of incomprehensibility and even fear. Organic chemistry provides an excellent example of this phenomenon. The discipline is replete with complex and initially abstract concepts, as a result the information may seem overwhelming, particularly for the young chemist. But as with most new subjects, consistent study and practice reveals patterns, commonalities, rules, and an apparent logic. Eventually, an "architecture" becomes more apparent as we grow to become more experienced chemists. To develop this intuition, it requires close study, repetition, and breadth of exposure. A significant element of that learning is intrinsic and simply requires time and immersion. However, to help with the development of this intuition, an organic chemist would also be wise to focus on mechanisms for organic reactions as a foundation or anchoring point. This, in combination with deep study, can help organize knowledge into skill and expertise. An understanding of reaction mechanisms provides a solid foundation for the field and a scaffold for further study and life-long learning. Mechanisms are highly useful because they can logically explain how a chemical bond in a molecule was formed or broken and help to rationalize the formation of the final synthetic target or an undesired side-product. Moreover, as we parse an increasing number of mechanisms, we begin to see the similarities and an invisible conceptual "thread" then forms in our mind's eye that was not previously apparent. It helps to organize thinking and brings sense to the otherwise foreign concepts such as reactive intermediates, transition states, charges, radicals, and mechanistic arrows.

The Approach. To help galvanize – and perhaps catalyze – the organic chemist's inductive ability and to provide a "go-to" reference for closer study, this book strives to present an abridged summary of some of the most important mechanisms. In today's terms, these are 100 MUST-KNOW Mechanisms. The author draws upon scientific knowledge developed through undergraduate and graduate years, including post-doctoral research and study focused on organic synthesis. With a keen awareness of the incremental learning process, the book curates and presents mechanisms by category, starting with the fundamental and basic mechanisms (e.g., *nucleophilic substitution* or *elimination*), and mechanisms associated with the most well-known named reactions (e.g., the ***Diels–Alder*** *reaction* or the ***Mitsunobu*** *reaction*). Additionally, the collection is complemented with historically important mechanisms (e.g., the *diazotization* or the *haloform reaction*). Finally, it includes some mechanisms dear to the author's heart, which he deems elegant or simply "cool" (e.g., the ***Paternò–Büchi*** *cycloaddition* or the *alkyne zipper reaction*).

Organization. The mechanisms are organized alphabetically by chapter for ease of reference, and numbered from 1 to 100. The dedicated student will consistently proceed through every single mechanism, giving each one time to study, practice with, memorize, and ponder. At the same time, the book can be used as a quick visual

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reference or as a starting point for further research and reading. The 100 mechanisms are selected for being classic and famous, core or fundamental, and useful in practice. Of course, a good degree of personal intuition is involved in the selection and it is definitely not a dogmatic ordering or a comprehensive anthology. The book is intended to be a visual guide as distinguished from a traditional text book. The presentation of each mechanism constitutes a complete InfoGraphic (or "MechanoGraphic") and provides distilled information focusing on key concepts, rules, acronyms, and terminology. It heavily focuses on the basic core – the starting amount of information, the extract – that a good organic chemist can commit to memory and understanding. Starting initially as a daily micro-blog post with a "hash tag" (#100MustKnowMechanisms) that gained a lot of support from students and chemists around the world, the book is really intended to bring together an array of mechanisms, organize them, provide additional historical context, and enable a conceptual space where the reader can focus on learning them as well as serve as a desk-reference or a "flip-book".

The book is color-coded: each key reaction is enclosed in a dark blue frame; each key mechanism (the center piece of the book) is presented in a red frame; other reactions and mechanisms related to the core 100 mechanisms covered in this book are usually summarized in grey frames. The book also collects a few useful rules, facts, and concepts that are presented in green frames. The reader may find several star diagrams, representing synthetic diversity, for example, throughout the book as well. Relevant comments and clarifications can be found in footnotes.

Sources. The underlying information stays very close to information usually covered in classic or key organic chemistry text books [1]. More specialized literature may be necessary in some cases (for organometallic or photochemical transformations, for example) [2]. The reader is also encouraged to familiarize themselves with some other supporting bibliography [3]. Where appropriate, it also references texts that the author trusts and cites for further in-depth study if the reader so chooses. Since this book strives to be an abridged visual illustration, students are encouraged to use other, more comprehensive books on the subject, especially those related to the *named reactions* in organic chemistry [4]. Additionally, open on-line sources, when thoughtfully selected, can also be very useful [5]. Such sources may be mentioned here when the information was deemed accurate, thorough, and supported by the references. This is further supplemented by the author's aggregate knowledge and education gained through college, graduate school, and post-doctoral academic research. The author also found the encyclopedia of organic reagents [6] to be an extremely useful "go-to" starting point in his personal experience and professional career, especially when embracing a new chemistry topic or using a new reagent. Moreover, each *MechanoGraphic* is supported by reference to the likely first original publication where the related reaction or mechanism was first mentioned (see the time-scale after each mechanism). Finally, several key and fundamental reviews; publications on recently elucidated mechanisms; and other research articles are referenced, as needed. The author uses his best judgement in each case. However, even though the

provided information was carefully checked, and presented in agreement with standard and accepted chemistry rules, this does not guarantee that it is free of all errors. A further caveat, the variety of text and scholarly references does not imply a comprehensive and chronological review of the literature and history – it is not a global historic review of mechanisms from 1800–2020. Mechanisms and our understanding of them can also change as this book is being prepared and the corresponding literature revised. Thus, the reader should supplement the use of the book with primary source reading and deeper study through a comprehensive textbook prepared by a cohort of experienced professors and experts. Here, the most common and known pathways, those that do not violate basic standard chemistry rules and that are frequently referenced in the classic and contemporary literature, are summarized visually.

A Few Things to Keep in Mind. It is also important that the reader remain flexible and mindful that mechanisms are represented based on our current understanding, taking into consideration basic chemistry rules, valency, electron pushing rules, charge preservation, Lewis dot structures, etc. They may not be the most "cutting-edge" or up-to-date (e.g., cross-coupling reactions that may not be well-understood). They may also be substrate-dependent and each reaction may undergo a slightly different pathway. Thus, the reader should not treat the book as a dogmatic guide, and should keep an open mind for new data, creativity, and view the book as part of a continuous debate in the subject.

Background Knowledge. To fully benefit from the book, the reader should have basic knowledge of organic chemistry. Figures are presented with an assumption that the reader understands common terms and symbols. Thus, basic concepts are not introduced or explained. Undergraduate students, graduate students, scientists, teachers, and professors in the discipline should be able to utilize the book. The book can also serve as a good condensed "refresher" for the experienced organic chemist who wants to "zero-in" on the most basic and fundamental core mechanisms as judged by the author.

The Inspiration and Further Reading. The author heavily draws upon his personal experience as a student of chemistry and later an academic researcher. Never having taken a formal course on mechanisms in organic chemistry, he approached the material initially through memorization as opposed to derivation. The first impression was fear and a sense of being overwhelmed. However, after many years of experience, more obvious patterns, trends, rules, and dependencies appear to have crystallized providing an inductive ability to navigate and identify the mechanisms behind reactions. This personal experience has definitely shaped the teaching philosophy of the book, and is further enhanced by the efficient way in which information can be conveyed through visuals and space. Moreover, as most individuals have a predisposition for visual learning – this book is more intuitively aligned with the way that we seem to learn the fastest. It strives to be a focused collection of the most useful, basic, and fundamental mechanisms. Started initially as a micro-blog post, the discussion, engagement, and interest it sparked indicated a clear need for a more-carefully prepared,

organized, and curated presentation in a format that could be placed in a physical library and easily internalized. The author hopes the book serves as a good starting point for the developing chemist who may need the most guidance and encouragement. No doubt it may stimulate constructive discussion, but nevertheless this will ultimately encourage and challenge everyone to learn, to search for a different answer, to think critically, and grow as a chemist and stay sharp as a scientist. Finally, knowledge is a fractal-like concept, the closer we look the more detail we see and learn. Here, we strive to reach a reasonable asymptote of precision and comprehensiveness given the purpose of the book. Further core reading [1], reference of primary and secondary sources [2–4], and on-line sources [5 and 6] as well as actual experimentation and practice will help paint the complete picture and prepare the organic chemist to be a well-rounded and informed scientist.

Contents

List of Acronyms and Abbreviations

≡	identical to [a depiction of a chemical structure]
1°	primary [e.g., carbocation] or first generation [e.g., catalyst]
2°	secondary [e.g., carbocation] or second generation [e.g., catalyst]
3°	tertiary [e.g., carbocation] or third generation [e.g., catalyst]
Ac	acetyl
acac	acetylacetonate
Ad_E2	**bi**molecular electrophilic addition
Ad_E3	**tri**molecular electrophilic addition
ADMET	acyclic diene metathesis [polymerization]
AIBN	azo*bis*isobutyronitrile; 2,2′-azo*bis*(2-methylpropionitrile)
Alk = R	alkyl group
anti	from opposite sides (in *anti*-addition or *anti*-elimination)
APA	3-aminopropylamine; 1,3-diaminopropane
aq	aqueous [work-up]
Ar	aryl; aromatic ring
B (B^-)	general Brønsted–Lowry base (proton acceptor)
B_2pin_2	*bis*(pinacolato)diboron; 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane
9-BBN	9-borabicyclo[3.3.1]nonane
BH (BH^+)	general Brønsted–Lowry acid (proton donor)
Bn	benzyl
Boc	*tert*-butoxycarbonyl; *t*-butoxycarbonyl
Bs	brosyl; 4-bromobenzenesulfonyl
Bu	butyl (if not specified = *n*-Bu)
CHD	1,4-cyclohexadiene
CM = XMET	[olefin] cross-metathesis
con	conrotatory
3-CR (MCR)	3-component reaction (multi-component reaction)
4-CR (MCR)	4-component reaction (multi-component reaction)
CuAAC	copper(I)-catalyzed azide-alkyne cycloaddition
CuTC	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
Cy_2BH	dicyclohexylborane
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide; 1,3-dicyclohexylcarbodiimide
DCM	dichloromethane; methylene chloride
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL = DIBAL-H	diisobutylaluminum hydride = $(i\text{-Bu})_2AlH$
dis	disrotatory
DMAP	4-dimethylaminopyridine; 4-(dimethylamino)pyridine
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
***E*-**	*entgegen* (*trans*- or opposite)
e^-	electron
E (or E^+)	electrophile

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E1	**uni**molecular elimination
E1cB (E1cb)	**uni**molecular elimination conjugate base
E2	**bi**molecular elimination
EDC = EDCI	1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride; *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
EDCI = EDC	1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride; *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
EDG (= ERG)	electron donating group (same as ERG)
E_i	internal or intramolecular elimination
eq	equivalent (e.g., 2 eq = 2 equivalents; 2 moles)
ERG (= EDG)	electron releasing group (same as EDG)
Et_2BH	diethylborane
EWG	electron withdrawing group
EYM	enyne metathesis
Grubbs 1°	the Grubbs catalyst first generation
Grubbs 2°	the Grubbs catalyst second generation
H_3B•THF	borane–tetrahydrofuran complex; borane tetrahydrofuran complex
H_3B•Me_2S = BMS	borane–dimethyl sulfide complex; borane dimethyl sulfide complex
HATU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
HBTU	*O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; 3-[bis(dimethylamino)methyliumyl]-3*H*-benzotriazol-1-oxide hexafluorophosphate
HET = ^{HET}Ar	heterocycle; heteroaromatic ring; heteroaryl
HOAt = HOAT	1-hydroxy-7-azabenzotriazole; 3-hydroxy-3*H*-1,2,3-triazolo[4,5-*b*]pyridine
HOBt = HOBT	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
hv	light (direct irradiation) or excited state
I_i(BR)	intermediate (biradical)
I_i(RP)	intermediate (radical pair)
IBX	2-iodoxybenzoic acid; *o*-iodoxybenzoic acid
IC	internal conversion
Ipc_2BH	di*iso*pinocampheylborane
$IpcBH_2$	mono*iso*pinocampheylborane
ISC	intersystem crossing
KAPA	potassium 3-aminopropylamide
L	ligand or leaving group
(*l*)	liquid [as in liquid ammonia: NH_3 (*l*)]
LA	Lewis acid
LAPA	lithium 3-aminopropylamide
LDA	lithium diisopropylamide = $(i\text{-Pr})_2NLi$
L_mPd	palladium(0) cross coupling catalyst
L_nPd	low-coordinate palladium(0) cross coupling catalyst
LUMO	lowest occupied molecular orbital
M	metal
[M]	metal catalyst (not specified)

M^{+3} = M(III)	oxidation state (oxidation number) of an element [e.g., Cu^{+2} = Cu(II); Pd^0 = Pd(0)]
M^{3+}	charge [e.g., Ti^{3+} in $TiCl_3$ versus Ti^{+3} = Ti(III)]
***m*-CPBA** (MCPBA)	*meta*-chloroperbenzoic acid; *m*-chloroperbenzoic acid; 3-chloroperbenzoic acid
MCR	multi-component reaction
Mes	mesityl (from mesitylene = 1,3,5-trimethylbenzene)
Ms	mesyl; methanesulfony = SO_2Me
n	nonbonding [molecular] orbital
NACM	nitrile-alkyne cross-metathesis
NBS	*N*-bromosuccinimide; 1-bromo-2,5-pyrrolidinedione
***N*-HBTU**	1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium hexafluorophosphate 3-oxide
NiAAC	nickel-catalyzed azide-alkyne cycloaddition
NMM	*N*-methylmorpholine; 4-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide; 4-methylmorpholine *N*-oxide
Ns	nosyl; 4-nitrobenzenesulfonyl or 2-nitrobenzenesulfonyl
Nu (or Nu^-)	nucleophile
NuH	general Brønsted–Lowry acid (proton donor, like BH)
[O]	general oxidant (e.g., $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$)
***O*-HBTU**	*N*-[(1*H*-benzotriazol-1-yloxy)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate
p [sp, sp^2, sp^3]	p orbital
P	product [in photochemical reactions]
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Ph_3P = TPP	triphenylphosphine
PhthNH	phthalimide (Phth = phthaloyl)
pK_a	acidity constant = $-\log_{10}(K_a)$
Pr	propyl (if not specified = *n*-Pr)
Py	pyridine
R	reactant; starting material [in photochemical reactions]
R ($-R_1$, $-R_2$, $-R'$, $-R''$, …)	[radical] group; alkyl group; substituent; [molecular] fragment
R^*	excited reactant [in photochemical reactions]
RCAM	ring-closing alkyne metathesis
RCEYM	ring-closing enyne metathesis
RCM	ring-closing metathesis
R_L	large group (substituent)
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerization
R_S	small group (substituent)
RuAAC	ruthenium-catalyzed azide-alkyne cycloaddition
s [sp, sp^2, sp^3]	s orbital
S_0	ground state
S_1	first [energy level] singlet excited state
S_2	second [energy level] singlet excited state
S_EAr = $S_E(Ar)$ = S_E2Ar	[**bi**molecular] aromatic electrophilic substitution = arenium ion mechanism

^{3}sens	sensitized irradiation [to the triplet excited state]
SET	single electron transfer
Sia_2BH	disiamylborane; *bis*(1,2-dimethylpropyl)borane
S_N1	**uni**molecular nucleophilic substitution
S_N2	**bi**molecular nucleophilic substitution
S_NAr = S_N2Ar	[**bi**molecular] aromatic nucleophilic substitution
$S_{RN}1$	**uni**molecular radical nucleophilic substitution
syn	from the same side (in *syn*-addition or *syn*-elimination)
T_1	first [energy level] triplet excited state
T_2	second [energy level] triplet excited state
TBAF	tetrabutylammonium (tetra-*n*-butylammonium) fluoride = *n*-Bu_4NF
Tf	triflyl; trifluoromethanesulfonyl = SO_2CF_3
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Thx_2BH_2	thexylborane; (2-methylpentan-2-yl)borane
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine; 1,2-*bis*(dimethylamino)ethane
TMS	trimethylsilyl = $SiMe_3$
TPAP	tetrapropylammonium (tetra-*n*-propylammonium) perruthenate = $(n\text{-Pr})_4NRuO_4$
TPP = Ph_3P	triphenylphosphine
Ts	tosyl; *p*-toluenesulfonyl
X (in –X)	halogen or a general leaving group (see L)
X (in =X)	variable atom; variable group (usually O or N)
XMET = CM	[olefin] cross-metathesis
***Z*-**	*zusammen* (*cis*- or same)
Z (in –Z)	variable group (often EWG)
α	alpha position (first position)
β	beta position (second position)
γ	gamma position (third position)
Δ	temperature; heat or ground state [in photochemical reactions]
δ+	partial positive charge (low electron density)
δ–	partial negative charge (high electron density)
π	involving a π–bond (for example, π–complex)
1π e^-, 2π e^-, ...	number of electrons in a π–orbital
σ	involving a σ–bond (for example, σ–complex)
σ*	[antibonding] sigma star [molecular] orbital
Φ_{ISC}	quantum yield [for intersystem crossing]

1 Electrophilic Addition Mechanism

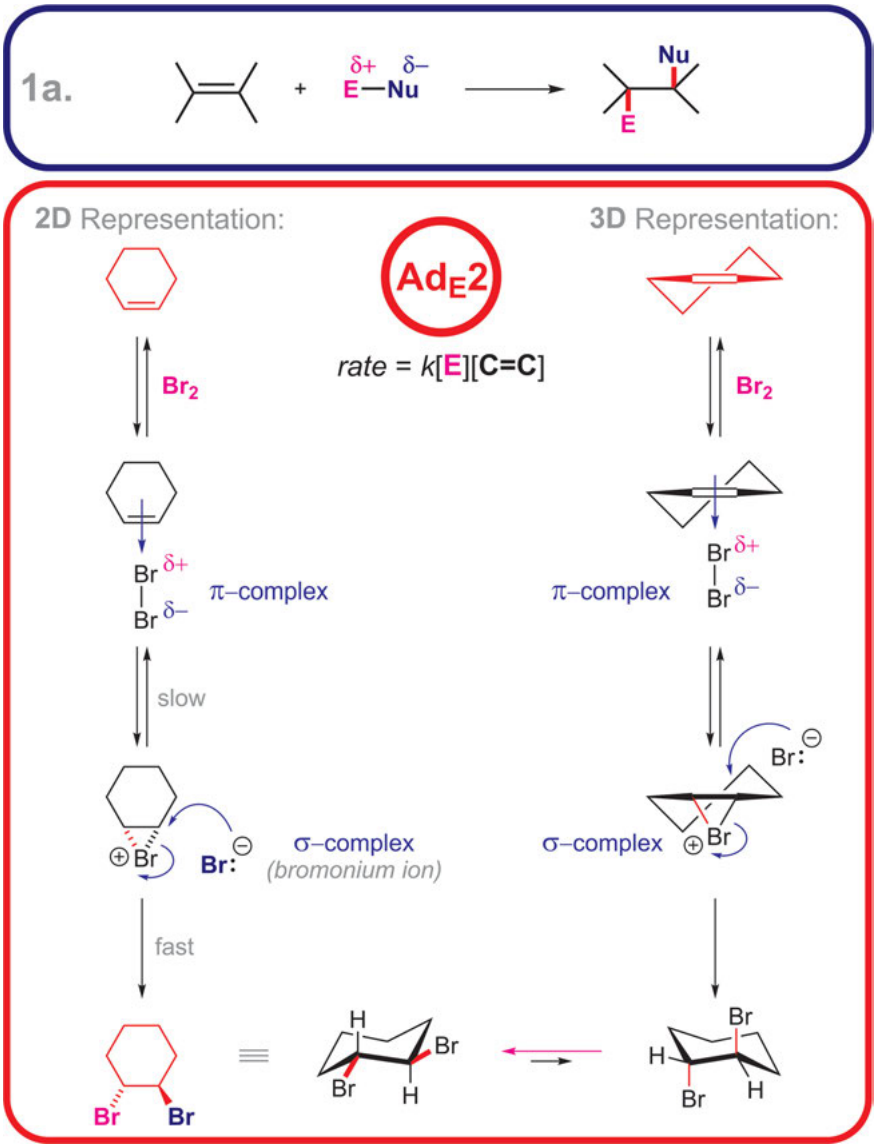

Fig. 1.1: Bimolecular electrophilic addition mechanism (**Ad$_E$2**).[1]

1 Symbol **Ad$_E$2** stands for **Ad**dition **E**lectrophilic **Bi**-molecular (**2**), that is, the rate of the reaction is ***second order*** and the rate-determining step (i.e., the *slow* step) depends on the concentration of two

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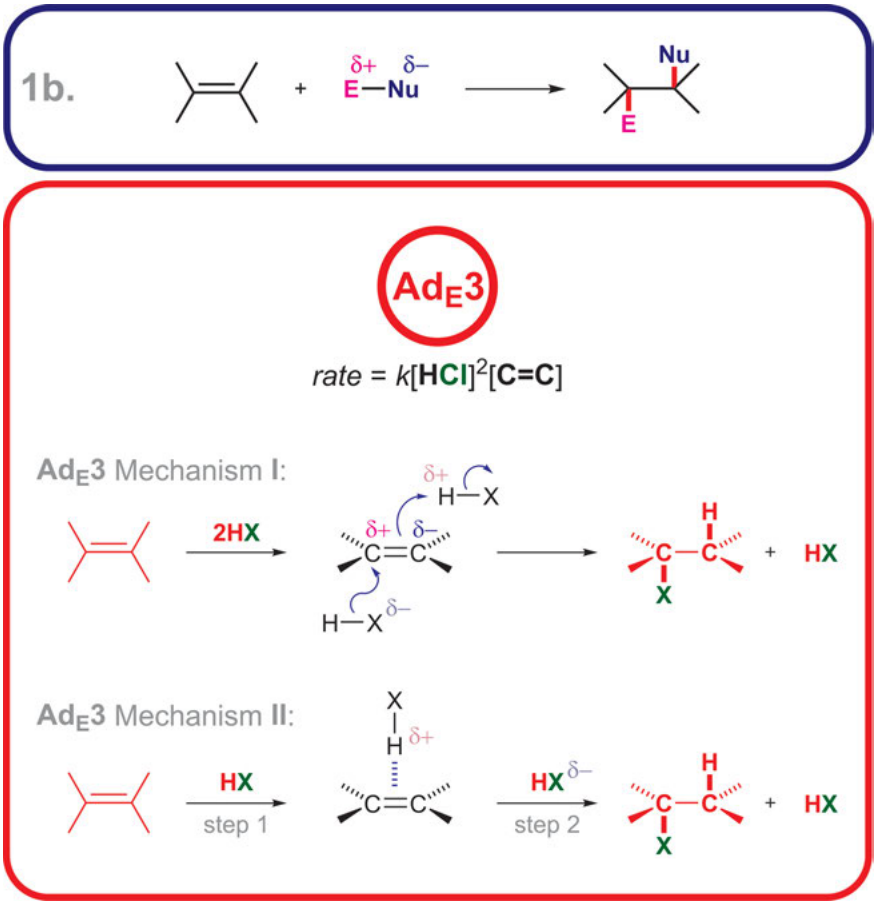

Fig. 1.2: Trimolecular electrophilic addition mechanism (**Ad$_E$3**).[2]

reactants. In the bromination of cyclohexene, it is the ***electrophile*** (**E** or **Br$_2$**) and ***alkene*** (**C=C**): *rate* = *k*[**E**]^1[**C=C**]^1.

2 Symbol **Ad$_E$3** stands for **Ad**dition **E**lectrophilic **Tri**-molecular (**3**), that is, the rate of the reaction is ***third order*** and the rate-determining step (i.e., the *slow* step) depends on the concentration of three reactants. In this less common example, it is the two ***electrophiles*** (**2HX** or **HCl** + **HCl**) and ***alkene*** (C=C): *rate* = *k*[**HCl**]^1[**HCl**]^1[**C=C**]^1 = *k*[**HCl**]^2[**C=C**]^1. In Mechanism I the collision of all three components is less probable and simultaneous. In more probable Mechanism II, a complex between the first HX and alkene is formed first (step 1), followed by step 2 (addition of the second HX).

2 Nucleophilic Substitution Mechanism

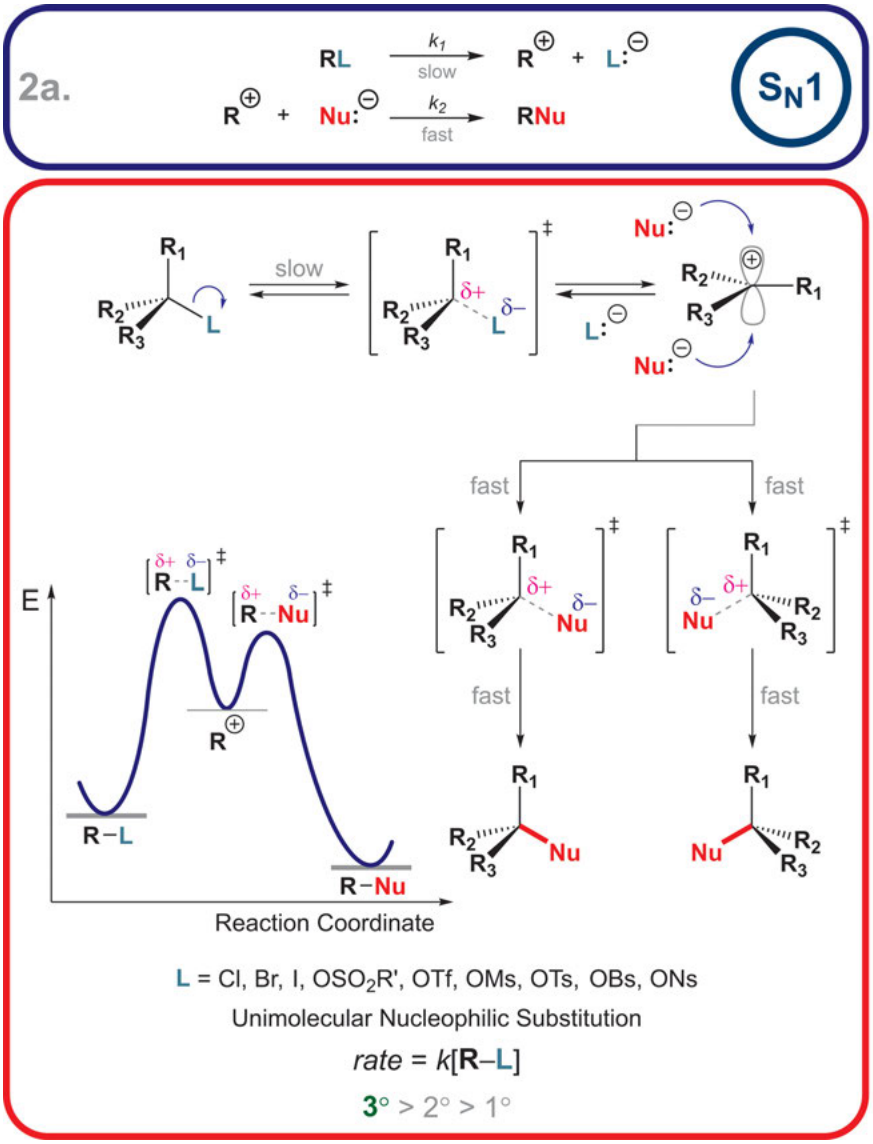

Fig. 2.1: Unimolecular nucleophilic substitution mechanism (S_N1).[3]

3 Symbol S_N1 stands for **S**ubstitution **N**ucleophilic **Uni**-molecular (**1**), that is, the rate of the reaction is ***first order*** and the rate-determining step (i.e., the *slow* step) depends on the concentration of one

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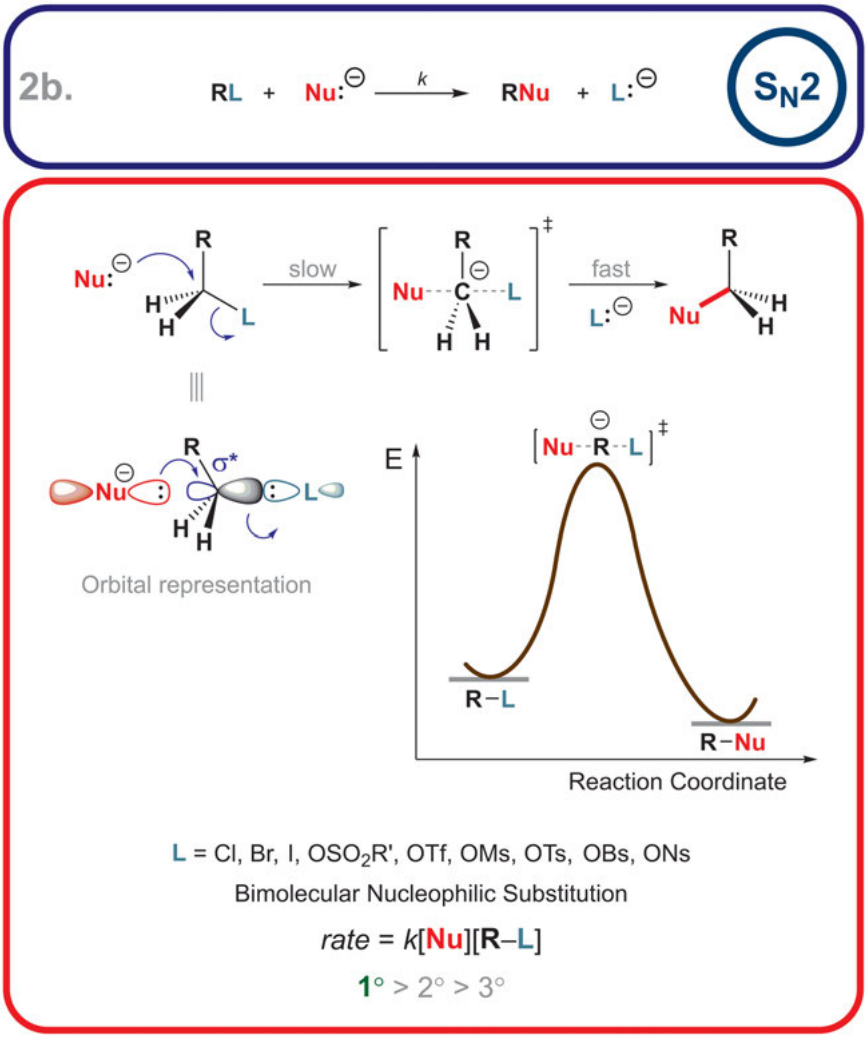

Fig. 2.2: Bimolecular nucleophilic substitution mechanism (S_N2).[4]

reactant. In this example, it is the ***starting material*** (substrate) containing a leaving group (**RL**): *rate* = *k*[**RL**]^1.

4 Symbol S_N2 stands for **S**ubstitution **N**ucleophilic **Bi**-molecular (**2**), that is, the rate of the reaction is ***second order*** and the rate-determining step (i.e., the *slow* step) depends on the concentration of two reactants. In this example, it is the ***nucleophile*** (**Nu**) and the ***starting material*** (**RL**): *rate* = *k*[**Nu**]^1[**RL**]^1.

3 Aromatic Electrophilic Substitution Mechanism

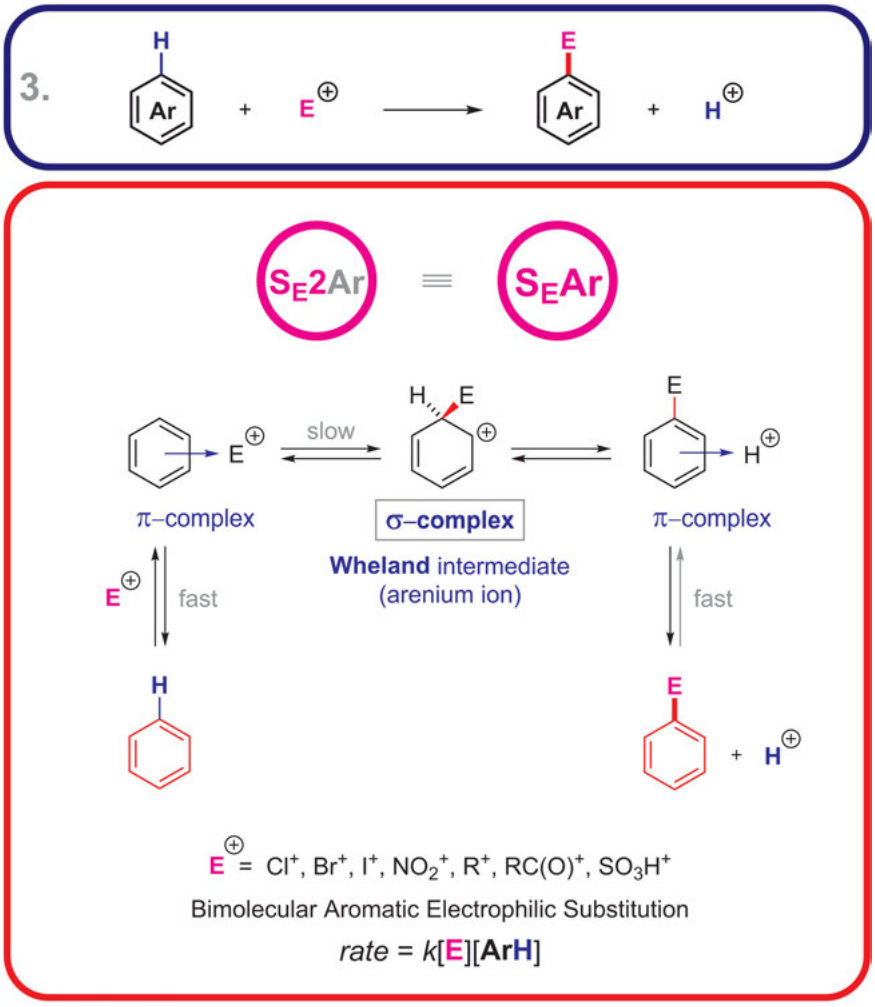

Fig. 3.1: The arenium ion mechanism (**S_EAr**).[5]

5 Symbol **S_EAr** or **S_E(Ar)** stands for **S**ubstitution **E**lectrophilic **Ar**enium (ion) (often confused with **Ar**omatic), that is, the ***arenium ion*** mechanism. In this example, it is a **Bi**-molecular (**2**) reaction, that is, the rate of the reaction is ***second order*** and the rate-determining step (i.e., the *slow* step) depends on the concentration of two reactants. It is the ***electrophile*** (**E**) and ***arene*** (**ArH**): *rate* = k[**E**]^1[**ArH**]^1. To emphasize that it is a bi-molecular mechanism, sometimes **S_E2Ar** or **S_E2(Ar)** notation is used (the use of a simple **S_E2** symbol can be confusing, since it can also apply to an Aliphatic Electrophilic Substitution).

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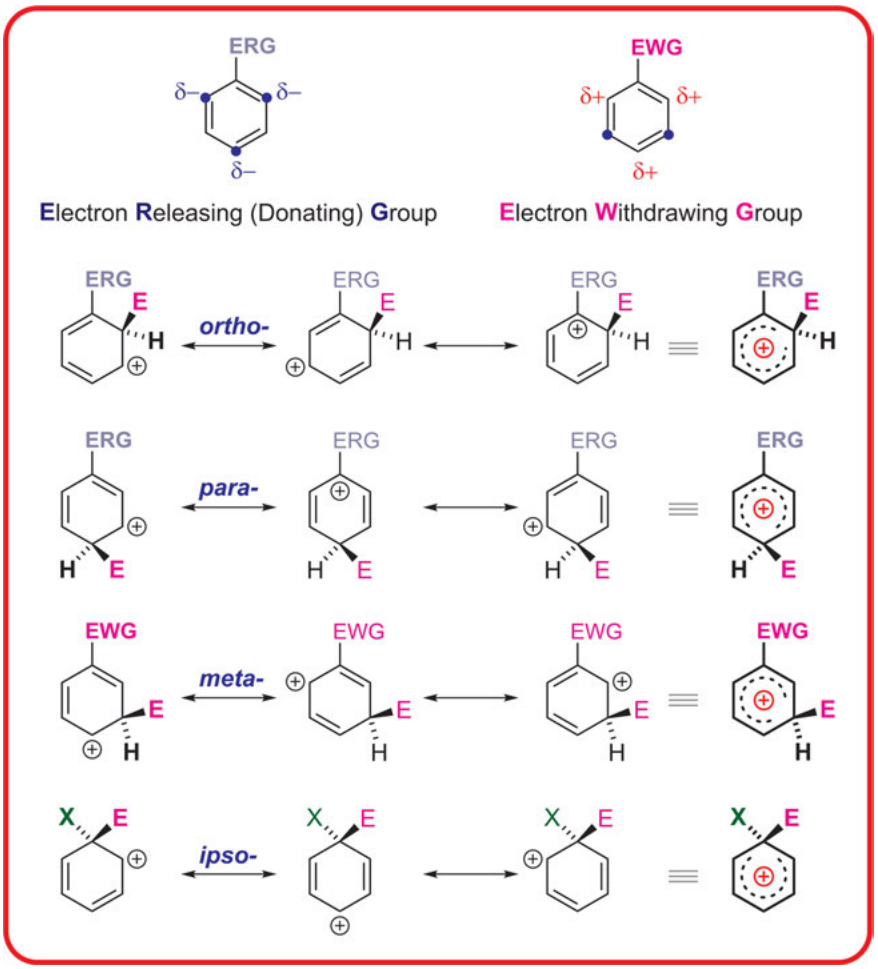

Fig. 3.2: The orientation of substitution with substrates containing EWG and ERG.[6]

6 In this book the terms Electron Releasing Group (ERG) and Electron Donating Group (EDG) are used interchangeably. Please note, ***ipso****-substitution* is provided only for the comparison with ***ortho***-, ***para***-, and ***meta***-*substitution*.

4 Aromatic Nucleophilic Substitution Mechanism

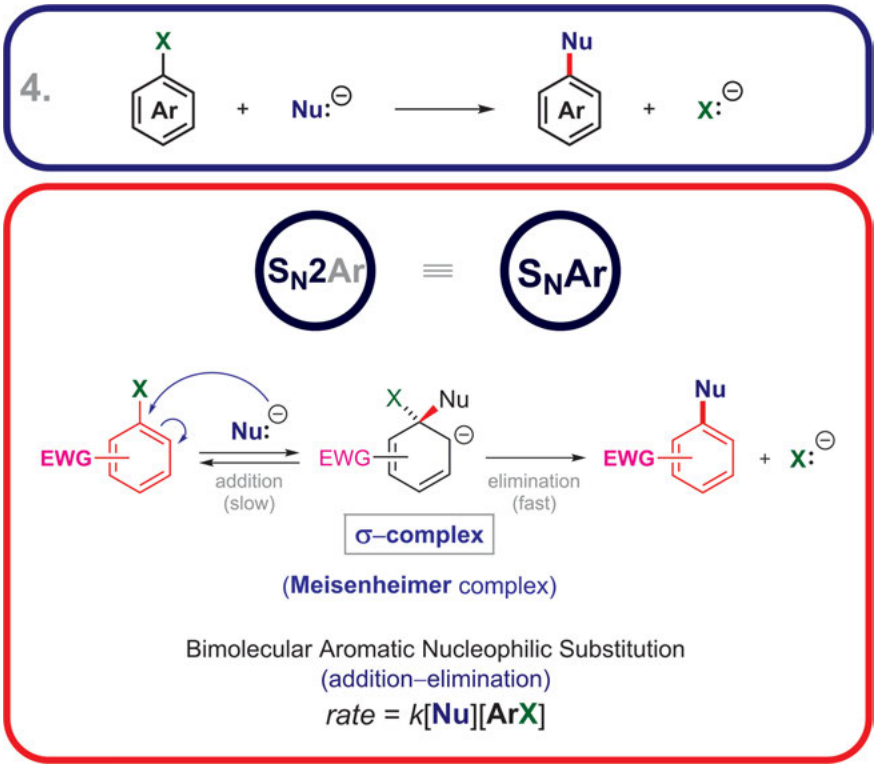

Fig. 4.1: Bimolecular aromatic nucleophilic substitution (addition-elimination) mechanism ($\mathbf{S_NAr}$).[7]

7 Symbol $\mathbf{S_NAr}$ stands for **S**ubstitution **N**ucleophilic **Ar**omatic; it is also called the *addition-elimination* mechanism. In this example, it is a **Bi**-molecular (**2**) reaction, that is, the rate of the reaction is ***second order*** and the rate-determining step (i.e., the *slow* step) depends on the concentration of two reactants. It is the ***nucleophile*** (**Nu**) and ***arene*** (**ArX**): *rate* = k[**Nu**]^1[**ArX**]^1. To emphasize that it is a bi-molecular mechanism, sometimes $\mathbf{S_N2Ar}$ notation is used.

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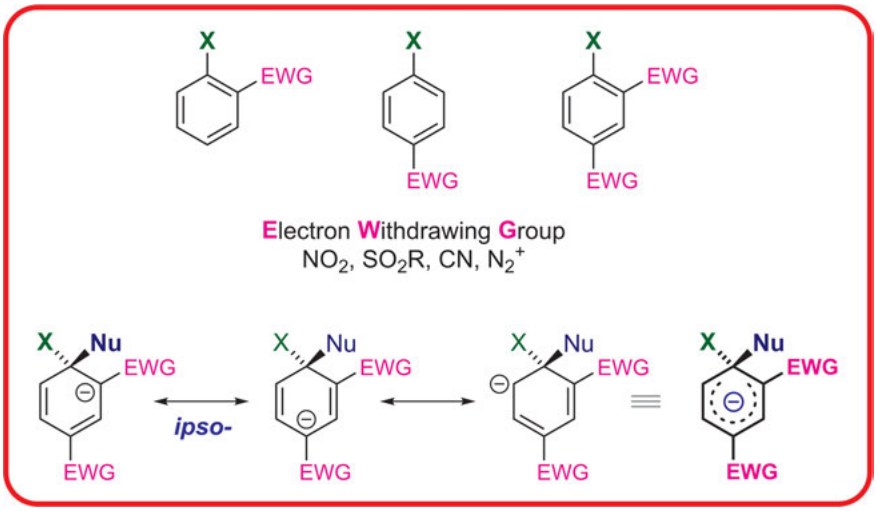

Fig. 4.2: Typical activated **S_NAr** substrates.[8]

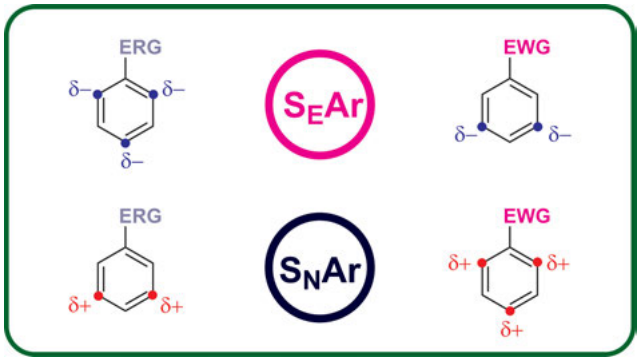

Fig. 4.3: The orientation of substitution in **S_EAr** and **S_NAr**.[9]

8 A typical **S_NAr** substrate usually contains an activating electron withdrawing group (EWG) and a leaving group (X).

9 In the **S_EAr** reaction, an EWG group orients (directs) the substitution in the *meta*-position and an ERG (EDG) directs the substitution in the *ortho*-position and/or *para*-position. However, in the **S_NAr** reaction, this trend is reversed: an EWG group orients (directs) the substitution in the *ortho*-position and/or *para*-position and ERG (EDG) directs the substitution in the *meta*-position.

5 Aromatic Radical Nucleophilic Substitution Mechanism

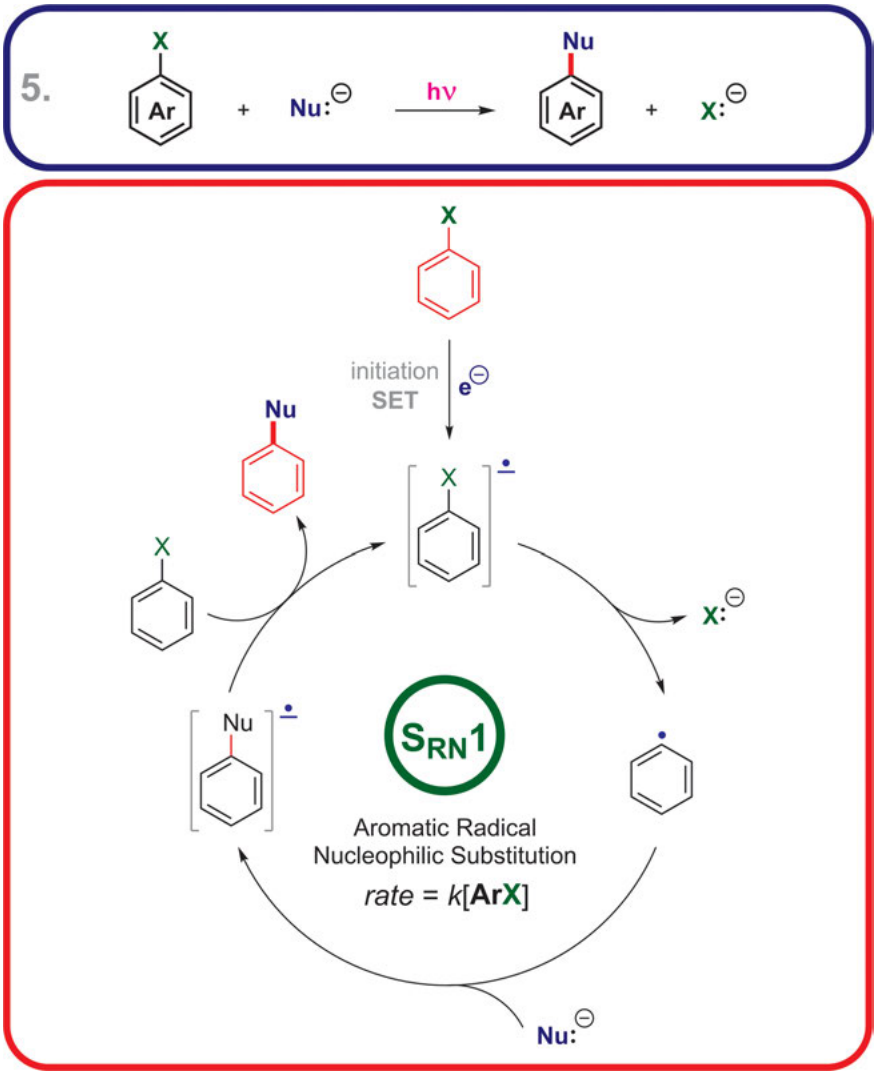

Fig. 5.1: Unimolecular aromatic radical nucleophilic substitution mechanism ($\mathbf{S_{RN}1}$).[10]

10 Symbol $\mathbf{S_{RN}1}$ stands for **S**ubstitution **R**adical **N**ucleophilic **Uni**-molecular (**1**), that is, the rate of the reaction is ***first order*** and the rate-determining step (the *slow* step) depends on the concentration of one reactant. In this example, it is the ***starting material*** that contains a leaving group (**ArX**): *rate* = k[**ArX**]^1.

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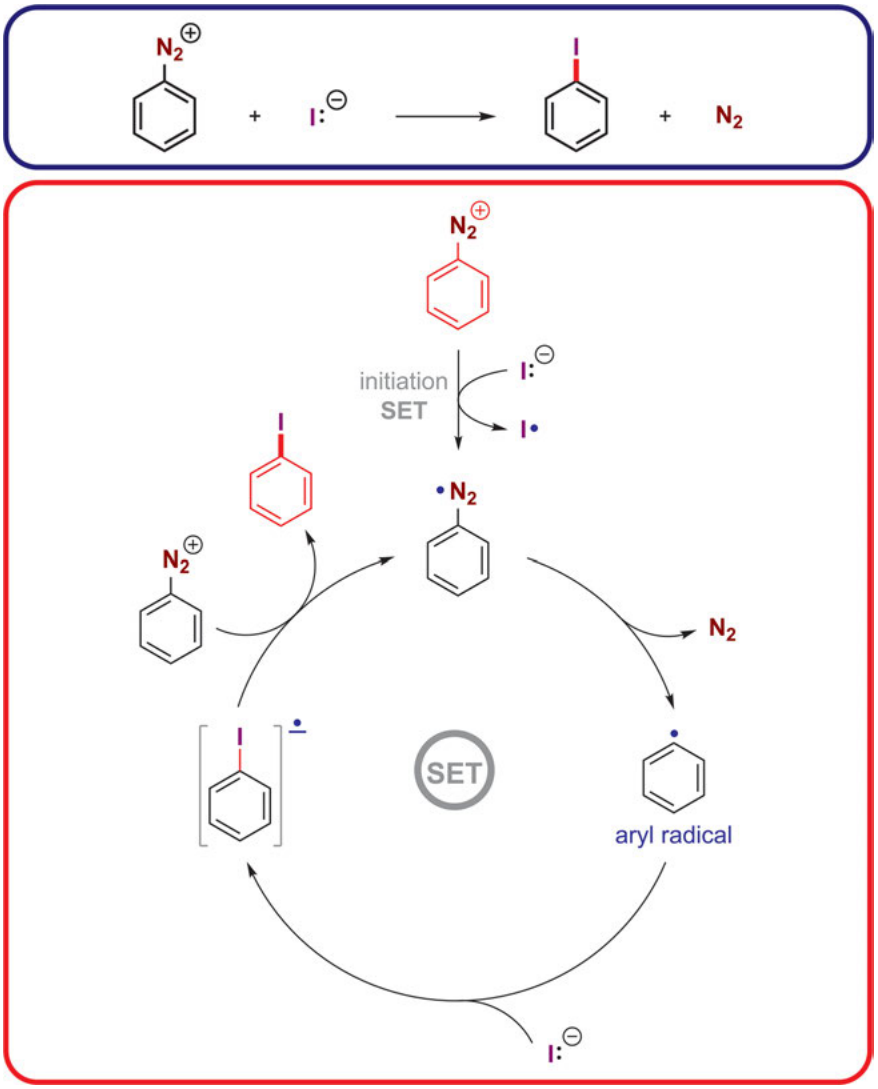

Fig. 5.2: Replacement of the diazonium group by iodide.[11]

11 The substitution of a diazonium group by iodide is an example of the **SET** (**S**ingle **E**lectron **T**ransfer) mechanism. Please note, the **S_{RN}1** mechanism and the **SET** mechanism are closely related and are not differentiated in this book. Jerry March [1a] distinguishes the $S_{RN}1$ mechanism (the initial attack of the aromatic substrate occurs by an electron donor) from the SET mechanism (the initial attack occurs by a nucleophile). The Sandmeyer reaction mechanism (not shown) is related [see https://doi.org/10.1002/cber.18840170219 and https://doi.org/10.1002/cber.188401702202, accessed December 5, 2019].

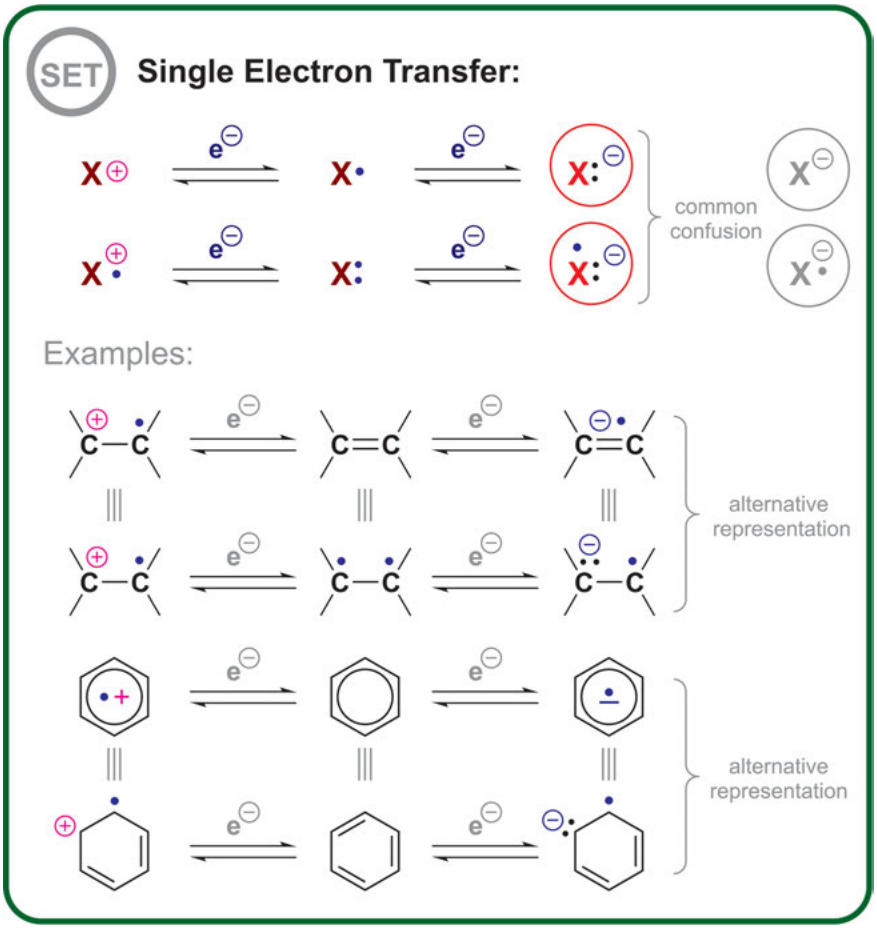

Fig. 5.3: Lewis electron dot structures of radical species involved in SET.[12]

12 This figure summarizes the Lewis (electron) dot structures of various SET processes: ***cation*** → ***radical*** → ***anion*** or ***cation-radical*** → ***di-radical*** or ***lone pair*** → ***anion-radical***, and provides several common examples. Please note, in the literature *cation-radical* is often called radical cation and *anion-radical* is called radical anion. In some instances, a *lone pair* associated with an *anion* or *anion-radical* is not represented for clarity (sometimes this simplification causes confusion).

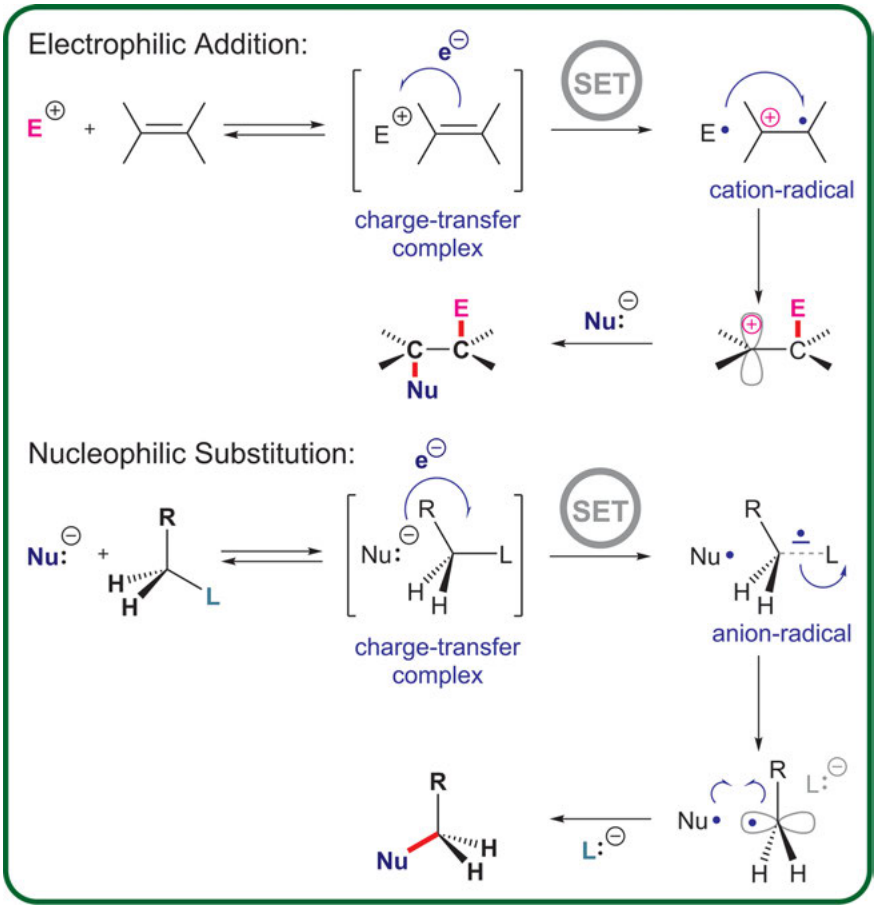

Fig. 5.4: The single electron transfer mechanism (**SET**) examples.[13]

13 An example of *Electrophilic Addition* described by the SET mechanism: a single electron transfer from an alkene to an electrophile and the formation of a *cation-radical* (radical cation). An example of *Nucleophilic Substitution* described by the SET mechanism: a single electron transfer from a nucleophile to a substrate and the formation of an *anion-radical* (radical anion) [3].

6 Elimination Mechanism

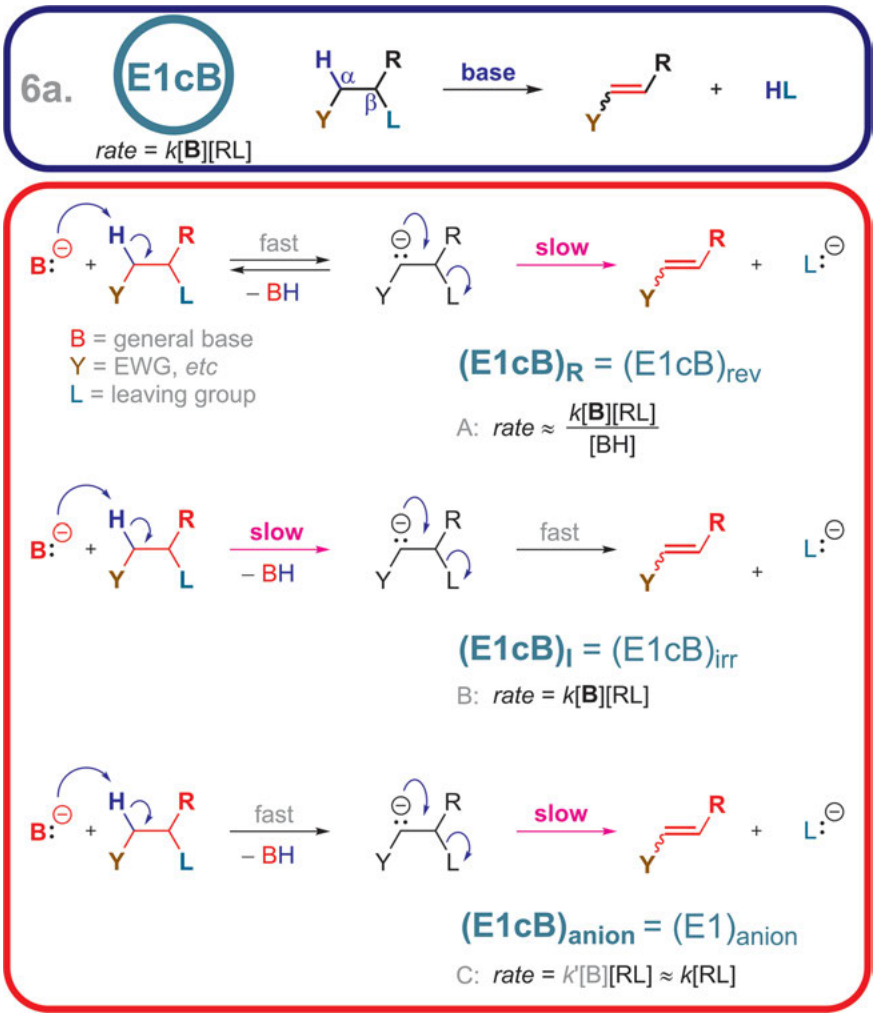

Fig. 6.1: Unimolecular β–elimination mechanism (**E1cB**).[14]

14 Symbol **E1cB** (**E1cb**) stands for **E**limination **Uni**-molecular (**1**) **c**onjugate **B**ase (**b**ase); it is also called the ***carbanion*** mechanism [McLennan DJ. The carbanion mechanism of olefin-forming elimination. *Q. Rev. Chem. Soc.* **1967**, 21 (4), 490–506]. The mechanism consists of two steps: the formation of a carbanion (step 1) and subsequent elimination (step 2). (Scenario A) Step 1 is fast and reversible (**R** or **rev**) and step 2 is rate-determining (slow): $\mathbf{(E1cB)_R = (E1cB)_{rev}}$. Here, the rate of the reaction is ***second order*** and the rate-determining step depends on the concentration of two reactants, that is, the ***base*** (**B**) and ***substrate*** (**RL**): $rate \approx k[\mathbf{B}]^1[\mathbf{RL}]^1/[\mathbf{BH}]$. (Scenario B) Step 1 is slow and irreversible (**I** or **irr**) (rate-determining) and step 2 is fast: $\mathbf{(E1cB)_I = (E1cB)_{irr}}$. Here, the rate of the reaction is ***sec-***

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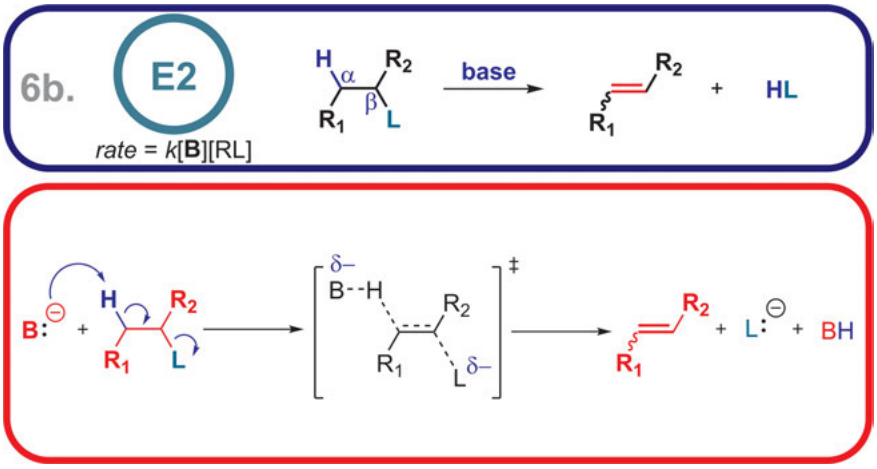

Fig. 6.2: Bimolecular β–elimination mechanism (**E2**).[15]

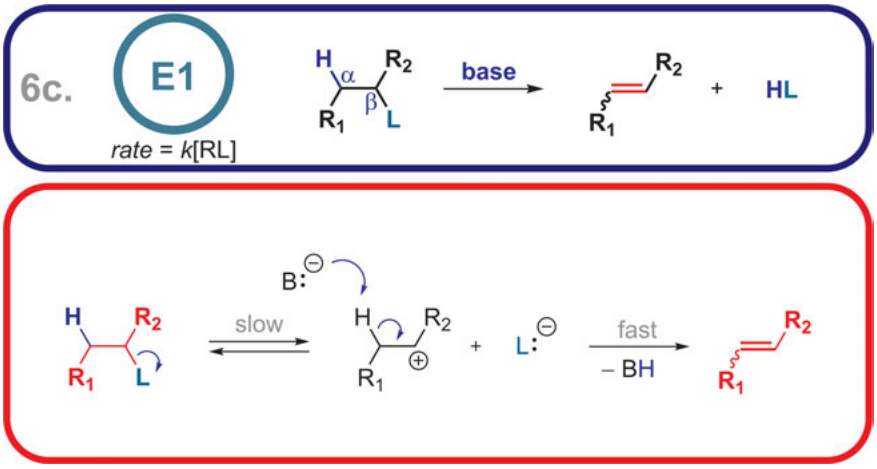

Fig. 6.3: Unimolecular β–elimination mechanism (**E1**).[16]

ond order and the rate-determining step depends on the concentration of two reactants, that is, the ***base*** (**B**) and ***substrate*** (**RL**): *rate* = *k*[**B**]^1[**RL**]^1. (Scenario C) Step 1 is fast and step 2 is rate-determining (slow): $\mathbf{(E1cB)_{anion}}$ = $\mathbf{(E1)_{anion}}$. Here, the rate of the reaction is ***first order*** and the rate-determining step depends on the concentration of one reactant, that is, the ***substrate*** (**RL**): *rate* ≈ *k*[**RL**]^1.

15 Symbol **E2** stands for **E**limination **Bi**-molecular (**2**), that is, the rate of the reaction is ***second order*** and the rate-determining step (i.e., the *slow* step) depends on the concentration of two reactants. In this example, it is the ***base*** (**B**) and the ***substrate*** (**RL**): *rate* = *k*[**B**]^1[**RL**]^1.

16 Symbol **E1** stands for **E**limination **Uni**-molecular (**1**), that is, the rate of the reaction is ***first order*** and the rate-determining step (i.e., the *slow* step) depends on the concentration of one reactant. In this example, it is the ***substrate*** (**RL**): *rate* = *k*[**RL**]^1.

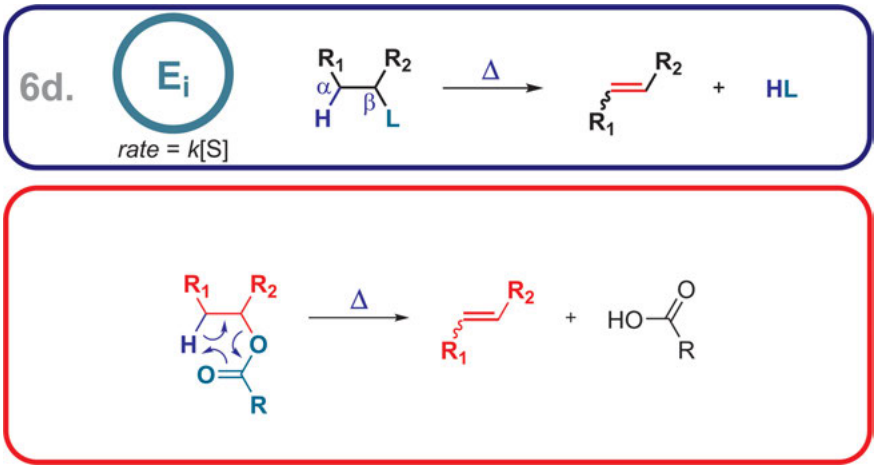

Fig. 6.4: Internal or Intramolecular β–elimination mechanism ($\mathbf{E_i}$).[17]

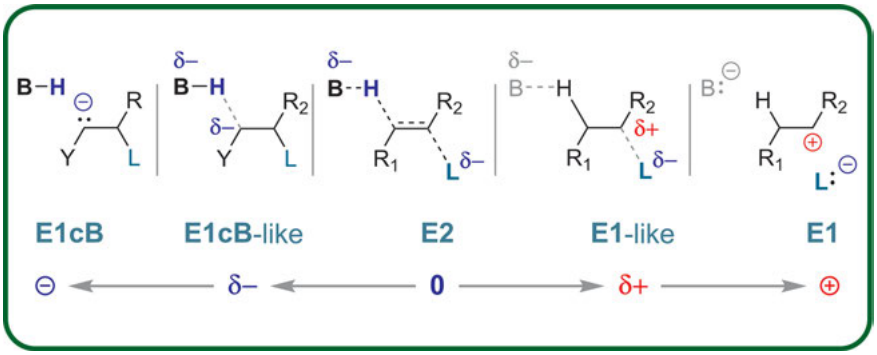

Fig. 6.5: **E1cB**, **E2**, and **E1** mechanisms.[18]

17 Symbol $\mathbf{E_i}$ stands for **E**limination **I**nternal or **I**ntramolecular. The rate of the reaction is ***first order*** and the rate-determining step (i.e., the *slow* step) depends on the concentration of one reactant. In this example, it is the ***substrate*** (**S**): $rate = k[\mathbf{S}]^1$.

18 The **E1cB** mechanism is also called the carbanion mechanism, its transition state is the most extreme case with a full negative charge. The **E2** mechanism is simultaneous and the transition state lies in the middle. A typical E2 reaction often competes with an S_N2 reaction and vice versa. The **E1** mechanism is exactly the opposite of E1cB and its transition state has a positive charge. A typical E1 reaction often competes with an S_N1 reaction and vice versa.

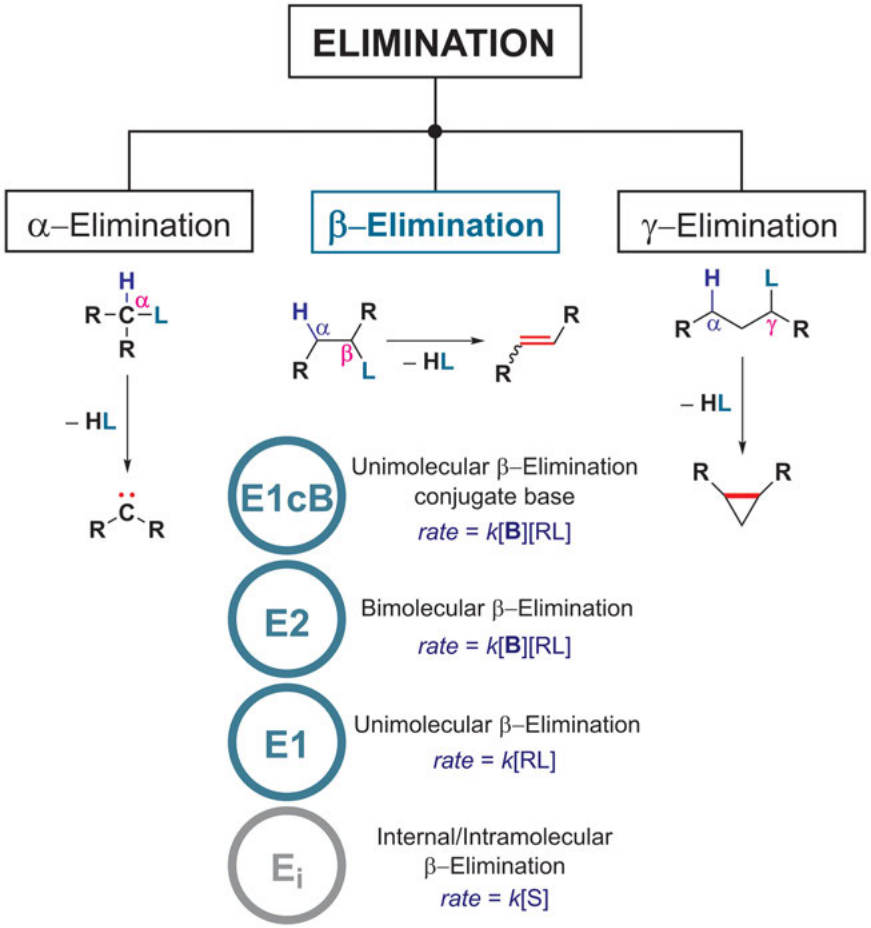

Fig. 6.6: The classification of characteristic elimination reactions.[19]

19 Only the key *β–elimination* examples are covered in this book.

7 Acyloin Condensation

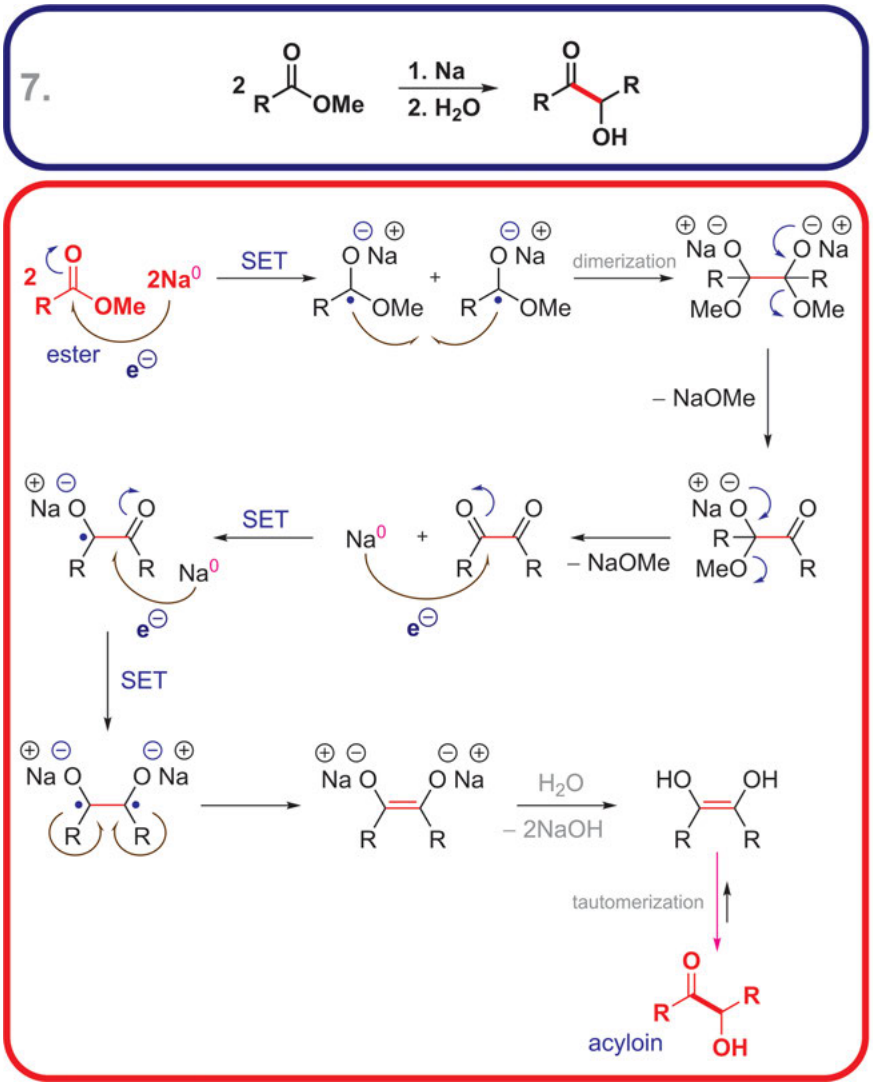

Fig. 7.1: The *acyloin condensation* mechanism.[20]

20 The reaction is also called the *acyloin ester condensation*. Please note, an *acyloin* is an α–hydroxy ketone.

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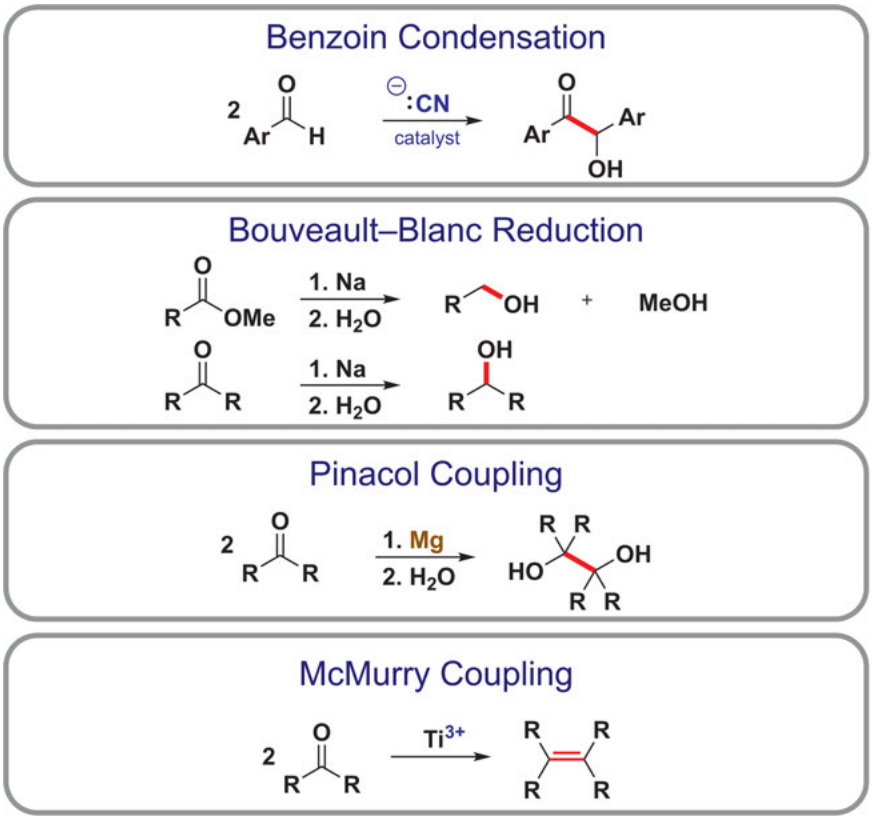

Fig. 7.2: Reactions related to the *acyloin condensation*.[21]

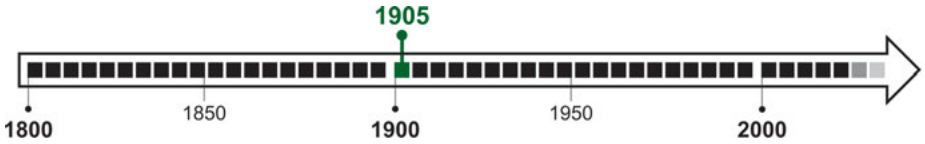

Fig. 7.3: The discovery of the *acyloin condensation*.[22]

21 Several reactions are mechanistically related to the *acyloin condensation*: the ***Bouveault–Blanc*** *reduction* [1a and 7a], the *pinacol coupling* and the ***McMurry*** *coupling* (both covered in Chapter 57). The *benzoin condensation* (covered in Chapter 15) undergoes a different mechanism, but it also yields α–hydroxy ketones containing aromatic groups *(benzoins)*.

22 The reaction was likely first described around 1905 [7b].

8 Alkyne Zipper Reaction

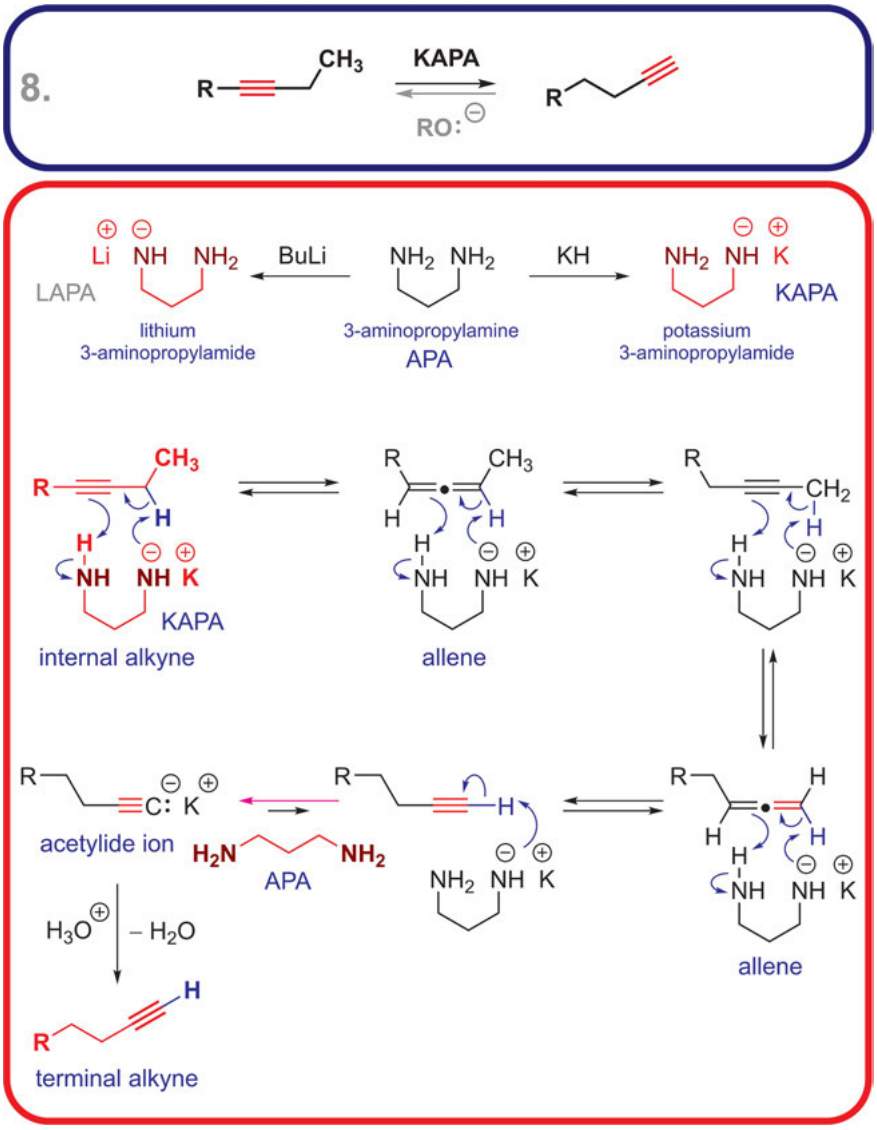

Fig. 8.1: The *alkyne zipper reaction* mechanism.[23]

23 The reaction is also called the *alkyne isomerization reaction* or the *alkyne-allene rearrangement*.

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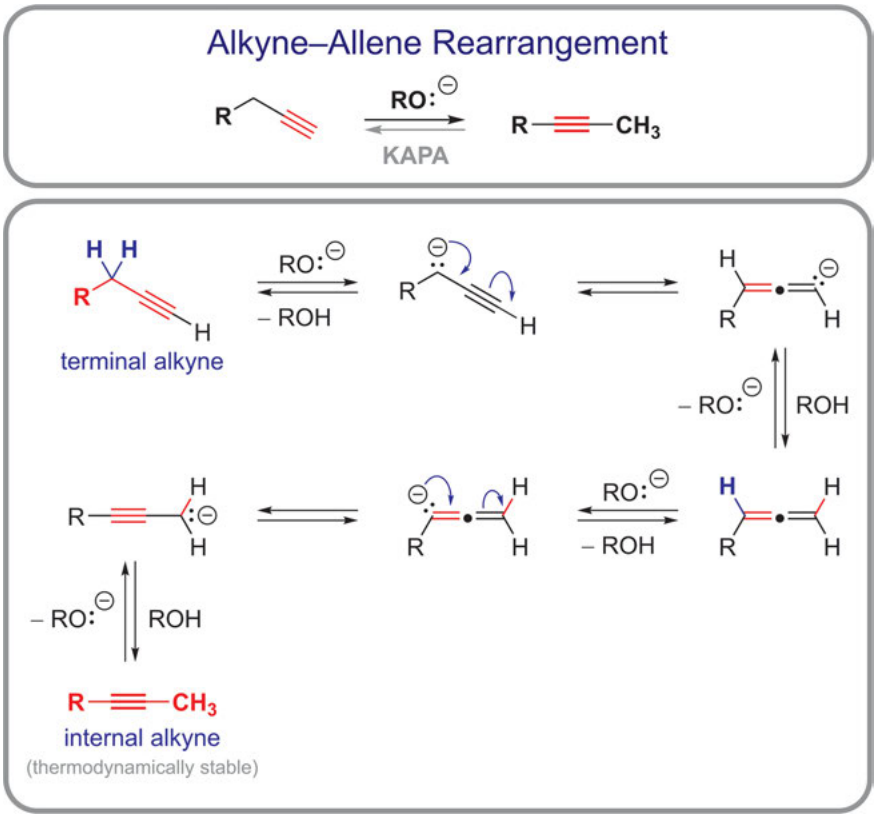

Fig. 8.2: The *alkyne-allene rearrangement* mechanism.[24]

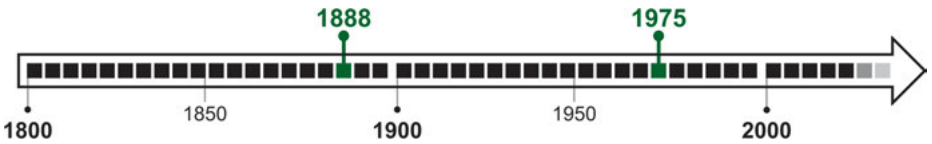

Fig. 8.3: The discovery of the *alkyne zipper reaction*.[25]

24 The *alkyne zipper reaction* with KAPA yields thermodynamically less stable *terminal alkyne*, whereas the typical *alkyne-allene rearrangement* usually produces thermodynamically more stable *internal alkyne*. Both reactions are reversible.

25 The reaction was likely first mentioned around 1888 by A. Favorsky (Favorskii) (in Russian A. E. Фаворский) [8a, 8b, 8c], the variation presented here was likely first described around 1975 [8d].

9 Arbuzov Reaction

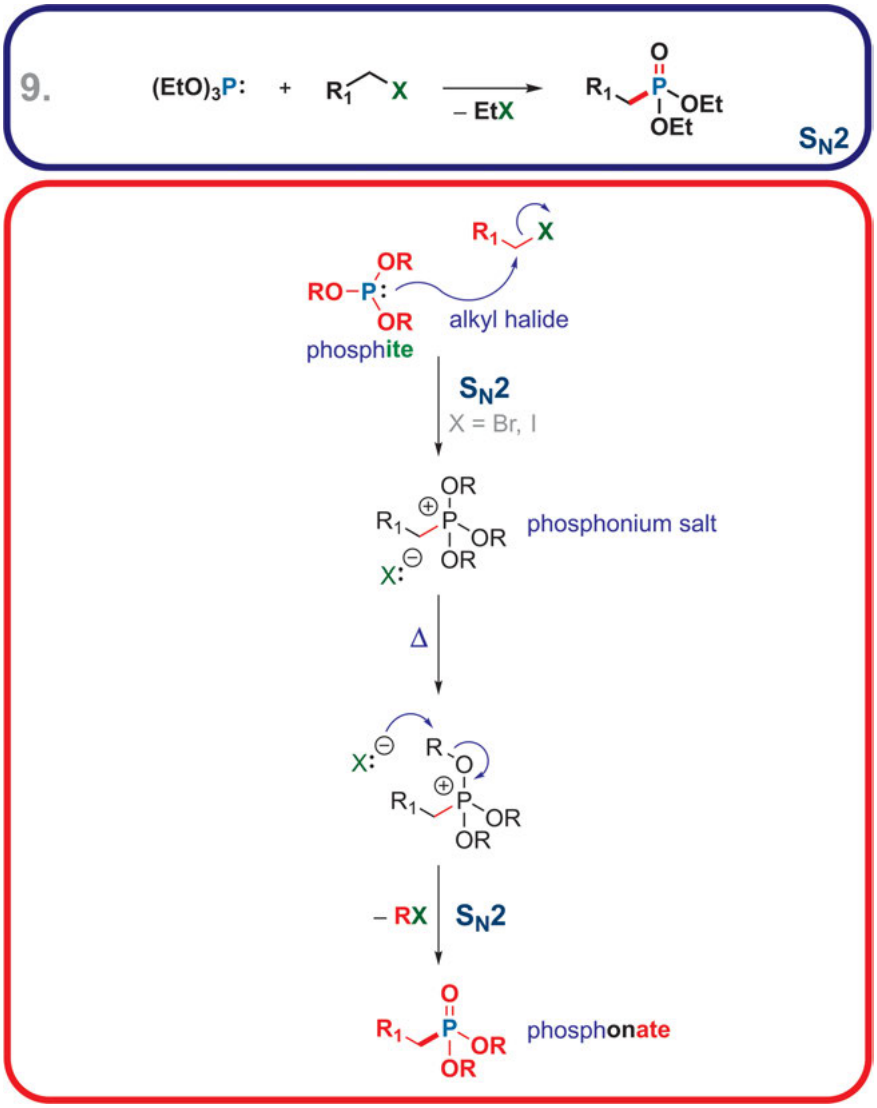

Fig. 9.1: The ***Arbuzov*** *reaction* mechanism.[26]

26 The ***Arbuzov*** *reaction* is an example of bimolecular **nucleophilic substitution** (S_N2), covered in Chapter 2. It is also referred to as the ***Michaelis–Arbuzov*** *reaction* or the ***Michaelis–Arbuzov*** *rearrangement*.

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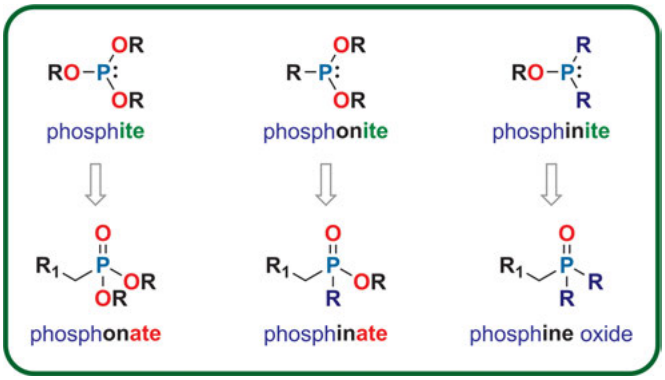

Fig. 9.2: The nomenclature of selected organophosphorus (III) and (V) compounds.[27]

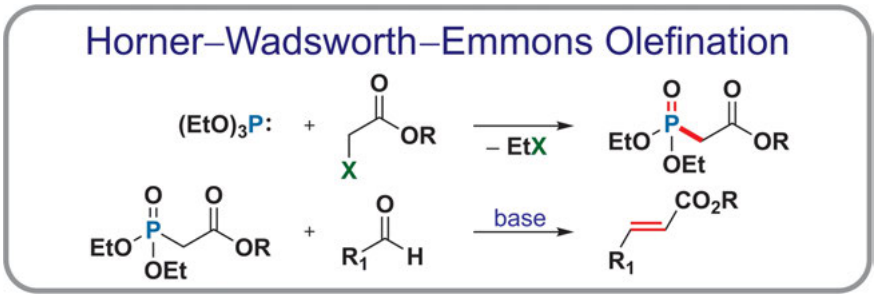

Fig. 9.3: The ***HWE*** olefination.[28]

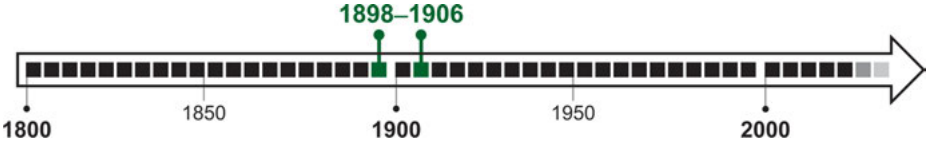

Fig. 9.4: The discovery of the ***Arbuzov*** *reaction*.[29]

27 A selected example of the complex organophosphorus nomenclature: the organophosphorus (III) compounds have a common suffix -***ite*** [phosph**ite**s $P(OR)_3$, phosphon**ite**s $P(OR)_2R$] and the organophosphorus (V) compounds have a common suffix -***ate*** [phosphon**ate**s $PO(OR)_2R$, phosphin**ate**s $PO(OR)R_2$] [9a].

28 The *phosphonates* produced in the ***Arbuzov*** *reaction* are essential in the ***Horner–Wadsworth–Emmons*** *(HWE) olefination* (covered in Chapter 50).

29 The reaction was likely first described around 1898 by Michaelis [9b] and around 1906 by Arbuzov [9c].

10 Arndt–Eistert Synthesis

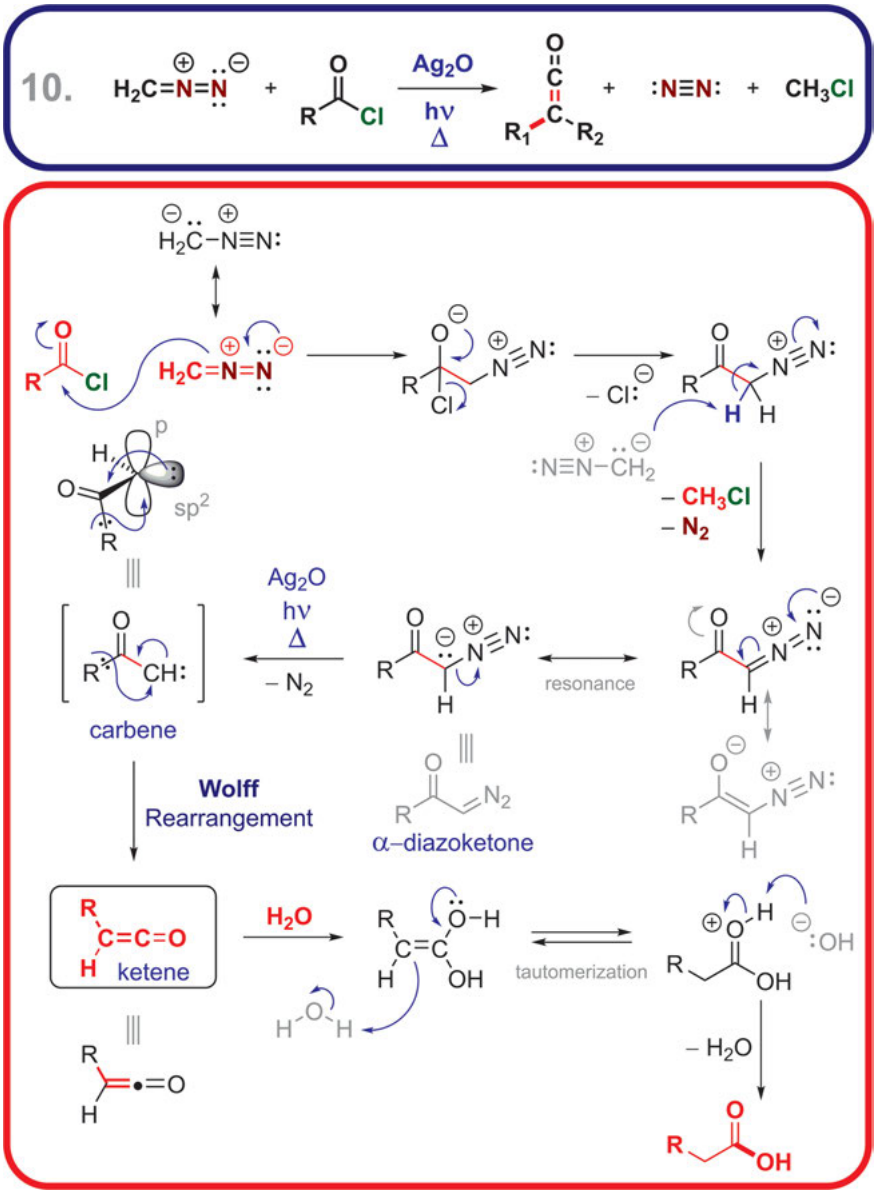

Fig. 10.1: The ***Arndt–Eistert*** *synthesis* mechanism.[30]

30 The ***Arndt–Eistert*** *synthesis* is also called the ***Arndt–Eistert*** *reaction (homologation)*. The ***Wolff*** *rearrangement* (α–diazoketone) is part of the ***Arndt–Eistert*** *synthesis* mechanism [10a].

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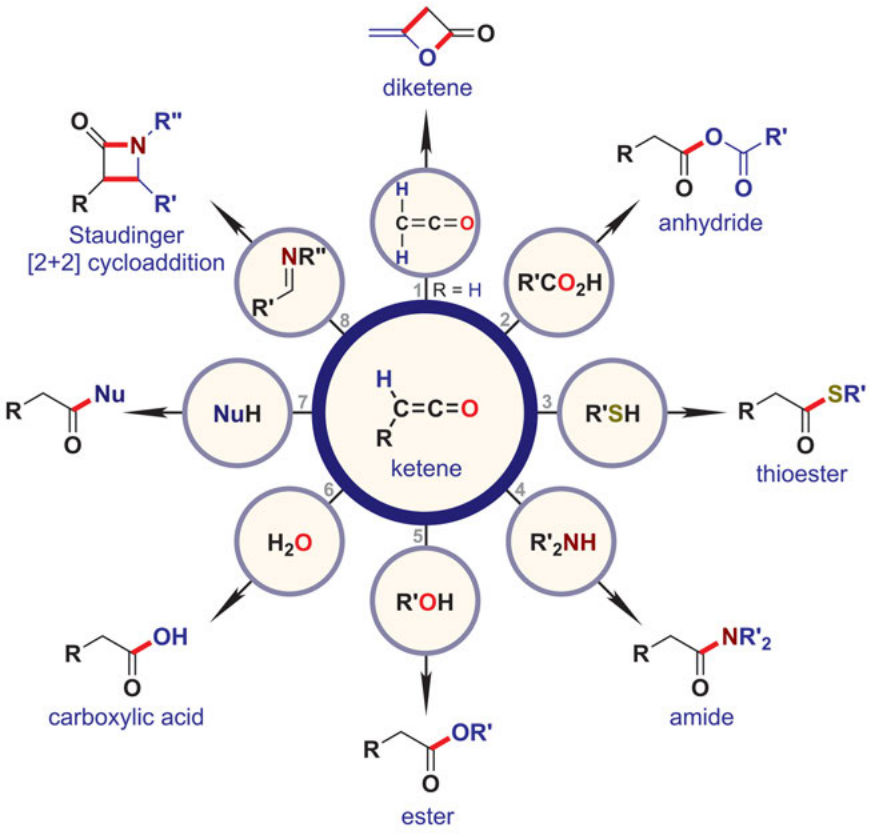

Fig. 10.2: The synthetic versatility of ketenes.[31]

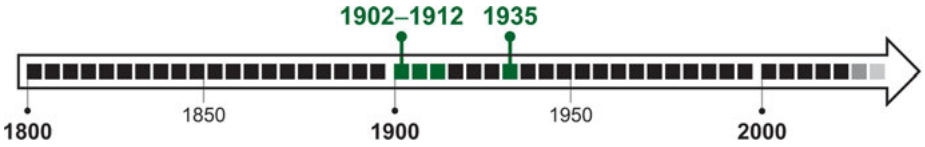

Fig. 10.3: The discovery of the ***Arndt–Eistert*** *synthesis*.[32]

31 The *ketenes* formed during the ***Arndt–Eistert*** *synthesis* can either be trapped by a variety of nucleophiles, or undergo [2+2] cycloaddition including dimerization.

32 The related reaction was likely first described by Wolff between 1902–1912 [10a, 10b] and by Arndt and Eistert around 1935 [10c].

11 Baeyer–Villiger Oxidation

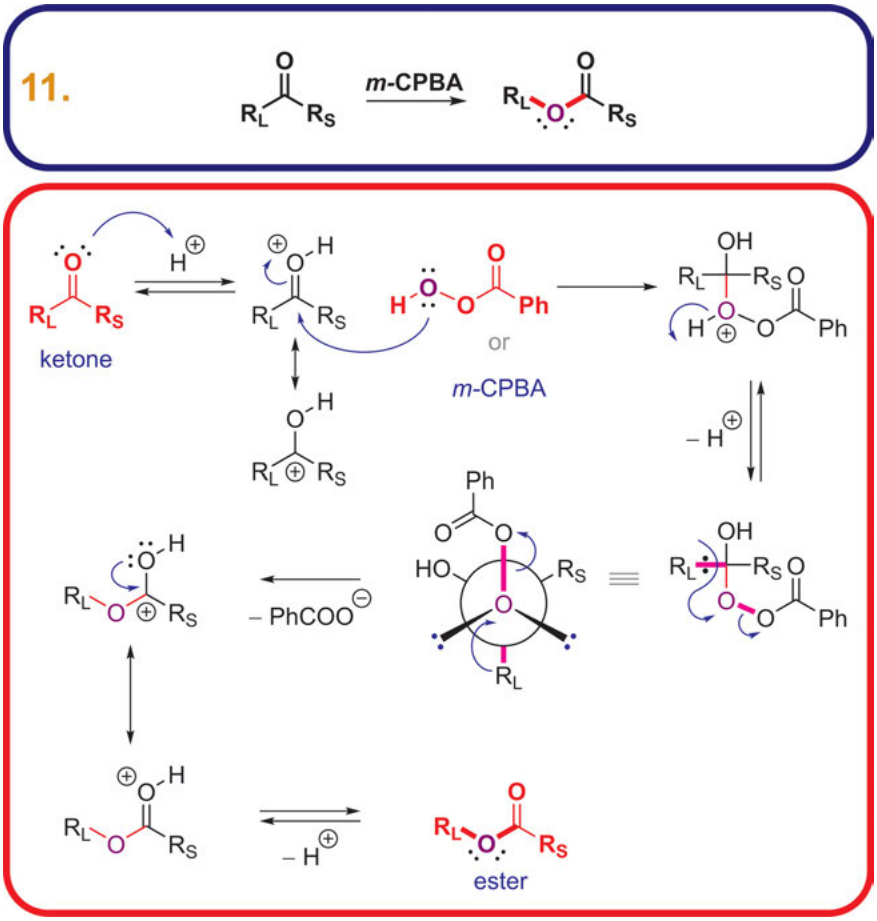

Fig. 11.1: The ***Baeyer–Villiger*** *oxidation* mechanism.[33]

33 The ***Baeyer–Villiger*** *oxidation* is also called the ***Baeyer–Villiger*** *rearrangement*.

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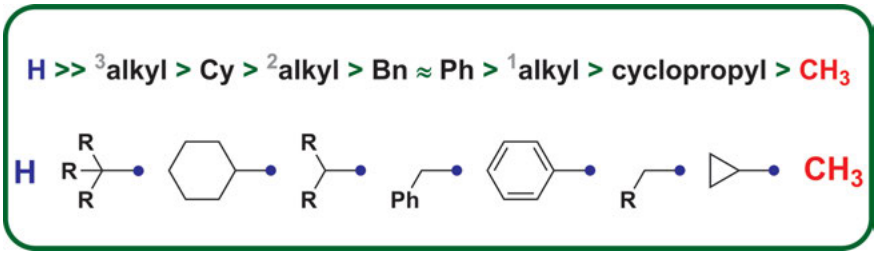

Fig. 11.2: The order of group migration in the ***Baeyer–Villiger*** *oxidation*.[34]

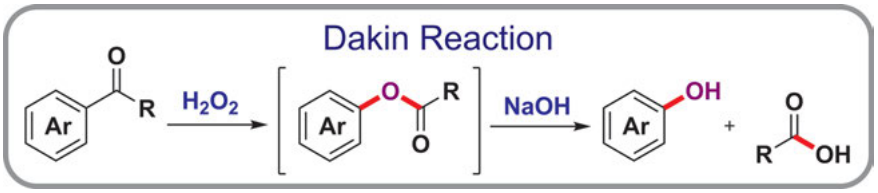

Fig. 11.3: The ***Dakin*** *reaction*.[35]

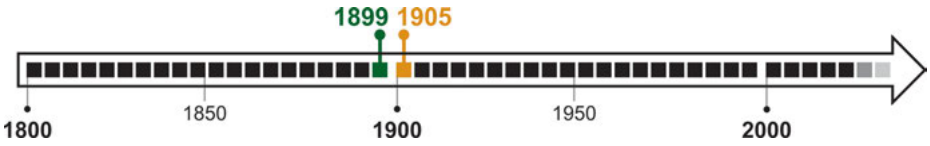

Fig. 11.4: The discovery of the ***Baeyer–Villiger*** *oxidation*.[36]

34 The order of group migration is essential for the *asymmetrical* ketones. Please note, this preference for migration is a general empirical trend and not an absolute rule [1].
35 The ***Dakin*** *reaction* (*oxidation*) is closely related to the ***Baeyer–Villiger*** *oxidation* and it usually yields *ortho*-hydroxy or *para*-hydroxy phenols (or phenols with a strong *ortho*- or *para*- ERG) [11a].
36 The reaction was likely first described around 1899 [11b]. In **1905**, Johann Friedrich Wilhelm Adolf von Baeyer received the Nobel Prize in Chemistry [11c].

12 Barton Decarboxylation

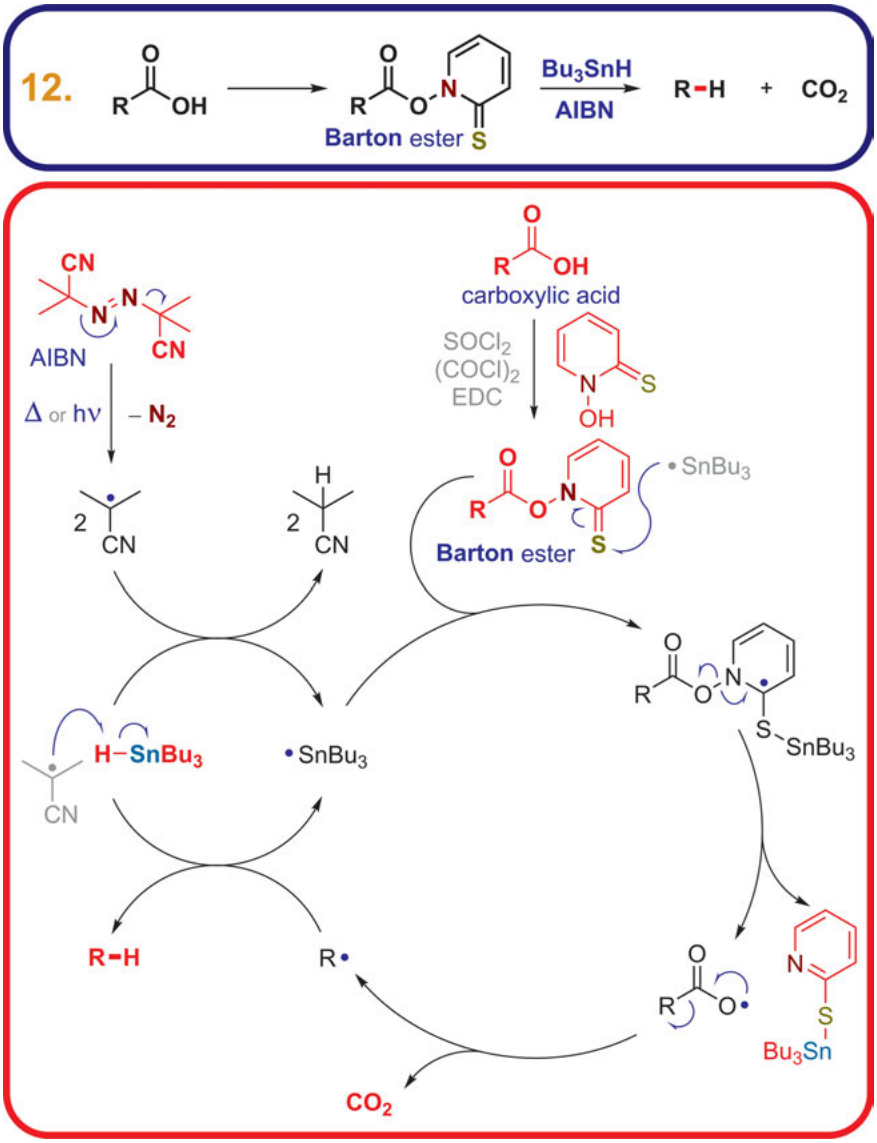

Fig. 12.1: The ***Barton*** *decarboxylation* mechanism.[37]

37 The ***Barton*** *decarboxylation* is a radical decarboxylation reaction of the ***Barton*** ester.

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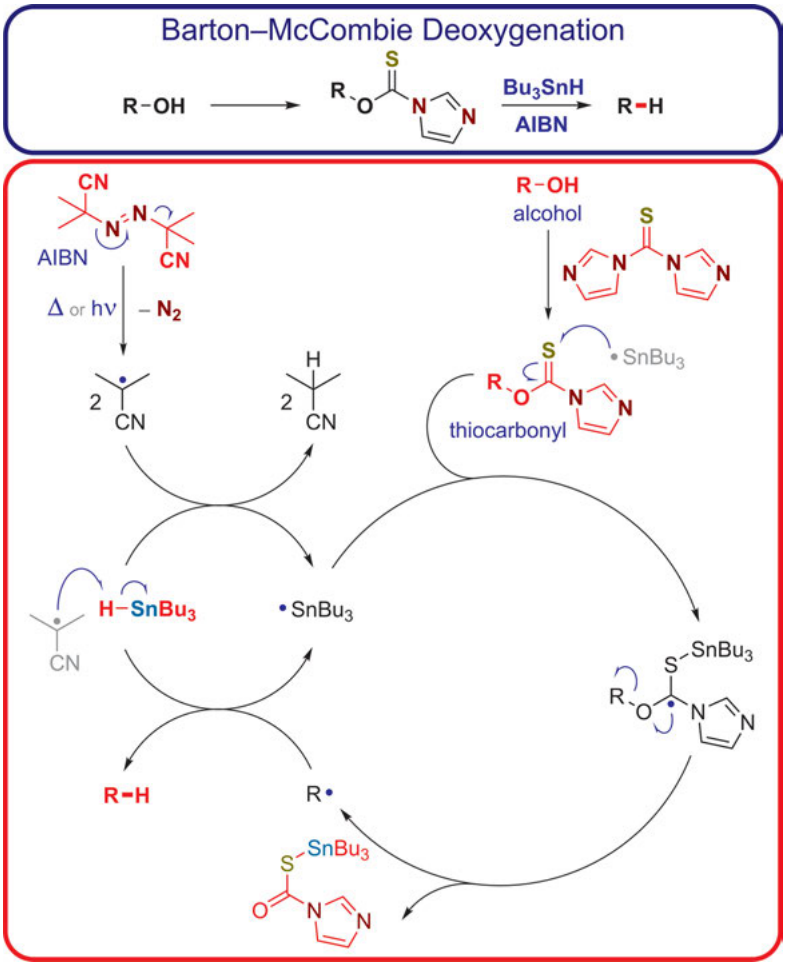

Fig. 12.2: The ***Barton–McCombie*** *deoxygenation* mechanism.[38]

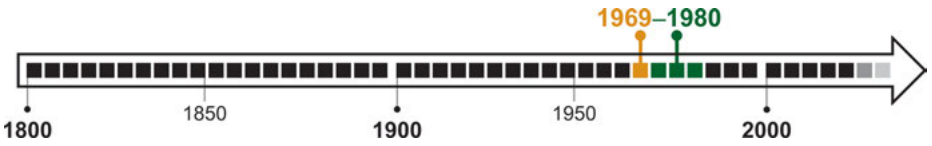

Fig. 12.3: The discovery of the ***Barton*** *decarboxylation*.[39]

38 The ***Barton–McCombie*** *deoxygenation* is a radical deoxygenation of a *thiocarbonyl*: *O*,*O*-thiocarbonate **RO**C(S)OR; *S*,*O*-dithiocarbonate = xanthate **RO**C(S)SR; or *O*-thiocarbamate **RO**C(S)NR_2.
39 The *decarboxylation* reaction was likely first described between 1980–1985 [12a, 12b] and the *deoxygenation* reaction was likely first described between 1975–1980 [12c, 12d]. In **1969**, Derek H. R. Barton (jointly with Odd Hassel) received the Nobel Prize in Chemistry [12e].

13 Baylis–Hillman Reaction

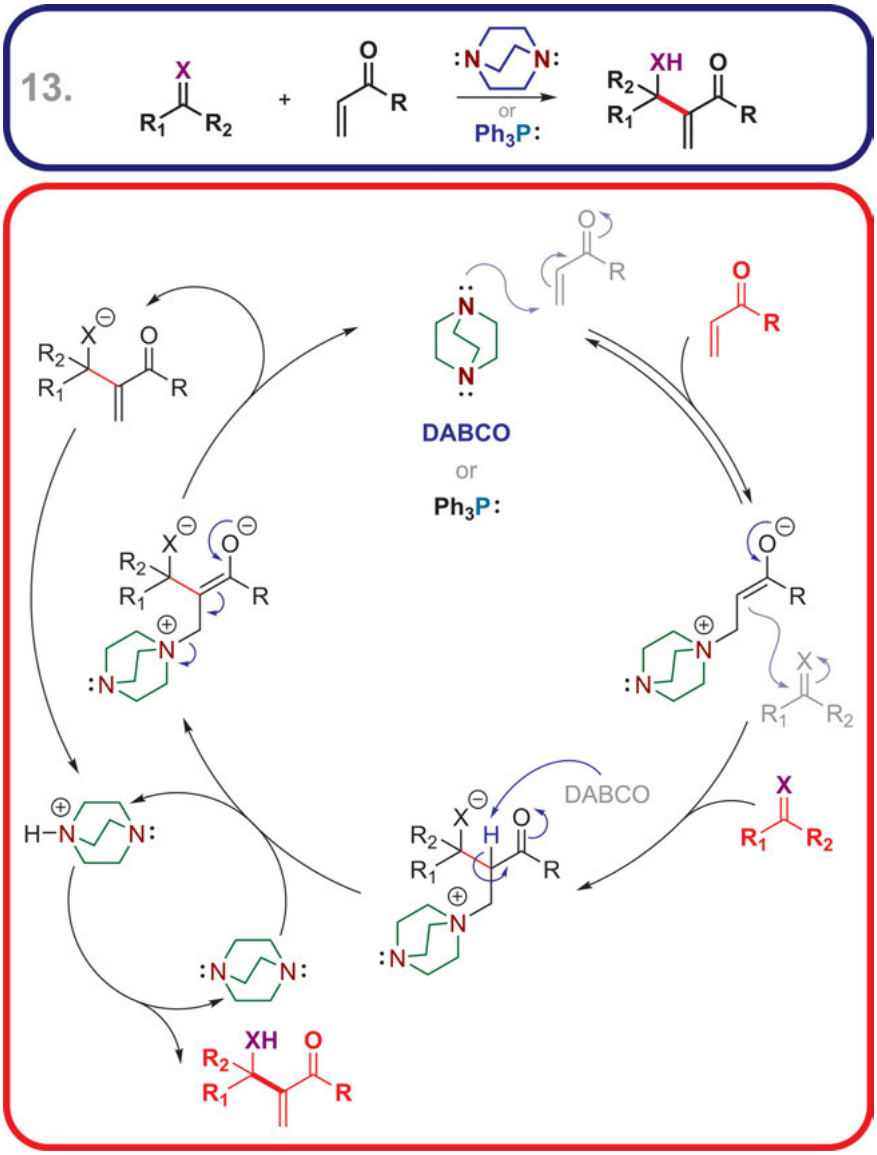

Fig. 13.1: The ***Baylis–Hillman*** *reaction* mechanism.[40]

40 The ***Baylis–Hillman*** *reaction* is also called the ***Morita–Baylis–Hillman*** *reaction*.

https://doi.org/10.1515/9783110608373-013

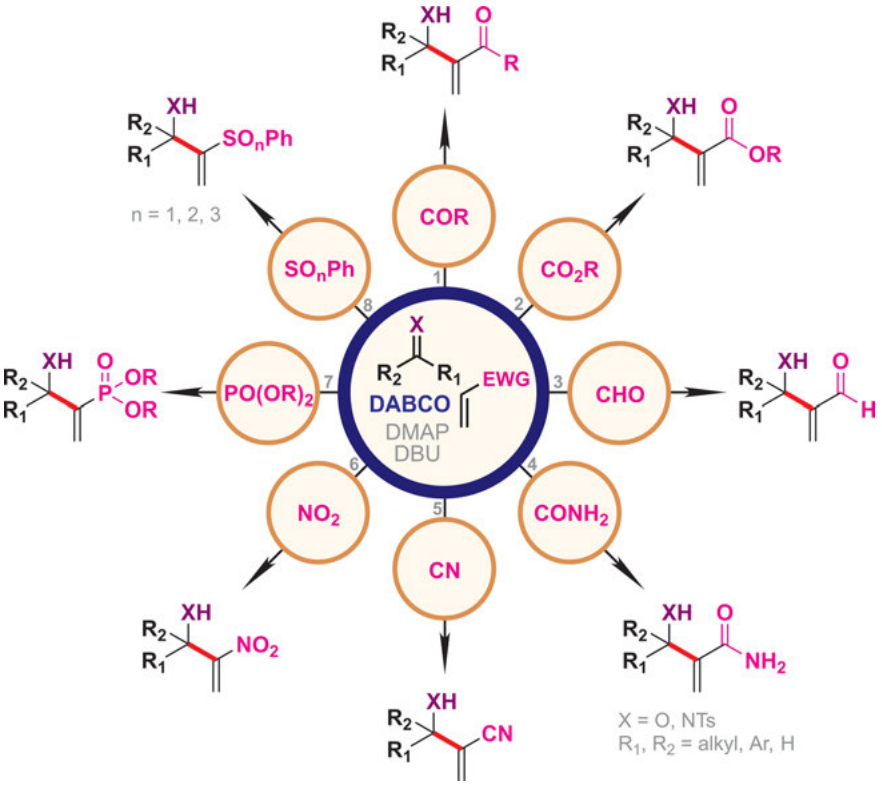

Fig. 13.2: The synthetic versatility of the ***Baylis–Hillman*** *reaction*.[41]

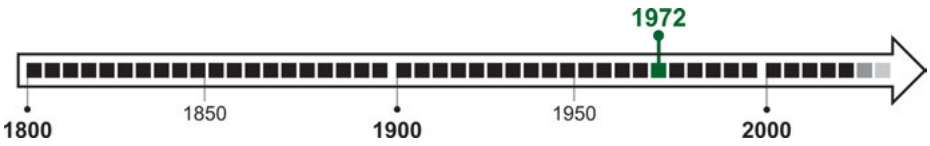

Fig. 13.3: The discovery of the ***Baylis–Hillman*** *reaction*.[42]

41 Many variations of the ***Baylis–Hillman*** *reaction* exist, depending on the nature of EWG (the *Michael* acceptor) and carbonyl compound (the electrophile). Please note, for X = NR it is called the *aza-**Baylis–Hillman** reaction.*

42 The reaction was likely first described around 1972 [13].

14 Beckmann Rearrangement

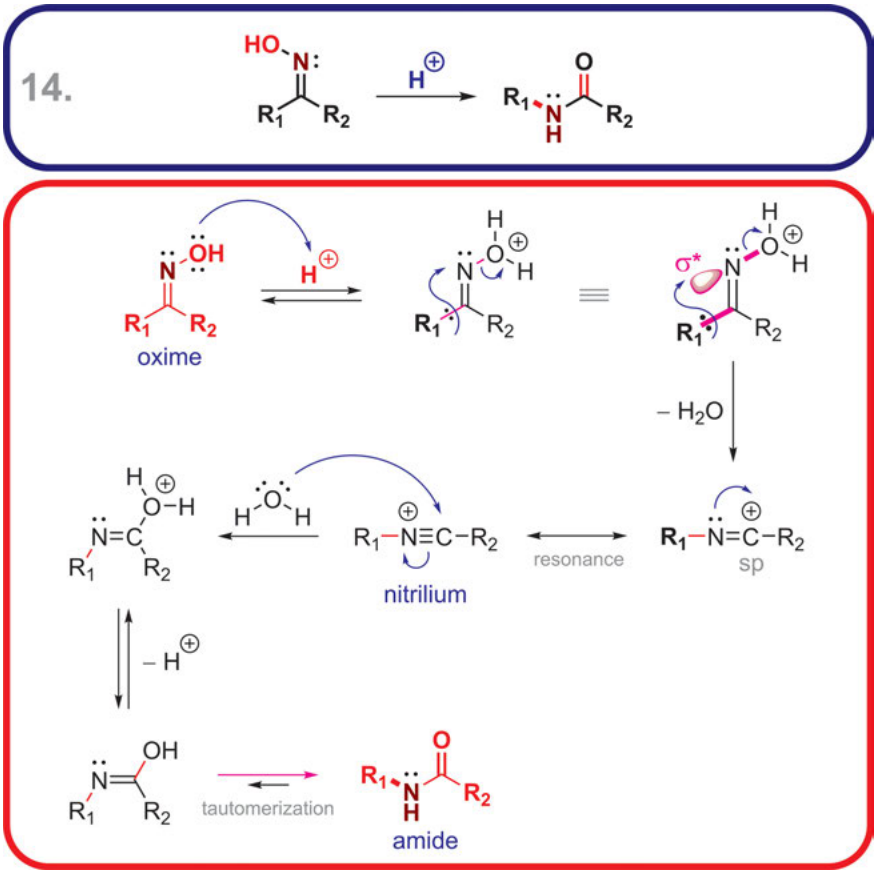

Fig. 14.1: The ***Beckmann*** *rearrangement* mechanism.[43]

43 The ***Beckmann*** *rearrangement* is seldom called the ***Beckmann*** *oxime-amide rearrangement*.

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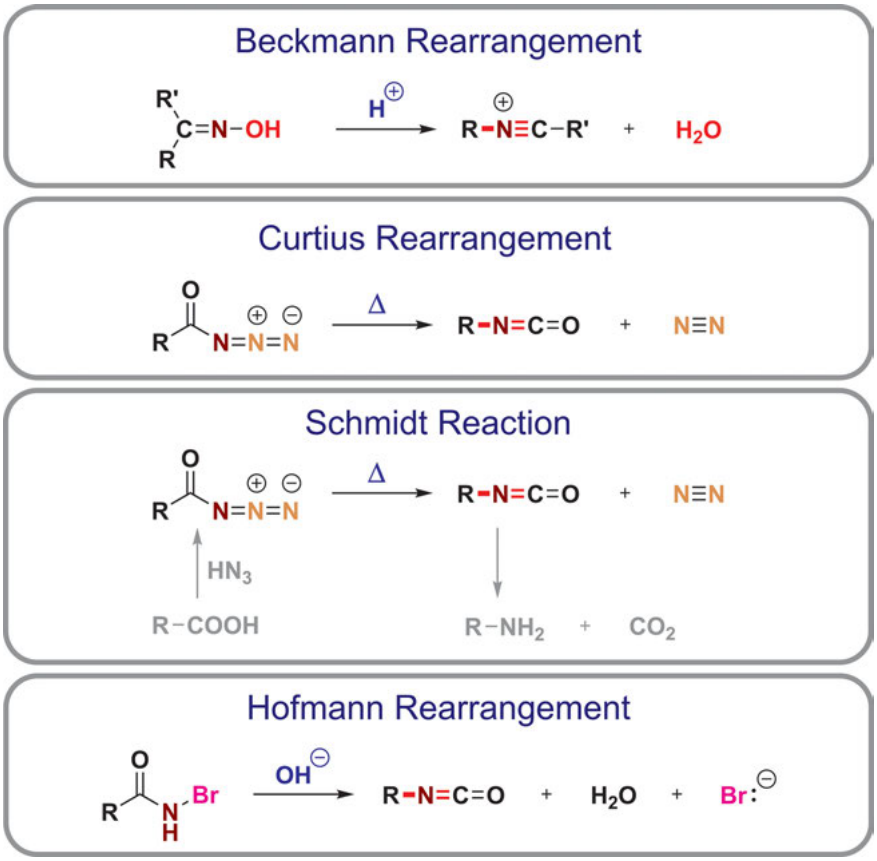

Fig. 14.2: Reactions related to the ***Beckmann*** *rearrangement*.[44]

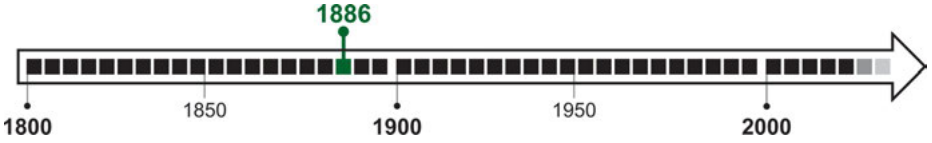

Fig. 14.3: The discovery of the ***Beckmann*** *rearrangement*.[45]

44 Several reactions are mechanistically related to the ***Beckmann*** *rearrangement*: the ***Curtius*** *rearrangement*, the ***Schmidt*** *reaction*, the ***Hofmann*** *rearrangement*, and the ***Lossen*** *rearrangement* (all covered in Chapter 31). The first example (the ***Beckmann*** *rearrangement*) is redrawn to emphasize the rearrangement of an *oxime* into a *nitrilium ion*. In other examples, the key step is the rearrangement of a *nitrene* (formed from a carbonyl derivative) into an *isocyanate*.

45 The reaction was likely first described around 1886 [14].

15 Benzoin Condensation

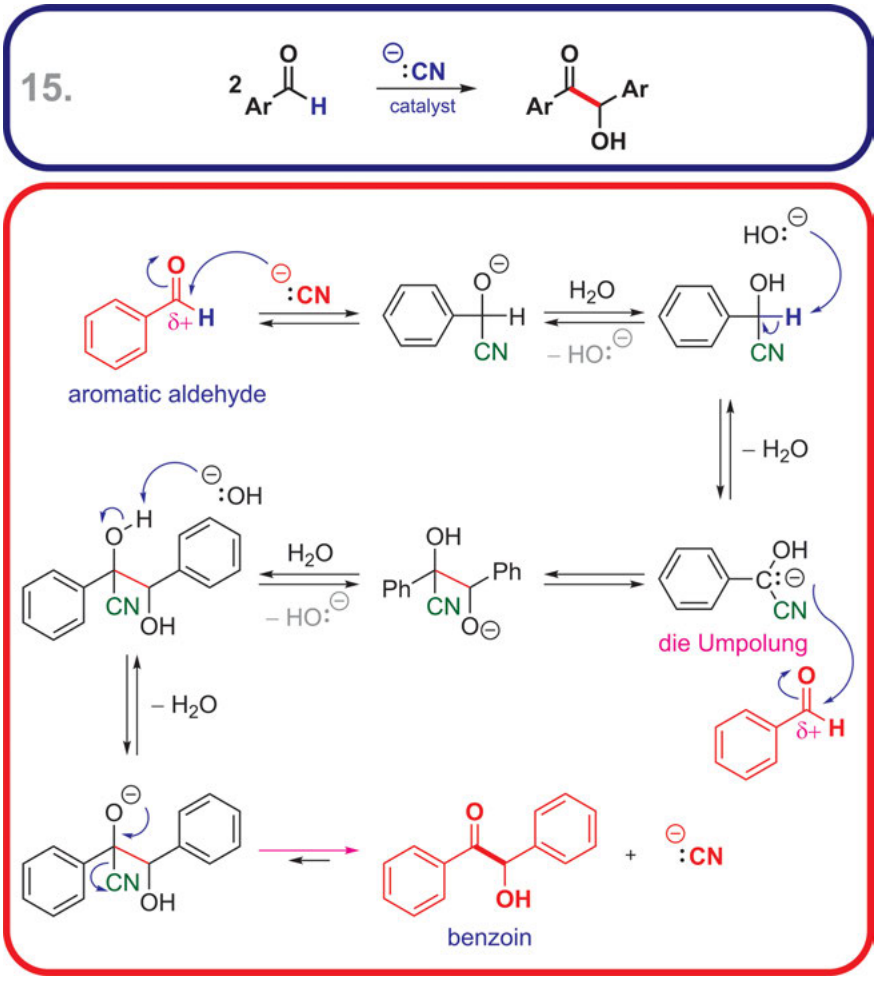

Fig. 15.1: The *benzoin condensation* mechanism.[46]

46 The *benzoin condensation* is one of the oldest reactions in organic chemistry.

https://doi.org/10.1515/9783110608373-015

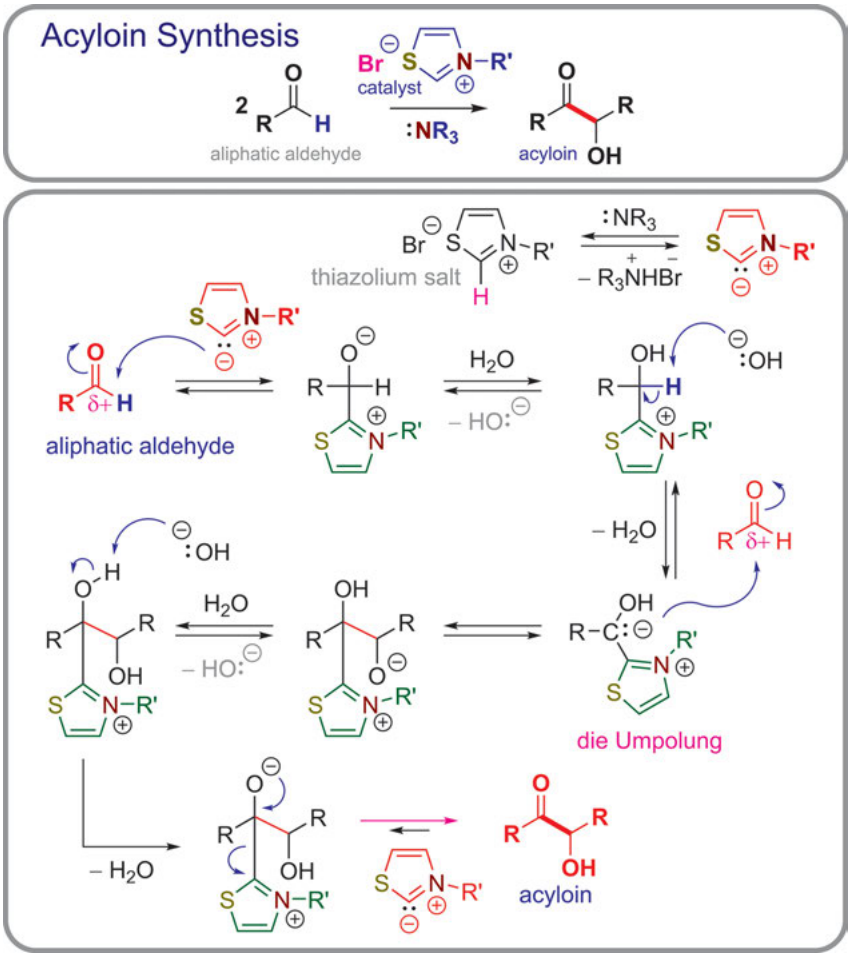

Fig. 15.2: The *acyloin synthesis* mechanism using thiazolium salts.[47]

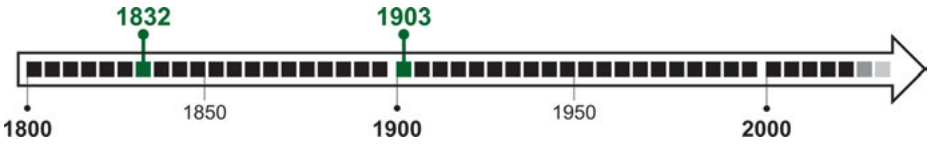

Fig. 15.3: The discovery of the *benzoin condensation*.[48]

47 The *benzoin condensation* involves two aromatic aldehydes and is catalyzed by **cyanide ion** forming aromatic α–hydroxy ketones *(benzoins)*. The *acyloin synthesis* is a condensation of two aliphatic aldehydes, it is catalyzed by **thiazolium salts** [15a, 15b] and yields aliphatic (or mixed) α–hydroxy ketones *(acyloins)*. The *acyloin synthesis* should not be confused with the *acyloin condensation* (Chapter 7).
48 The reaction was likely first described around 1832 and the mechanism in 1903 [15c, 15d].

16 Benzyne Mechanism

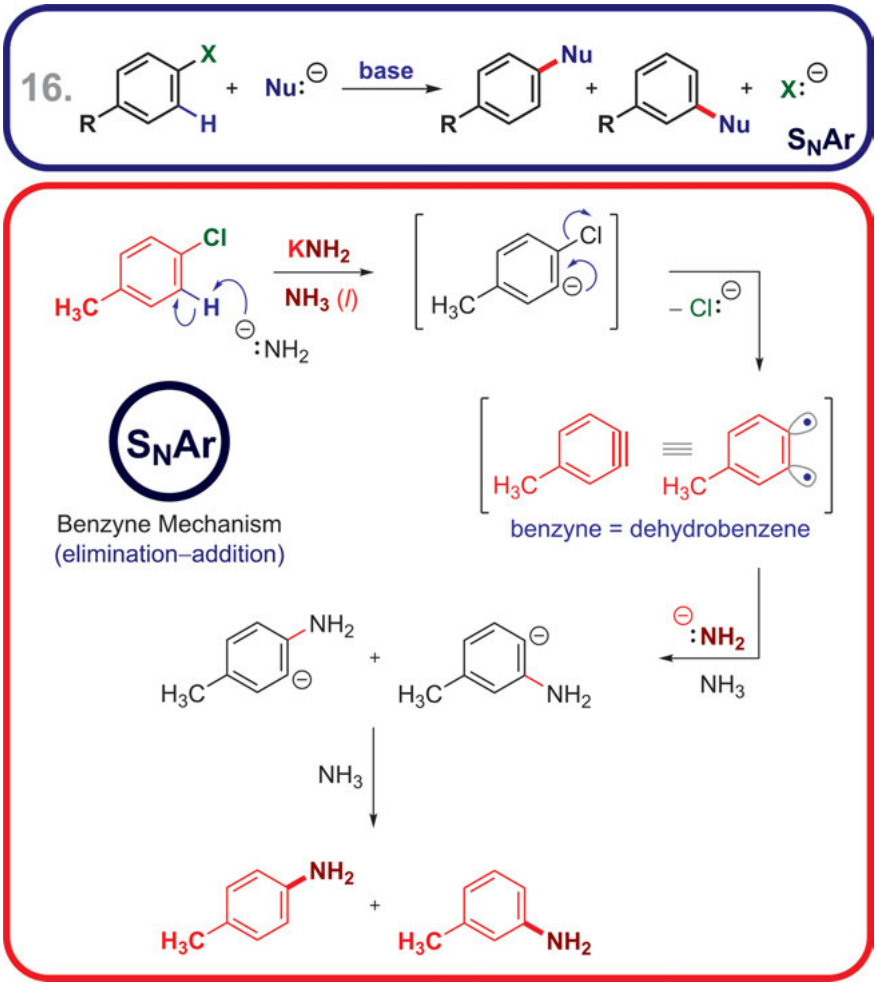

Fig. 16.1: The *benzyne (elimination-addition)* mechanism.[49]

49 The *benzyne mechanism* is one of the fundamental **aromatic nucleophilic substitution** mechanisms; it is also called the *elimination-addition* mechanism, that is, the opposite of **S_NAr** (**S_N2Ar**), or the *addition-elimination* mechanism (covered in Chapter 4).

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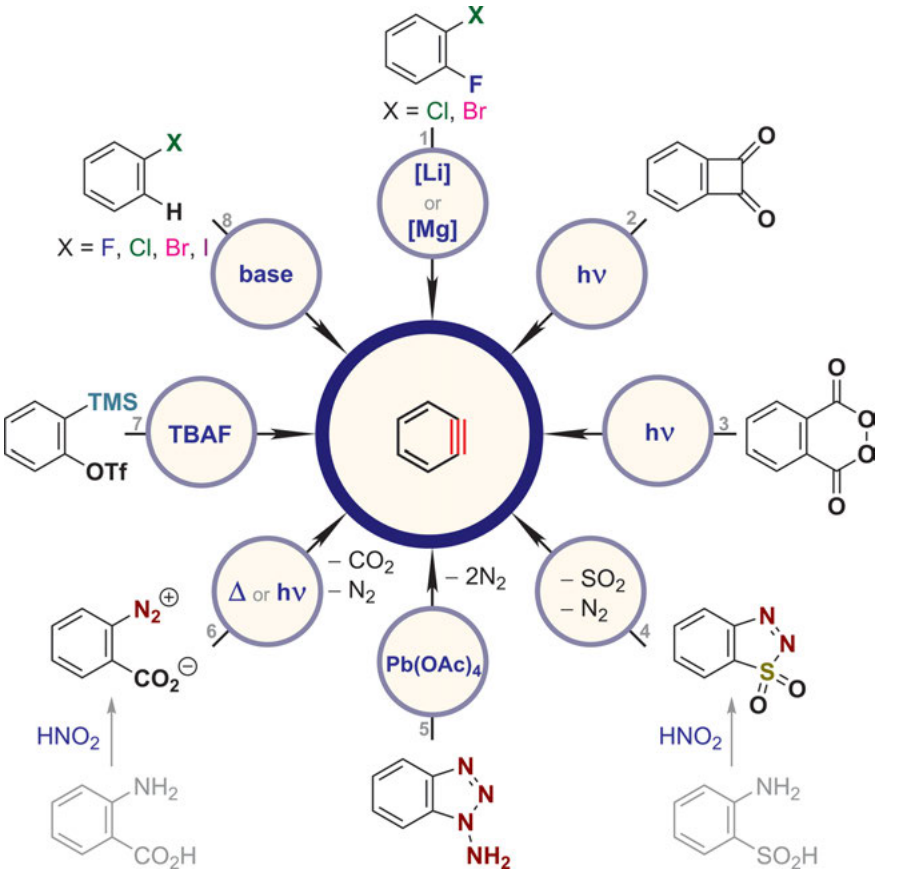

Fig. 16.2: Various synthetic methods leading to the formation of benzyne.[50]

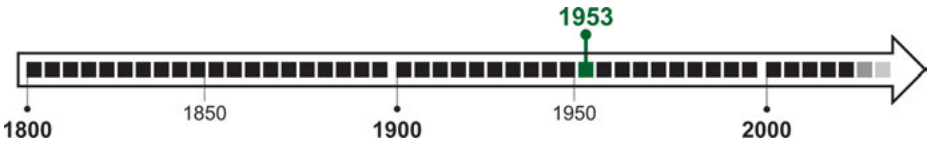

Fig. 16.3: The discovery of the *benzyne mechanism*.[51]

50 Since its first discovery, numerous methods evolved leading to the formation of the *benzyne* intermediate *(aryne)*. Please note, *benzyne (aryne)* can also be called *dehydrobenzene (dehydroarene)* [16a, 16b].

51 The mechanism in its present form was likely first proposed around 1953 [16c].

17 Bergman Cyclization

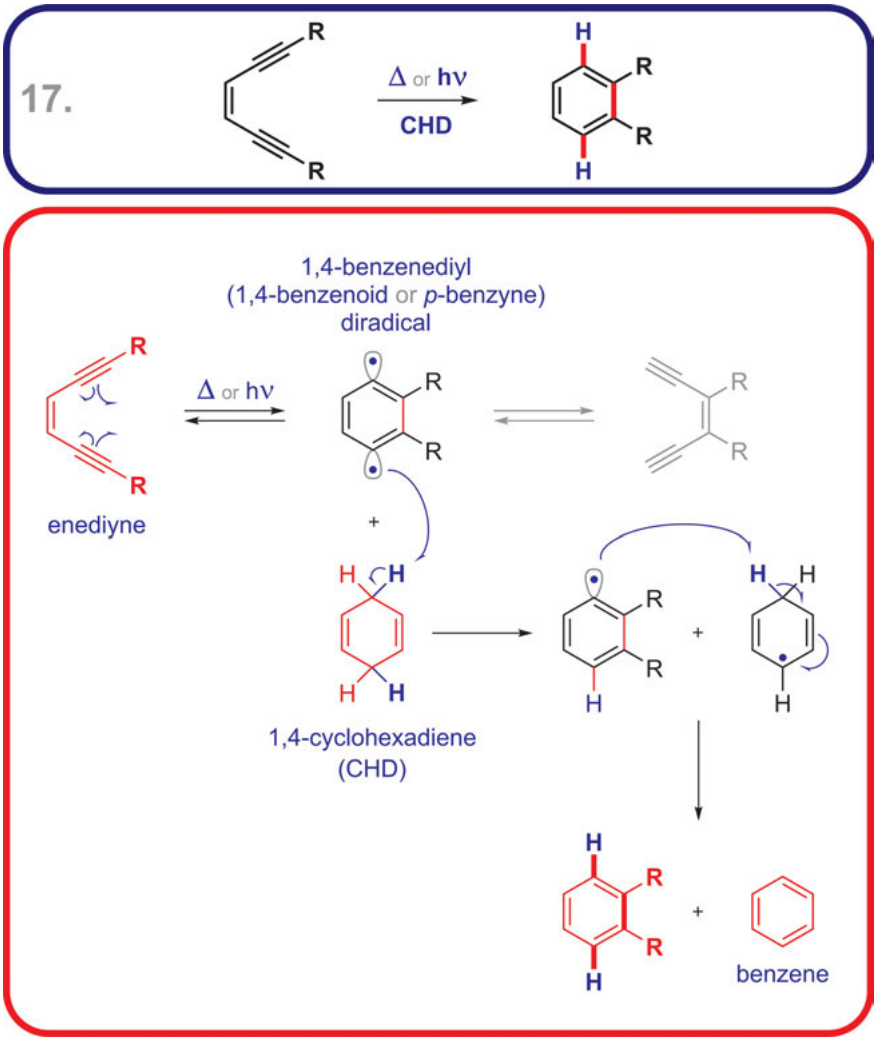

Fig. 17.1: The ***Bergman*** *cyclization* mechanism.[52]

52 The ***Bergman*** *cyclization* is also known as the ***Bergman*** *reaction (isomerization, cycloaromatization).*

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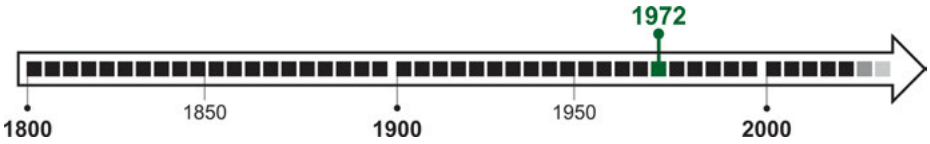

Fig. 17.2: The discovery of the ***Bergman*** *cyclization*.[53]

53 The reaction was likely first described around 1972 [17].

18 Birch Reduction

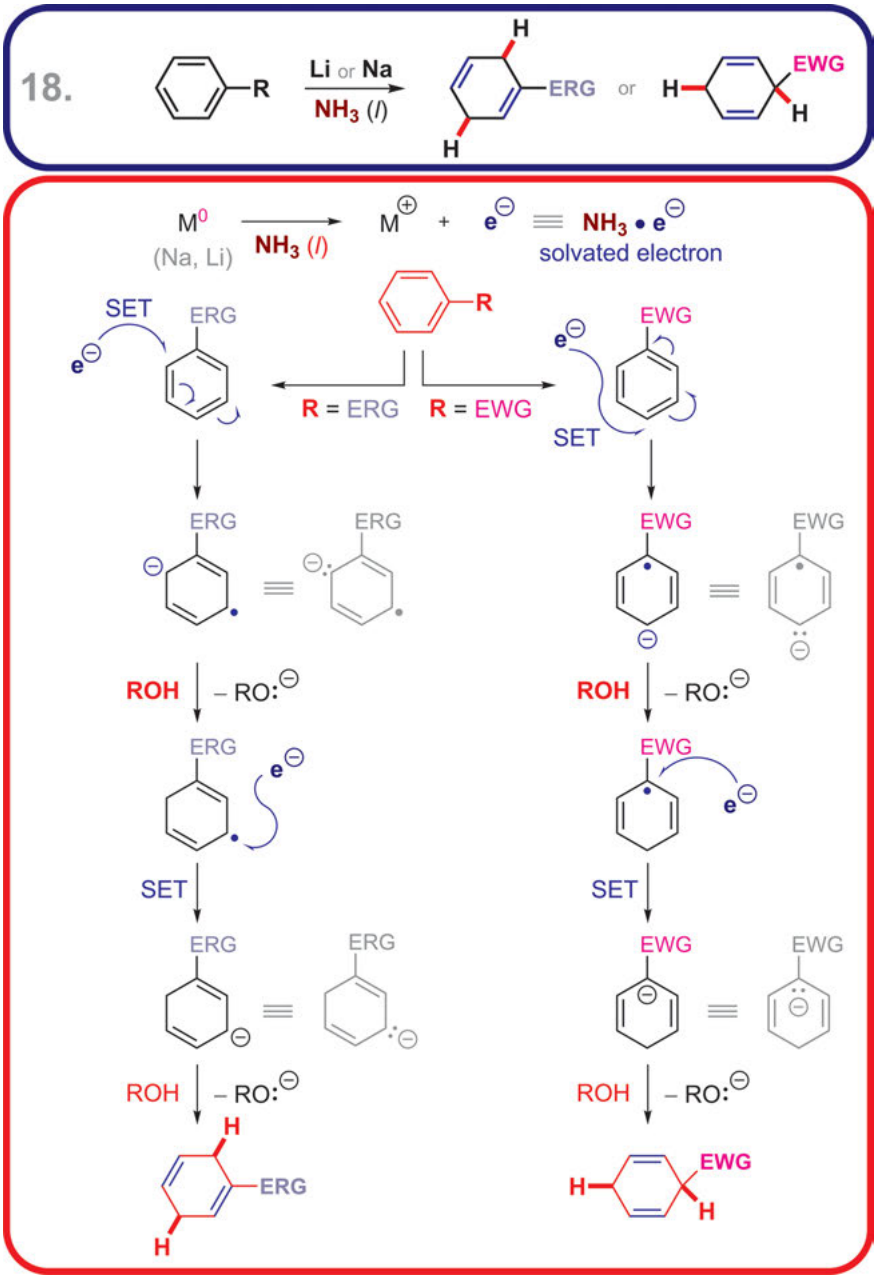

Fig. 18.1: The ***Birch*** *reduction* mechanism.[54]

https://doi.org/10.1515/9783110608373-018

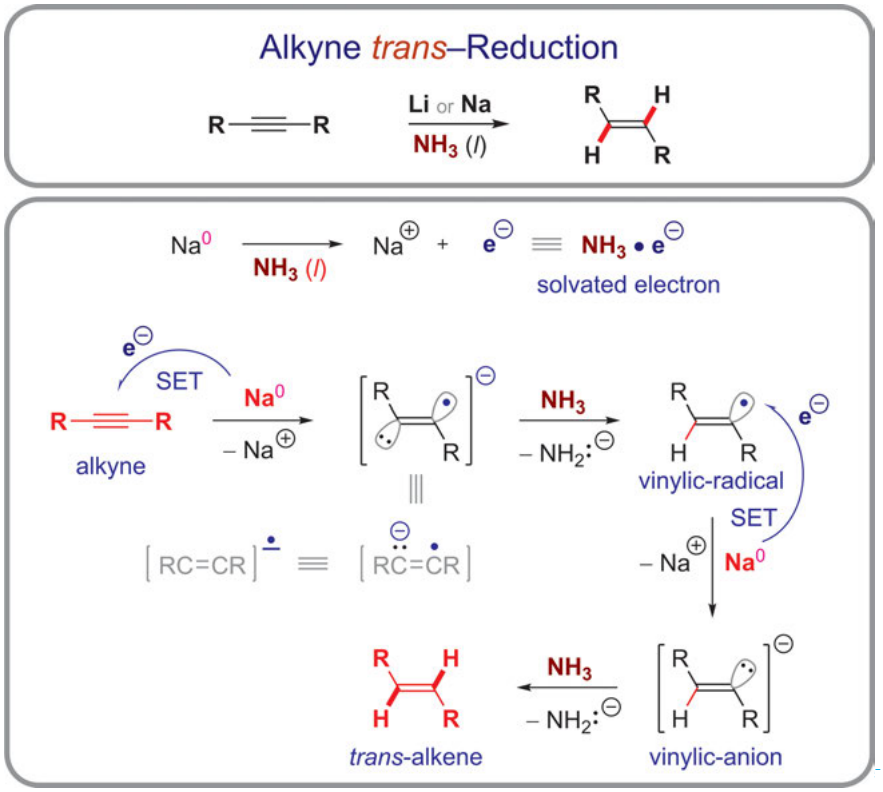

Fig. 18.2: The *alkyne trans-reduction* mechanism.[55]

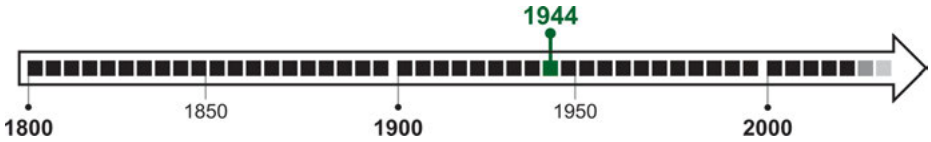

Fig. 18.3: The discovery of the ***Birch*** *reduction*.[56]

54 The first step in the ***Birch*** *reduction* mechanism is a *single electron transfer* (SET) (see Chapter 5). The regiochemistry of the formed products depends on the nature of the substitution (ERG versus EWG).
55 The *alkyne trans-reduction (alkyne metal reduction)* mechanism is much like the ***Birch*** *reduction*. Please note, under the ***Birch*** *reduction* conditions *alkynes* are reduced to ***trans****-alkenes* [18a, 18b]. Under Pd/C-catalyzed conditions, the ***cis****-alkene* is usually the major product.
56 The reaction was likely first described around 1944 [18c].

19 Bischler–Napieralski Cyclization

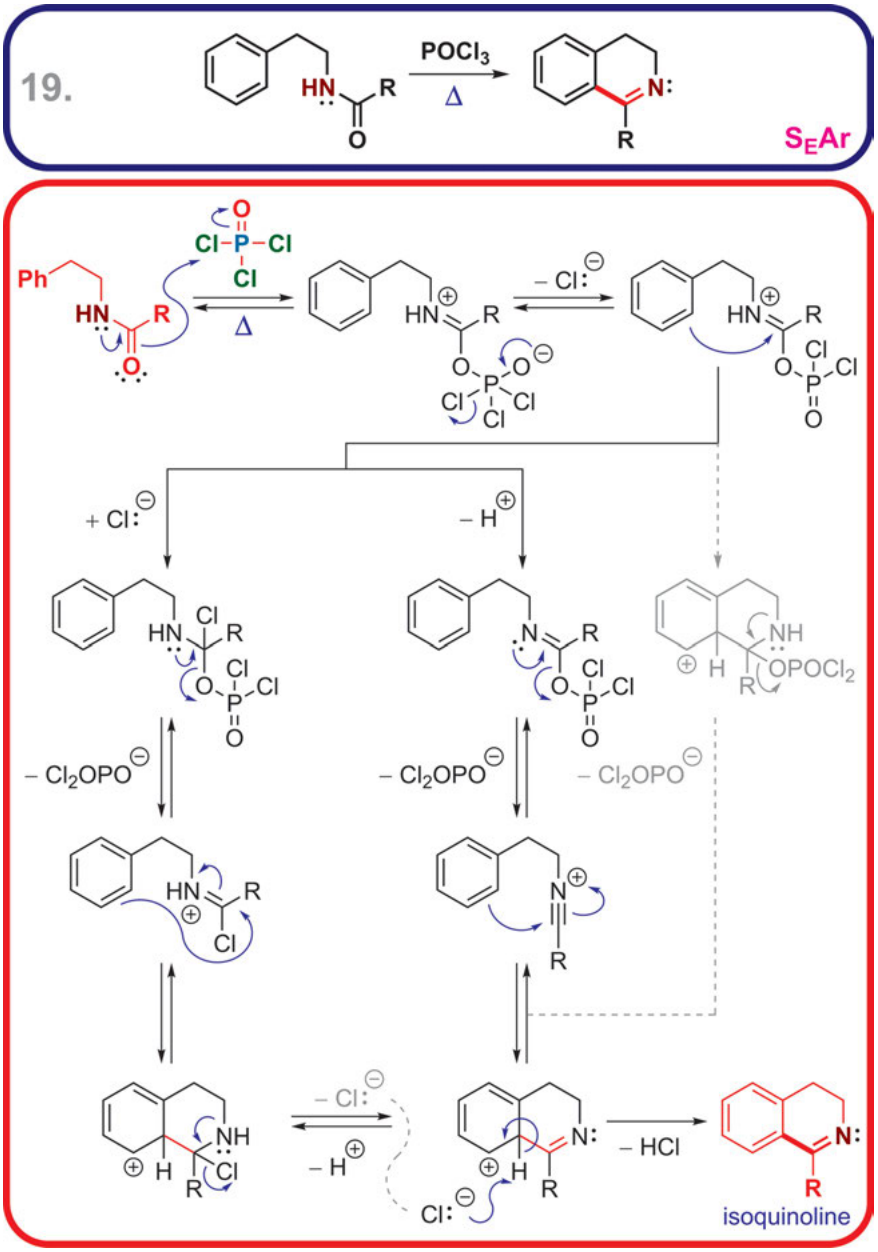

Fig. 19.1: The ***Bischler–Napieralski*** *cyclization* mechanism.[57]

https://doi.org/10.1515/9783110608373-019

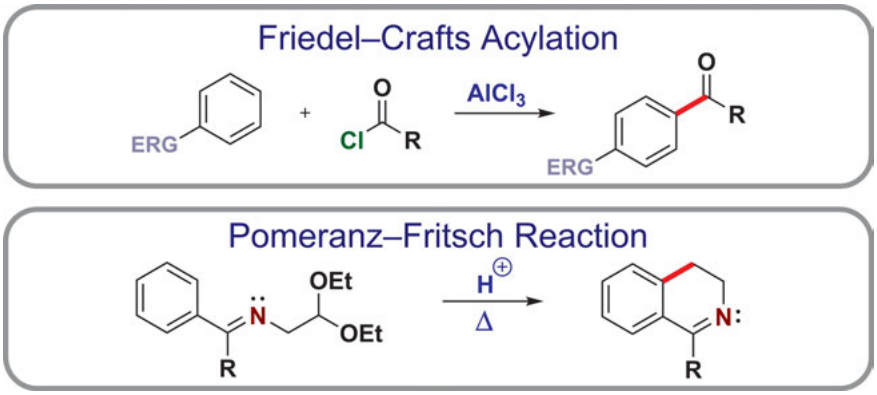

Fig. 19.2: Reactions related to the ***Bischler–Napieralski*** *cyclization*.[58]

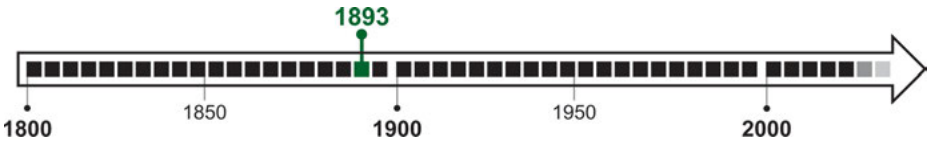

Fig. 19.3: The discovery of the ***Bischler–Napieralski*** *cyclization*.[59]

57 The ***Bischler–Napieralski*** *cyclization* also called the ***Bischler–Napieralski*** *reaction*. It is a classic example of **aromatic electrophilic substitution** (the ***arenium ion*** mechanism or $\mathbf{S_EAr}$, Chapter 3).
58 Several named reactions are related to the ***Bischler–Napieralski*** *cyclization*: the ***Friedel–Crafts*** *acylation* and *alkylation* (covered in Chapter 39), and the closely related ***Pomeranz–Fritsch*** *reaction*, which is an alternative way to make *isoquinolines* [19a, 19b].
59 The reaction was likely first described around 1893 [19c].

20 Brown Hydroboration

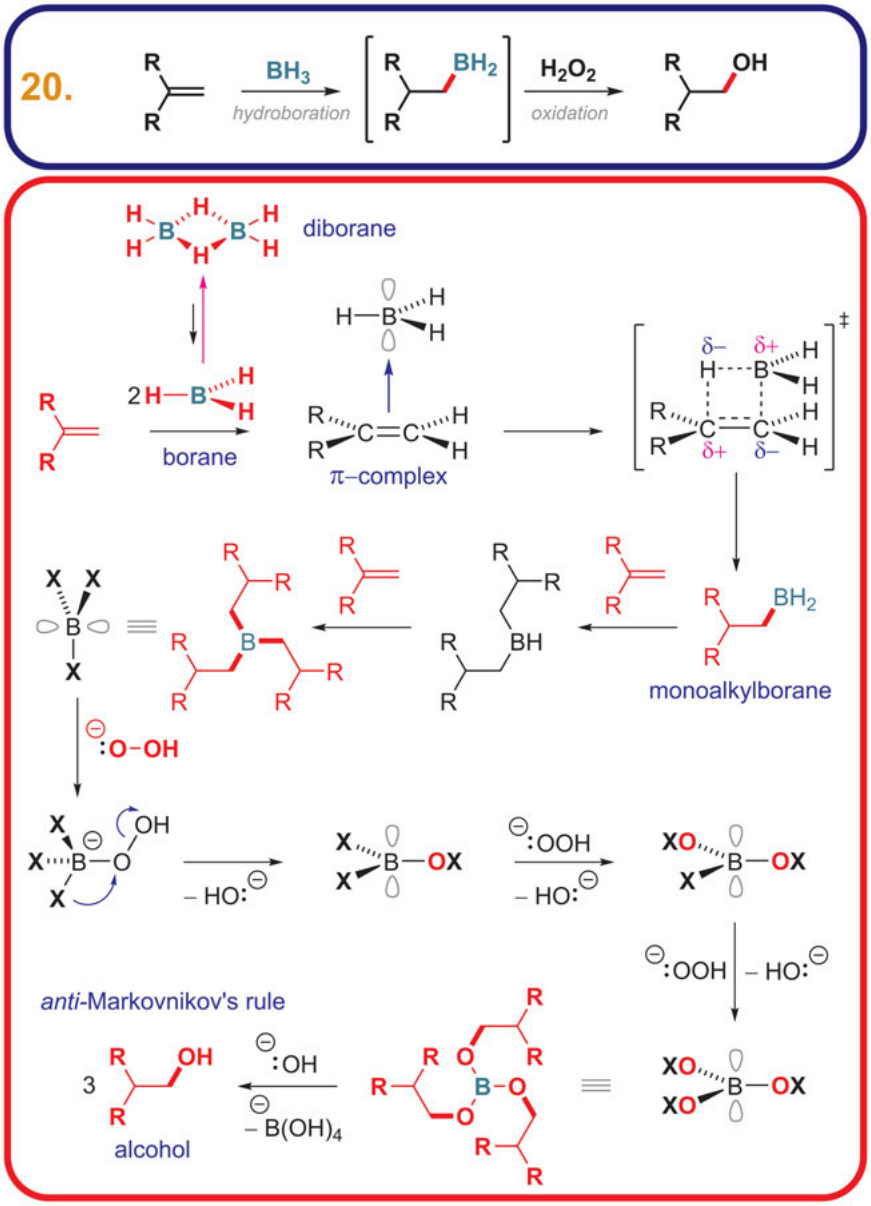

Fig. 20.1: The ***Brown*** *hydroboration* mechanism.[60]

https://doi.org/10.1515/9783110608373-020

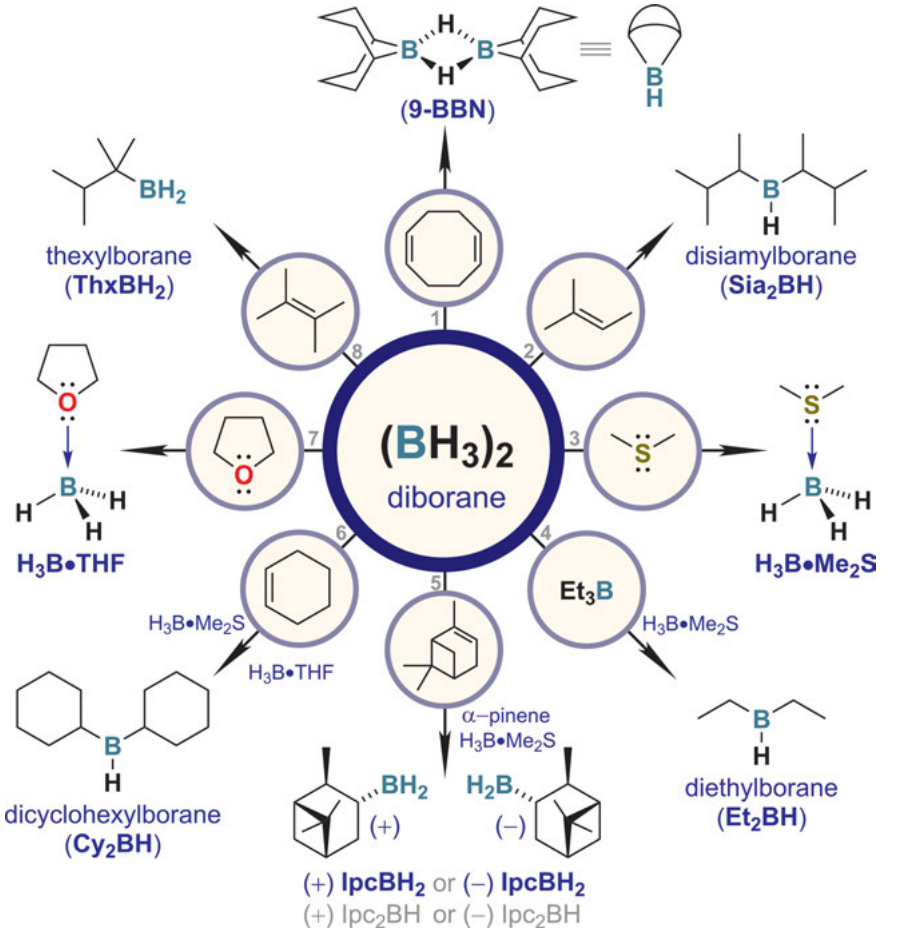

Fig. 20.2: Various borane derivatives formed from diborane.[61]

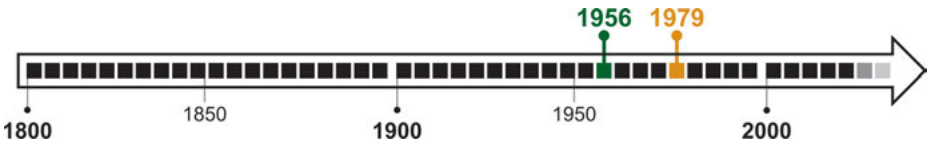

Fig. 20.3: The discovery of the ***Brown*** *hydroboration*.[62]

60 The ***Brown*** *hydroboration* is also known as the *hydroboration-oxidation*. The mechanism is believed to be concerted and ***anti-Markovnikov's*** product is usually formed. Compare to Chapter 52.

61 There are numerous examples of the borane complexes (BH_3•X); the monoalkylborane (RBH_2); and dialkylborane (R_2BH) reagents, which can be prepared from the *diborane* (B_2H_6) via the *hydroboration reaction*: 9-BBN reagent is one of the most important among them [20a].

62 The reaction was likely described around 1956 [20b]. In **1979**, Herbert C. Brown (jointly with Georg Wittig) received the Nobel Prize in Chemistry for the development of boron chemistry [20c].

21 Buchwald–Hartwig Cross Coupling

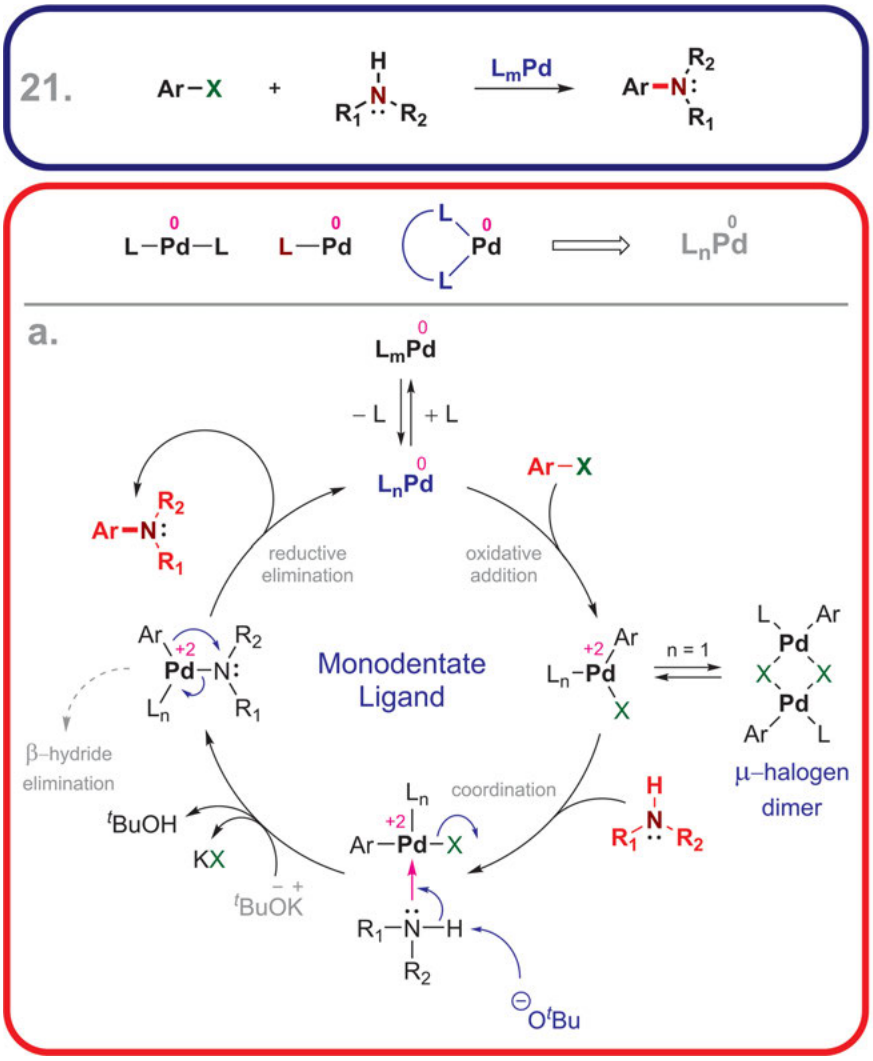

Fig. 21.1: The ***Buchwald–Hartwig*** *cross coupling* mechanism (monodentate ligand).[63]

63 The ***Buchwald–Hartwig*** *cross coupling (amination)* is a type of ***Pd****-catalyzed cross coupling* reaction (C–N bond formation using *aryl halides* and *amines*). The mechanism varies and is usually substrate and ligand dependent. For teaching purposes, a simplified and general example is shown, which may take place in the presence of a *monodentate ligand*.

https://doi.org/10.1515/9783110608373-021

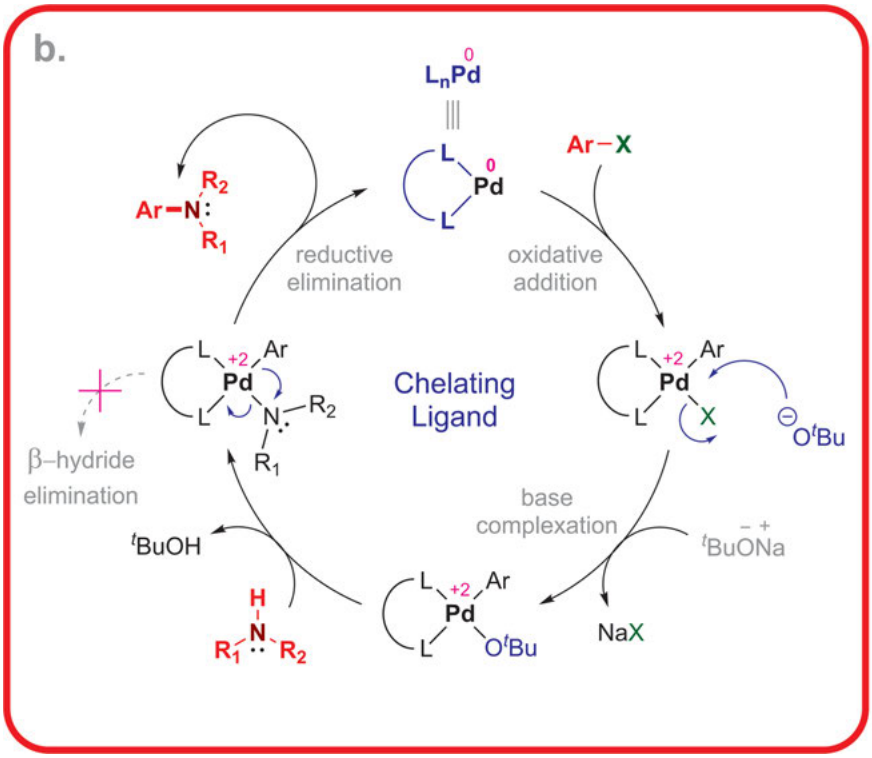

Fig. 21.2: The ***Buchwald–Hartwig*** *cross coupling* mechanism (chelating ligand).[64]

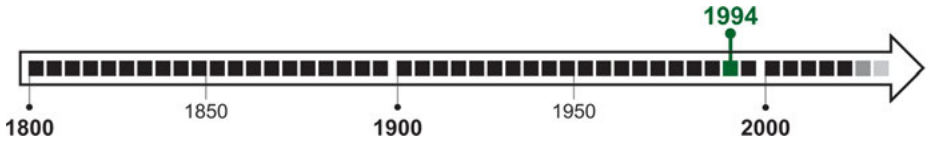

Fig. 21.3: The discovery of the ***Buchwald–Hartwig*** *cross coupling*.[65]

64 For teaching purposes, a simplified and general example is shown, which may take place in the presence of a *chelating ligand*.

65 The reaction was likely first described around 1994 [21].

22 Cannizzaro Reaction

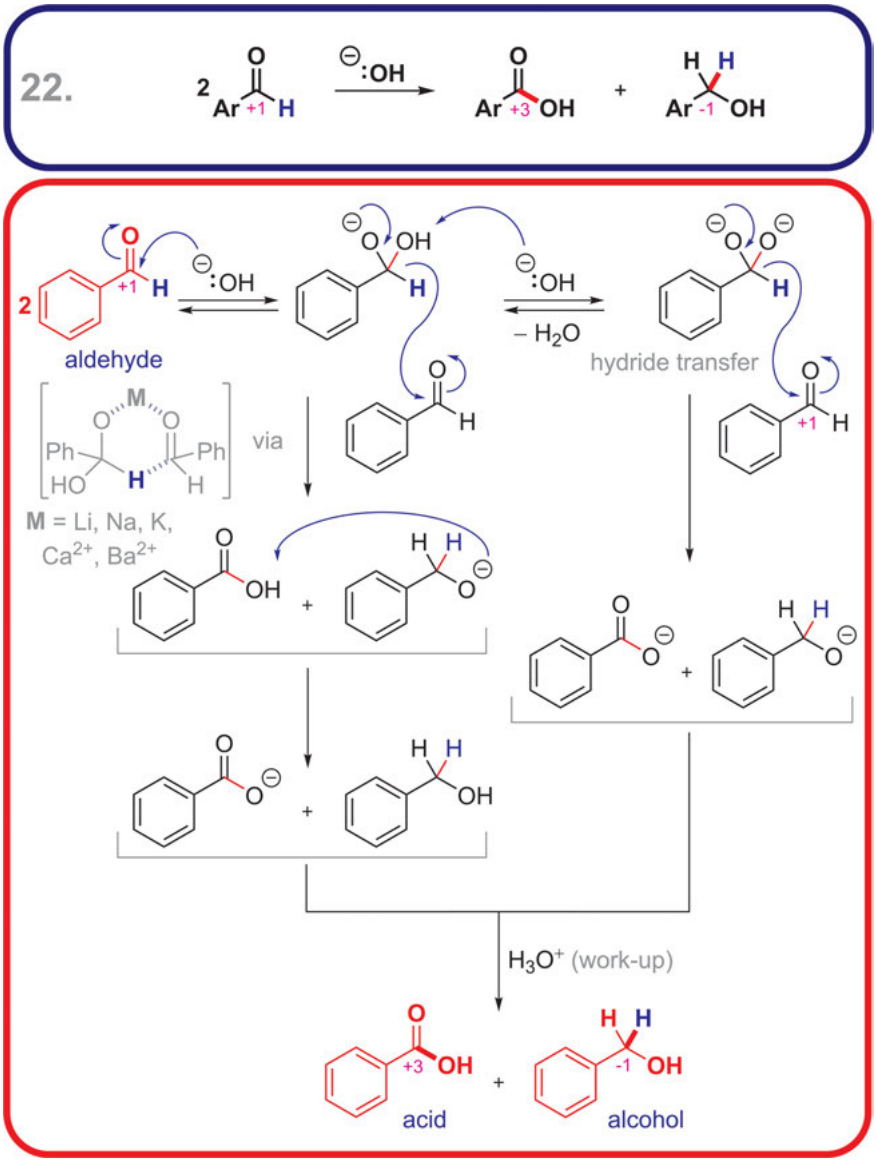

Fig. 22.1: The ***Cannizzaro*** *reaction* mechanism.[66]

66 The ***Cannizzaro*** *reaction* is seldom called the ***Cannizzaro*** *disproportionation (RedOx) reaction*. It is one of the oldest reactions in organic chemistry.

https://doi.org/10.1515/9783110608373-022

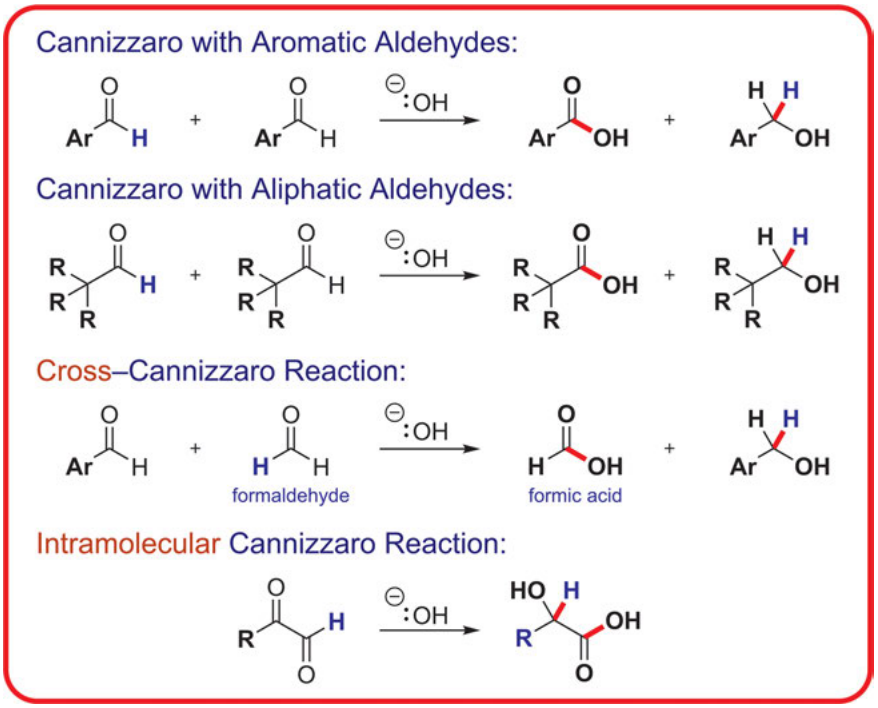

Fig. 22.2: Variations of the ***Cannizzaro*** *reaction*.[67]

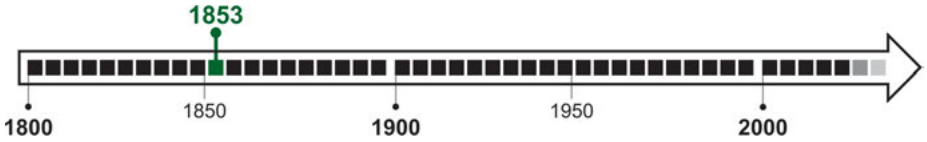

Fig. 22.3: The discovery of the ***Cannizzaro*** *reaction*.[68]

67 There are many variations of the ***Cannizzaro*** *reaction*: the ***Cannizzaro*** *reaction* with aromatic and aliphatic aldehydes containing no α–hydrogen atoms, and the *cross-**Cannizzaro** reaction* and the *intramolecular **Cannizzaro** reaction* [1].

68 The reaction was likely first described around 1853 [22].

23 Chan–Evans–Lam Cross Coupling

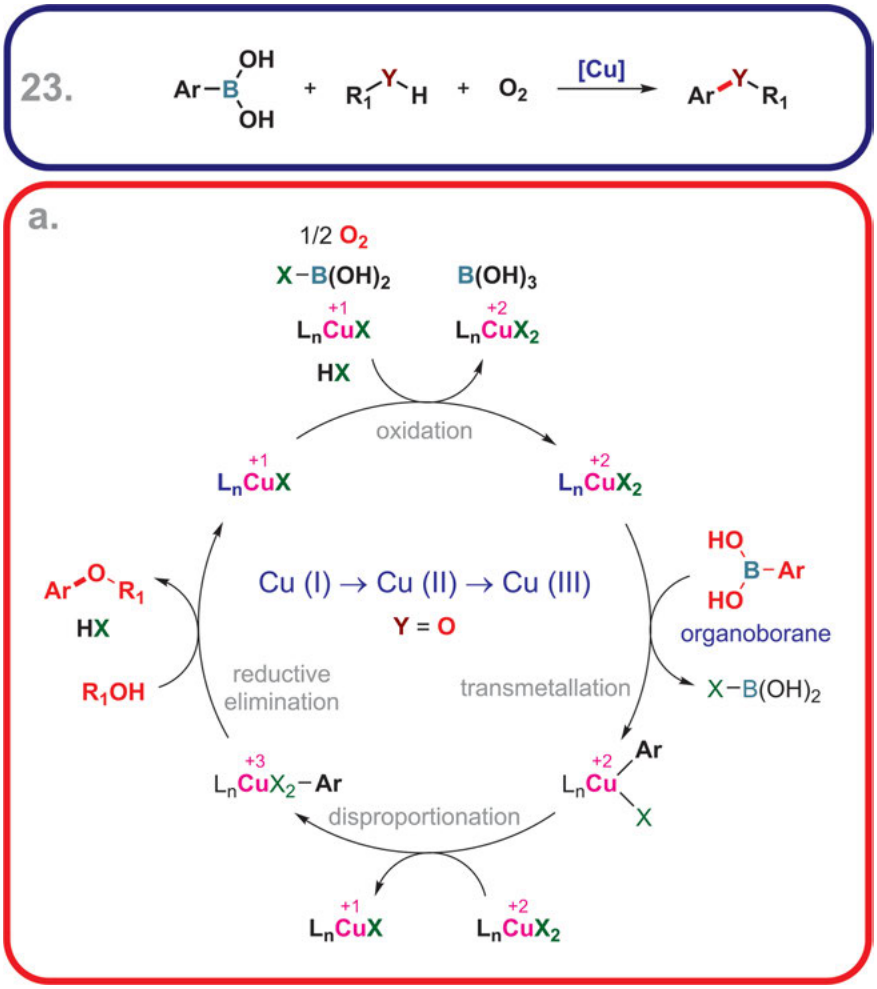

Fig. 23.1: The ***Chan–Evans–Lam*** *cross coupling* mechanism (Y = O).[69]

69 The ***Chan–Evans–Lam*** *cross coupling* (also simply called the ***Chan–Lam*** *cross coupling*) is a type of ***Cu****-catalyzed cross coupling* reaction (C–O and C–N bond formation using *aryl boronic acids* and *alcohols* or *amines*). The mechanism is not well-understood and is usually very substrate and ligand dependent. For teaching purposes, a simplified and general example is shown, which may take place in etherification reactions (C–O bond formation, Y = O) [23a, 23b].

https://doi.org/10.1515/9783110608373-023

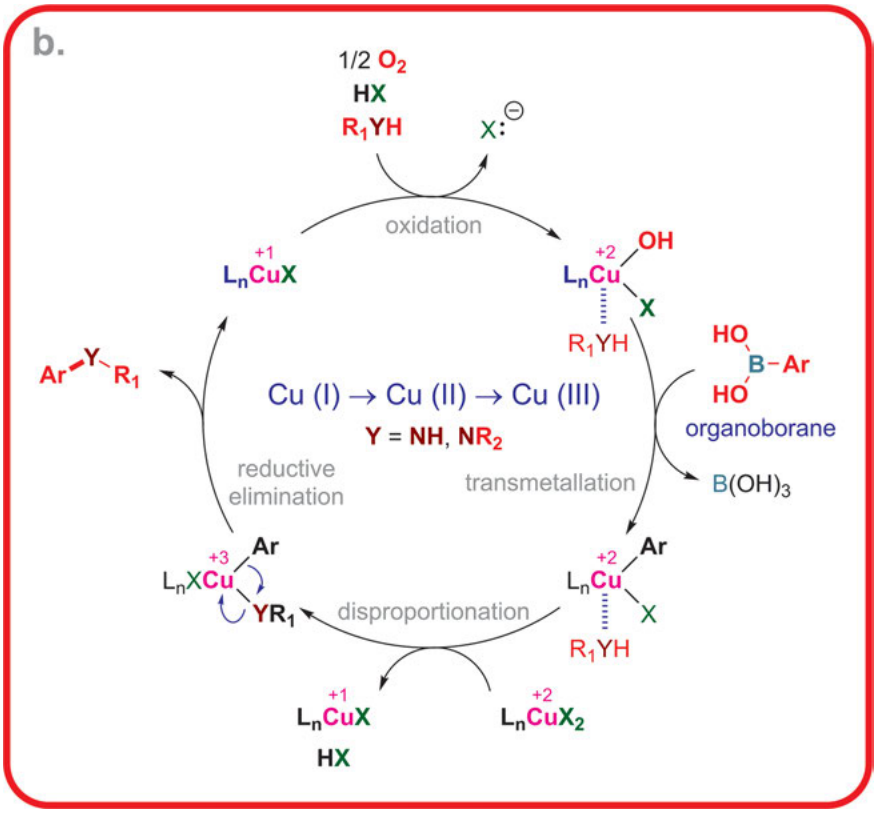

Fig. 23.2: The ***Chan–Evans–Lam*** *cross coupling* mechanism (Y = NH, NR_2).[70]

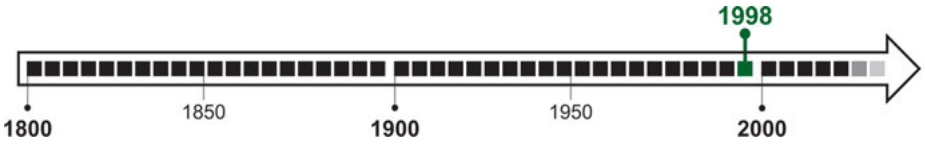

Fig. 23.3: The discovery of the ***Chan–Evans–Lam*** *cross coupling*.[71]

70 The mechanism is not well-understood and is usually very substrate and ligand dependent. For teaching purposes, a simplified and general example is shown, which may take place in amination reactions (C–N bond formation, Y = NH, NR_2) [23c].

71 The reaction was likely first described around 1998 [23d, 23e, 23f].

24 Chichibabin Amination

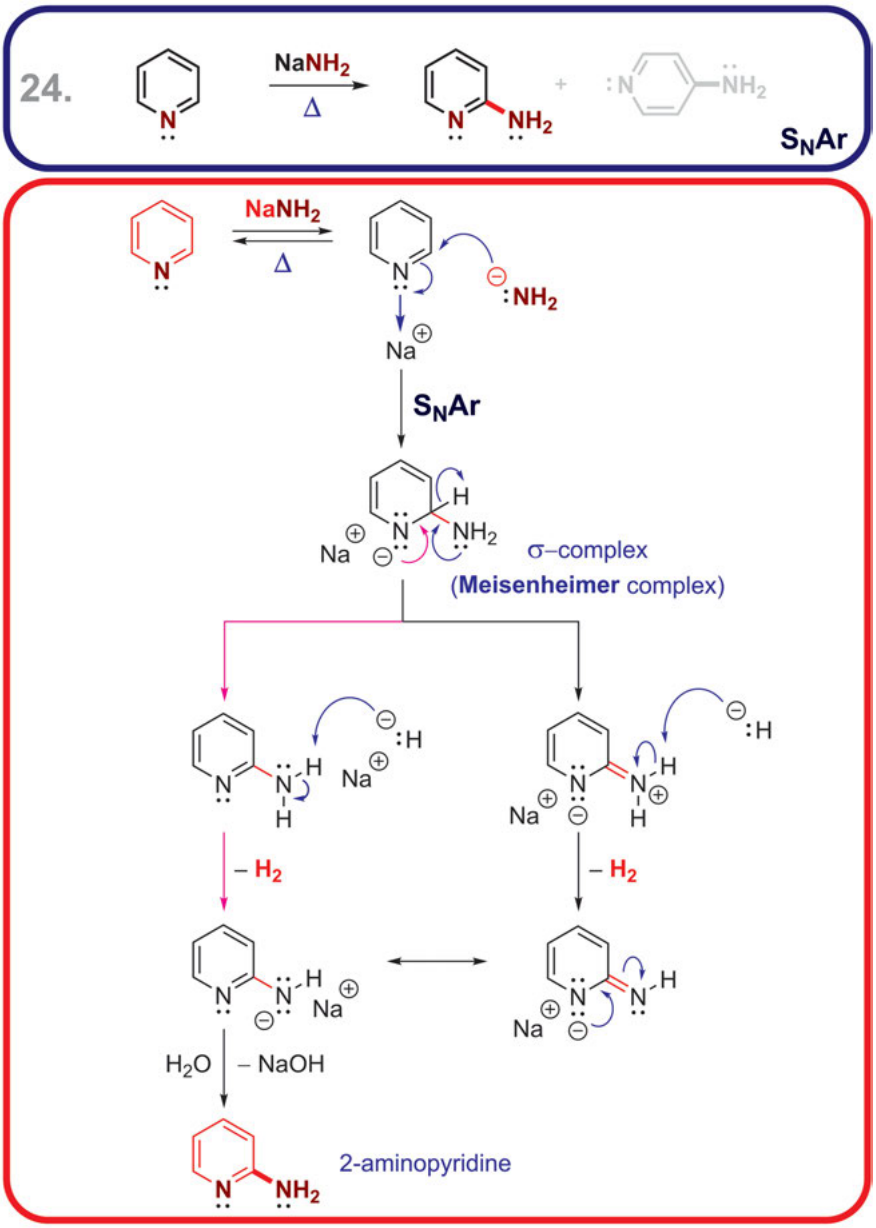

Fig. 24.1: The ***Chichibabin*** *amination* mechanism.[72]

https://doi.org/10.1515/9783110608373-024

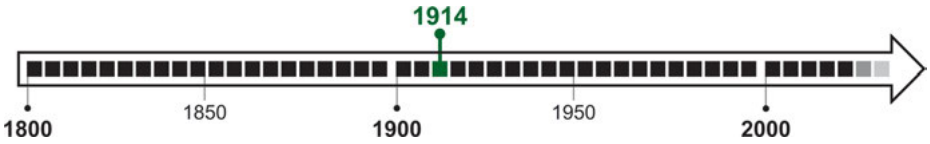

Fig. 24.2: The discovery of the ***Chichibabin*** *amination*.[73]

72 The ***Chichibabin*** *amination* (in Russian Чичибабин) is also called the ***Chichibabin*** *reaction*. It is a classic example of **aromatic nucleophilic substitution**. Specifically, it undergoes the *addition-elimination* mechanism: **S_NAr** (**S_N2Ar**), covered in Chapter 4.

73 The reaction was likely first described around 1914 [24].

25 Claisen Condensation

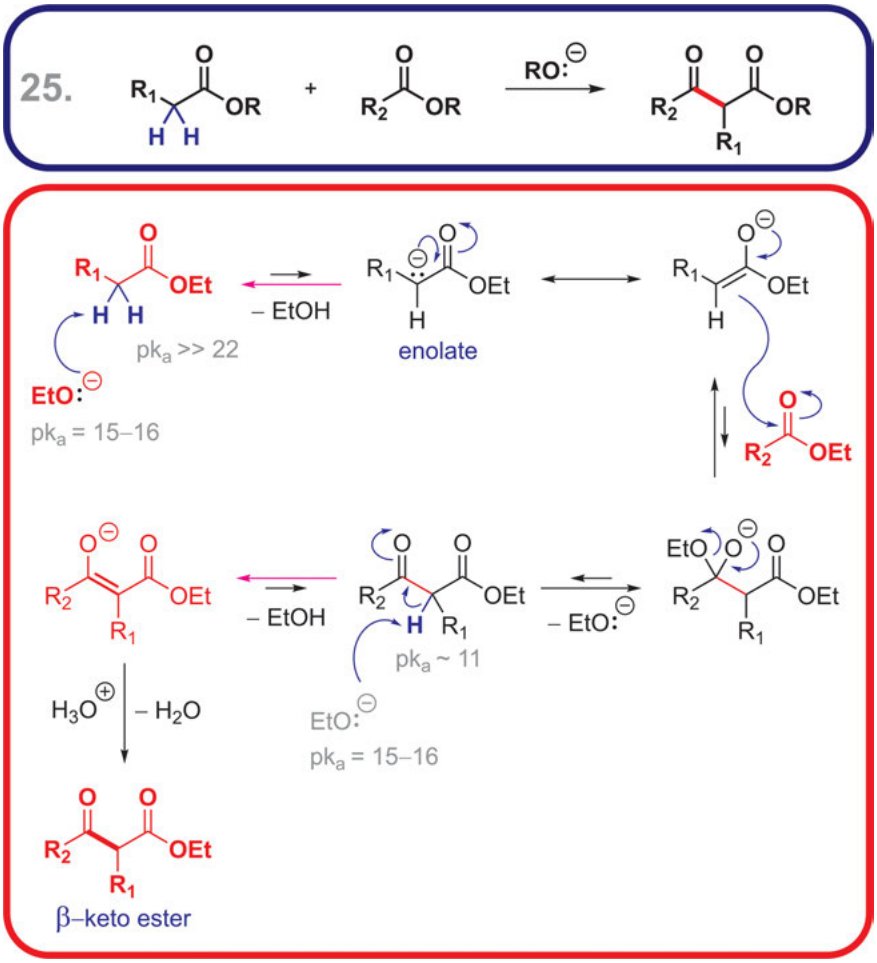

Fig. 25.1: The ***Claisen*** *condensation* mechanism.[74]

74 The ***Claisen*** *condensation* is a condensation reaction between an *ester* and another carbonyl compound containing two enolizable H-atoms (α–hydrogen atoms).

https://doi.org/10.1515/9783110608373-025

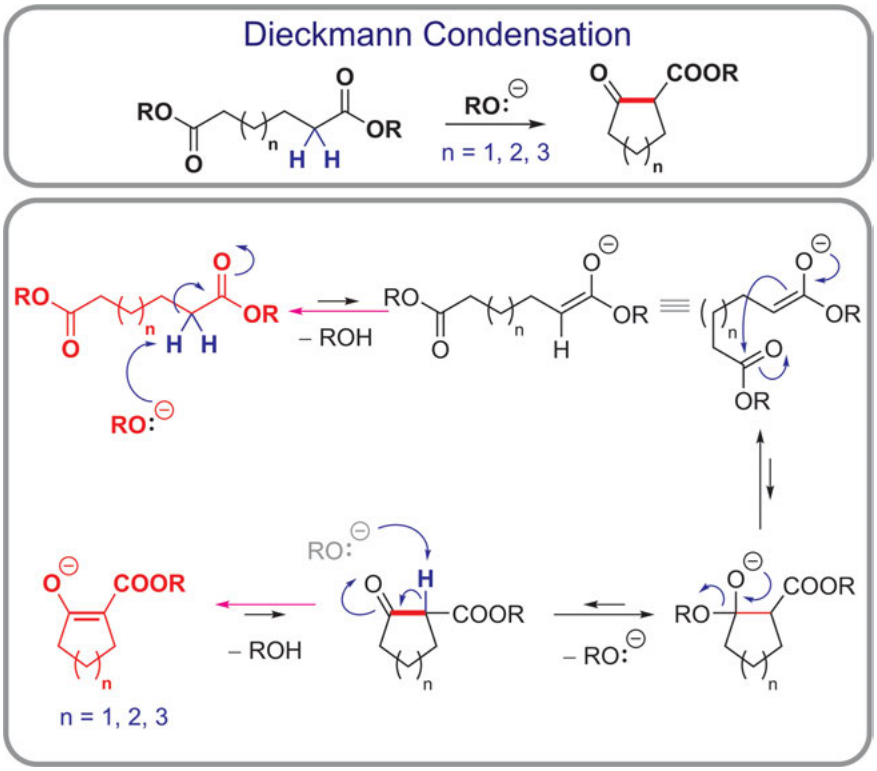

Fig. 25.2: The ***Dieckmann*** *condensation* mechanism.[75]

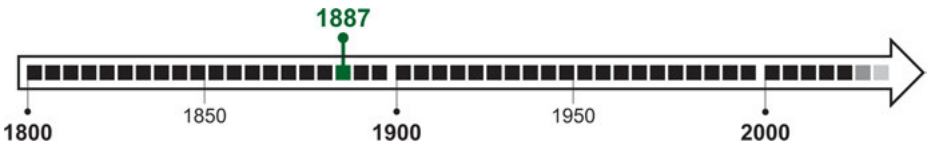

Fig. 25.3: The discovery of the ***Claisen*** *condensation*.[76]

75 The ***Dieckmann*** *condensation* is the *intramolecular* ***Claisen*** *condensation* and their mechanisms are almost identical. The ***Dieckmann*** *condensation* is ideal for the formation of 5-, 6-, and 7-membered rings [25a].

76 The reaction was likely first described around 1887 [25b].

26 Claisen Rearrangement

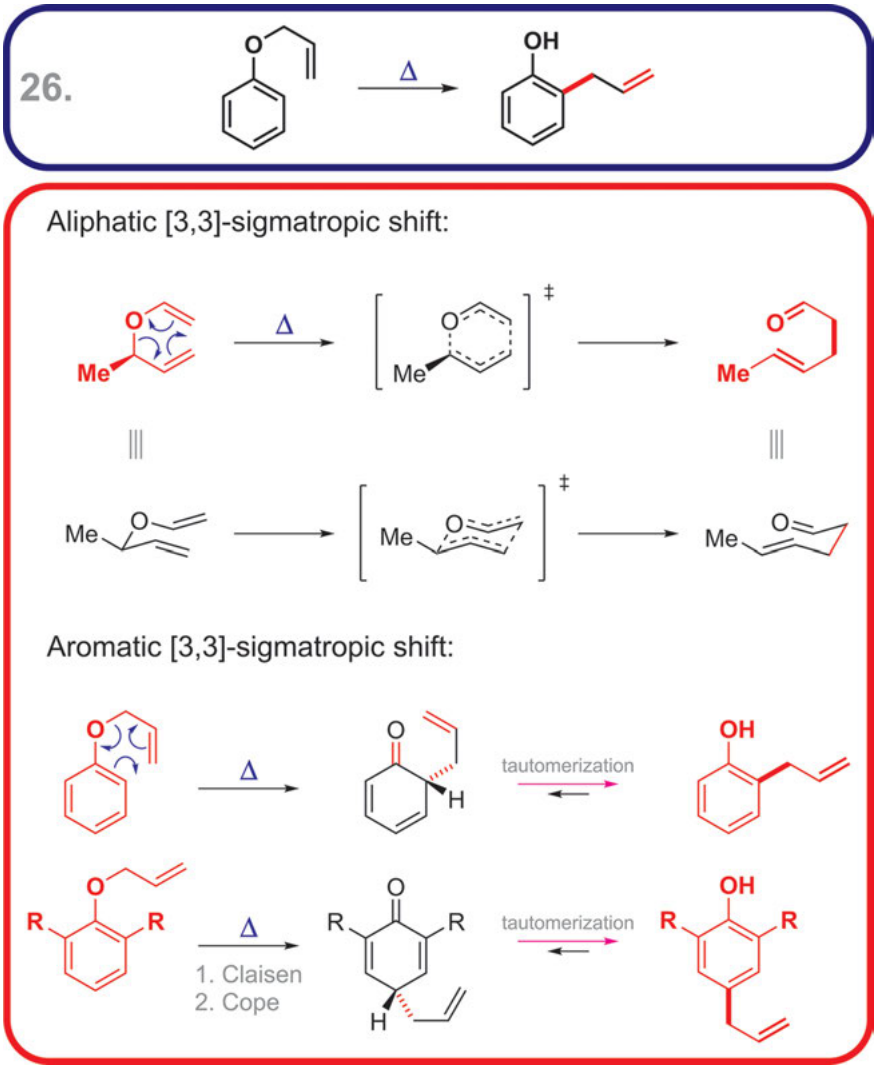

Fig. 26.1: The ***Claisen*** *rearrangement* mechanism.[77]

77 The ***Claisen*** *rearrangement* (different from the ***Claisen*** *condensation* and much like the ***Cope*** *rearrangement*, see Chapter 28) is a pericyclic reaction with a concerted mechanism. This is a classic example of a [3,3′]-*sigmatropic rearrangement (shift)*.

https://doi.org/10.1515/9783110608373-026

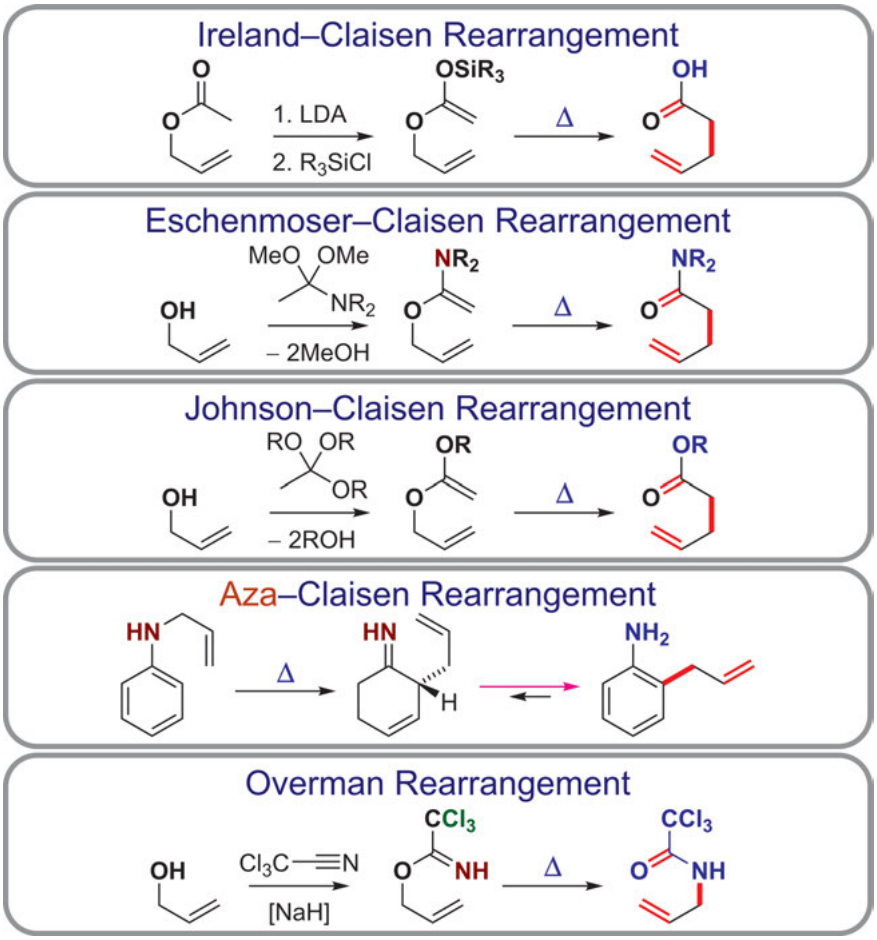

Fig. 26.2: Reactions related to the ***Claisen*** *rearrangement*.[78]

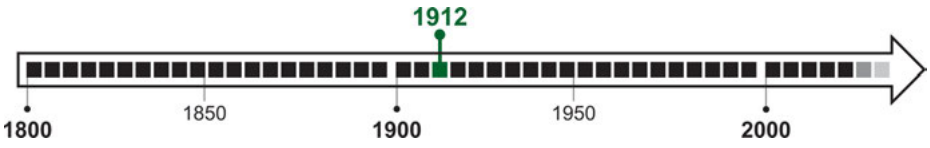

Fig. 26.3: The discovery of the ***Claisen*** *rearrangement*.[79]

78 There are numerous variations and modifications of the ***Claisen*** *rearrangement reaction*, to name a few: the ***Ireland–Claisen*** *rearrangement*, the ***Eschenmoser–Claisen*** *rearrangement*, the ***Johnson–Claisen*** *rearrangement*, the *aza-**Claisen** (aza-**Cope**) rearrangement*, the ***Overman*** *rearrangement*, and others [26a].

79 The reaction was likely first described around 1912 [26b].

27 Cope Elimination

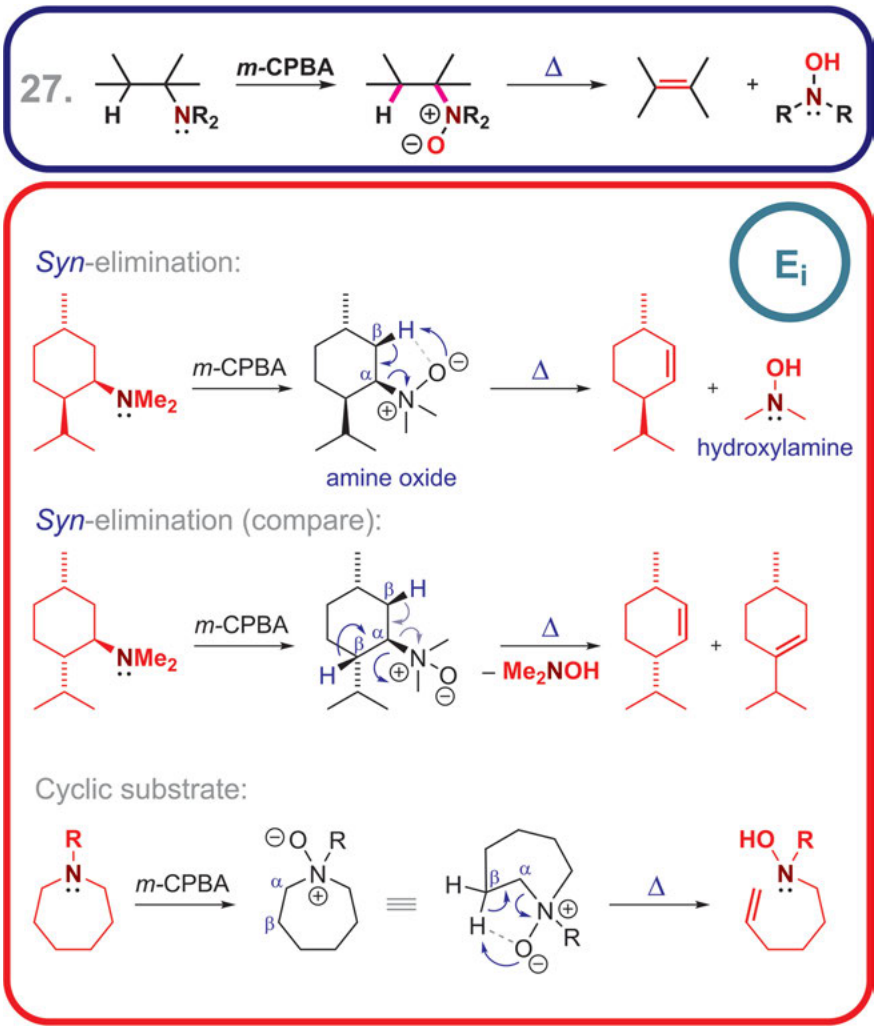

Fig. 27.1: The ***Cope*** *elimination* mechanism.[80]

80 The ***Cope*** *elimination* or the ***Cope*** *reaction* is an example of the *5-membered* **internal** or **intramolecular β–elimination** reaction ($\mathbf{E_i}$), mentioned in Chapter 6.

https://doi.org/10.1515/9783110608373-027

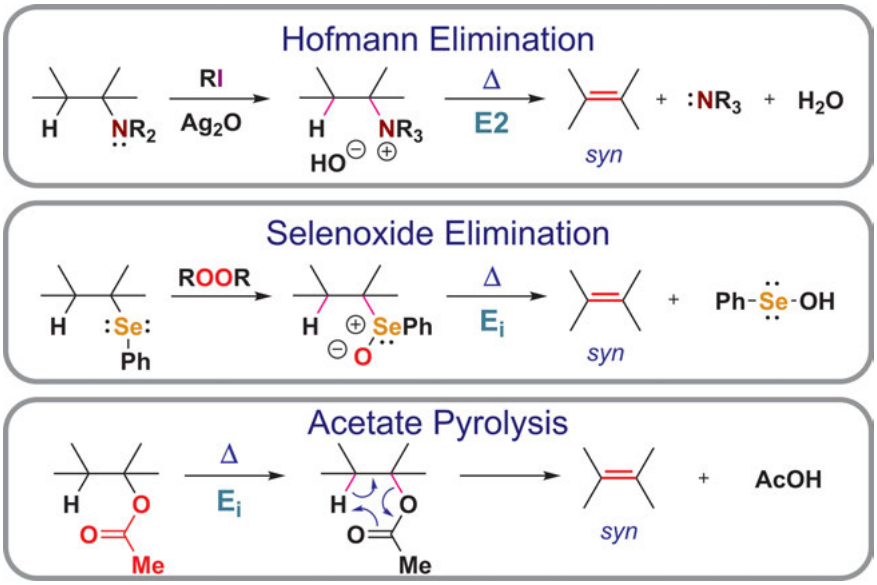

Fig. 27.2: Reactions related to the ***Cope*** *elimination*.[81]

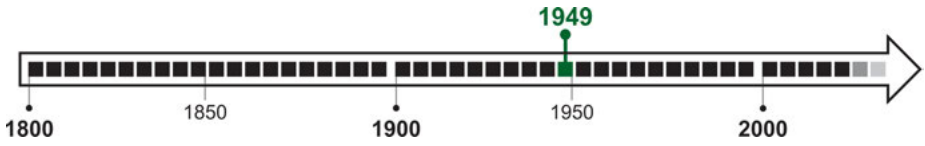

Fig. 27.3: The discovery of the ***Cope*** *elimination*.[82]

81 Several reactions are related to the ***Cope*** *elimination*: the ***Hofmann*** *elimination* (usually E2-type elimination, rarely E_i, covered in Chapter 49), the *selenoxide elimination* [27a, 27b], the *acetate pyrolysis* [1], and others (not mentioned here).

82 The reaction was likely first described around 1949 [27c].

28 Cope Rearrangement

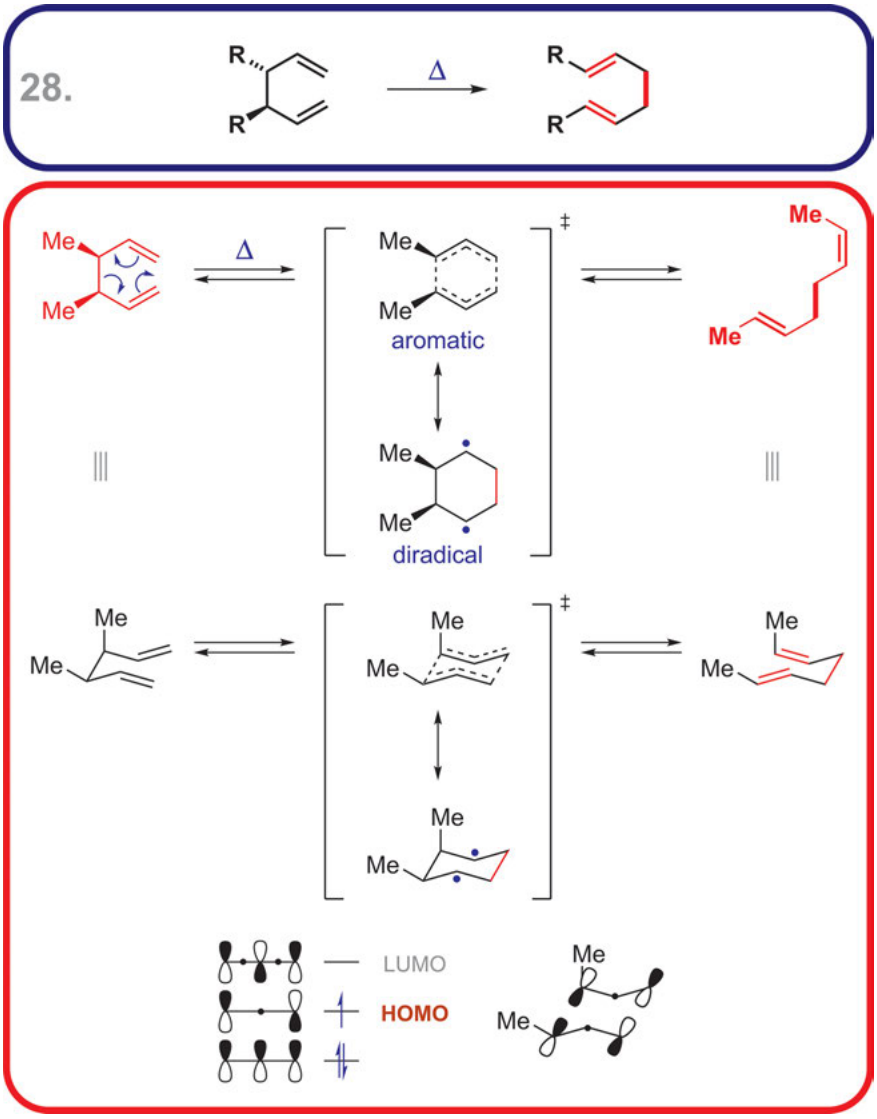

Fig. 28.1: The ***Cope*** *rearrangement* mechanism.[83]

83 The ***Cope*** *rearrangement* (different from the ***Cope*** *elimination* and much like the ***Claisen*** *rearrangement*, see Chapter 26) is a pericyclic reaction with a concerted mechanism. This is a classic example of a [3,3′]-*sigmatropic rearrangement* (also referred to as [3,3′]-*sigmatropic shift*).

https://doi.org/10.1515/9783110608373-028

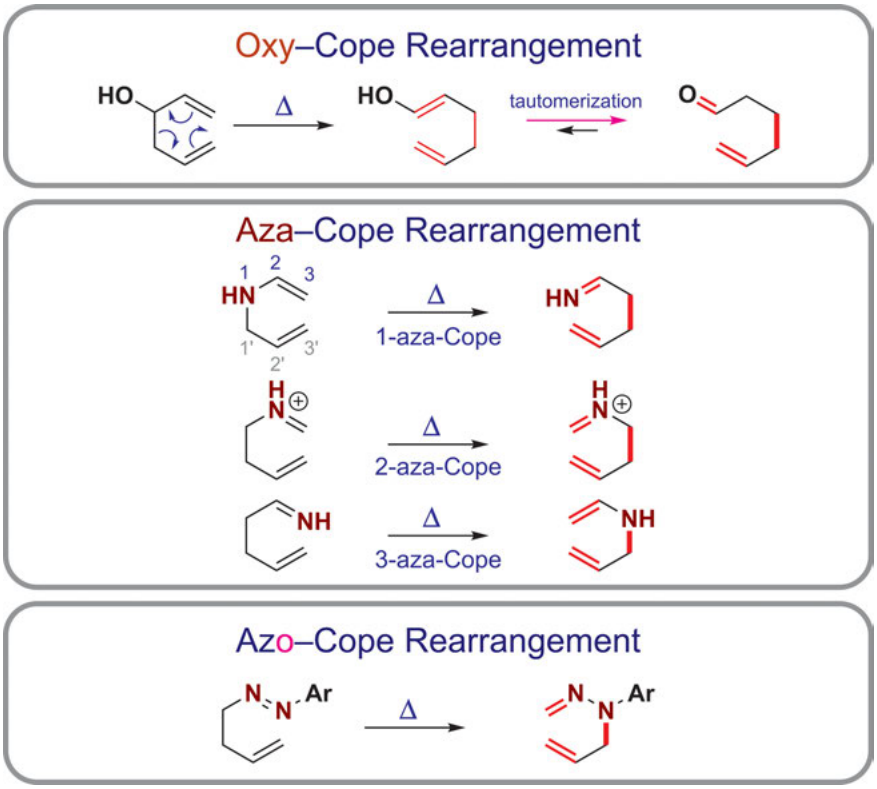

Fig. 28.2: Reactions related to the ***Cope*** *rearrangement*.[84]

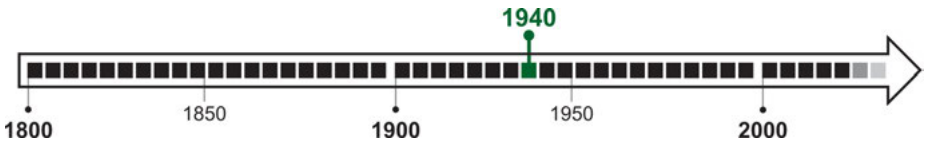

Fig. 28.3: The discovery of the ***Cope*** *rearrangement*.[85]

84 There are numerous variations of the ***Cope*** *rearrangement* [1], such as: the *(anionic) oxy-**Cope** rearrangement*, the *aza-**Cope*** and/or *aza-**Claisen** rearrangement* (confusing), the *azo-**Cope** rearrangement* [28a].

85 The reaction was likely first described around 1940 [28b].

29 Criegee & Malaprade Oxidation

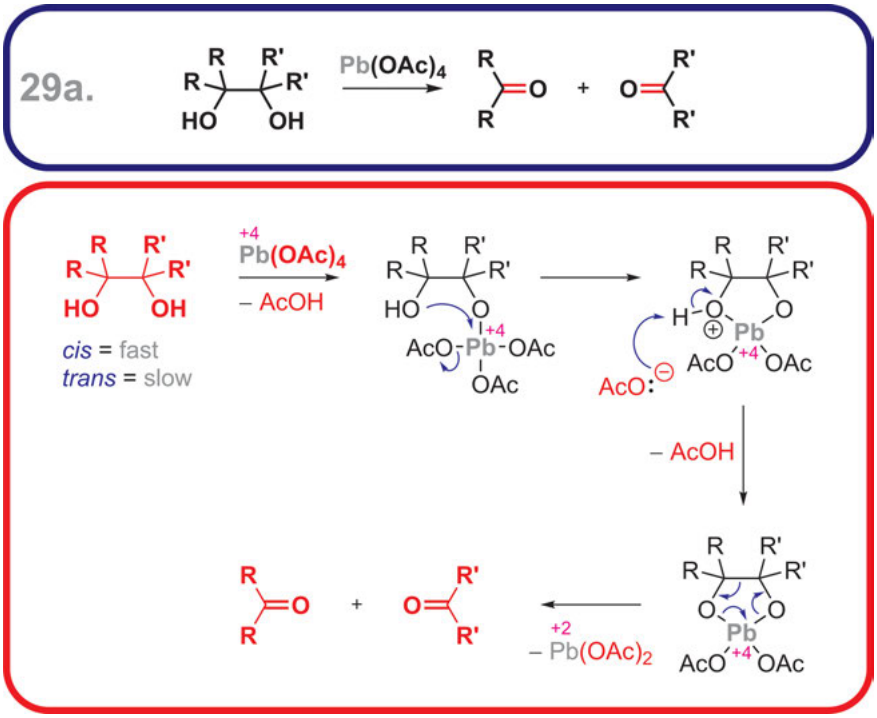

Fig. 29.1: The ***Criegee*** *oxidation* mechanism.[86]

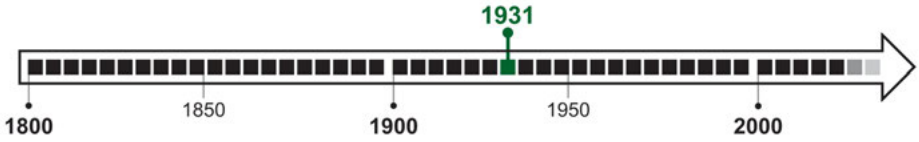

Fig. 29.2: The discovery of the ***Criegee*** *oxidation*.[87]

86 The ***Criegee*** *oxidation* or simply the ***Criegee*** *reaction* is different from the ***Criegee*** *mechanism* proposed for *ozonolysis* (covered in Chapter 70).

87 The reaction was likely first described around 1931 [29a].

https://doi.org/10.1515/9783110608373-029

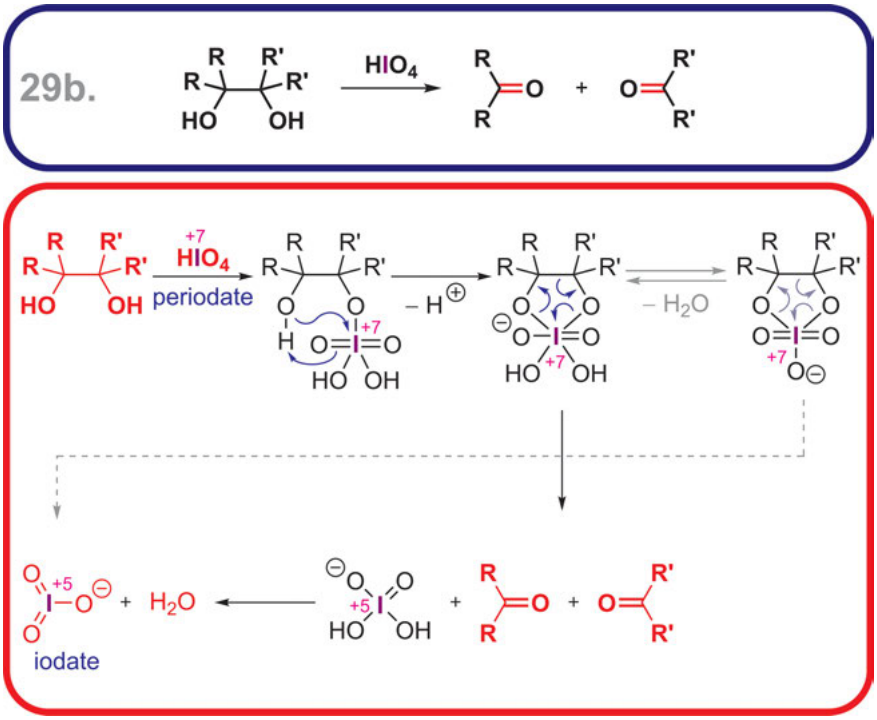

Fig. 29.3: The ***Malaprade*** *oxidation* mechanism.[88]

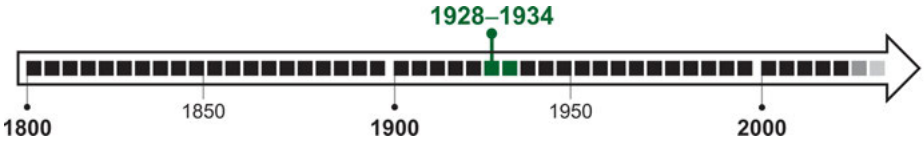

Fig. 29.4: The discovery of the ***Malaprade*** *oxidation*.[89]

88 The ***Malaprade*** *oxidation* is analogous to the ***Criegee*** *reaction*.

89 The reaction was likely first described between 1928 and 1934 [29b, 29c].

30 CuAAC

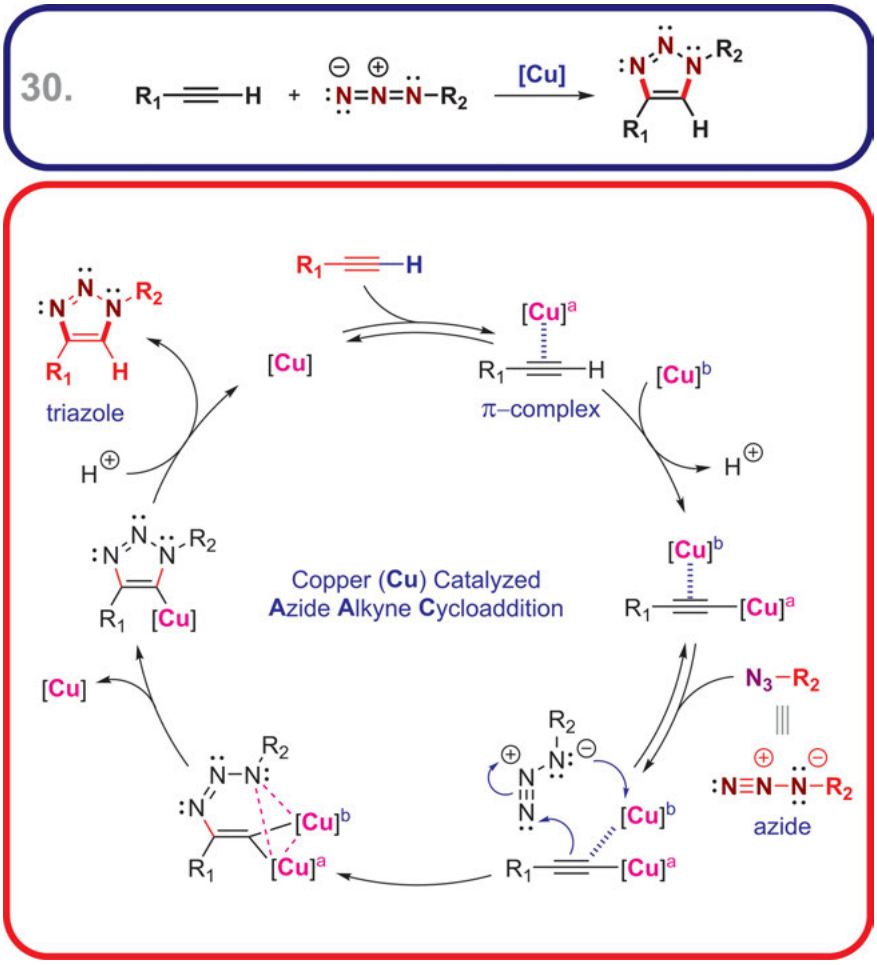

Fig. 30.1: The **CuAAC** mechanism.[90]

90 The acronym **CuAAC** stands for **Cu**-catalyzed **A**zide-**A**lkyne **C**ycloaddition (Copper(I)-catalyzed azide-alkyne cycloaddition). It is also often referred to as "**click chemistry**". Formally, it is a *1,3-dipolar cycloaddition reaction* or a (3+2)-*cycloadditon reaction*. Please note, the notation (3+2) means the atom count is used; the notation [4+2] means the electron count involved in the reaction is used [30a]. IUPAC does not recommend mixed usage, but it is seen frequently in the literature: [3+2].

https://doi.org/10.1515/9783110608373-030

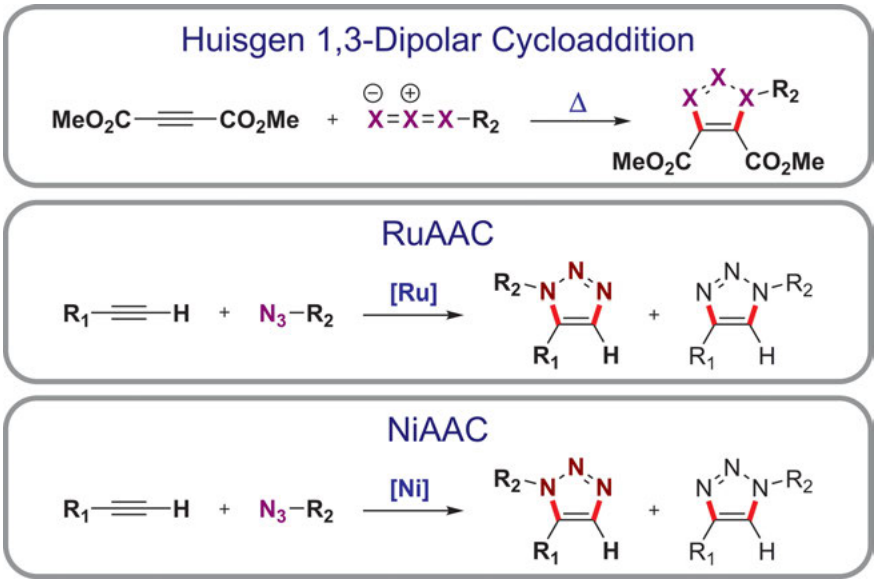

Fig. 30.2: Reactions related to the **CuAAC**.[91]

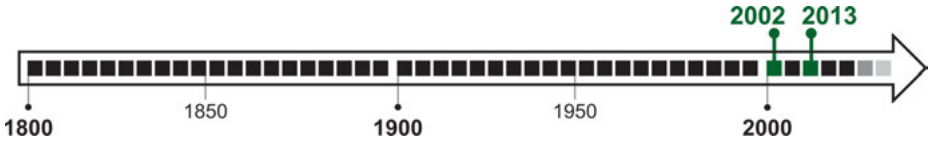

Fig. 30.3: The discovery of the **CuAAC**.[92]

91 The ***Huisgen*** *cycloaddition* [30b, 30c] is not catalytic but related to **CuAAC**. The *azide-alkyne cycloaddition* can also be catalyzed by Ruthenium (**RuAAC**) or Nickel (**NiAAC**), however, it undergoes a different mechanism (not shown).

92 The reaction was likely first described around 2002 [30d, 30e] and the mechanism, in its current form, proposed around 2013 [30f].

31 Curtius Rearrangement

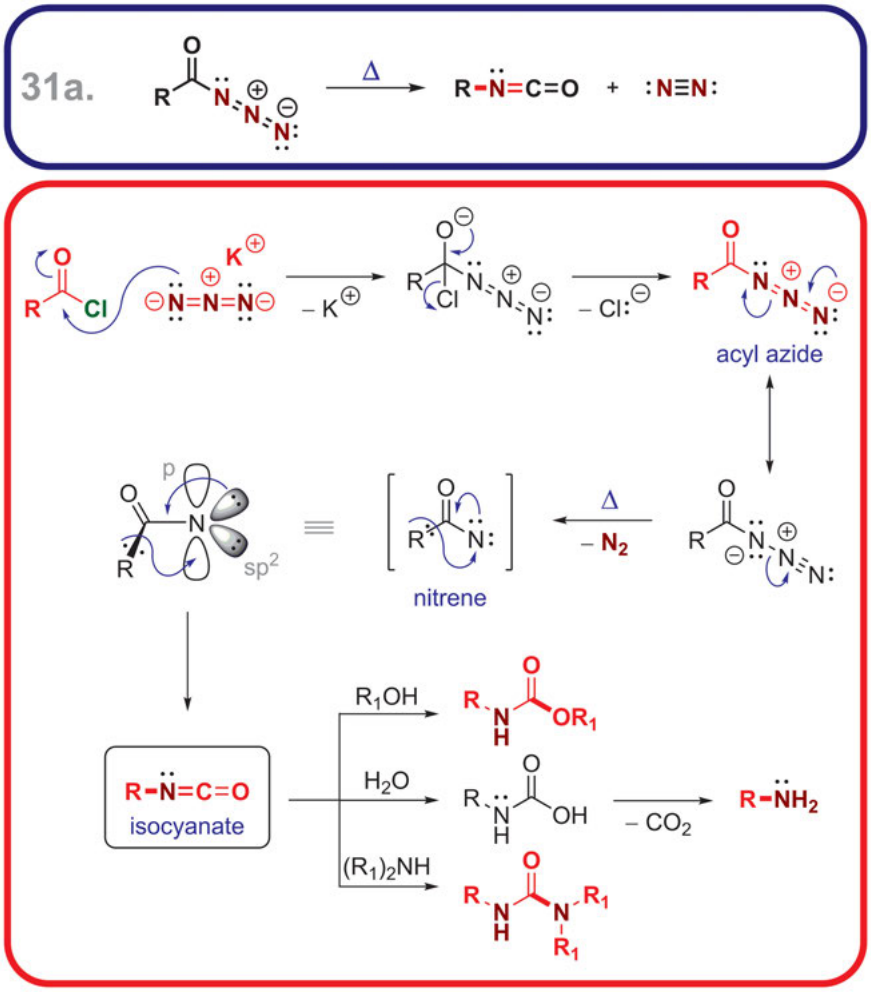

Fig. 31.1: The ***Curtius*** *rearrangement* mechanism.[93]

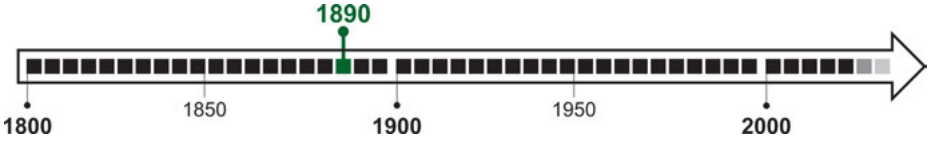

Fig. 31.2: The discovery of the ***Curtius*** *rearrangement*.[94]

93 The ***Curtius*** *rearrangement* is also called the ***Curtius*** *reaction*.

https://doi.org/10.1515/9783110608373-031

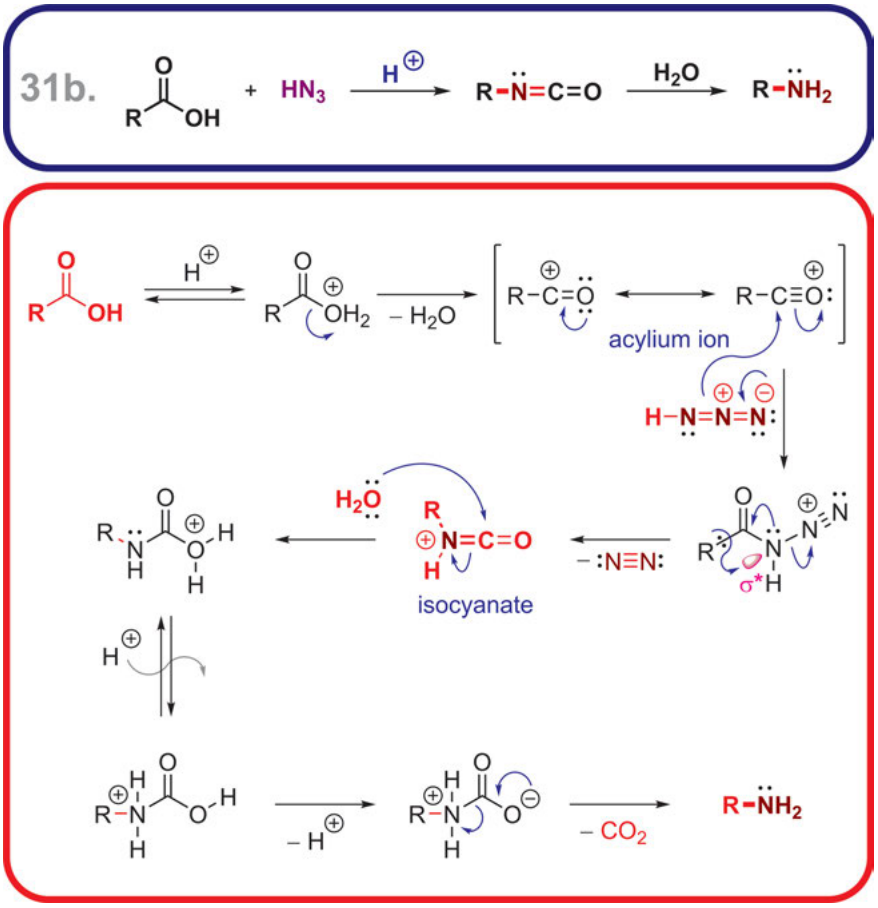

Fig. 31.3: The ***Schmidt*** *reaction* mechanism.[95]

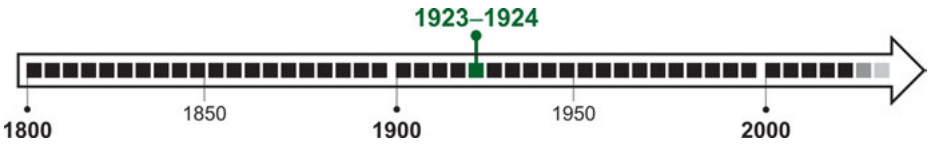

Fig. 31.4: The discovery of the ***Schmidt*** *reaction* mechanism.[96]

94 The reaction was likely first described around 1890 [31a, 31b].
95 The ***Schmidt*** *reaction* is also a rearrangement.
96 The reaction was likely first described between 1923–1924 [31c, 31d].

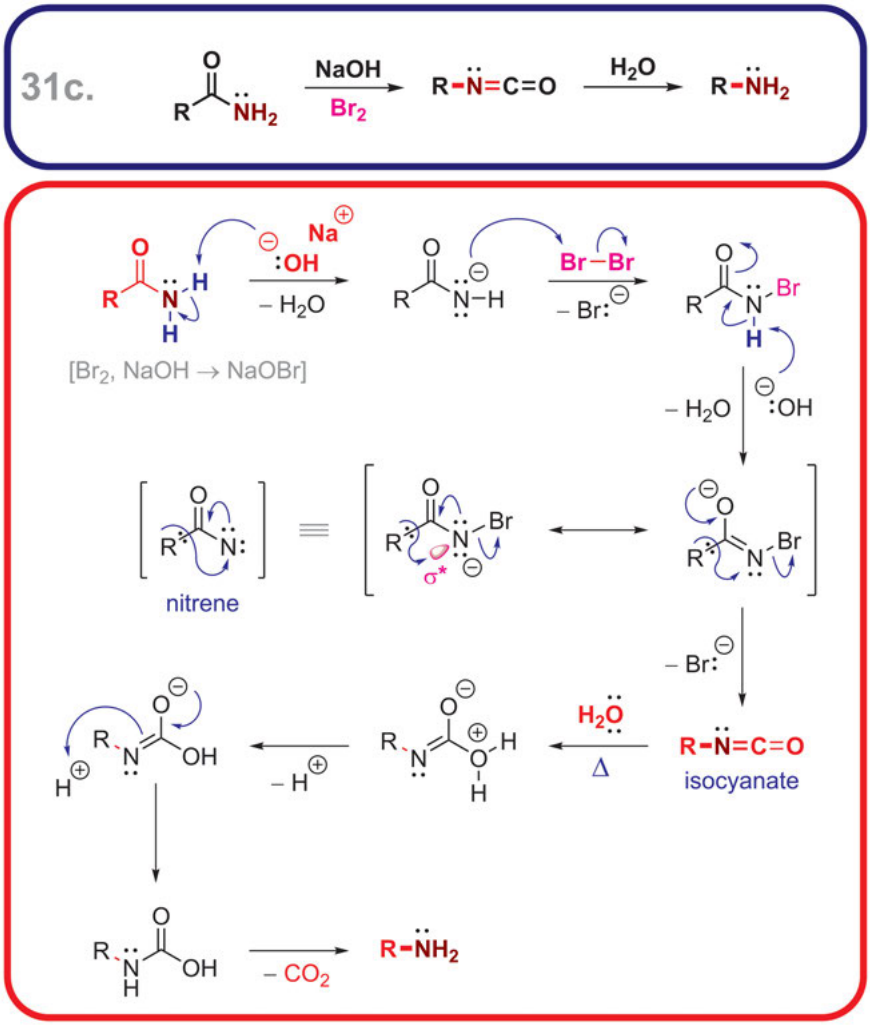

Fig. 31.5: The ***Hofmann*** *rearrangement* mechanism.[97]

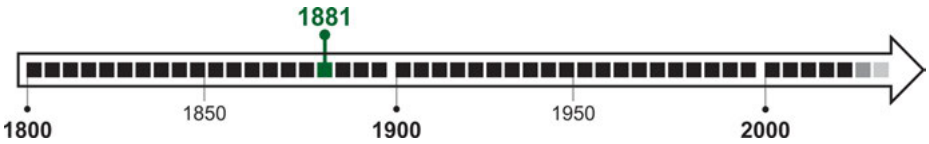

Fig. 31.6: The discovery of the ***Hofmann*** *rearrangement*.[98]

97 The ***Hofmann*** *rearrangement* is also known as the ***Hofmann*** *reaction*. It is completely different from the ***Hofmann*** *elimination*, see Chapter 49.

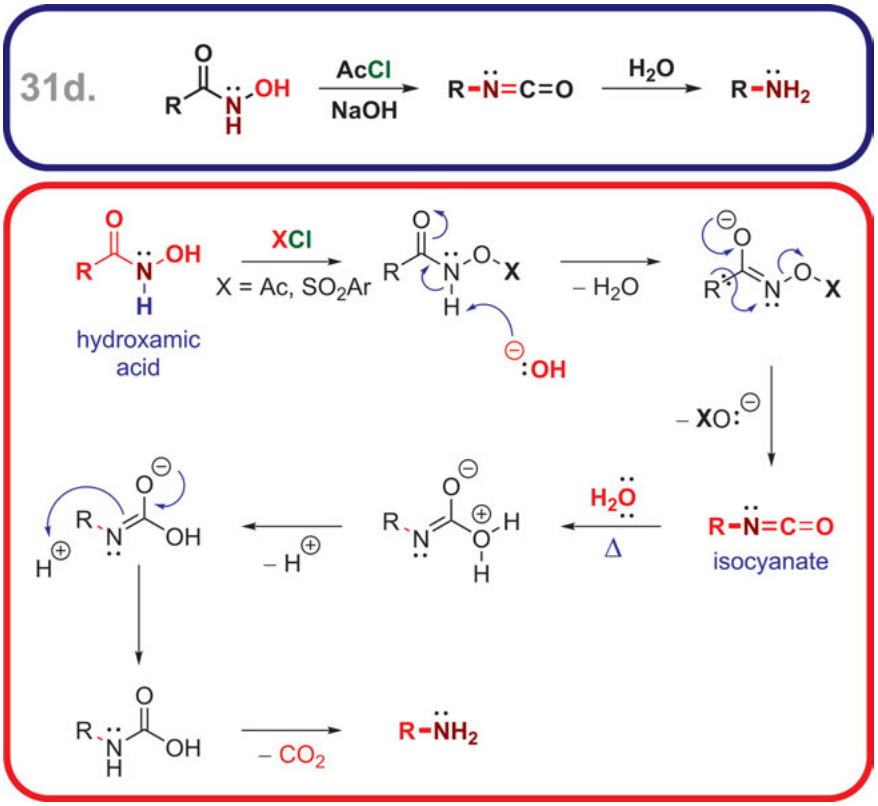

Fig. 31.7: The ***Lossen*** *rearrangement* mechanism.[99]

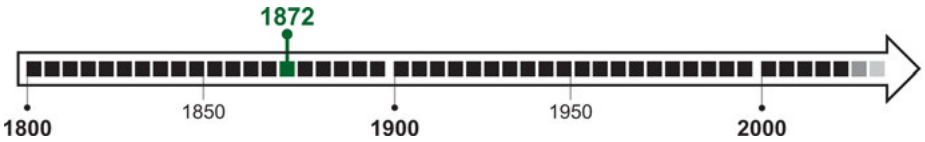

Fig. 31.8: The discovery of the ***Lossen*** *rearrangement*.[100]

98 The reaction was likely first described around 1881 [31e].

99 The ***Lossen*** *rearrangement* is much like these reactions and is related to the ***Beckmann*** *rearrangement*, covered in Chapter 14.

100 The reaction was likely first described around 1872 [31f].

32 Darzens Condensation

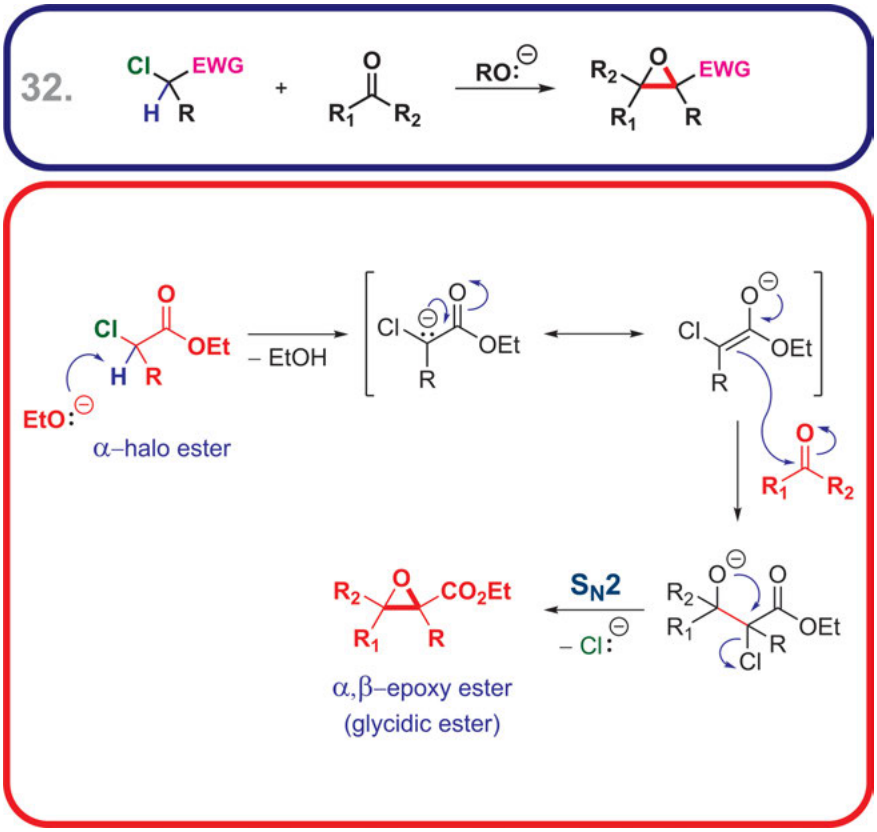

Fig. 32.1: The ***Darzens*** *condensation* mechanism.[101]

101 The ***Darzens*** *condensation* is also called the ***Darzens*** *glycidic ester condensation* or the ***Darzens*** *reaction*. Please note, a *glycidic ester* is an α,β–epoxy ester.

https://doi.org/10.1515/9783110608373-032

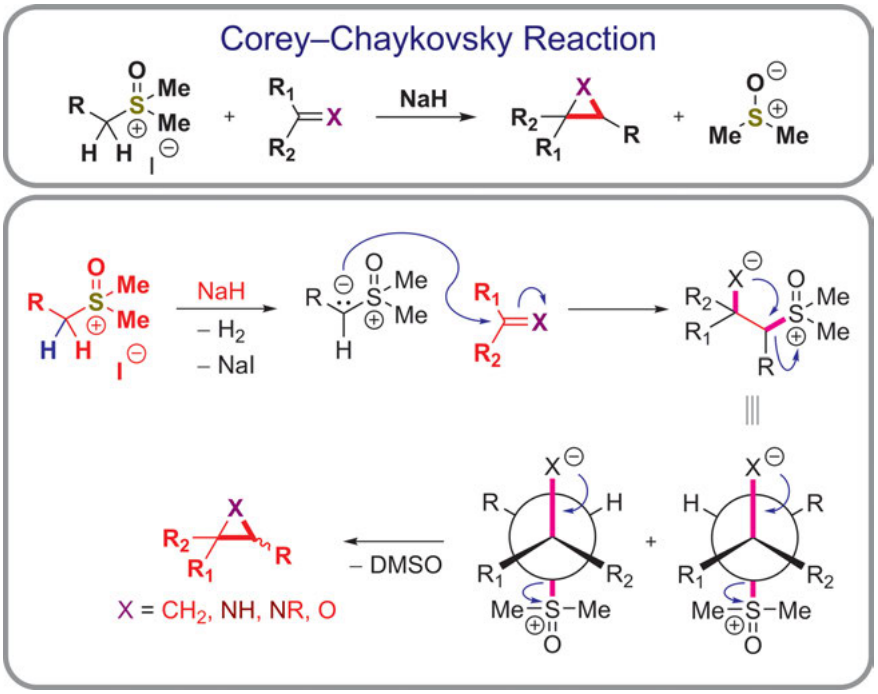

Fig. 32.2: The ***Corey–Chaykovsky*** *reaction* mechanism.[102]

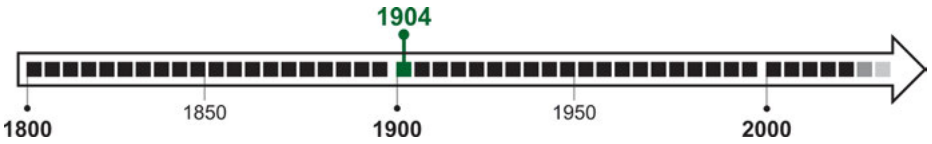

Fig. 32.3: The discovery of the ***Darzens*** *condensation*.[103]

102 The ***Corey–Chaykovsky*** *reaction* (also known as the ***Johnson–Corey–Chaykovsky*** *reaction*) [32a, 32b] is related to both the ***Darzens*** *condensation*, and the ***Wittig*** *reaction* (covered in Chapter 98).
103 The reaction was likely first described around 1904 [32c].

33 Dess–Martin Oxidation

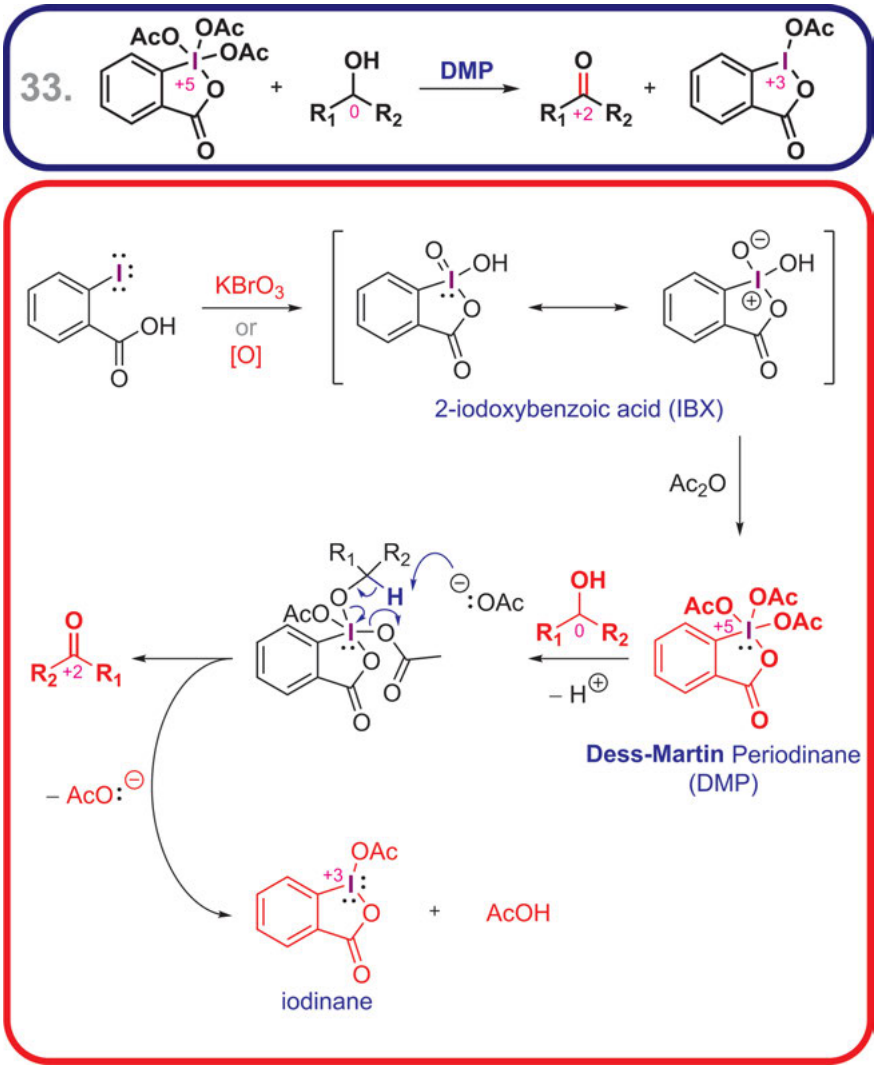

Fig. 33.1: The ***Dess–Martin*** *oxidation* mechanism.[104]

104 The ***Dess–Martin*** *oxidation* is based on the use of a named reagent: the ***Dess–Martin*** *periodinane* (**DMP**) [33a, 33b].

https://doi.org/10.1515/9783110608373-033

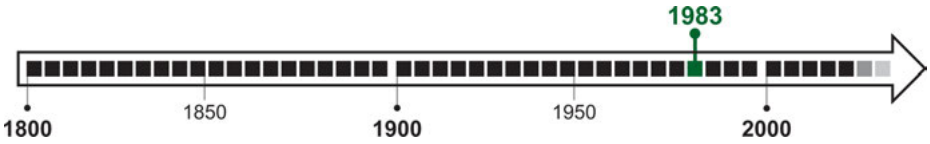

Fig. 33.2: The discovery of the ***Dess–Martin*** *oxidation*.[105]

105 The reaction was likely first described around 1983 [33c].

34 Diazotization (Diazonium Salt)

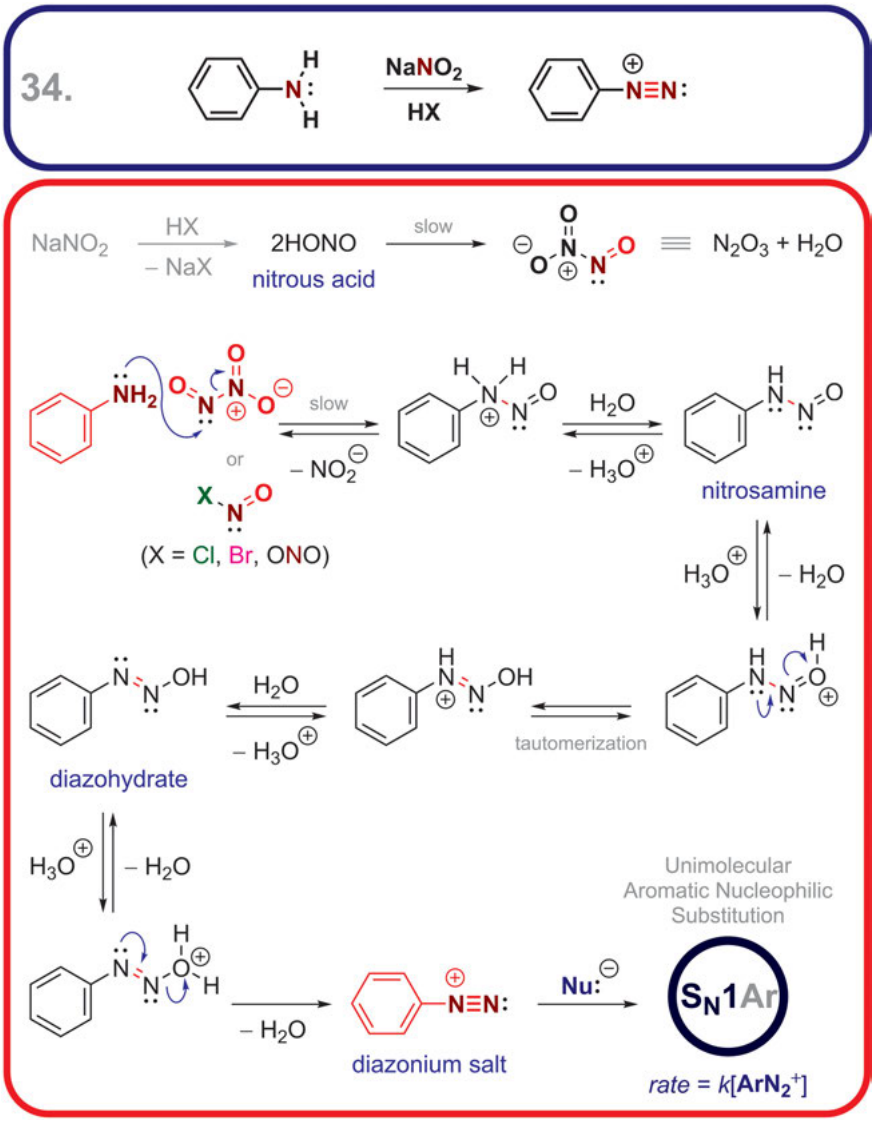

Fig. 34.1: The *diazonium salt formation (diazotization)* mechanism.[106]

106 The *diazonium salt formation reaction* is also known as the ***diazotization*** [1] (the term is also preferred in this book), or the *diazoniation* [1a], or the *diazotation* [34a].

https://doi.org/10.1515/9783110608373-034

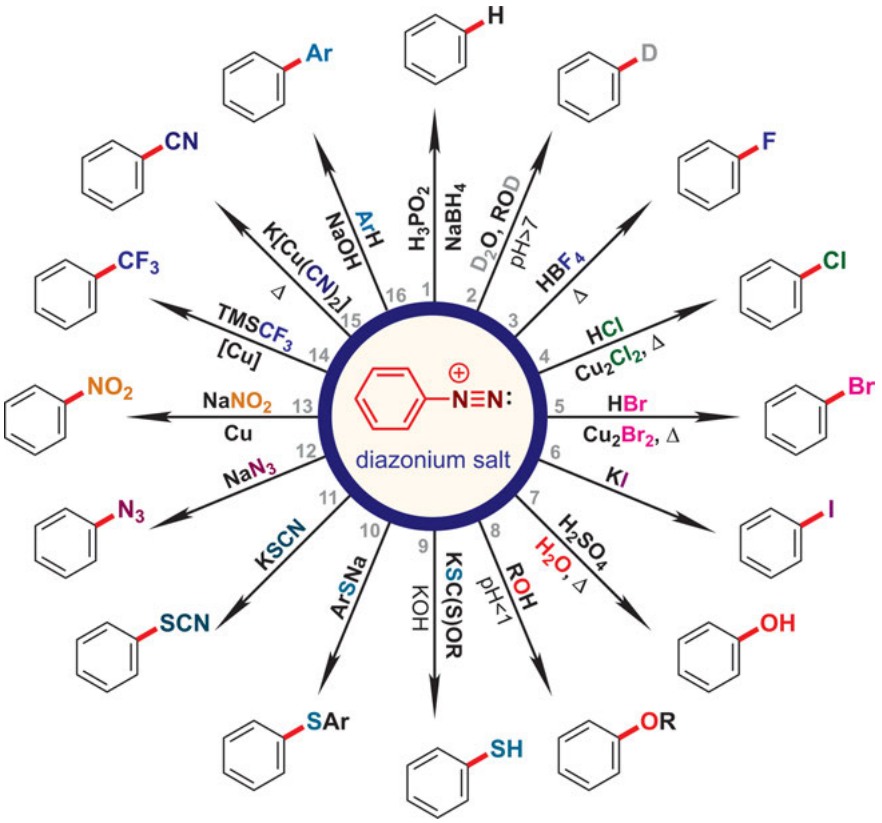

Fig. 34.2: Synthetic versatility of the diazonium salts.[107]

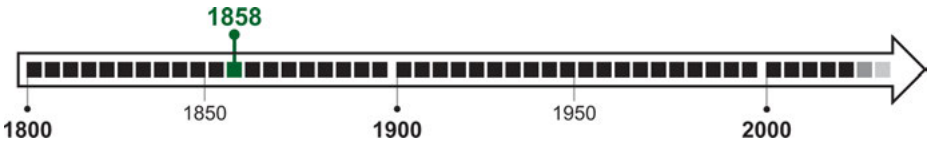

Fig. 34.3: The discovery of the *diazotization reaction*.[108]

107 The *diazonium salts* formed during the *diazotization* process have wide synthetic application and they can react with a variety of nucleophiles. These reactions go through the **aromatic nucleophilic substitution** mechanism (**S_N1Ar** or sometimes **$S_{RN}1$**). Symbol **S_N1Ar** stands for **S**ubstitution **N**ucleophilic **Ar**omatic. It is a **Uni**-molecular (1) reaction, that is, the rate of the reaction is first order and the rate-determining step (i.e., the slow step) depends on the concentration of one reactant, the diazonium salt (**ArN_2^+**): *rate* = k[**ArN_2^+**]**[1]**. This mechanism is different from the *addition-elimination* mechanism (**S_NAr** or **S_N2Ar**), covered in Chapter 4, because the first step is elimination and the formation of an *aryl cation*. Please note, it is also different from the *benzyne* mechanism (the *elimination-addition* mechanism) covered in Chapter 16.

108 The reaction was likely first described around 1858 [34b].

35 Diels–Alder Cycloaddition

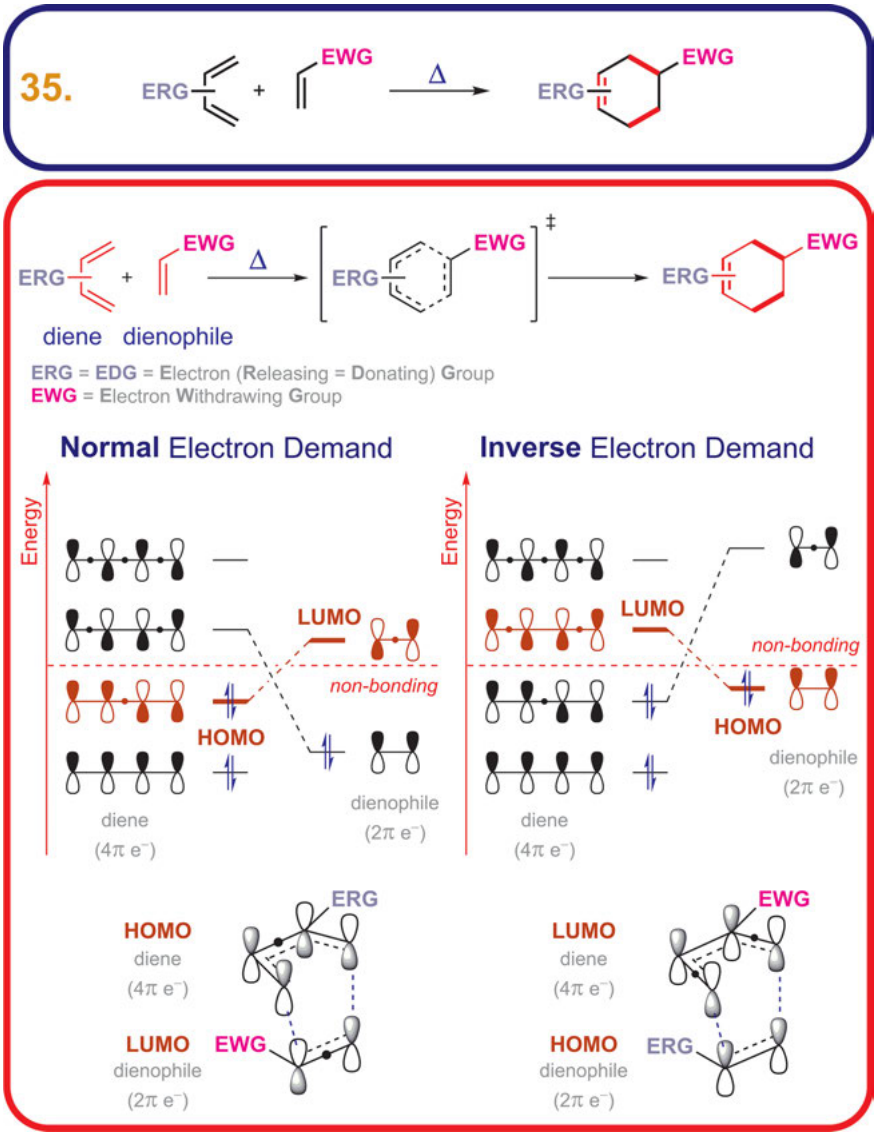

Fig. 35.1: The ***Diels–Alder*** *cycloaddition* mechanism.[109]

109 The ***Diels–Alder*** *cycloaddition*, the ***Diels–Alder*** *reaction* or the **[4+2]**-*cycloaddition reaction* is a pericyclic reaction with a concerted mechanism. Please note, the notation (4+2) means the atom count is used; the notation [4+2] means the electron count involved in the reaction is used [30a]. Compare to the *1,3-dipolar cycloaddition* (Chapter 30).

https://doi.org/10.1515/9783110608373-035

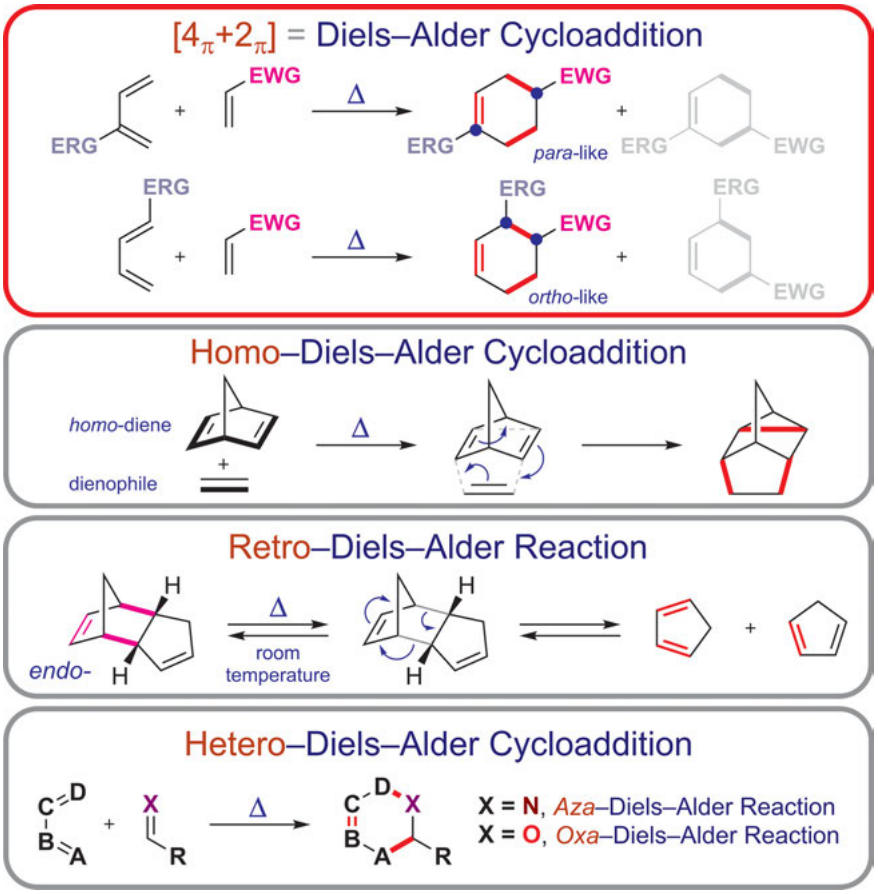

Fig. 35.2: Reactions related to the ***Diels–Alder*** *cycloaddition*.[110]

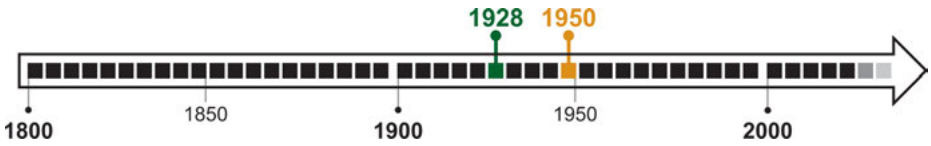

Fig. 35.3: The discovery of the ***Diels–Alder*** *cycloaddition*.[111]

110 There are numerous variations of this reaction: the *homo-**Diels–Alder** cycloaddition*, the *retro-**Diels–Alder** reaction*, the *hetero-**Diels–Alder** cycloaddition*, and many others (not shown). Please note the regiochemistry observed in the first case of the **[4_π+2_π]** = ***Diels–Alder*** *cycloaddition*.

111 The reaction was likely first described around 1928 [35a, 35b]. In **1950**, Otto Paul Hermann Diels and Kurt Alder received the Nobel Prize in Chemistry for the discovery of the diene synthesis [35c].

36 Di–π–Methane Rearrangement

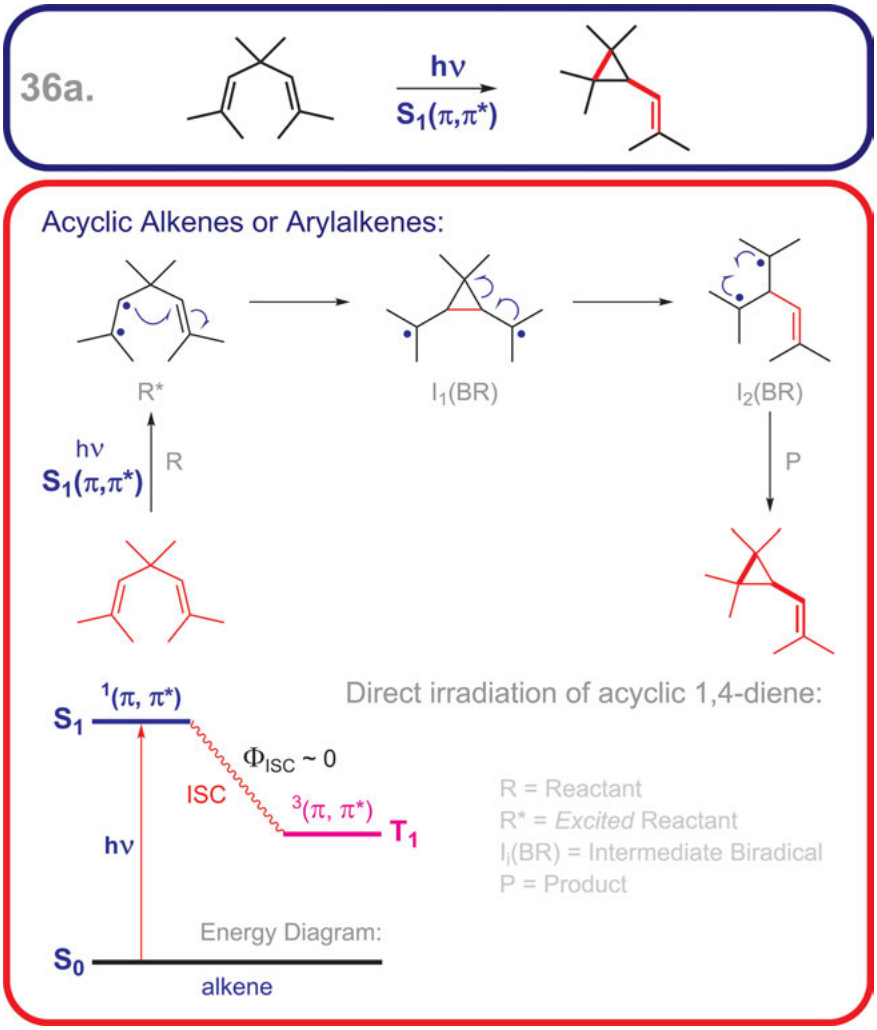

Fig. 36.1: The *Di–π–Methane rearrangement* mechanism: direct irradiation.[112]

112 The *Di–π–Methane rearrangement* (**DPM**) is rarely called the ***Zimmerman*** *reaction*. If the reaction undergoes *direct irradiation*: the reaction occurs from the singlet excited state $\mathbf{S_1}$, in this case $\mathbf{^1(\pi, \pi^*)}$ [2b].

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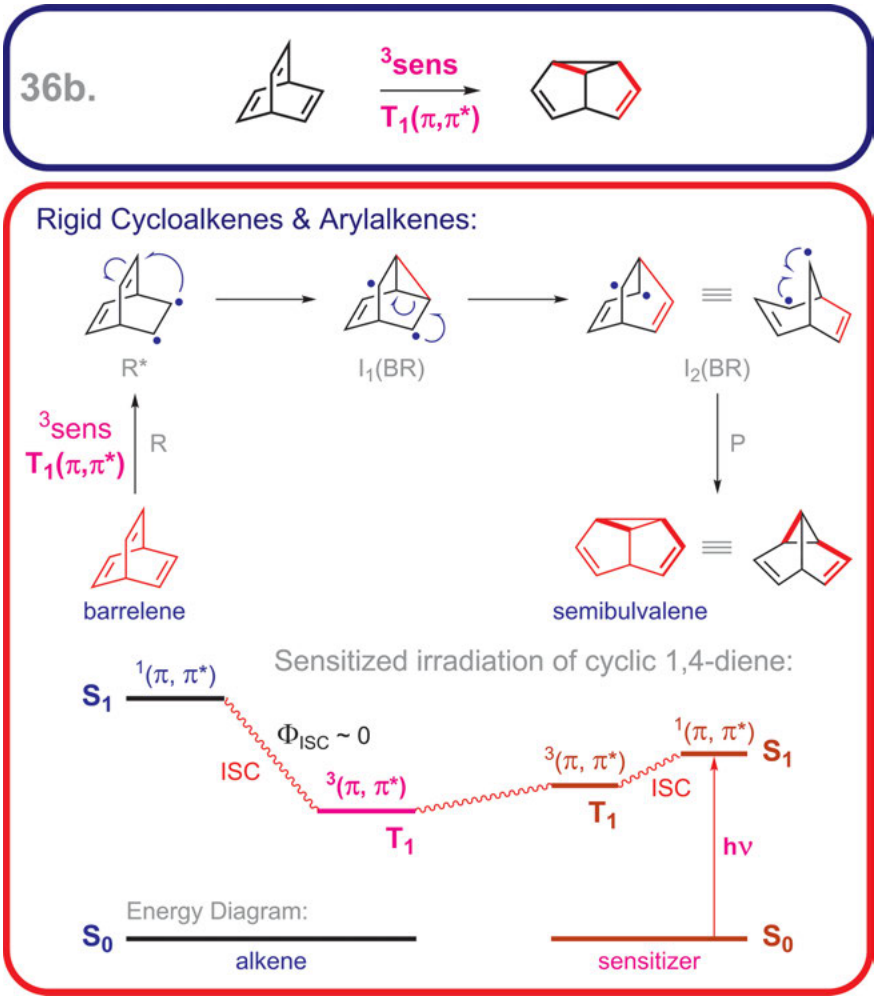

Fig. 36.2: The *Di–π–Methane rearrangement* mechanism: sensitized irradiation.[113]

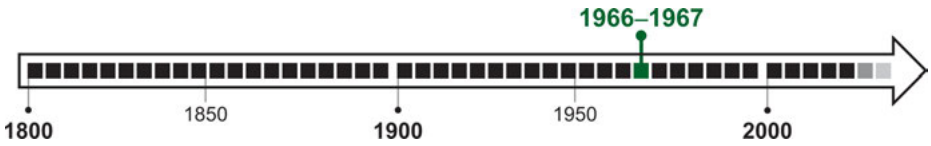

Fig. 36.3: The discovery of the *Di–π–Methane rearrangement*.[114]

113 The *Di–π–Methane rearrangement* in the presence of a *photosensitizer*, that is the reaction undergoes the *sensitized irradiation*: the product formation occurs from the triplet excited state $\mathbf{T_1}$, here $^{3}\mathbf{(\pi, \pi^*)}$ [2b].

114 The reaction was likely first described between 1966–1967 [36].

37 Favorskii Rearrangement

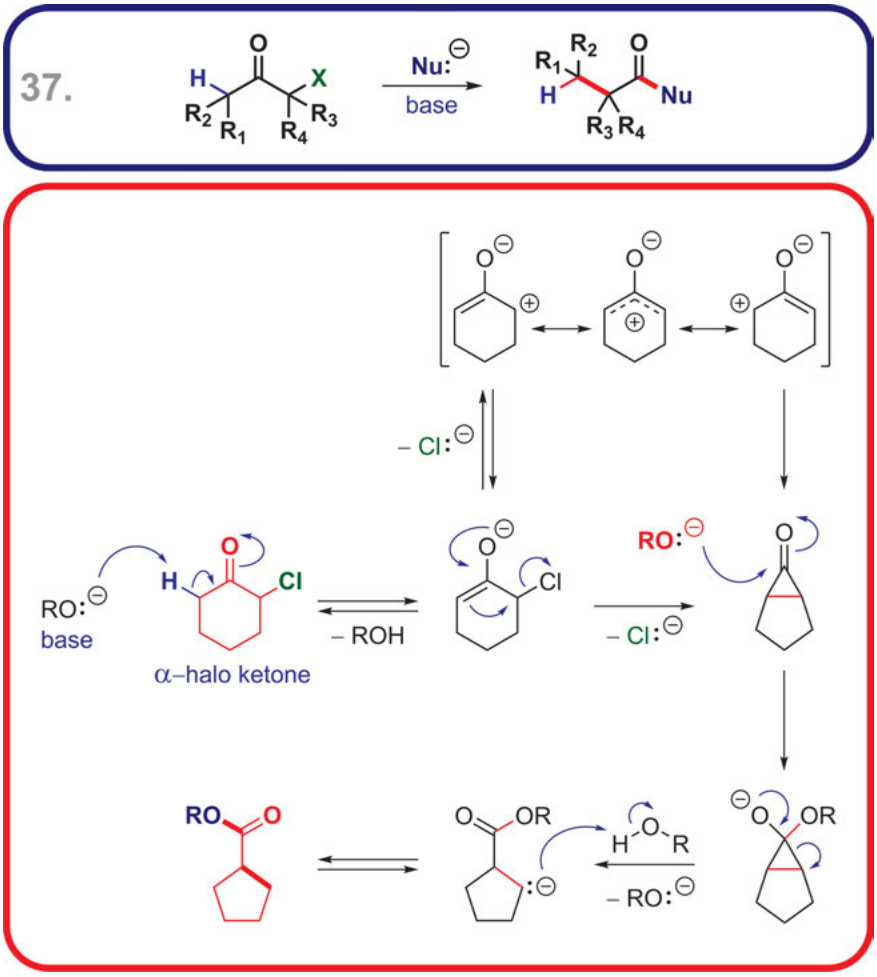

Fig. 37.1: The ***Favorskii*** *rearrangement* mechanism.[115]

115 The ***Favorskii*** *rearrangement* (also spelled Favorsky, in German transliteration Faworsky, and in Russian Алексей Евграфович Фаворский or А. Е. Фаворский) is different from the ***Favorskii*** *reaction* (not shown here).

https://doi.org/10.1515/9783110608373-037

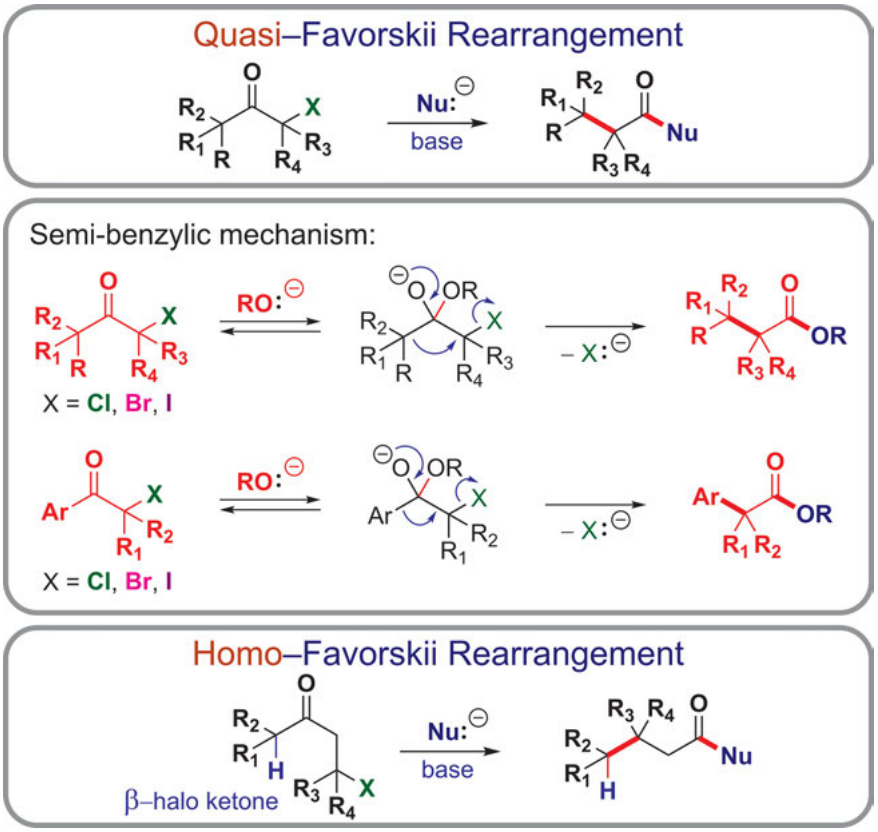

Fig. 37.2: The *quasi-**Favorskii** rearrangement* mechanism and related reactions.[116]

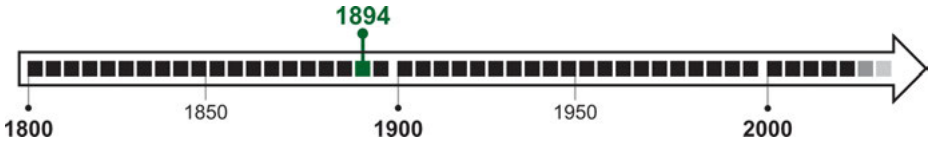

Fig. 37.3: The discovery of the ***Favorskii** rearrangement*.[117]

116 There are numerous variations of this reaction: for example, the *quasi-**Favorskii** rearrangement*, which undergoes a process similar to the *semi-benzylic* mechanism [37a, 37b], the *homo-**Favorskii** rearrangement*, and others (not shown).

117 The reaction was likely first described around 1894 [37c, 37d].

38 Fischer Indole Synthesis

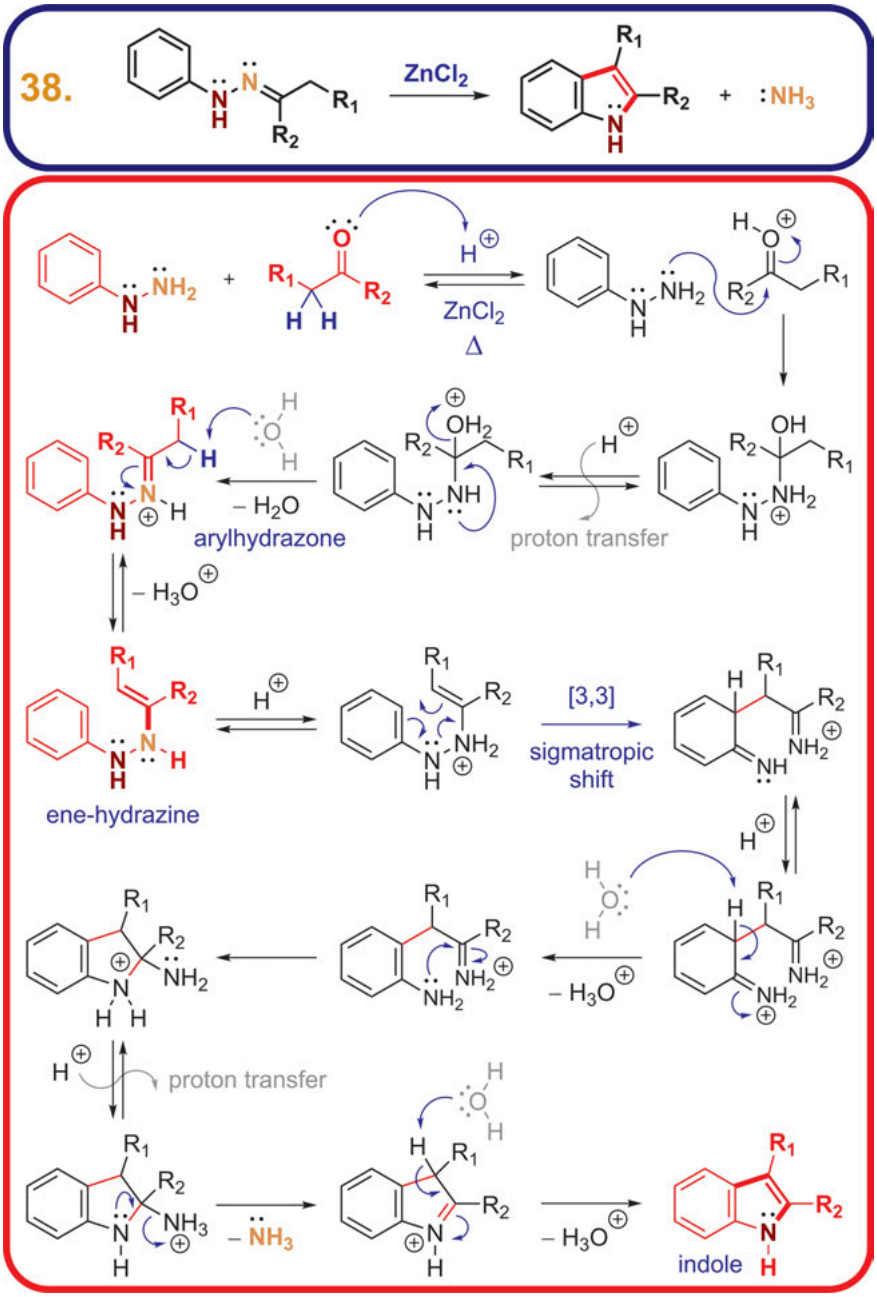

Fig. 38.1: The ***Fischer*** *indole synthesis* mechanism.[118]

https://doi.org/10.1515/9783110608373-038

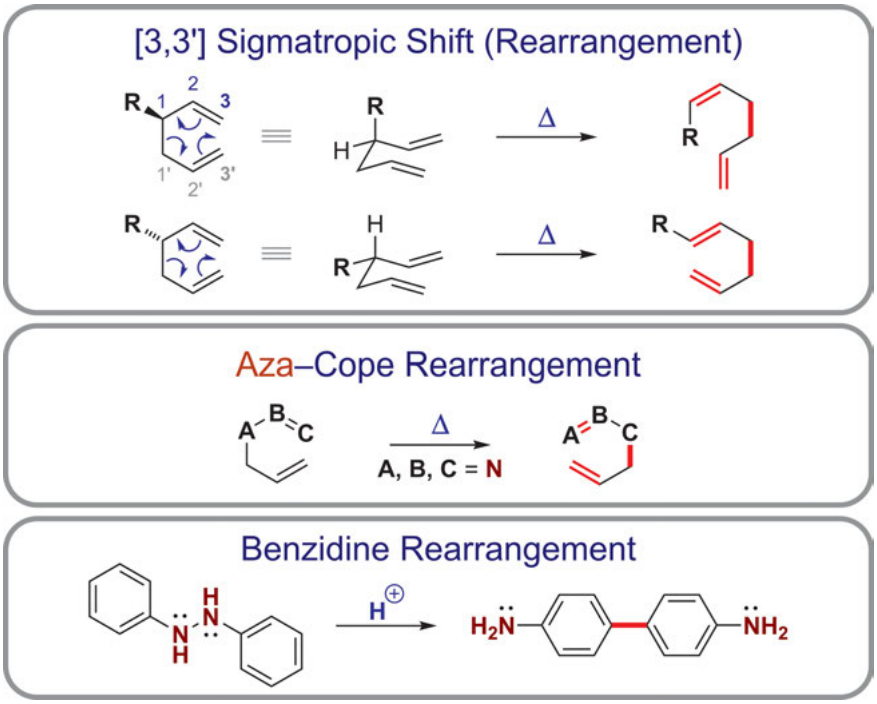

Fig. 38.2: Reactions related to the ***Fischer*** *indole synthesis*.[119]

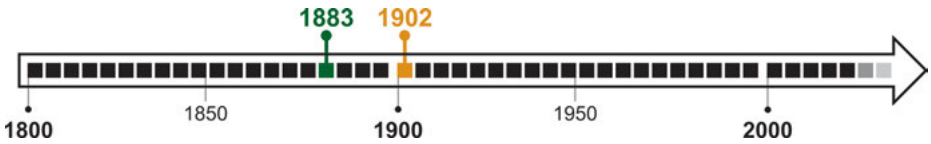

Fig. 38.3: The discovery of the ***Fischer*** *indole synthesis*.[120]

118 he ***Fischer*** *indole synthesis* (different from the ***Fischer*** *esterification*) is one of the most important reactions in organic chemistry. The key mechanistic step is the [3,3′]-*sigmatropic shift (rearrangement)*.
119 The key mechanistic step is related to the ***Cope*** *rearrangement*, the *aza*-***Cope*** and/or *aza*-***Claisen*** *rearrangement* (Chapter 28). Other reactions related to this transformation include the ***Benzidine*** *rearrangement* (its mechanism is not well-understood) [1, 38a].
120 The reaction was likely first described around 1883 [38b, 38c]. In **1902**, Emil Fischer received the Nobel Prize in Chemistry [38d].

39 Friedel–Crafts Acylation & Alkylation

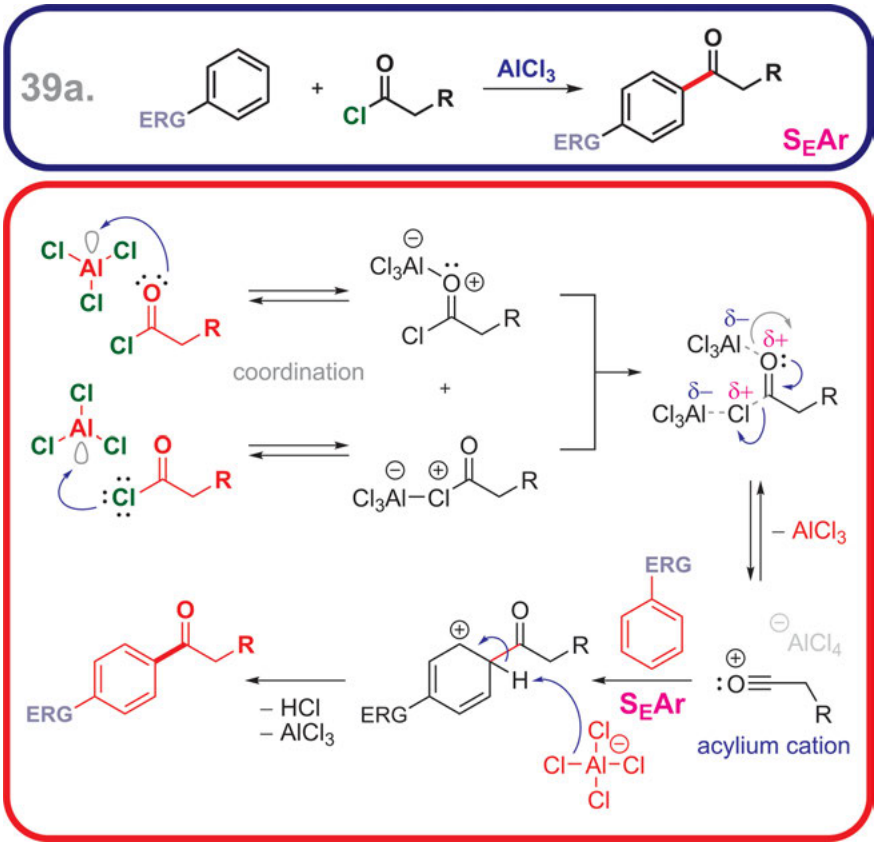

Fig. 39.1: The ***Friedel–Crafts*** *acylation* mechanism.[121]

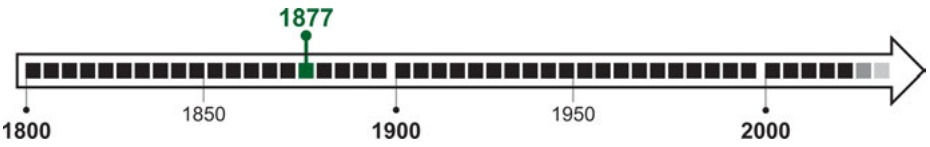

Fig. 39.2: The discovery of the ***Friedel–Crafts*** *acylation*.[122]

121 The ***Friedel–Crafts*** *acylation* mechanism is an example of the **aromatic electrophilic substitution** (the *arenium ion* mechanism or **S_EAr**, covered in Chapter 3). The linear *acyl halides* react via *acylium cation* and form *aryl ketones* with linear alkyl chains.
122 The reaction was likely first described around 1877 [39a].

https://doi.org/10.1515/9783110608373-039

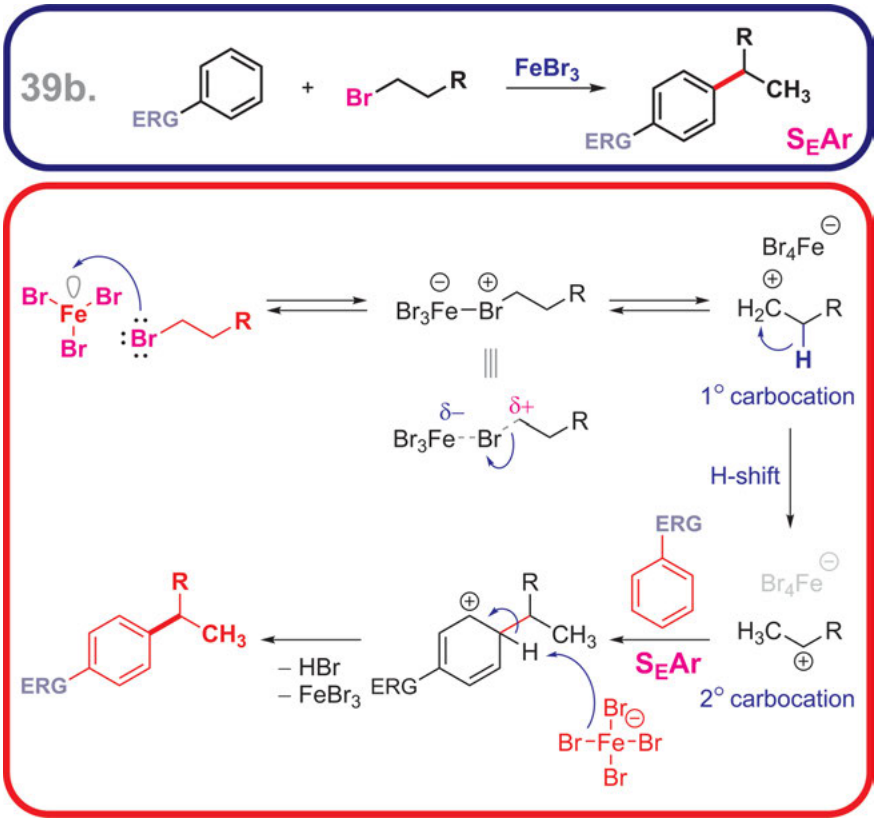

Fig. 39.3: The ***Friedel–Crafts*** *alkylation* mechanism.[123]

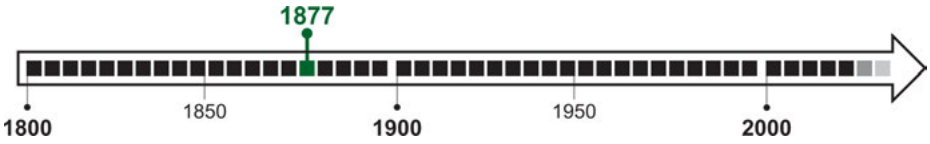

Fig. 39.4: The discovery of the ***Friedel–Crafts*** *alkylation*.[124]

123 The ***Friedel–Crafts*** *alkylation* is also the **aromatic electrophilic substitution**. The linear *alkyl halides* undergo the *carbocation rearrangement* (also called the ***Wagner–Meerwein*** *rearrangement* covered in Chapter 96) and always produce branched products.
124 The reaction was likely first described around 1877 [39b].

40 Gabriel Synthesis

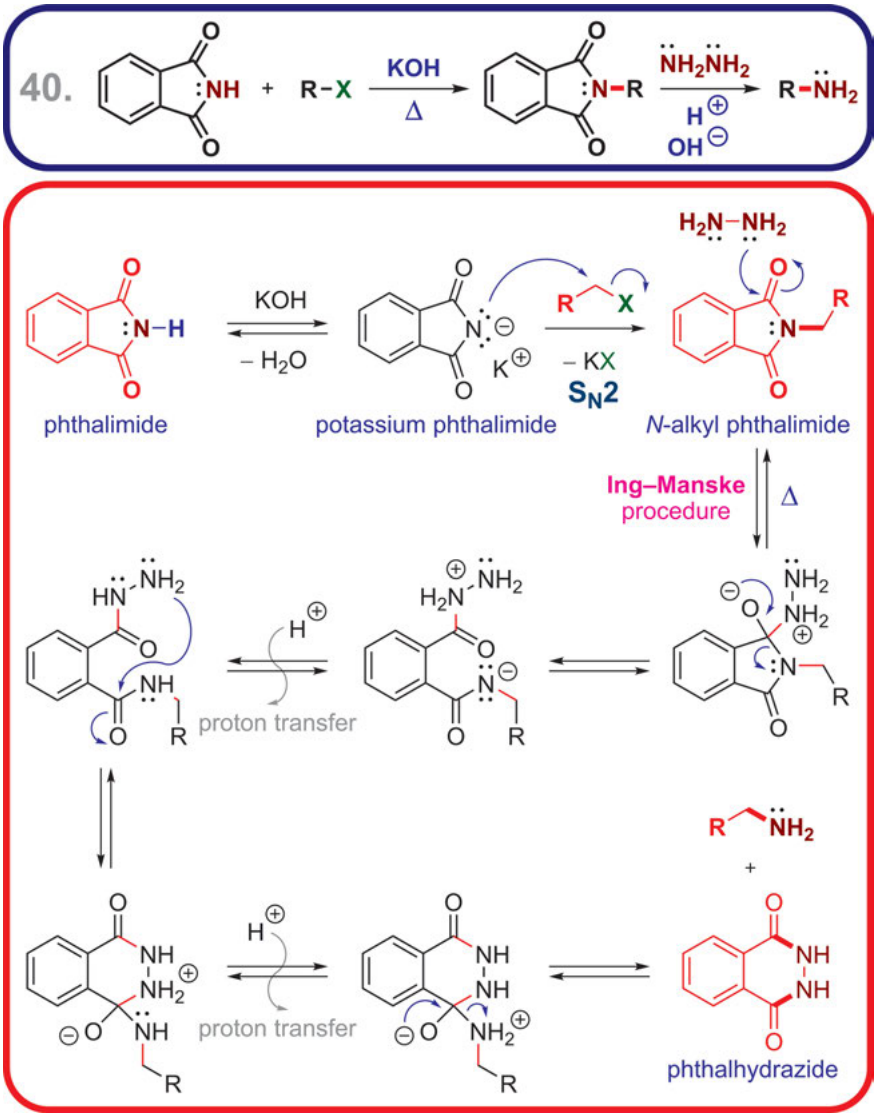

Fig. 40.1: The ***Gabriel*** *synthesis* mechanism.[125]

125 The ***Gabriel*** *synthesis* is a chemical reaction that converts *alkyl halides* to *primary (1°) amines* via the $\mathbf{S_N2}$ reaction using *phthalimide*. The ***Ing–Manske*** *procedure* [40a] is a chemical reaction that converts *N-alkyl phthalimide* to *primary (1°) amine* using *hydrazine*.

https://doi.org/10.1515/9783110608373-040

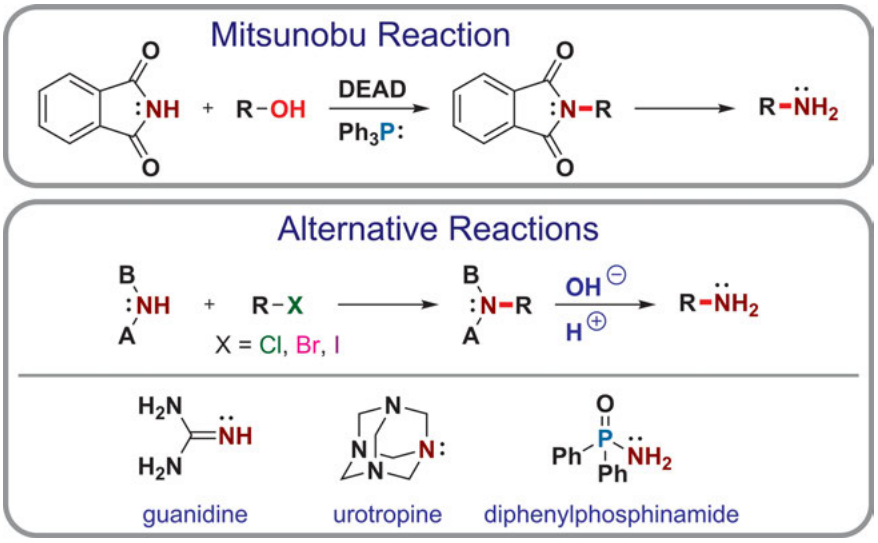

Fig. 40.2: Reactions related to the ***Gabriel*** *synthesis*.[126]

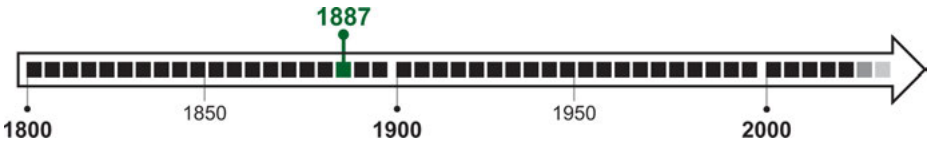

Fig. 40.3: The discovery of the ***Gabriel*** *synthesis*.[127]

126 There are alternative synthetic transformations to yield *primary amines*: the ***Mitsunobu*** *reaction* (covered in Chapter 61) or other $\mathbf{S_N2}$ reactions using various **N** (nitrogen) nucleophiles. Some of them are named reactions as well: the ***Delépine*** *reaction* (*urotropine* is the nitrogen nucleophile) [40b].
127 The reaction was likely first described around 1887 [40c].

41 Gewald Reaction

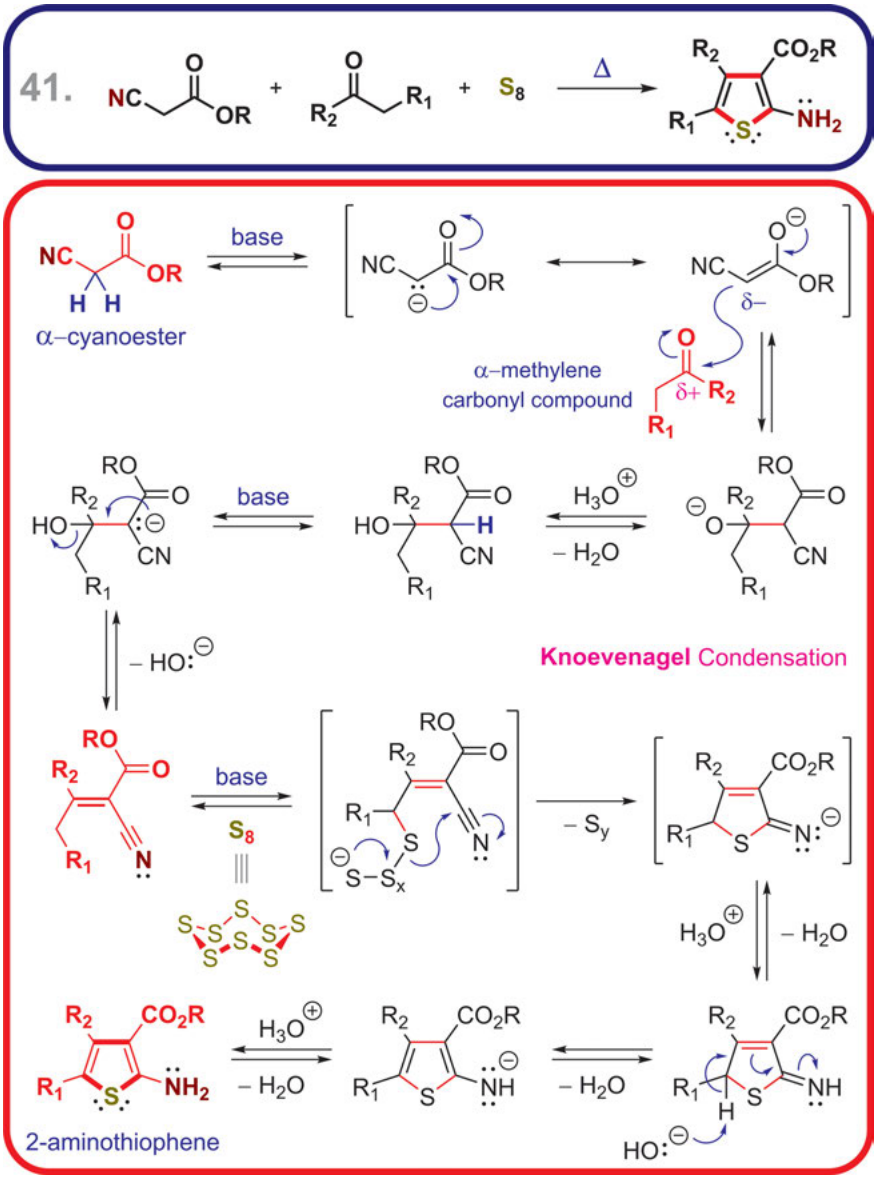

Fig. 41.1: The ***Gewald*** *reaction* mechanism.[128]

128 The ***Gewald*** *reaction*, also called the ***Gewald*** *condensation*, is a three-component reaction (3-CR) producing *2-aminothiophenes*. The key condensation step is the ***Knoevenagel*** *condensation* [41a].

https://doi.org/10.1515/9783110608373-041

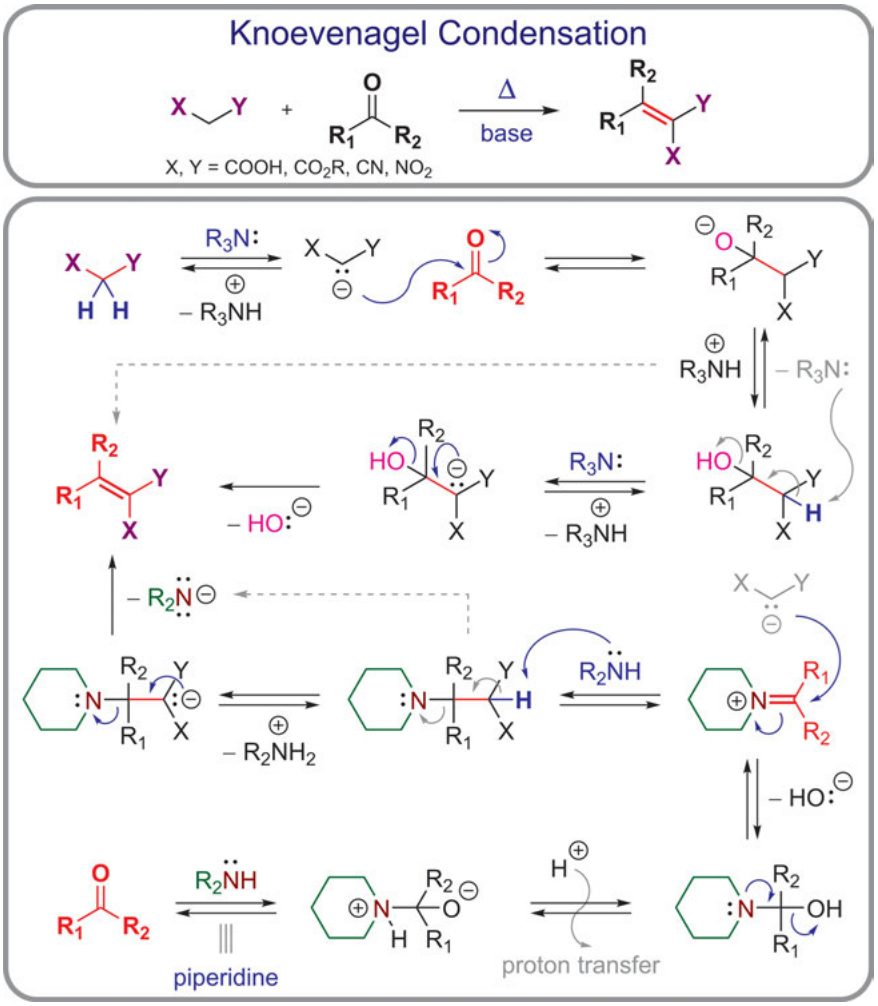

Fig. 41.2: The ***Knoevenagel*** *condensation* mechanism.[129]

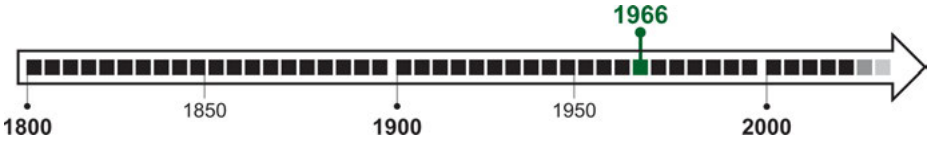

Fig. 41.3: The discovery of the ***Gewald*** *reaction*.[130]

129 The ***Knoevenagel*** *condensation* is a variation of the *aldol condensation* followed by *crotonation* (covered in Chapter 83). The reaction is often catalyzed by *piperidine*.

130 The reaction was likely first described around 1966 [41b].

42 Glaser–Eglinton–Hay Coupling

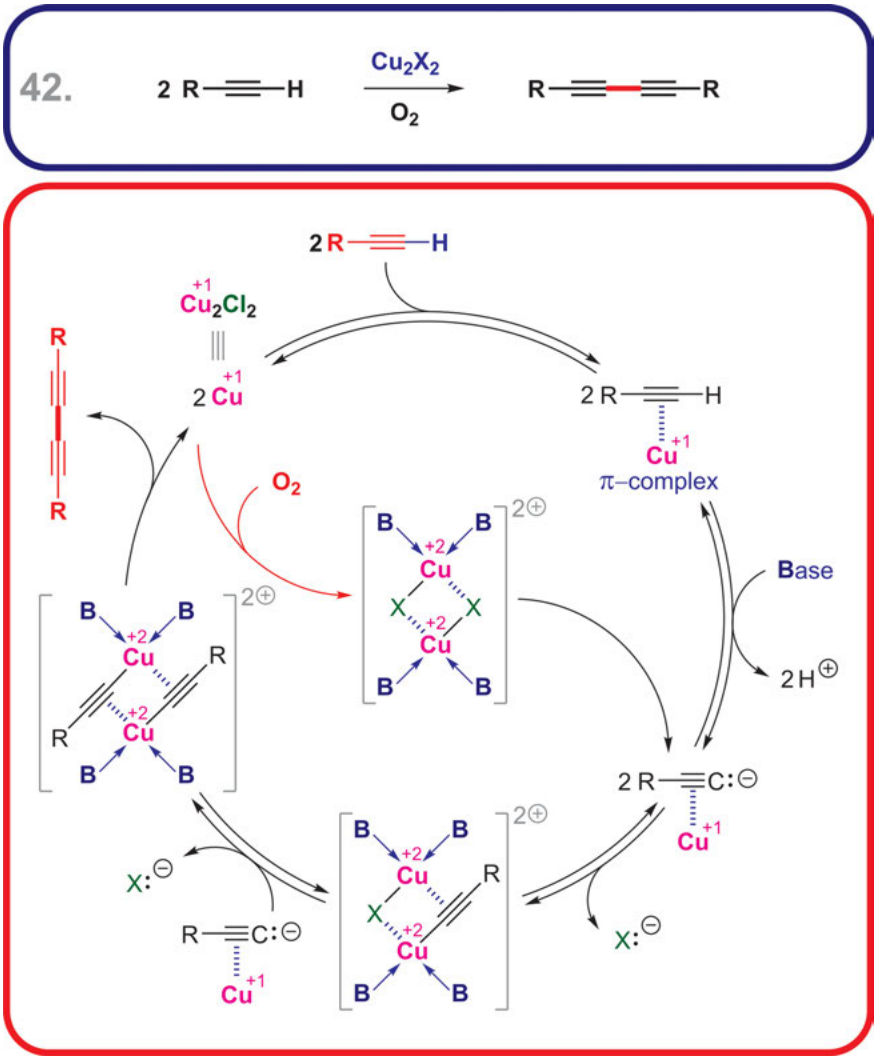

Fig. 42.1: The ***Glaser–Eglinton–Hay*** *coupling* mechanism.[131]

131 The ***Glaser–Eglinton–Hay*** *coupling* is a general name for three named reactions: the ***Glaser*** *coupling*, the ***Eglinton*** *coupling*, and the ***Hay*** *coupling*. It is one of many examples of ***Cu****-mediated dimerization* of *terminal alkynes*. In all three cases, the formed products are symmetrical.

https://doi.org/10.1515/9783110608373-042

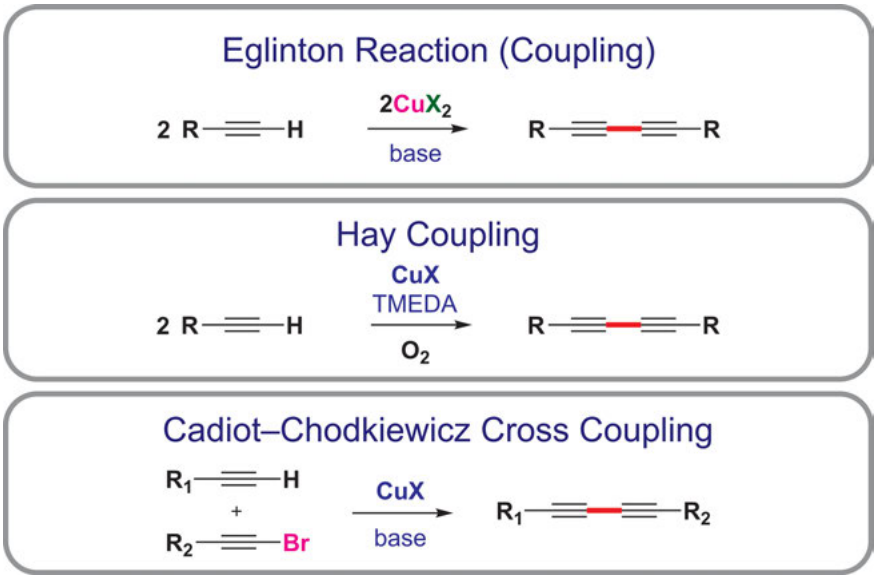

Fig. 42.2: Reactions related to the ***Glaser–Eglinton–Hay*** *coupling*.[132]

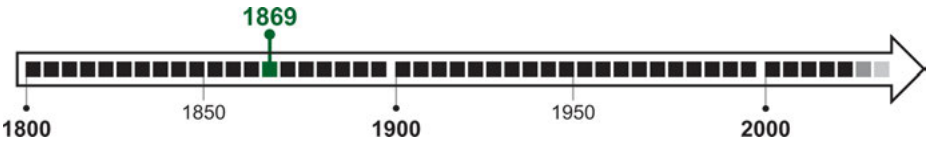

Fig. 42.3: The discovery of the ***Glaser–Eglinton–Hay*** *coupling*.[133]

132 More specifically: in the ***Eglinton*** *coupling*, the product is (a) symmetrical, (b) **Cu** is used as a stoichiometric reagent [42a, 42b]; in the ***Glaser*** *coupling*, the product is (a) symmetrical, (b) **CuX** is used as a catalyst with NH_3 or NH_4OH [42c]; in the ***Hay*** *coupling*, the product is (a) symmetrical, (b) **CuX**•TMDA complex is used as a catalyst [42d, 42e]; in the ***Cadiot–Chodkiewicz*** *coupling*, the product is (a) **asymmetrical**, (b) **Cu** is used as a catalyst [42f], and other examples [1, 4].

133 The reaction was likely first described around 1869 [42c].

43 Grignard Reaction

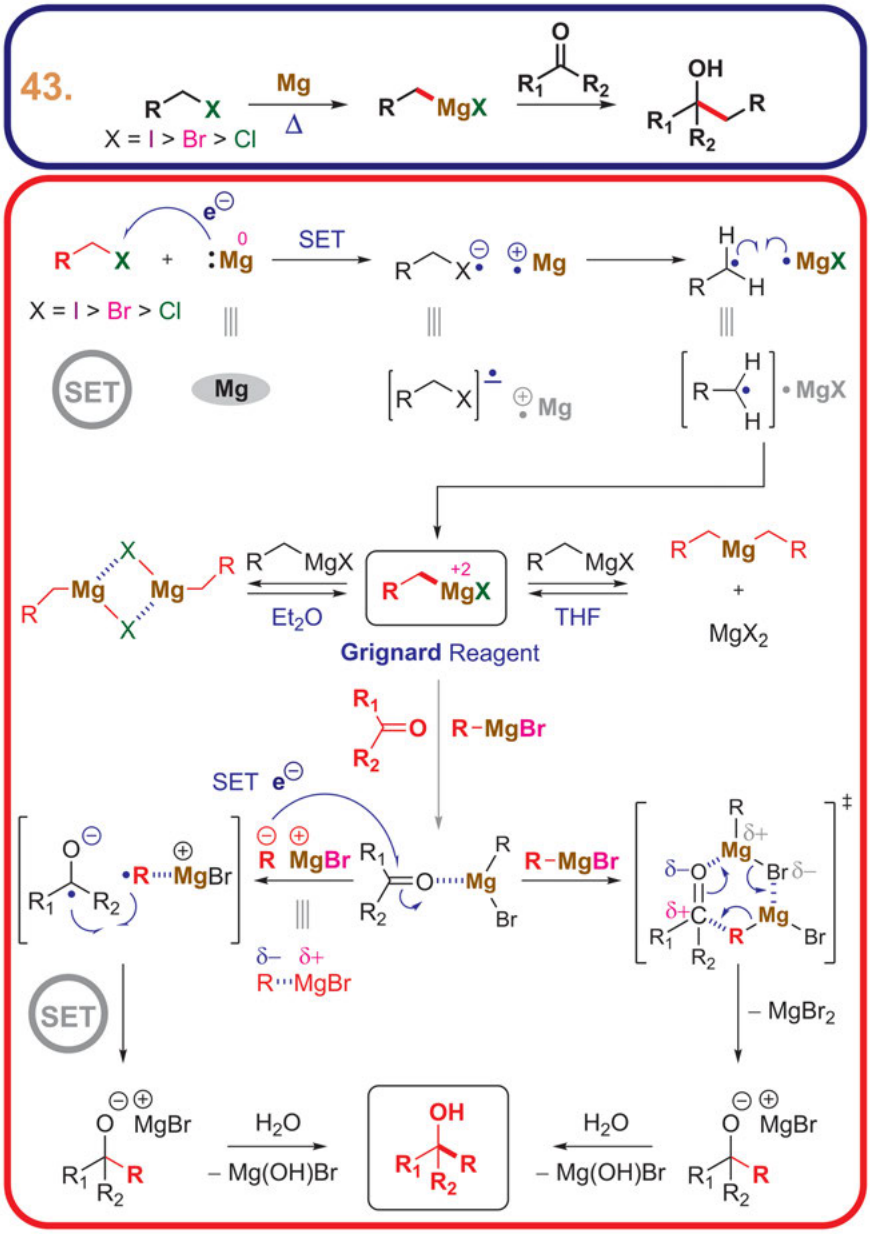

Fig. 43.1: The ***Grignard*** *reaction* mechanism.[134]

https://doi.org/10.1515/9783110608373-043

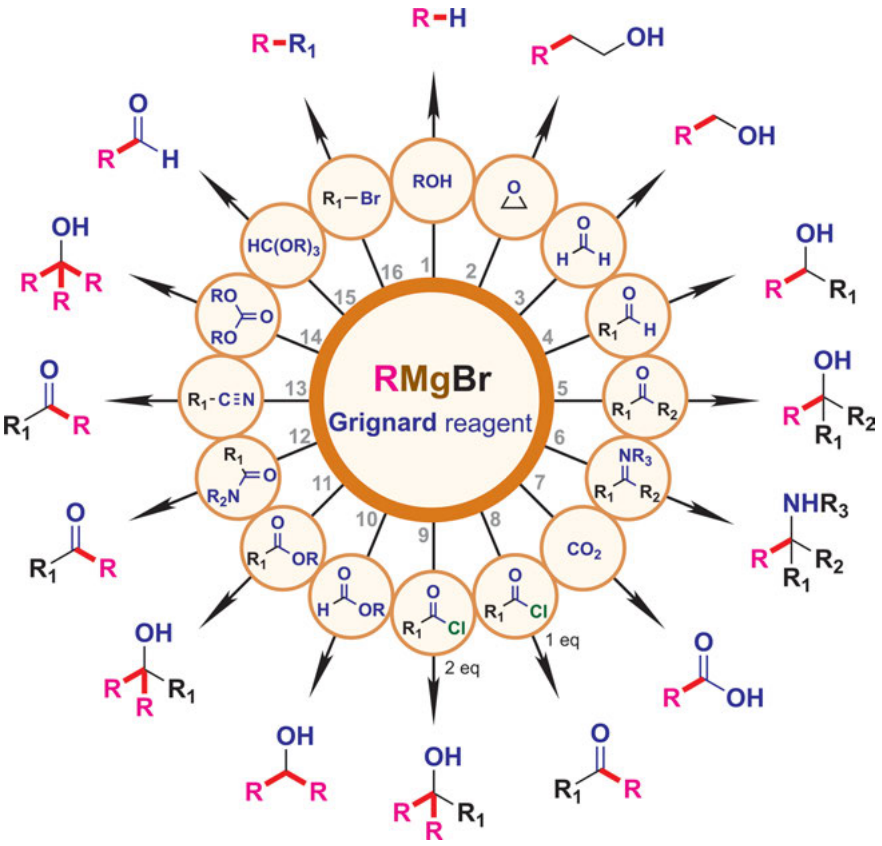

Fig. 43.2: Synthetic versatility of the ***Grignard*** *reagent*.[135]

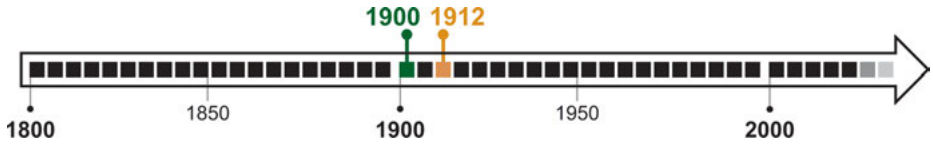

Fig. 43.3: The discovery of the ***Grignard*** *reaction*.[136]

134 The ***Grignard*** *reaction* is based on the use of a named reagent: the ***Grignard*** *reagent* (**RMgX**). The mechanism is not well-understood and most likely involves a **single electron transfer** (**SET**) (Chapter 5).
135 The ***Grignard*** *reagent* has wide synthetic applications, it can react with a variety of electrophiles (electrophilic centers): 1. alcohols, deuterated water; 2. epoxides; 3. formaldehyde; 4. aldehydes; 5. ketones; 6. imines; 7. carbon dioxide (disulfide); 8. acyl chlorides (1 eq); 9. acyl chlorides (excess); 10. formates; 11. esters; 12. amides; 13. nitriles; 14. carbonates; 15. orthoesters; 16. alkyl halides; and others [1].
136 The reaction was likely first described around 1900 [43a]. In **1912**, Victor Grignard (jointly with Paul Sabatier) received the Nobel Prize in Chemistry for the discovery of the ***Grignard*** *reagent* (and other achievements in chemistry) [43b].

44 Grob Fragmentation

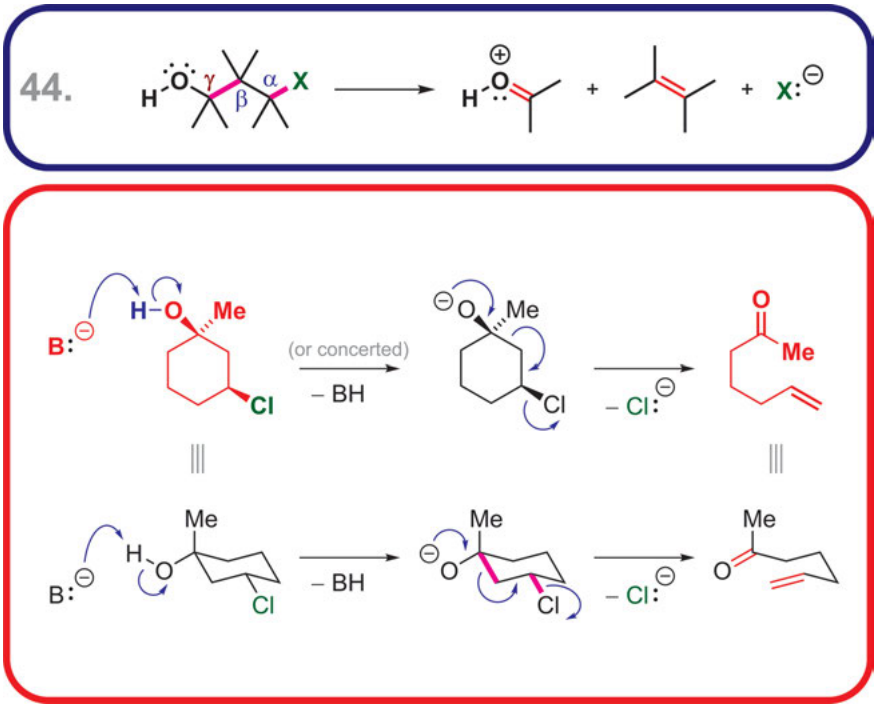

Fig. 44.1: The ***Grob*** *fragmentation* mechanism.[137]

137 The ***Grob*** *fragmentation* mechanism is most likely related to the **β–elimination** mechanisms (in this case 1,4-elimination) covered in Chapter 6. The common feature of this fragmentation is the formation of three species: positively charged *(electrofuge)*, neutral unsaturated fragment, and negatively charged *(nucleofuge)*. A stepwise or concerted mechanism can take place.

https://doi.org/10.1515/9783110608373-044

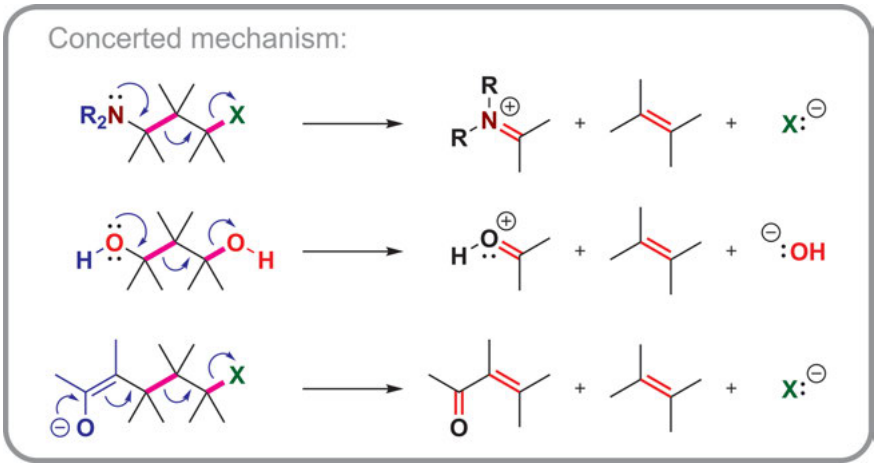

Fig. 44.2: Variations of the ***Grob*** *fragmentation*.[138]

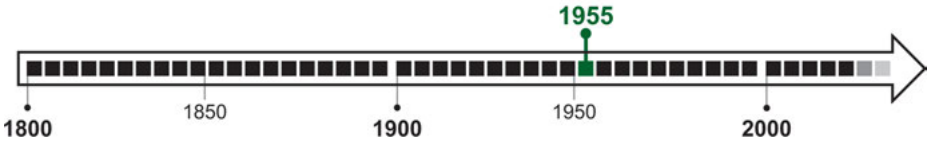

Fig. 44.3: The discovery of the ***Grob*** *fragmentation*.[139]

138 There are many variations of the ***Grob*** *fragmentation* involving: γ–hydroxy halides (shown here); γ–amino halides; 1,3-diols; and others [44a].

139 The reaction was likely first described around 1955 [44b, 44c].

45 Haloform Reaction

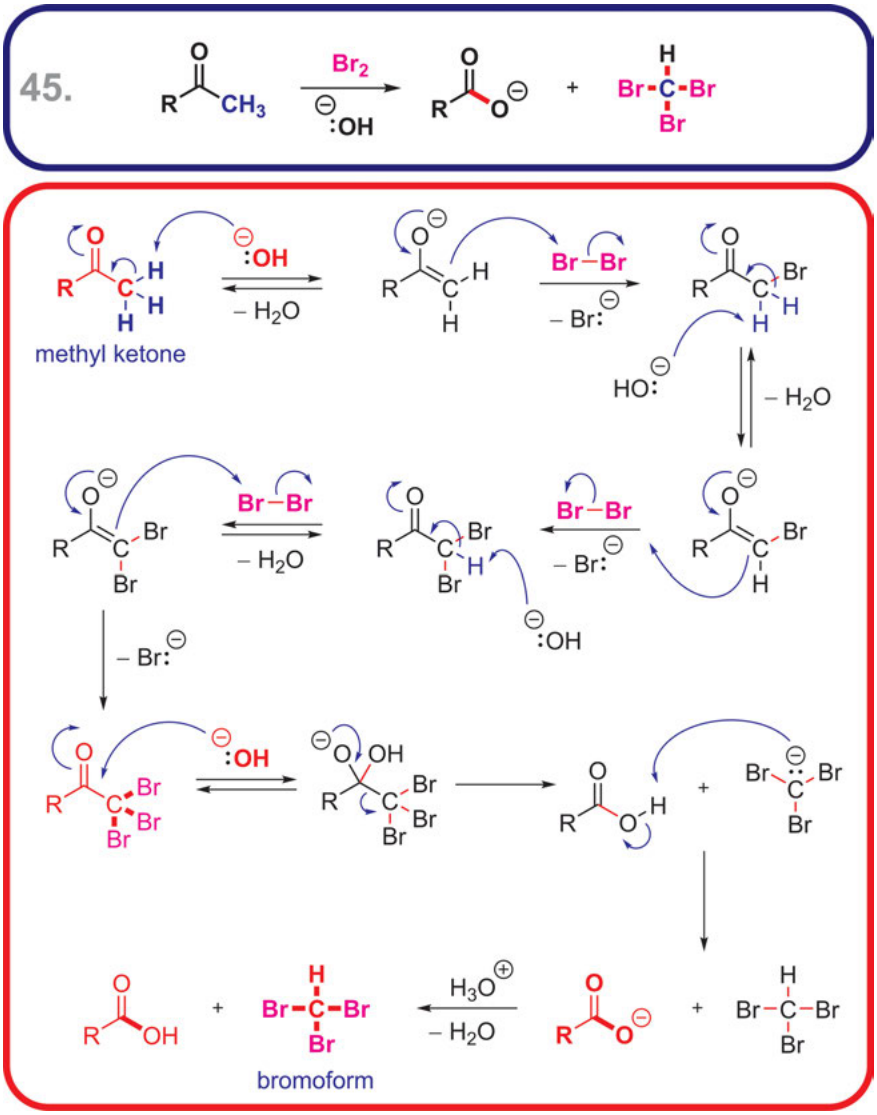

Fig. 45.1: The *haloform reaction* mechanism.[140]

140 The *haloform reaction* is one of the oldest reactions in organic chemistry. It is an example of **aliphatic electrophilic substitution**, which is not covered in this book (Chapter 3).

https://doi.org/10.1515/9783110608373-045

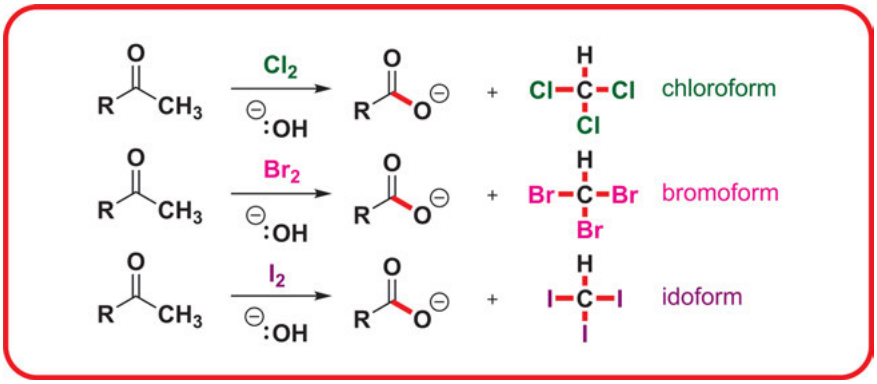

Fig. 45.2: Variations of the *haloform reaction*.[141]

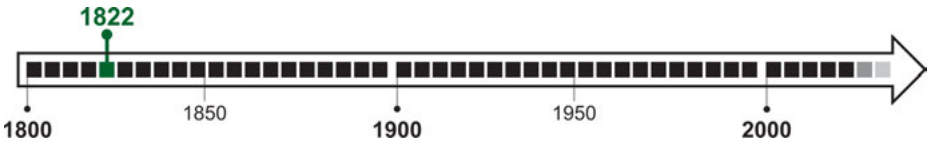

Fig. 45.3: The discovery of the *haloform reaction*.[142]

141 The *haloform reaction* can be carried out with most halogens: (Cl) the *chloroform reaction*; (Br) the *bromoform reaction*, (I) the *iodoform reaction*, also known as the *iodoform test* or the ***Lieben iodoform test*** (it is used as an indication of the methyl ketones presence) [45].
142 The reaction was likely first described between 1822 and 1870 [45].

46 Heck Cross Coupling

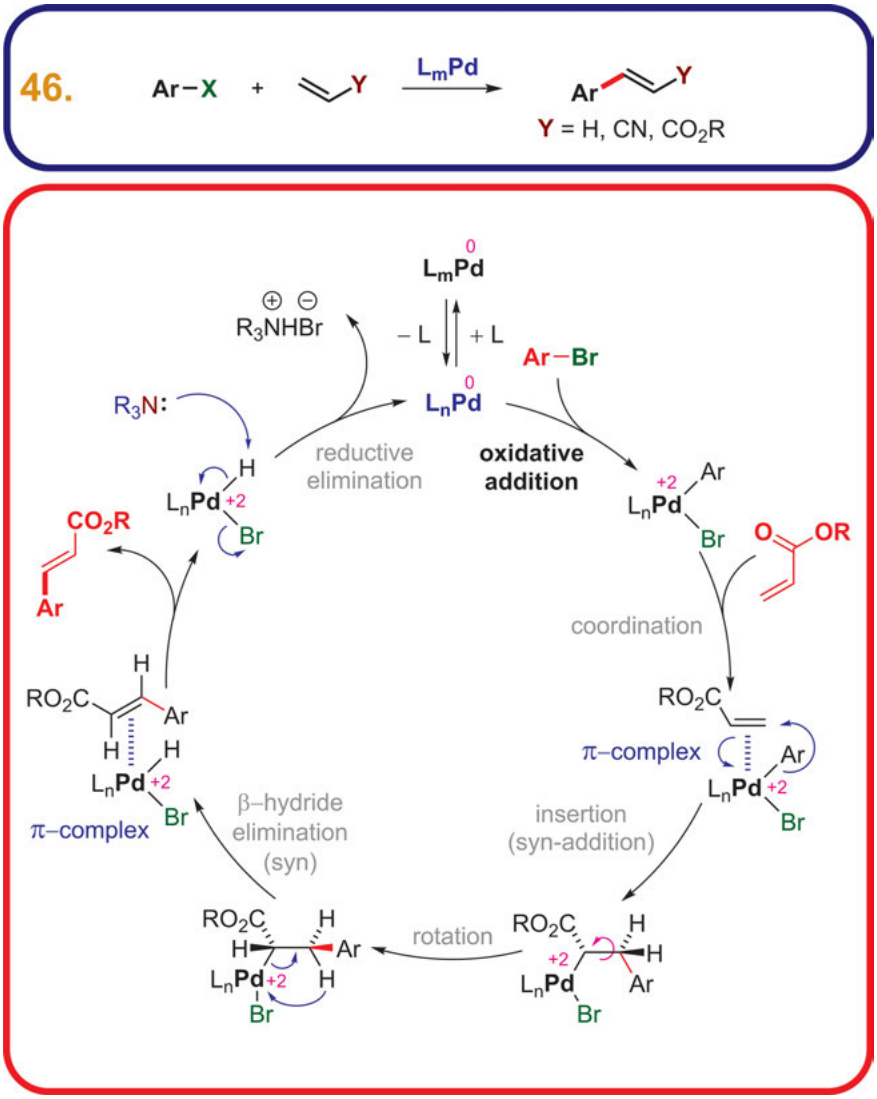

Fig. 46.1: The ***Heck*** *cross coupling* mechanism.[143]

143 The ***Heck*** *cross coupling* or the ***Heck*** *reaction* is also called the ***Mizoroki–Heck*** *reaction*. It is one of the most important types of ***Pd***-*catalyzed cross coupling* reactions (C–C bond formation using *aryl halides* and *alkenes*). For teaching purposes, a simplified and general mechanism is shown.

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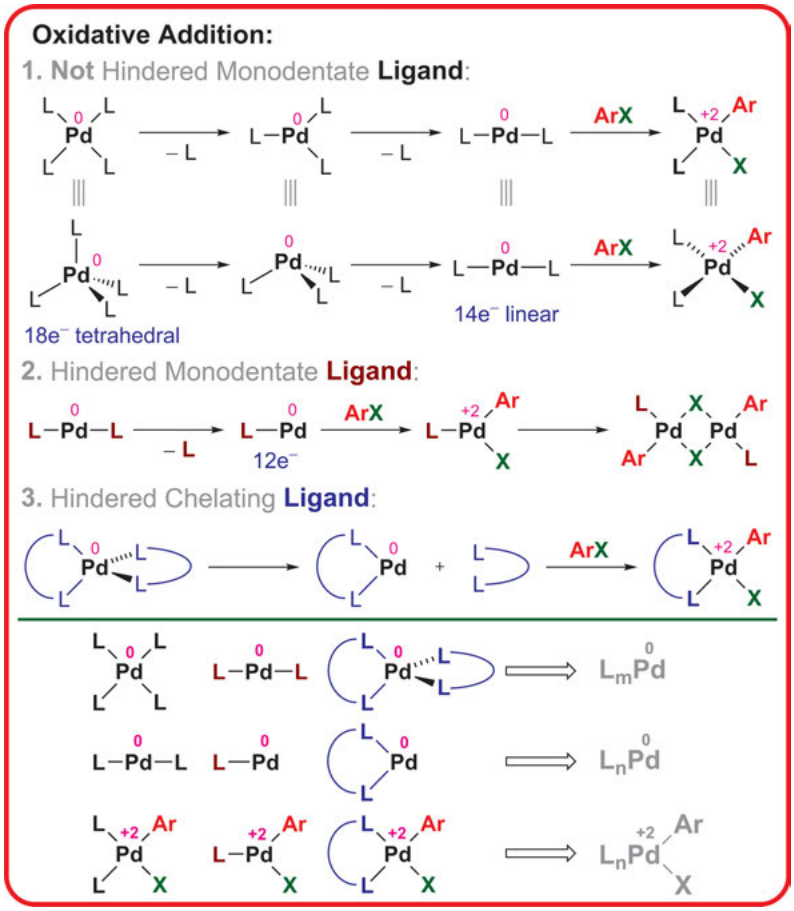

Fig. 46.2: General illustration of the *oxidative addition* step.[144]

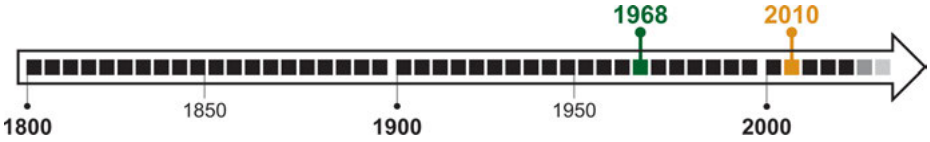

Fig. 46.3: The discovery of the ***Heck*** *cross coupling*.[145]

144 The *oxidative addition* step can be represented in several ways in the literature; including a catalyst with: 1. a *not (less) hindered monodentate ligand*; 2. a *large hindered monodentate ligand*; 3. a *hindered chelating (bidentate) ligand*. For simplicity, unspecified representation will be used henceforth: **L_mPd** or **L_nPd** [2a].

145 The reaction was likely first described around 1968 [46a, 46b]. In **2010**, Richard F. Heck (jointly with Ei-ichi Negishi and Akira Suzuki) received the Nobel Prize in Chemistry for the development of **Pd**-catalyzed cross coupling reactions [46c].

47 Hell–Volhard–Zelinsky Reaction

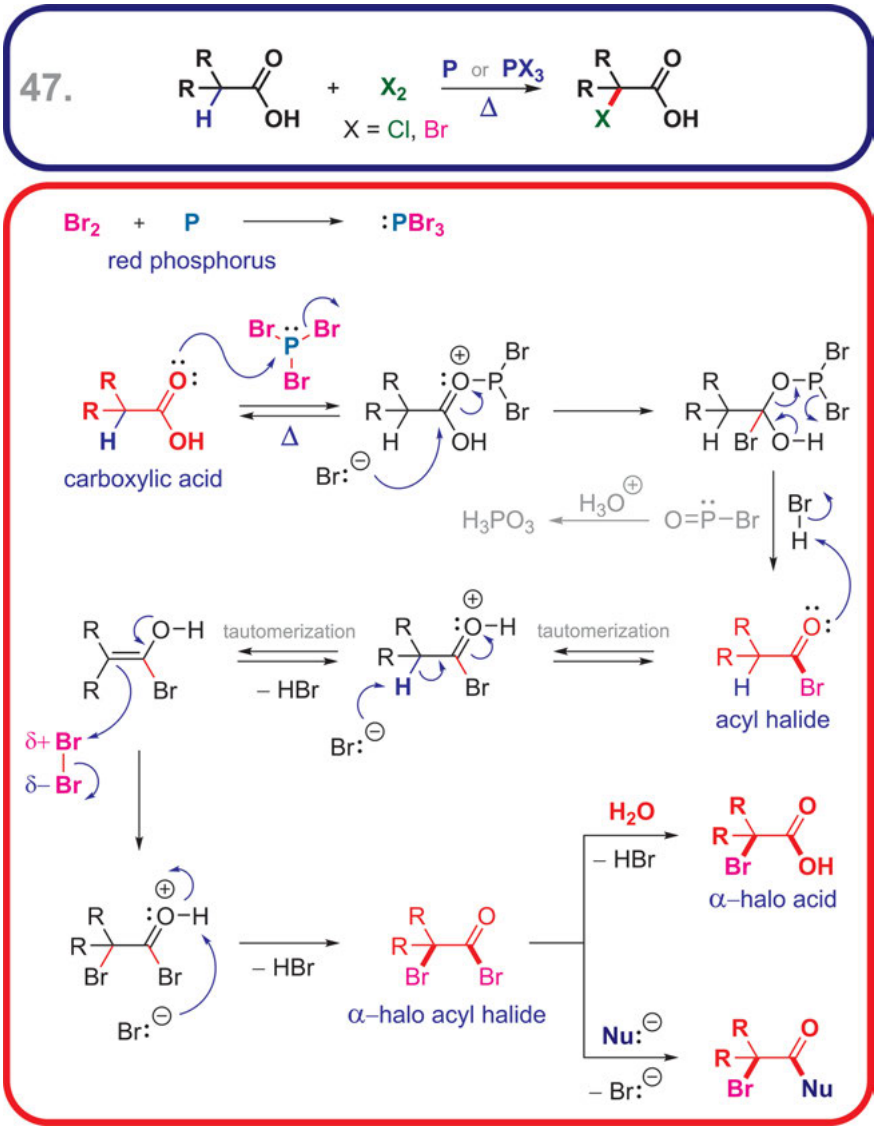

Fig. 47.1: The ***Hell–Volhard–Zelinsky*** *reaction* mechanism.[146]

146 The ***Hell–Volhard–Zelinsky*** *reaction* is also known as the ***Hell–Volhard–Zelinsky*** *(HVZ) halogenation*. It is a type of *aliphatic electrophilic substitution* (briefly mentioned in Chapter 3). Mechanistically, it is also related to the *haloform reaction* (see Chapter 45).

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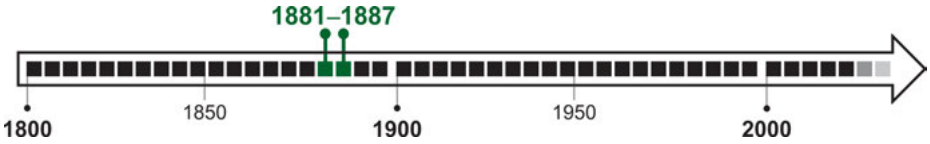

Fig. 47.2: The discovery of the ***Hell–Volhard–Zelinsky*** *reaction*.[147]

147 The reaction was likely first described around 1881 by Hell [47a], and around 1887 by both Volhard and Zelinsky [47b] and [47c].

48 Hiyama Cross Coupling

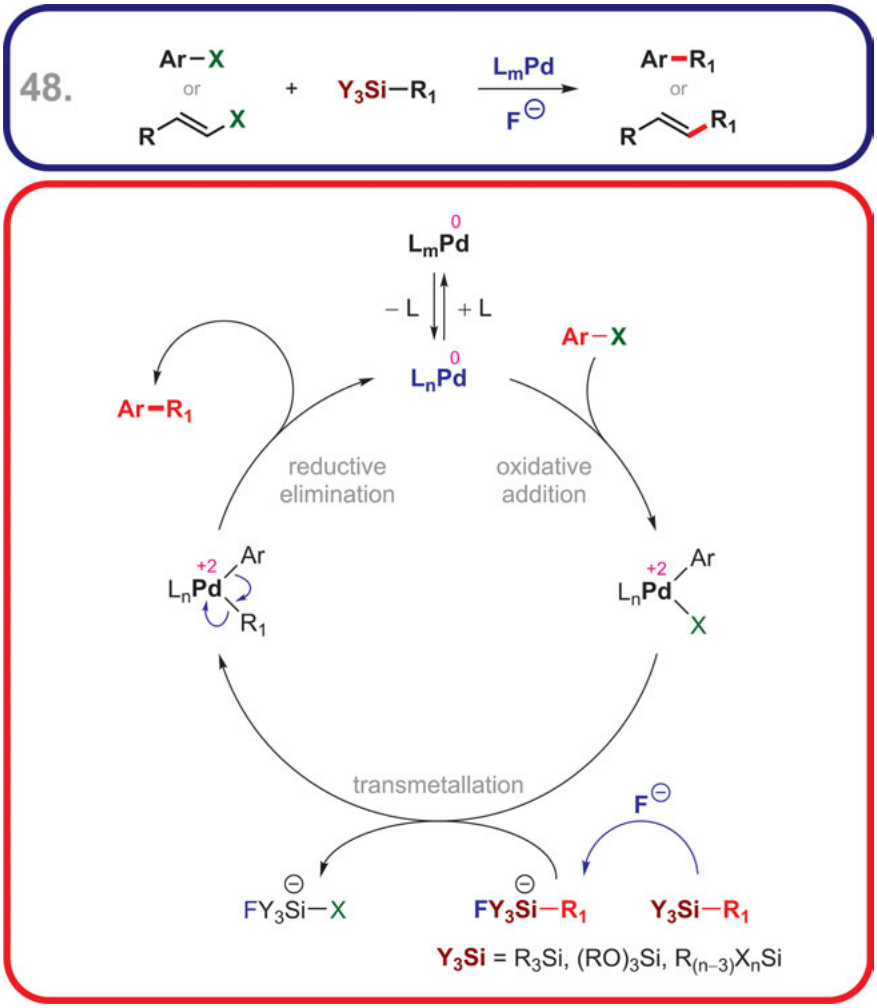

Fig. 48.1: The ***Hiyama*** *cross coupling* mechanism.[148]

148 The ***Hiyama*** *cross coupling* is a type of ***Pd****-catalyzed cross coupling* reaction (C–C bond formation using *aryl halides* and *organosilanes*). For teaching purposes, a simplified and general mechanism is shown.

https://doi.org/10.1515/9783110608373-048

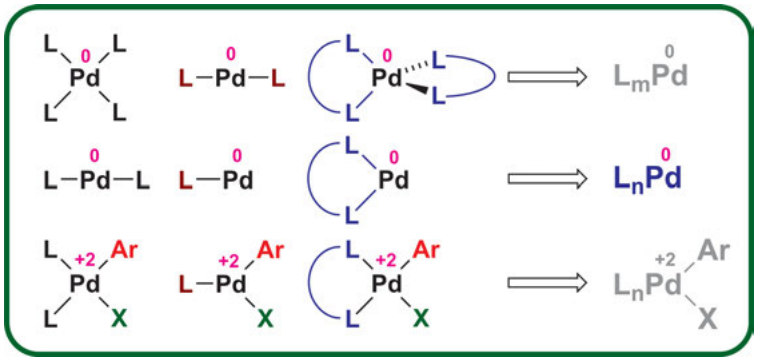

Fig. 48.2: The *oxidative addition* step representation.[149]

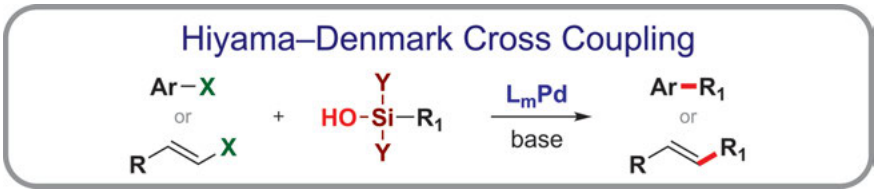

Fig. 48.3: Variations of the ***Hiyama*** *cross coupling*.[150]

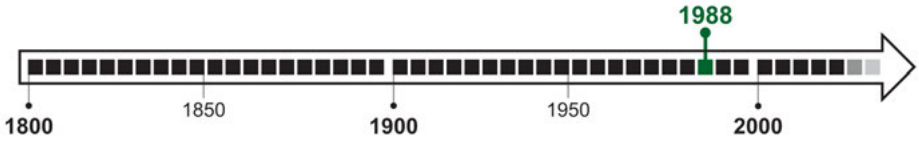

Fig. 48.4: The discovery of the ***Hiyama*** *cross coupling*.[151]

149 As it was explained in Chapter 46, the representation of the *oxidative addition* step can vary. For simplicity and consistency, a general depiction of a *catalyst-ligand* complex is used: **L_mPd** or **L_nPd** [2a].

150 A modification of the ***Hiyama*** *cross coupling* is called the ***Hiyama–Denmark*** *cross coupling* reaction [48a]. It is also a type of ***Pd****-catalyzed cross coupling* reaction (C–C bond formation using *aryl halides* and *organosilanols*).

151 The reaction was likely first described around 1988 [48b].

49 Hofmann Elimination

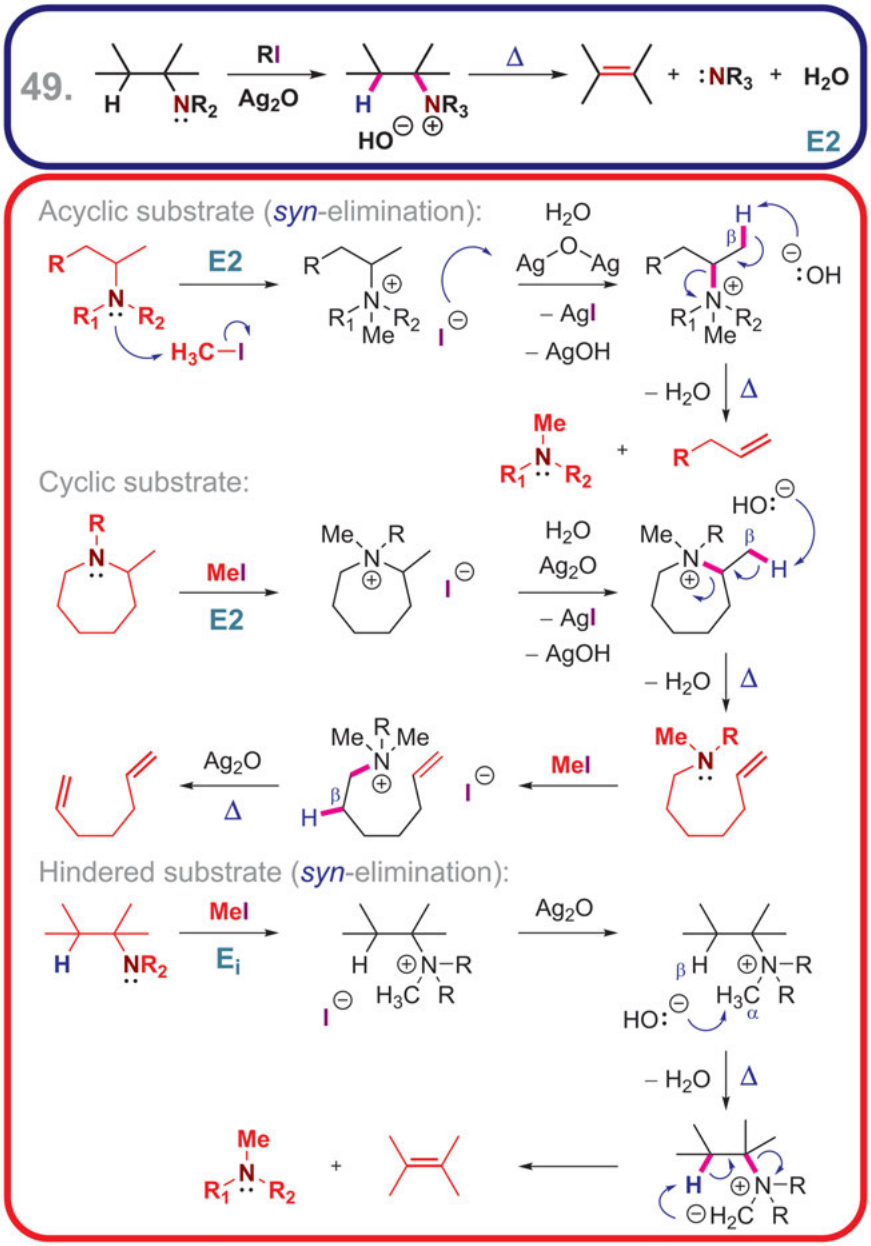

Fig. 49.1: The ***Hofmann*** *elimination* mechanism.[152]

https://doi.org/10.1515/9783110608373-049

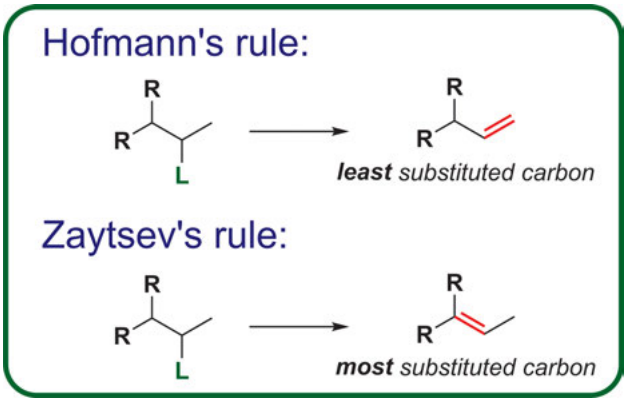

Fig. 49.2: ***Hofmann's*** *rule* and ***Zaytsev's*** *rule*.[153]

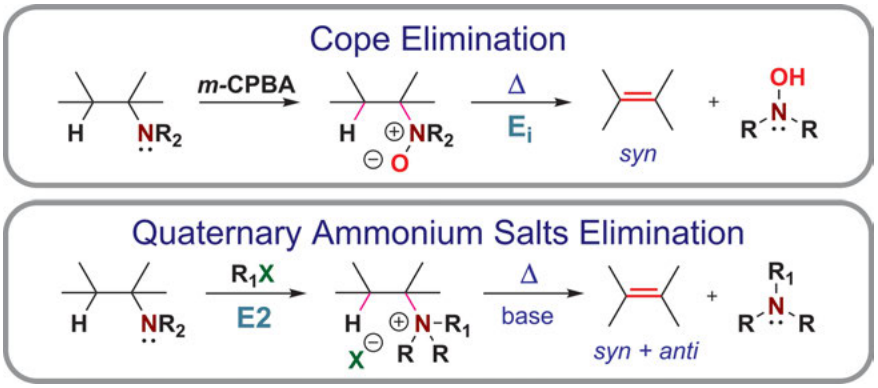

Fig. 49.3: Reactions related to the ***Hofmann*** *elimination*.[154]

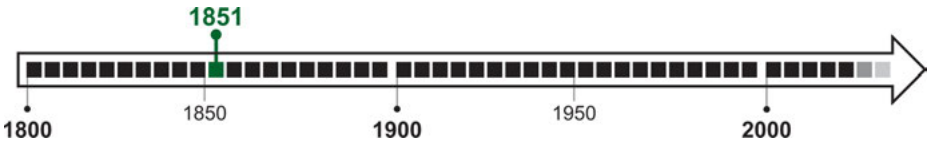

Fig. 49.4: The discovery of the ***Hofmann*** *elimination*.[155]

152 The ***Hofmann*** *elimination* is also known as the ***Hofmann*** *degradation*. This should not be confused with the ***Hofmann*** *rearrangement* (Chapter 31). It is an example of **β–elimination** reaction, Chapter 6.
153 The products of the ***Hofmann*** *elimination* obey *Hofmann's rule*: the double bond is at the *least substituted carbon*. If the double bond is at the *most substituted carbon*, then it conforms with *Zaytsev's rule* (also spelled Saytzeff, and in Russian Александр Михайлович Зайцев or A. M. Зайцев) [49a].
154 Several reactions are related to the ***Hofmann*** *elimination*: the ***Cope*** *elimination* ($\mathbf{E_i}$ mechanism, Chapter 27), the fragmentation of quaternary ammonium salts (**E2** mechanism), and others [1, 49b].
155 The reaction was likely first described around 1851 [49c, 49d].

50 Horner–Wadsworth–Emmons Olefination

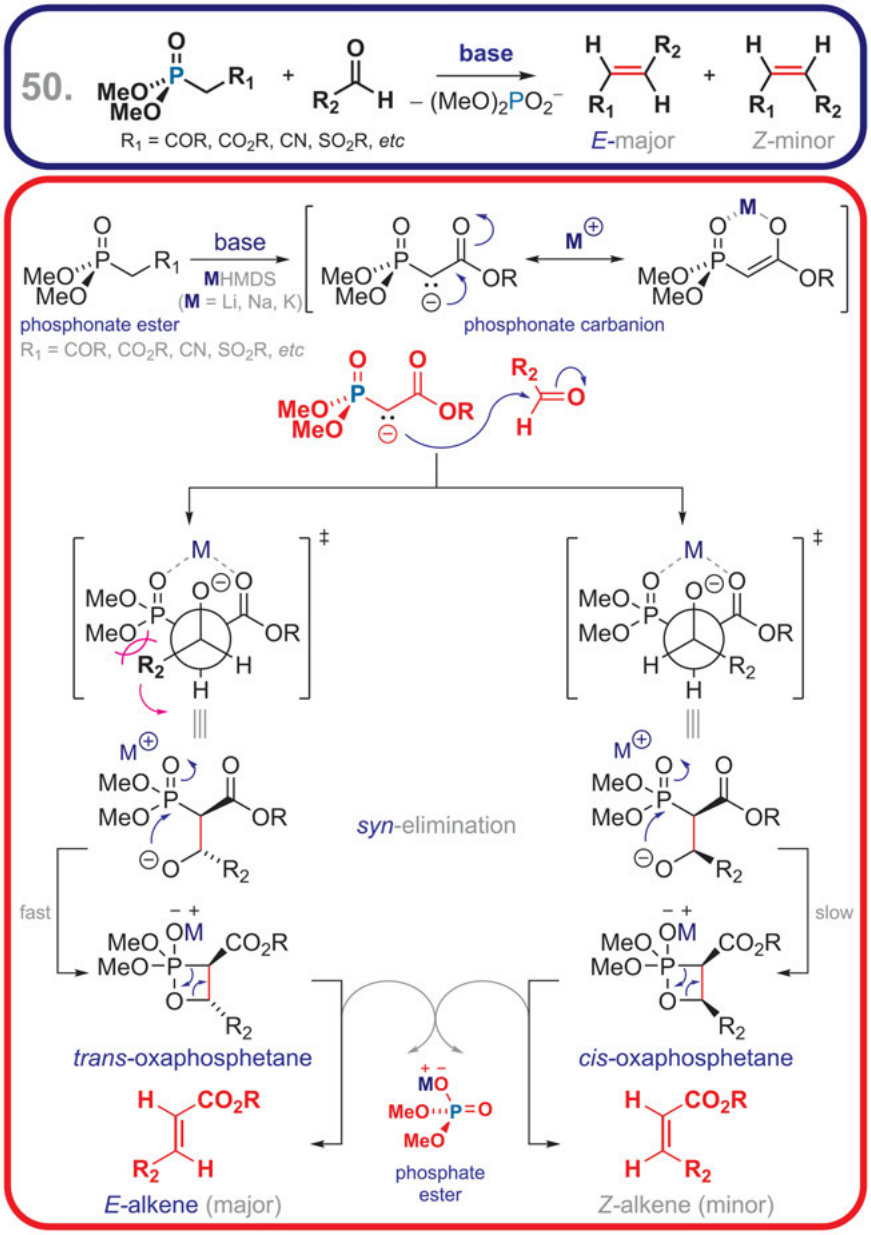

Fig. 50.1: The ***Horner–Wadsworth–Emmons*** *olefination* mechanism.[156]

https://doi.org/10.1515/9783110608373-050

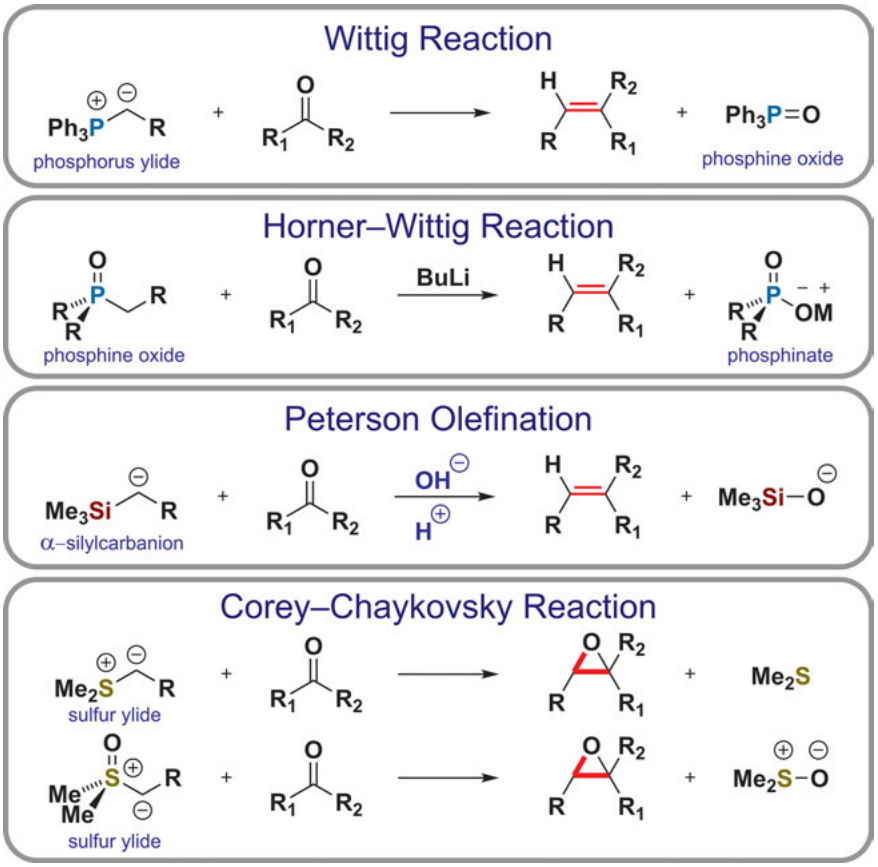

Fig. 50.2: Reactions related to the ***Horner–Wadsworth–Emmons*** *olefination*.[157]

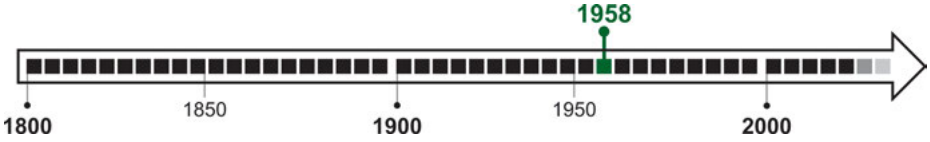

Fig. 50.3: The discovery of the ***Horner–Wadsworth–Emmons*** *olefination*.[158]

156 The ***Horner–Wadsworth–Emmons*** *(HWE) olefination* is also called the ***HWE*** *reaction*. The reaction relies on the use of *phosphonates* prepared via the ***Arbuzov*** *reaction* (Chapter 9).

157 Several reactions are related to the ***HWE*** *olefination*: the ***Wittig*** *reaction* (Chapter 98, it relies on the *phosphorus ylides* formed from the *phosphonium salts*), the ***Horner–Wittig*** *reaction* (relies on the *ylides* formed from the *phosphine oxides*) [1] and [50a], the ***Peterson*** *olefination* (relies on the *organosilanes*) [50b], the ***Corey–Chaykovsky*** *reaction* (relies on the *sulfur ylides*, Chapter 32).

158 The reaction was likely first described around 1958 [50c, 50d, 50e].

51 Jones Oxidation

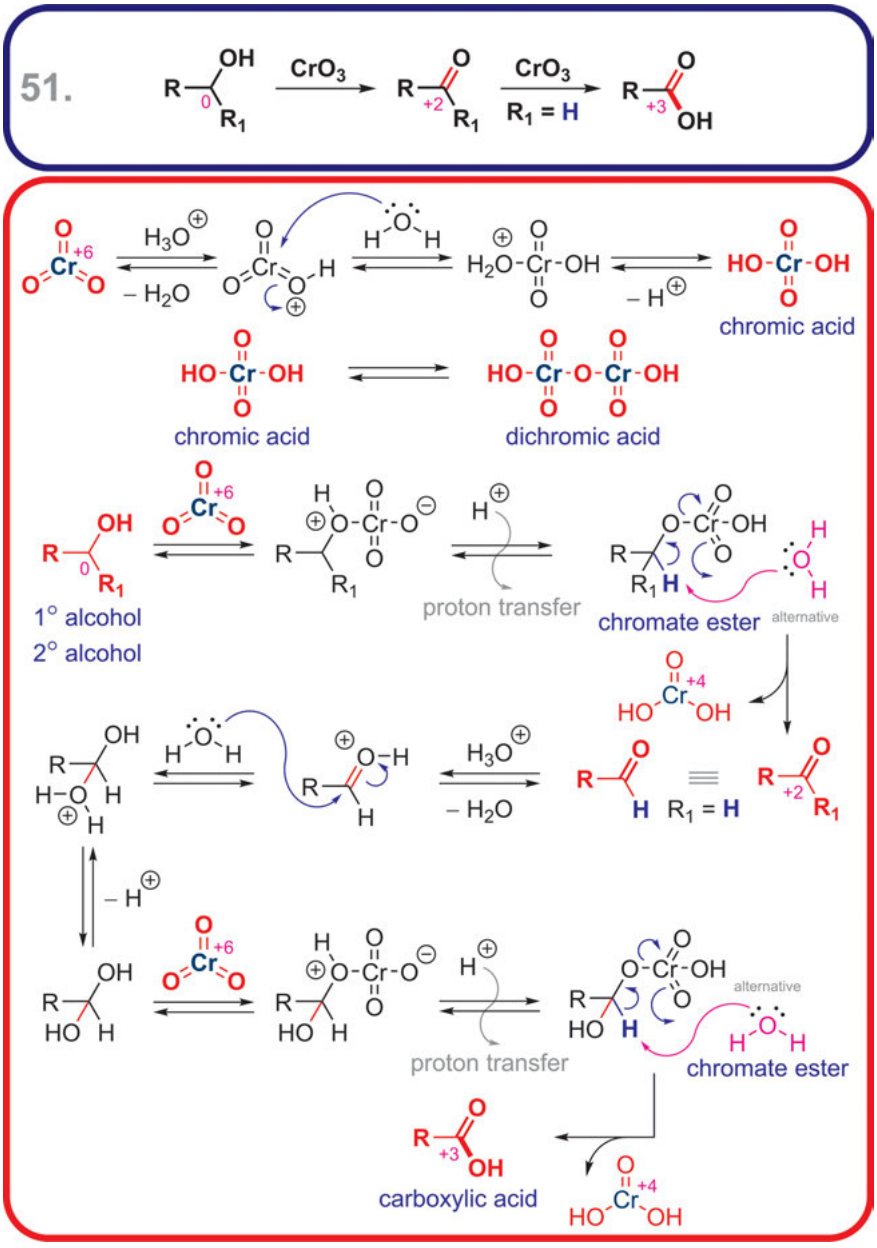

Fig. 51.1: The ***Jones** oxidation* mechanism.[159]

https://doi.org/10.1515/9783110608373-051

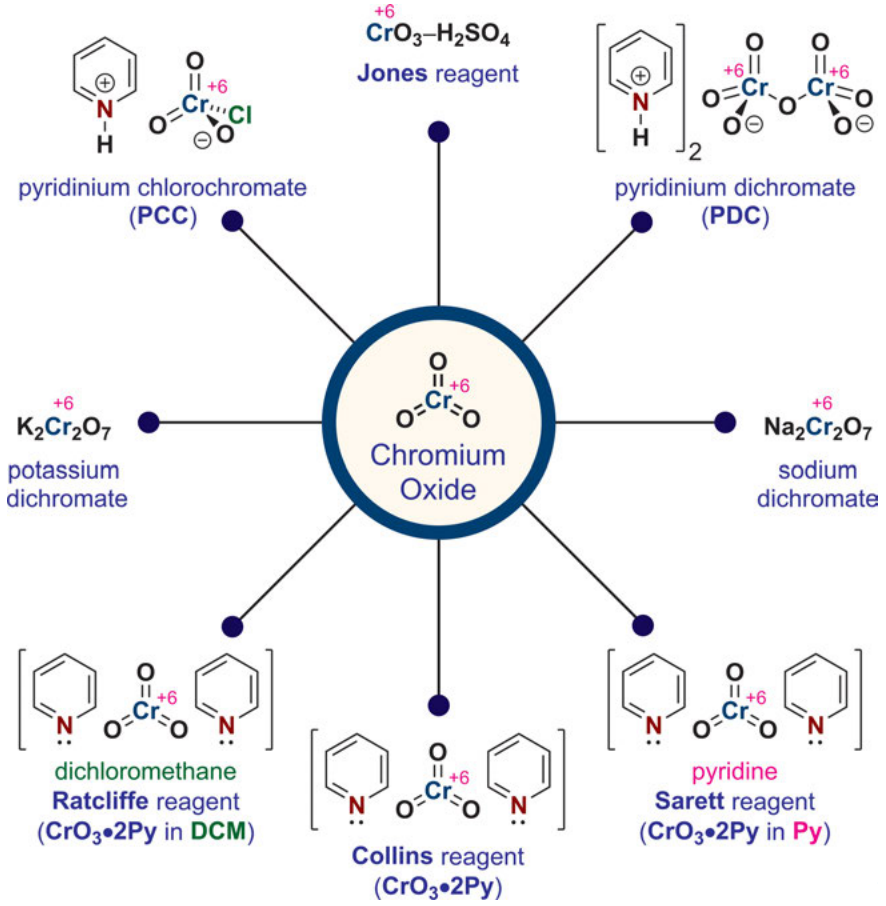

Fig. 51.2: Various oxidizing reagents formed from chromium oxide (VI).[160]

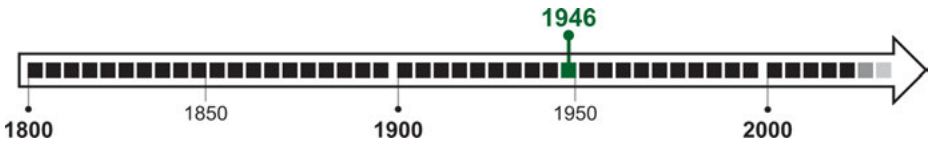

Fig. 51.3: The discovery of the ***Jones*** *oxidation*.[161]

159 The ***Jones*** *oxidation* is based on the use of the same named reagent: the ***Jones*** *reagent* [51a].

160 There are numerous examples of chromium oxidizing reagents, which can be prepared from chromium oxide (VI): *pyridinium chlorochromate* (PCC) [51b, 51c] is one of the most important among them.

161 The reaction was likely first described around 1946 [51d].

52 Kucherov Reaction

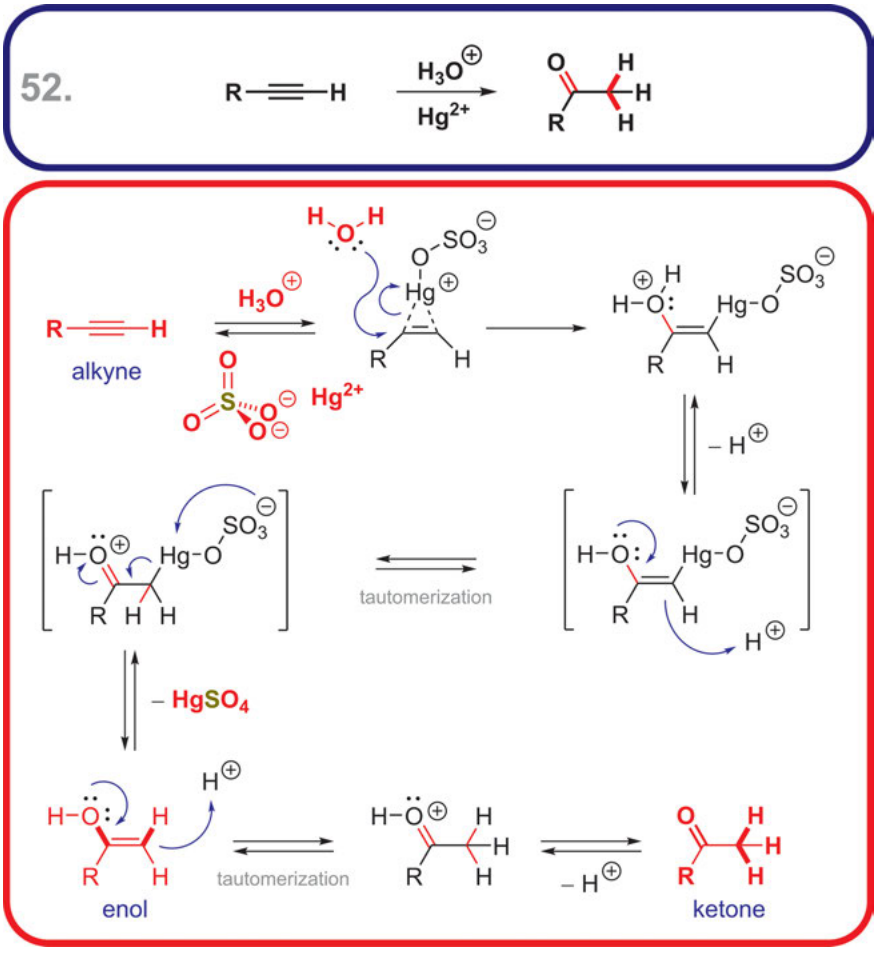

Fig. 52.1: The ***Kucherov*** *reaction* mechanism.[162]

162 The ***Kucherov*** *reaction* (in Russian Кучеров) is rare and very seldom called by its name. Mechanistically, it is an example of the **electrophilic addition** (to an alkyne) more broadly covered in Chapter 1. The reaction follows *Markovnikov's rule* (in Russian Владимир Васильевич Марковников or В. В. Марковников): hydrogen (H^+, or any other electrophilic part of a molecule) is at the least substituted carbon (or H adds to the carbon with more H atoms) [52a].

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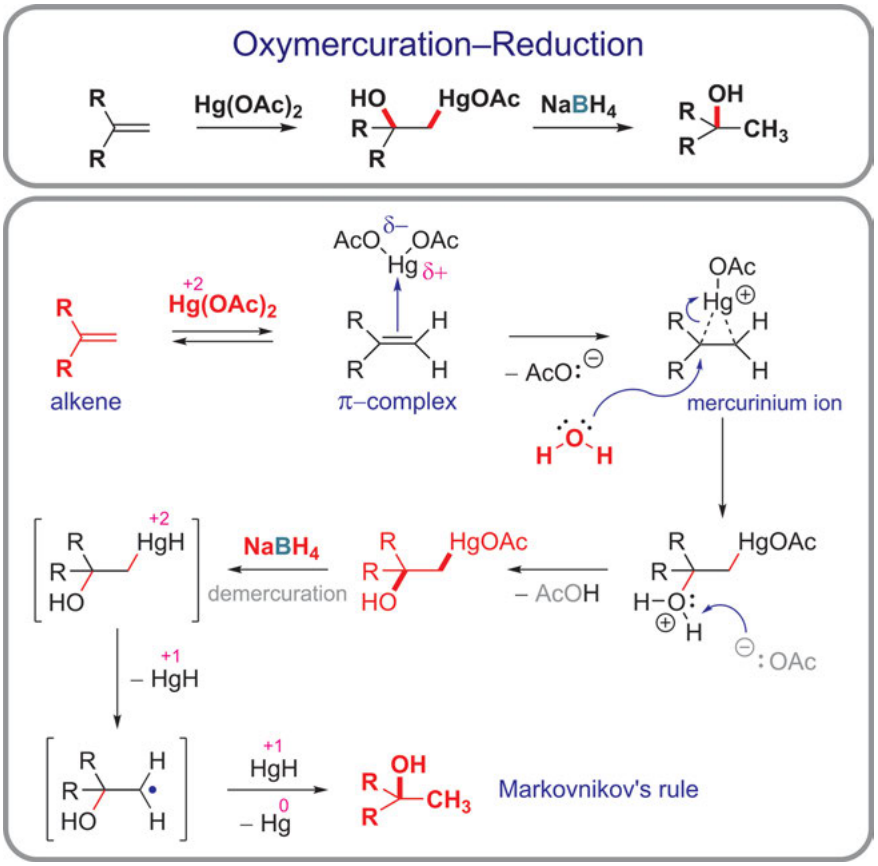

Fig. 52.2: The *oxymercuration reaction* mechanism.[163]

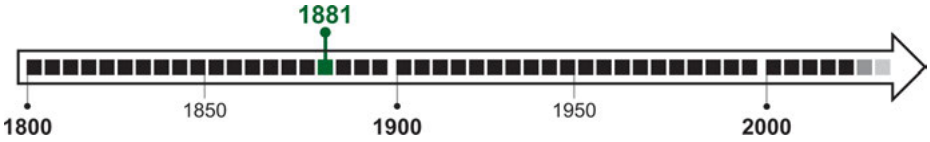

Fig. 52.3: The discovery of the ***Kucherov*** *reaction*.[164]

163 The *oxymercuration reaction* (the *oxymercuration-reduction reaction*) is related to the ***Kucherov*** *reaction*. It is also an **electrophilic addition** reaction predominantly forming products (alcohols) according to *Markovnikov's rule*. Please note, the *hydroboration-oxidation* (Chapter 20), yields ***anti-Markovnikov's*** products: hydrogen is at the most substituted carbon (or H adds to the carbon with less H atoms).

164 The reaction was likely first described around 1881 [52b].

53 Kumada Cross Coupling

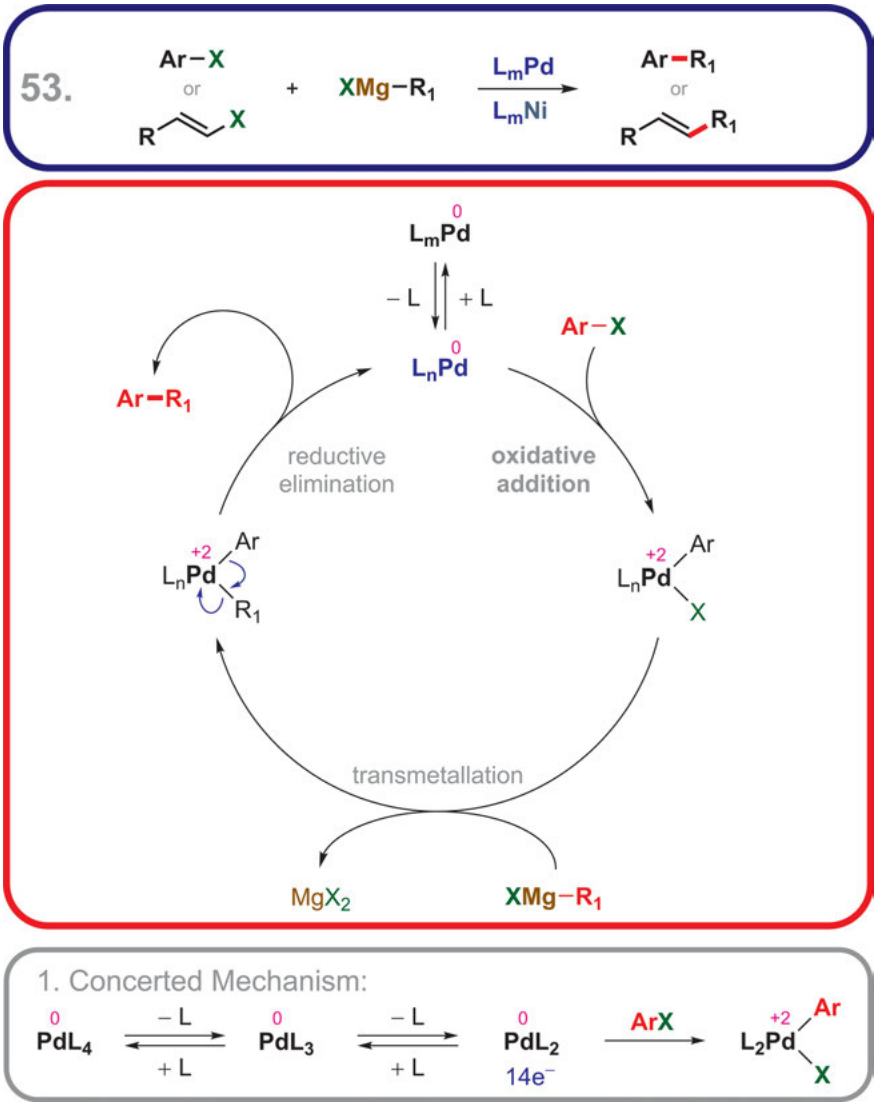

Fig. 53.1: The **Pd**-catalyzed ***Kumada*** *cross coupling* mechanism.[165]

165 The ***Kumada*** *cross coupling* (or the ***Kumada–Corriu*** cross coupling) is a type of ***Pd****-catalyzed cross coupling* reaction (C–C bond formation using *aryl halides* and the ***Grignard*** *reagent = organo-magnesium compound*). For teaching purposes, a simplified and general mechanism is shown. Note, (1) *concerted oxidative addition* step to a low-coordinate ($14e^-$) **Pd**-complex is more complicated [2a].

https://doi.org/10.1515/9783110608373-053

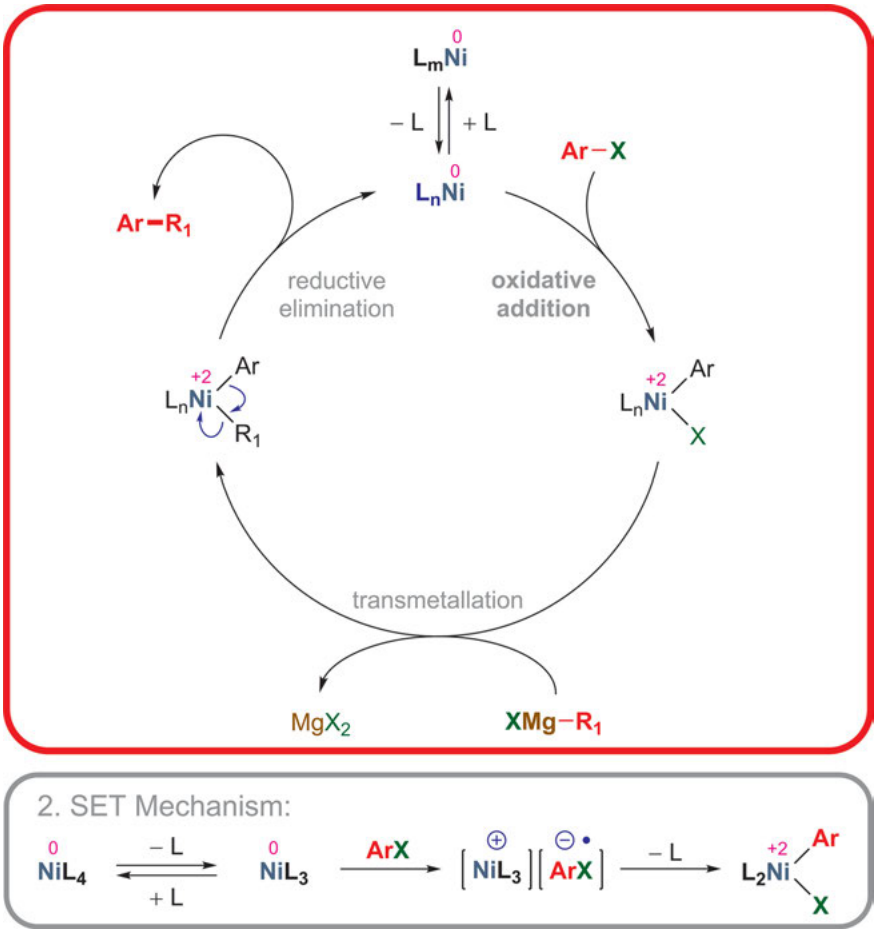

Fig. 53.2: The **Ni**-catalyzed ***Kumada*** *cross coupling* mechanism.[166]

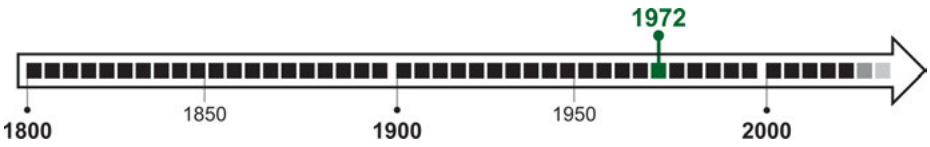

Fig. 53.3: The discovery of the ***Kumada*** *cross coupling*.[167]

166 The ***Kumada*** *cross coupling* can be ***Ni****-catalyzed*. Note, a possible example of a (2) *SET oxidative addition* step to a **Ni**-complex (not necessarily at play in the example shown) [2a].
167 The reaction was likely first described around 1972 [53].

54 Ley–Griffith Oxidation

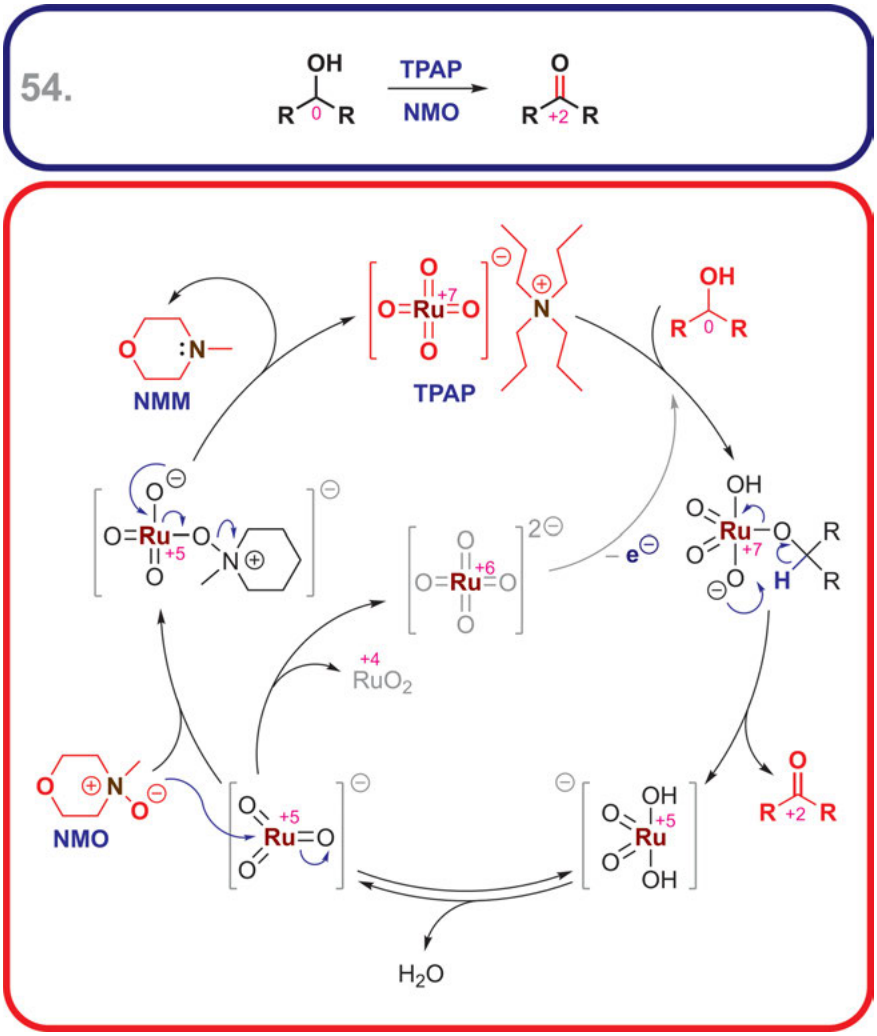

Fig. 54.1: The ***Ley–Griffith*** *oxidation* mechanism.[168]

168 The ***Ley–Griffith*** *oxidation* is based on the use of a named reagent: the ***Ley–Griffith*** *reagent* (**TPAP**) [54a].

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Fig. 54.2: Reactions related to the ***Ley–Griffith*** *oxidation*.[169]

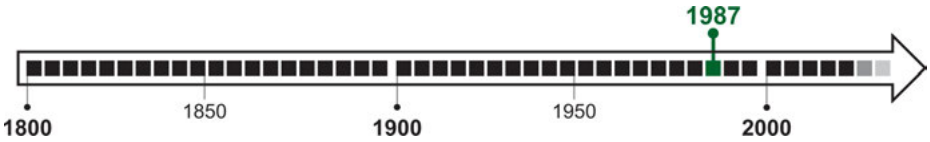

Fig. 54.3: The discovery of the ***Ley–Griffith*** *oxidation*.[170]

169 The ***Upjohn*** *dihydroxylation* (covered in Chapter 93) is related to the ***Ley–Griffith*** *oxidation*.
170 The reaction was likely first described around 1987 [54b].

55 Liebeskind–Srogl Cross Coupling

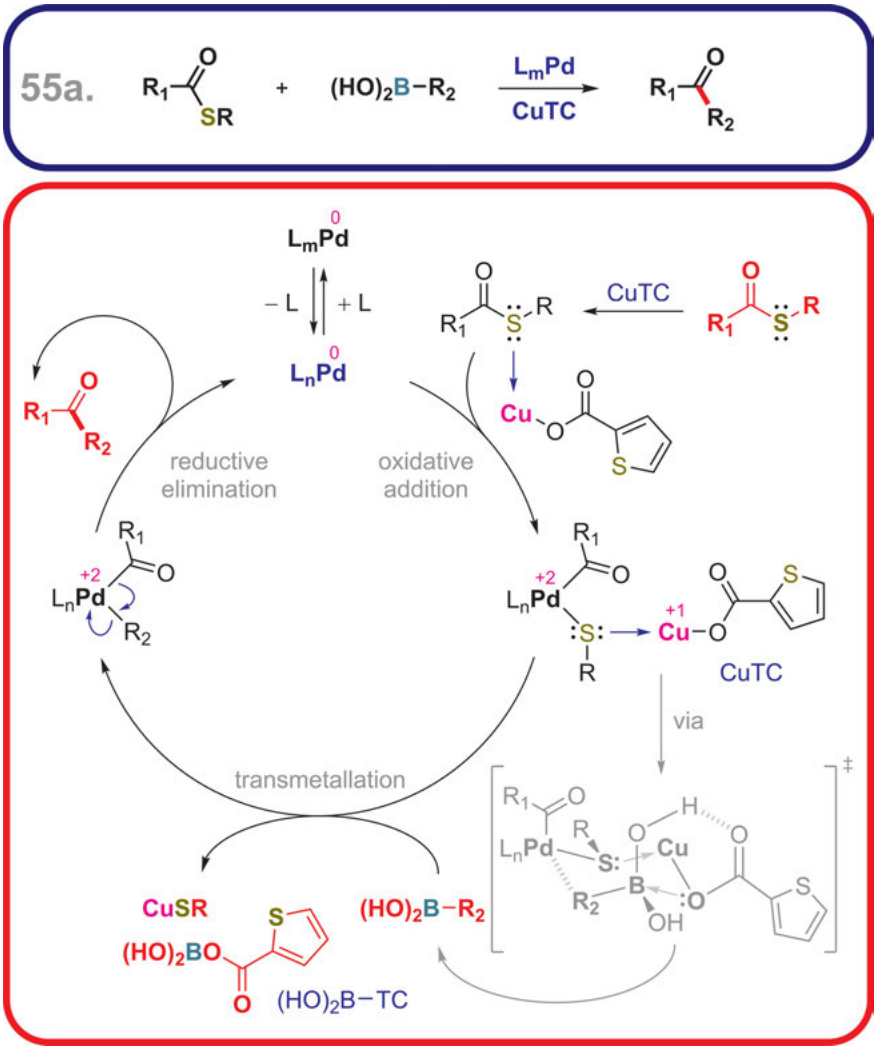

Fig. 55.1: The ***Liebeskind–Srogl*** *cross coupling* (thioesters) mechanism.[171]

171 The ***Liebeskind–Srogl*** *cross coupling* of *thioesters* is a type of ***Pd****-catalyzed cross coupling* reaction (C–C bond formation using *thioesters* and *boronic acids*). For teaching purposes, only a simplified general mechanism is shown.

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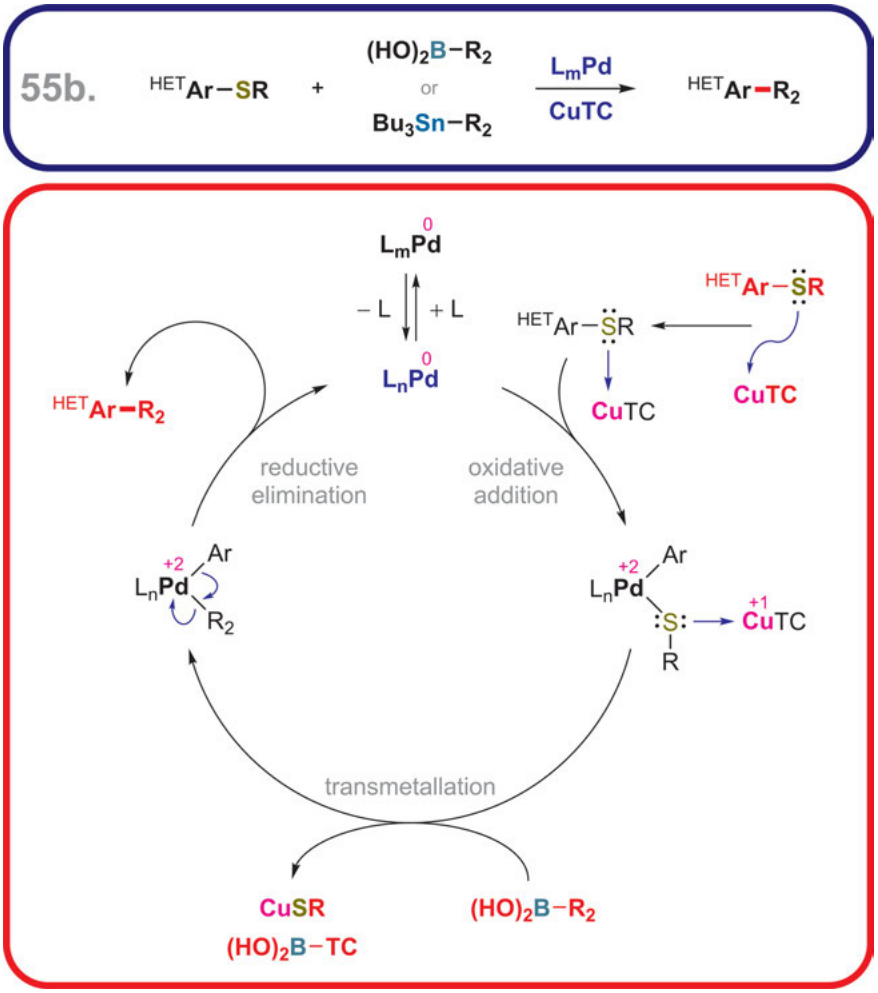

Fig. 55.2: The ***Liebeskind–Srogl*** *cross coupling* (thioethers) mechanism.[172]

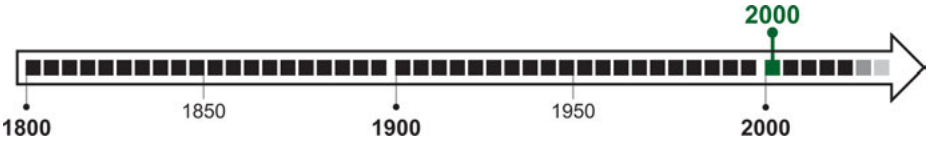

Fig. 55.3: The discovery of the ***Liebeskind–Srogl*** *cross coupling*.[173]

172 The ***Liebeskind–Srogl*** *cross coupling* of *thioethers* is a variation (C–C bond formation using *thioethers (ArSR)* and *boronic acids* or *organotin reagents = organostannanes*). For teaching purposes, only a simplified general mechanism is shown.

173 The reaction was likely first described around 2000 [55].

56 Mannich Reaction

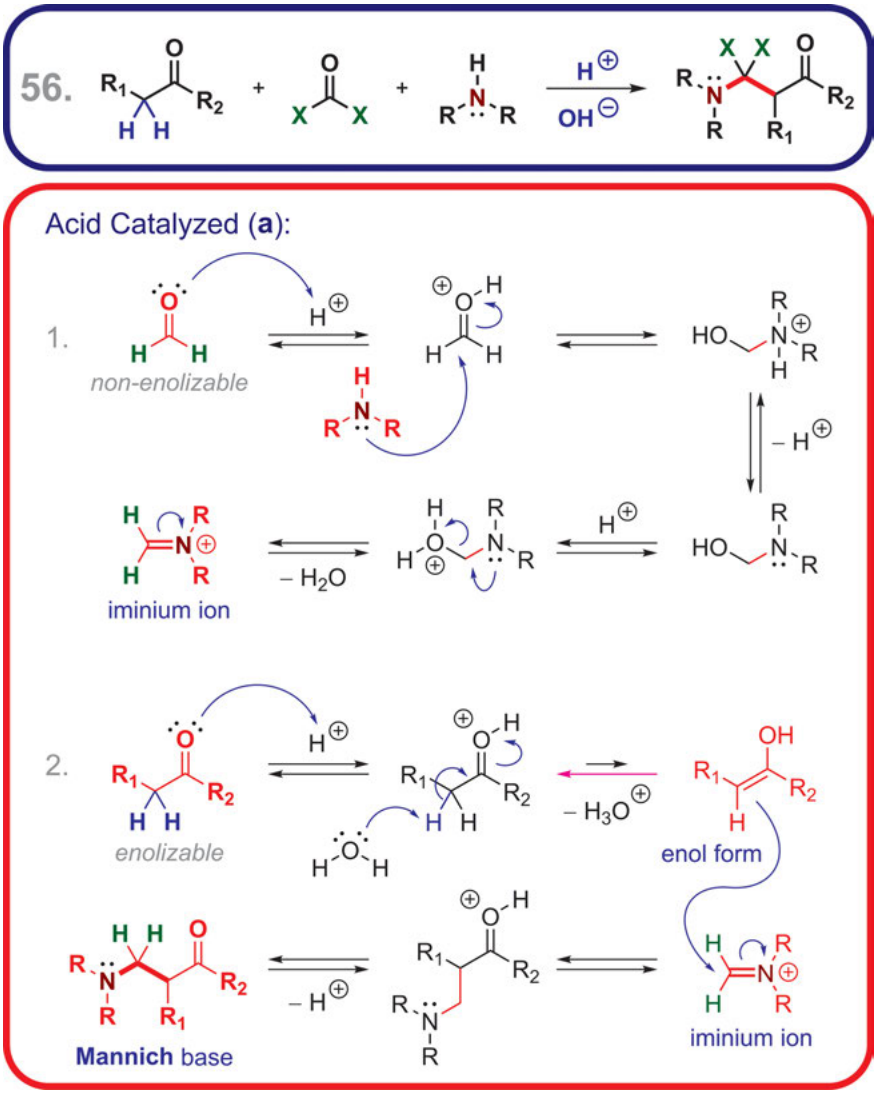

Fig. 56.1: The ***Mannich*** *reaction* mechanism (acid catalyzed).[174]

174 The ***Mannich*** *reaction* is also known as *the* ***Mannich*** *condensation.* This three-component reaction (3-CR) can be catalyzed in (a) acidic media (via an *iminium ion* intermediate). The final product (β–amino carbonyl) is also called a ***Mannich*** *base.*

https://doi.org/10.1515/9783110608373-056

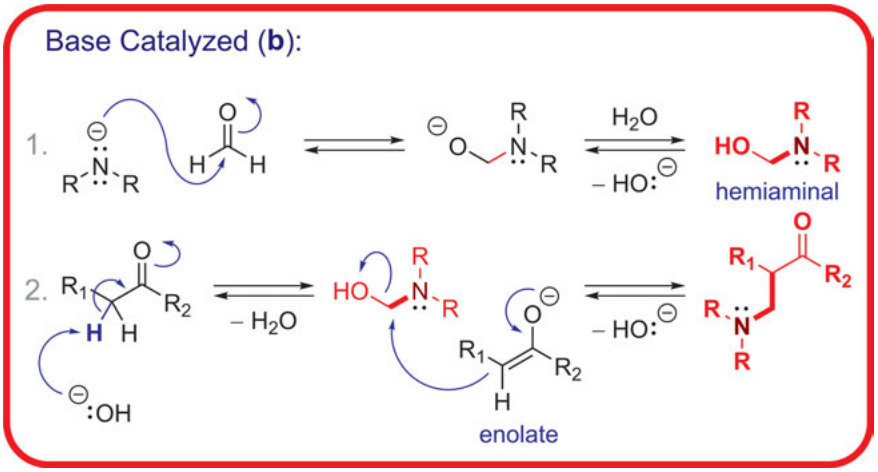

Fig. 56.2: The ***Mannich*** *reaction* mechanism (base catalyzed).[175]

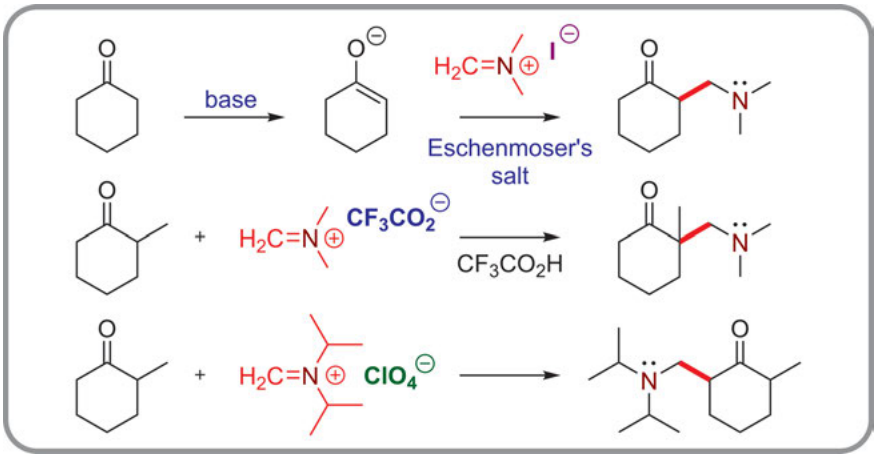

Fig. 56.3: Variations of the ***Mannich*** *reaction*.[176]

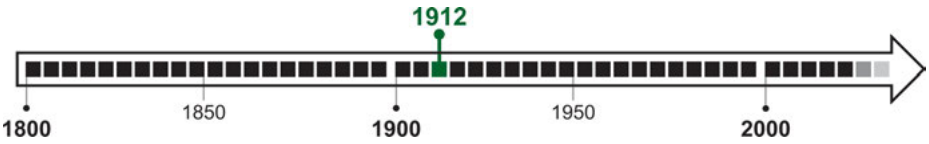

Fig. 56.4: The discovery of the ***Mannich*** *reaction*.[177]

175 The ***Mannich*** *reaction* can be also catalyzed in (b) basic media (via a *hemiaminal* intermediate).
176 There are several iterations of the ***Mannich*** *reaction* based on availability of the preformed iminium ions: ***Eschenmoser's*** *salts* or ***Böhme's*** *salts* (not shown here) [56a].
177 The reaction was likely first described around 1912 [56b].

57 McMurry Coupling

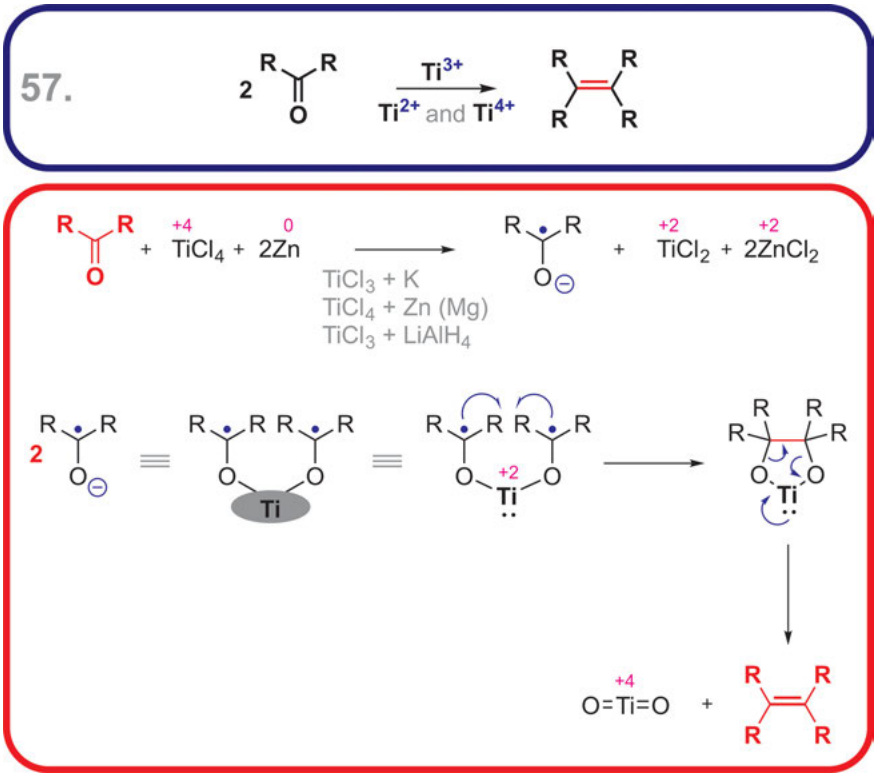

Fig. 57.1: The ***McMurry*** *coupling* mechanism.[178]

178 The ***McMurry*** *coupling* or the ***McMurry*** *reaction* mechanism is not fully understood. It is believed the *low-valent titanium* species play a major role: Ti (0) + Ti (II) + Ti (III).

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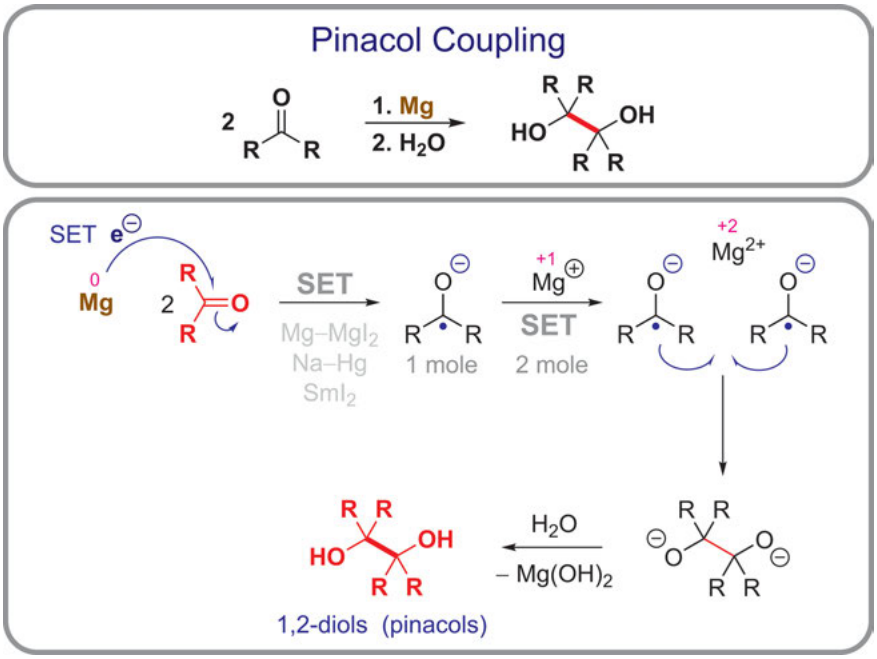

Fig. 57.2: The *pinacol coupling* mechanism.[179]

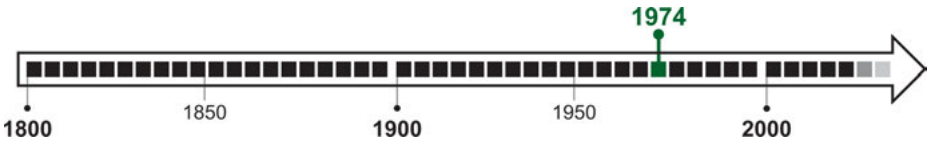

Fig. 57.3: The discovery of the ***McMurry*** *coupling*.[180]

179 The *pinacol coupling* undergoes a **single electron transfer** (SET) mechanism [57a, 57b]. This reaction is related to the ***McMurry*** *coupling* and the *acyloin condensation* (covered in Chapter 7). Please do not confuse the *pinacol coupling* with the *pinacol-pinacolone rearrangement* covered in Chapter 76.
180 The reaction was likely first described around 1974 [57c].

58 Meerwein–Ponndorf–Verley Reduction

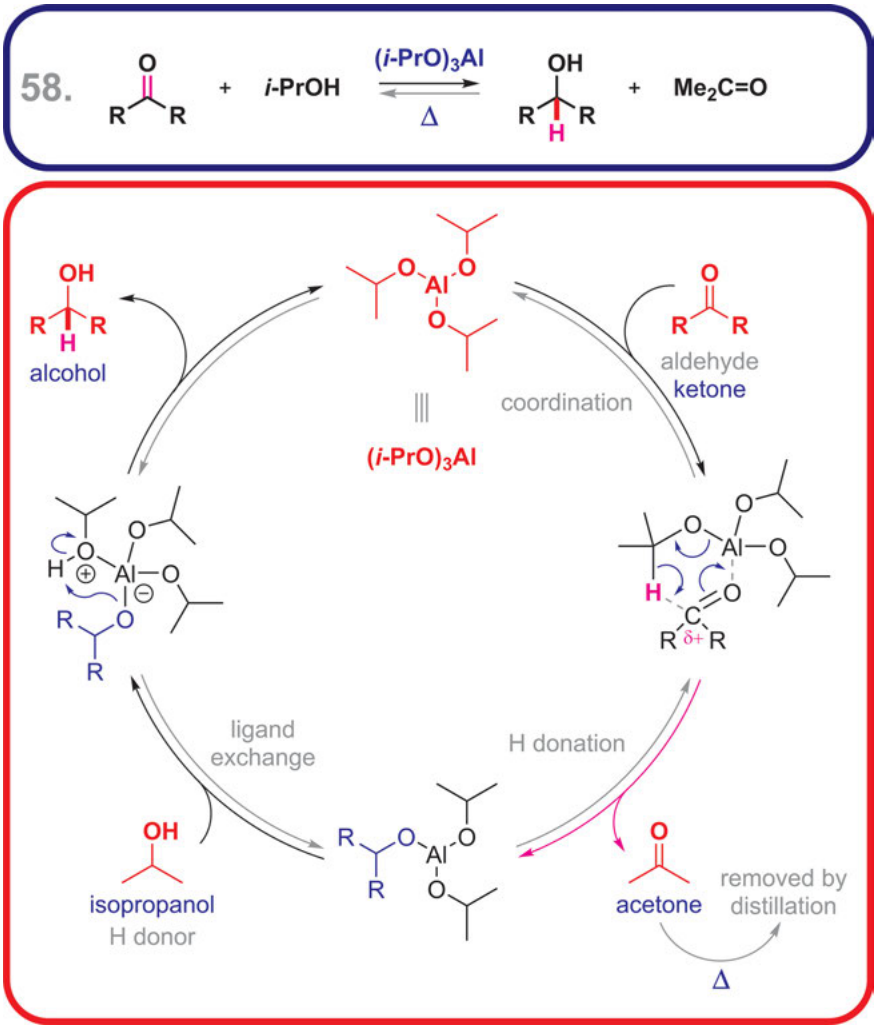

Fig. 58.1: The ***Meerwein–Ponndorf–Verley*** *reaction* mechanism.[181]

181 The ***Meerwein–Ponndorf–Verley*** *(MPV) reduction* is reversible. The reversed oxidation is called the ***Oppenauer*** *oxidation*. The equilibrium can be shifted towards reduction by removing formed *acetone* from the reaction mixture (via distillation).

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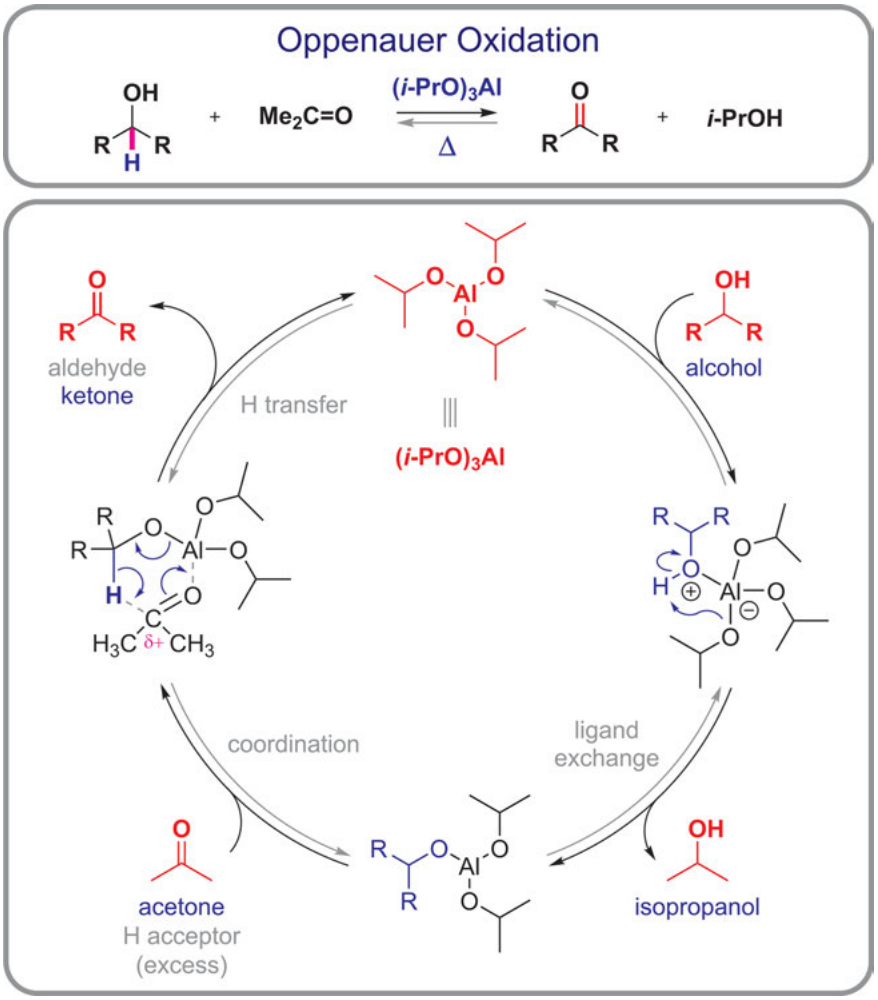

Fig. 58.2: The ***Oppenauer*** *oxidation* mechanism.[182]

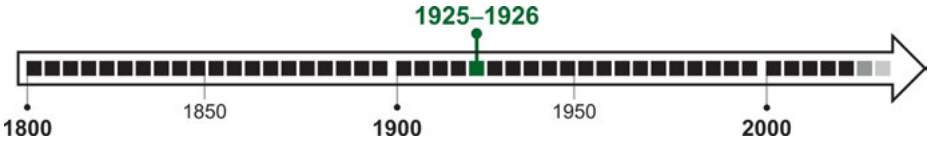

Fig. 58.3: The discovery of the ***Meerwein–Ponndorf–Verley*** *reaction*.[183]

182 The ***Oppenauer*** *oxidation* is a reversed process of the ***MPV*** *reduction* (see Chapter 69).
183 The reaction was likely first described around 1925 by Meerwein and Verley [58a, 58b], and then in 1926 by Ponndorf [58c].

59 Michael Addition

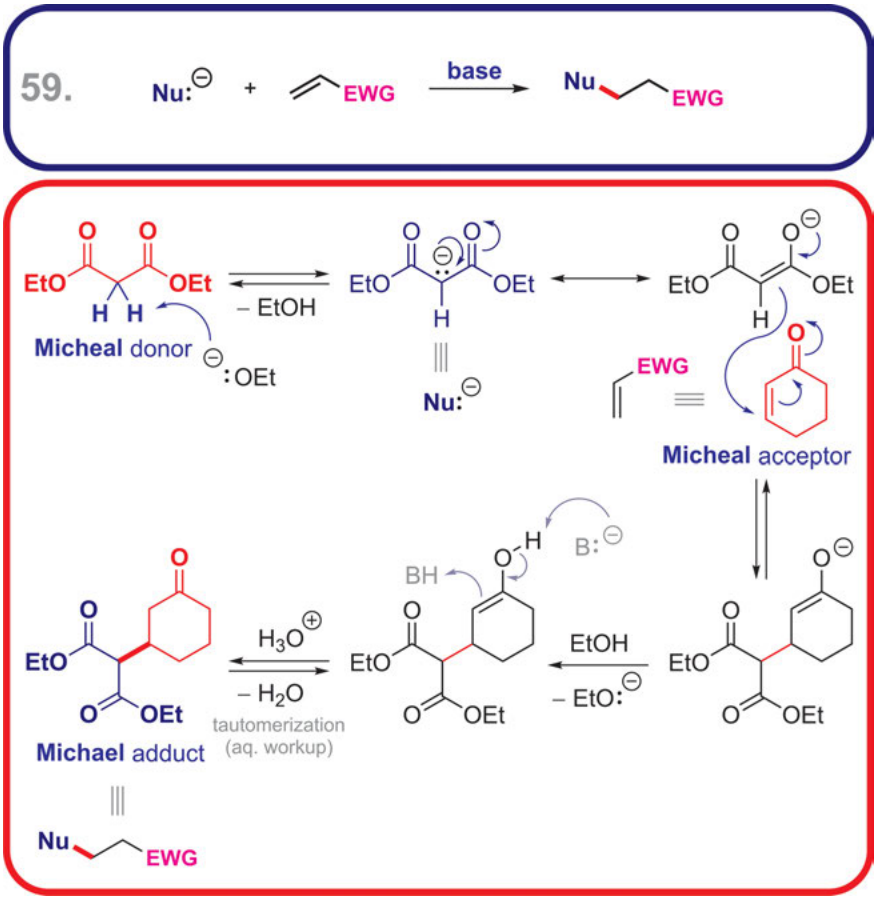

Fig. 59.1: The ***Michael*** *addition* mechanism.[184]

184 The ***Michael*** *addition* or the ***Michael*** *conjugate addition* is also simply called *the* ***Michael*** *reaction*. The products are known as ***Michael*** *adducts*. It is one of the most important reactions in organic chemistry.

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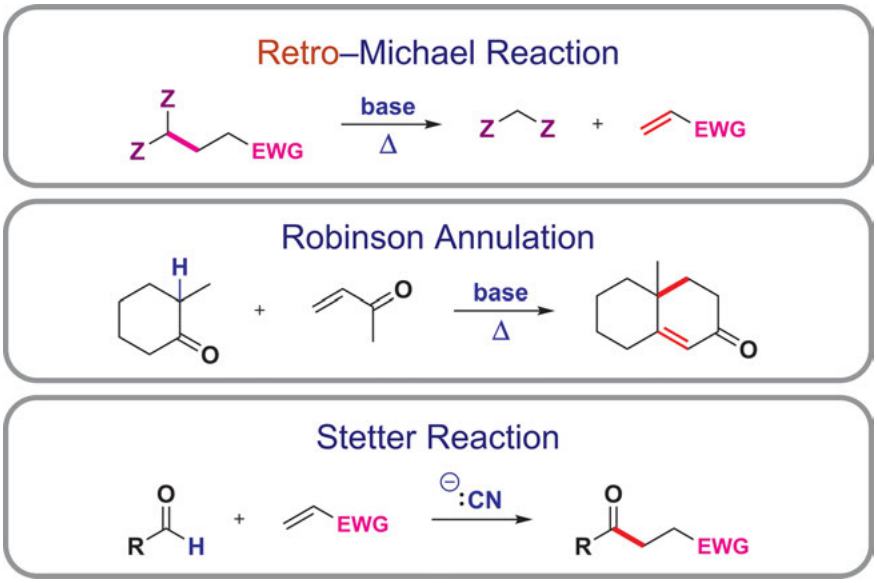

Fig. 59.2: Reactions related to the ***Michael*** *addition*.[185]

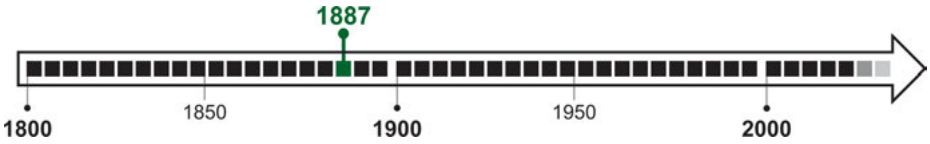

Fig. 59.3: The discovery of the ***Michael*** *addition*.[186]

185 There are variations of this reaction; for example, the *retro-**Michael** addition* and the ***Robinson*** *annulation* (covered in Chapter 83). Please note, the mechanism of the ***Stetter*** *reaction* (not shown) [59a] is related to both the ***Michael*** *addition* and to the *benzoin condensation* (covered in Chapter 15).
186 The reaction was likely first described around 1887 [59b].

60 Minisci Reaction

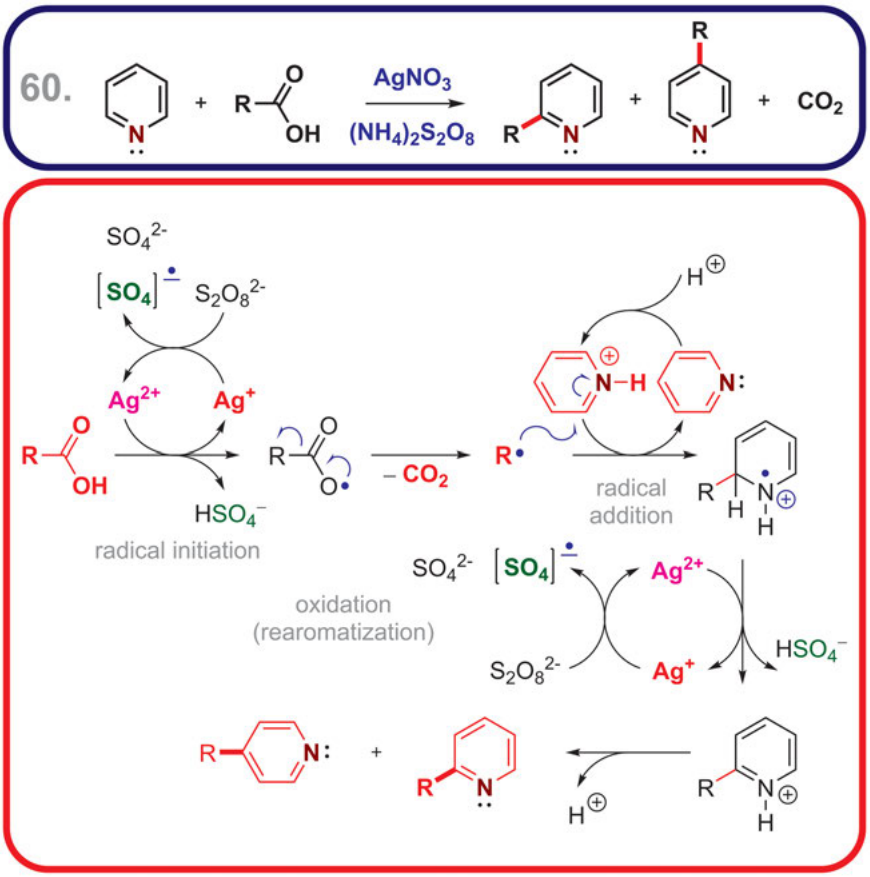

Fig. 60.1: The ***Minisci*** *reaction* mechanism.[187]

187 The ***Minisci*** *reaction* is a type of **free radical substitution** (not covered in this book). The closely related mechanistic examples are the $\mathbf{S_{RN}1}$ mechanism (covered in Chapter 5), the ***Barton*** *decarboxylation* (covered in Chapter 12), and the ***Wohl–Ziegler*** *reaction* (covered in Chapter 99).

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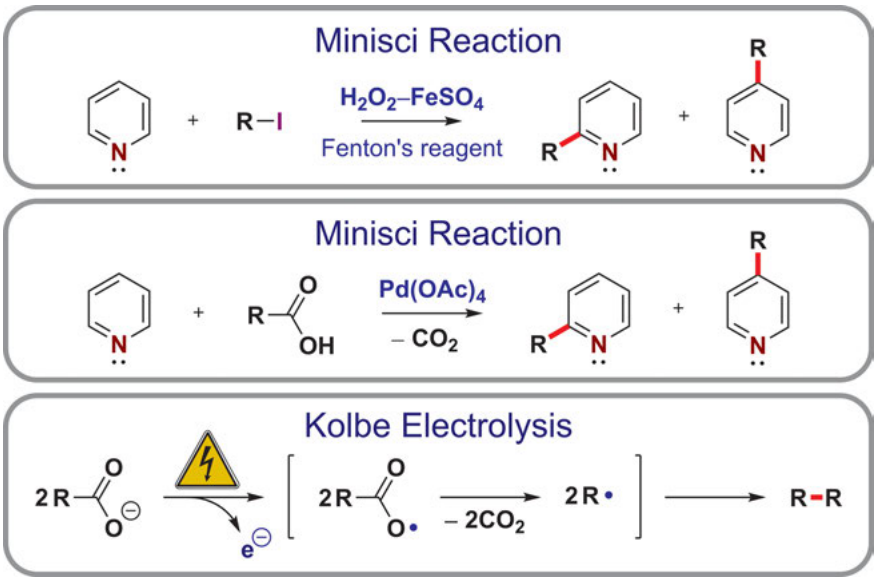

Fig. 60.2: Variations of the ***Minisci*** *reaction*.[188]

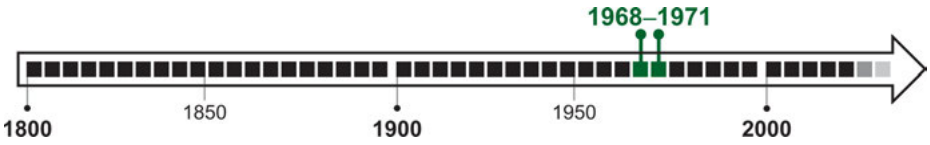

Fig. 60.3: The discovery of the ***Minisci*** *reaction*.[189]

188 There are several variations of the ***Minisci*** *reaction* depending on the free radical sources: ***Fenton's*** *reagent* [60a] and alkyl iodides; lead (IV) acetate [60b] and carboxylic acids. The ***Kolbe*** *electrolysis* or the ***Kolbe*** *reaction* is also related [60c].

189 The reaction was likely first described between 1968–1971 [60d, 60e].

61 Mitsunobu Reaction

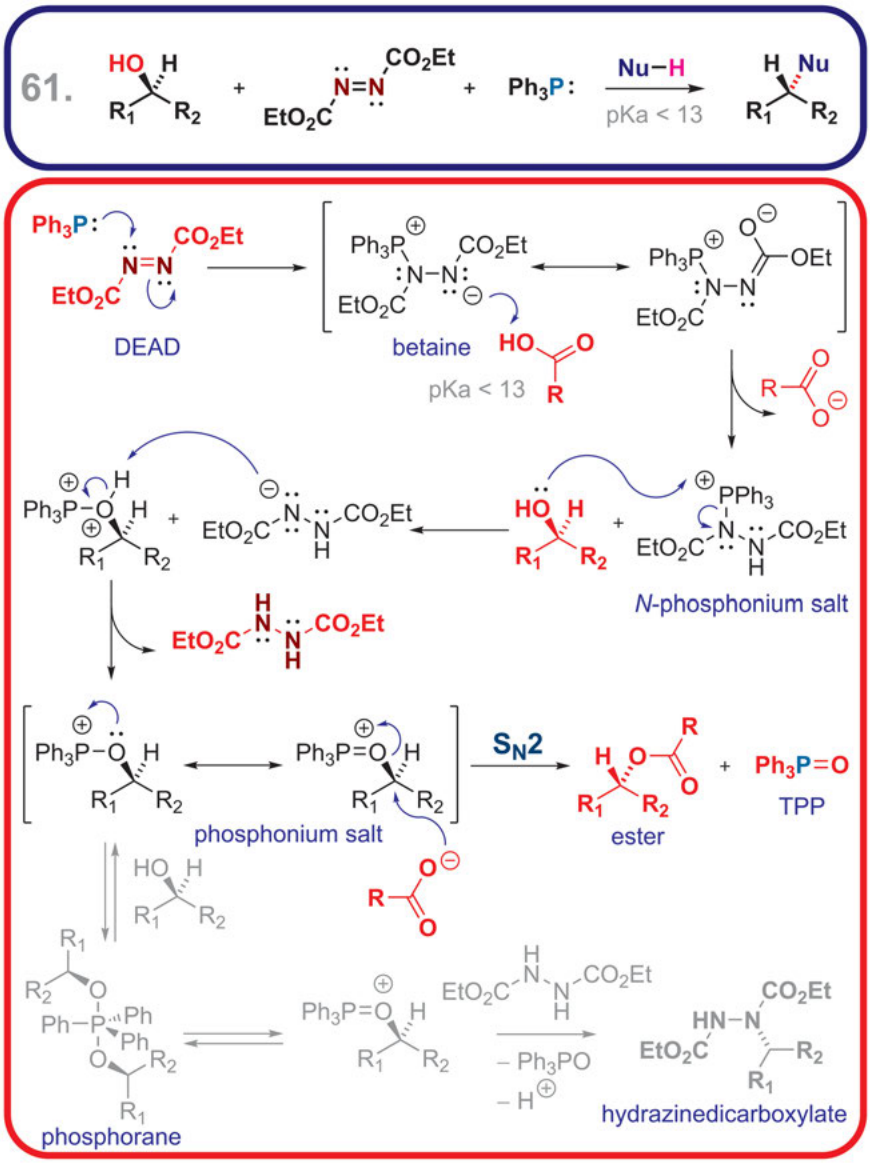

Fig. 61.1: The ***Mitsunobu*** *reaction* mechanism.[190]

190 The ***Mitsunobu*** *reaction* mechanism is complicated but related to the (aliphatic) **nucleophilic substitution** (S_N2) covered in Chapter 2. Note, the pK_a of the NuH acid should be generally < 13 [61a].

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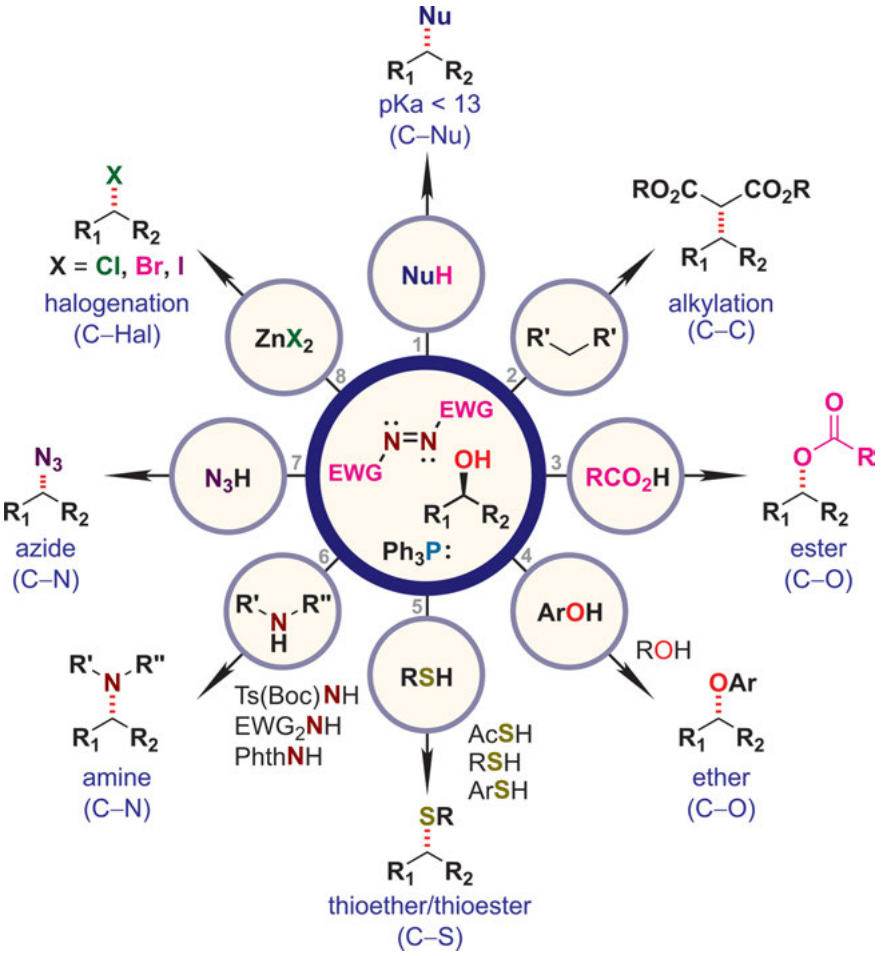

Fig. 61.2: Synthetic versatility of the ***Mitsunobu*** *reaction*.[191]

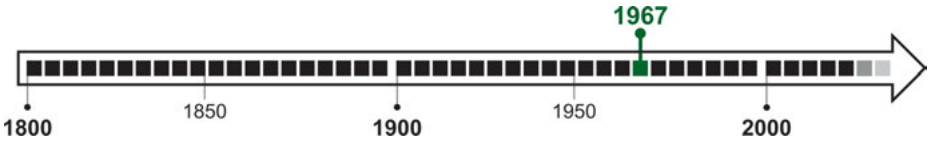

Fig. 61.3: The discovery of the ***Mitsunobu*** *reaction*.[192]

191 The ***Mitsunobu*** *reaction* has wide synthetic application and can convert alcohols into various products using different nucleophiles (Nu): 1. R–Nu, $pK_a < 13$; 2. alkylated products C–C; 3. esters C–O; 4. ethers C–O; 5. thioethers or thioesters C–S; 6. amines C–N; 7. azides C–N; 8. alkyl halides C–X; and others [61b, 61c].

192 The reaction was likely first described around 1967 [61d, 61e].

62 Miyaura Borylation

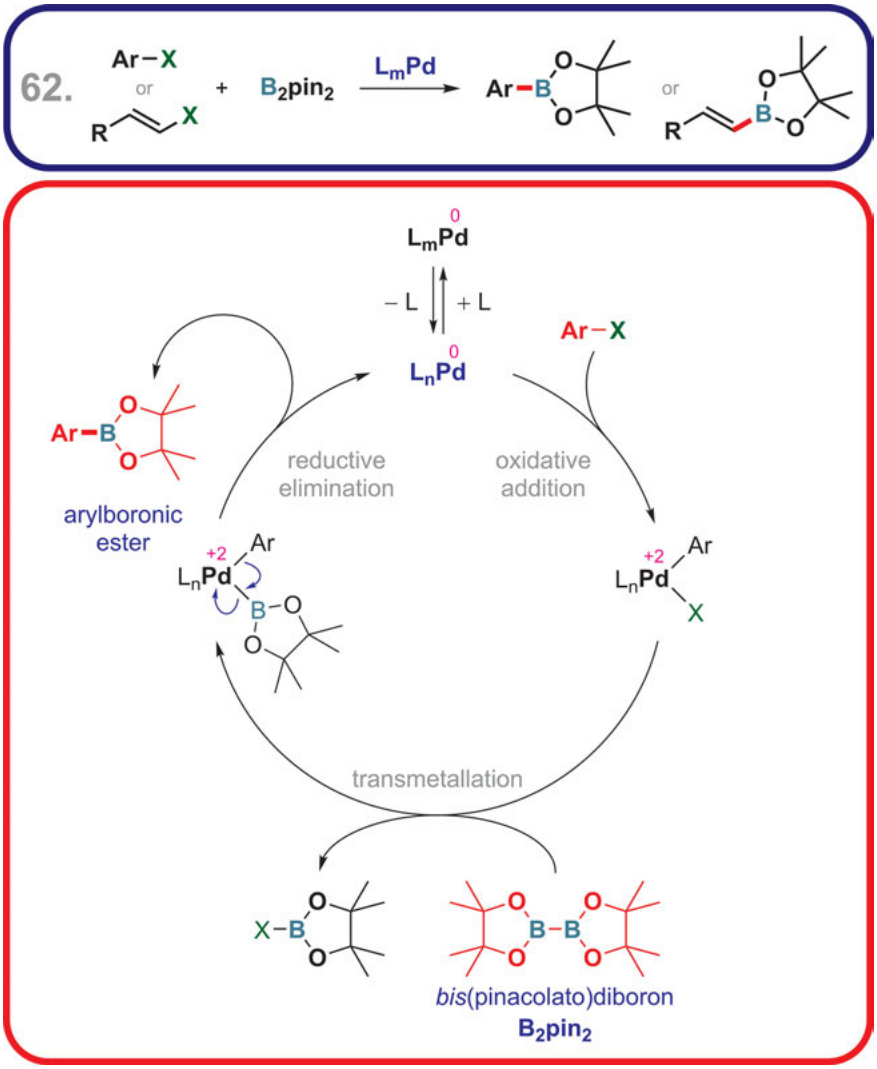

Fig. 62.1: The ***Miyaura*** *borylation* mechanism.[193]

193 The ***Miyaura*** *borylation* is a type of **Pd**-*catalyzed cross coupling* reaction (C–B bond formation using *aryl halides* and *bis(pinacolato)diboron* or $\mathbf{B_2pin_2}$ [62a]). For teaching purposes, a simplified and general mechanism is shown. The synthesized *boronic esters* (and their related *boronic acids*) are one of the most important reagents in synthetic organic and medicinal chemistry.

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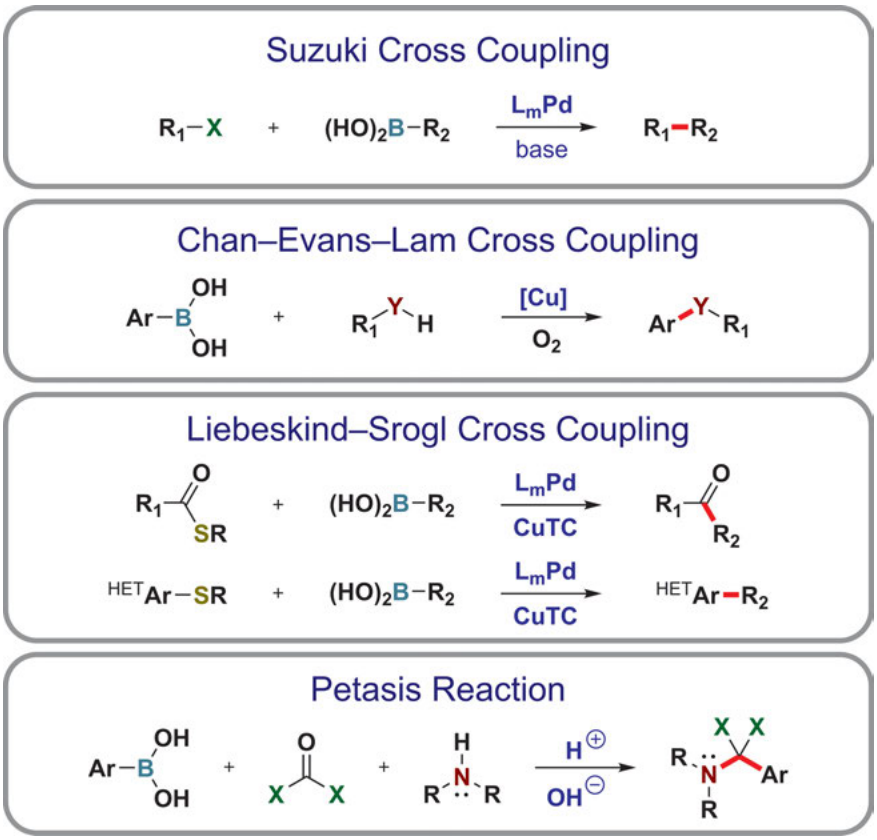

Fig. 62.2: Synthetic application of boronic esters and acids.[194]

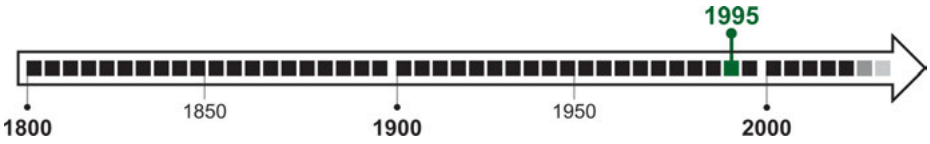

Fig. 62.3: The discovery of the ***Miyaura*** *borylation*.[195]

194 Many *key cross-coupling* reactions utilize *boronic esters* (and their related *boronic acids*): the ***Suzuki*** *cross coupling* (covered in Chapter 89), the ***Chan–Evans–Lam*** *cross coupling* (covered in Chapter 23), ***Liebeskind–Srogl*** *cross coupling* (covered in Chapter 55). The ***Petasis*** *reaction* is a mechanistically different three-component (3-CR) reaction, but it uses boronic acids as well [62b].

195 The reaction was likely first described around 1995 [62c].

63 Mukaiyama RedOx Hydration

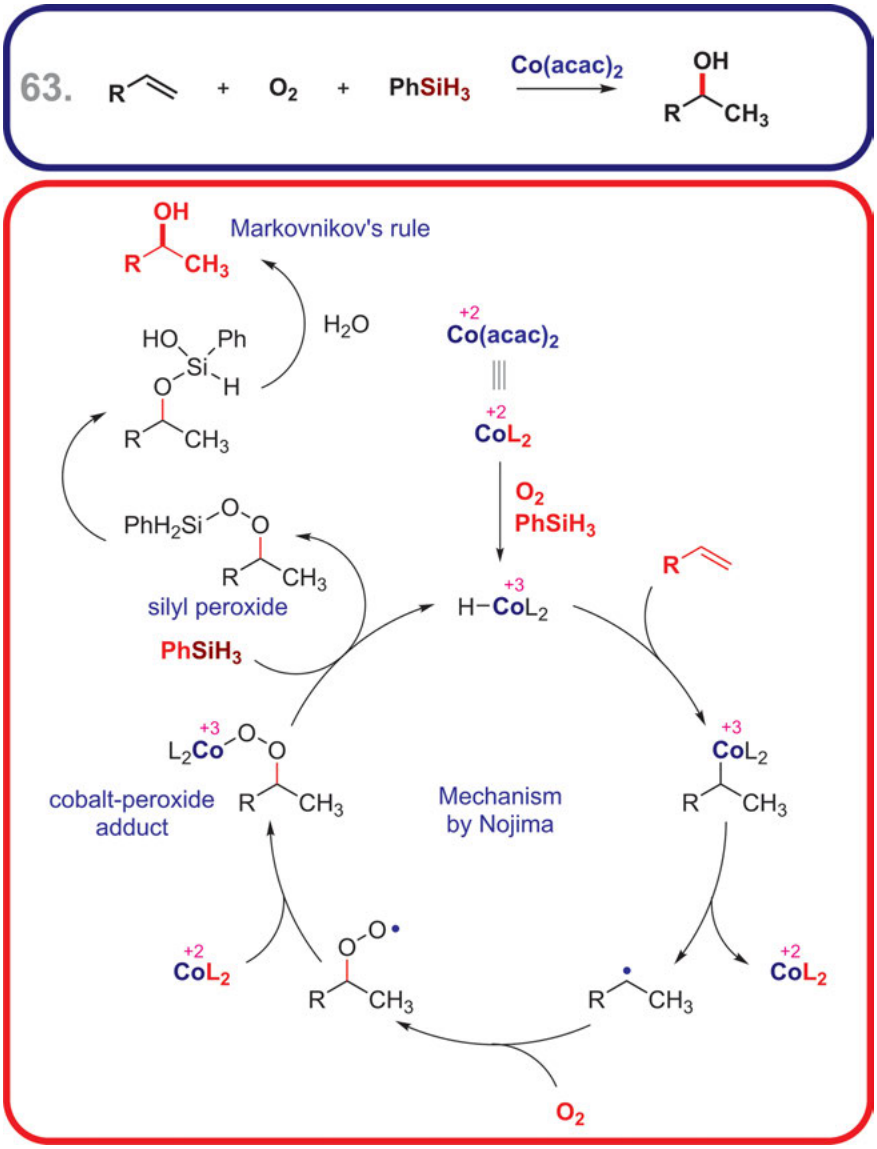

Fig. 63.1: The ***Mukaiyama*** *RedOx hydration* mechanism by **Nojima**.[196]

196 The revised ***Mukaiyama*** *RedOx hydration* mechanism is recently proposed by **Nojima** [63a].

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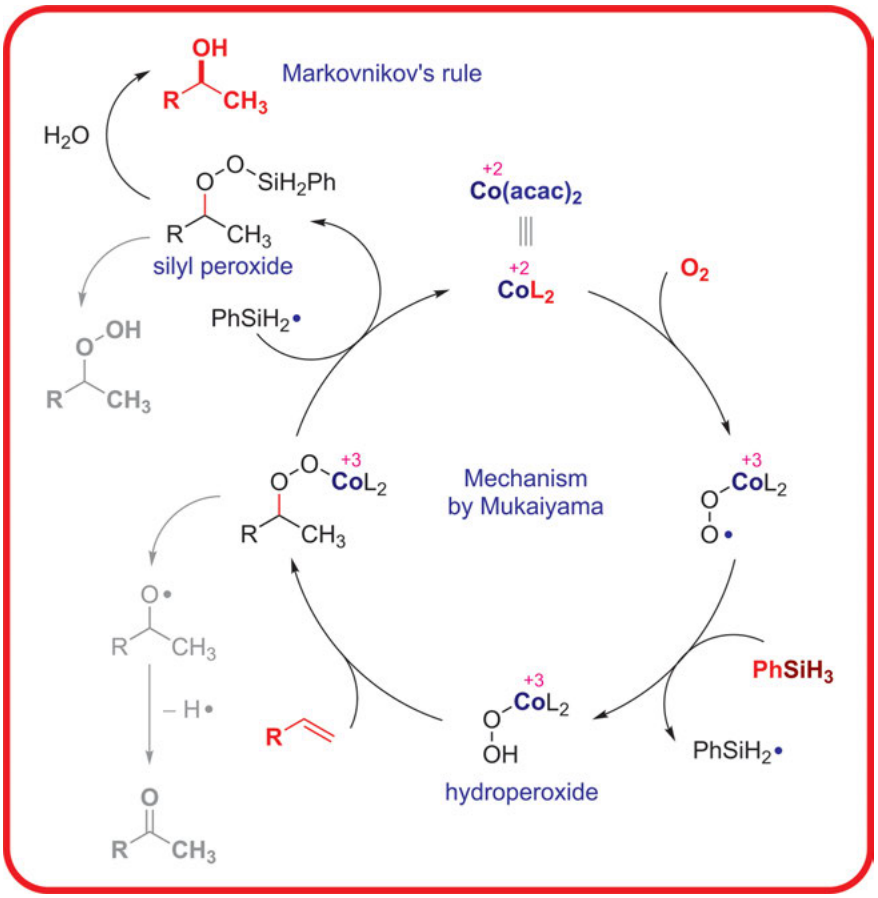

Fig. 63.2: The ***Mukaiyama*** *oxidation-reduction hydration* mechanism by **Mukaiyama**.[197]

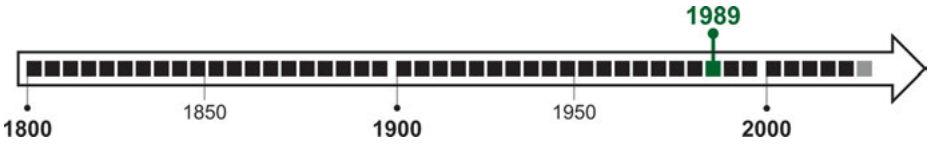

Fig. 63.3: The discovery of the ***Mukaiyama*** *oxidation-reduction hydration*.[198]

197 The original ***Mukaiyama*** *oxidation-reduction hydration* mechanism by **Mukaiyama** [63b, 63c, 63d]. The ***Mukaiyama*** *oxidation-reduction hydration* should not be confused with the ***Mukaiyama*** *aldol addition reaction* (not shown here). The reaction follows *Markovnikov's rule*. The ***Mukaiyama*** *oxidation-reduction hydration* is a safe alternative to the *oxymercuration-reduction reaction* (Chapter 20 and 52).

198 The reaction was likely first described around 1989 [63b, 63c, 63d].

64 Nazarov Cyclization

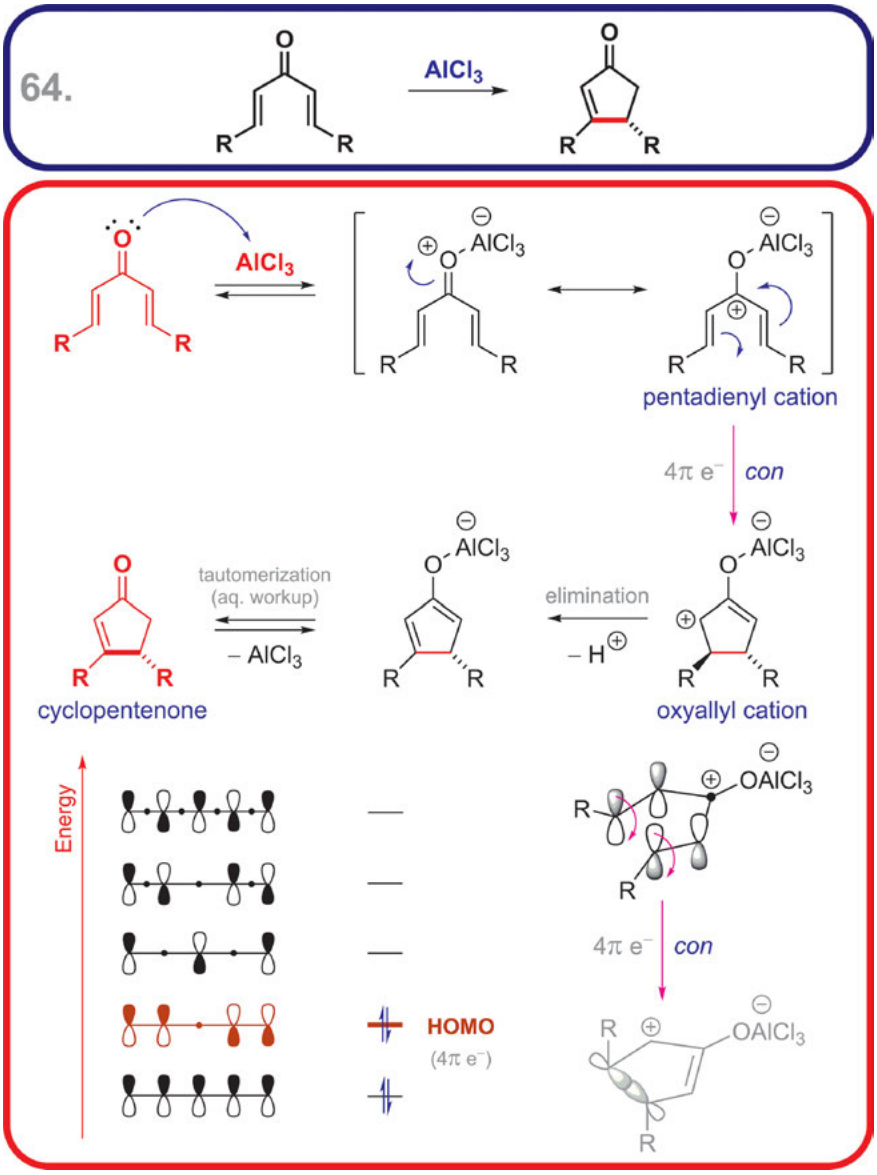

Fig. 64.1: The ***Nazarov*** *cyclization* mechanism.[199]

199 The ***Nazarov*** *cyclization reaction* is a pericyclic reaction with a concerted mechanism. This is an example of a [4π] ***con****rotatory electrocyclization.*

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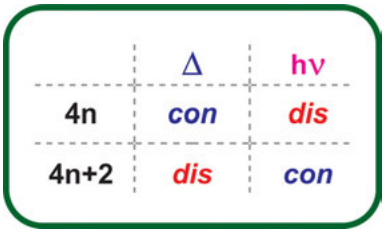

Fig. 64.2: The ***Woodward–Hoffmann*** *rules* (the pericyclic selection rules).[200]

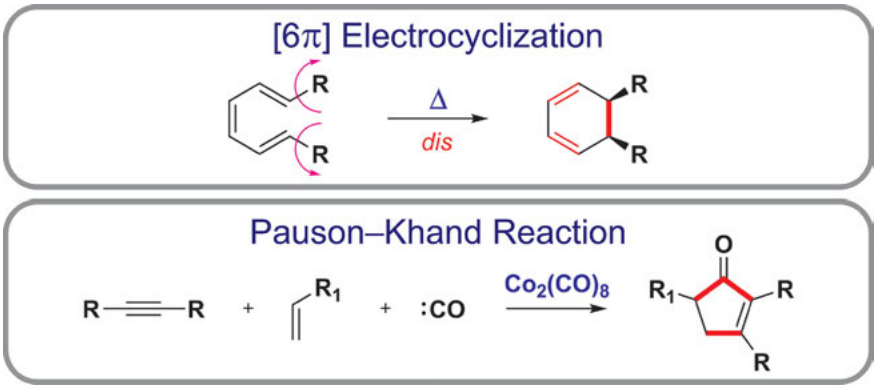

Fig. 64.3: Reactions related to the ***Nazarov*** *cyclization*.[201]

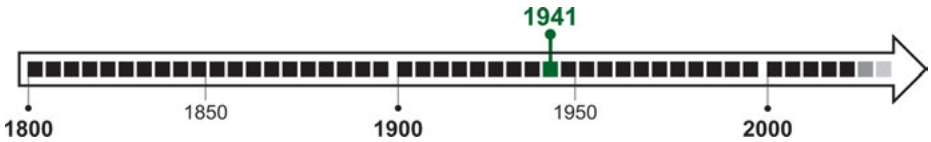

Fig. 64.4: The discovery of the ***Nazarov*** *cyclization*.[202]

200 The ***Woodward–Hoffmann*** *rules* (the pericyclic selection rules) [64a, 64b] for the *electrocyclization reactions*. Please note, the ***Nazarov*** *cyclization* is a ***con****rotatory* process (**4n** = 4π), which is allowed at the ground state = under thermal conditions or control (Δ). An example of [6π] *electrocyclization* below should be a ***dis****rotatory* process (**4n+2** = 6π), which is allowed at the ground state (Δ). The outcome at the excited state = under photochemical conditions or control (hν) should be reverse [64c].

201 There are numerous examples of other [4n] *electrocyclic* and [4n+2] *electrocyclic reactions*. The ***Pauson–Khand*** *reaction* (see Chapter 73) undergoes a different mechanism, but it also yields *cyclopentenones*.

202 The reaction was likely first described around 1941 [64d, 64e], see also [64f, 64g].

65 Nef Reaction

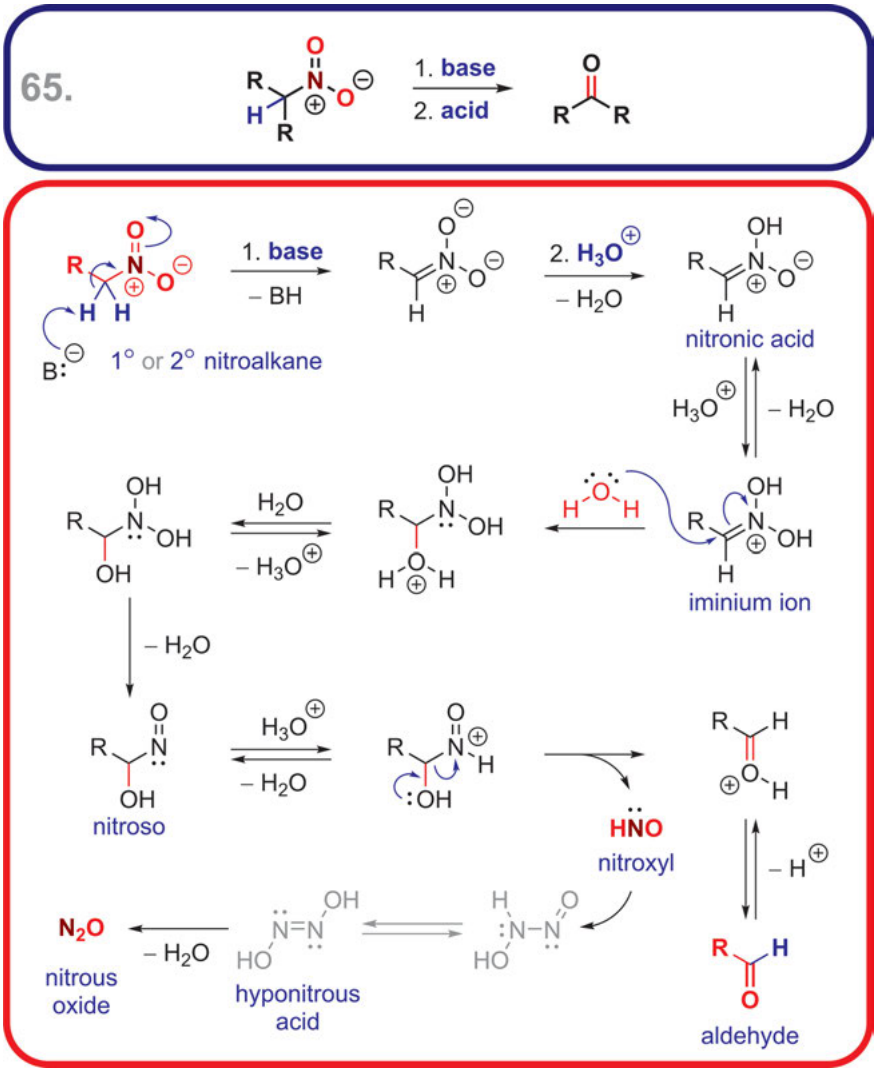

Fig. 65.1: The ***Nef*** *reaction* mechanism (base-acid-catalyzed).[203]

203 The classic ***Nef*** *reaction* is catalyzed by an acid and yields *aldehydes* and *ketones*. A base is needed to convert a primary (1°) or secondary (2°) *nitroalkane* into its conjugate base *(nitronic acid)*. The tertiary (3°) nitroalkanes do not react.

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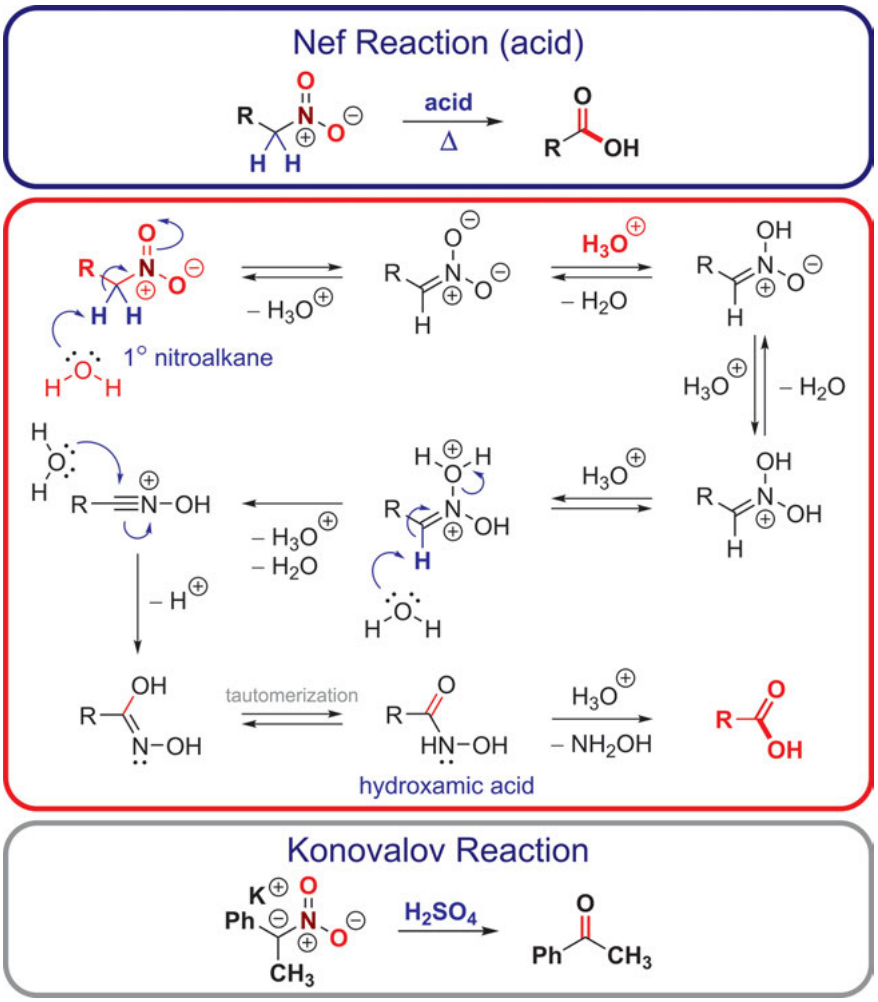

Fig. 65.2: The ***Nef*** *reaction* mechanism (acid-catalyzed).[204]

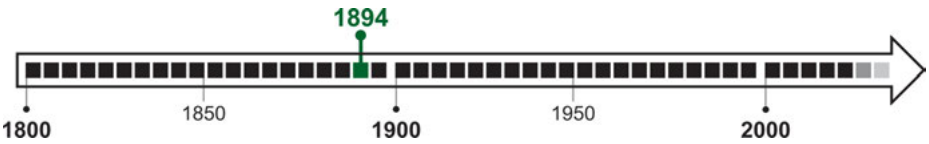

Fig. 65.3: The discovery of the ***Nef*** *reaction*.[205]

204 The mechanism of the ***Nef*** *reaction* can change and go through a *hydroxamic acid* intermediate if a strong acid (exclusively) is used with a primary (1°) *nitroalkane*. In this case, a *carboxylic acid* is formed [1] and [65a]. Please note, the reaction was likely first reported by Konovalov [65b].
205 The reaction was likely first described around 1894 [65c, 65d].

66 Negishi Cross Coupling

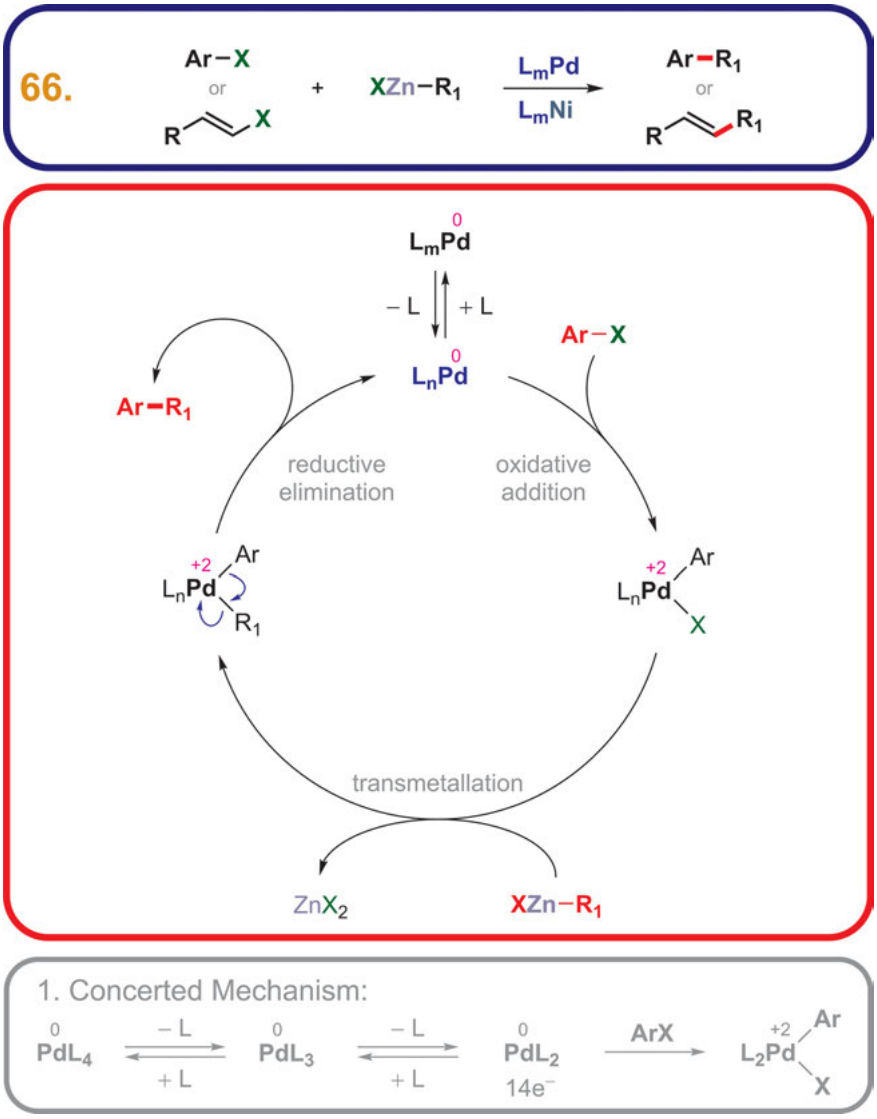

Fig. 66.1: The **Pd**-catalyzed ***Negishi*** *cross coupling* mechanism.[206]

206 The ***Negishi*** *cross coupling* is a type of ***Pd****-catalyzed cross coupling* reaction (C–C bond formation using *aryl halides* and *organozinc compounds*). For teaching purposes, a simplified and general mechanism is shown. Note, (1) *concerted oxidative addition* step to a low-coordinate ($14e^-$) **Pd**-complex is more complicated [2a].

https://doi.org/10.1515/9783110608373-066

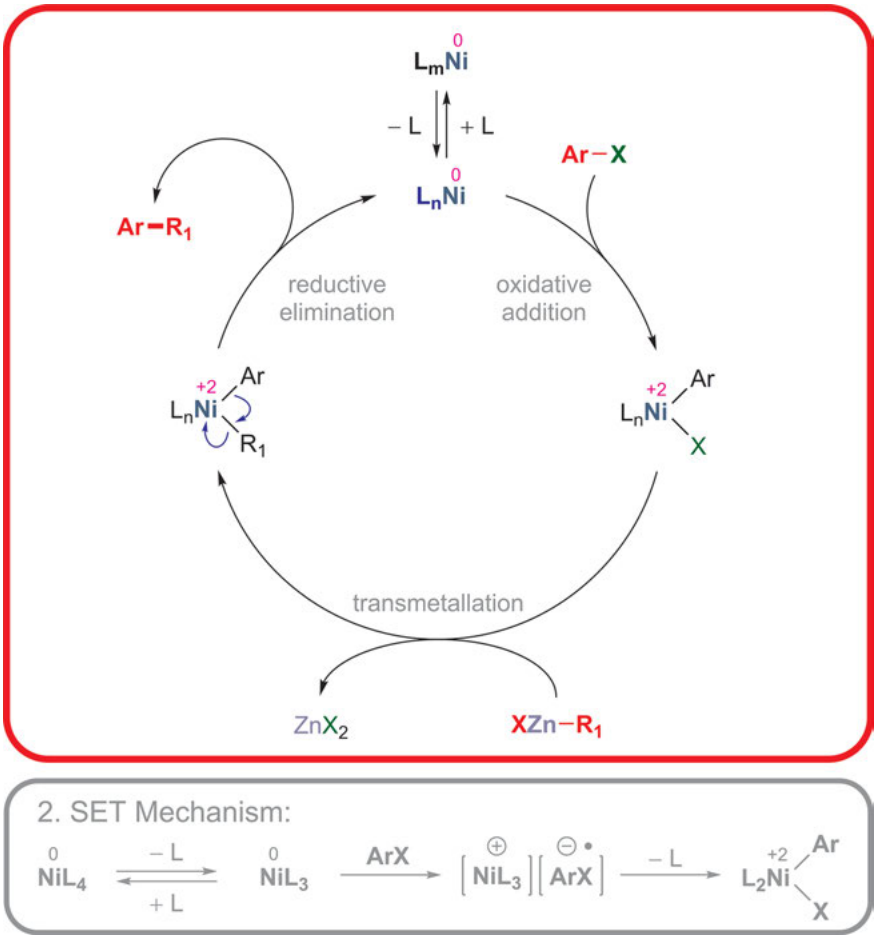

Fig. 66.2: The **Ni**-catalyzed ***Negishi*** *cross coupling* mechanism.[207]

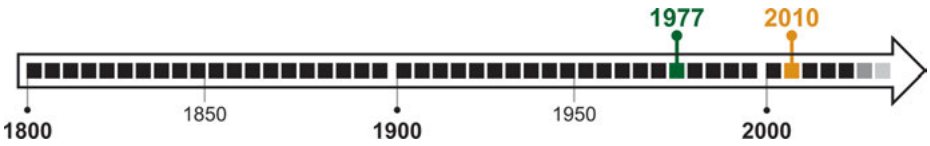

Fig. 66.3: The discovery of the ***Negishi*** *cross coupling*.[208]

207 The ***Negishi*** *cross coupling* can be ***Ni***-*catalyzed*. Note, a possible example of a (2) *SET oxidative addition* step to a **Ni**-complex (not necessarily at play in the example shown) [2a].

208 The reaction was likely first described around 1977 [66]. In **2010**, Ei-ichi Negishi (jointly with Richard F. Heck and Akira Suzuki) received the Nobel Prize in Chemistry for the development of **Pd**-catalyzed cross coupling reactions [46c].

67 Norrish Type I & II Reaction

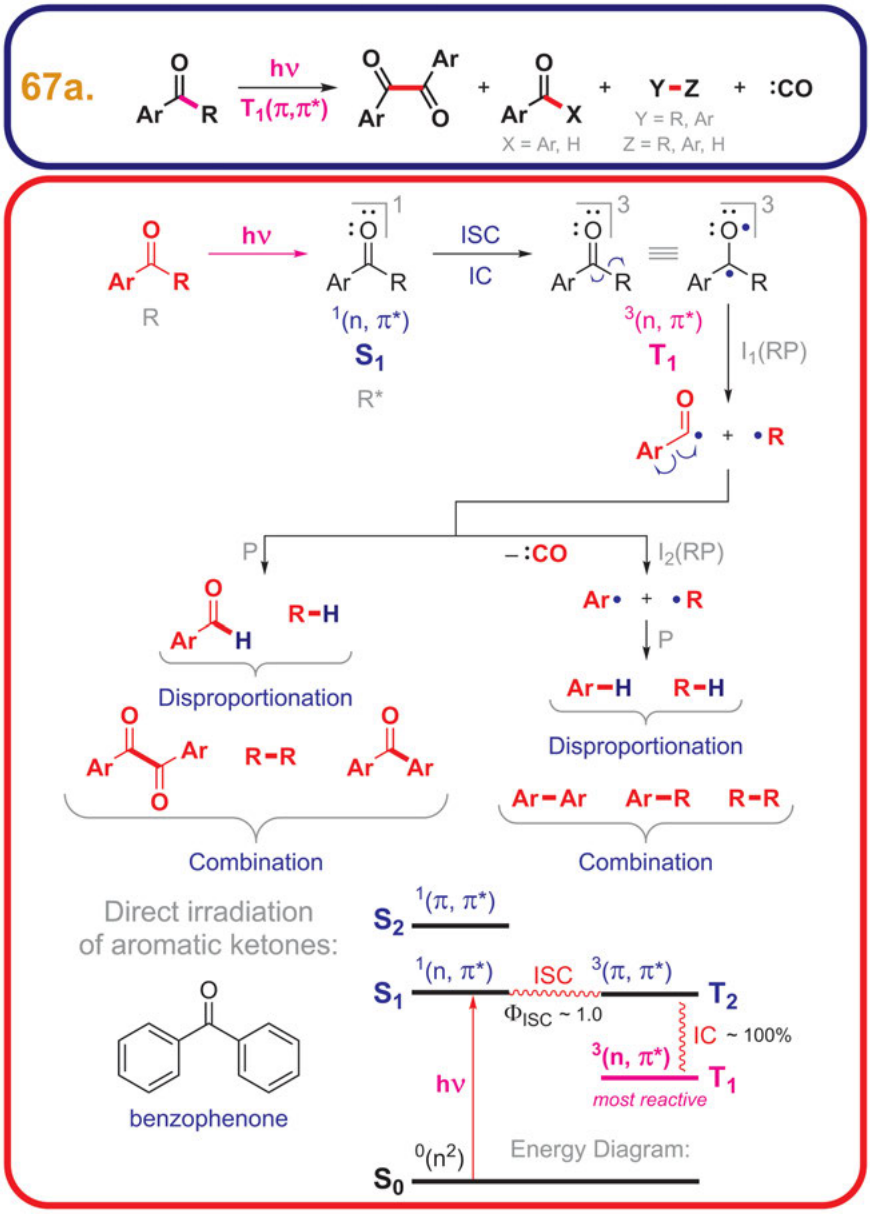

Fig. 67.1: The ***Norrish Type I*** *reaction* mechanism.[209]

209 The ***Norrish Type I*** *reaction* is a photochemical decomposition (**α–cleavage**) of *aldehydes* and

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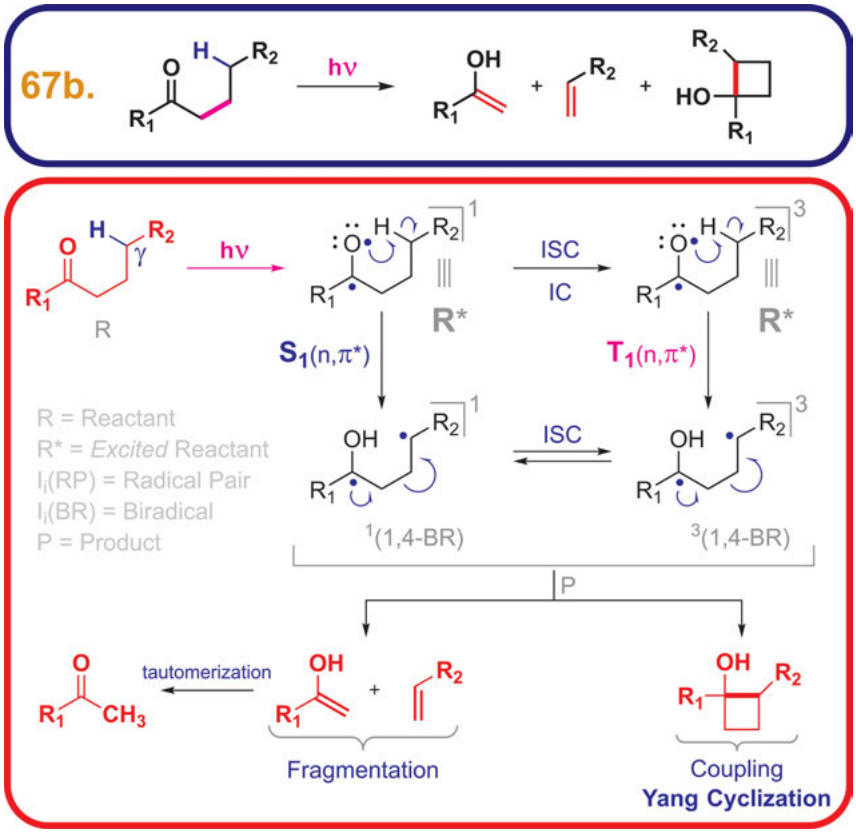

Fig. 67.2: The ***Norrish Type II*** *reaction* mechanism.[210]

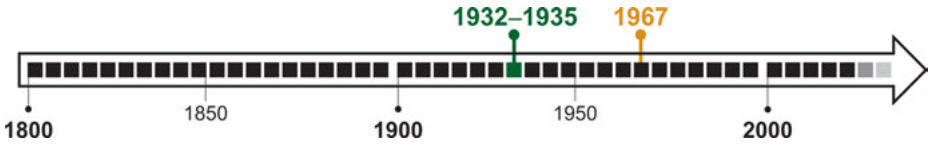

Fig. 67.3: The discovery of the ***Norrish*** *fragmentation*.[211]

ketones. The products may be formed because of initial *fragmentation* and subsequent *disproportionation* or *(re)combination* of formed radical species. Upon *direct irradiation* of aromatic ketones (i.e., benzophenone) the reaction usually occurs from the triplet excited state $\mathbf{T_1 = {}^3(n, \pi^*)}$ [2b].

210 The ***Norrish Type II*** *reaction* is a photochemical intramolecular **γ–H abstraction**. The products may be formed due to *fragmentation*, *(re)combination* or the ***Yang*** *cyclization* of 1,4-biradicals. The reaction may occur from the singlet $\mathbf{S_1 = {}^1(n, \pi^*)}$ or triplet excited state $\mathbf{T_1 = {}^3(n, \pi^*)}$ [2b].

211 The **Type I** and **II** reactions were likely first described between 1932–1935 [67a, 67b, 67c, 67d] or possibly earlier, see also [67e, 67f]. In **1967**, Ronald George Wreyford Norrish (jointly with Manfred Eigen and George Porter) received the Nobel Prize in Chemistry [67g].

68 Olefin (Alkene) Metathesis

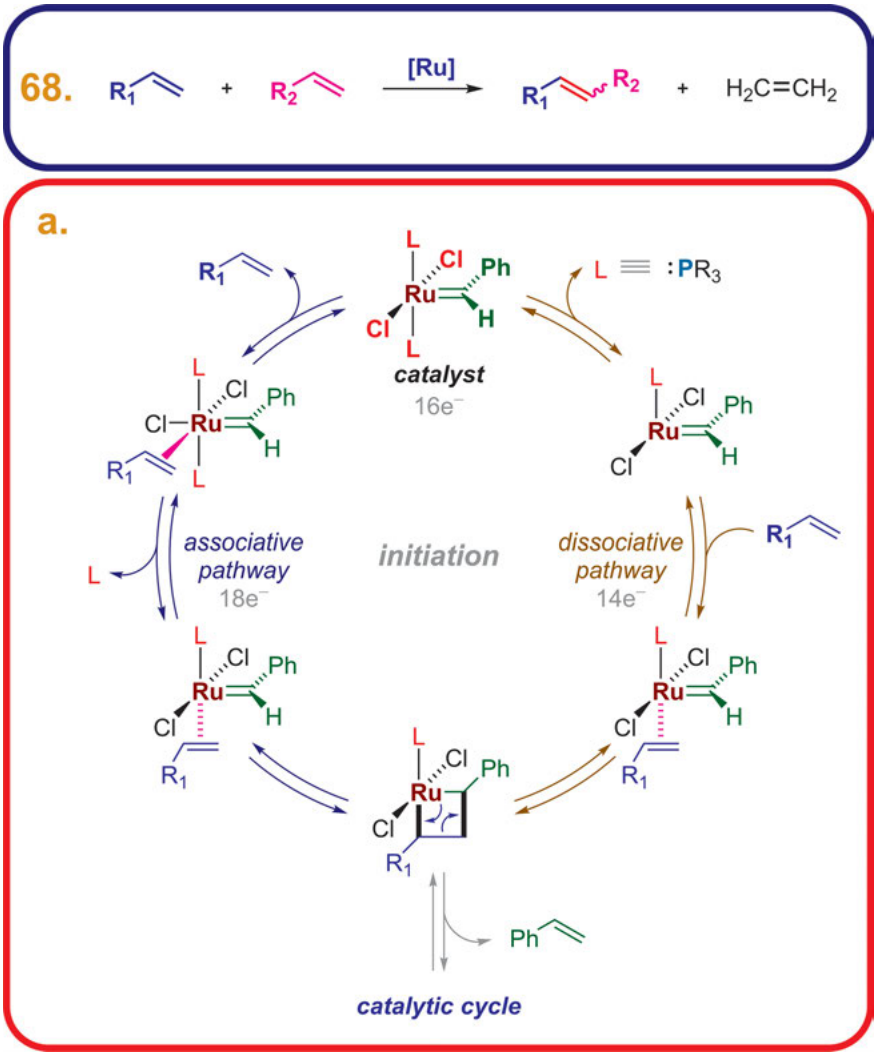

Fig. 68.1: The *olefin (alkene) metathesis* mechanism (initiation).[212]

212 The ***Ru**-catalyzed olefin (alkene) metathesis* mechanism starts with the stable *catalyst (16e⁻) initiation cycle (**a**)*: theoretically it can go either via a dissociative pathway (14e⁻), or an associative pathway (18e⁻), an interchange pathway is not shown here [68a].

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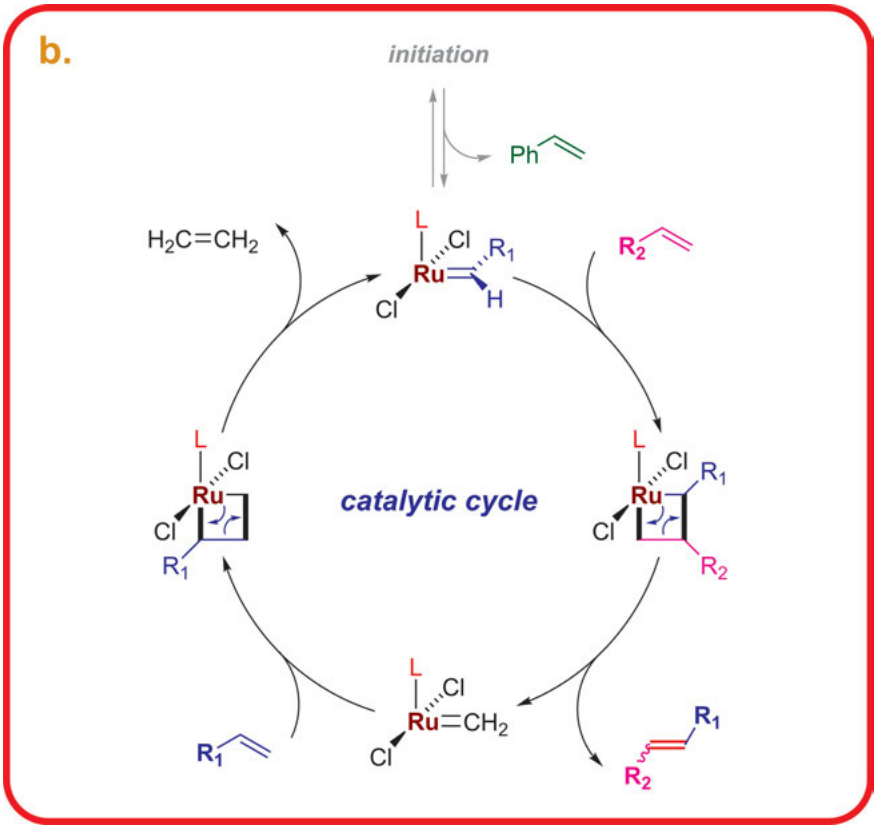

Fig. 68.2: The *olefin (alkene) metathesis* mechanism (catalytic cycle).[213]

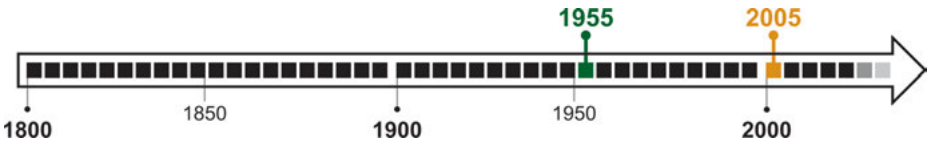

Fig. 68.3: The discovery of the *olefin metathesis*.[214]

213 After the loss of *styrene*, the *main catalytic cycle* (***b***) continues with the "active" catalyst. Please note, the mechanism is rather complex and varies significantly depending on the substrate and catalyst. For teaching purposes, a simplified and general example is shown.

214 The reaction was likely first described around 1955 [68b, 68c]. In **2005**, Yves Chauvin, Robert H. Grubbs and Richard R. Schrock received the Nobel Prize in Chemistry for the development of the *metathesis* transformations [68d].

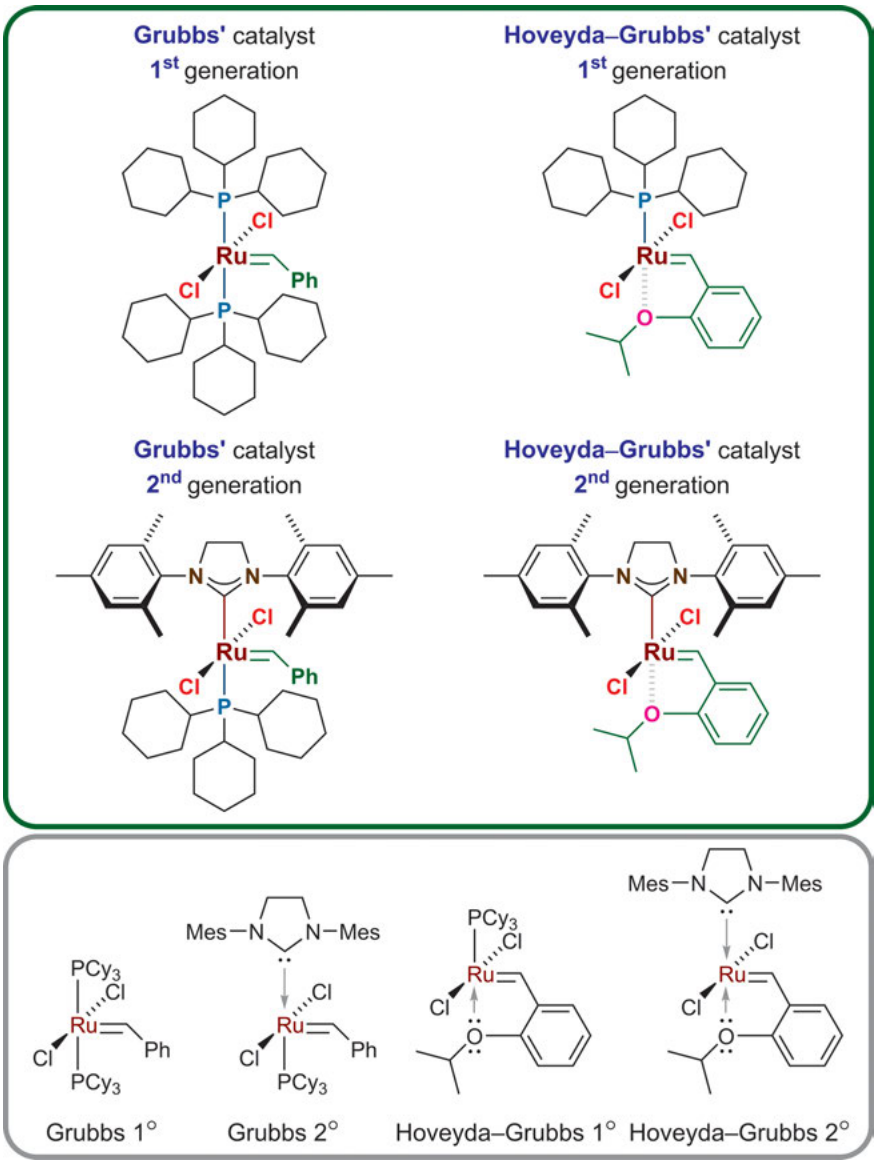

Fig. 68.4: The main *olefin (alkene) metathesis* catalysts.[215]

215 The most common catalysts used in the ***Ru**-catalyzed olefin (alkene) metathesis* are ***Grubbs'** catalysts* (1st and 2nd generation) [68e, 68f] and ***Hoveyda–Grubbs'** catalysts* (1st and 2nd generation) [68g].

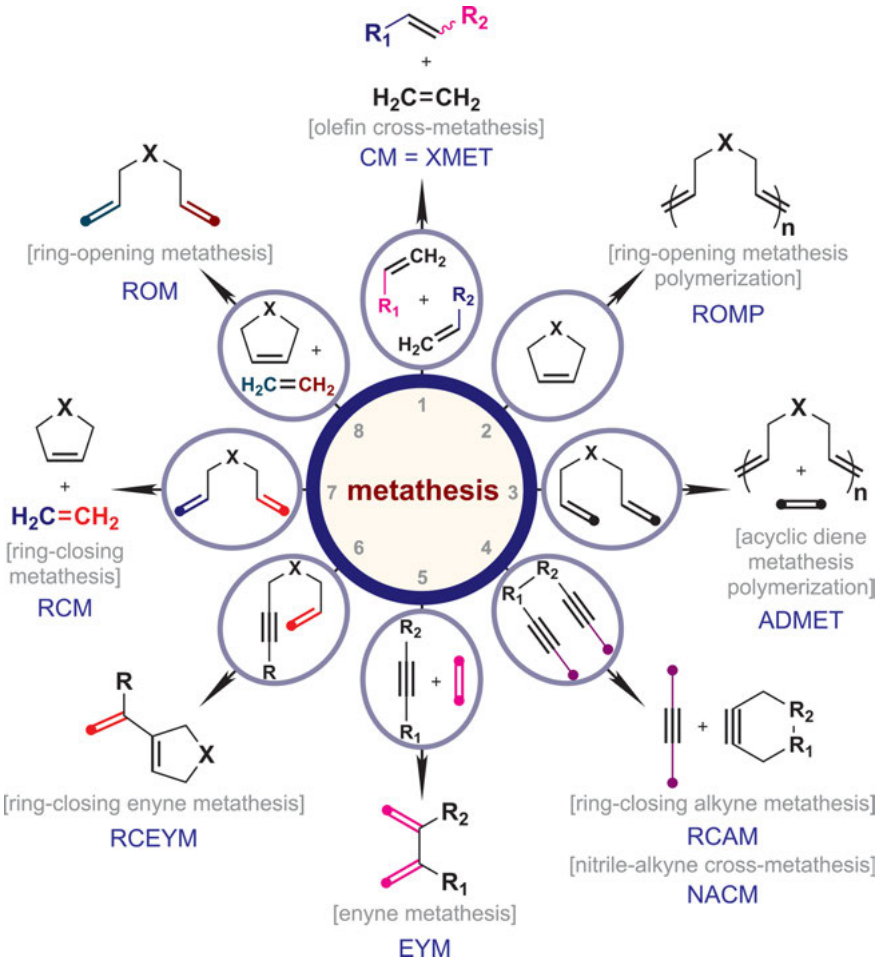

Fig. 68.5: Classification of *metathesis* reactions.[216]

216 The metathesis reactions can be classified as: 1. CM = XMET (olefin cross-metathesis); 2. ROMP (ring-opening metathesis polymerization); 3. ADMET (acyclic diene metathesis polymerization); 4. RCAM (ring-closing alkyne metathesis) and NACM (nitrile-alkyne cross-metathesis); 5. EYM (enyne metathesis); 6. RCEYM (ring-closing enyne metathesis); 7. **RCM** (ring-closing metathesis); 8. ROM (ring-opening metathesis).

69 Oppenauer Oxidation

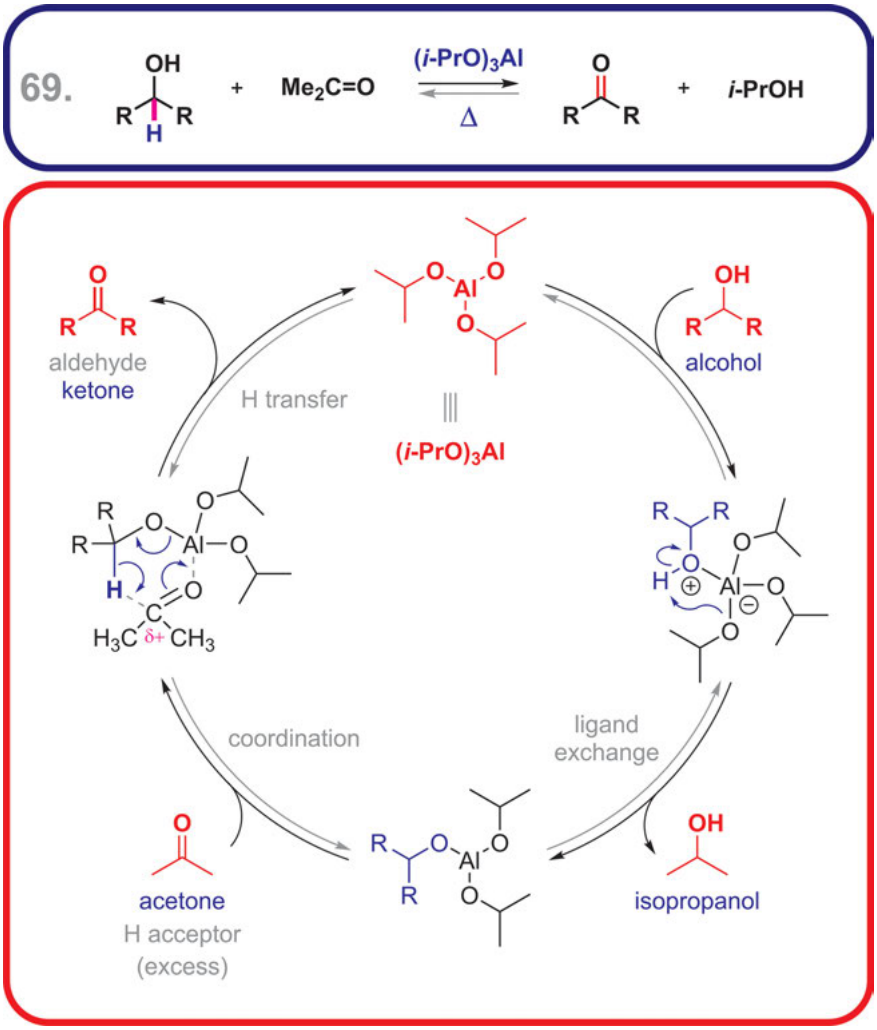

Fig. 69.1: The ***Oppenauer*** *oxidation* mechanism.[217]

217 The ***Oppenauer*** *oxidation* is reversible. The reversed reduction is called the ***Meerwein–Ponndorf–Verley*** *(MPV) reduction*. The equilibrium can be shifted towards oxidation by adding the excess of *acetone*.

https://doi.org/10.1515/9783110608373-069

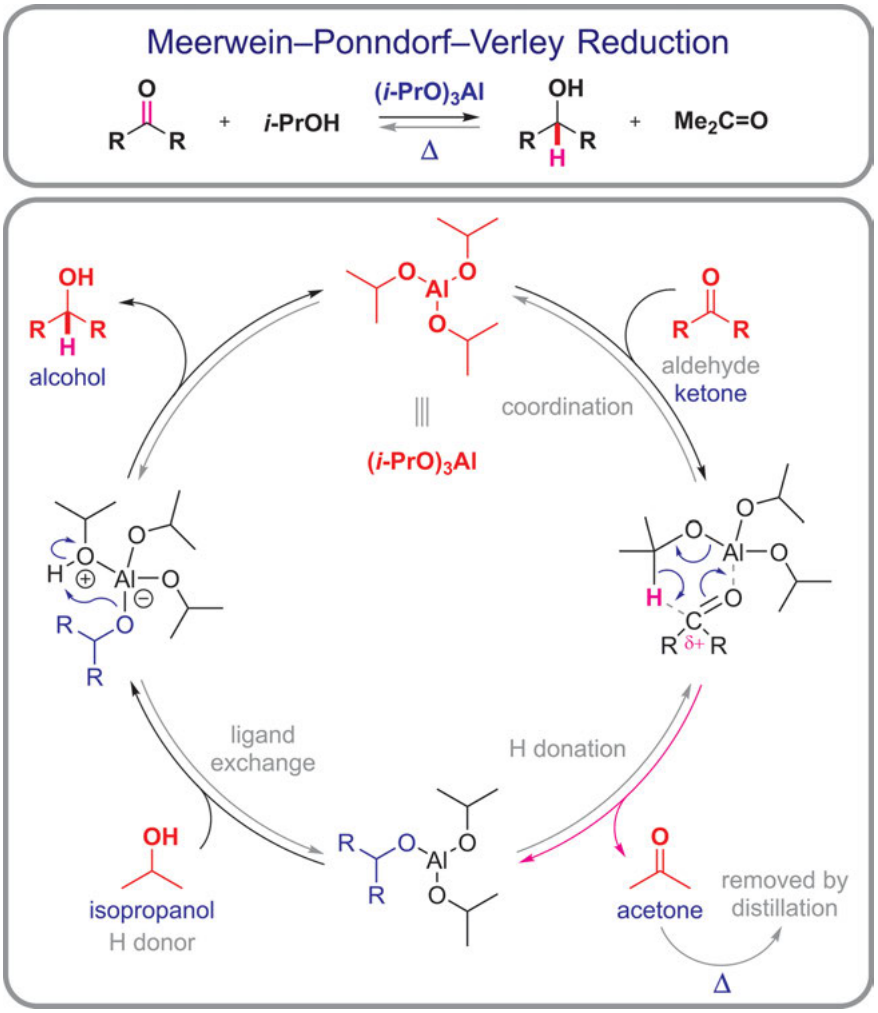

Fig. 69.2: The ***Meerwein–Ponndorf–Verley*** *reaction* mechanism.[218]

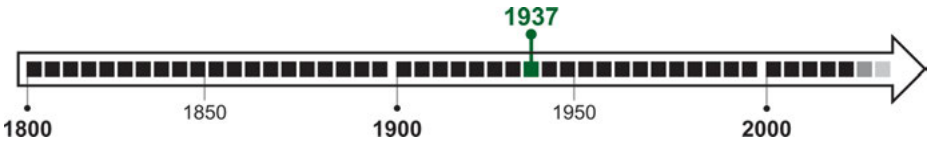

Fig. 69.3: The discovery of the ***Oppenauer*** *oxidation*.[219]

218 The ***Meerwein–Ponndorf–Verley*** *reduction* is a reversed process of the ***Oppenauer*** *oxidation*. It is also covered in Chapter 58.

219 The reaction was likely first described around 1937 [69].

70 Ozonolysis

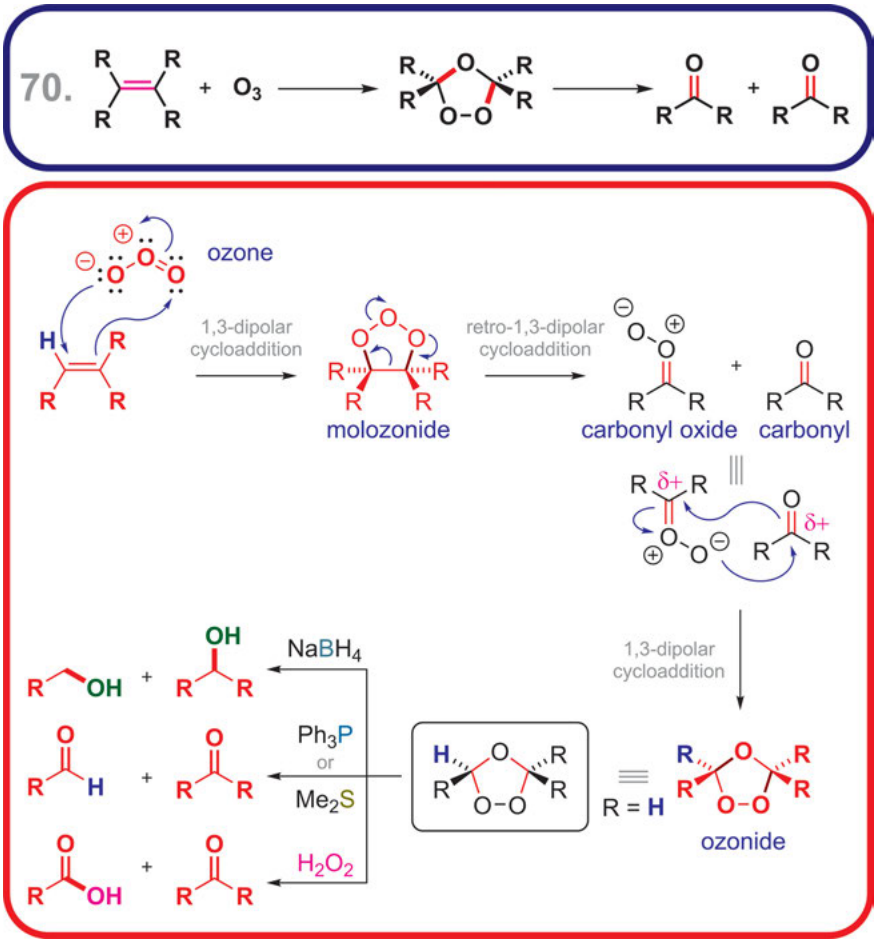

Fig. 70.1: The *ozonolysis* mechanism (the ***Criegee*** mechanism).[220]

220 The *ozonolysis* mechanism was first proposed by Criegee [70a, 70b, 70c], thus it is often called the ***Criegee*** *mechanism* (it is different from *the* ***Criegee*** *oxidation* covered in Chapter 29). Formally, the first step of *ozonolysis* is a *1,3-dipolar cycloaddition reaction* or a (3+2)-*cycloadditon reaction*.

https://doi.org/10.1515/9783110608373-070

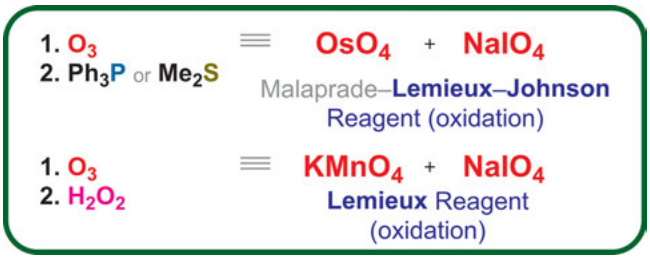

Fig. 70.2: Alternative to the *ozonolysis* reaction conditions.[221]

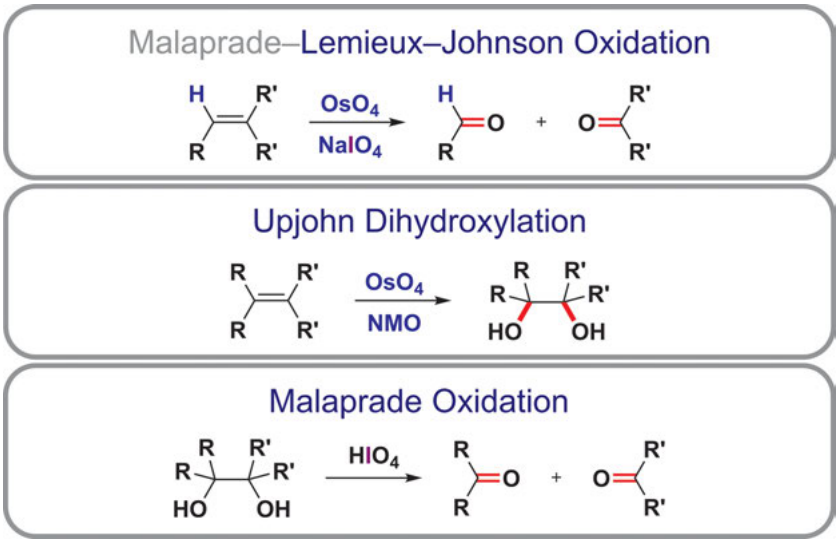

Fig. 70.3: Reactions related to the *ozonolysis*.[222]

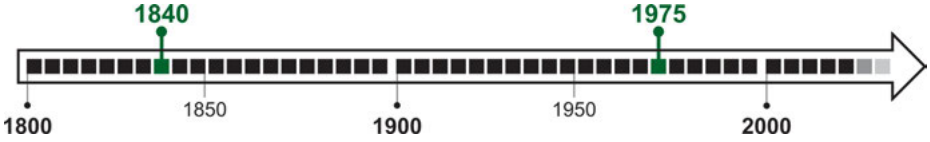

Fig. 70.4: The discovery of the *ozonolysis*.[223]

221 The *Malaprade–**Lemieux–Johnson** reagent* [70d] is an alternative to the use of *ozone* [70e], followed by Ph_3P or Me_2S to form *aldehydes* and *ketones*. The ***Lemieux*** reagent [70f] is an alternative to the use of *ozone*, followed by H_2O_2, to form *carboxylic acids* and *ketones*.

222 The *Malaprade–**Lemieux–Johnson** reaction (oxidation)* is an alternative to the *ozonolysis reaction* under Ph_3P or Me_2S conditions. The ***Upjohn** dihydroxylation* (covered in Chapter 93) followed by the ***Malaprade** oxidation* (covered in Chapter 29) can be also used as an alternative to *ozonolysis*.

223 The reaction was likely first described around 1840 [70g], the mechanism was proposed around 1975 [70b, 70c].

71 Paal–Knorr Syntheses

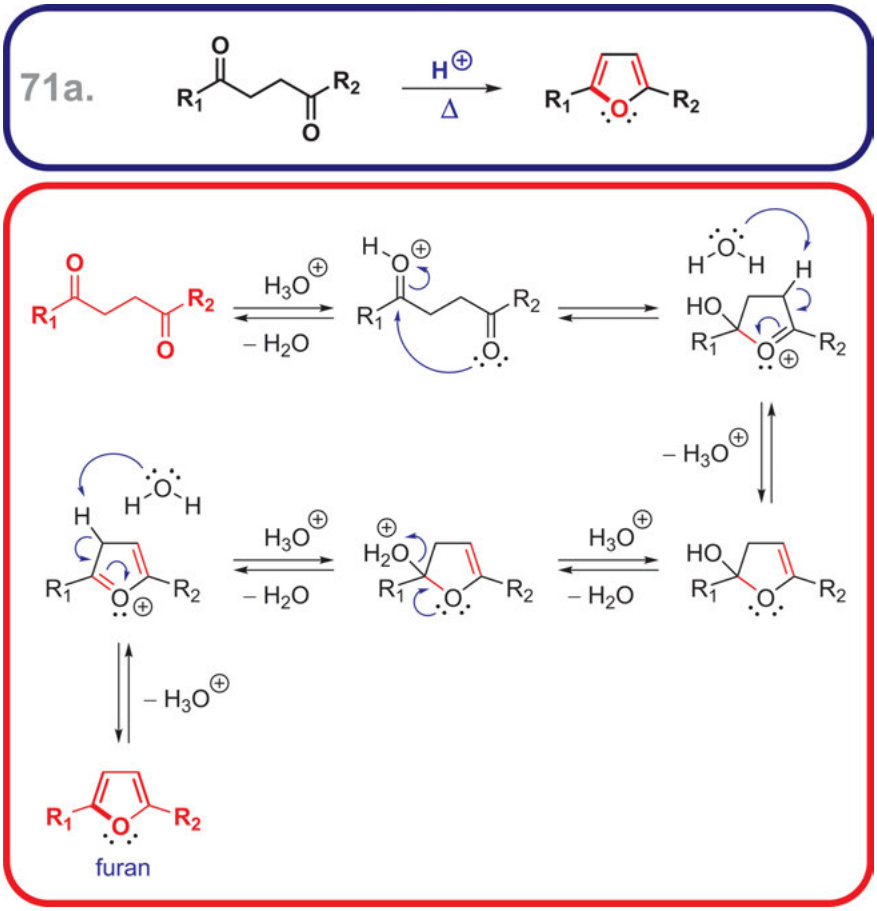

Fig. 71.1: The ***Paal–Knorr*** *furan synthesis* mechanism.[224]

224 The ***Paal–Knorr*** *synthesis* is a reaction that was initially proposed for the synthesis of *furans* and *pyrroles*: the ***Paal–Knorr*** *furan synthesis*.

https://doi.org/10.1515/9783110608373-071

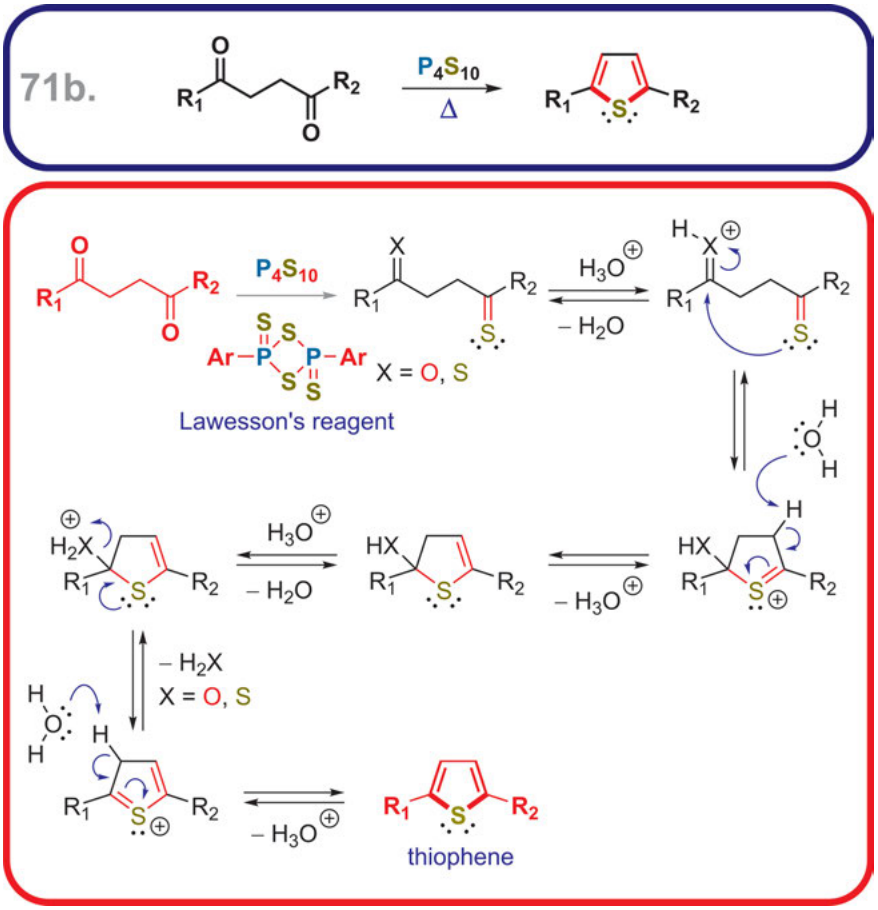

Fig. 71.2: The ***Paal–Knorr*** *thiophene synthesis* mechanism.[225]

225 The ***Paal–Knorr*** *thiophene synthesis* was adopted for the preparation of *thiophenes*, for example by using ***Lawesson's*** *reagent* [71a].

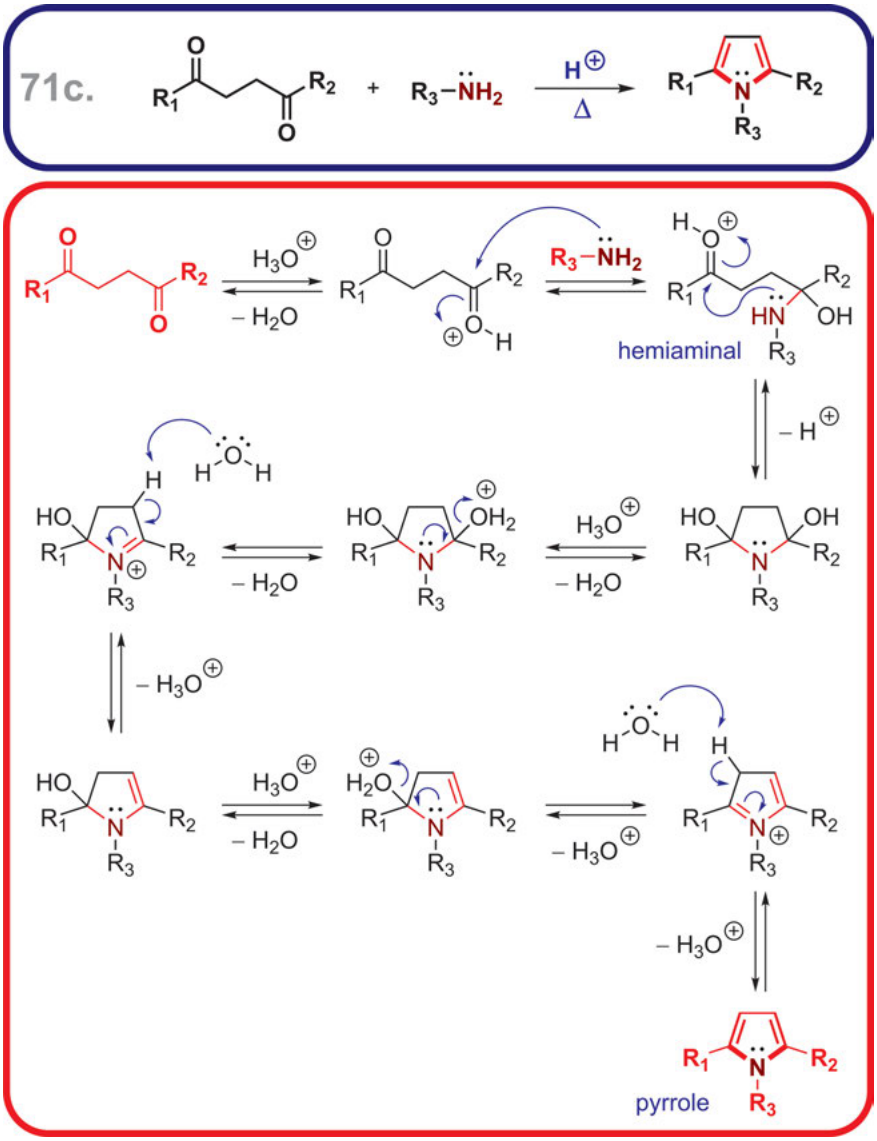

Fig. 71.3: The ***Paal–Knorr*** *pyrrole synthesis* mechanism.[226]

226 The ***Paal–Knorr*** *pyrrole synthesis* is a reaction that was initially proposed for the synthesis of *pyrroles*. It should not be confused with the ***Knorr*** *pyrrole synthesis* (not shown).

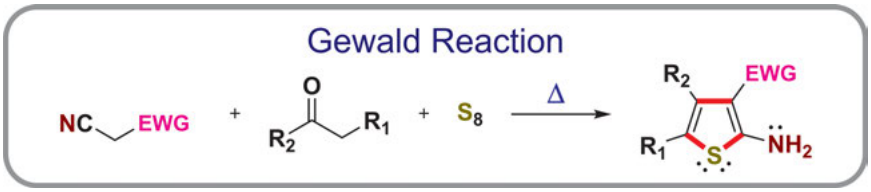

Fig. 71.4: Reactions related to the ***Paal–Knorr*** *thiophene synthesis*.[227]

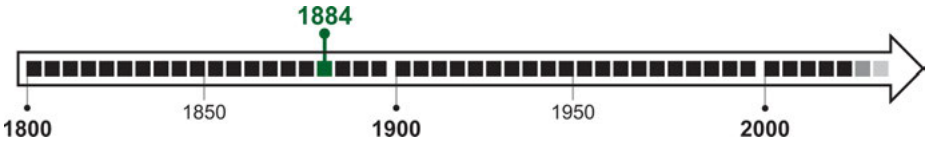

Fig. 71.5: The discovery of the ***Paal–Knorr*** *syntheses*.[228]

227 Thiophenes (2-aminothiophenes) can be prepared via the ***Gewald*** *condensation* (see Chapter 41).
228 The reaction was likely first described around 1884 [71b, 71c].

72 Paternò–Büchi Reaction

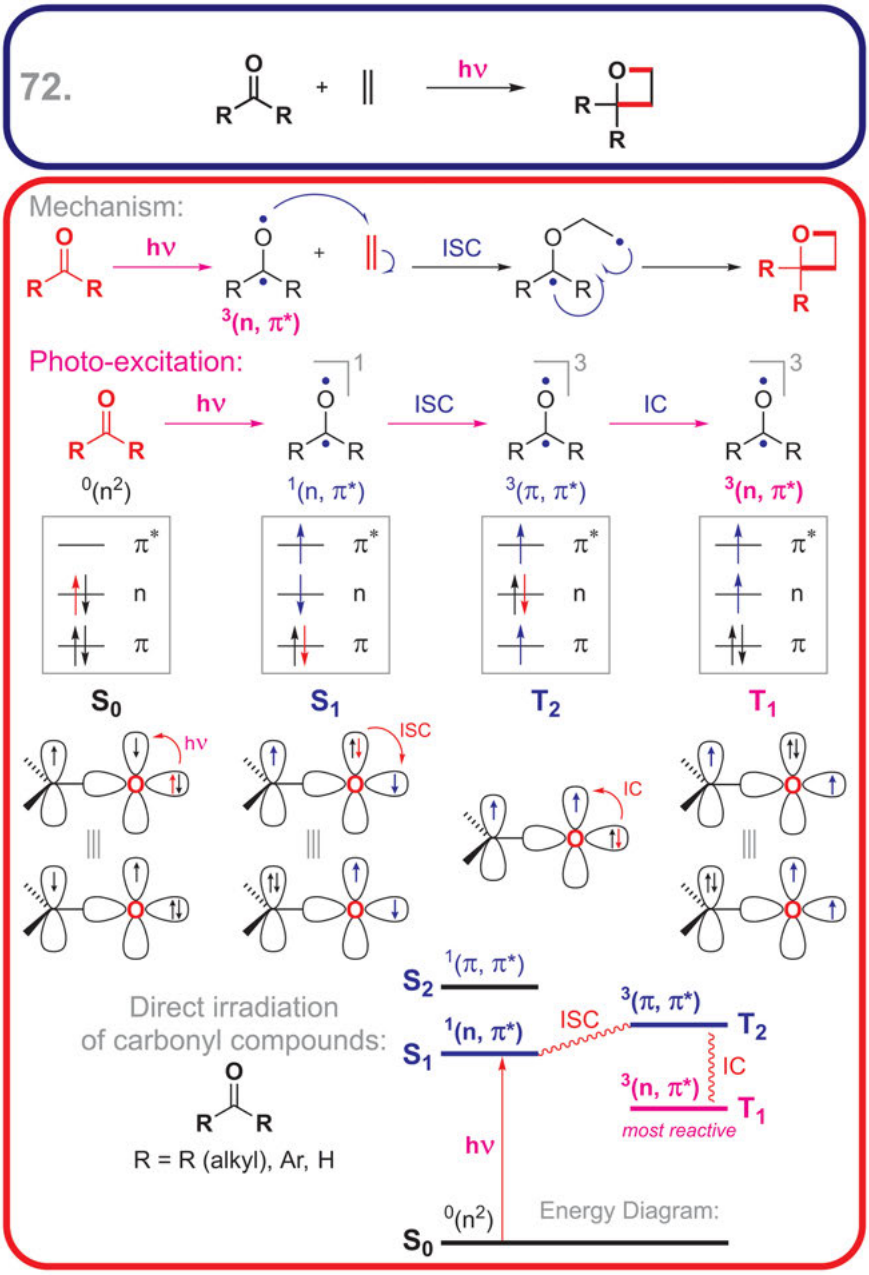

Fig. 72.1: The ***Paternò–Büchi*** *reaction* mechanism.[229]

https://doi.org/10.1515/9783110608373-072

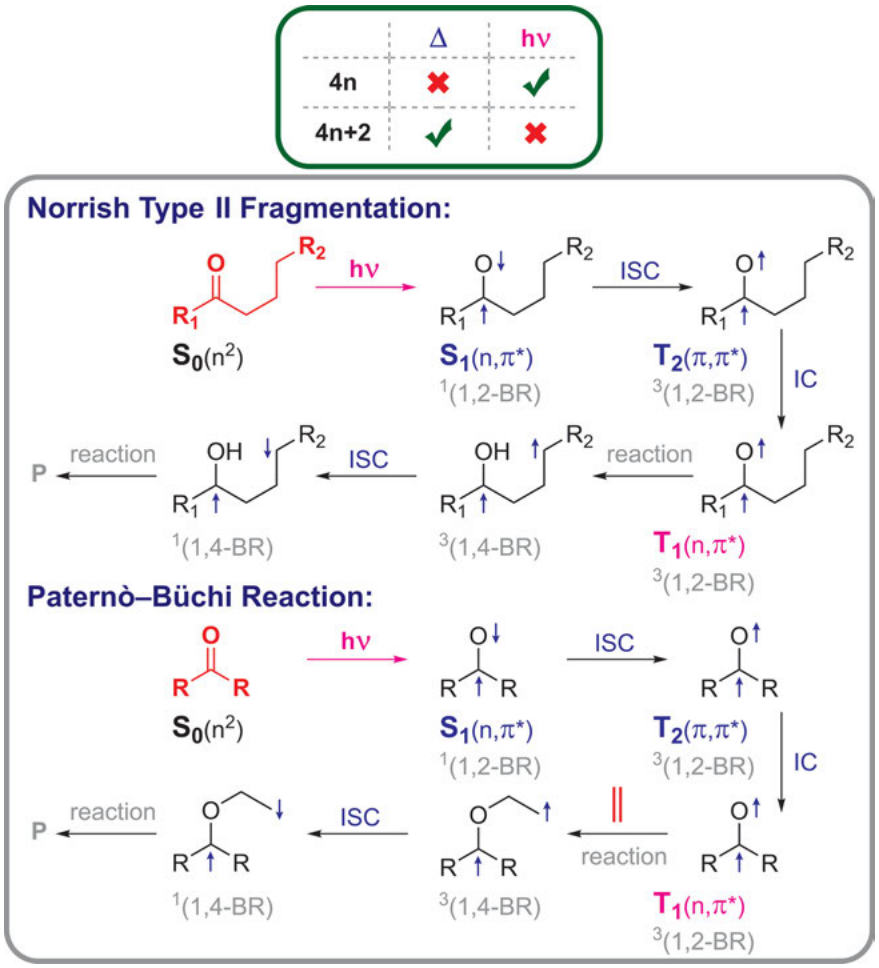

Fig. 72.2: The ***Norrish Type II*** *reaction* vs the ***Paternò–Büchi*** *reaction* mechanism.[230]

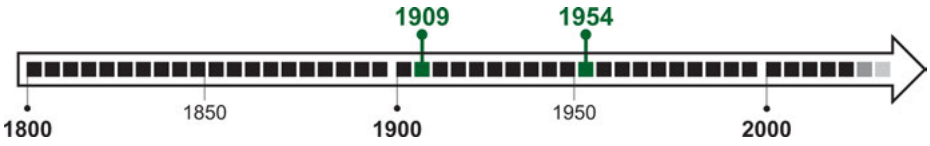

Fig. 72.3: The discovery of the ***Paternò–Büchi*** *reaction*.[231]

229 The ***Paternò–Büchi*** *reaction* is a photochemical **[2_π+2_π]** or **[2+2]**-*cycloaddition reaction*. The ***Woodward–Hoffmann*** *rules* [64a, 64b, 64c]: this reaction (**4n** = 4π) is not allowed at the ground state = under thermal conditions (Δ) but allowed at the excited state = under photochemical conditions (hν) [2b].

230 Compare the mechanistic similarities between the ***Norrish Type II*** *reaction* (covered in Chapter 67) and the ***Paternò–Büchi*** *cycloaddition reaction* [2b].

231 The reaction was likely described by Paternò around 1909 [72a] and by Büchi in 1954 [72b].

73 Pauson–Khand Reaction

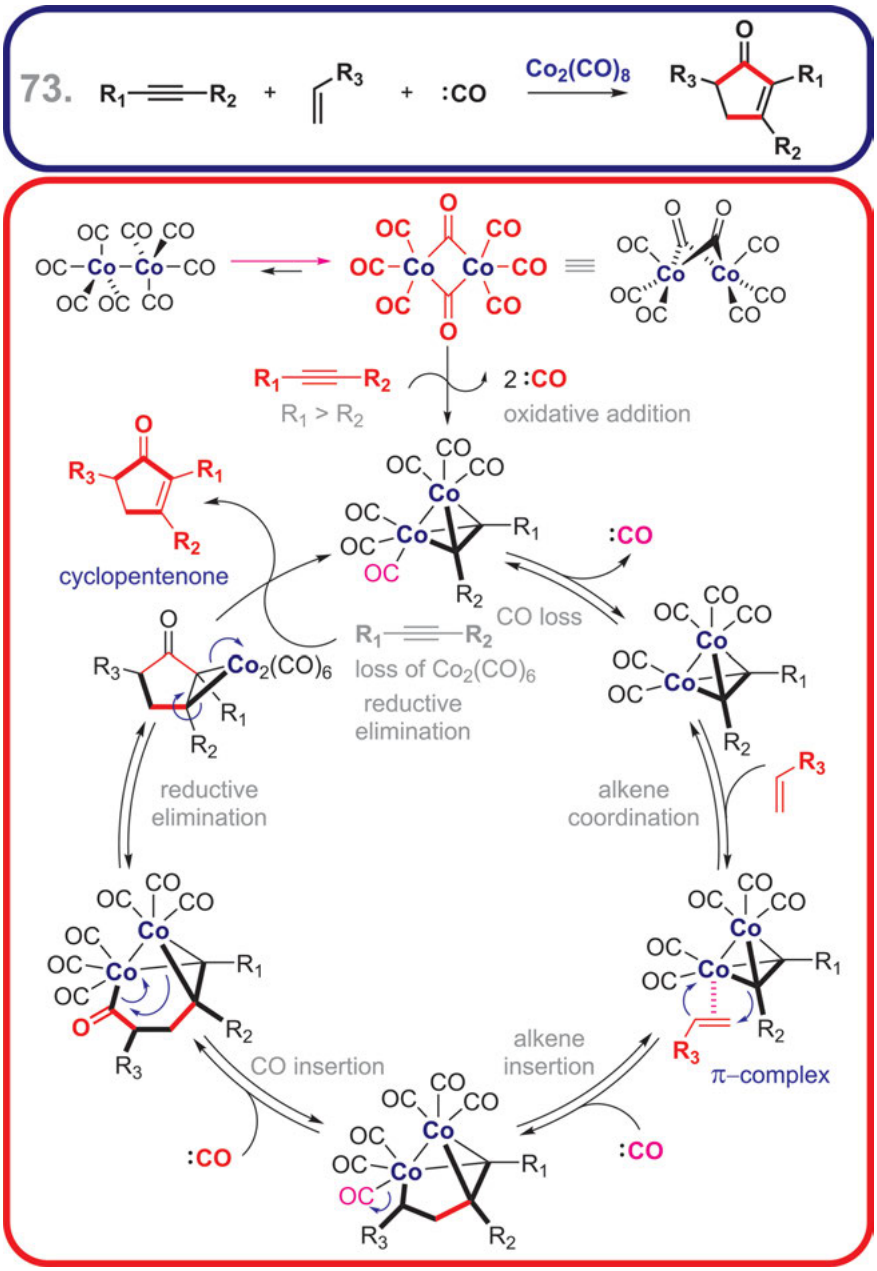

Fig. 73.1: The ***Pauson–Khand*** *reaction* mechanism.[232]

https://doi.org/10.1515/9783110608373-073

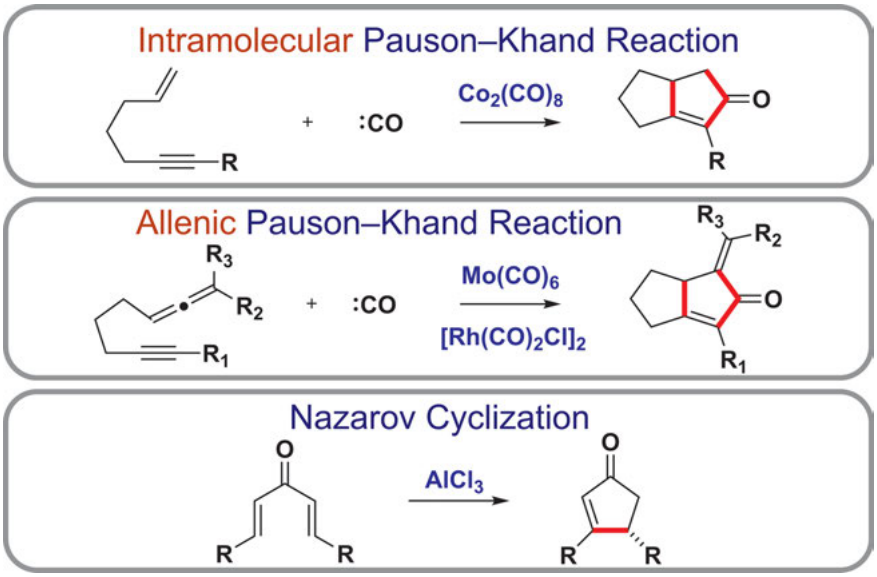

Fig. 73.2: Variations of the ***Pauson–Khand*** *reaction*.[233]

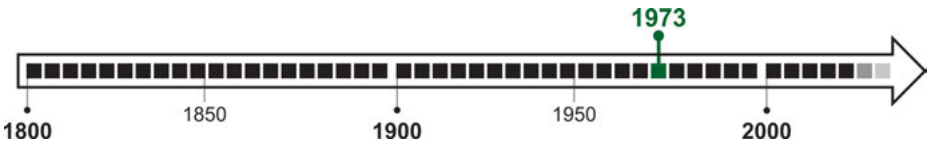

Fig. 73.3: The discovery of the ***Pauson–Khand*** *reaction*.[234]

232 The ***Pauson–Khand*** *reaction* is a ***Co****-catalyzed* (2+2+1)*-cycloaddition reaction.*

233 There are several variations of this reaction: the *intramolecular* ***Pauson–Khand*** *reaction*, the *allenic* ***Pauson–Khand*** *reaction*, and others (not shown) [73a]. Other metals can catalyze it: **Mo**, **Rh**, *etc*. The ***Nazarov*** *cyclization* undergoes a different [4π] ***con****rotatory electrocyclization* mechanism (Chapter 64), but it also yields *cyclopentenones*.

234 The reaction was likely first described around 1973 [73b, 73c, 73d].

74 Peptide (Amide) Coupling

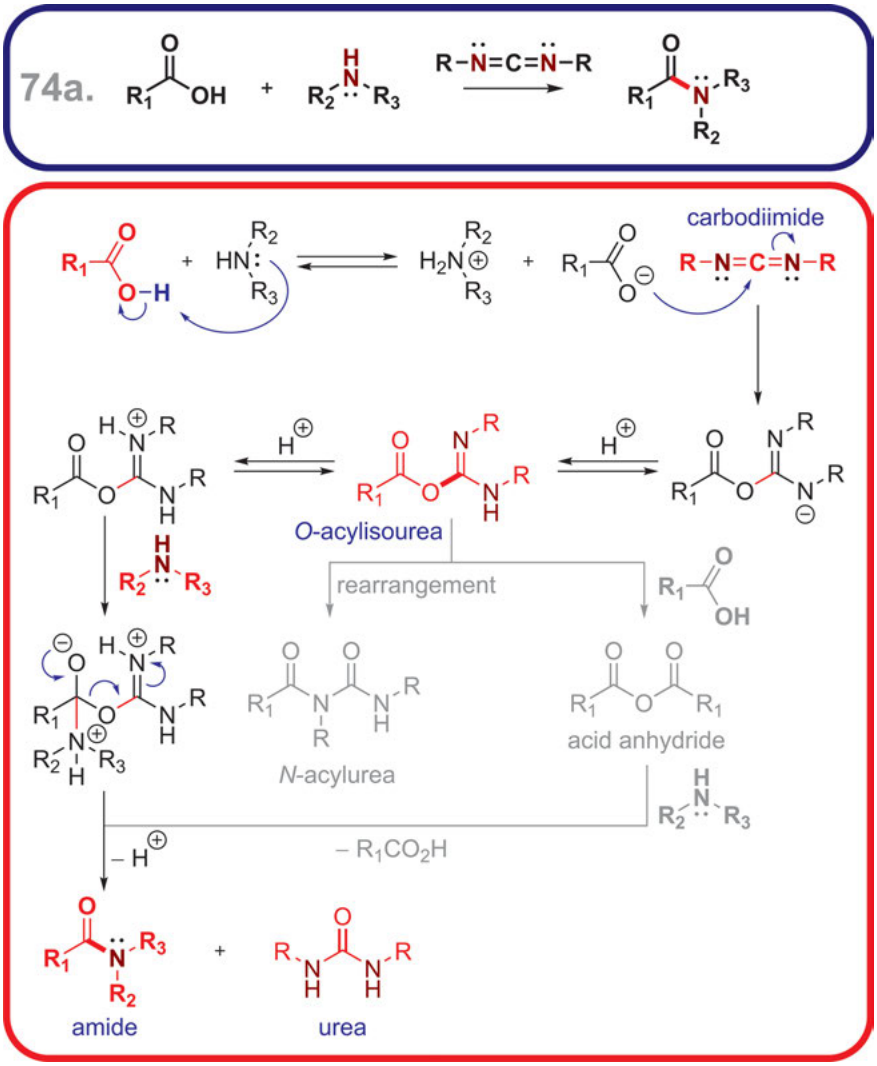

Fig. 74.1: The *peptide (amide) coupling* (DCC) mechanism.[235]

235 The *peptide (amide) coupling* mechanism based on the use of *carbodiimide* coupling reagents (DCC) [74a, 74b].

https://doi.org/10.1515/9783110608373-074

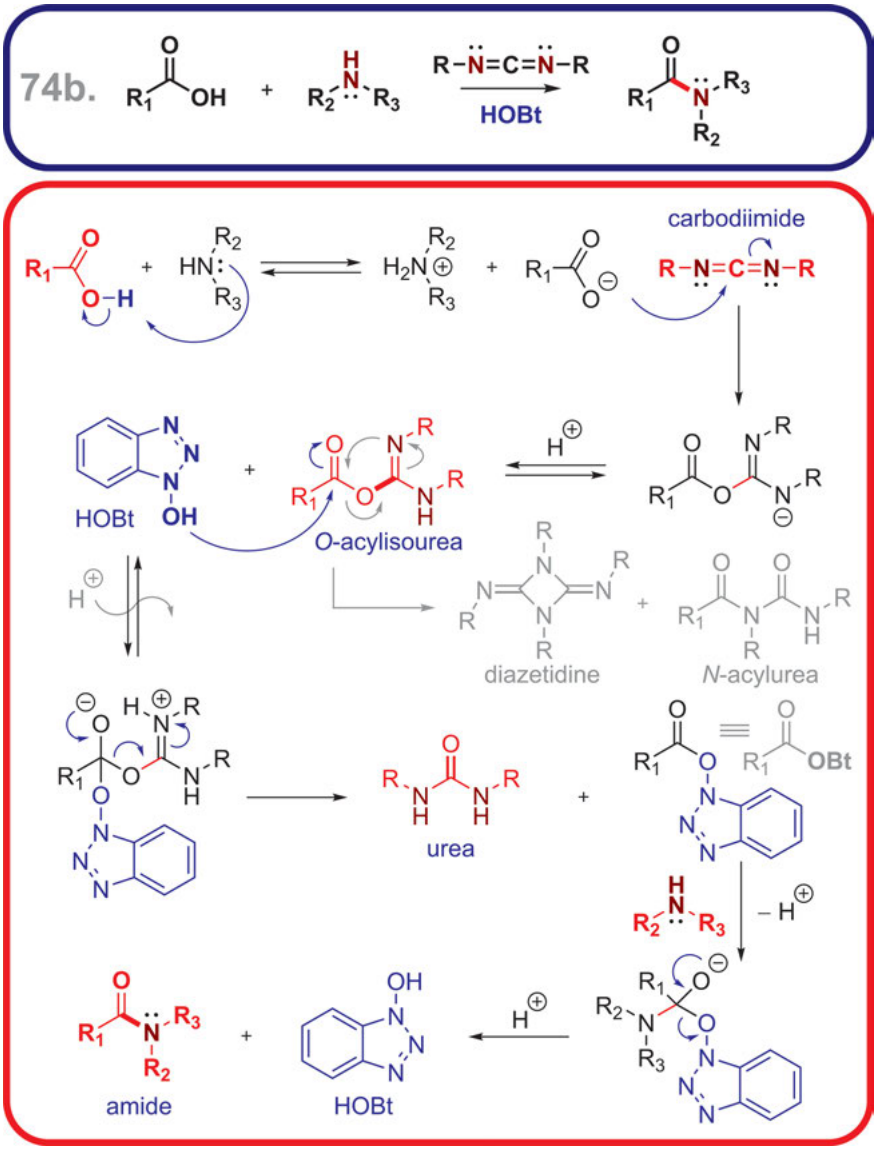

Fig. 74.2: The *peptide (amide) coupling* (DCC + HOBt) mechanism.[236]

236 The *peptide (amide) coupling* mechanism based on the use of *carbodiimide* coupling reagents and *additives* (DCC and HOBt) [74a, 74b].

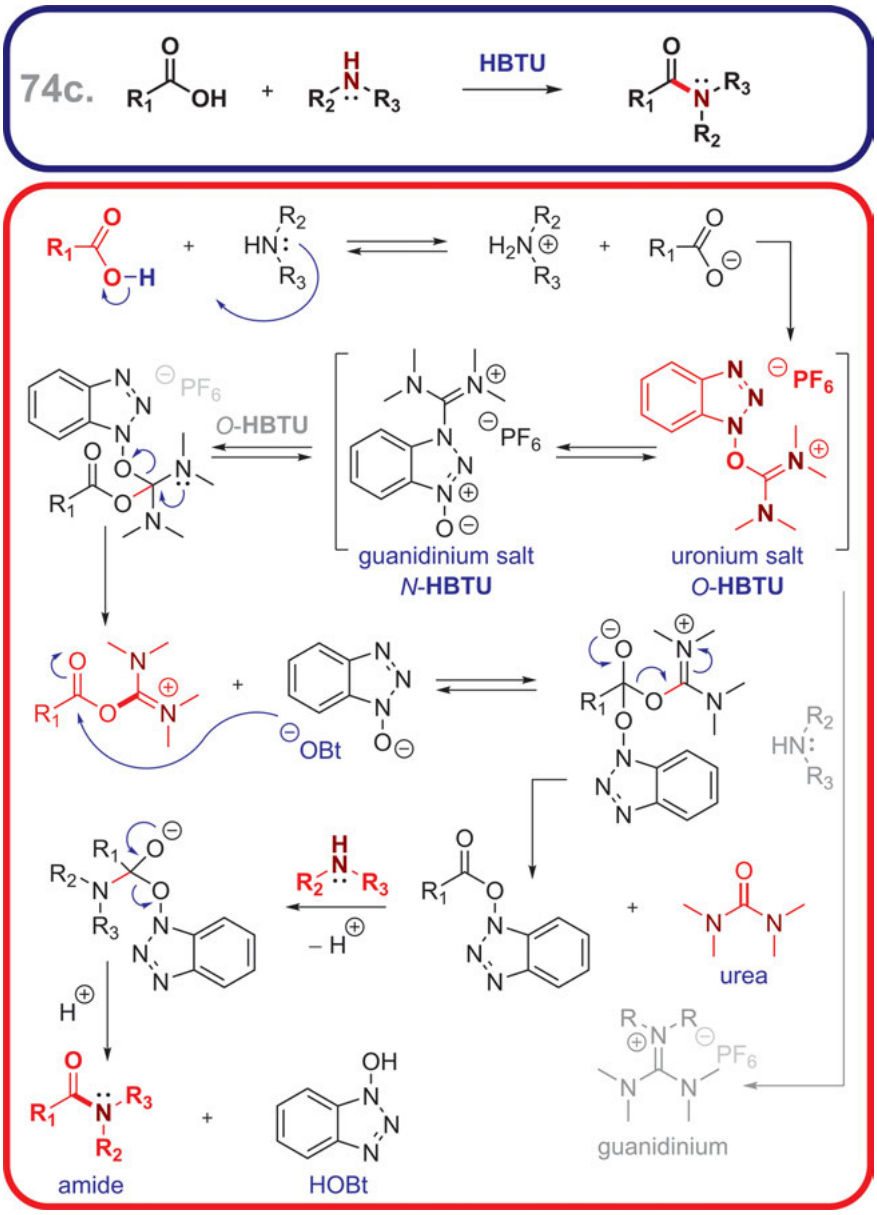

Fig. 74.3: The *peptide (amide) coupling* (HBTU) mechanism.[237]

237 The *peptide (amide) coupling* mechanism based on the use of *benzotriazole = guanidinium/uronium salts* coupling reagents (HBTU) [74c].

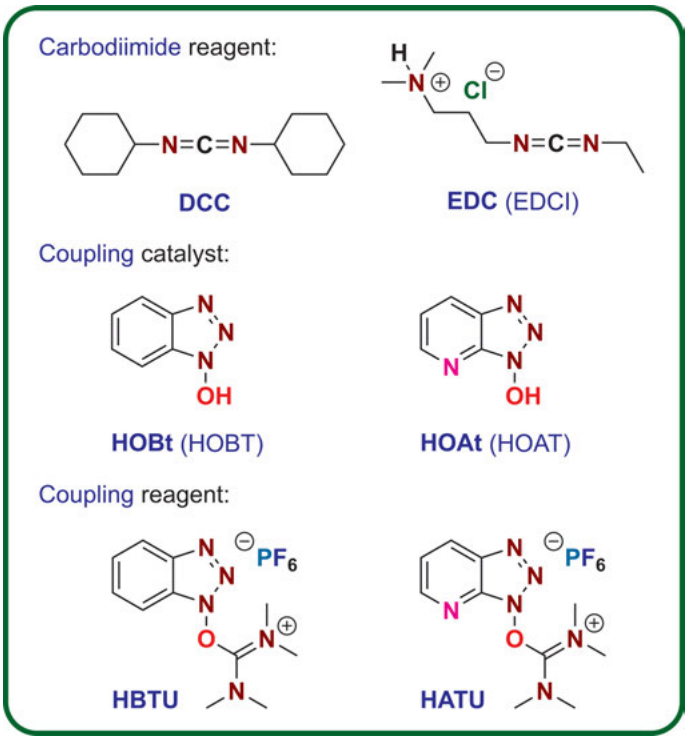

Fig. 74.4: The main *peptide (amide) coupling* reagents and catalysts.[238]

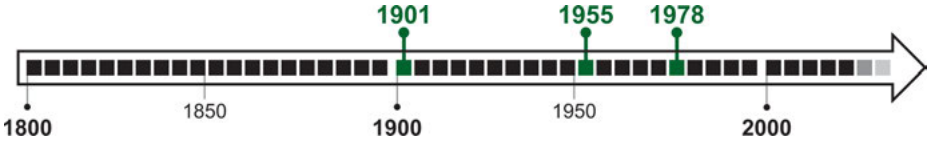

Fig. 74.5: The discovery of the *peptide (amide) coupling*.[239]

238 The most common reagents used in the *peptide (amide) coupling* or the *peptide synthesis* are the ***carbodiimide*** *reagents* (DCC [74d], EDC [74e], and many other); ***guanidinium/uronium salts*** (HBTU [74f], HATU [74g]; and many more like *phosphonium salts* PyBOP [74h]). The most common additives (catalysts) used in the *peptide synthesis* are HOBt [74i] and HOAt, among others.

239 A. The *peptide (amide) coupling* reaction was likely first described around 1901 [74j]. B. DCC coupling reagent was likely first described around 1955 [74k]. C. HBTU coupling reagent was likely first described around 1978 [74l].

75 Pictet–Spengler Reaction

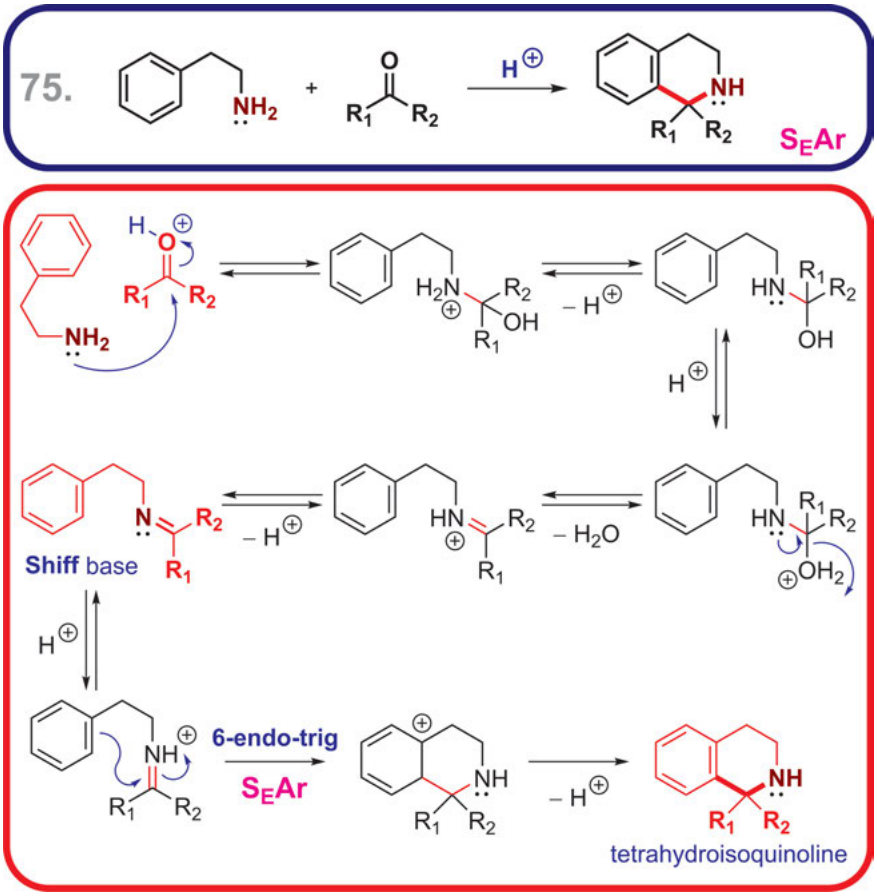

Fig. 75.1: The ***Pictet–Spengler*** *reaction* mechanism.[240]

240 The ***Pictet–Spengler*** *reaction* or the ***Pictet–Spengler*** *condensation* mechanism is a combination of the ***Mannich*** *condensation* = the *imine condensation (the* ***Shiff*** *base)* (see Chapter 56) and the **aromatic electrophilic substitution** (the ***arenium ion*** mechanism or **S_EAr**, which was covered in Chapter 3).

https://doi.org/10.1515/9783110608373-075

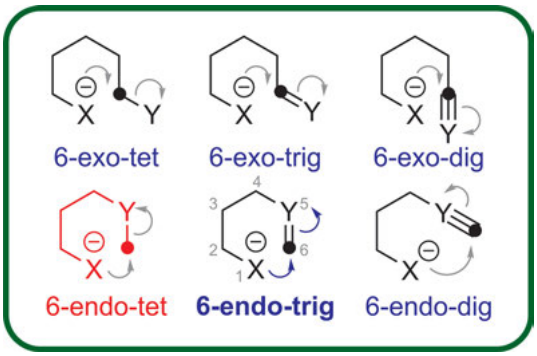

Fig. 75.2: ***Baldwin's*** *rules*.[241]

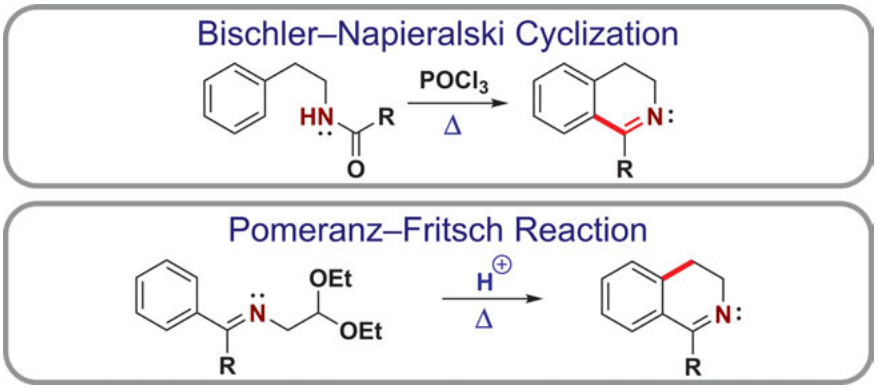

Fig. 75.3: Reactions related to the ***Pictet–Spengler*** *reaction*.[242]

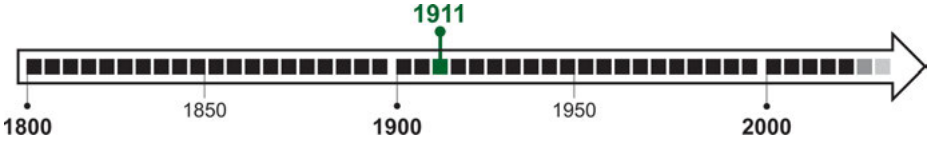

Fig. 75.4: The discovery of the ***Pictet–Spengler*** *reaction*.[243]

241 The cyclization (**S_EAr**) step is allowed according to *Baldwin's rules*: **6-endo-trig** [75a].

242 Several named reactions are related to the ***Pictet–Spengler*** *reaction*: the ***Bischler–Napieralski*** *cyclization* (Chapter 19), and closely related the ***Pomeranz–Fritsch*** *reaction* [19a, 19b]. Both reactions yield *isoquinolines*.

243 The reaction was likely first described around 1911 [75b].

76 Pinacol–Pinacolone Rearrangement

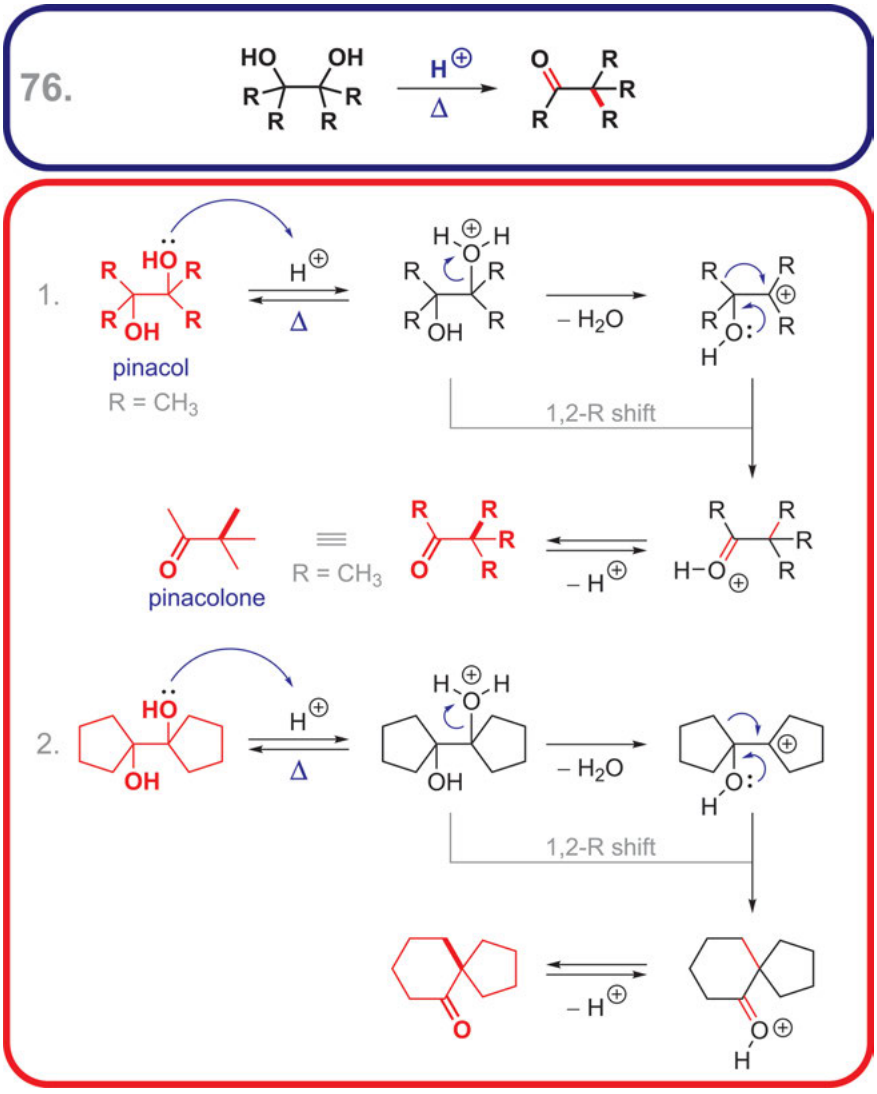

Fig. 76.1: The *pinacol-pinacolone rearrangement* mechanism.[244]

244 The *pinacol-pinacolone rearrangement* or simply the *pinacol rearrangement* mechanism is distantly related to the ***Wagner–Meerwein*** *rearrangement* covered in Chapter 96. The *pinacol-pinacolone rearrangement* should not be confused with the *pinacol coupling* covered in Chapter 57. Please also note: *2,3-dimethylbutane-2,3-diol* is called ***pinacol*** and *3,3-dimethyl-2-butanone* is called ***pinacolone***.

https://doi.org/10.1515/9783110608373-076

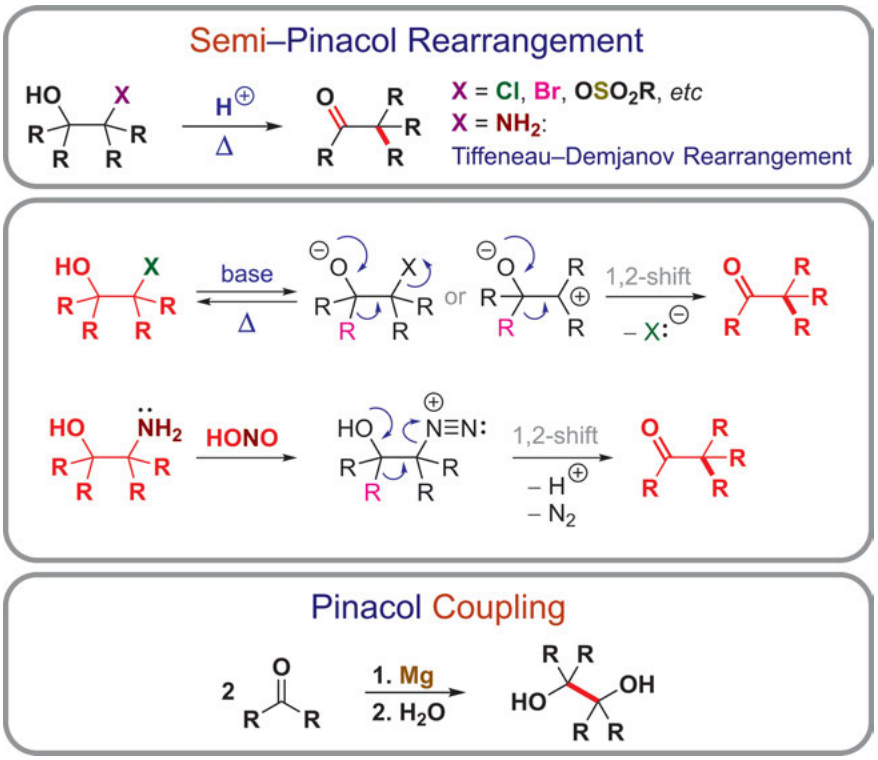

Fig. 76.2: The *semi-pinacol rearrangement* mechanism.[245]

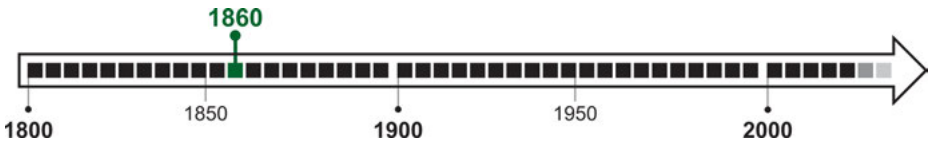

Fig. 76.3: The discovery of the *pinacol-pinacolone rearrangement*.[246]

245 The *semi-pinacol rearrangement* mechanism [1] is analogous to the *pinacol rearrangement*. It occurs in *α–substituted alcohols*. If X = NH_2, the reaction is called the ***Tiffeneau–Demjanov*** *rearrangement* [76a, 76b].

246 The reaction was likely first described around 1860 [76c].

77 Polonovski Reaction

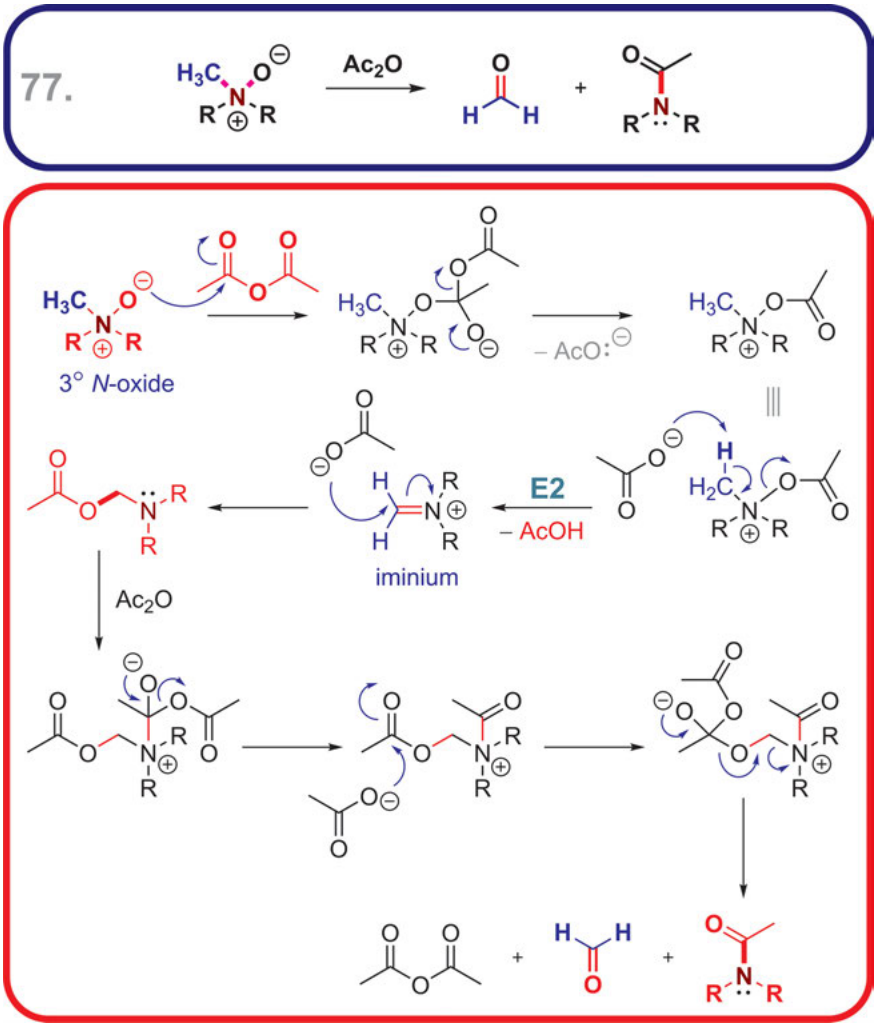

Fig. 77.1: The ***Polonovski*** *reaction* mechanism.[247]

247 The ***Polonovski*** *reaction* can be called the ***Polonovski*** *rearrangement*. The key intermediate is an *iminium ion* (see the ***Mannich*** *reaction* in Chapter 56).

https://doi.org/10.1515/9783110608373-077

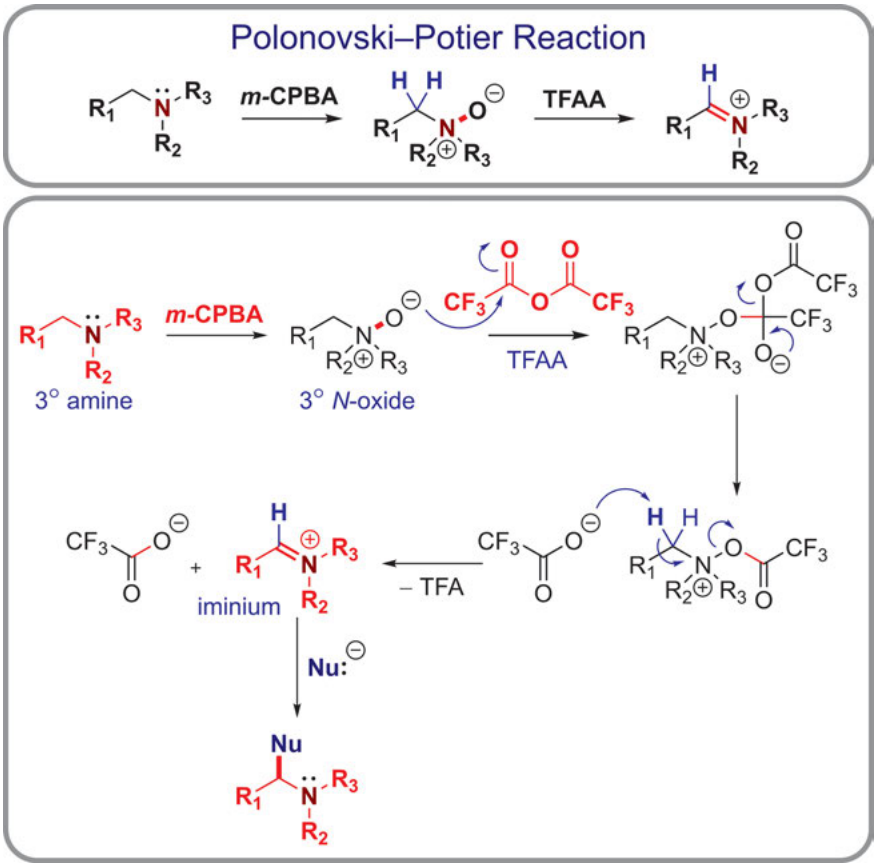

Fig. 77.2: The ***Polonovski–Potier*** *reaction* mechanism.[248]

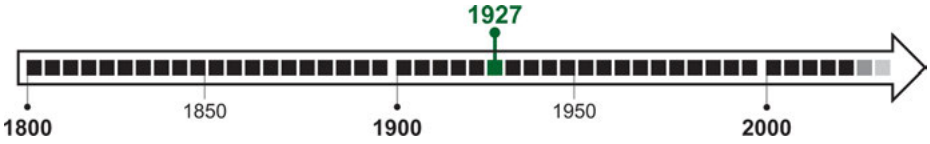

Fig. 77.3: The discovery of the ***Polonovski*** *reaction*.[249]

248 The ***Polonovski–Potier*** *reaction* is closely related [77a, 77b]. *Trifluoroacetic anhydride* (TFAA) is used instead of *acetic anhydride* and the *iminium ion* can be trapped with various nucleophiles.
249 The reaction was likely first described around 1927 [77c].

78 Prilezhaev Epoxidation

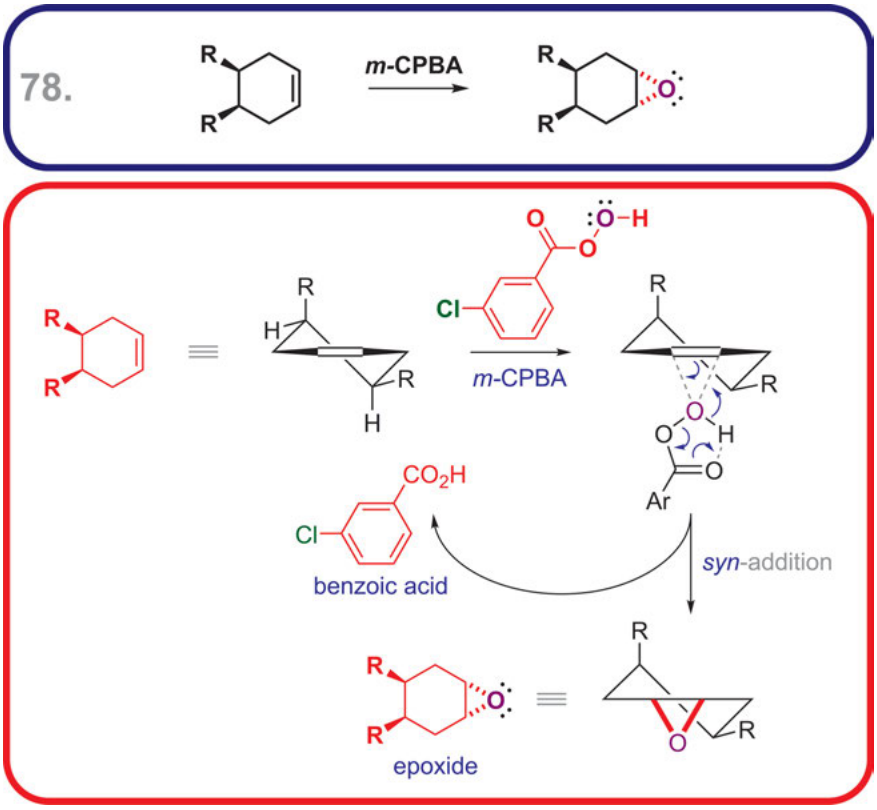

Fig. 78.1: The ***Prilezhaev*** *epoxidation* mechanism.[250]

250 The ***Prilezhaev*** *reaction* (in Russian Прилежаев) is a type of epoxidation, and it is often called the ***Prilezhaev*** *epoxidation*.

https://doi.org/10.1515/9783110608373-078

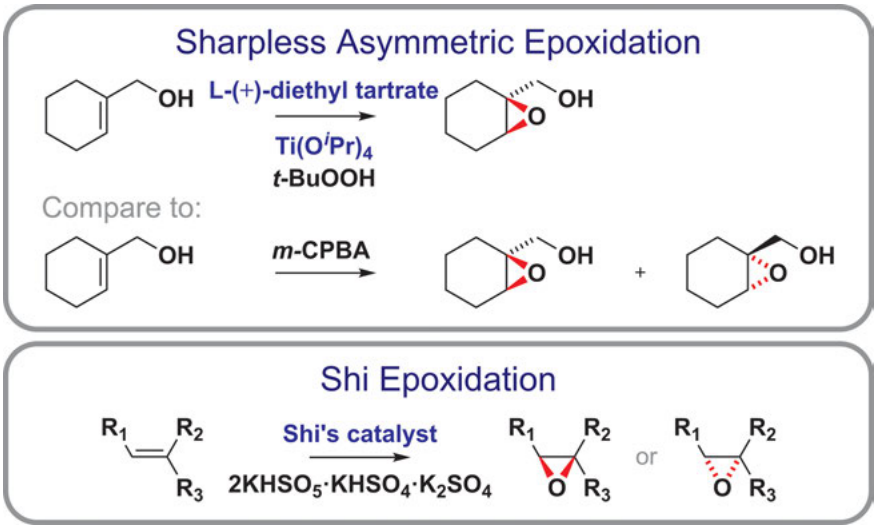

Fig. 78.2: Reactions related to the ***Prilezhaev*** *epoxidation*.[251]

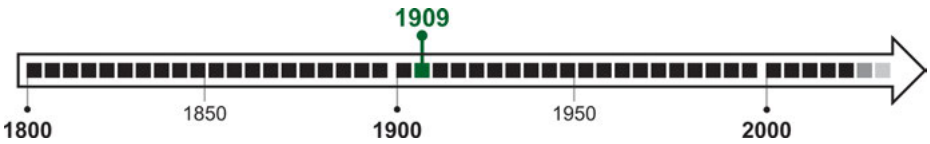

Fig. 78.3: The discovery of the ***Prilezhaev*** *epoxidation*.[252]

251 There are many ways to synthesize *epoxides*, such as: the ***Sharpless*** *asymmetric epoxidation* [78a] (compare to the ***Prilezhaev*** *epoxidation* where a mixture of enantiomers is formed); the ***Shi*** *asymmetric epoxidation* [78b], and many more other examples (not shown) [1].

252 The reaction was likely first described around 1909 [78c].

79 Prins Reaction

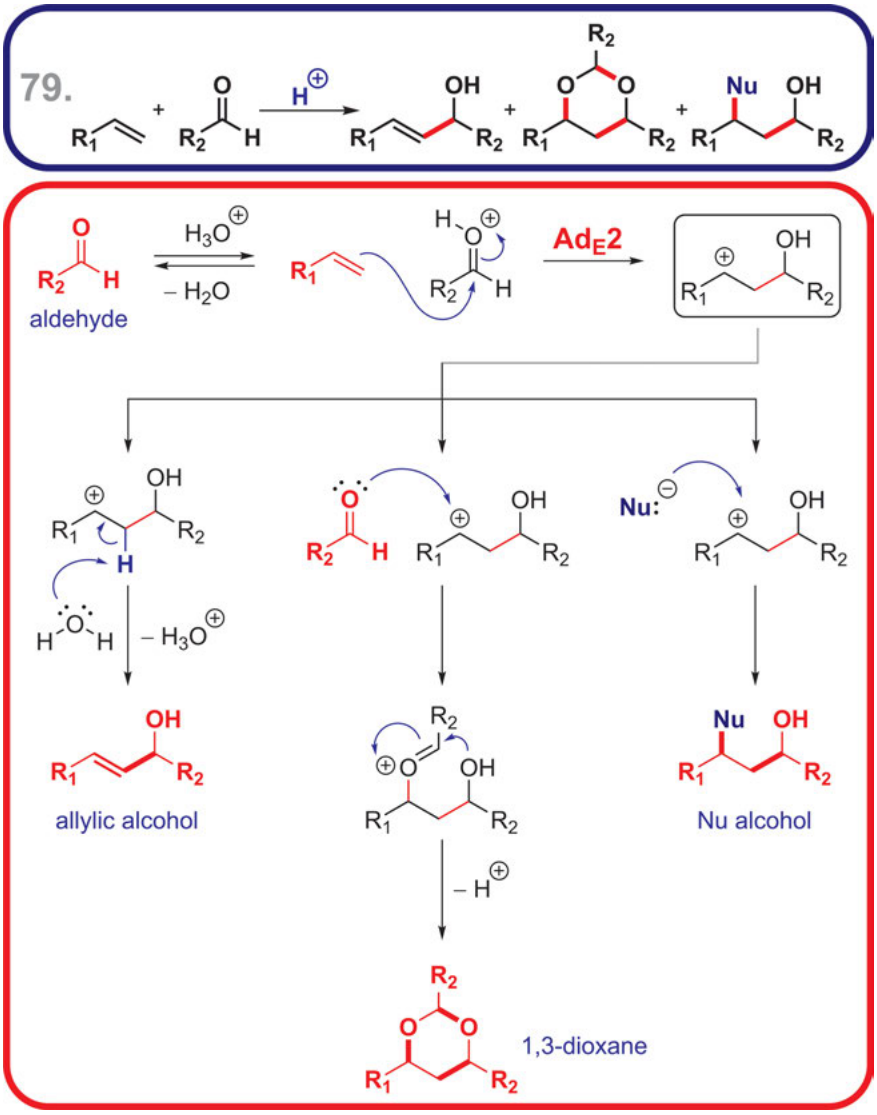

Fig. 79.1: The ***Prins*** *reaction* mechanism.[253]

253 The ***Prins*** *reaction* is a type of *condensation* with various possible products. Mechanistically (addition of a protonated *aldehyde* to an *alkene*), it is an example of the **electrophilic addition** covered in Chapter 1.

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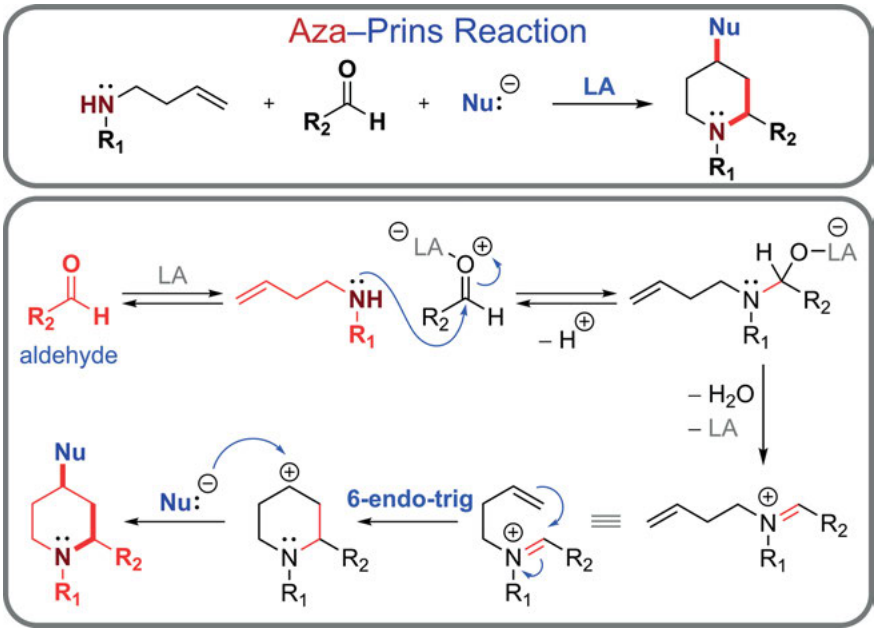

Fig. 79.2: The *aza-**Prins** reaction* mechanism.[254]

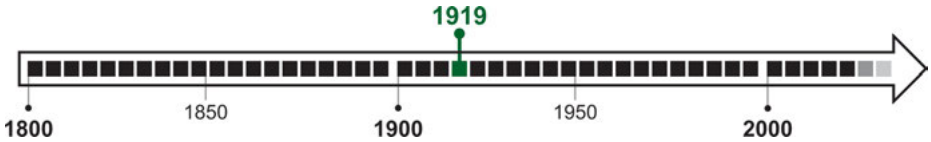

Fig. 79.3: The discovery of the ***Prins** reaction*.[255]

254 The *aza-**Prins** reaction* mechanism is related to the ***Prins** reaction* [79a, 79b]. It yields the *piperidine* core (see *Baldwin's rules* mentioned in Chapter 75: **6-endo-trig**). Other variations exist, for example the ***Prins**–pinacol reaction* (not shown here) [79c].

255 The reaction was likely first described around 1919 [79d, 79e].

80 Pummerer Rearrangement

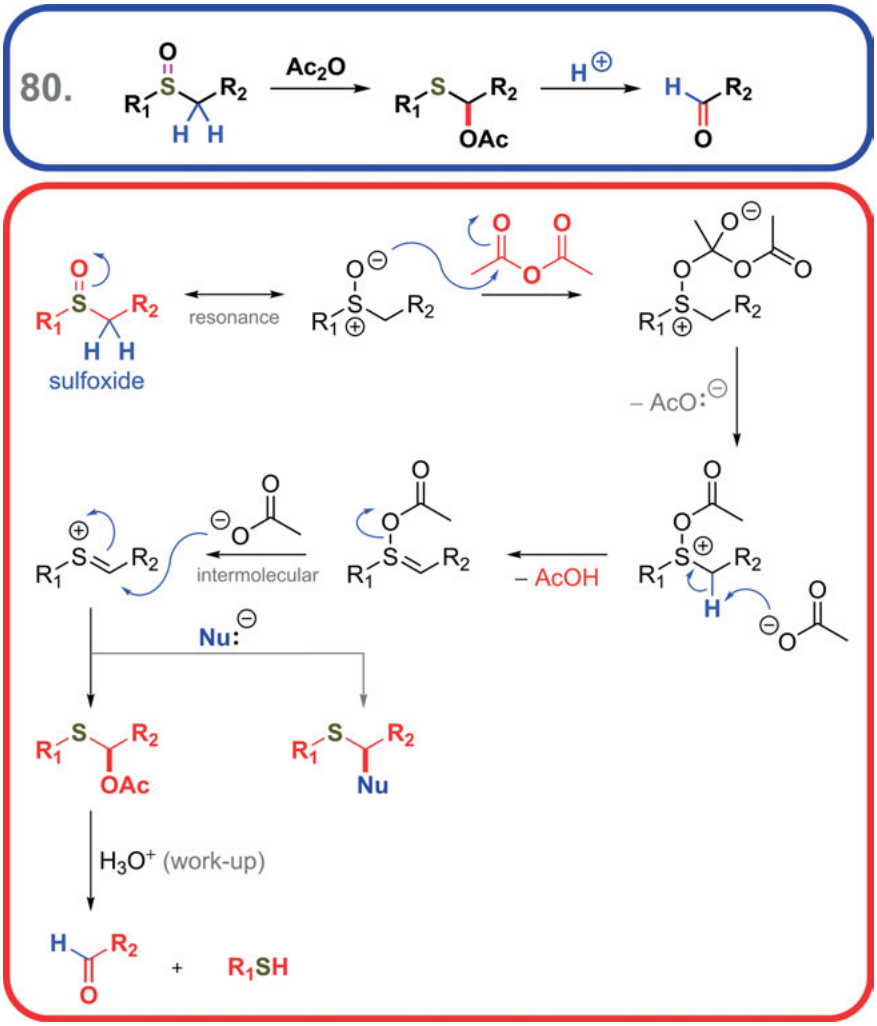

Fig. 80.1: The ***Pummerer*** *rearrangement* mechanism.[256]

256 The ***Pummerer*** *rearrangement* can be called the ***Pummerer*** *fragmentation*.

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Fig. 80.2: Reactions related to the ***Pummerer*** *rearrangement*.[257]

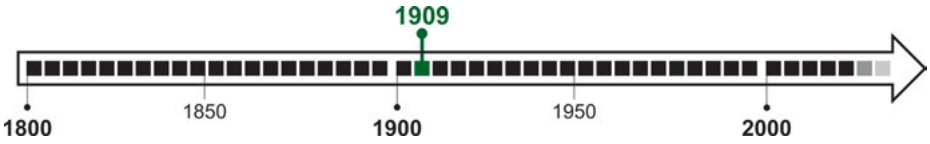

Fig. 80.3: The discovery of the ***Pummerer*** *rearrangement*.[258]

257 The ***Polonovski*** *reaction* mechanism (see Chapter 77) is related to the ***Pummerer*** *rearrangement*. An *amine oxide* (in the ***Polonovski*** *reaction*) plays similar role as a *sulfoxide* (in the ***Pummerer*** *rearrangement*).

258 The reaction was likely first described around 1909 [80].

81 Ramberg–Bäcklund Rearrangement

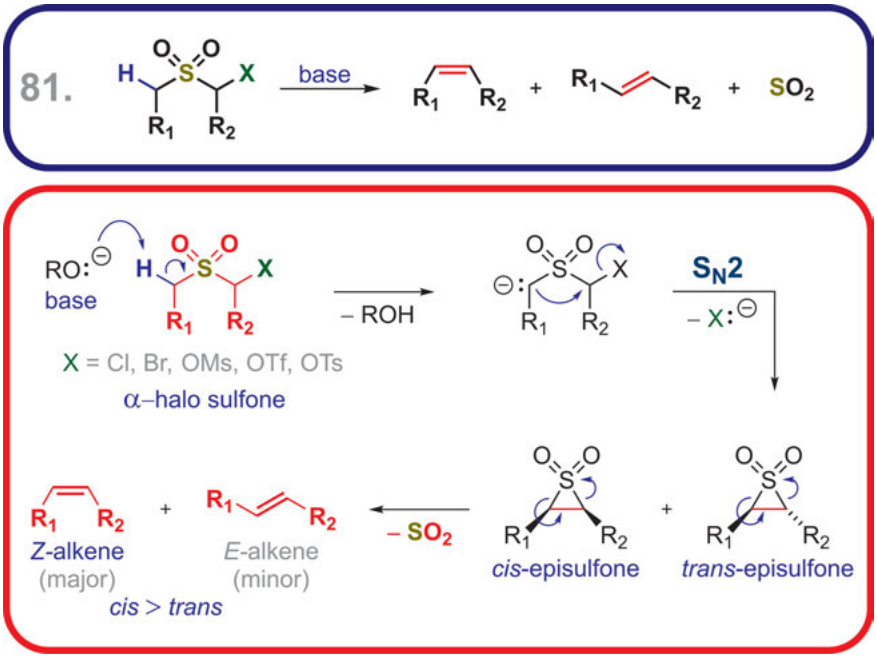

Fig. 81.1: The ***Ramberg–Bäcklund*** *rearrangement* mechanism.[259]

259 The ***Ramberg–Bäcklund*** *rearrangement* or the ***Ramberg–Bäcklund*** *reaction* mechanism is a combination of the bimolecular **nucleophilic substitution** (S_N2), covered in Chapter 2, and subsequent concerted **elimination** *(cheletropic elimination reaction)* [1a] and [81a].

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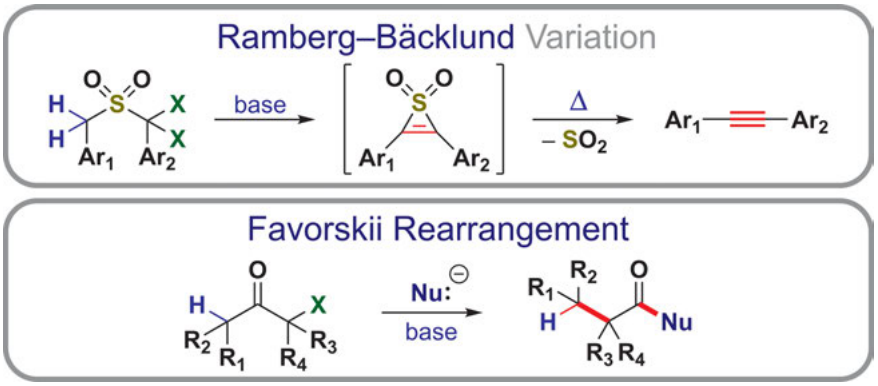

Fig. 81.2: Reactions related to the ***Ramberg–Bäcklund*** *rearrangement*.[260]

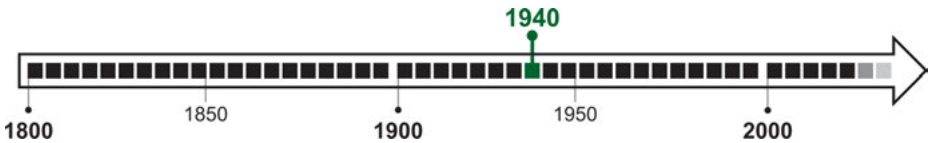

Fig. 81.3: The discovery of the ***Ramberg–Bäcklund*** *rearrangement*.[261]

260 There are several variations of the ***Ramberg–Bäcklund*** *rearrangement*; for example, the formation of *alkynes* instead of *alkenes* [81b] and [1a]. The S_N2 step in the ***Favorskii*** *rearrangement* (covered in Chapter 37) is related to the ***Ramberg–Bäcklund*** *rearrangement*.

261 The reaction was likely first described around 1940 [81c].

82 Reformatsky Reaction

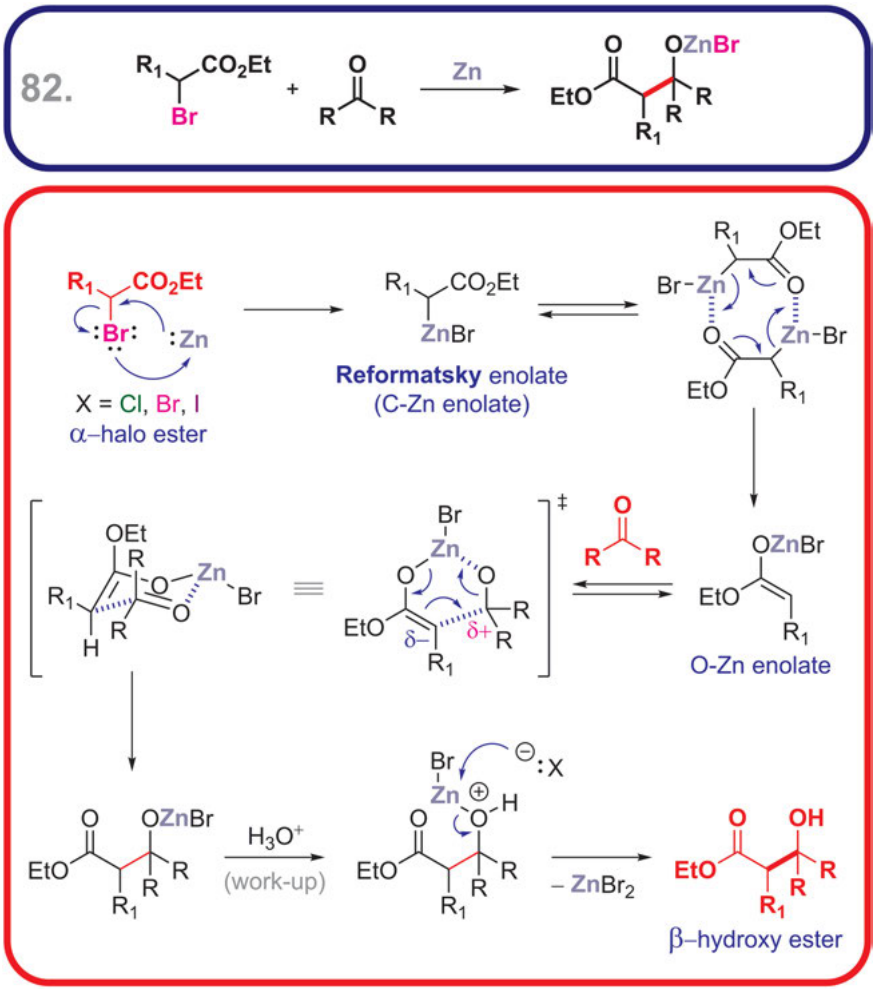

Fig. 82.1: The ***Reformatsky*** *reaction* mechanism.[262]

262 The ***Reformatsky*** *reaction (condensation)* (also spelled Reformatskii, and in Russian Сергей Николаевич Реформатский or С. Н. Реформатский) mechanistically is much like the *aldol condensation* reaction (see Chapter 83).

https://doi.org/10.1515/9783110608373-082

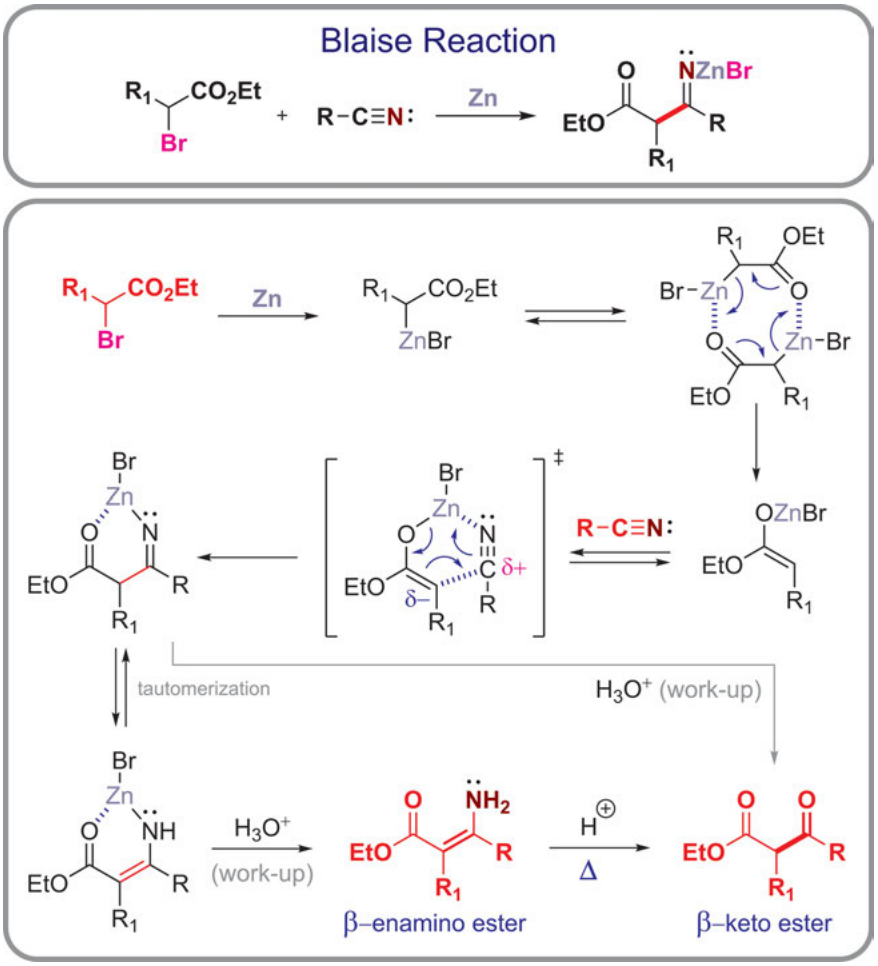

Fig. 82.2: The ***Blaise*** *reaction* mechanism.[263]

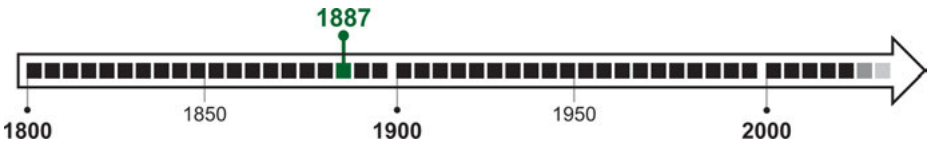

Fig. 82.3: The discovery of the ***Reformatsky*** *reaction*.[264]

263 The ***Blaise*** *reaction* is a variation of the ***Reformatsky*** *reaction* [82a, 82b]. In this case, the preformed ***Reformatsky*** *enolate (C-Zn or O-Zn enolate)* reacts with a *nitrile* instead of an *aldehyde* or *ketone*.

264 The reaction was likely first described around 1887 [82].

83 Robinson Annulation

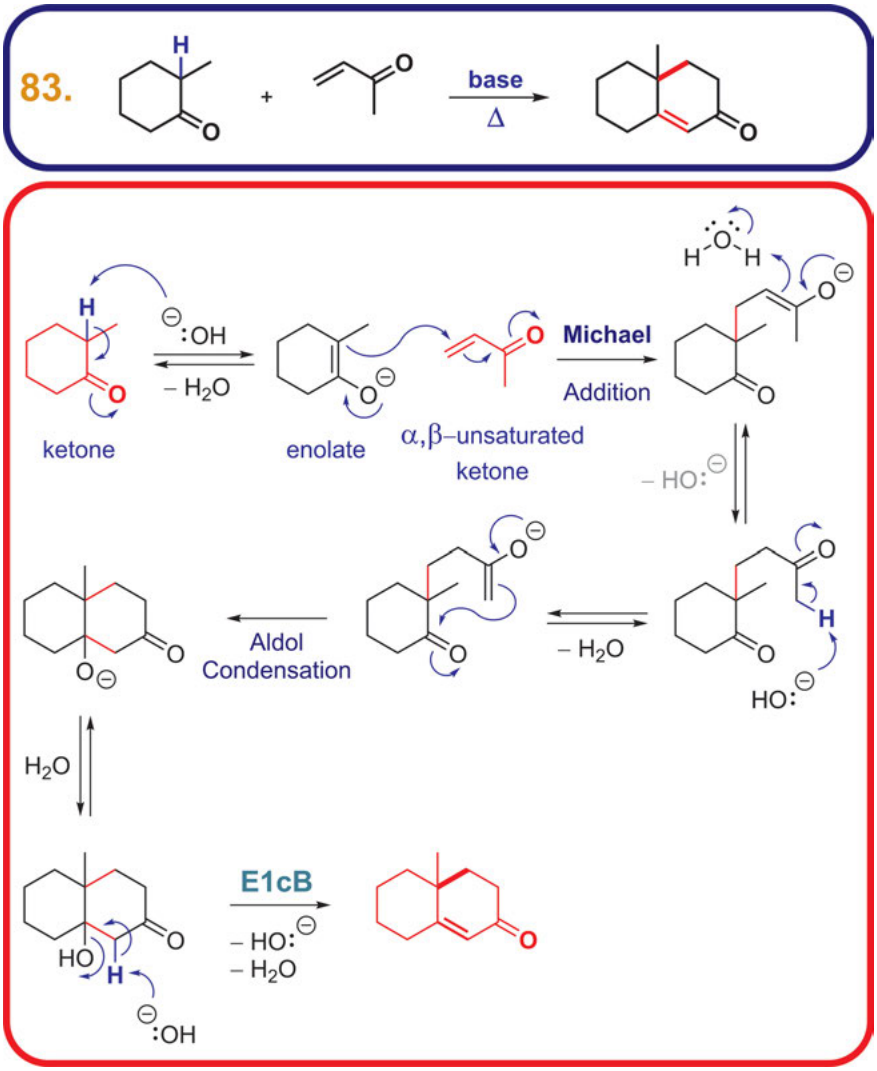

Fig. 83.1: The ***Robinson*** *annulation* mechanism.[265]

265 The ***Robinson*** *annulation* mechanism is a cascade of the ***Michael*** *conjugate addition* (see Chapter 59), followed by the *aldol condensation*, and finally **E1cB** *elimination* (see Chapter 6).

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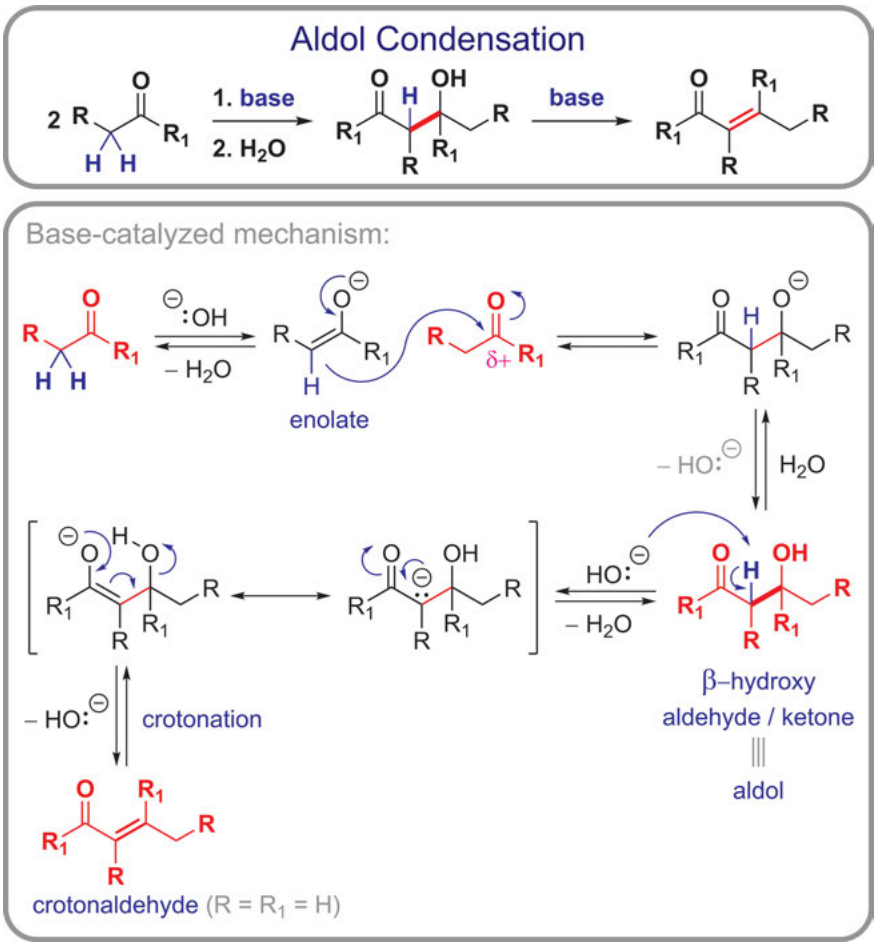

Fig. 83.2: The *aldol condensation* mechanism.[266]

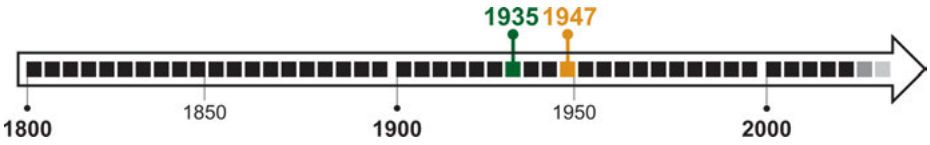

Fig. 83.3: The discovery of the ***Robinson*** *annulation*.[267]

266 The *base-catalyzed aldol condensation* can yield *β–hydroxy aldehydes (**aldols**)* or ketones. The formed *aldols* can undergo an elimination and yield *crotonaldehydes* (the *croton condensation = crotonation)* [1].

267 The reaction was likely first described around 1935 [83a]. In **1947**, Sir Robert Robinson received the Nobel Prize in Chemistry for his work related to alkaloids [83b].

84 Shapiro Reaction

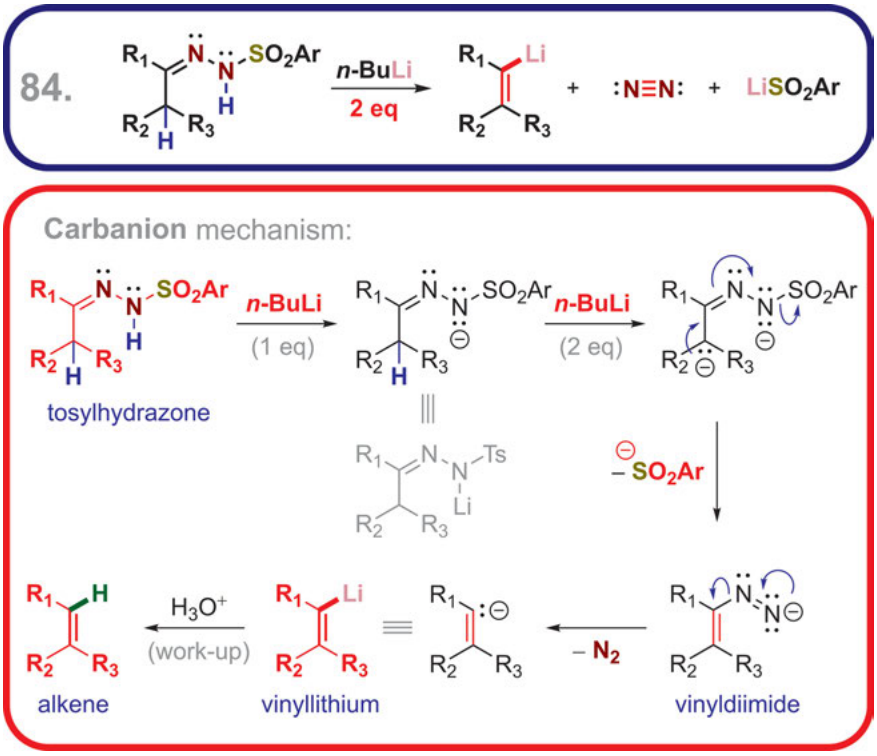

Fig. 84.1: The ***Shapiro*** *reaction* mechanism.[268]

268 The ***Shapiro*** *reaction* is a type of **elimination** reaction that undergoes the *carbanion* mechanism.

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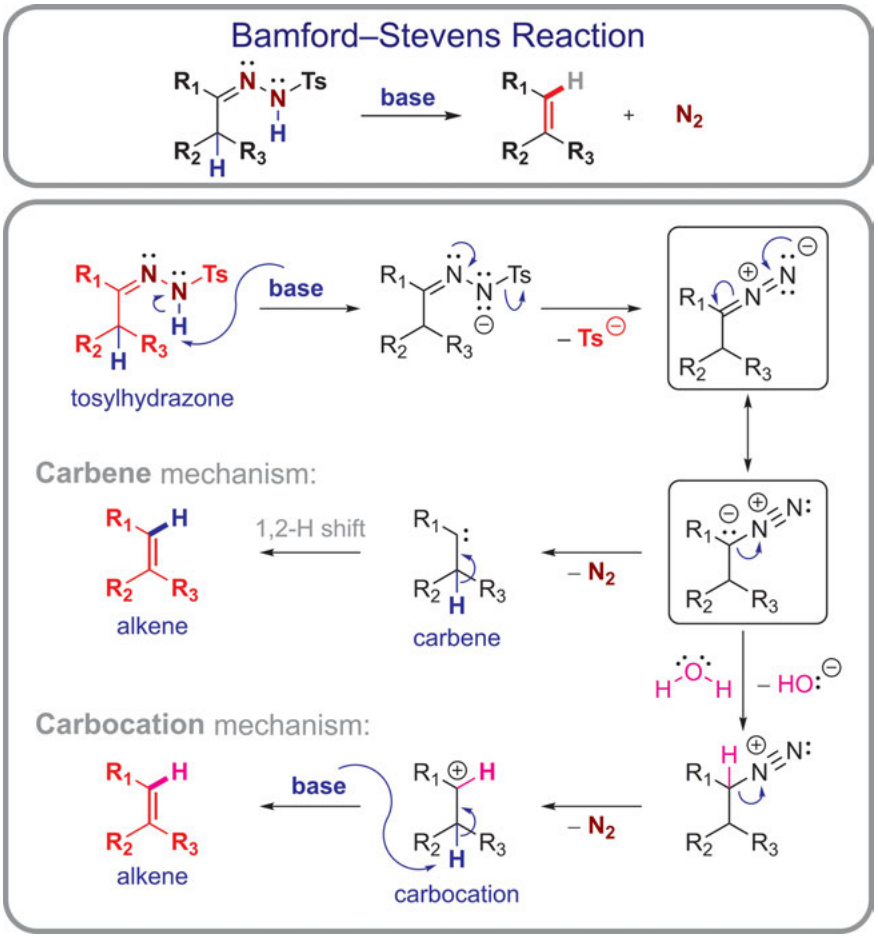

Fig. 84.2: The ***Bamford–Stevens*** *reaction* mechanism.[269]

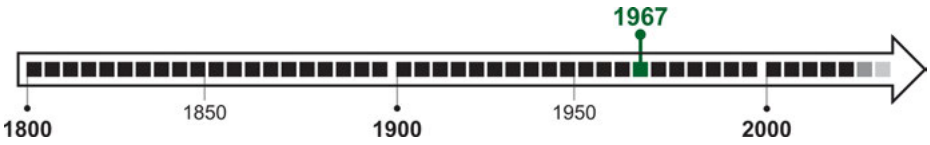

Fig. 84.3: The discovery of the ***Shapiro*** *reaction*.[270]

269 The ***Bamford–Stevens*** *reaction* is a more general variation of the ***Shapiro*** *reaction*. Two mechanisms are possible: the *carbene* mechanism and the *carbocation* mechanism (the *carbenium ion* mechanism) [84a].

270 The reaction was likely first described around 1967 [84b], see also [84c, 84d].

85 Sonogashira Cross Coupling

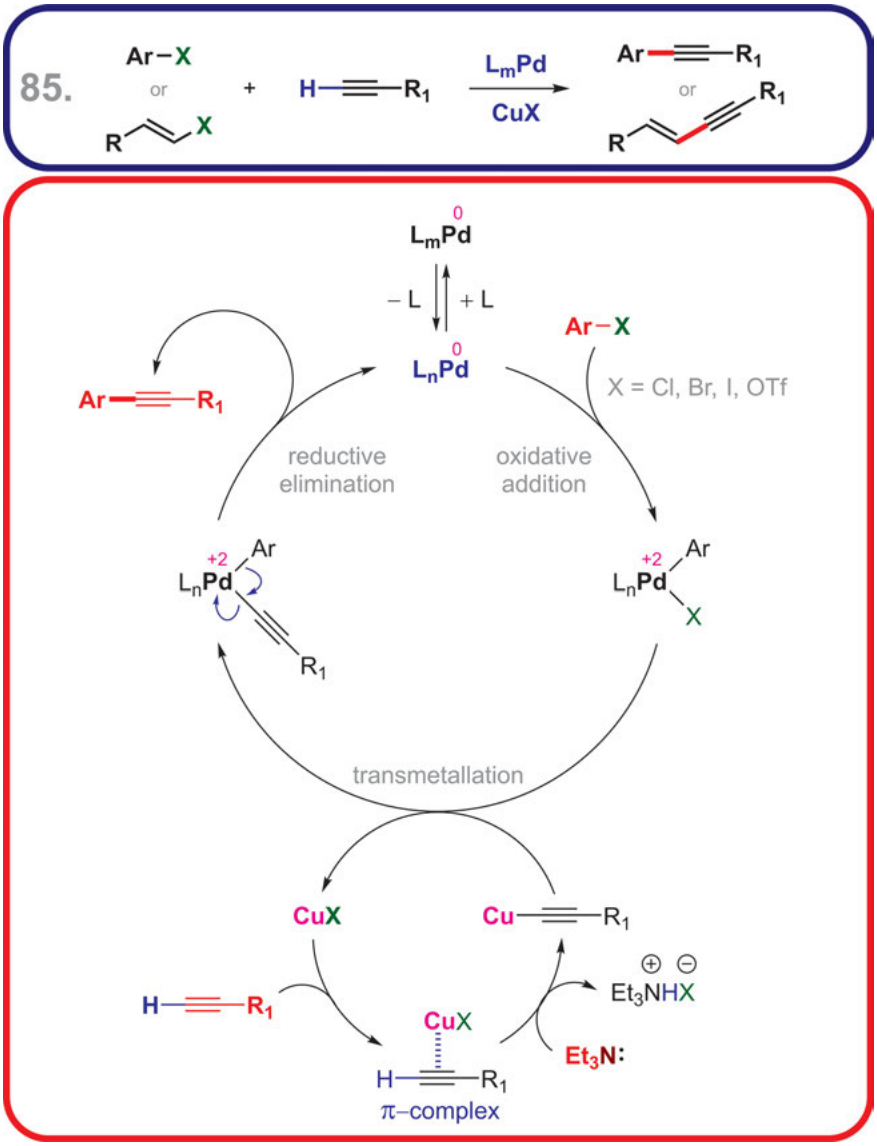

Fig. 85.1: The ***Sonogashira*** *cross coupling* mechanism.[271]

271 The ***Sonogashira*** *cross coupling* is a type of mixed ***Pd****-catalyzed* and ***Cu****-co-catalyzed cross coupling* reaction (C–C bond formation using *aryl halides* and *terminal alkynes*). For teaching purposes, a simplified and general mechanism (with two catalytic cycles using **Pd** and **Cu**) is shown.

https://doi.org/10.1515/9783110608373-085

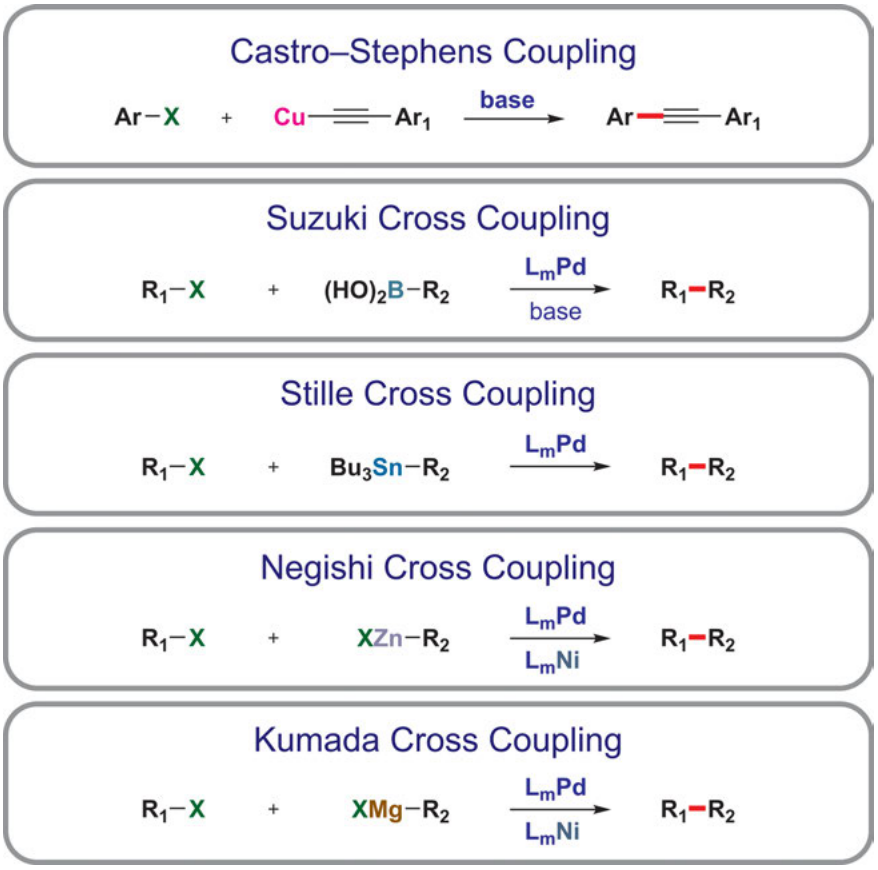

Fig. 85.2: Reactions related to the ***Sonogashira*** *cross coupling*.[272]

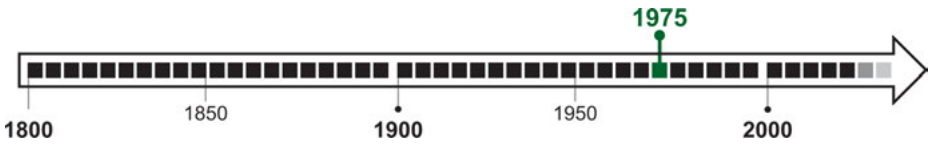

Fig. 85.3: The discovery of the ***Sonogashira*** *cross coupling*.[273]

272 The ***Castro–Stephens*** *cross coupling* is ***Cu****-catalyzed* and closely related (C–C bond formation using *aryl halides* and pre-formed or *in situ* generated *copper(I) acetylides*) [85a]. Other cross coupling reactions are also related to the ***Sonogashira*** *cross coupling:* the ***Suzuki*** (Chapter 89), the ***Stille*** (Chapter 88), the ***Negishi*** (Chapter 66), and the ***Kumada*** *cross coupling* (Chapter 53).

273 The reaction was likely first described around 1975 [85b].

86 Staudinger Reaction

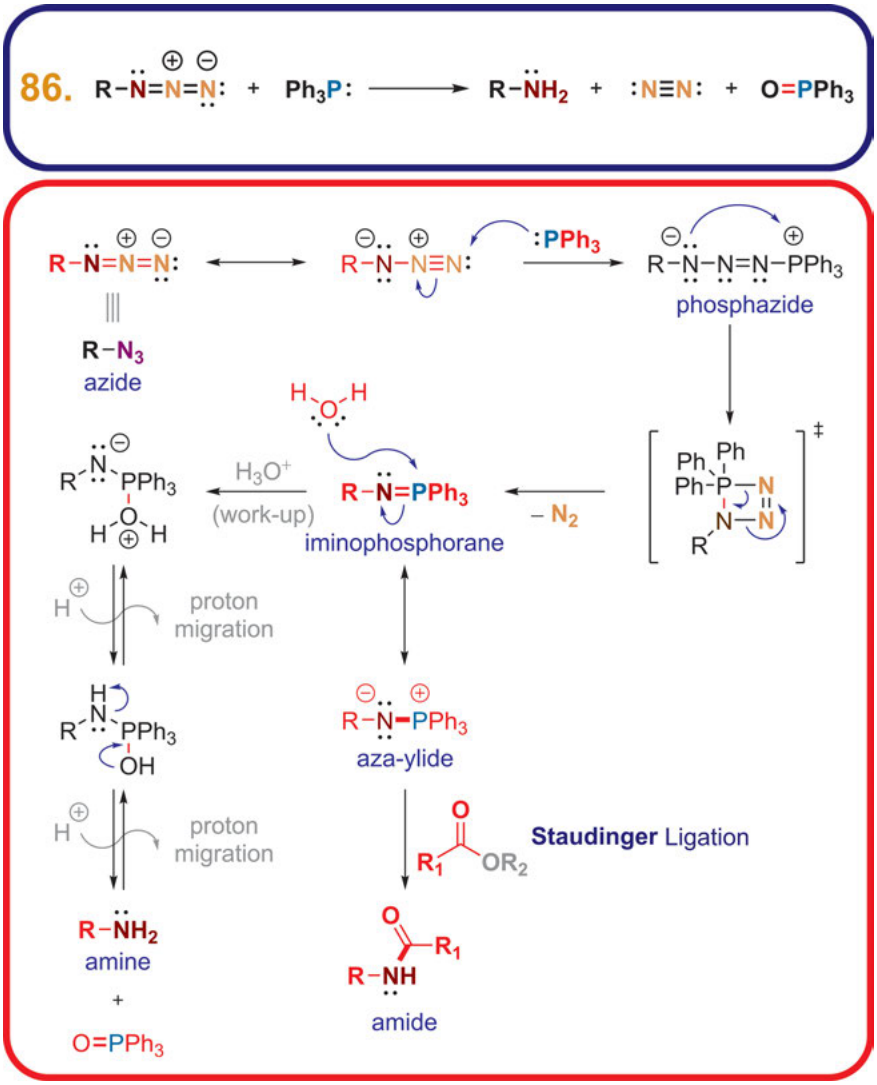

Fig. 86.1: The ***Staudinger*** *reaction* mechanism.[274]

274 The ***Staudinger*** *reaction (reduction)* is a reduction of *azides* to primary amines using *triphenylphosphine*. It should not be confused with the ***Staudinger*** *synthesis or* the ***Staudinger*** *ketene cycloaddition reaction* (for example, formation of *β–lactams*) [86a, 86b].

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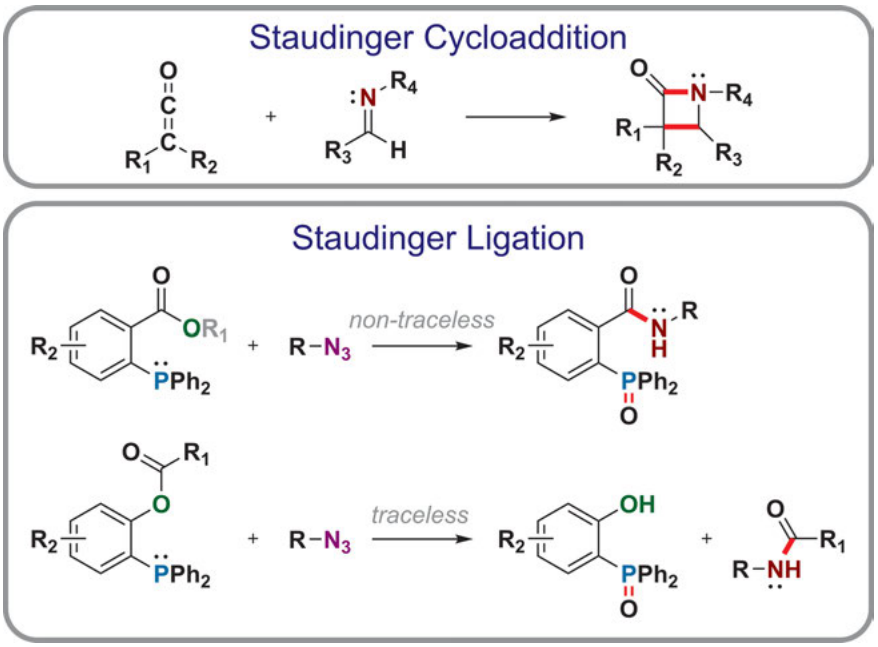

Fig. 86.2: The ***Staudinger*** *cycloaddition* and *ligation*.[275]

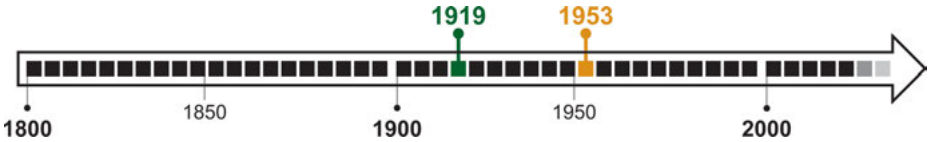

Fig. 86.3: The discovery of the ***Staudinger*** *reaction*.[276]

275 The ***Staudinger*** *ligation* [86c, 86d] is a modification of the ***Staudinger*** *reaction*: in this case, the generated *aza-ylide* is trapped with an *ester* to form an *amide* bond. There are two general types: *non-traceless* and *traceless* ***Staudinger*** *ligation* [86e].

276 The reaction was likely first described around 1919 [86f]. In **1953**, Hermann Staudinger received the Nobel Prize in Chemistry for his work in macromolecular chemistry [86g].

87 Steglich Esterification

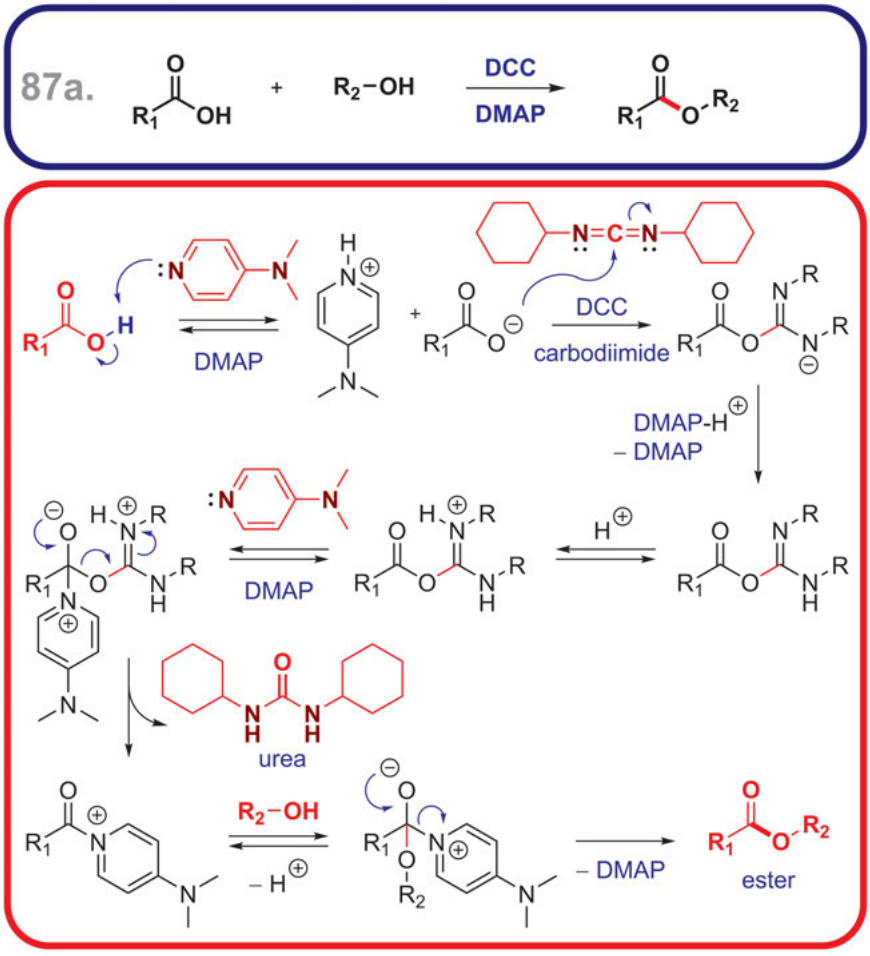

Fig. 87.1: The ***Steglich*** *esterification* mechanism (DCC + DMAP).[277]

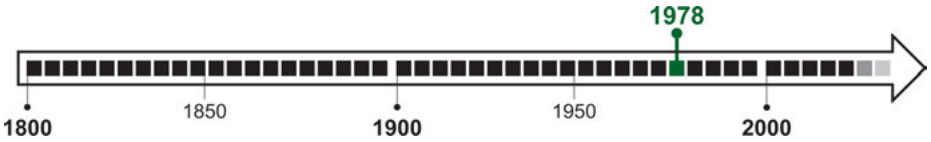

Fig. 87.2: The discovery of the ***Steglich*** *esterification*.[278]

277 The ***Steglich*** *esterification* is an *ester coupling reaction* (compare to the *peptide (amide) coupling* mechanism in Chapter 74 or the ***Fischer*** *esterification* – not covered here). The mechanism involves

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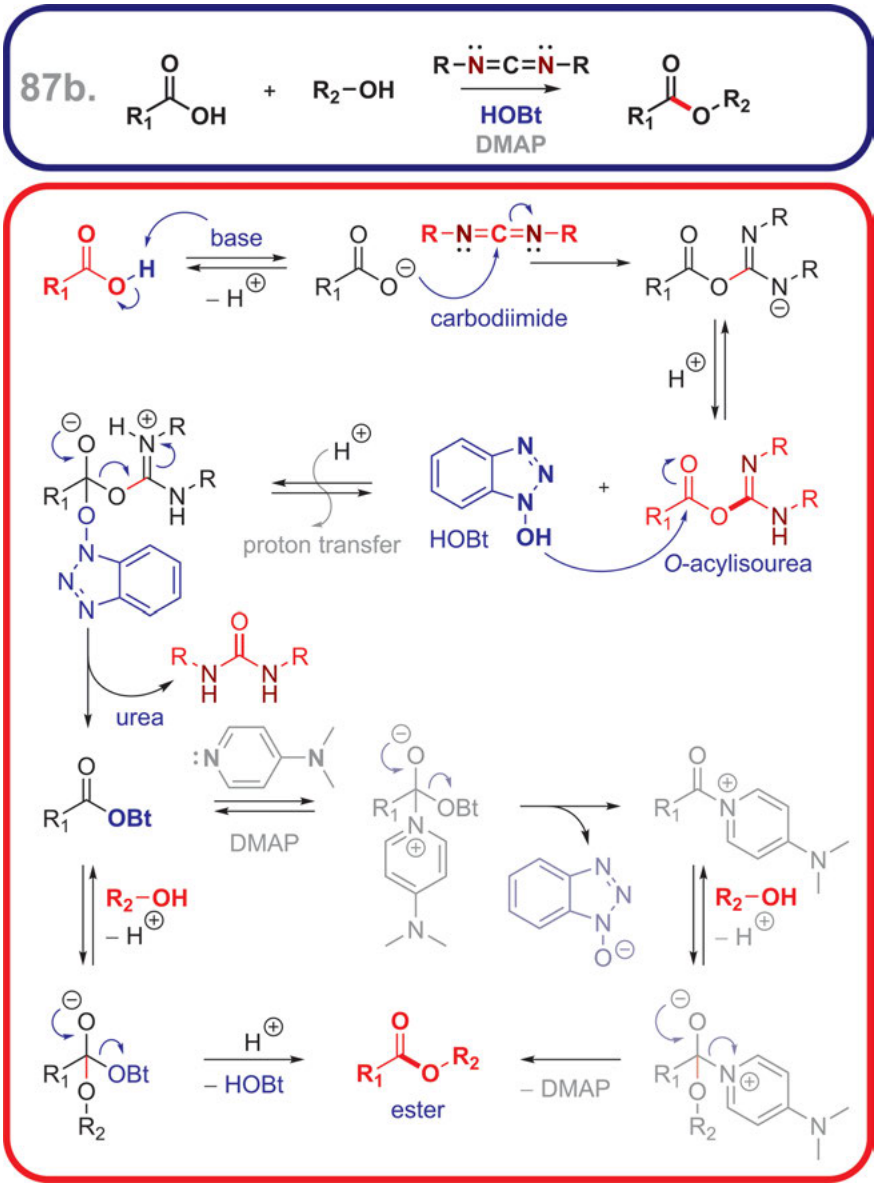

Fig. 87.3: The ***Steglich*** *esterification* mechanism (DCC + HOBt + DMAP).[279]

the use of *carbodiimide* coupling reagents (DCC) and DMAP catalyst [87a].

278 The reaction was likely first described around 1978 [87b].

279 The ***Steglich*** *esterification* can be carried out with DCC in the presence of other *peptide (amide) coupling additives* (for example, HOBt) with or without DMAP catalyst.

88 Stille Cross Coupling

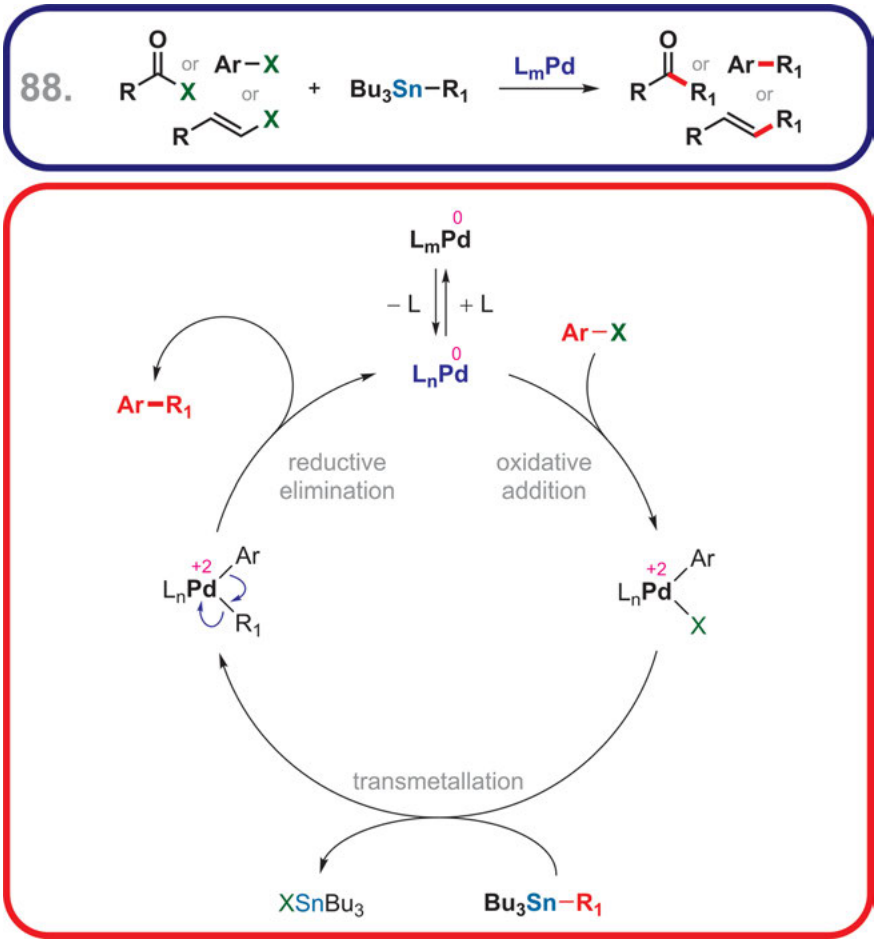

Fig. 88.1: The ***Stille*** *cross coupling* mechanism.[280]

280 The ***Stille*** *cross coupling* or the ***Migita–Kosugi–Stille*** *cross coupling* is a versatile type of ***Pd***-*catalyzed cross coupling* reaction (C–C bond formation using *aryl halides* or other *electrophiles* and *organotin compounds* = *organostannanes*). For teaching purposes, a simplified and general mechanism is shown.

https://doi.org/10.1515/9783110608373-088

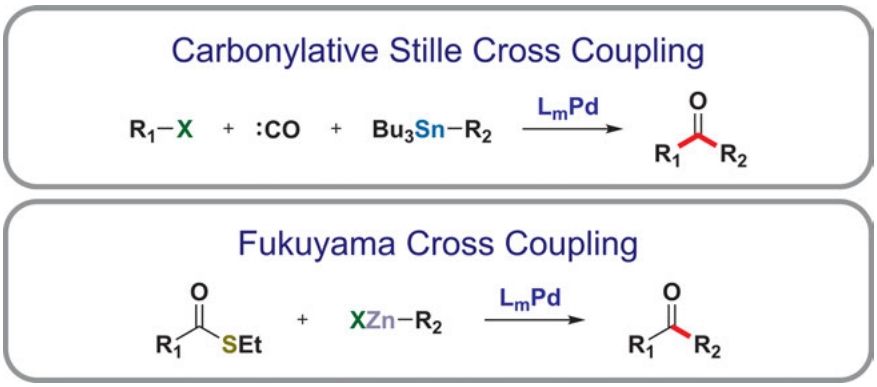

Fig. 88.2: Reactions related to the ***Stille*** *cross coupling*.[281]

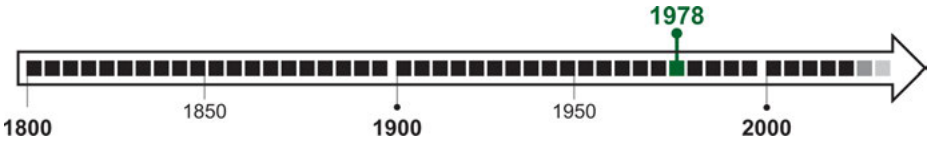

Fig. 88.3: The discovery of the ***Stille*** *cross coupling*.[282]

281 The *carbonylative* ***Stille*** *cross coupling* is related to the ***Stille*** *cross coupling*. It is a method to form *ketones* (two C–C bond formations using *aryl halides* or other *electrophiles*, *organostannanes*, and *carbon monoxide*) [88a]. Ketones can also be formed via the ***Fukuyama*** *cross coupling* (C–C bond formation using *thioesters* and *organozinc compounds*) [88b] or the ***Liebeskind–Srogl*** *cross coupling* covered in Chapter 55 (C–C bond formation using *thioesters* and *boronic acids*).

282 The reaction was likely first described around 1978 [88c, 88d].

89 Suzuki Cross Coupling

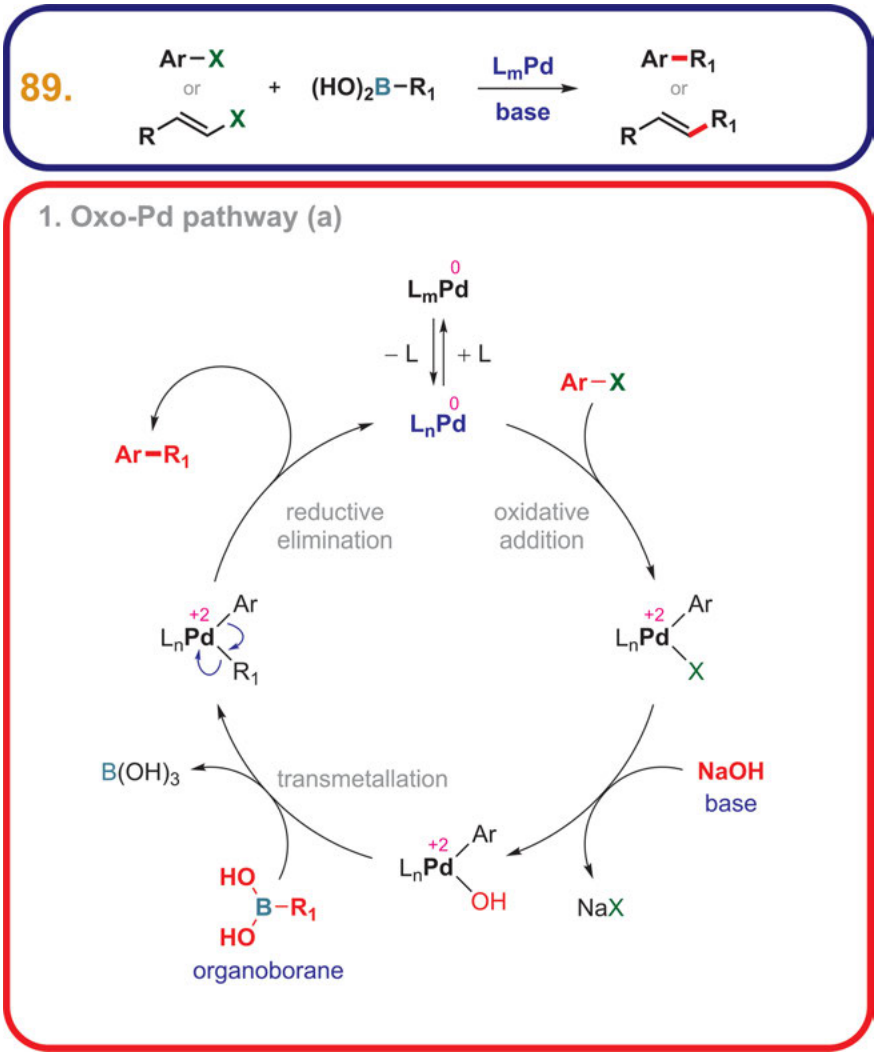

Fig. 89.1: The ***Suzuki*** *cross coupling* mechanism (oxo-**Pd** pathway (**a**)).[283]

283 The ***Suzuki*** *cross coupling* or the ***Suzuki–Miyaura*** *cross coupling* is a type of ***Pd****-catalyzed cross coupling* reaction (C–C bond formation using *aryl halides* and *organoboronic acids*). It is one of the most important reactions in synthetic organic and medicinal chemistry. The *oxo-****Pd*** *pathway* (**a**) is the preferred mechanism [89a].

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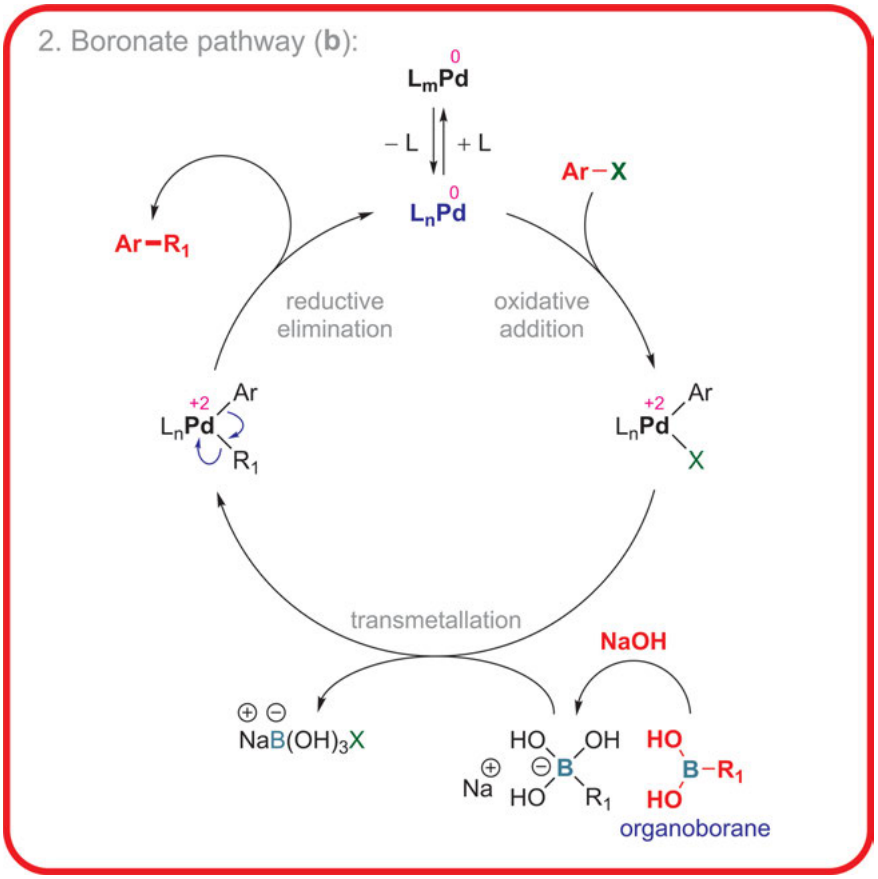

Fig. 89.2: The ***Suzuki*** *cross coupling* mechanism (boronate pathway (**b**)).[284]

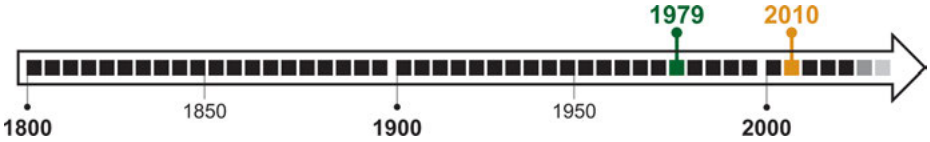

Fig. 89.3: The discovery of the ***Suzuki*** *cross coupling*.[285]

284 The reaction mechanism can also be explained by the *boronate pathway* (**b**). For teaching purposes, a simplified and general mechanism is shown [89b].

285 The reaction was likely first described around 1979 [89c, 89d]. In **2010**, Akira Suzuki (jointly with Richard F. Heck and Ei-ichi Negishi) received the Nobel Prize in Chemistry for the development of **Pd**-catalyzed cross coupling reactions [46c].

90 Swern Oxidation

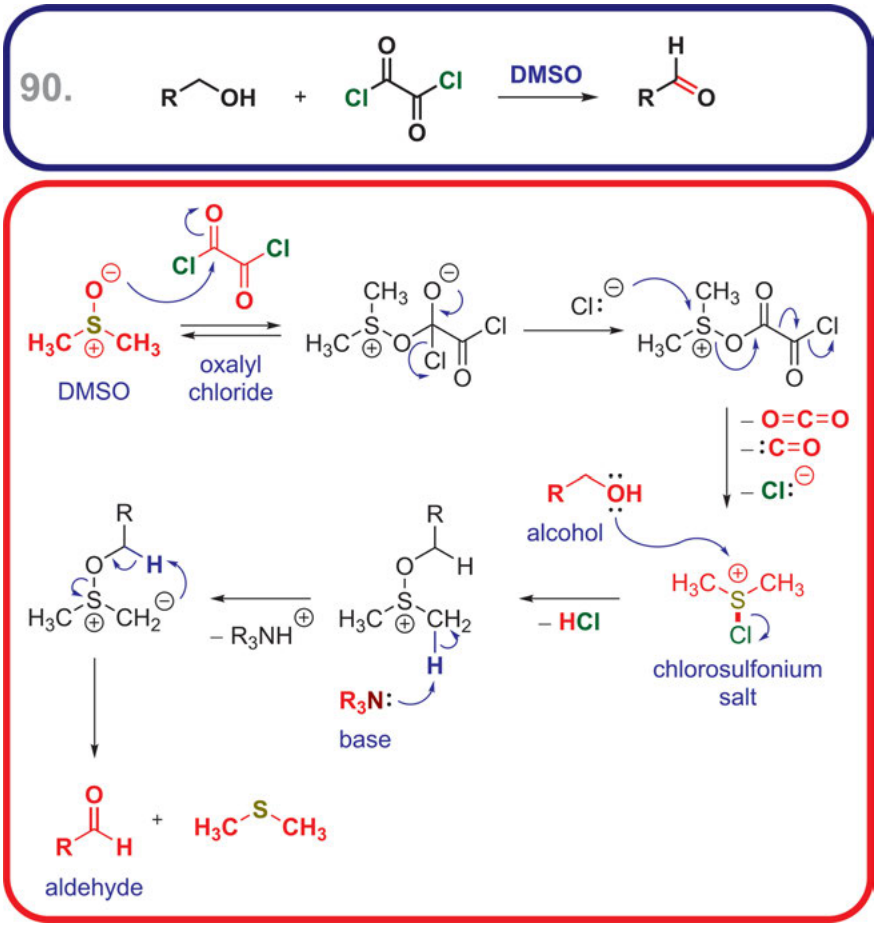

Fig. 90.1: The ***Swern*** *oxidation* mechanism.[286]

286 The ***Swern*** *oxidation* is one of the most important reactions in synthetic organic and medicinal chemistry.

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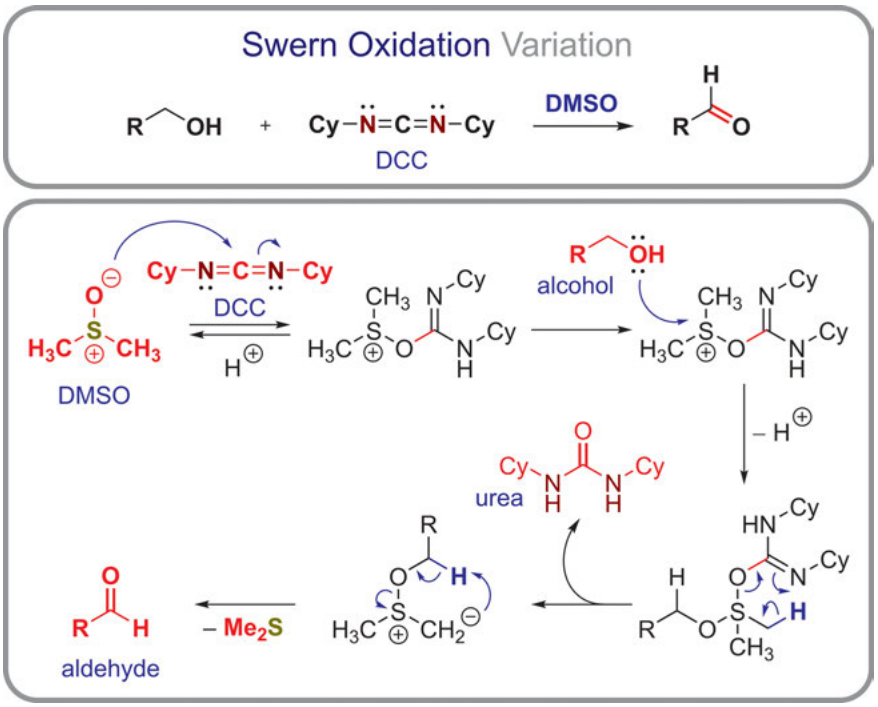

Fig. 90.2: The ***Swern*** *oxidation* variation mechanism (DCC + DMSO).[287]

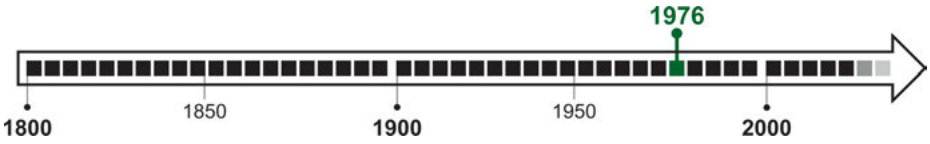

Fig. 90.3: The discovery of the ***Swern*** *oxidation*.[288]

287 There are numerous variations of the ***Swern*** *oxidation*: the ***Swern*** *variation* using TFAA and DMSO [90a] or *carbodiimide reagent* (DCC) and DMSO [90b]. Several important named oxidation reactions yield *ketones* from *alcohols*: the ***Dess–Martin*** *oxidation* (Chapter 33), the ***Jones*** *oxidation* (Chapter 51).

288 The reaction was likely first described around 1976 [90a], see also [90c, 90d].

91 Ugi Reaction

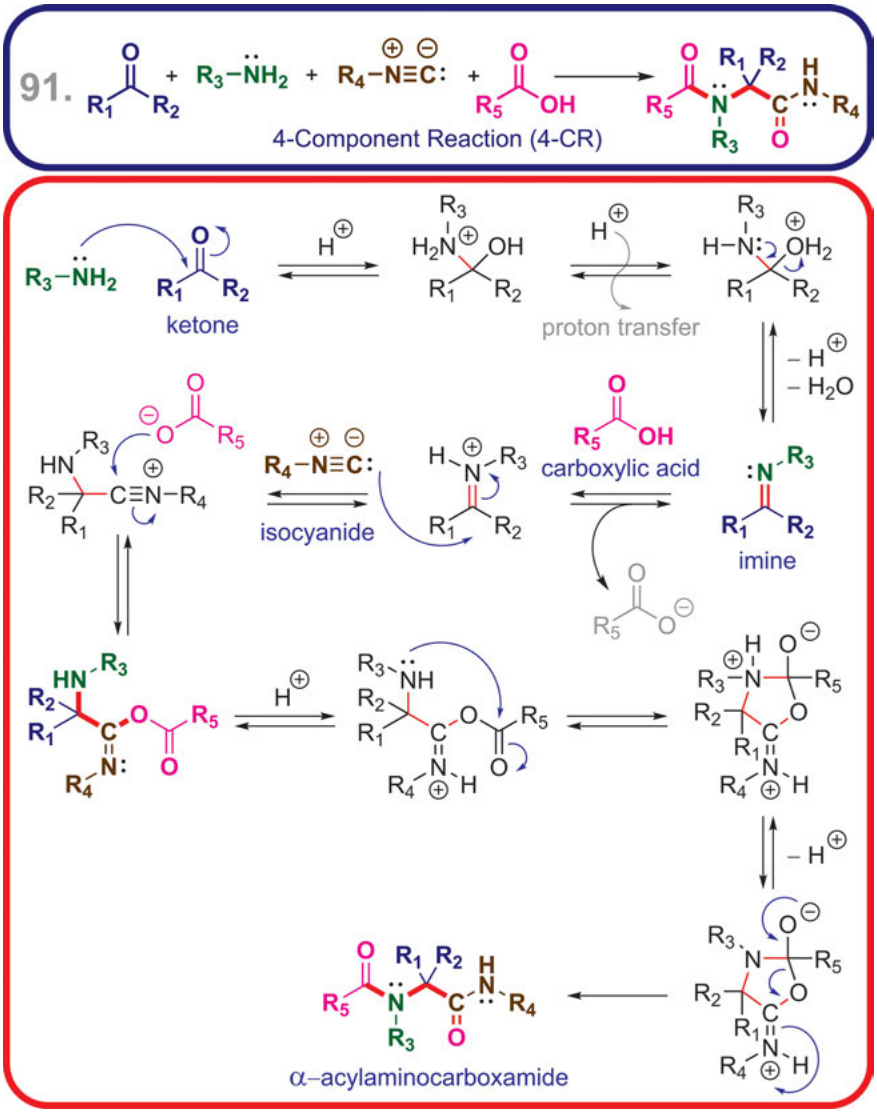

Fig. 91.1: The ***Ugi*** *reaction* mechanism.[289]

289 The ***Ugi*** *reaction* or the ***Ugi*** *condensation* is a type of multi-component reaction (MCR): a four-component reaction (4-CR).

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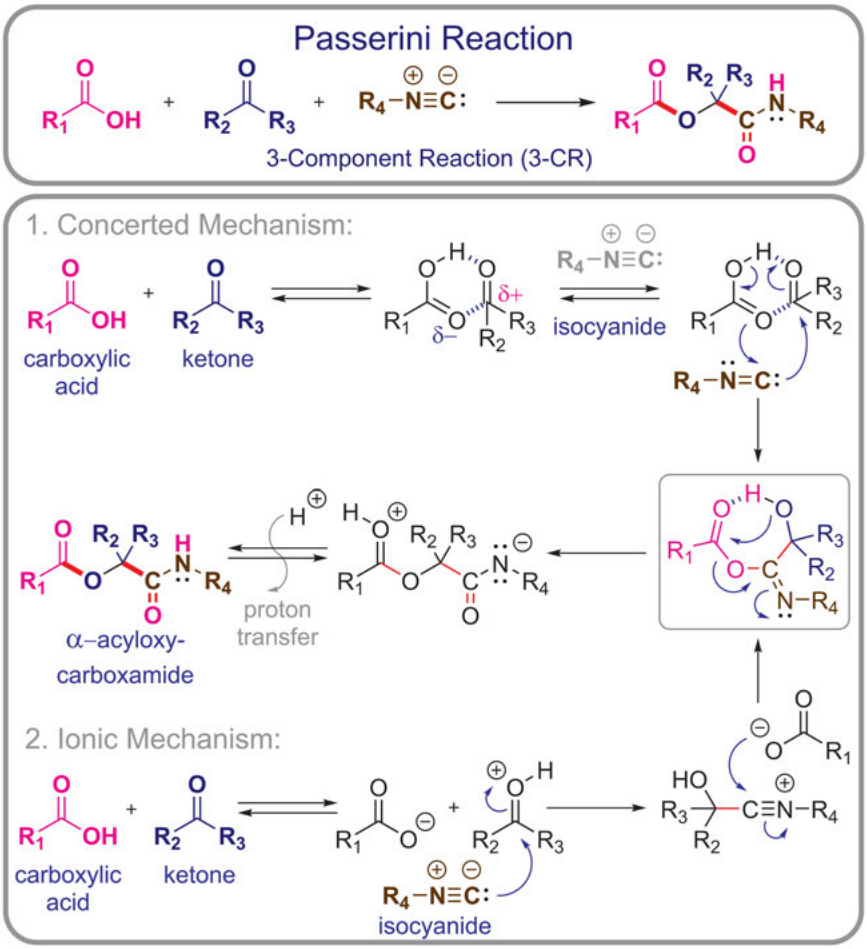

Fig. 91.2: The ***Passerini*** *reaction* mechanism.[290]

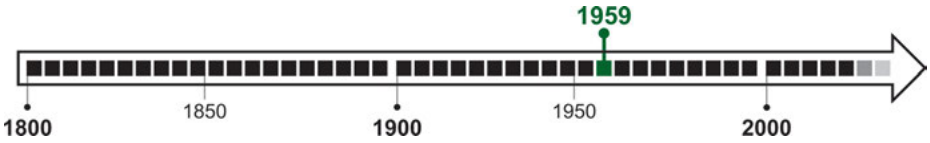

Fig. 91.3: The discovery of the ***Ugi*** *reaction*.[291]

290 The ***Passerini*** *reaction* is mechanistically related to the ***Ugi*** *reaction* [91a, 91b]. The product formation can be rationalized either via 1. the *concerted* mechanism or 2. the *ionic* mechanism. Other 3-CR's were also mentioned in this book: the ***Gewald*** *reaction* (Chapter 41), the ***Mannich*** *reaction* (Chapter 56), the ***Petasis*** *reaction* (Chapter 62), the ***Pauson–Khand*** *reaction* (Chapter 73).

291 The reaction was likely first described around 1959 [91c].

92 Ullmann Aryl–Aryl Coupling

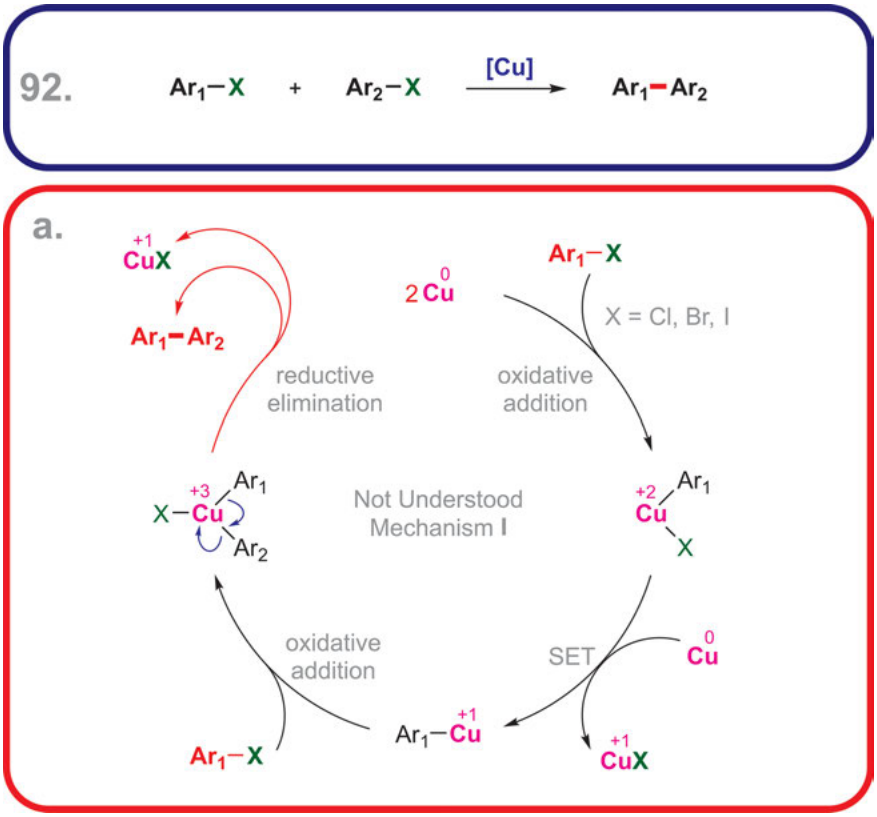

Fig. 92.1: The ***Ullmann*** *aryl–aryl coupling* mechanism I.[292]

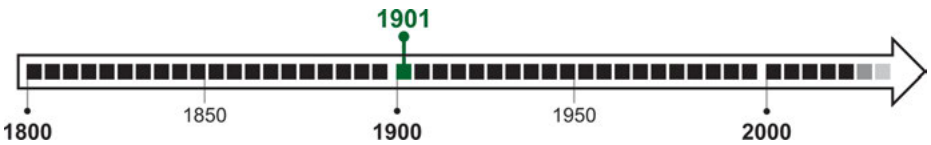

Fig. 92.2: The discovery of the ***Ullmann*** *aryl–aryl coupling*.[293]

292 The ***Ullmann*** *aryl–aryl coupling* or the ***Ullmann*** *reaction* is a ***Cu****-mediated coupling* (C–C bond formation using *aryl halides*). The mechanism is not fully understood. A possible formation of *organo-copper* intermediates (Cu(I) or Cu(II)) is postulated: mechanism I (**a**).
293 The reaction was likely first described around 1901 [92a, 92b].

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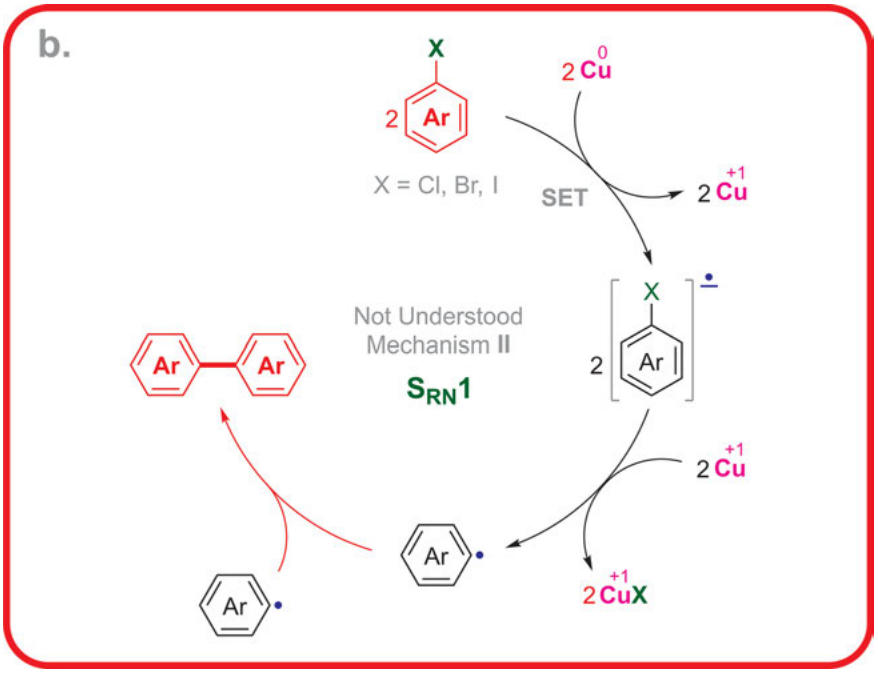

Fig. 92.3: The ***Ullmann*** *aryl–aryl coupling* mechanism II.[294]

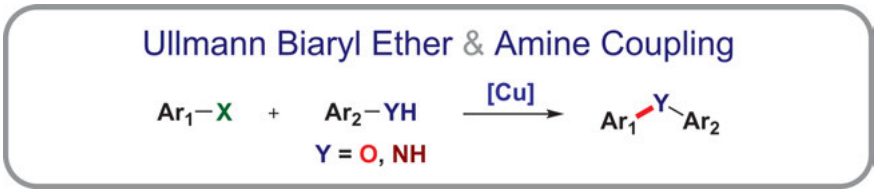

Fig. 92.4: The ***Ullmann*** *biaryl ether & amine coupling*.[295]

294 The **aromatic radical nucleophilic substitution** ($\mathbf{S_{RN}1}$) mechanism (Chapter 5) is another explanation for the formation of the *symmetrical* or *asymmetrical biaryl* products: mechanism II (**b**).

295 The ***Ullmann*** *biaryl ether* and *biaryl amine coupling* reaction is more synthetically useful [92c, 92d]. It is also a ***Cu****-mediated coupling* (C–O and C–N bond formation using *aryl halides* with *phenols* or *anilines*) [92e]. An alternative way to synthesize *aryl ethers* and *amines* is via the ***Chan–Evans–Lam*** *cross coupling* (Chapter 23).

93 Upjohn Dihydroxylation

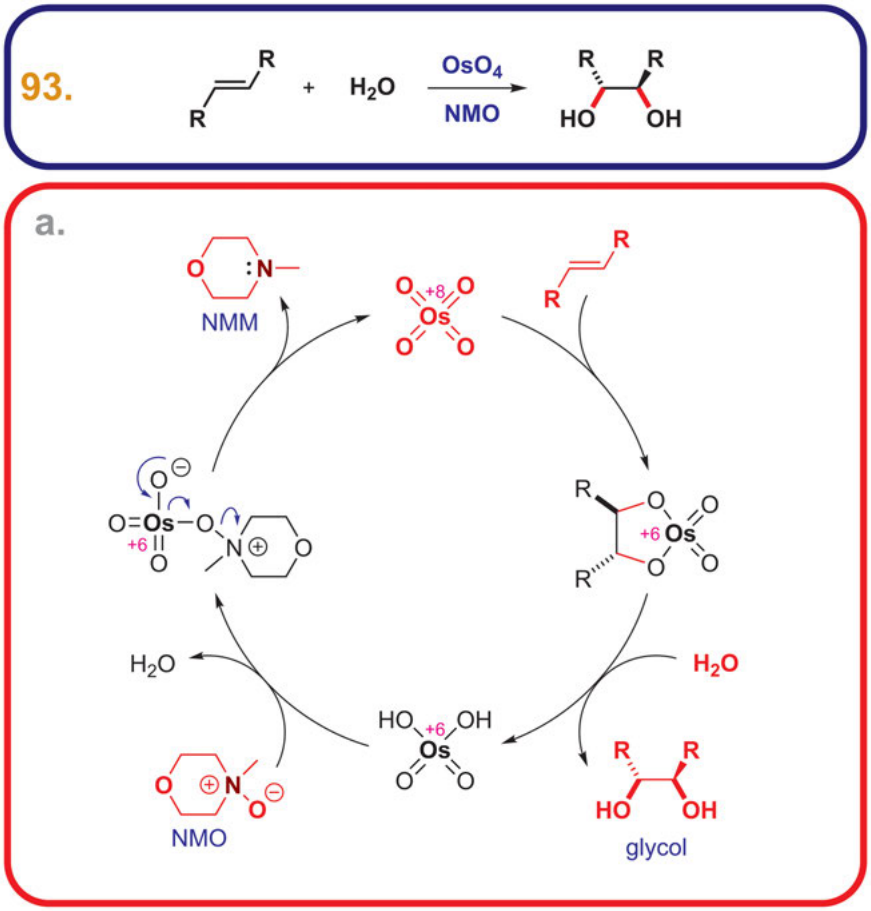

Fig. 93.1: The ***Upjohn*** *dihydroxylation* mechanism (a).[296]

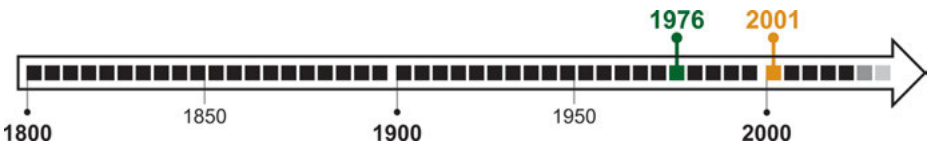

Fig. 93.2: The discovery of the ***Upjohn*** *dihydroxylation*.[297]

296 The ***Upjohn*** *dihydroxylation* (**a**) yields racemic products (*cis-1,2-glycols* = *cis*-1,2-diols) [93a].
297 The reaction was likely first described around 1976 [93f]. In **2001**, K. Barry Sharpless (together with William S. Knowles and Ryoji Noyori) received the Nobel Prize in Chemistry for the development

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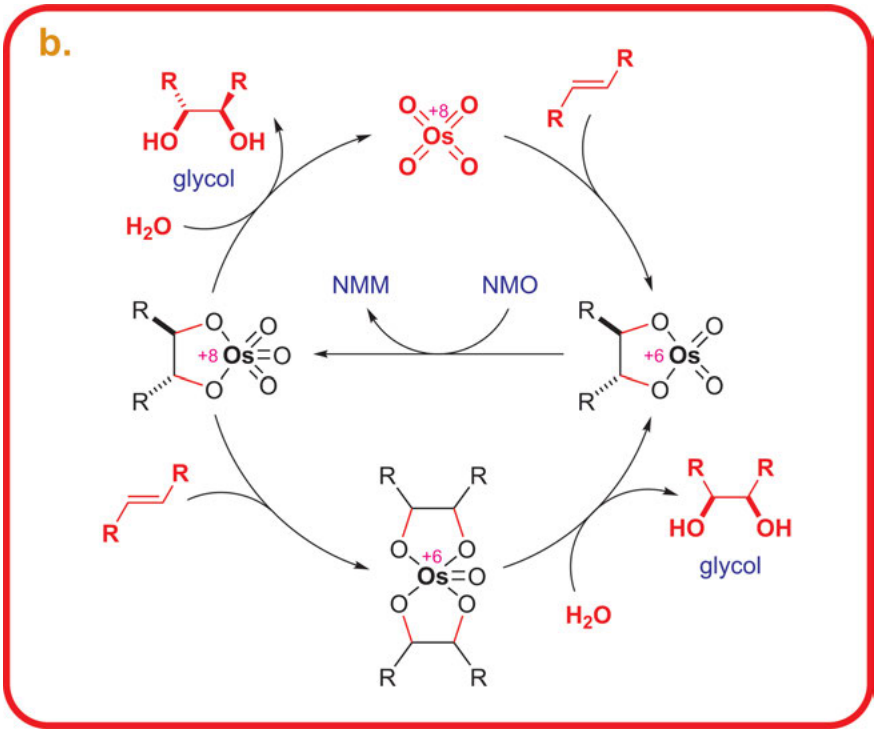

Fig. 93.3: The ***Upjohn*** *dihydroxylation* mechanism (b).[298]

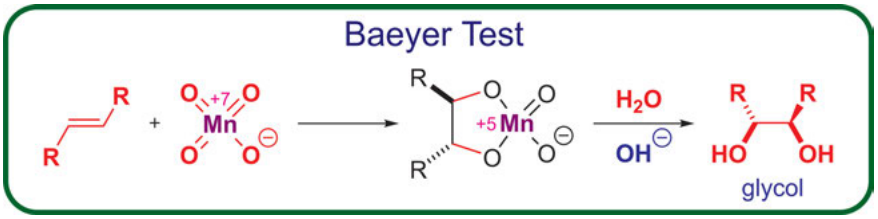

Fig. 93.4: The ***Baeyer*** *test*.[299]

of chirally catalyzed oxidation and hydrogenation reactions [93g].

298 The ***Sharpless*** *asymmetric dihydroxylation* is exemplified in a simplified mechanism (**b**). It is an asymmetric variation of the ***Upjohn*** *dihydroxylation* and it yields enantiomerically pure products [93b, 93c, 93d].

299 The ***Baeyer*** *test (**Baeyer's** test)* (potassium permanganate-based TLC stain) is a reaction related to the ***Upjohn*** *dihydroxylation*. It is used to detect the presence of *double bonds (unsaturation)* [93e].

94 Vilsmeier–Haack Reaction

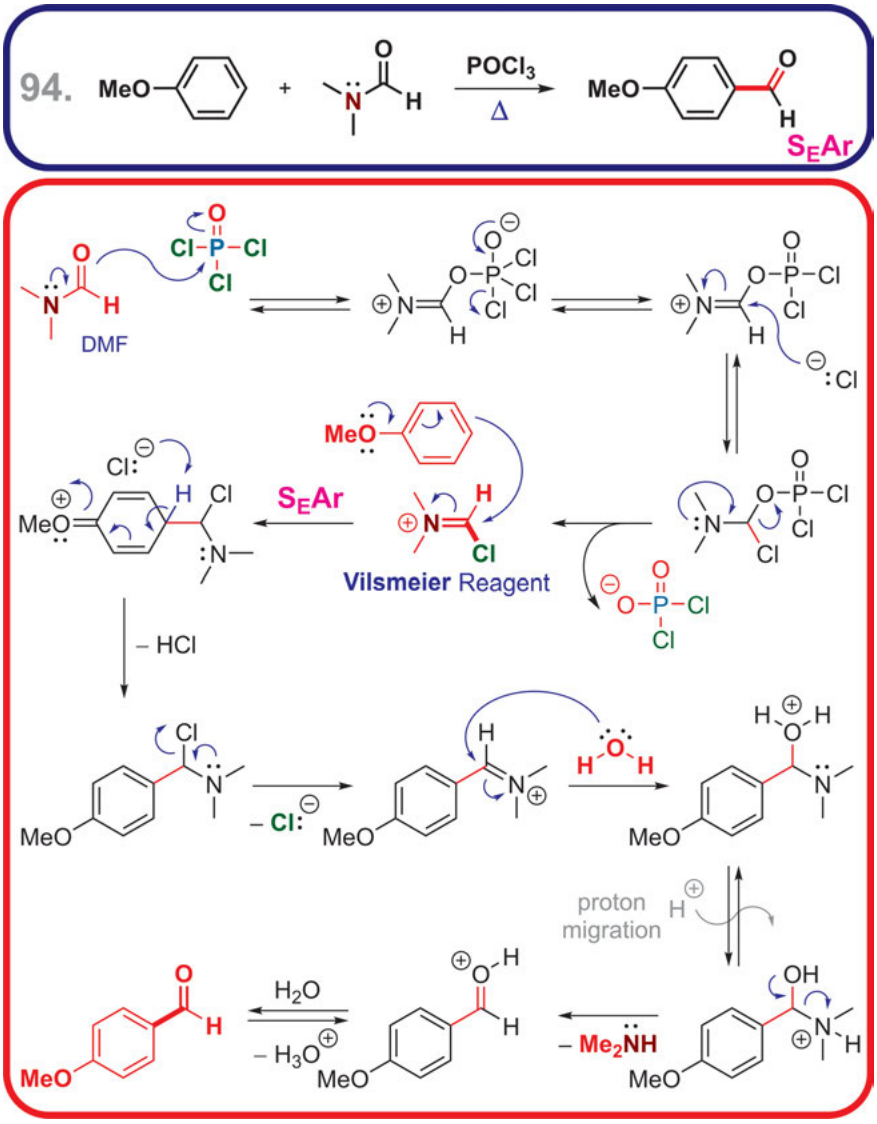

Fig. 94.1: The ***Vilsmeier–Haack*** *reaction* mechanism.[300]

300 The ***Vilsmeier–Haack*** *reaction* or the ***Vilsmeier–Haack*** *formylation* is a classic example of **aromatic electrophilic substitution** (the ***arenium ion*** mechanism = **S_EAr**, covered in Chapter 3).

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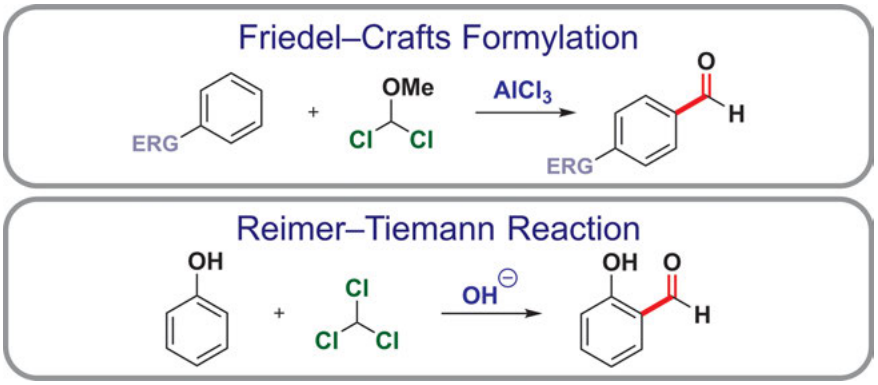

Fig. 94.2: Reactions related to the ***Vilsmeier–Haack*** *reaction*.[301]

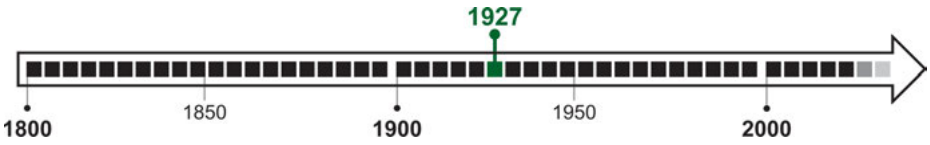

Fig. 94.3: The discovery of the ***Vilsmeier–Haack*** *reaction*.[302]

301 A few named reactions are related to the ***Vilsmeier–Haack*** *reaction*: the ***Friedel–Crafts*** *formylation* using *dichloro(methoxy)methane* (the ***Friedel–Crafts*** reaction is covered in Chapter 39), the ***Reimer–Tiemann*** *reaction* using *chloroform* (limited to the *ortho*-formylation of *phenols*) [94a], and others (not shown here) [1].

302 The reaction was likely first described around 1927 [94b].

95 Wacker Oxidation

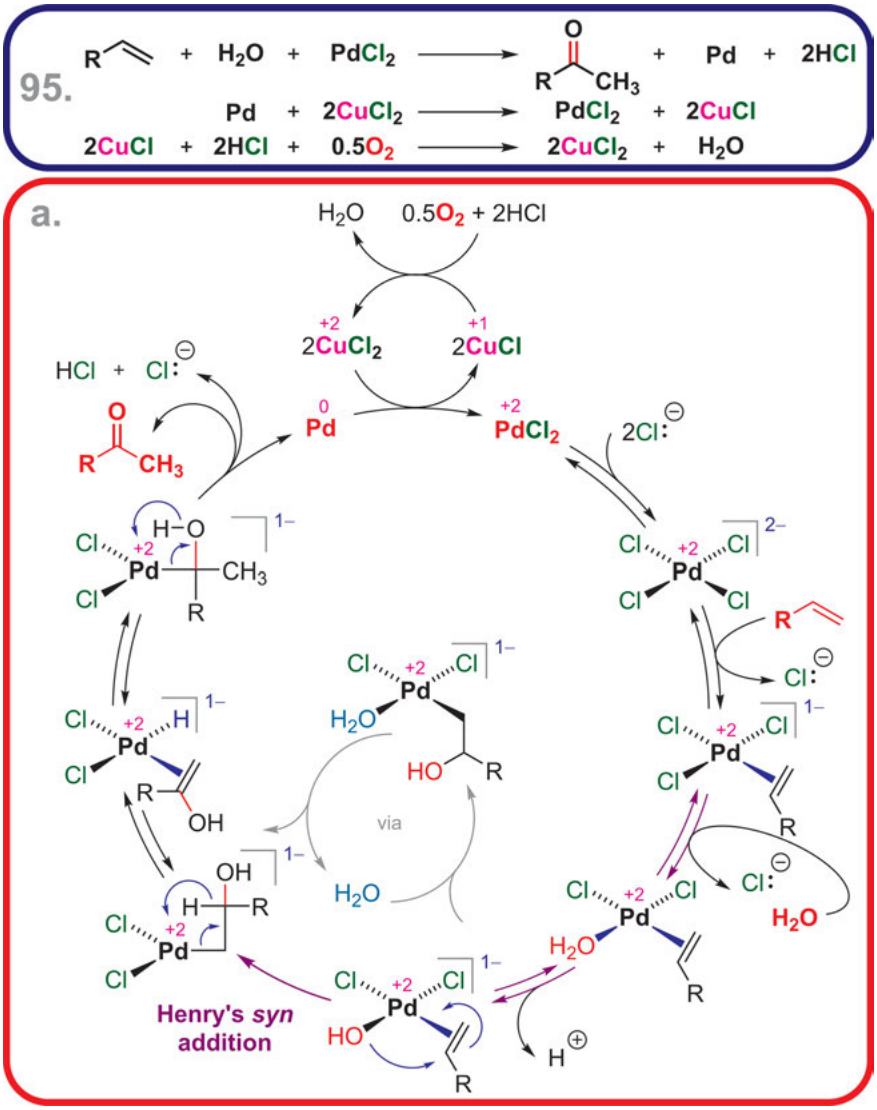

Fig. 95.1: The ***Wacker*** *oxidation* mechanism (a).[303]

303 The ***Wacker*** *oxidation* or the ***Wacker*** *process* is a ***Pd****-catalyzed* and ***Cu****-co-catalyzed* alkene (olefin) oxidation. The mechanism can vary: mechanism (**a**) is proposed by Henry: ***Henry's*** *syn addition* (inner-sphere) [95a, 95b].

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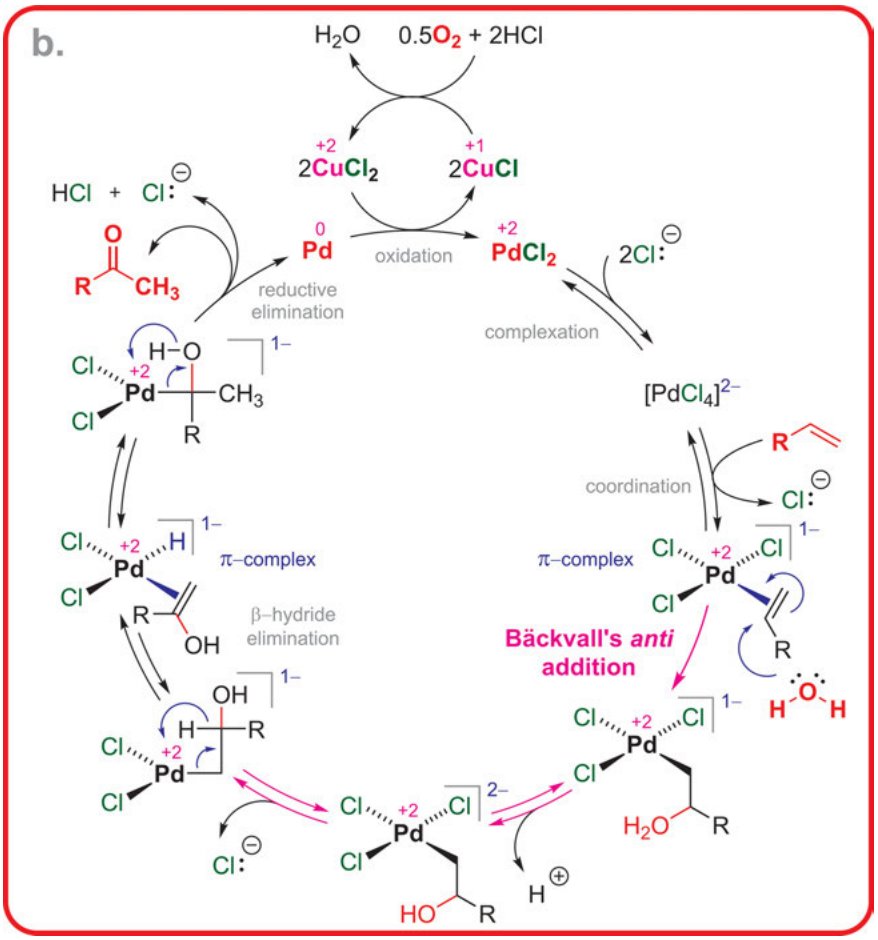

Fig. 95.2: The ***Wacker*** *oxidation* mechanism (b).[304]

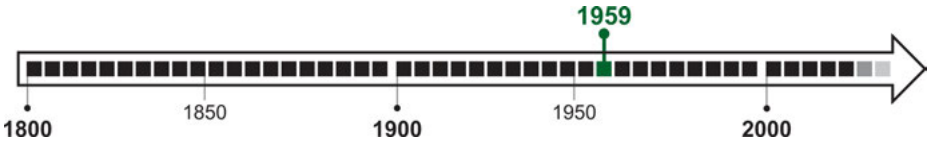

Fig. 95.3: The discovery of the ***Wacker*** *oxidation*.[305]

304 Mechanism (**b**) is proposed by Bäckvall: ***Bäckvall's*** *anti addition* (outer-sphere) [95a, 95b].
305 The reaction was likely first described around 1959 [95c].

96 Wagner–Meerwein Rearrangement

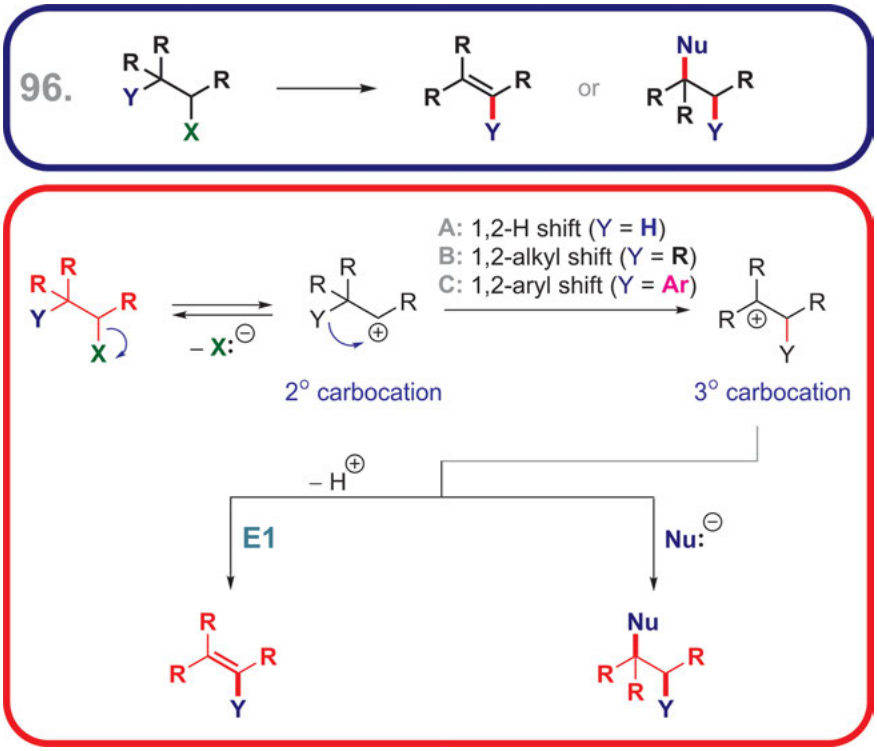

Fig. 96.1: The *general* ***Wagner–Meerwein*** *rearrangement* mechanism.[306]

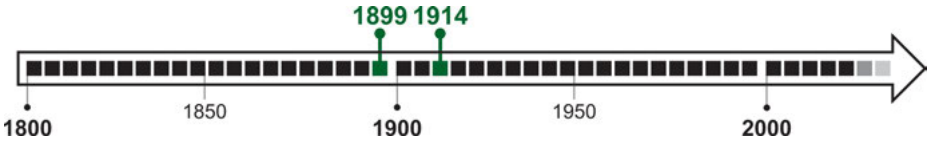

Fig. 96.2: The discovery of the ***Wagner–Meerwein*** *rearrangement*.[307]

306 The ***Wagner–Meerwein*** *rearrangement* is a rearrangement of new formed *carbocations* into more stable carbocations (1° → 2° → 3°). This reaction is related to the *pinacol-pinacolone rearrangement* and the ***Tiffeneau–Demjanov*** *rearrangement* (Chapter 76).

307 The reaction was likely first described around 1899 by Wagner [96a, 96b] and 1914 by Meerwein [96c].

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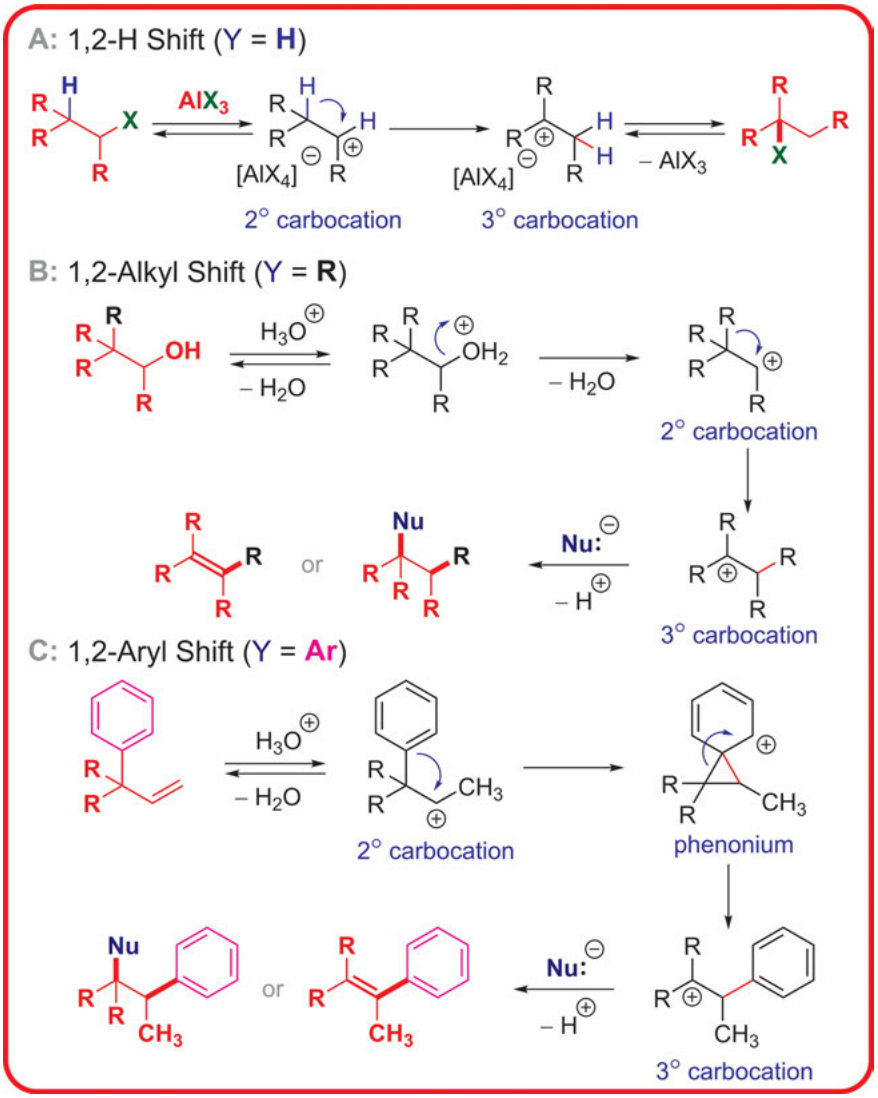

Fig. 96.3: The ***Wagner–Meerwein*** *rearrangement* mechanism (A, B, and C).[308]

308 The generated *carbocations* rearrange into more stable species via either (a) 1,2-H shift (Y = H); (b) 1,2-alkyl shift (Y = R); or (c) 1,2-aryl shift (Y = Ar). **β–Elimination** reactions (**E1**) often accompany the ***Wagner–Meerwein*** *rearrangement* [1].

97 Weinreb Ketone Synthesis

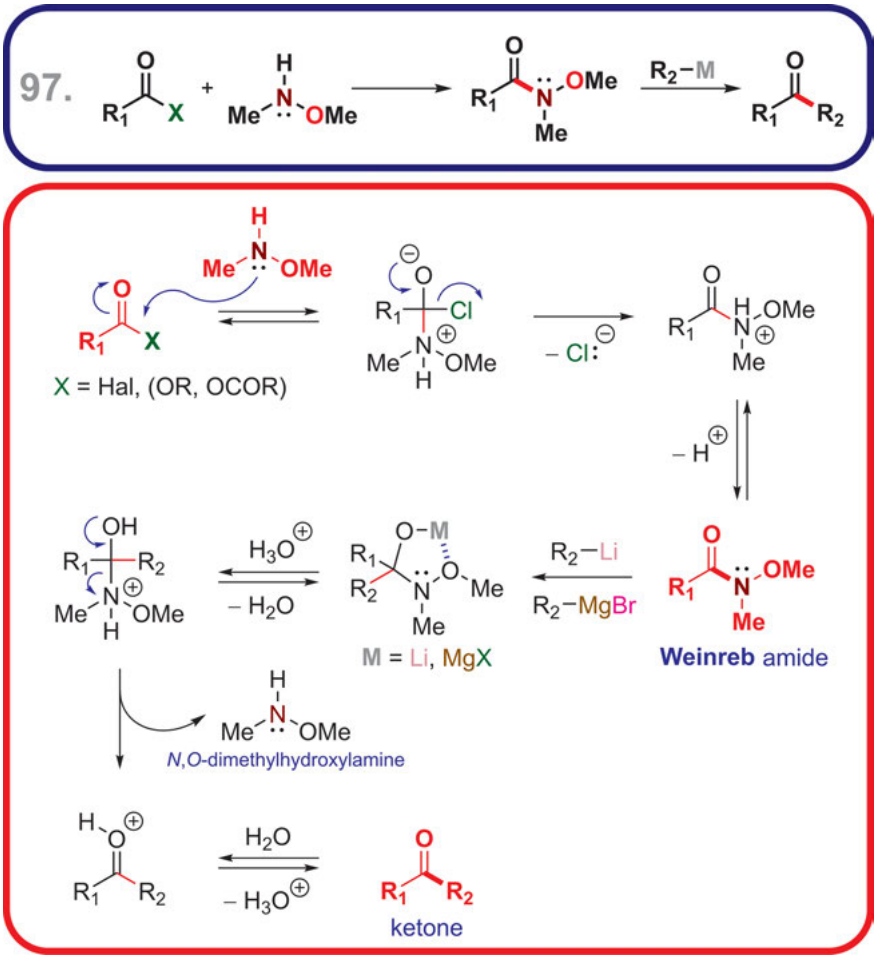

Fig. 97.1: The ***Weinreb*** *ketone synthesis* mechanism.[309]

309 The ***Weinreb*** *ketone synthesis* is a synthetic procedure (preparation of *ketones*) based on the use of a named reagent: the ***Weinreb*** *amide (**Weinreb–Nahm** amide)* [97a].

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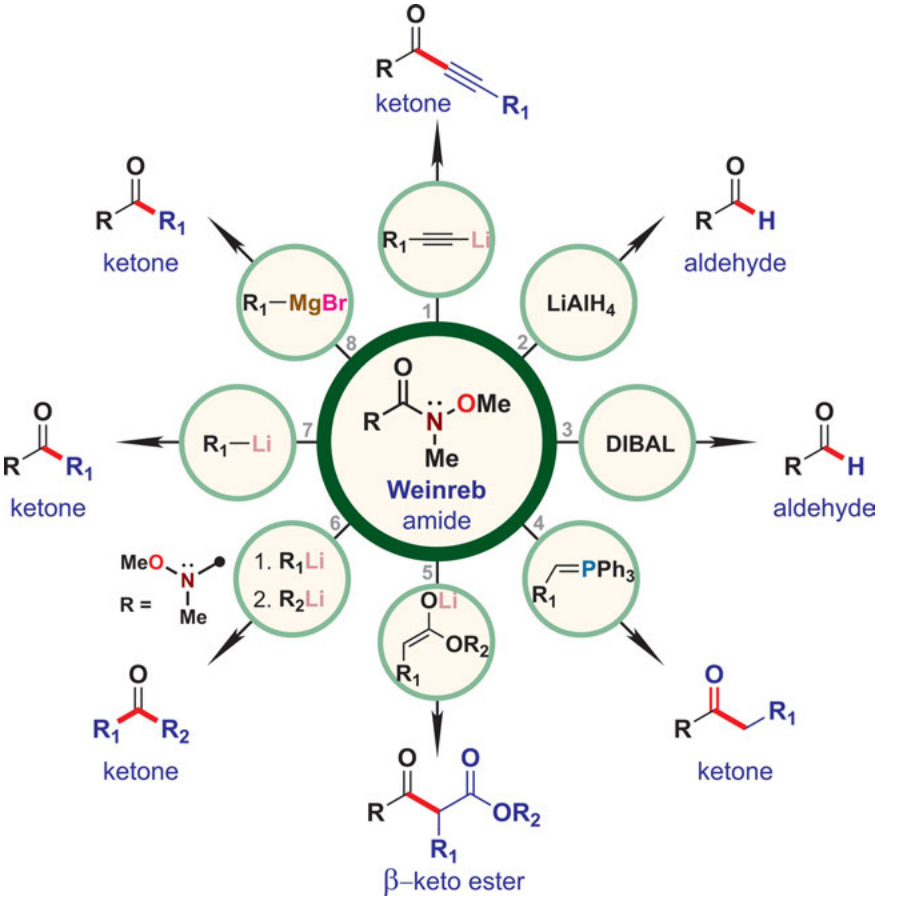

Fig. 97.2: Synthetic versatility of the ***Weinreb*** *amide*.[310]

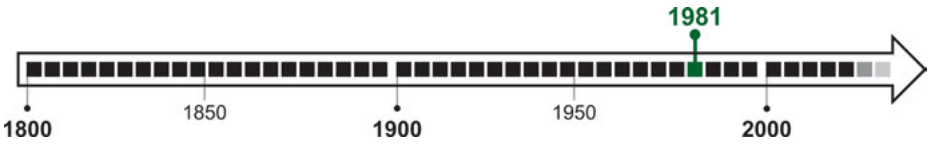

Fig. 97.3: The discovery of the ***Weinreb*** *ketone synthesis*.[311]

310 The ***Weinreb*** *amide* has wide synthetic application and it can react with a variety of nucleophilic reagents: (a) *organolithium* and *organomagnesium* = ***Grignard*** *reagents*; (b) reducing reagents like DIBAL; (c) *phosphorus ylides* or *phosphoranes* [97b]; and others [1].

311 The reaction was likely first described around 1981 [97c].

98 Wittig Reaction

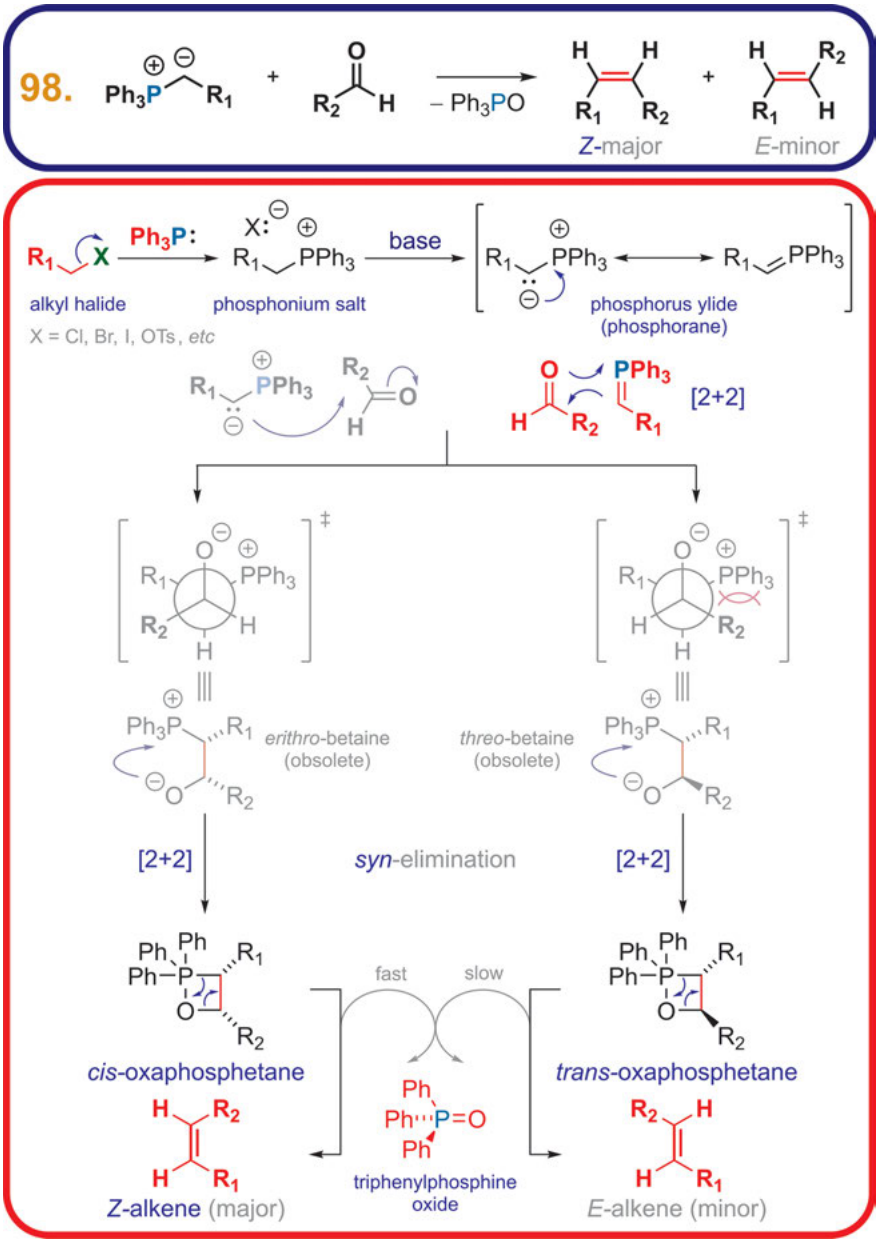

Fig. 98.1: The ***Wittig*** *reaction* mechanism.[312]

https://doi.org/10.1515/9783110608373-098

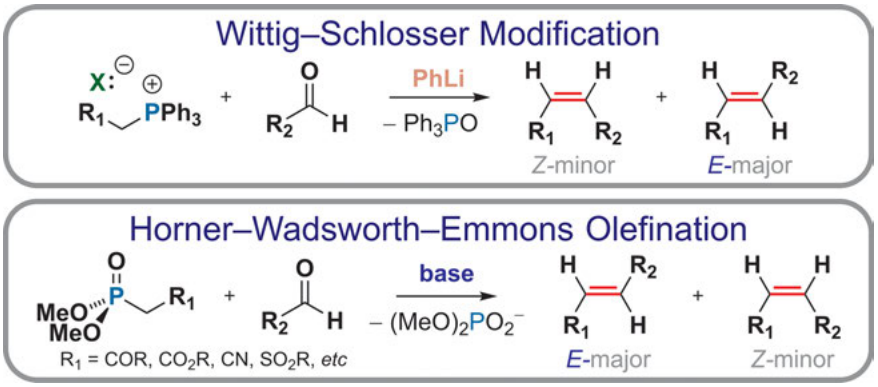

Fig. 98.2: Reactions related to the ***Wittig*** *reaction*.[313]

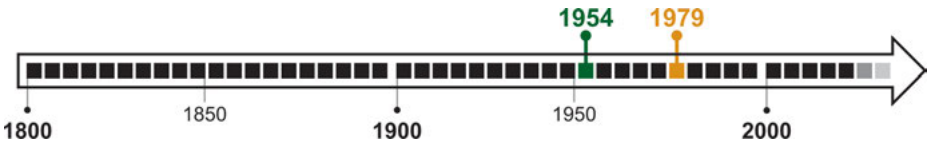

Fig. 98.3: The discovery of the ***Wittig*** *reaction*.[314]

312 The ***Wittig*** *reaction* or *the* ***Wittig*** *olefination* relies on the use of *phosphorus ylides* or *phosphoranes* formed from the *phosphonium salts* [98a].

313 Several reactions are closely related to the ***Wittig*** *reaction*: the ***Wittig–Schlosser*** *modification* (favoring *E*-alkenes with an excess of **PhLi** as a base) [98b]. The ***Horner–Wadsworth–Emmons*** *olefination* (Chapter 50) relies on the use of *phosphonates* [$PO(OR)_2R$], which can be made via the ***Arbuzov*** *reaction* (Chapter 9).

314 The reaction was likely first described around 1954 [98c, 98d]. In **1979**, Georg Wittig (jointly with Herbert C. Brown) received the Nobel Prize in Chemistry for the development of phosphorus (and boron) chemistry [20c].

99 Wohl–Ziegler Reaction

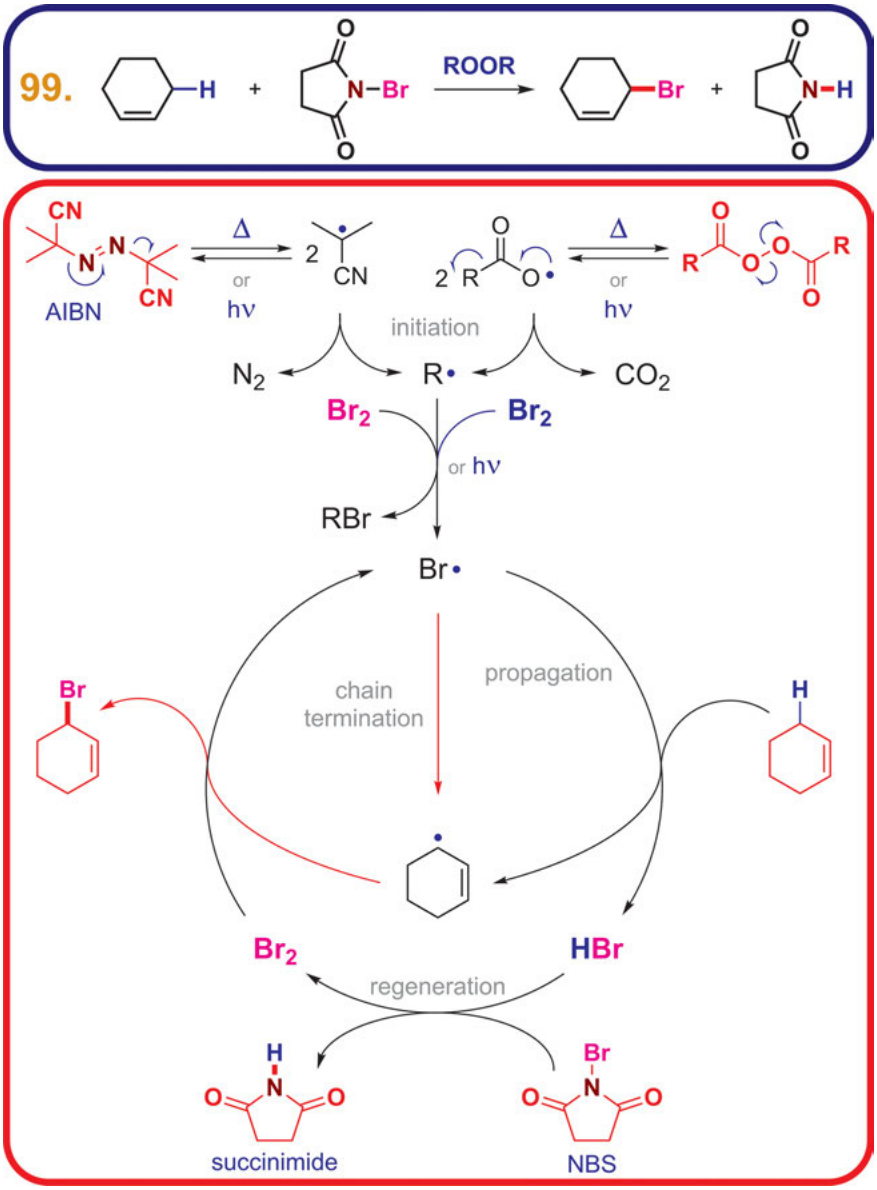

Fig. 99.1: The ***Wohl–Ziegler*** *reaction* mechanism.[315]

315 The ***Wohl–Ziegler*** *reaction*, or the ***Wohl–Ziegler*** *bromination*, is a type of the **free radical substitution** (see the ***Minisci*** *reaction* in Chapter 60).

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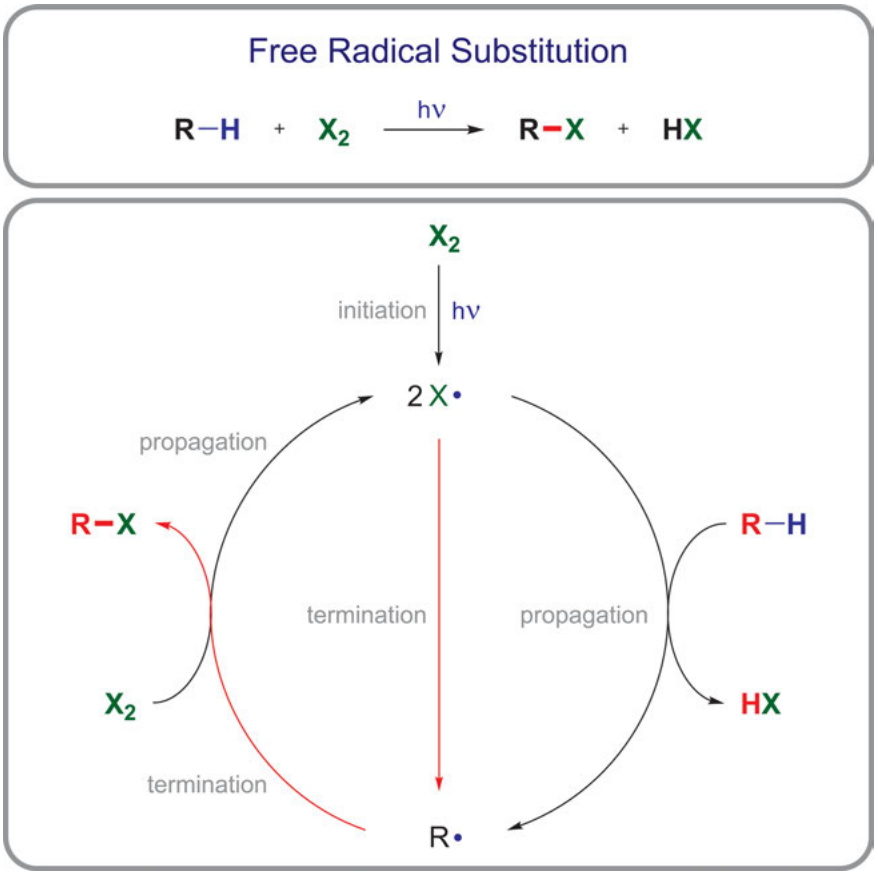

Fig. 99.2: The *free radical substitution* mechanism.[316]

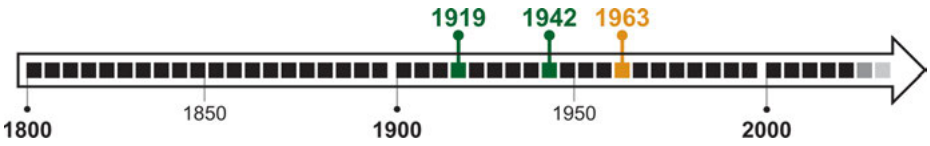

Fig. 99.3: The discovery of the ***Wohl–Ziegler*** *reaction*.[317]

316 The *free radical substitution* mechanisms usually feature three major steps: (**a**) *initiation*; (**b**) chain *propagation*; and (**c**) chain *termination*. A *free radical chlorination* of *alkanes* is a typical example [1].
317 The reaction was likely first described around 1919 by Wohl [99a] and around 1942 by Ziegler [99b]. In **1963**, Karl Ziegler (jointly with Giulio Natta) received the Nobel Prize in Chemistry [99c].

100 Wolff–Kishner Reduction

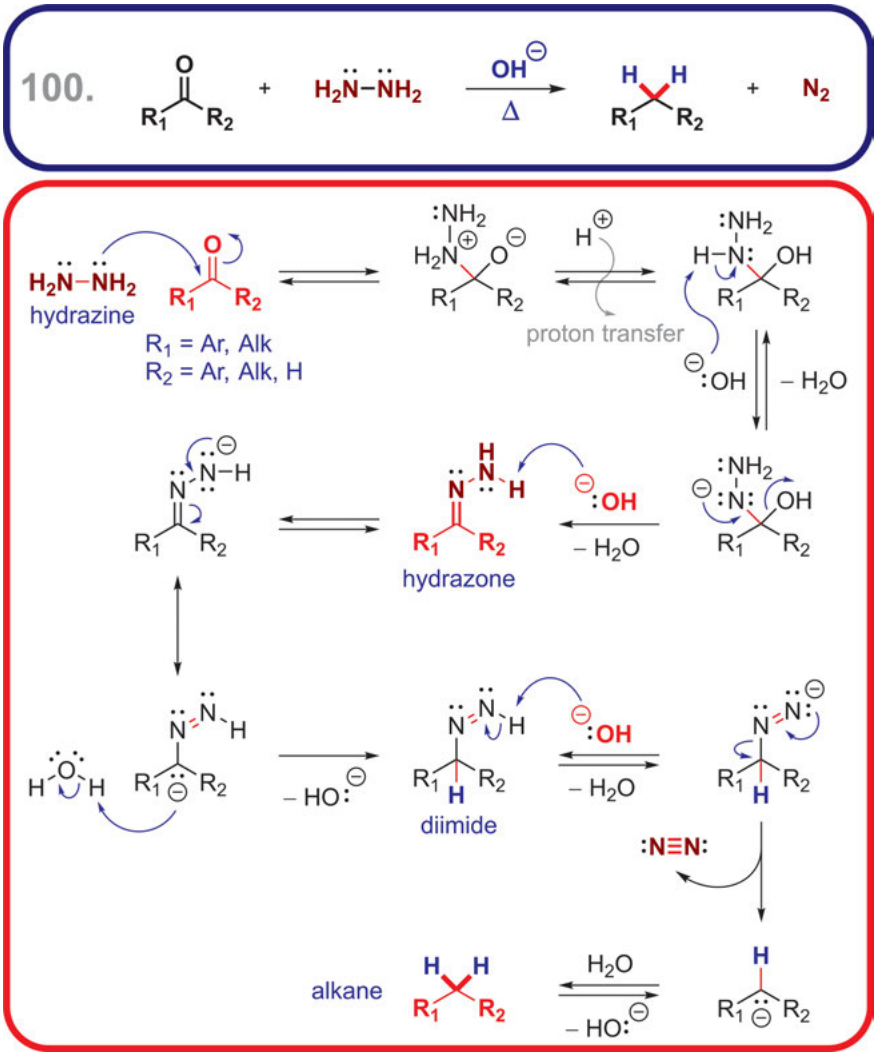

Fig. 100.1: The ***Wolff–Kishner*** *reduction* mechanism.[318]

318 There are many modifications of the ***Wolff–Kishner*** *reduction*: for example, the ***Huang–Minlon*** *modification*, and many others (not shown) [100a].

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Fig. 100.2: Reactions related to the ***Wolff–Kishner*** *reduction*.[319]

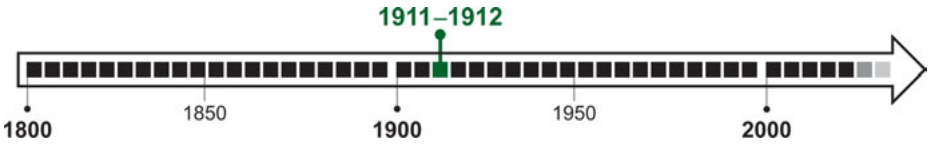

Fig. 100.3: The discovery of the ***Wolff–Kishner*** *reduction*.[320]

319 The ***Clemmensen*** *reduction* is closely related to the ***Wolff–Kishner*** *reduction* in terms of the product type formation but not the mechanism [100b].

320 The reaction was likely first described around 1911 by Kishner [100c] and around 1912 by Wolff [100d].

Acknowledgments

I envision this reference book to be one part of the intellectual and physical library that the developing chemist builds as they gain experience and expertise. This immersion, in conjunction with further learning, can provide an invaluable scientific intuition. Mechanisms have become an integral part of my continued study, research, and learning in organic chemistry and I hope this book imparts some of that to the field.

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Special thanks are owned to my family, friends, and peers in the scientific community, and my students. The confluence of an idea and diligence makes possible great progress. But this combination must also be fueled by the compassion, support, and patience of those around us. I am very grateful that this constellation aligned for me and made possible the environment in which I could prepare this book. Moreover, as always, I am most grateful to my students and followers on social media. As I share and teach, I also continue to learn about the discipline as well as myself, always striving to understand, grow, and get closer to truth.

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