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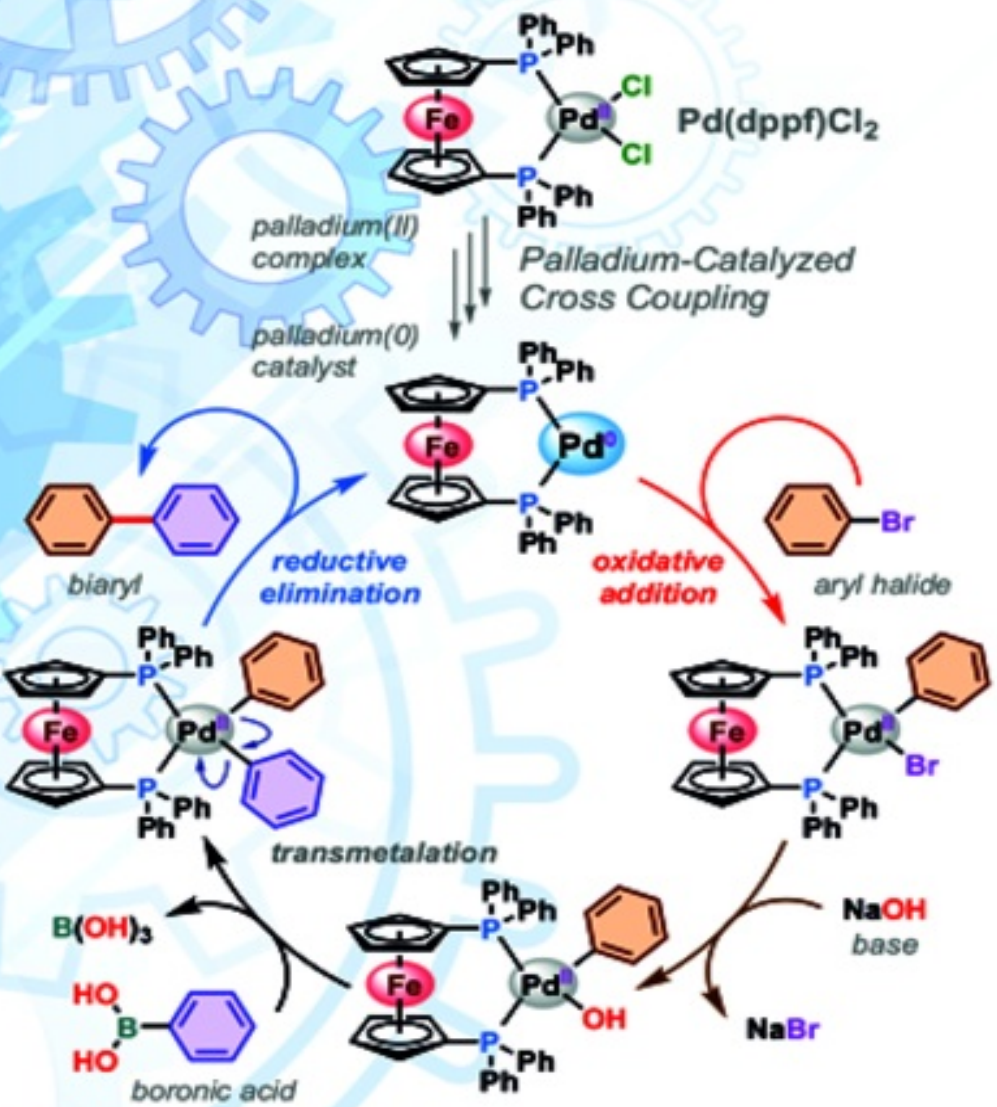
Roman A. Valiulin

ORGANIC CHEMISTRY: 100 MUST-KNOW MECHANISMS

2ND EDITION



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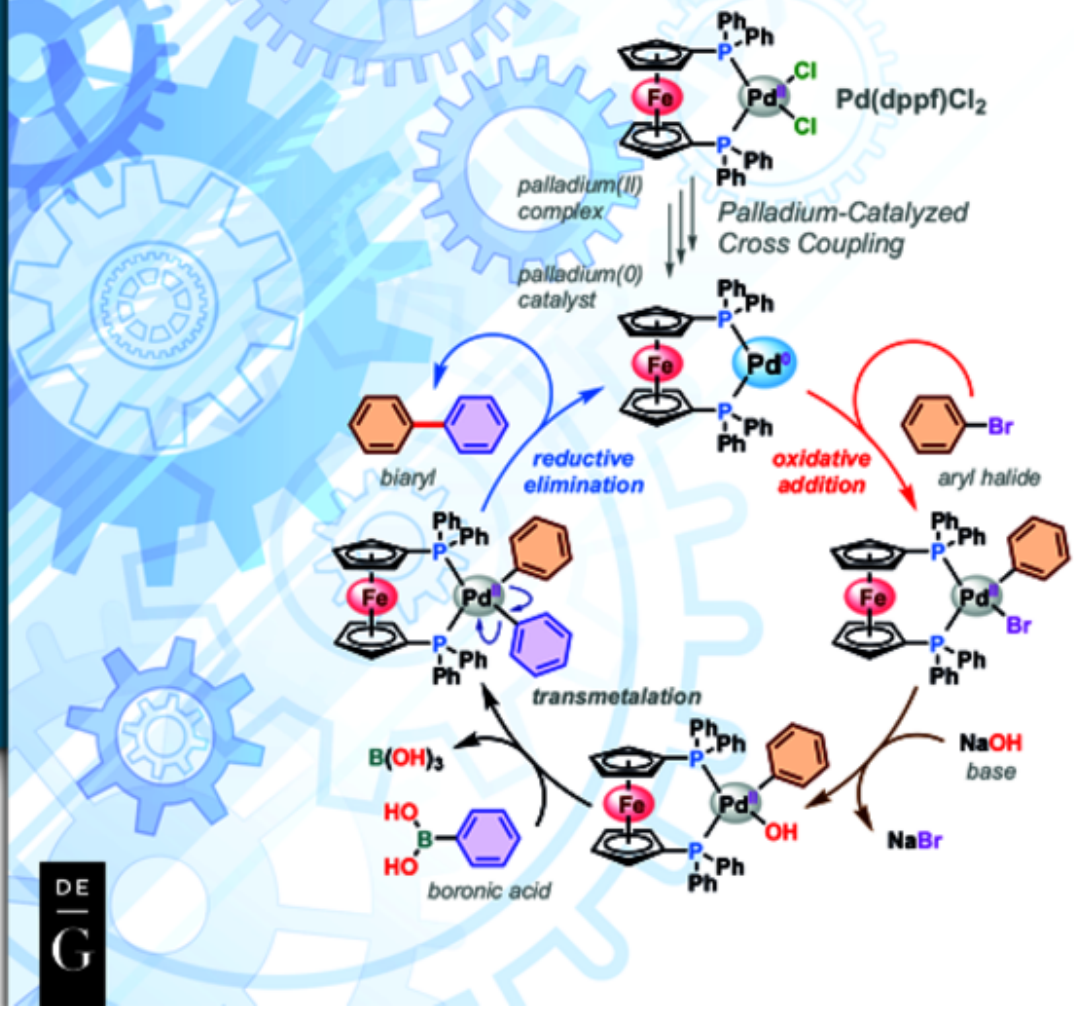

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De Gruyter Textbook

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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

Second Edition

This edition of *Organic Chemistry: 100 Must-Know Mechanisms* is an enriched and improved version of the first book with over 40 new illustrations. It builds upon the existing 100 fundamental mechanisms mentioned in the previous book and adds other mechanisms related to the original 100 with engaging, supplementary examples. The book is also fine-tuned with features that can help broaden its usefulness to earlier-stage students of chemistry and related sciences.

Formal ***Lewis*** (dot) structures are added to all the previously mentioned intermediates in each mechanism, keeping track of the movement of electrons and making the schemes more comprehensive. This improvement is a valuable enhancement for those still learning organic chemistry and expands usefulness to undergraduate students and college students in STEM fields whose area of major concentration is not chemistry. The original 100 mechanistic schemes are also visually improved: the chemical structures are more vivid and consistent throughout the book. Additionally, newly formed bonds are highlighted in red color and accentuated using bold lines for each final product or key intermediate.

In the first version, many related mechanisms were only mentioned by name. The second edition expands upon those examples and has numerous new mechanistic schemes. For example, the reader will find a new illustration of the ***Bouveault–Blanc*** *reduction* mechanism of esters and ketones, a separate ***Wolff*** *rearrangement,* which was previously mentioned only as a part of the ***Arndt–Eistert*** *synthesis* mechanism. Other new illustrations include the ***Dakin*** *reaction* mechanism, the ***Myers–Saito*** *cyclization* mechanism, the ***Pomeranz–Fritsch*** *reaction*

mechanism, an example of *the* ***Benzidine*** *rearrangement* mechanism, the ***Delépine*** *reaction* mechanism, the ***Peterson*** *olefination* mechanism, the ***Kabachnik–Fields*** *reaction* mechanism, the ***Petasis*** *reaction* mechanism, the ***Stetter*** *reaction* mechanism for aromatic and aliphatic aldehydes, the ***Fischer*** *esterification* mechanism – and its comparison to the ***Mitsunobu*** *ester synthesis* and the stereochemical outcome of both reactions involving a chiral alcohol – the ***Ullmann*** *biaryl ether coupling* mechanism catalyzed by Cu(I) complex with a neutral bidentate ligand, the ***Reimer–Tiemann*** *reaction* mechanism, and the ***Clemmensen*** *reduction* mechanism. The *nontraceless* and *traceless* ***Staudinger*** *ligation* mechanisms are also highlighted, making them especially relevant after the announcement of the 2022 *Nobel Prize* in Chemistry for the development of click chemistry and bioorthogonal chemistry [30g, 30h].

Moreover, many of the original mechanistic schemes depicted in the first edition of this book were general, covering a vast scope of chemical structures and often using a general R-group representation, instead of a particular example of an actual organic compound. This edition is enhanced with a variety of real-case examples, such as the bromination and nitration of an aromatic ring (an example of the aromatic electrophilic substitution), the ***Beckmann*** *rearrangement* mechanism of cyclohexanone oxime, the ***Chichibabin*** *amination* mechanism of quinoline, a sequence of the ***Cope*** *rearrangements* involving (3*R*,4*R*)-3,4-dimethylhexa-1,5-diene, (2*E*,4*R*,5*R*,6*E*)-4,5-dimethylocta-2,6-diene, (2*Z*,4*R*,5*R*,6*E*)-4,5-dimethylocta-2,6-diene, and (2*Z*,4*R*,5*S*,6*E*)-4,5-dimethylocta-2,6-diene, several variations of the ***Diels–Alder*** *cycloaddition* reactions using various *dienes* and *dienophiles,* the ***Favorskii*** *rearrangement* mechanism of 2-chlorocyclohexan-1-one, the ***Grob*** *fragmentation* mechanism of (1*R*,3*S*)-3-chloro-1-methylcyclohexan-1-ol, the ***Bischler–Napieralski*** *cyclization* mechanism of *N*-phenethylacetamide, the

***Polonovski** reaction* mechanism (*N*-demethylation) of a morphinan derivative, and the ***Suzuki** cross-coupling* mechanism catalyzed by either **$Pd(dppf)Cl_2$** or tetrakis(triphenylphosphine)palladium(0): **$Pd(PPh_3)_4$**. Also noteworthy, an educational example of the *ozonolysis* reaction mechanism of (–)-α-fenchene and anomalous (interrupted) *ozonolysis* reaction mechanisms are presented as well, in addition to the synthesis of cubane-1,4-dicarboxylic acid (with the key ***Favorskii** rearrangement* transformation step), the rearrangement mechanism of bicyclo[2.2.2]octane system (an example of the ***Hell–Volhard–Zelinsky** reaction*), and two plausible mechanisms of *adamantane* rearrangement undergoing a sequence of numerous ***Wagner–Meerwein** rearrangement* steps.

This edition continues in the tradition of the first: presenting information efficiently by using clear, balanced, and intuitive visuals and infographic diagrams. Like a stone sculpture, this version is a refined and more finely chiseled version of the first. The goal is to build upon what worked well, update the content where needed, and to add key pieces of information or notation, with the ultimate objective of making the book more useful to more students of chemistry and the sciences. Of course, we cannot promise perfection, because it, like an asymptote, is unreachable, but we hope that you will find this version to be a valuable addition or update to your scientific library.

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 postdoctoral

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*), 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 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 textbook. 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 centerpiece 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 gray or black 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 textbooks [→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 online 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 postdoctoral 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 a 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 judgment 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 to 2023. 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, and so on. 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 a 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 microblog 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], online sources [→5, →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.

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
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 first generation Grubbs catalyst
Grubbs 2°	The second generation Grubbs catalyst
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
hν	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	Multicomponent 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., $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)
***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 (e.g., π-complex)
1π e⁻, 2π e⁻, …	Number of electrons in a π-orbital
σ	Involving a σ-bond (e.g., σ-complex)
σ*	(Antibonding) sigma star (molecular) orbital
Φ_{ISC}	Quantum yield (for intersystem crossing)

1 Electrophilic Addition Mechanism

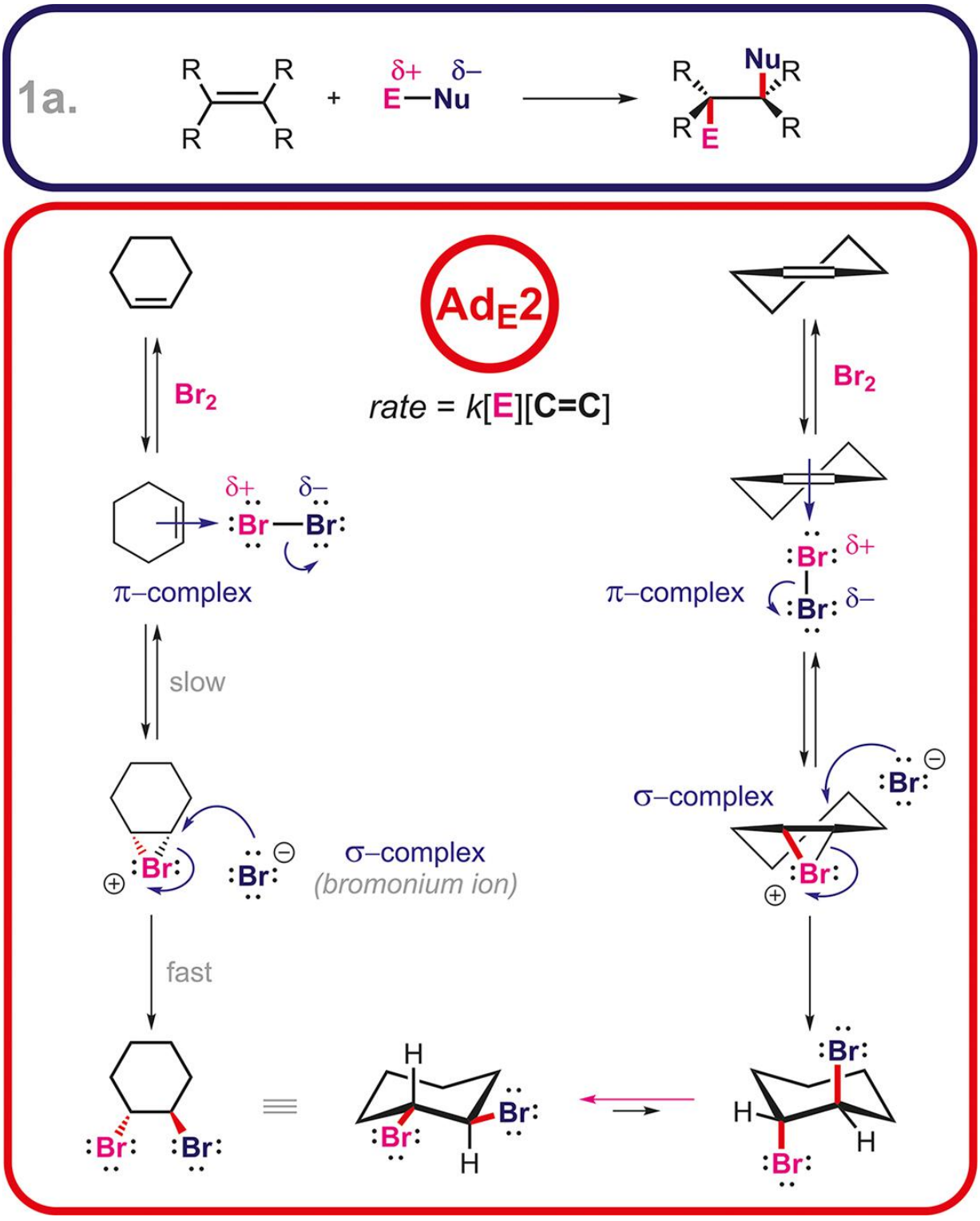


Fig. 1.1: Bimolecular electrophilic addition mechanism (**Ad$_E$2**).[1]

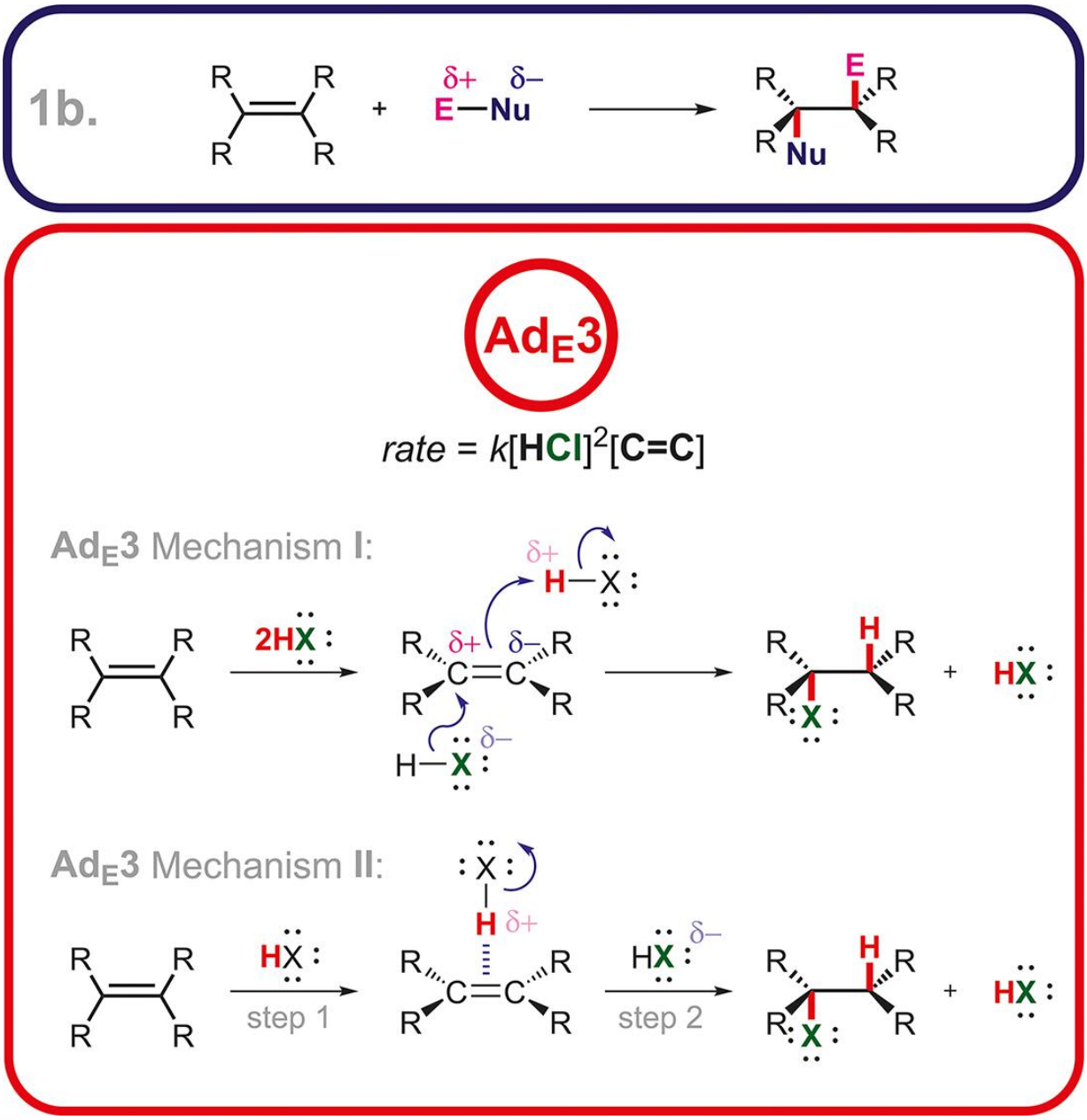


Fig. 1.2: Trimolecular electrophilic addition mechanism (**Ad$_E$3**).[2]

2 Nucleophilic Substitution Mechanism

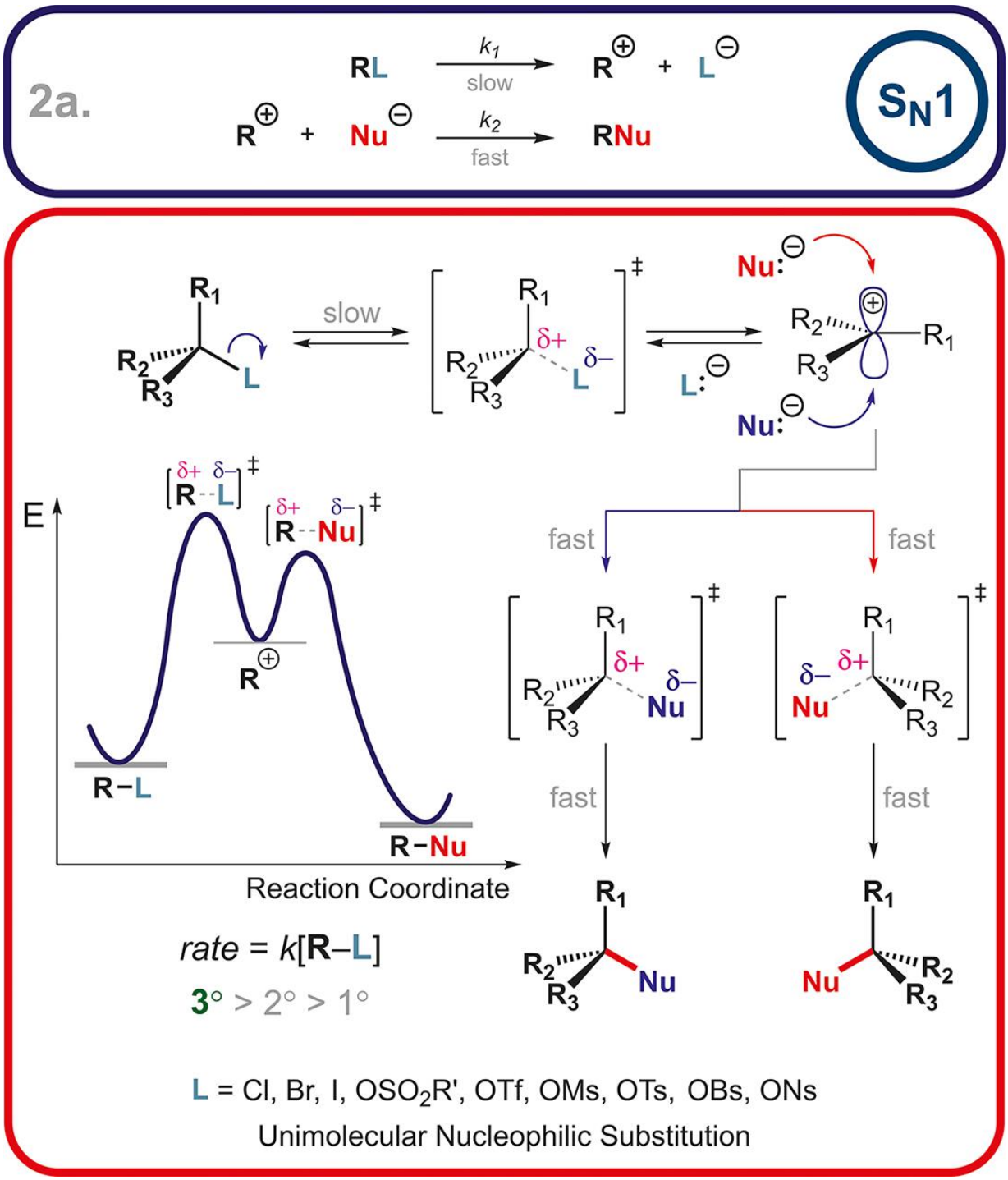


Fig. 2.1: Unimolecular nucleophilic substitution mechanism (**S_N1**).[3].

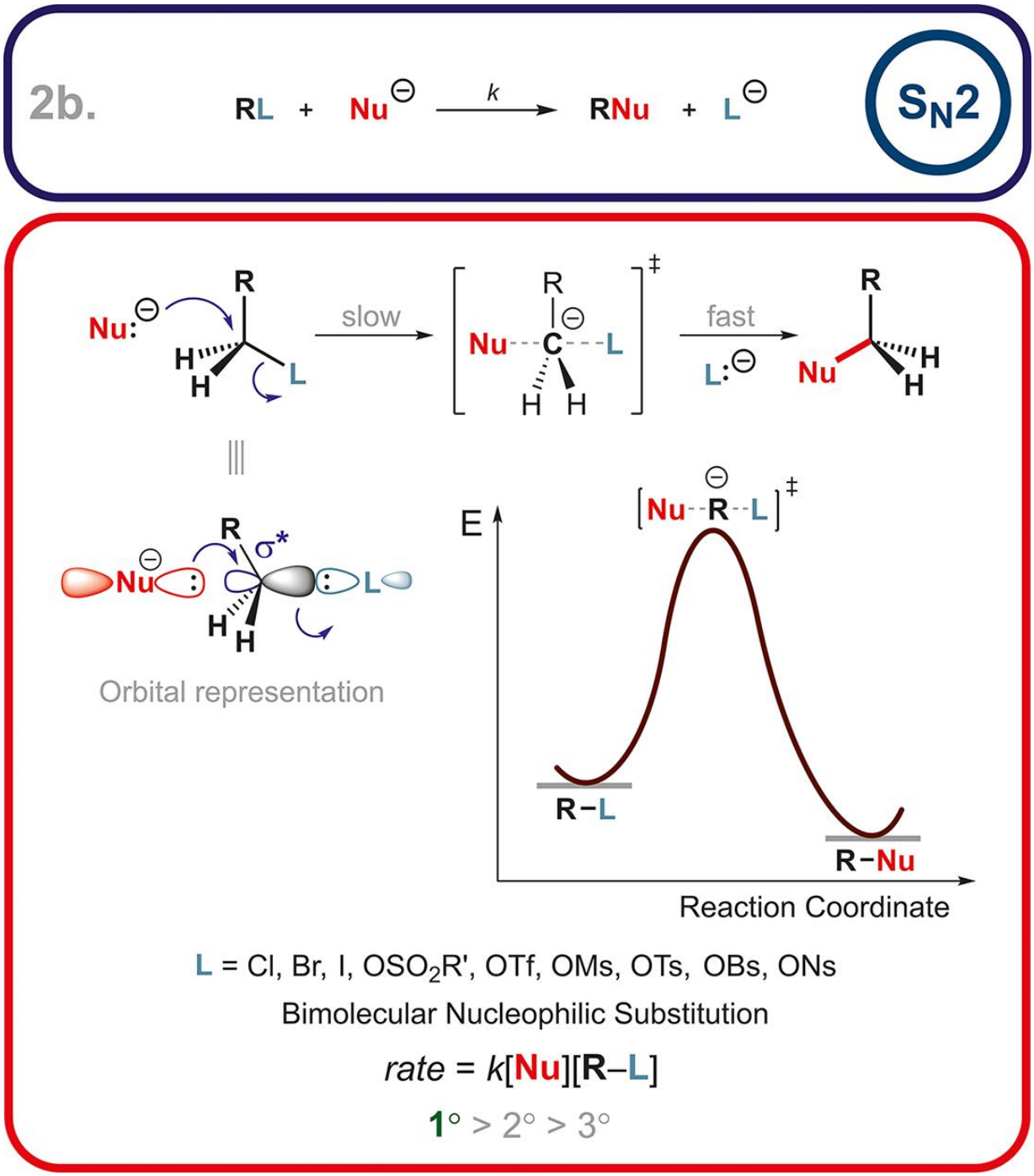


Fig. 2.2: Bimolecular nucleophilic substitution mechanism (**S_N2**).[4].

3 Aromatic Electrophilic Substitution Mechanism

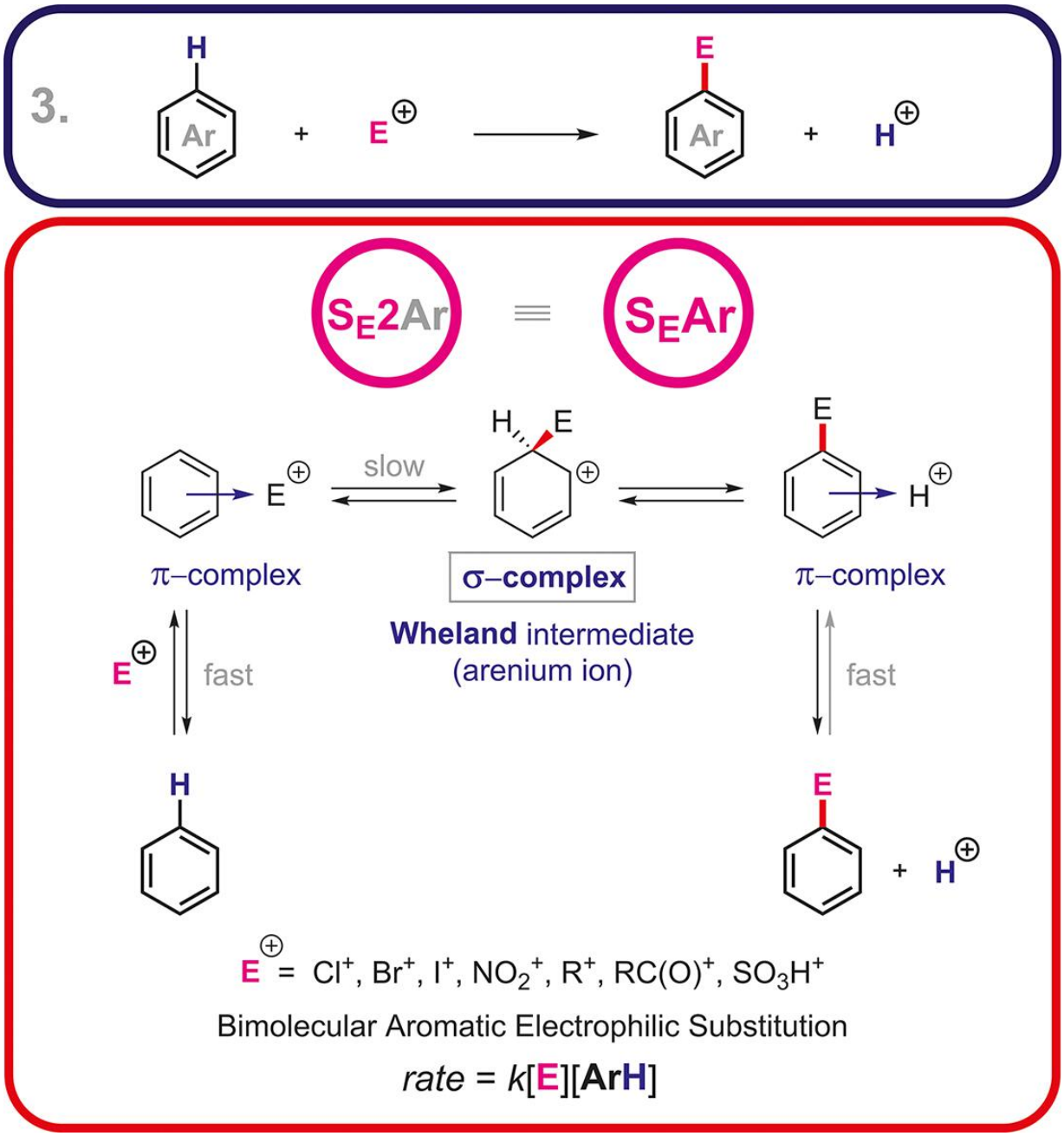


Fig. 3.1: The arenium ion mechanism (**S_EAr**).[5]

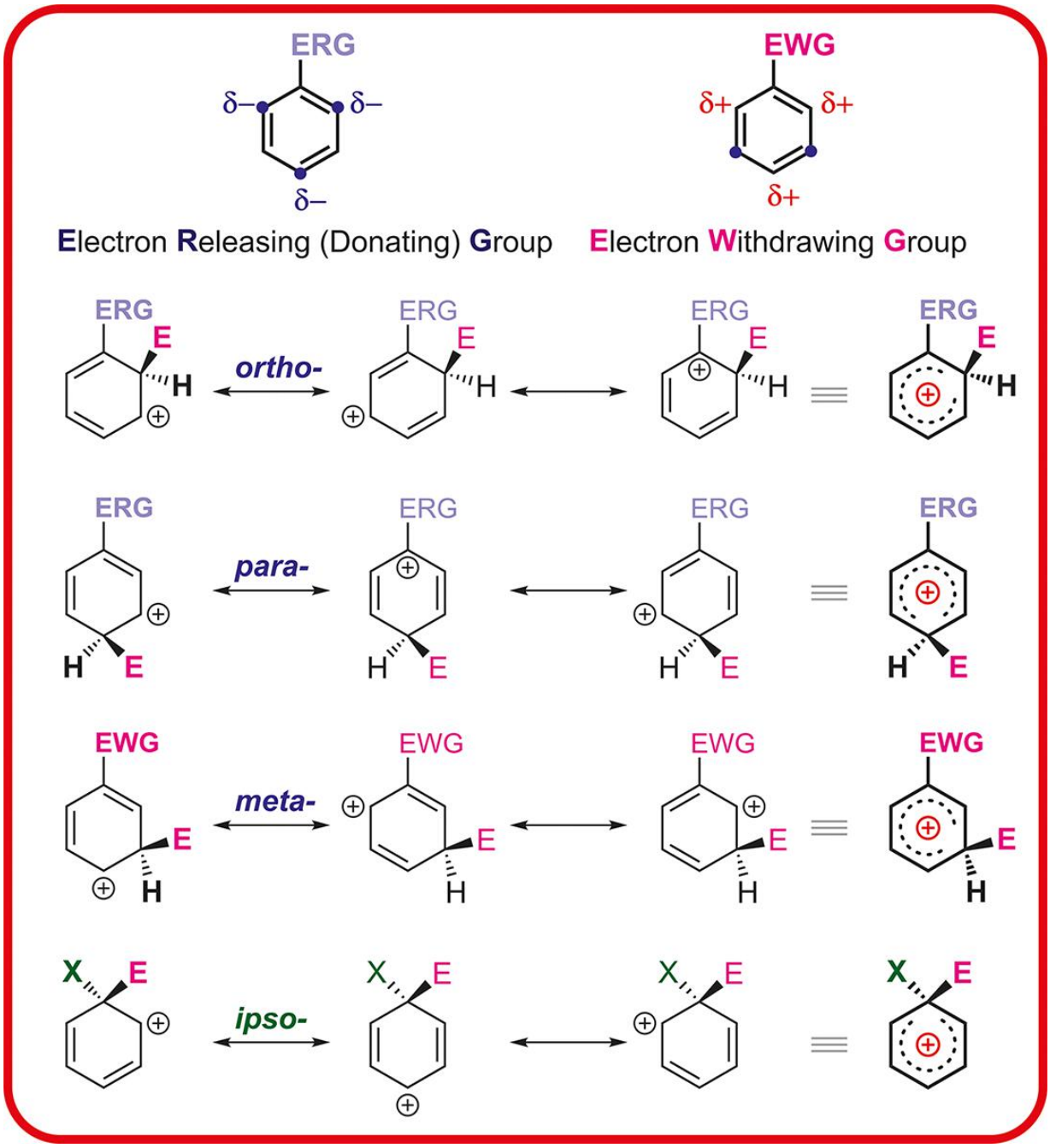


Fig. 3.2: The orientation of substitution with substrates containing EWG and ERG.[6]

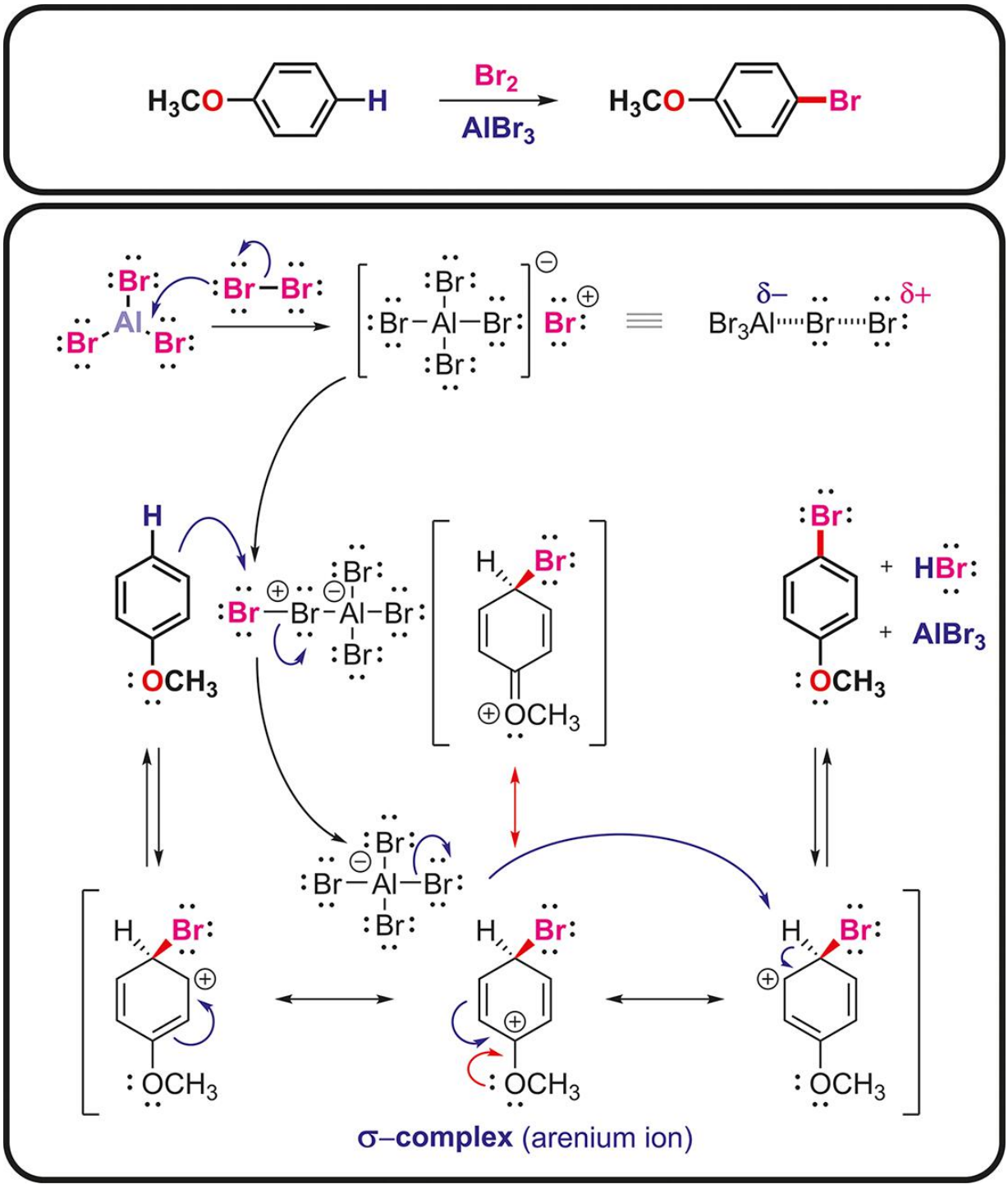


Fig. 3.3: Bromination of anisole.[7]

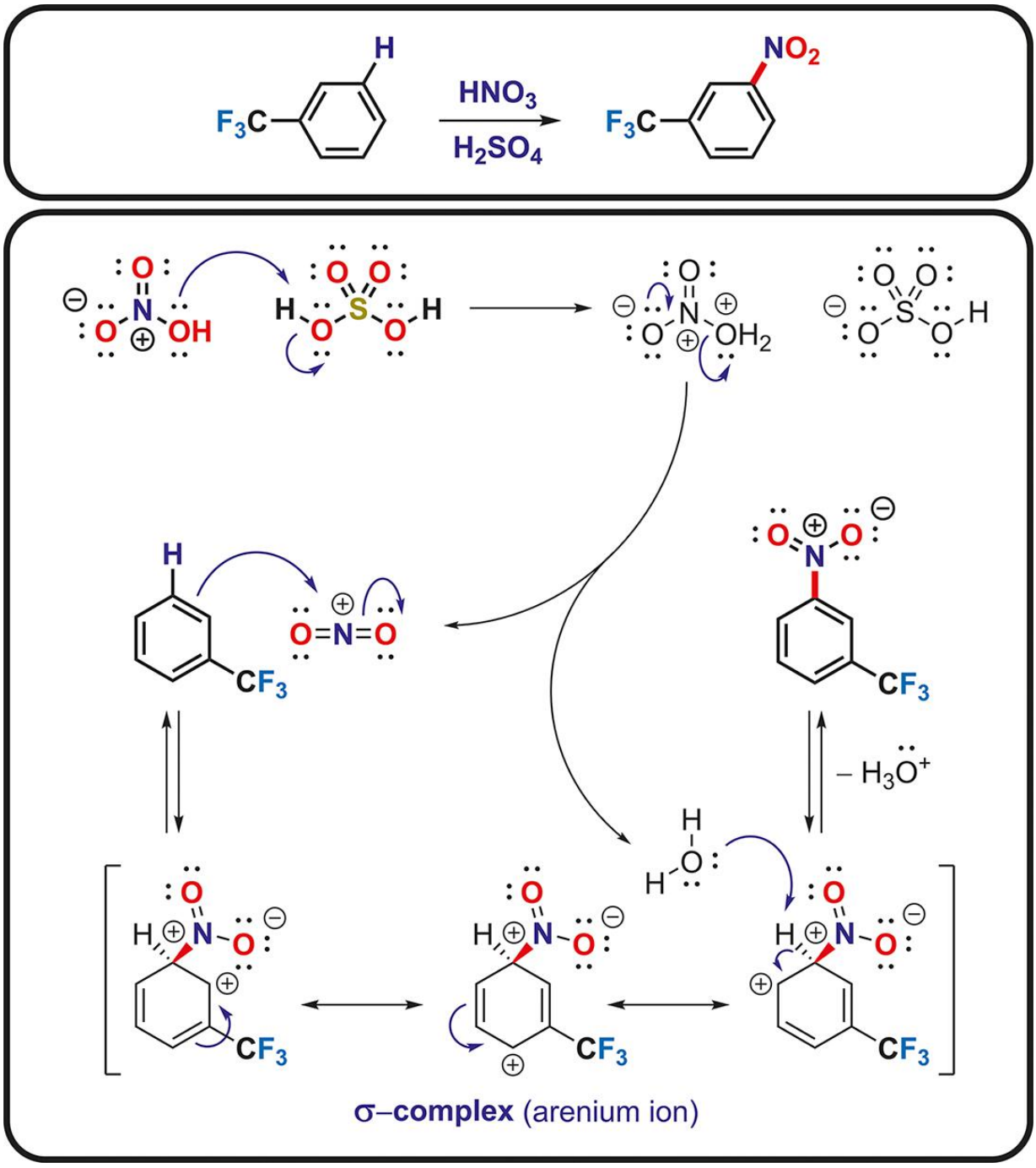


Fig. 3.4: Nitration of (trifluoromethyl)benzene.[8]

4 Aromatic Nucleophilic Substitution Mechanism

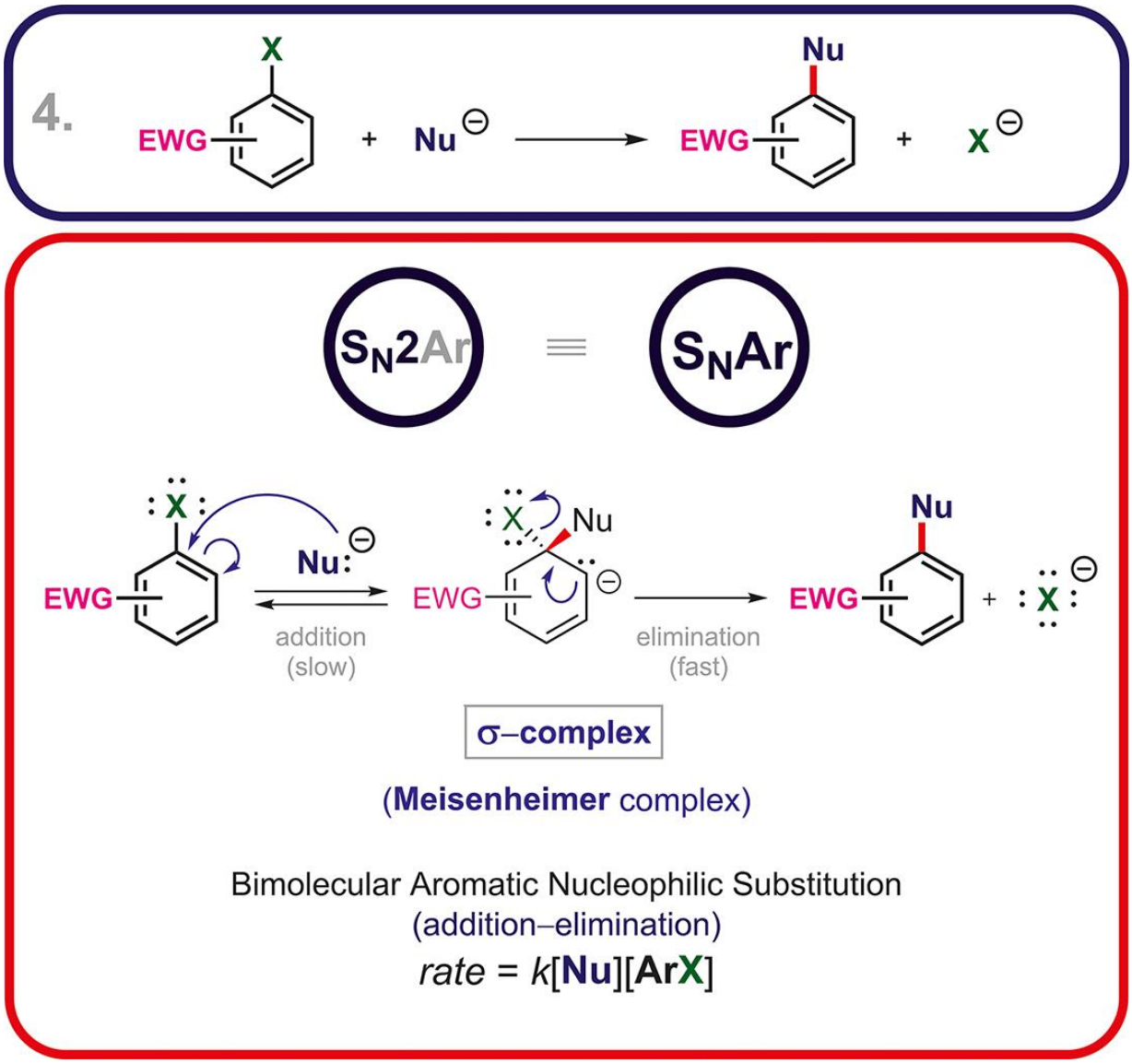


Fig. 4.1: Bimolecular aromatic nucleophilic substitution (addition–elimination) mechanism (**S_NAr**).[9]

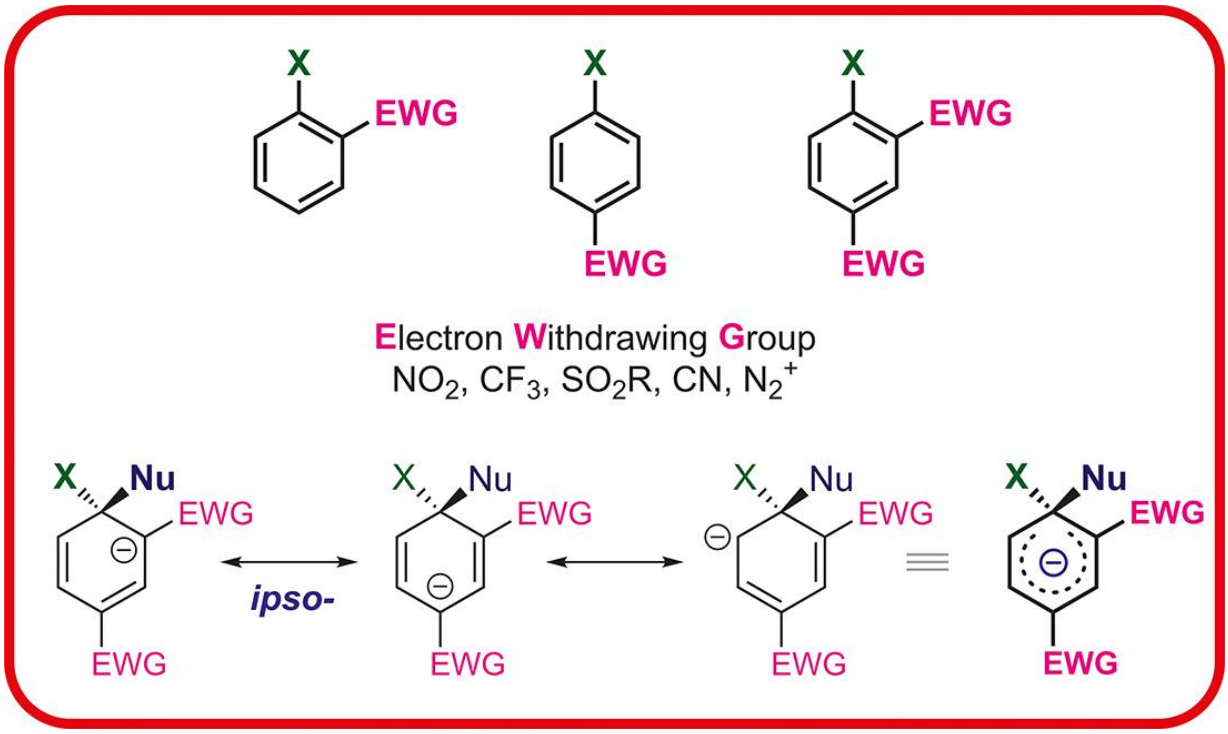


Fig. 4.2: Typical activated **S_NAr** substrates.[10]

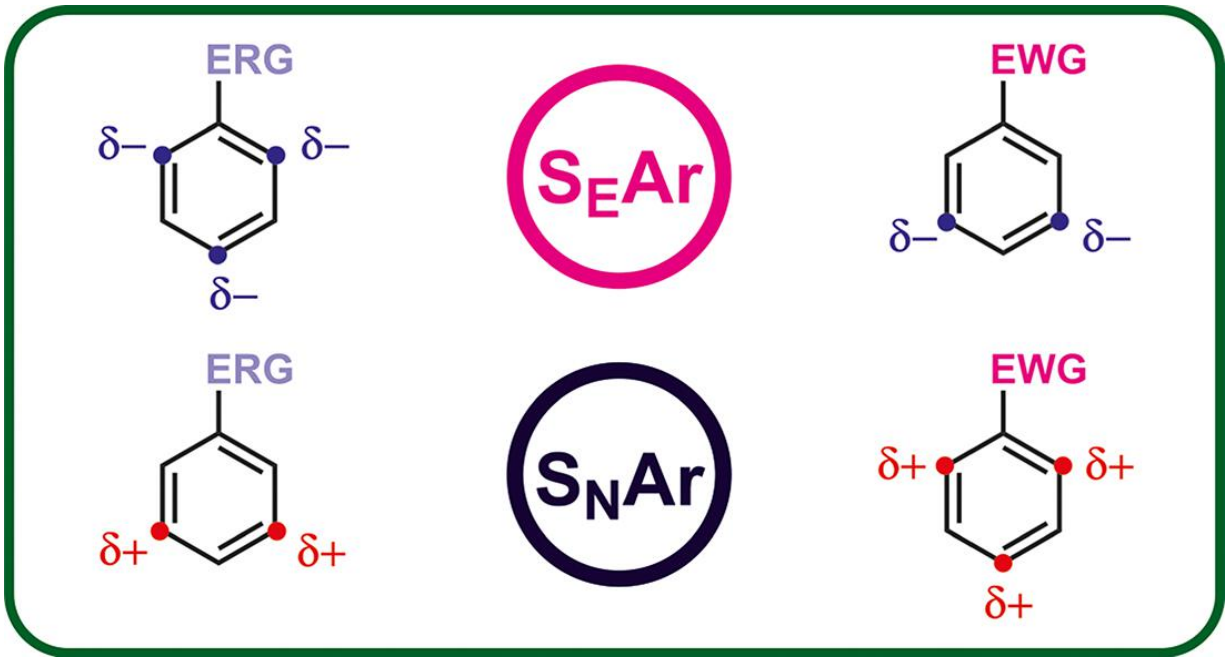


Fig. 4.3: The orientation of substitution in **S_EAr** and **S_NAr**.[11]

5 Aromatic Radical Nucleophilic Substitution Mechanism

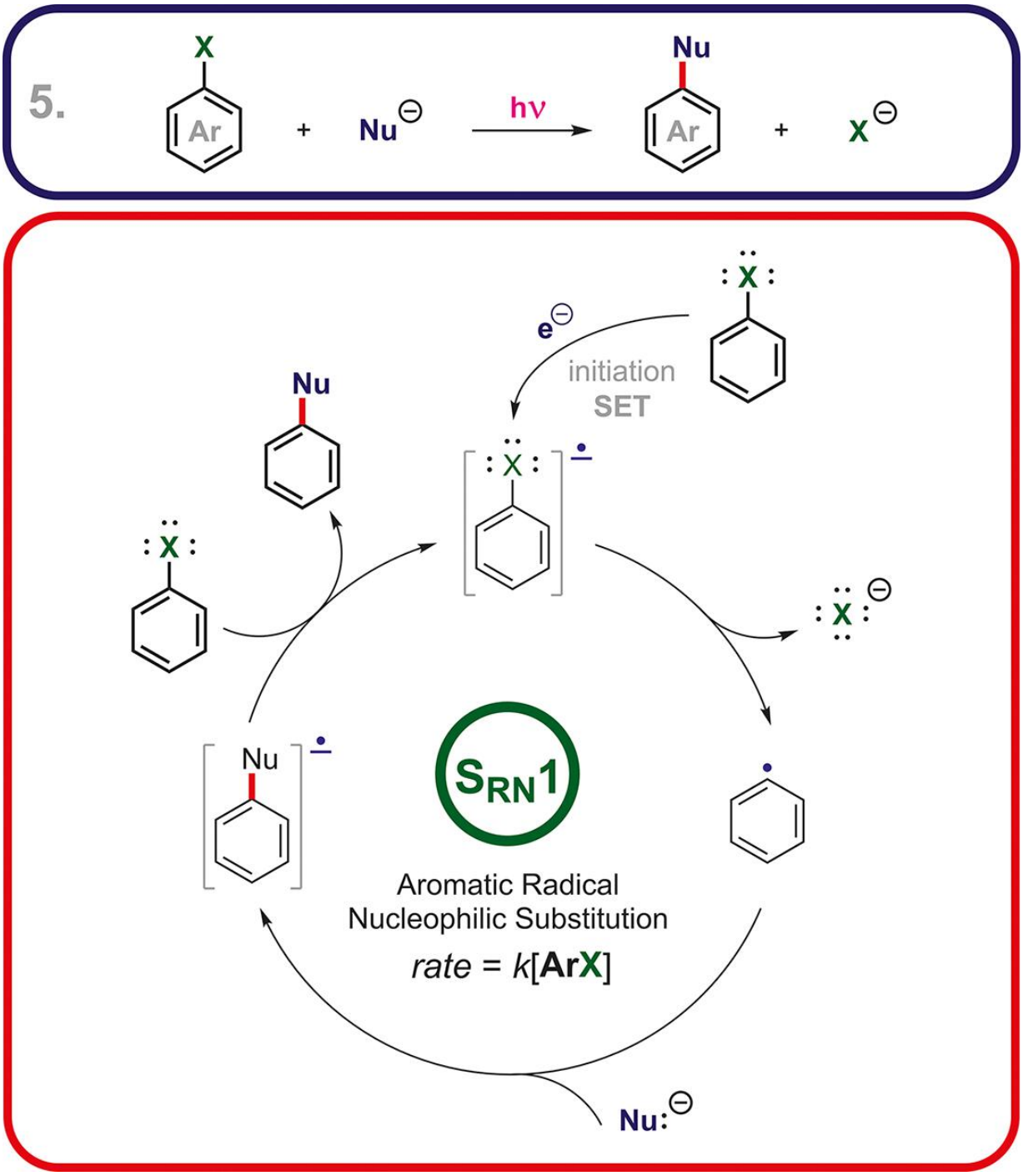


Fig. 5.1: Unimolecular aromatic radical nucleophilic substitution mechanism ($\mathbf{S_{RN}1}$).[12]

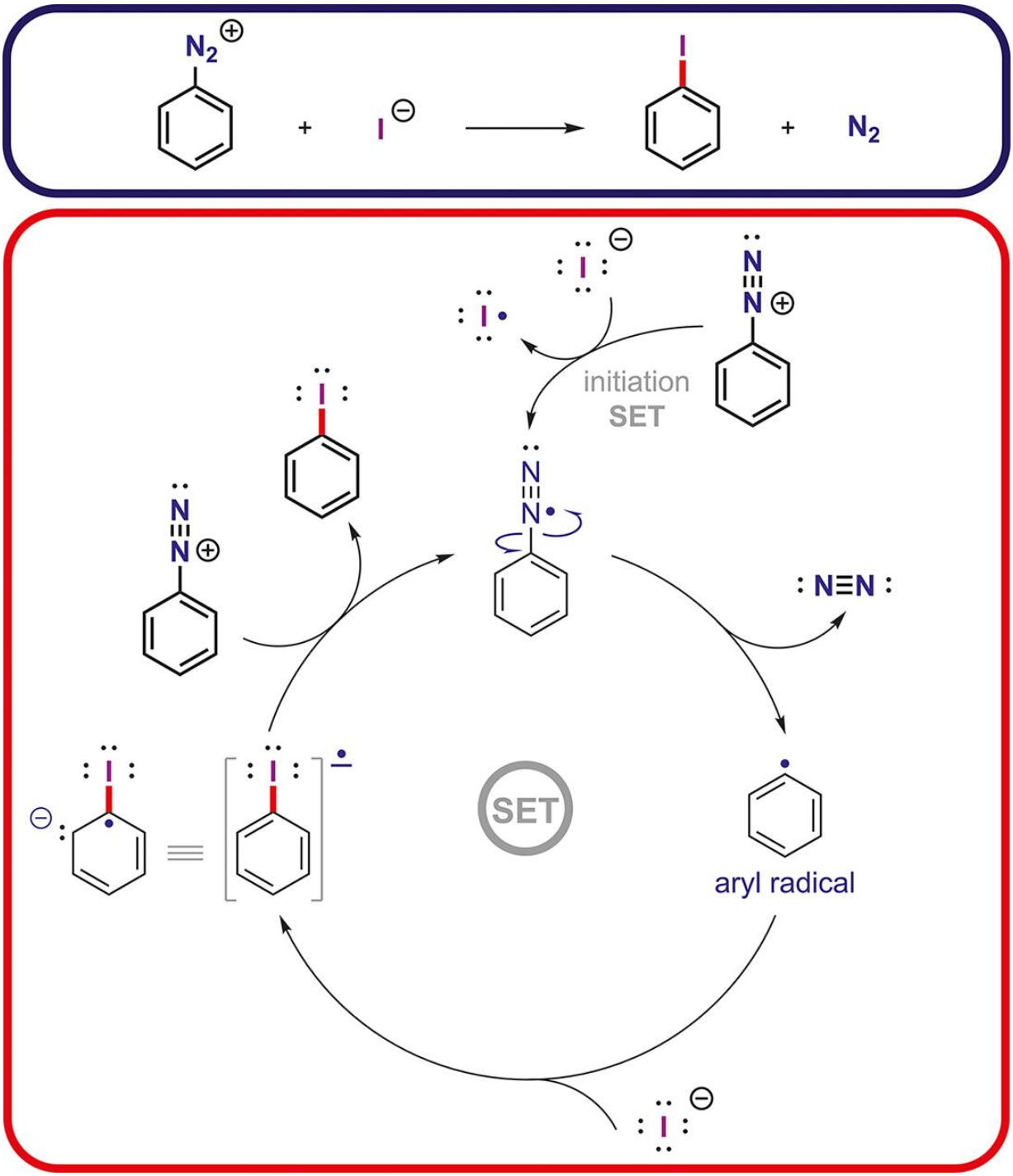


Fig. 5.2: Replacement of the diazonium group by iodide.[13]

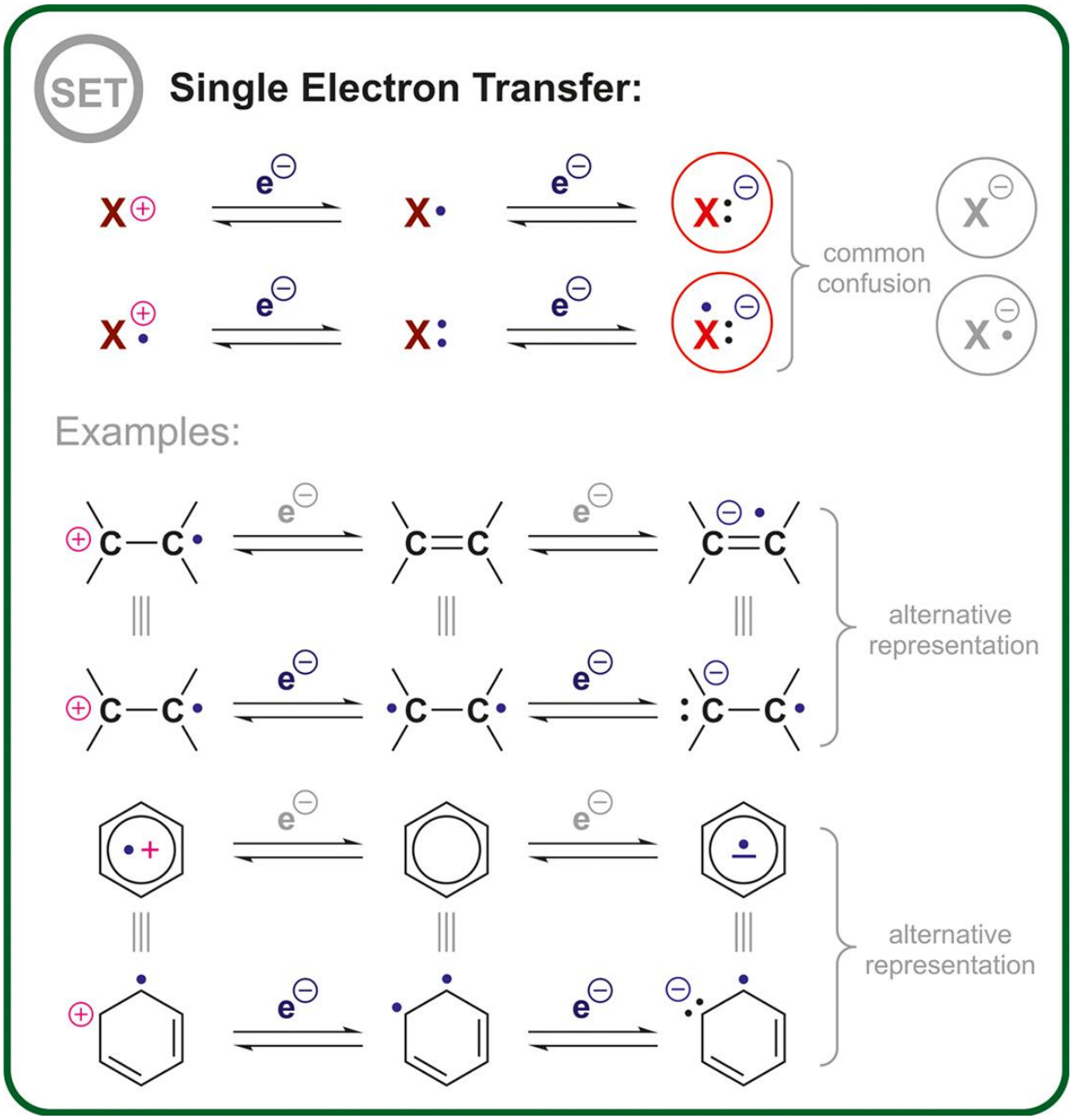


Fig. 5.3: Lewis electron dot structures of radical species involved in SET.[14]

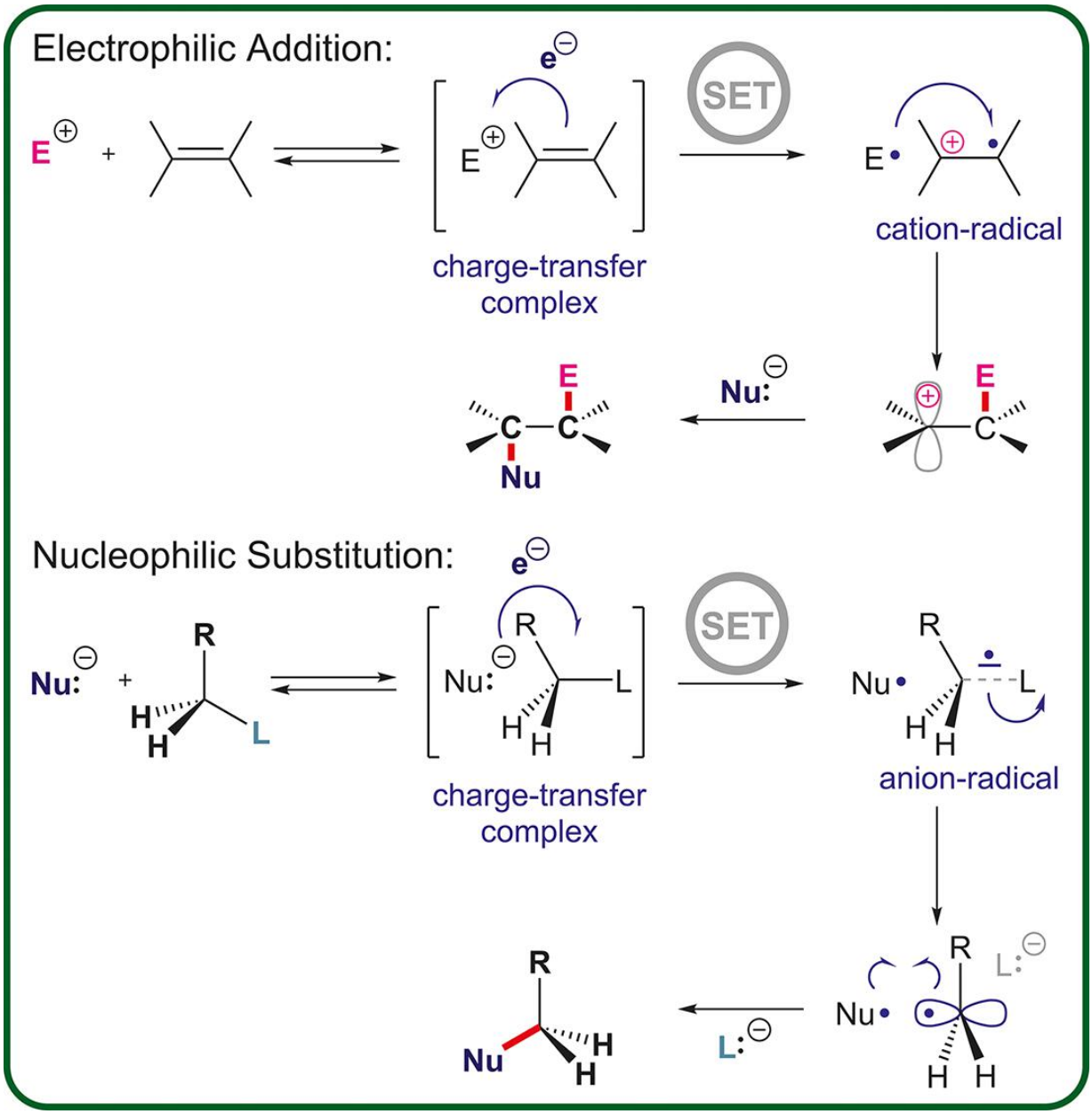


Fig. 5.4: The single electron transfer mechanism (**SET**) examples.[15]

6 Elimination Mechanism

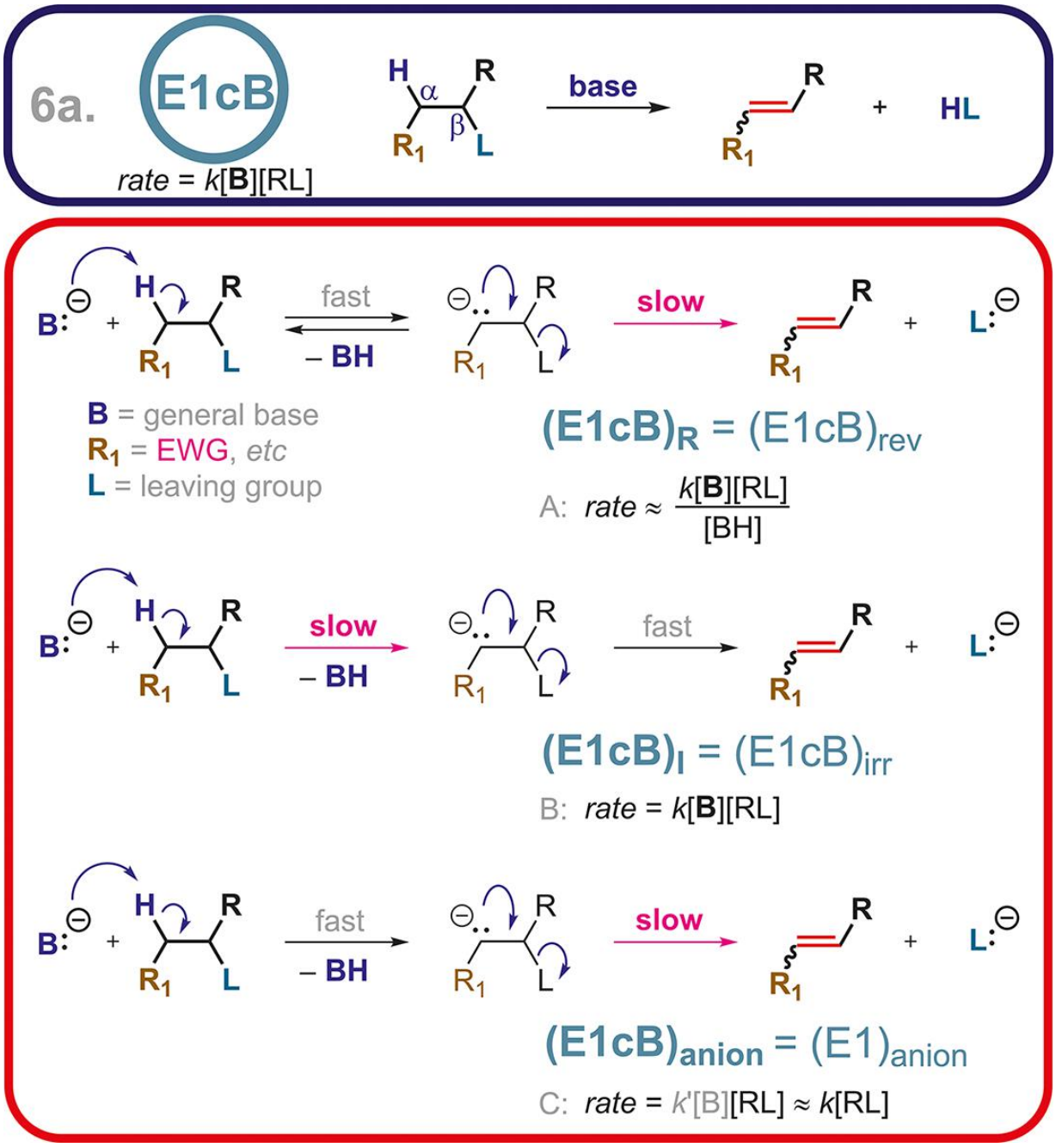


Fig. 6.1: Unimolecular β-elimination mechanism (**E1cB**).[16].

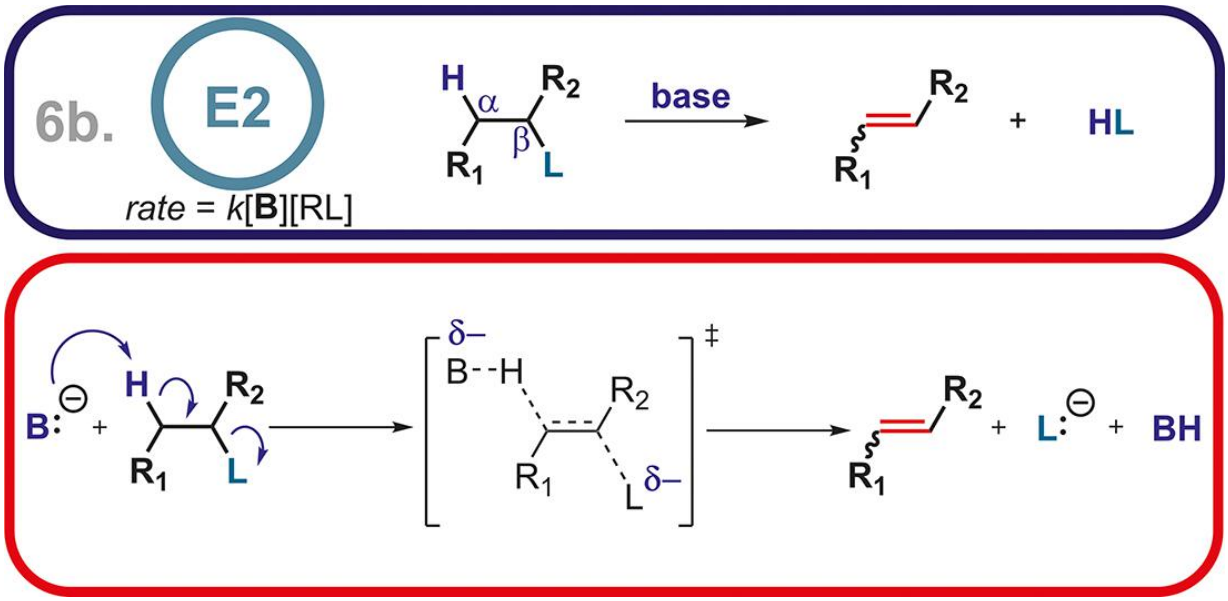


Fig. 6.2: Bimolecular β-elimination mechanism (**E2**).[17].

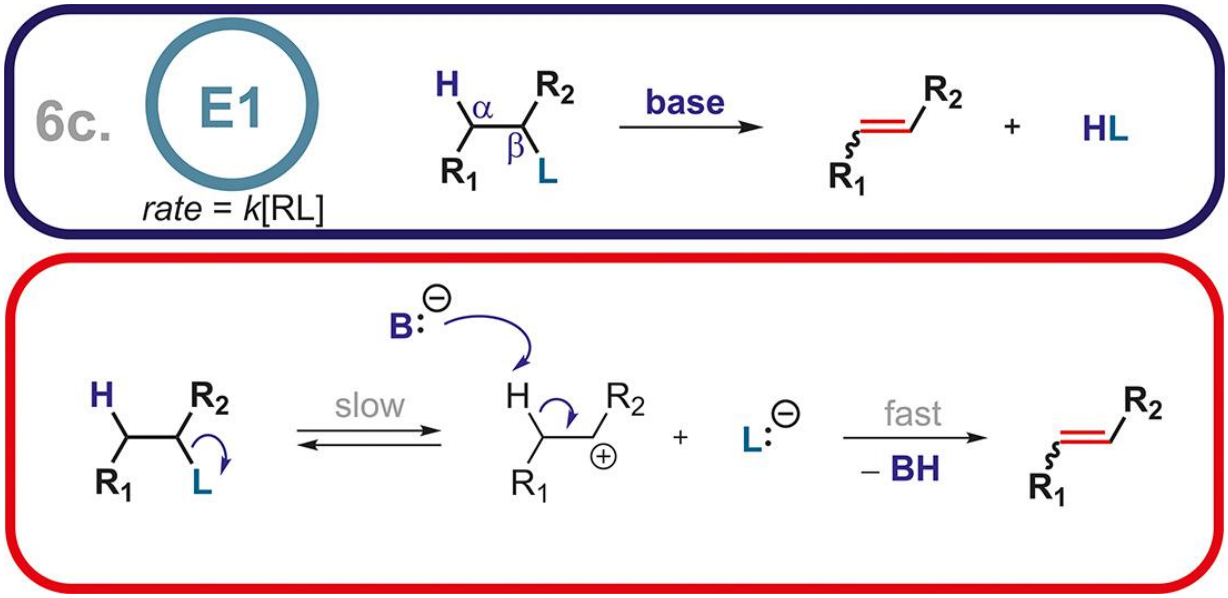


Fig. 6.3: Unimolecular β-elimination mechanism (**E1**).[18].

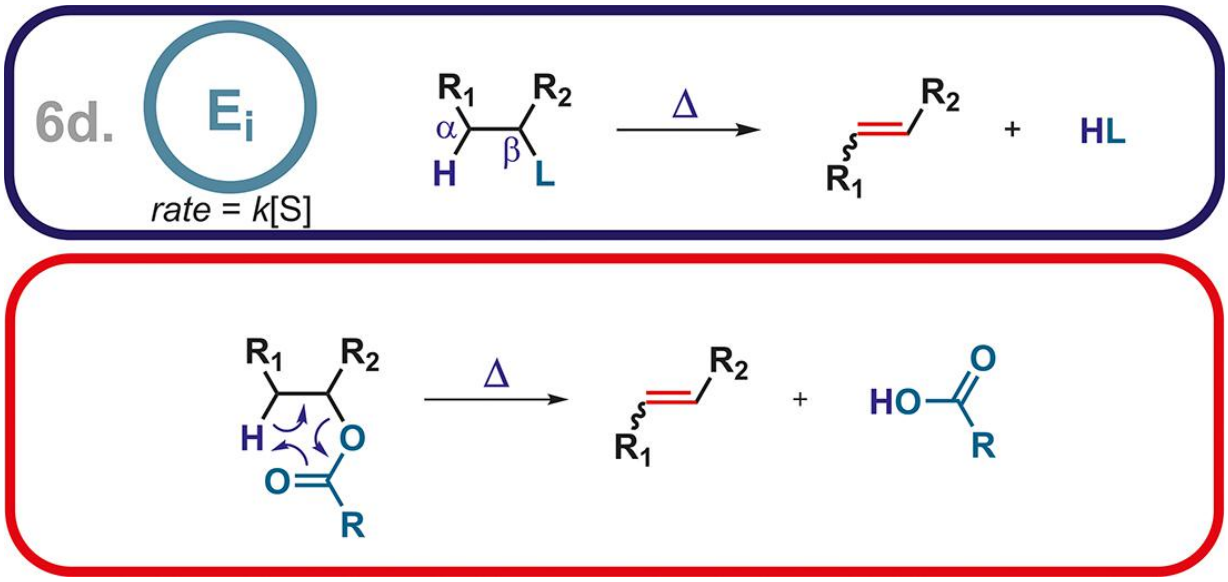


Fig. 6.4: Internal or intramolecular β-elimination mechanism (**E_i**).[19].

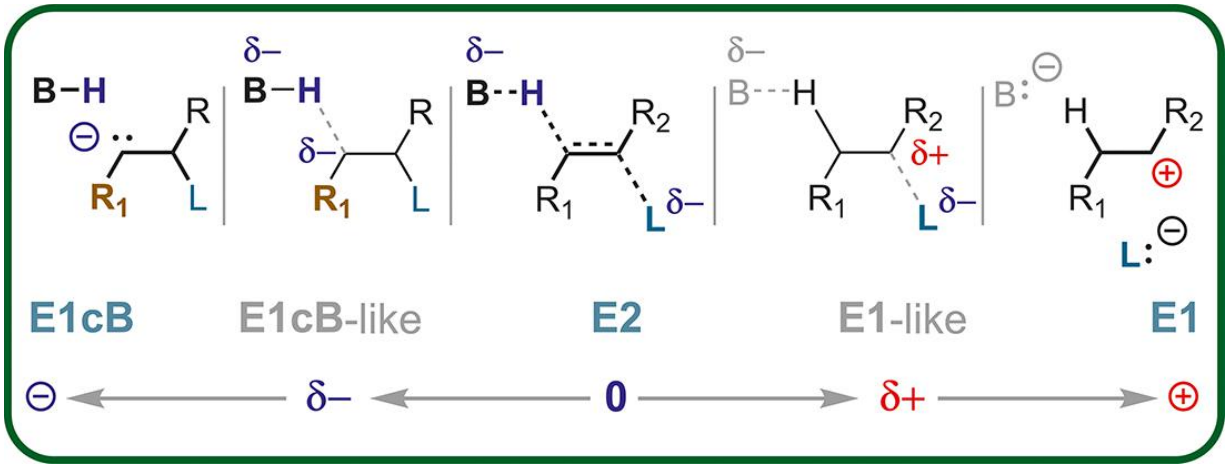


Fig. 6.5: **E1cB**, **E2**, and **E1** mechanisms.[20].

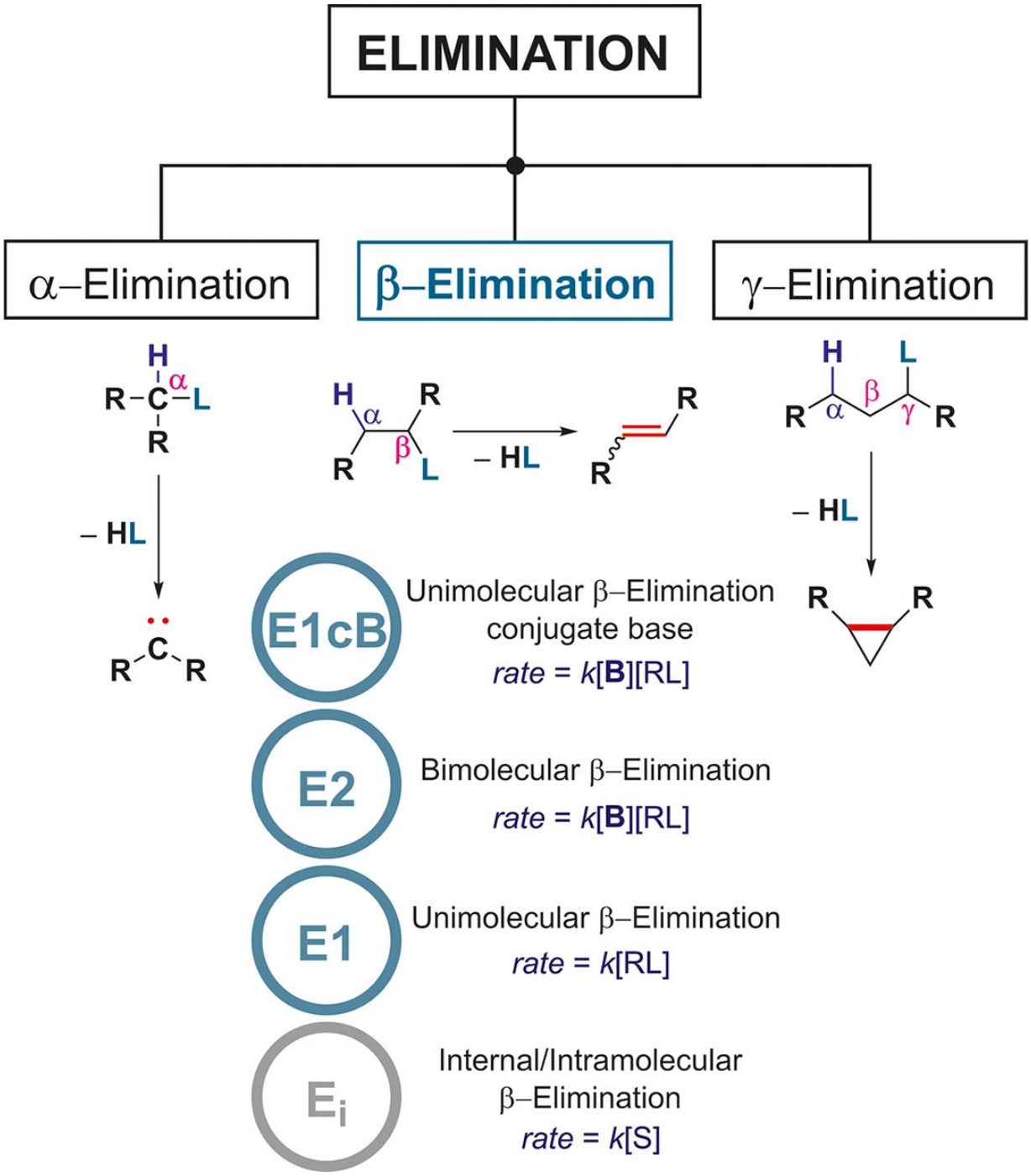


Fig. 6.6: The classification of characteristic elimination reactions.[21].

7 Acyloin Condensation

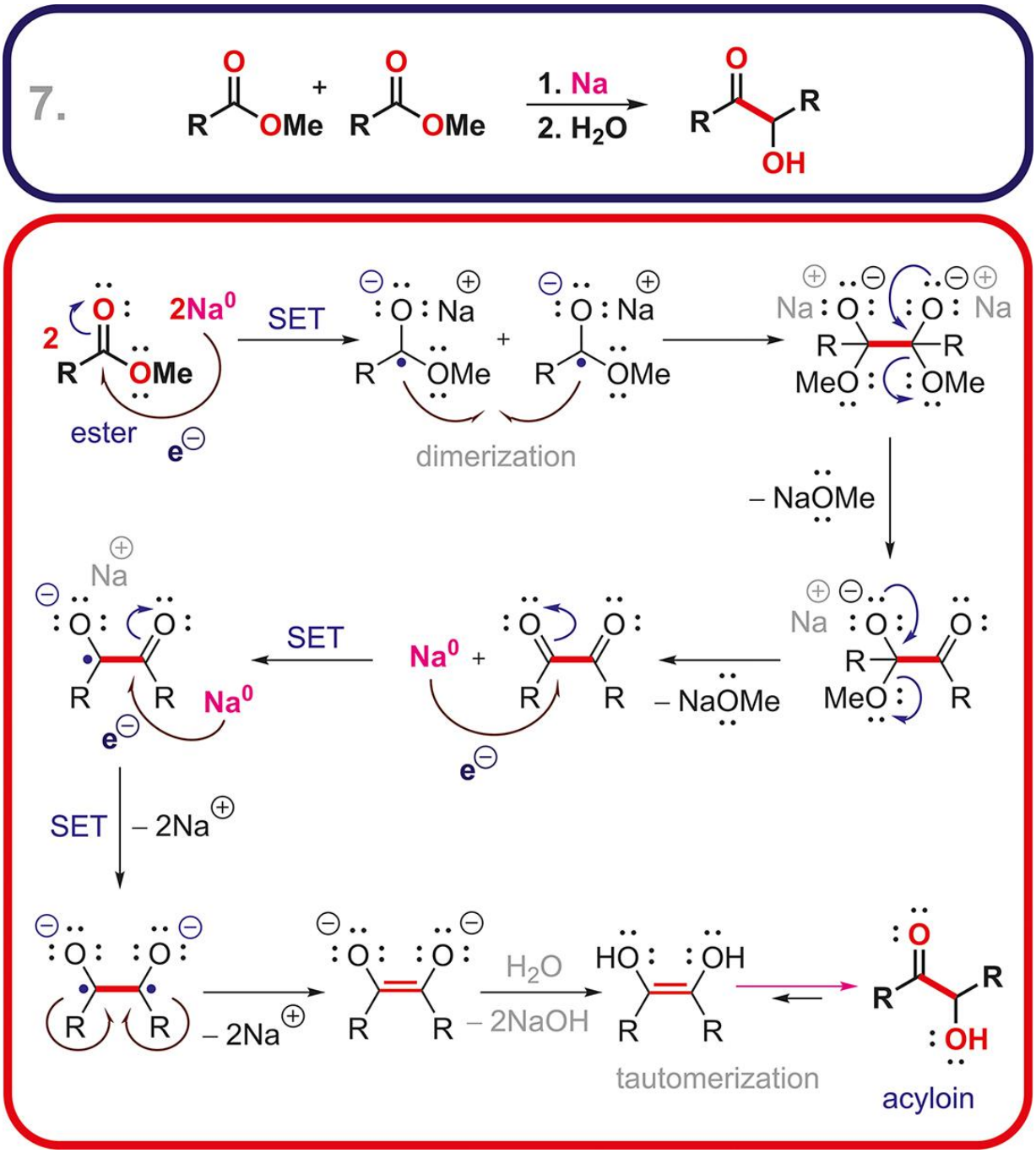


Fig. 7.1: The *acyloin condensation* mechanism.[22]

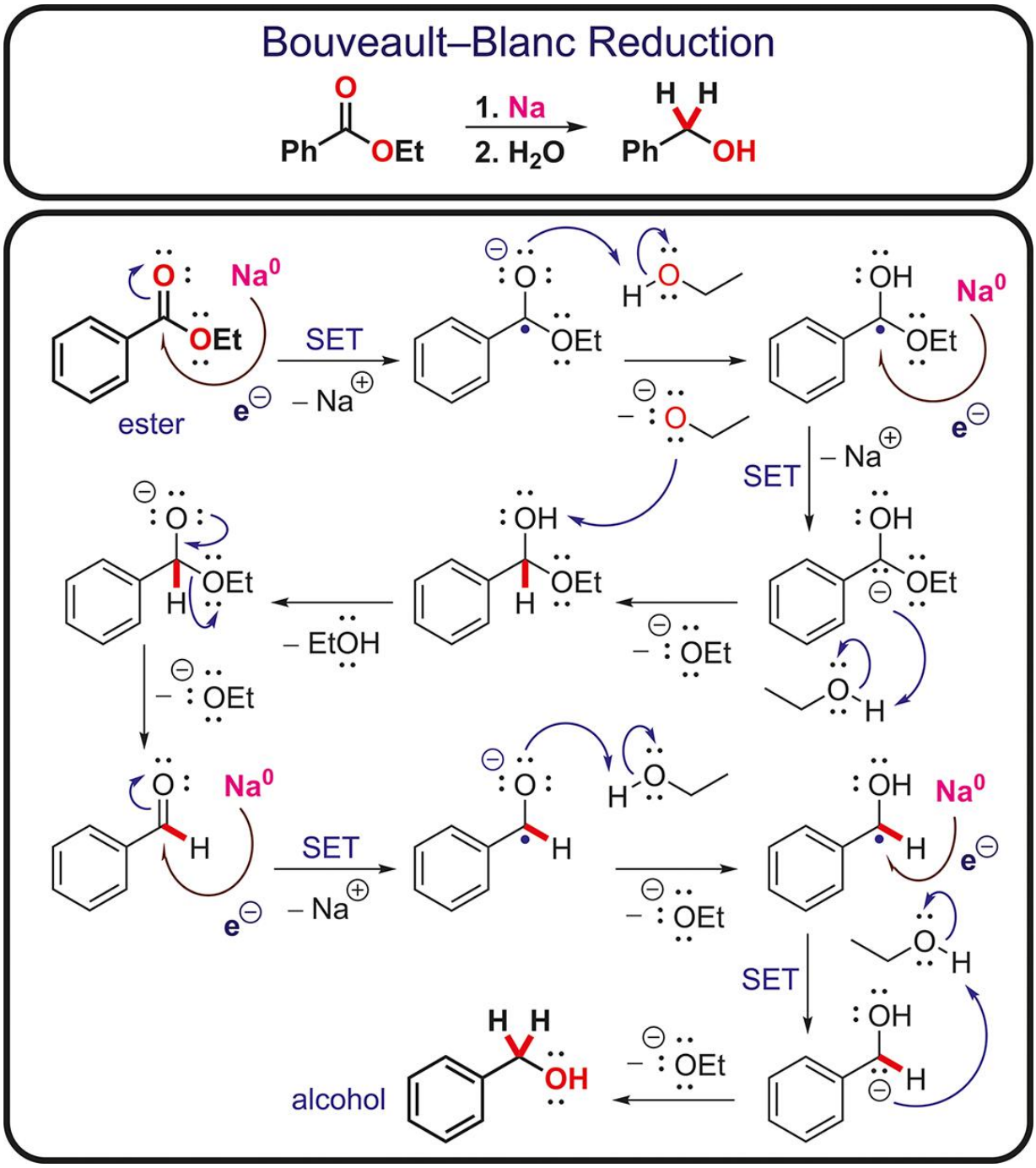


Fig. 7.2: The ***Bouveault–Blanc*** *reduction* mechanism (ester reduction).[23]

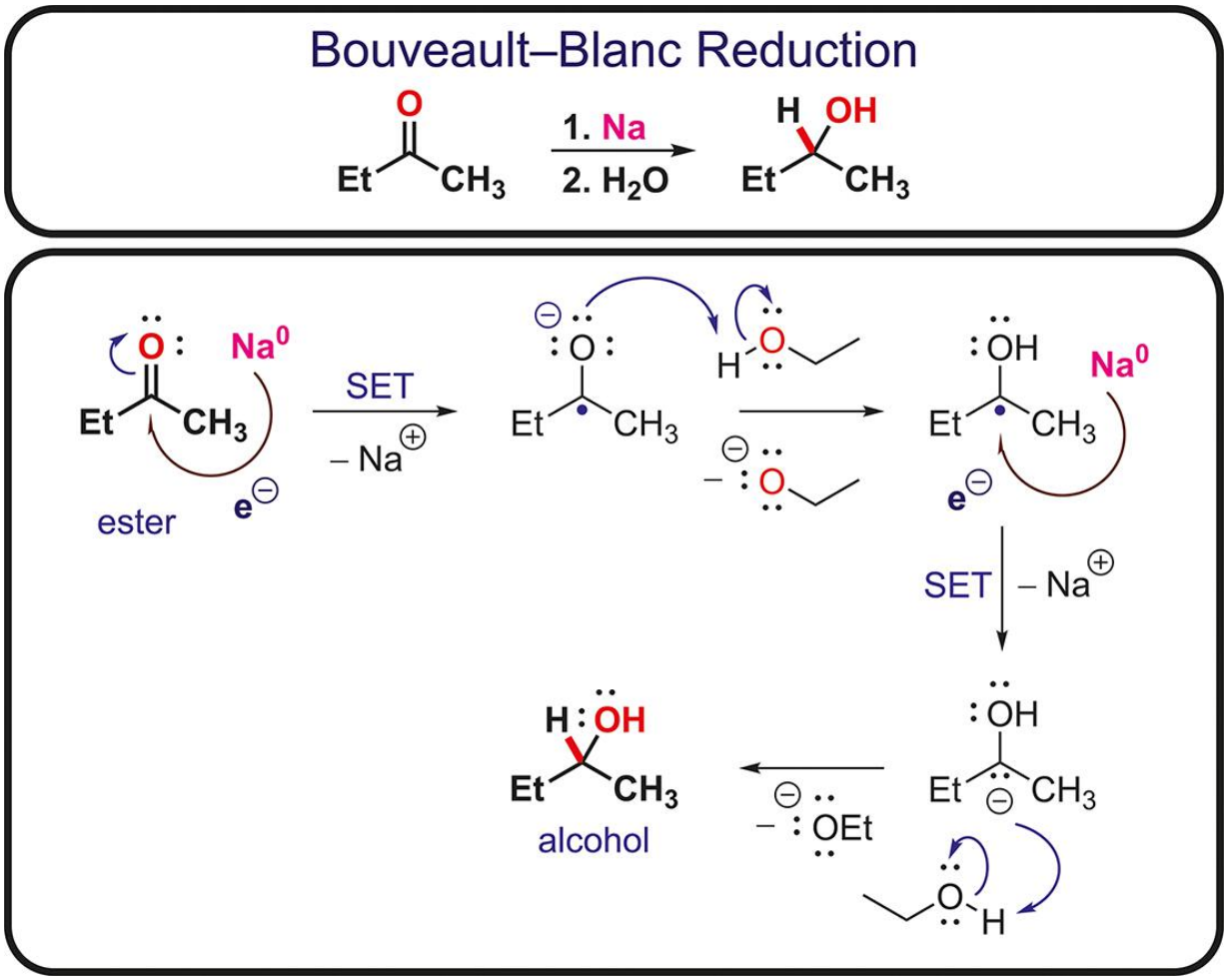


Fig. 7.3: The ***Bouveault–Blanc*** *reduction* mechanism (ketone reduction).[24]

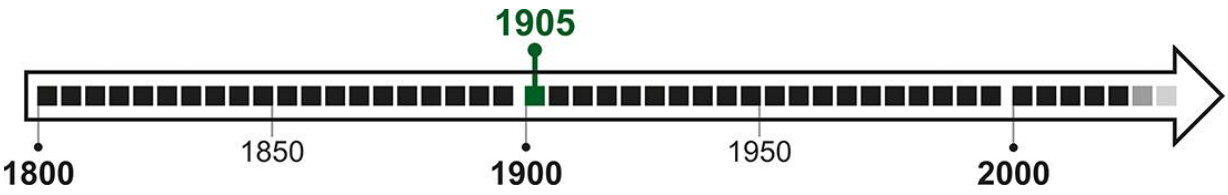


Fig. 7.4: The discovery of the *acyloin condensation*.[25]

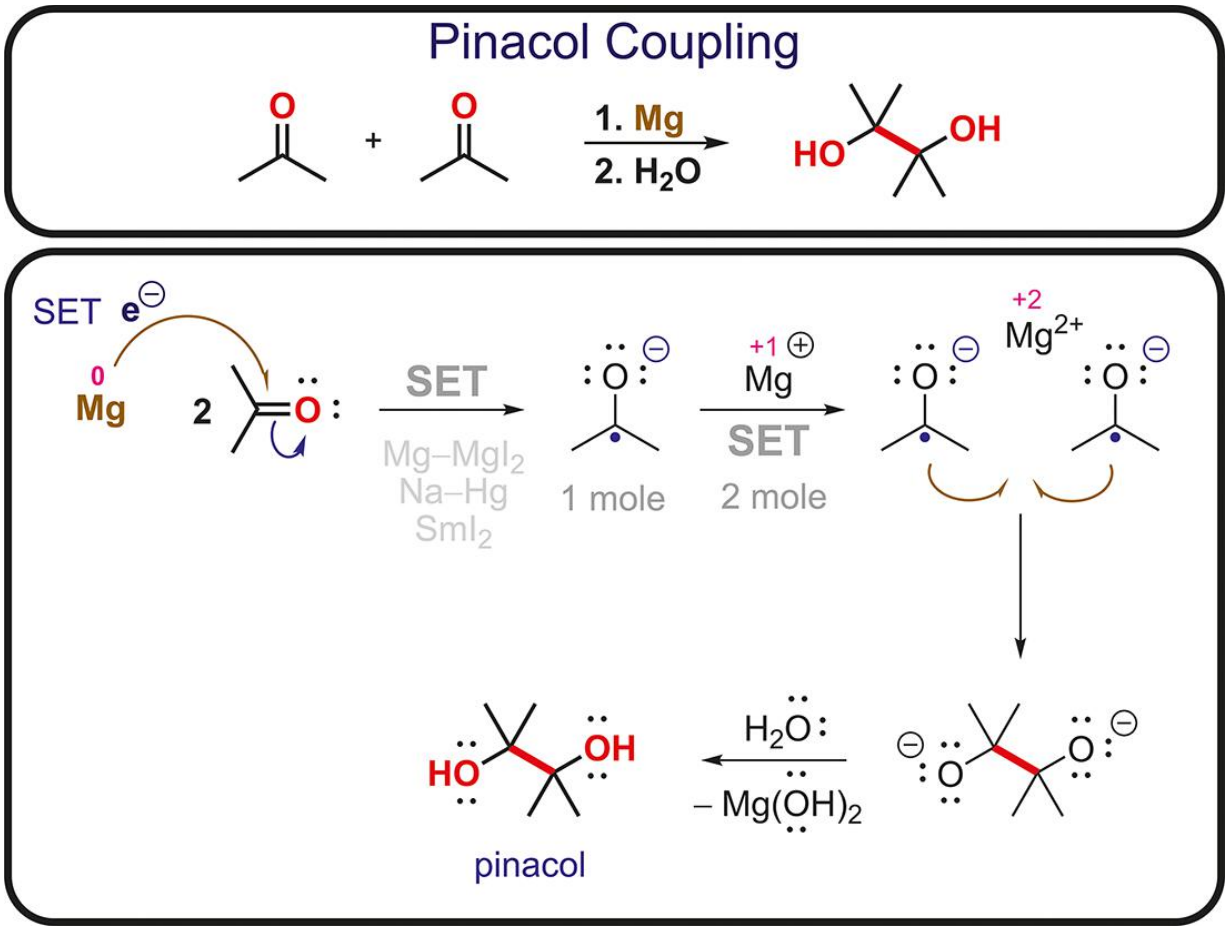


Fig. 7.5: The *pinacol coupling* mechanism.[26]

8 Alkyne Zipper Reaction

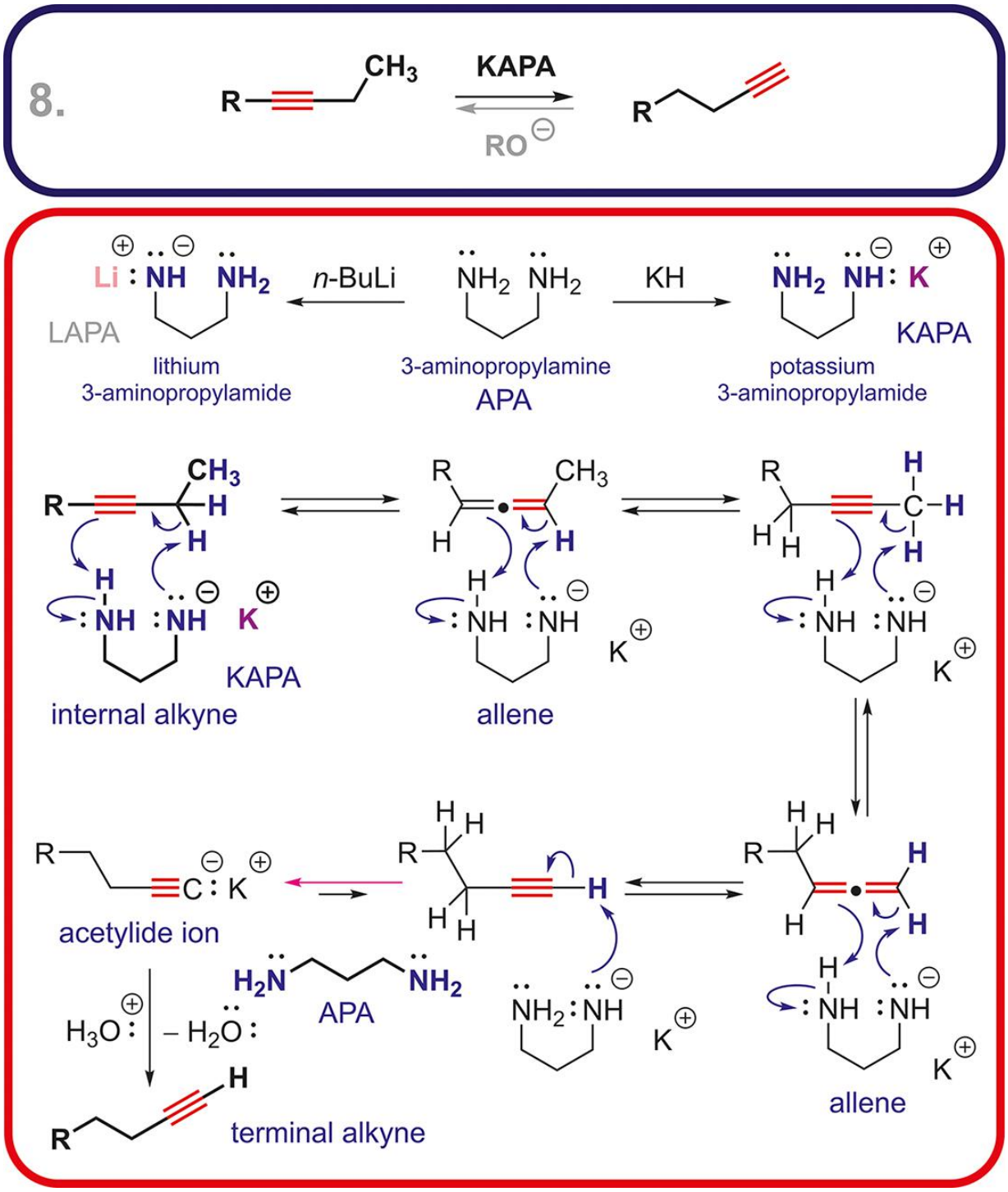


Fig. 8.1: The *alkyne zipper reaction* mechanism.[27]

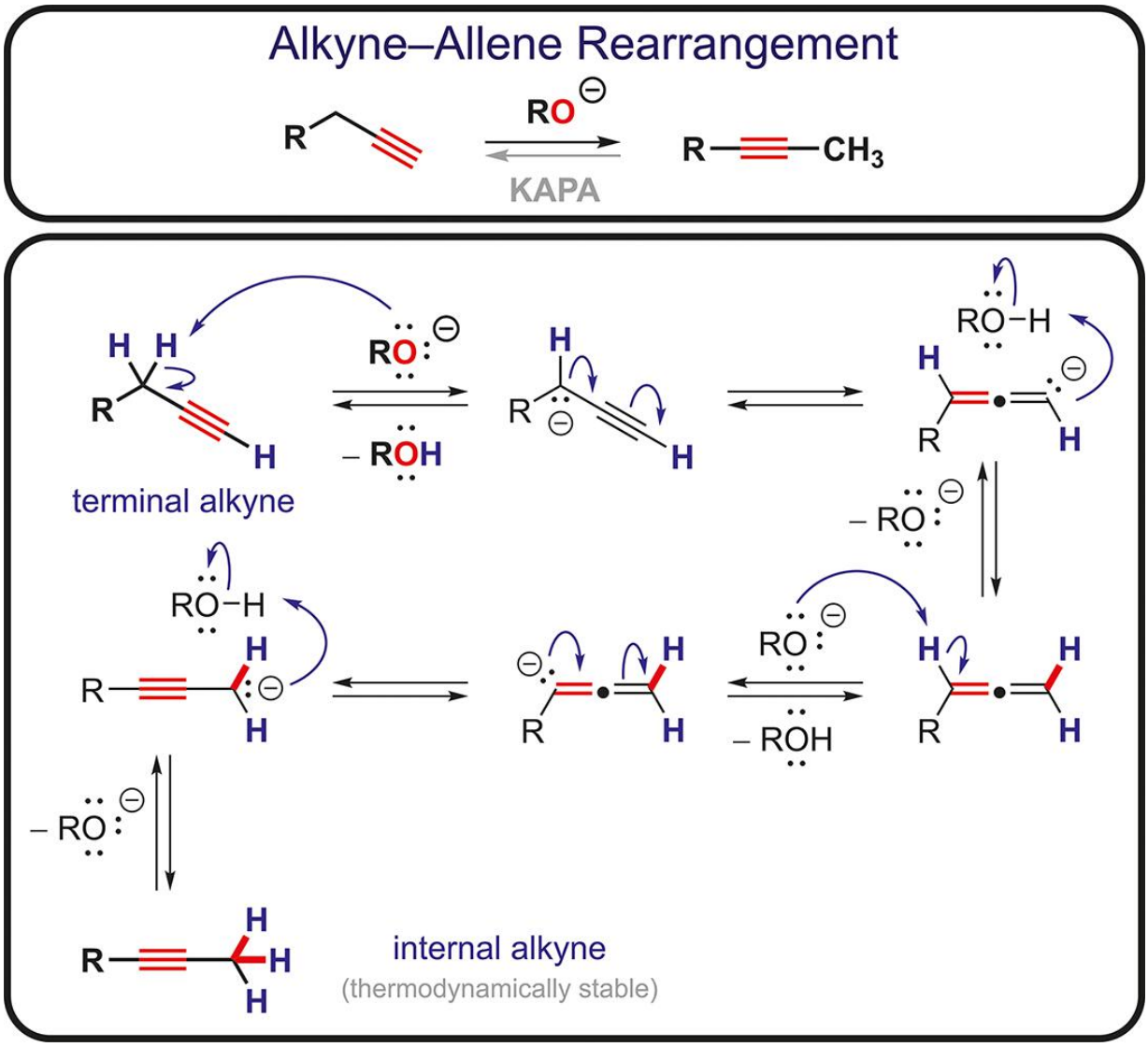


Fig. 8.2: The *alkyne–allene rearrangement* mechanism.[28]

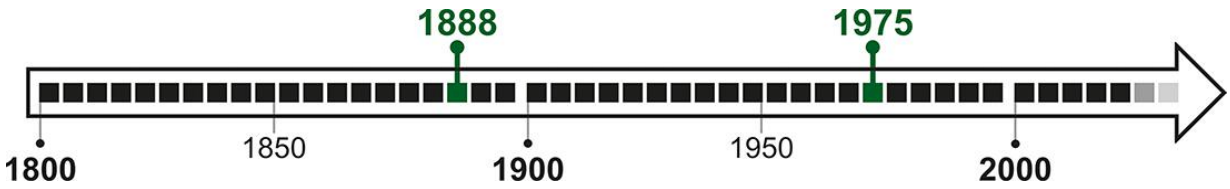


Fig. 8.3: The discovery of the *alkyne zipper reaction*.[29]

9 Arbuzov Reaction

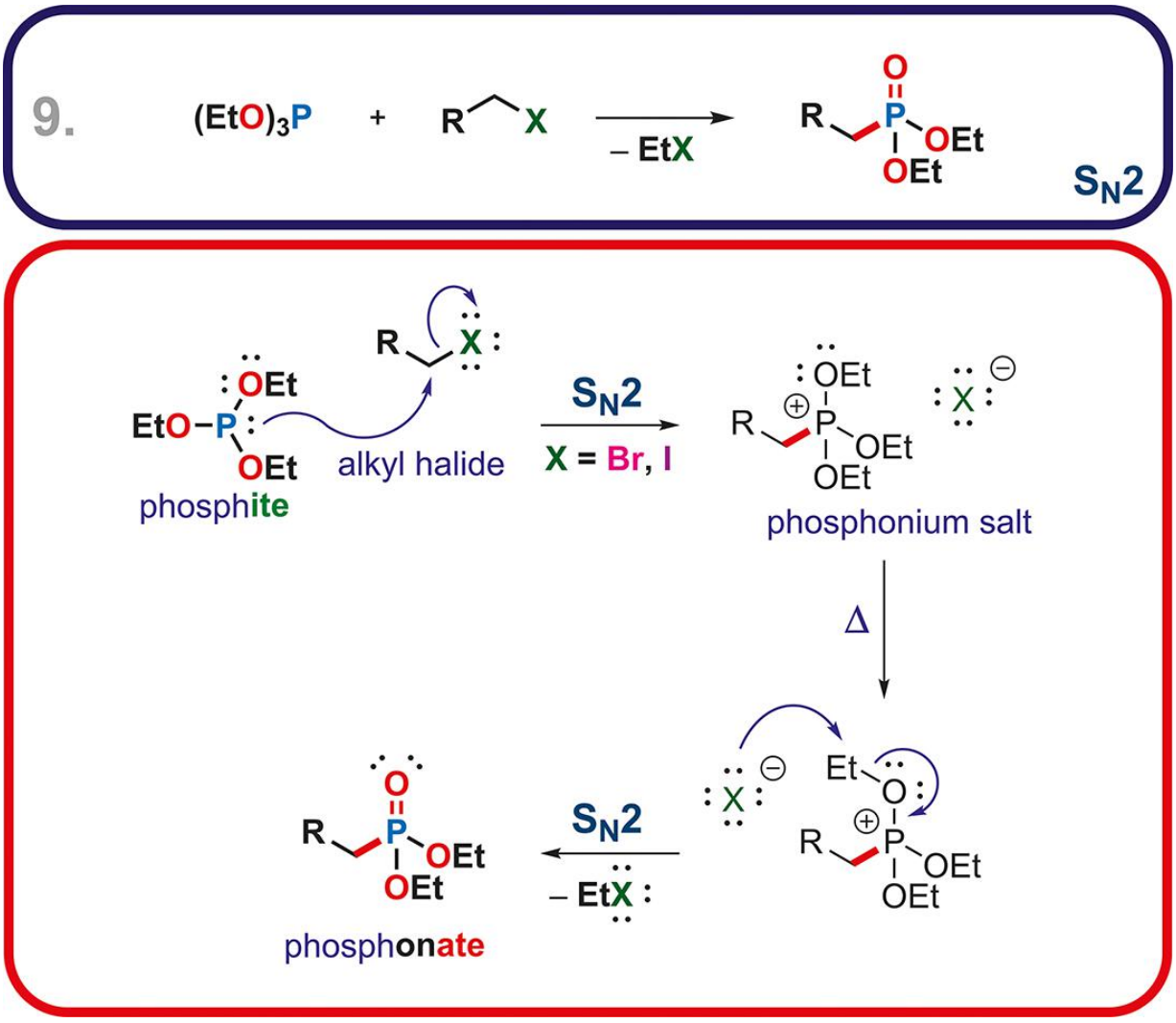


Fig. 9.1: The ***Arbuzov*** *reaction* mechanism.[30]

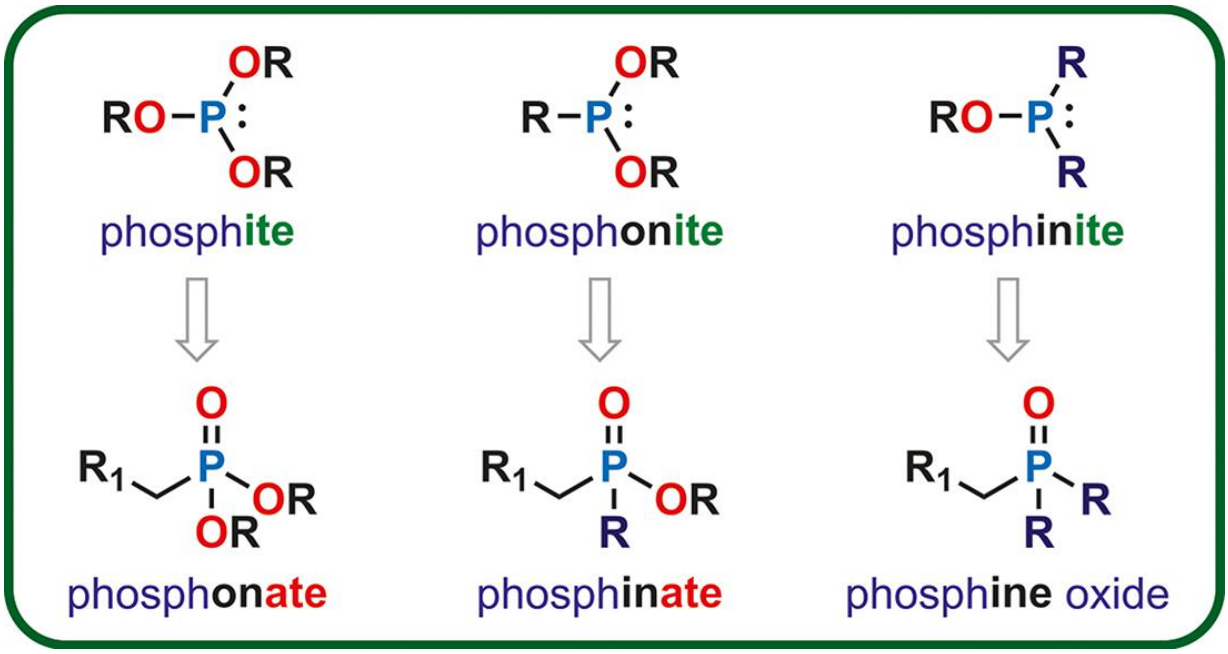


Fig. 9.2: The nomenclature of selected organophosphorus(III) and (V) compounds.[31]

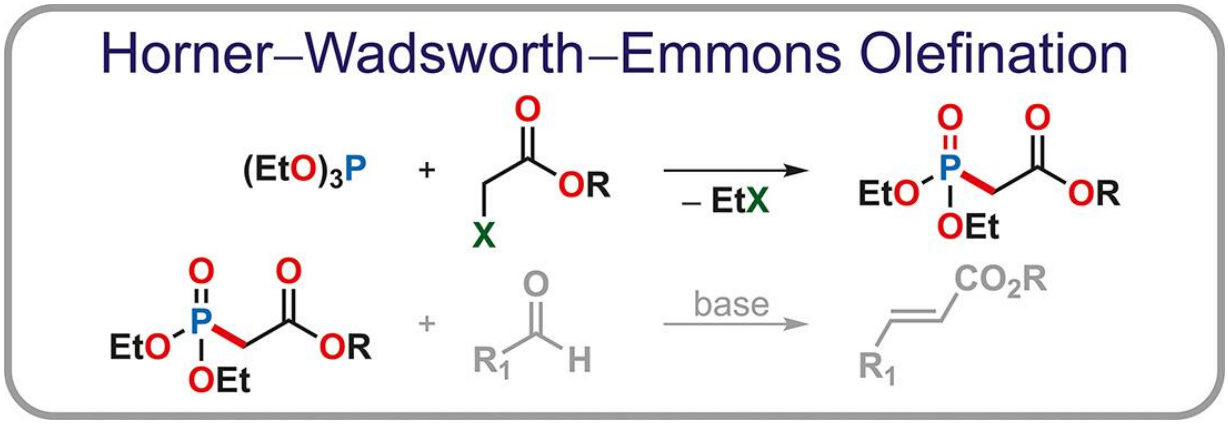


Fig. 9.3: The ***HWE*** olefination.[32]

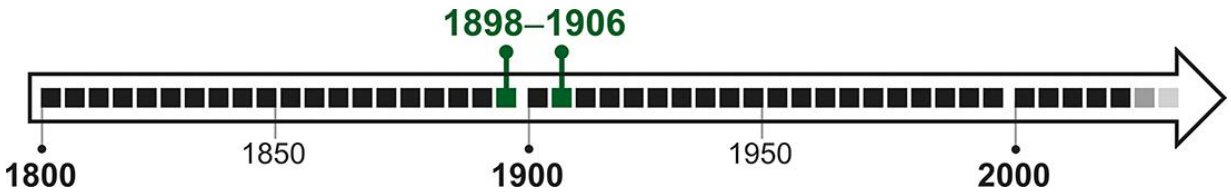


Fig. 9.4: The discovery of the ***Arbuzov*** *reaction*.[33]

10 Arndt–Eistert Synthesis

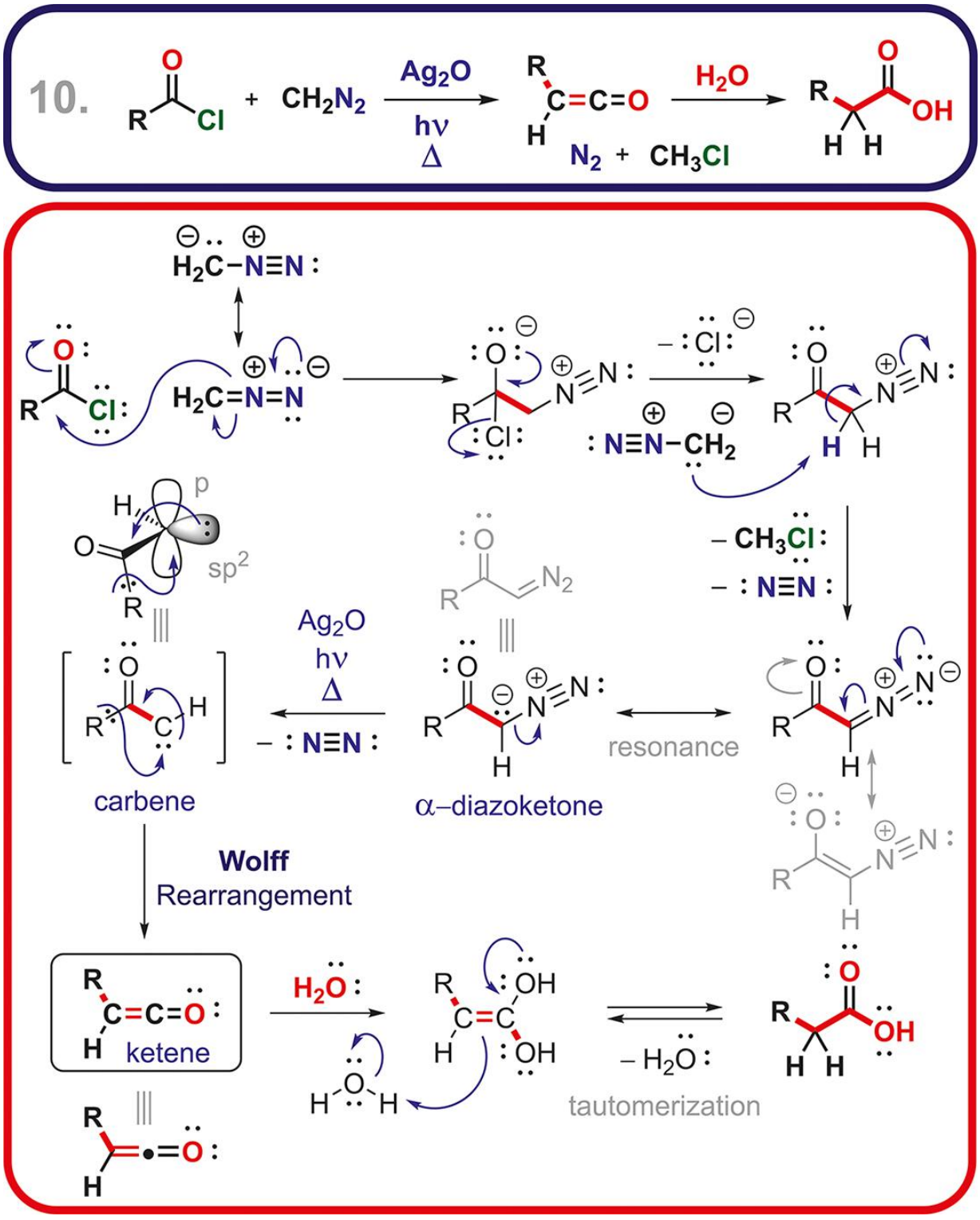


Fig. 10.1: The ***Arndt–Eistert*** *synthesis* mechanism.[34]

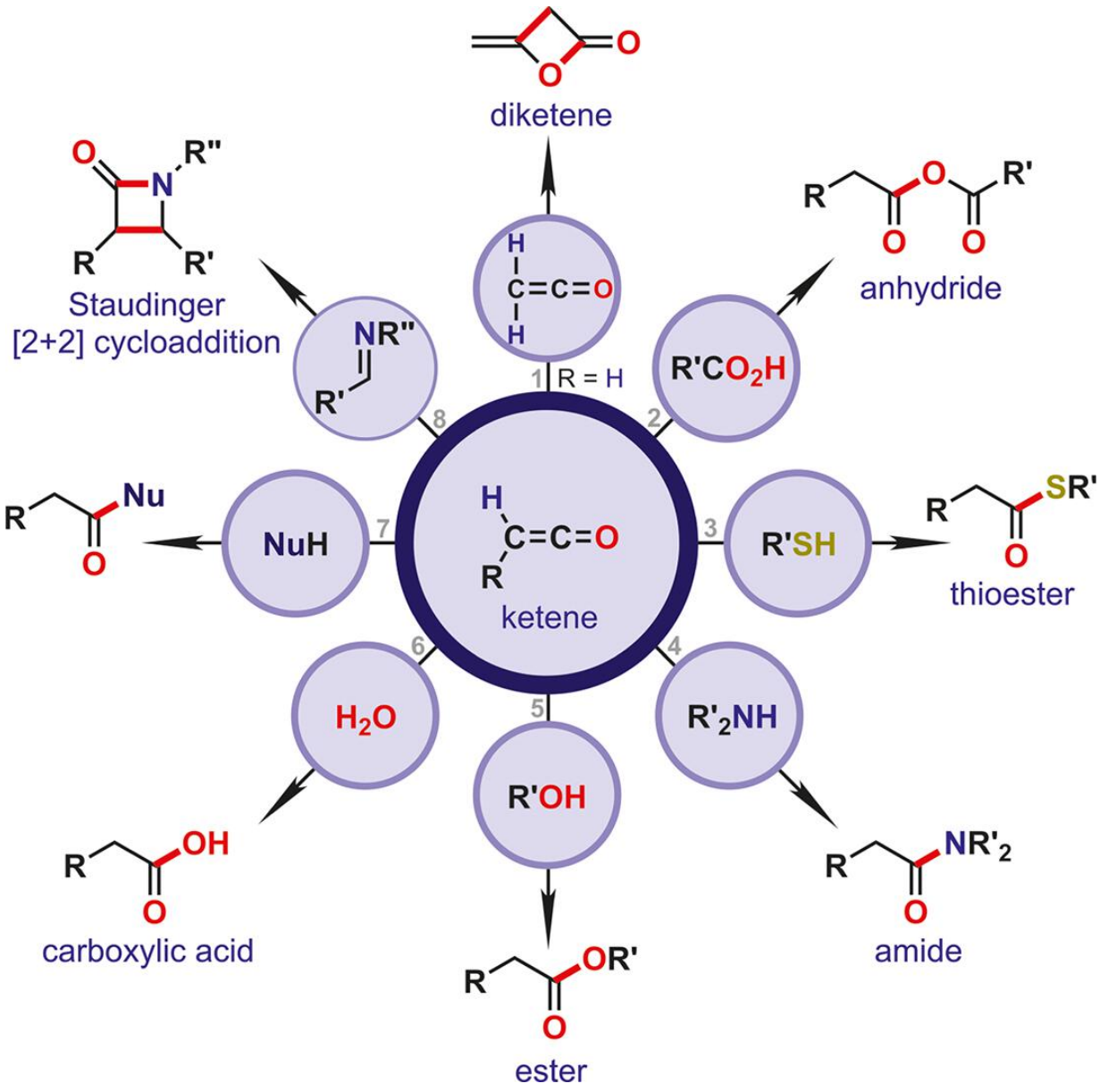


Fig. 10.2: The synthetic versatility of ketenes.[35]

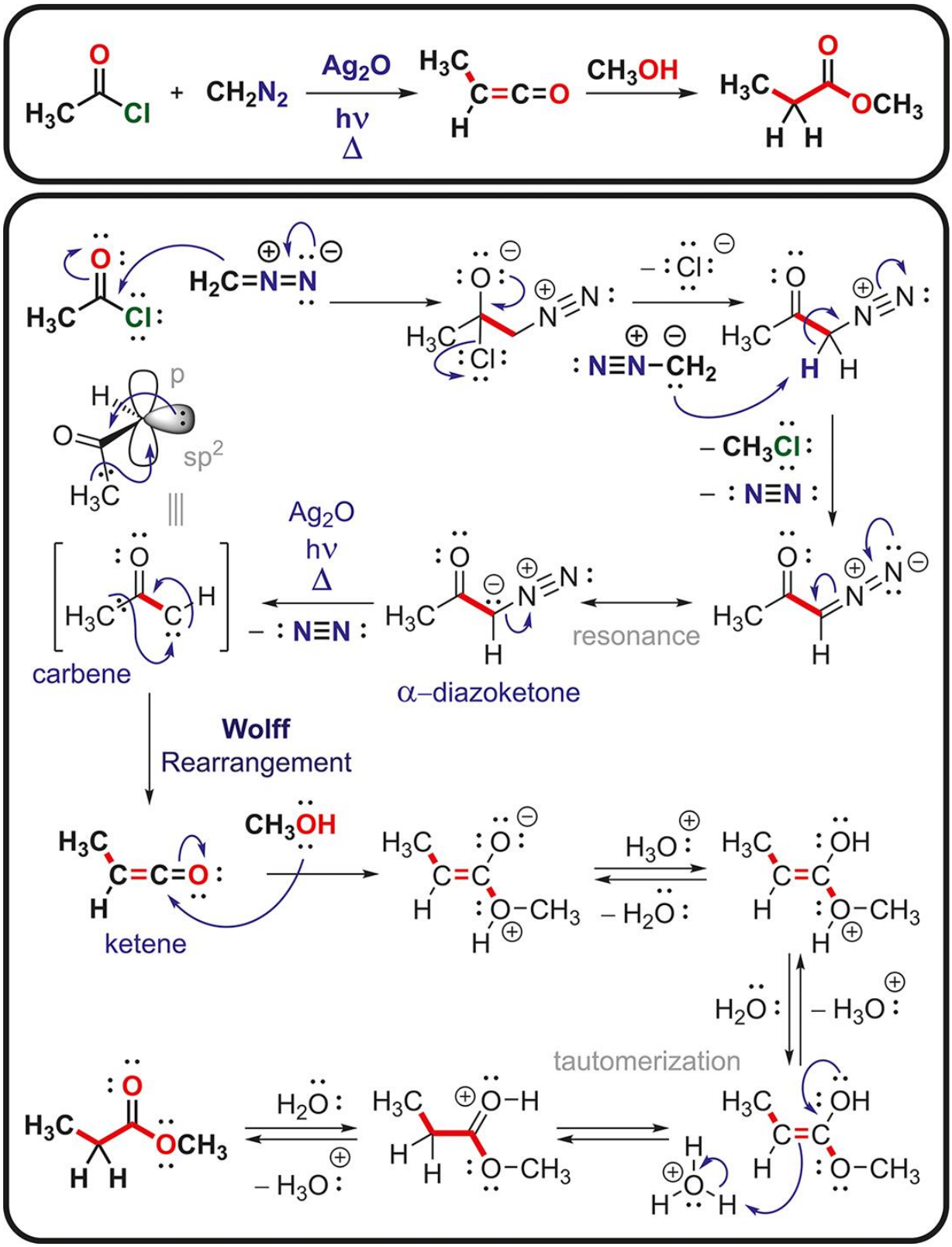


Fig. 10.3: The ***Arndt–Eistert*** *reaction* mechanism.[36]

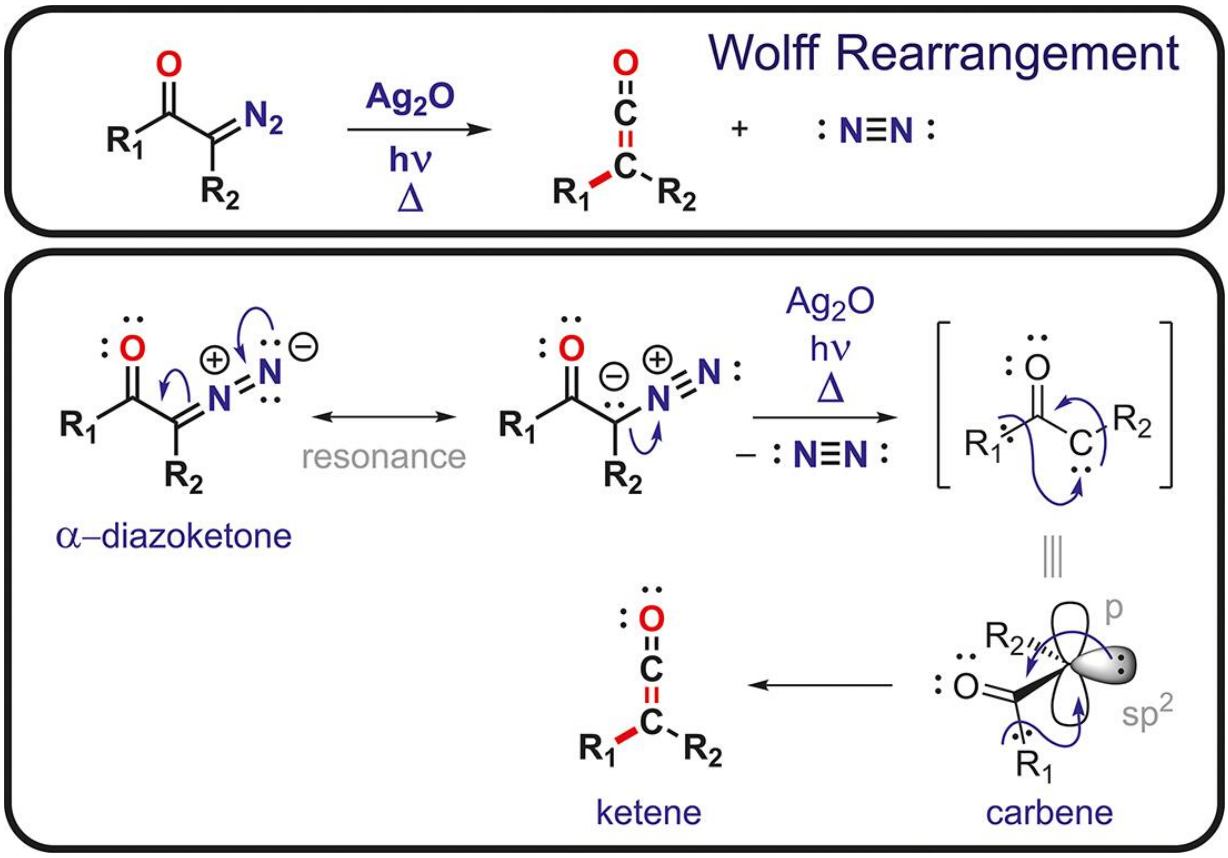


Fig. 10.4: The ***Wolff*** *rearrangement* mechanism.[37]

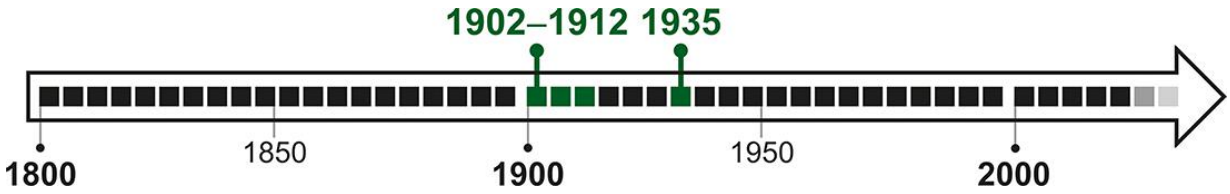


Fig. 10.5: The discovery of the ***Arndt–Eistert*** *synthesis*.[38]

11 Baeyer–Villiger Oxidation

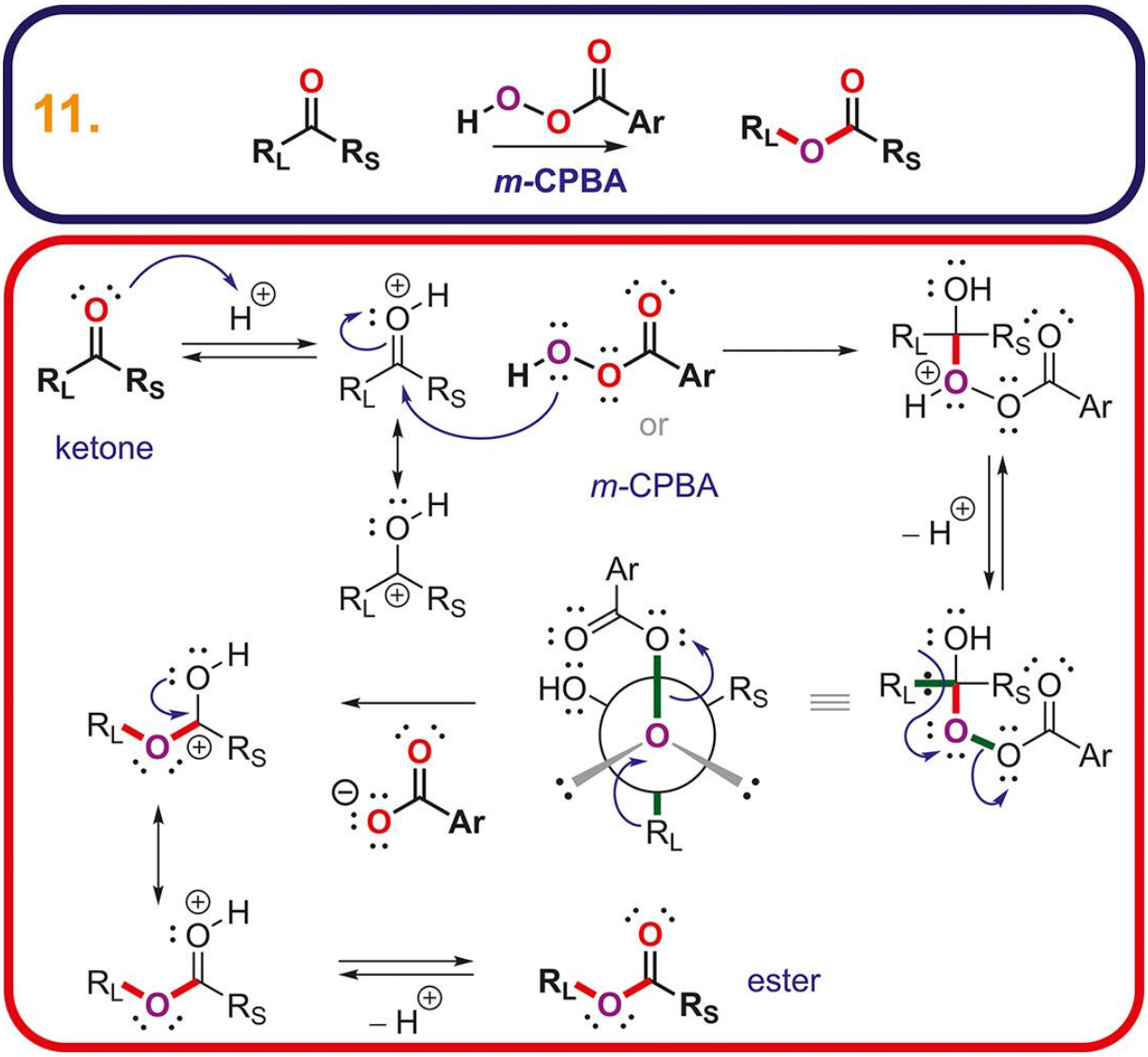


Fig. 11.1: The ***Baeyer–Villiger*** *oxidation* mechanism.[39]

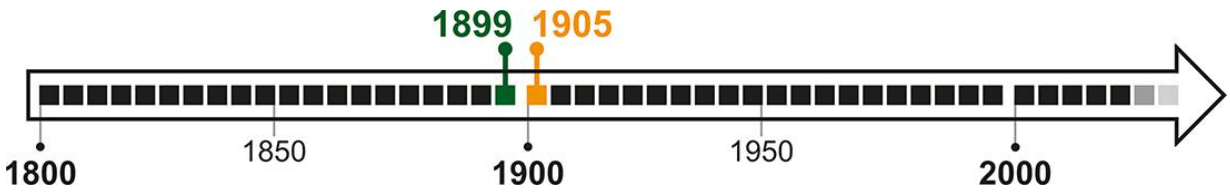


Fig. 11.2: The discovery of the ***Baeyer–Villiger*** *oxidation*.[40]

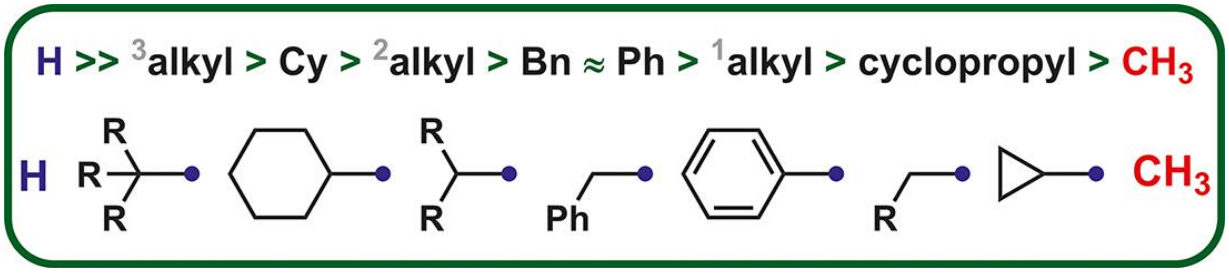


Fig. 11.3: The order of group migration in the ***Baeyer–Villiger*** *oxidation*.[41]

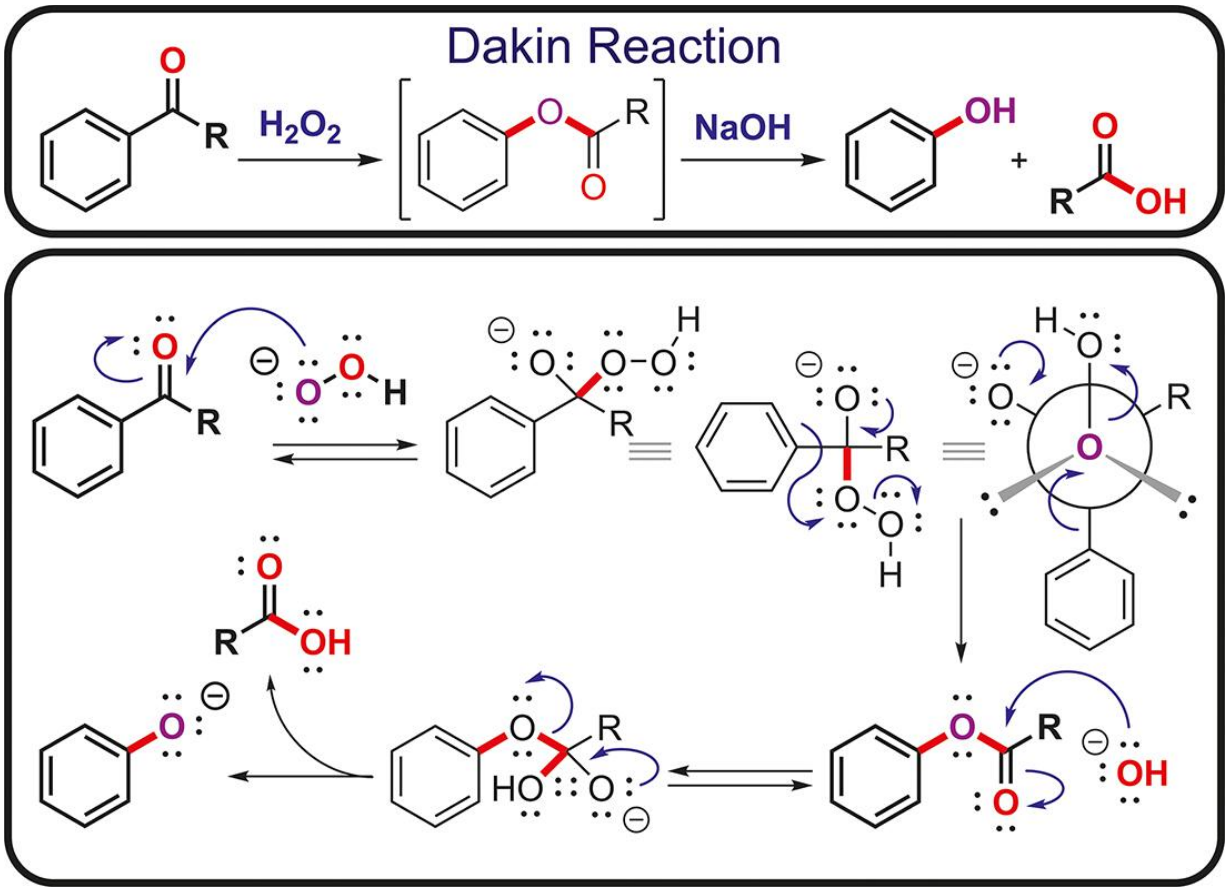


Fig. 11.4: The ***Dakin*** *reaction* mechanism.[42]

12 Barton Decarboxylation

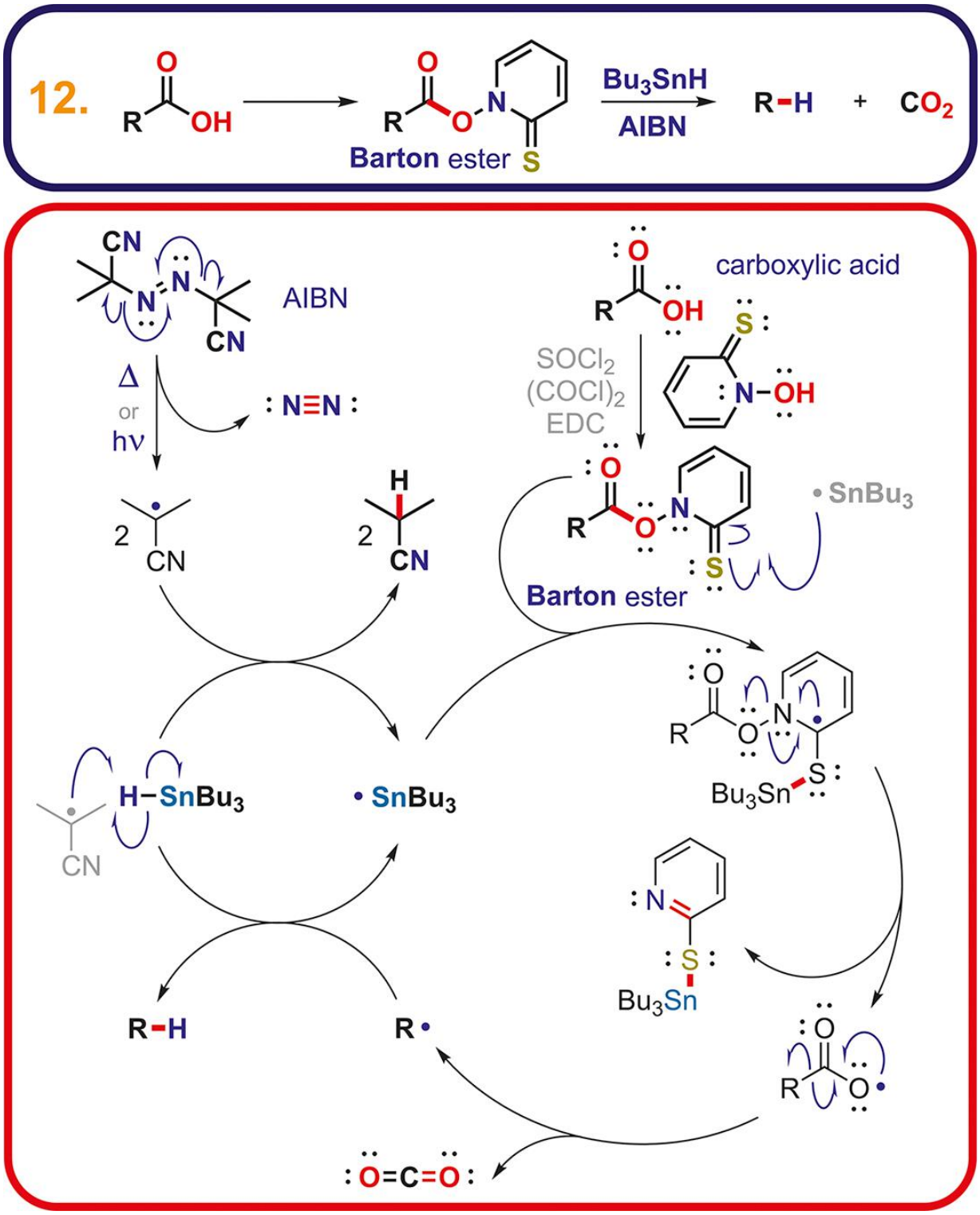


Fig. 12.1: The ***Barton*** *decarboxylation* mechanism.[43].

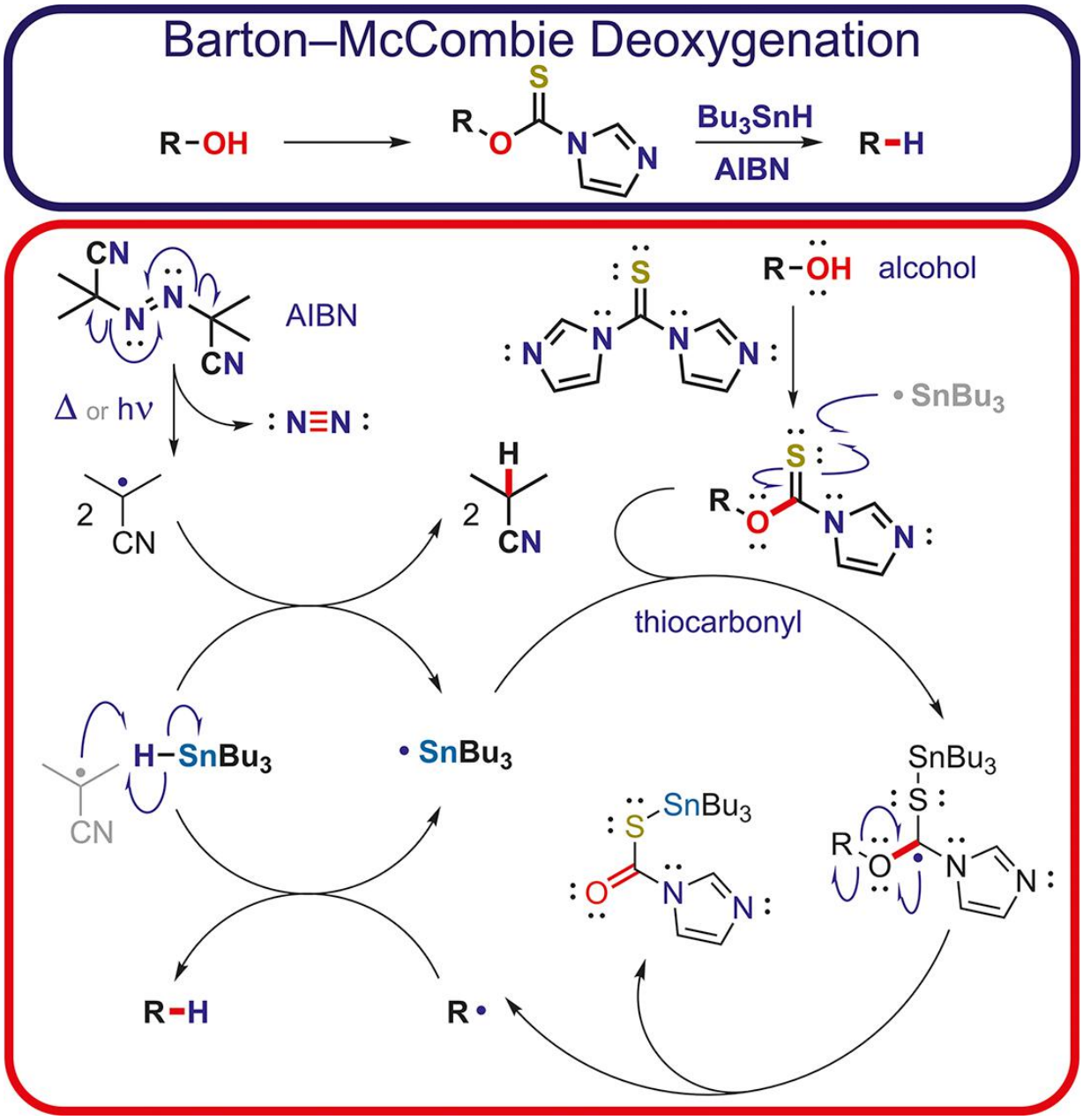


Fig. 12.2: The ***Barton–McCombie*** *deoxygenation* mechanism.[44].

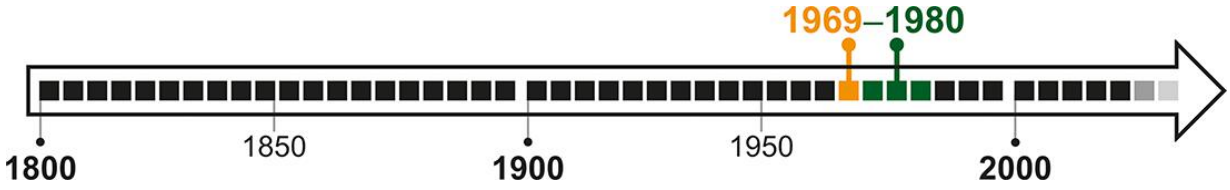


Fig. 12.3: The discovery of the ***Barton*** *decarboxylation*.[45].

13 Baylis–Hillman Reaction

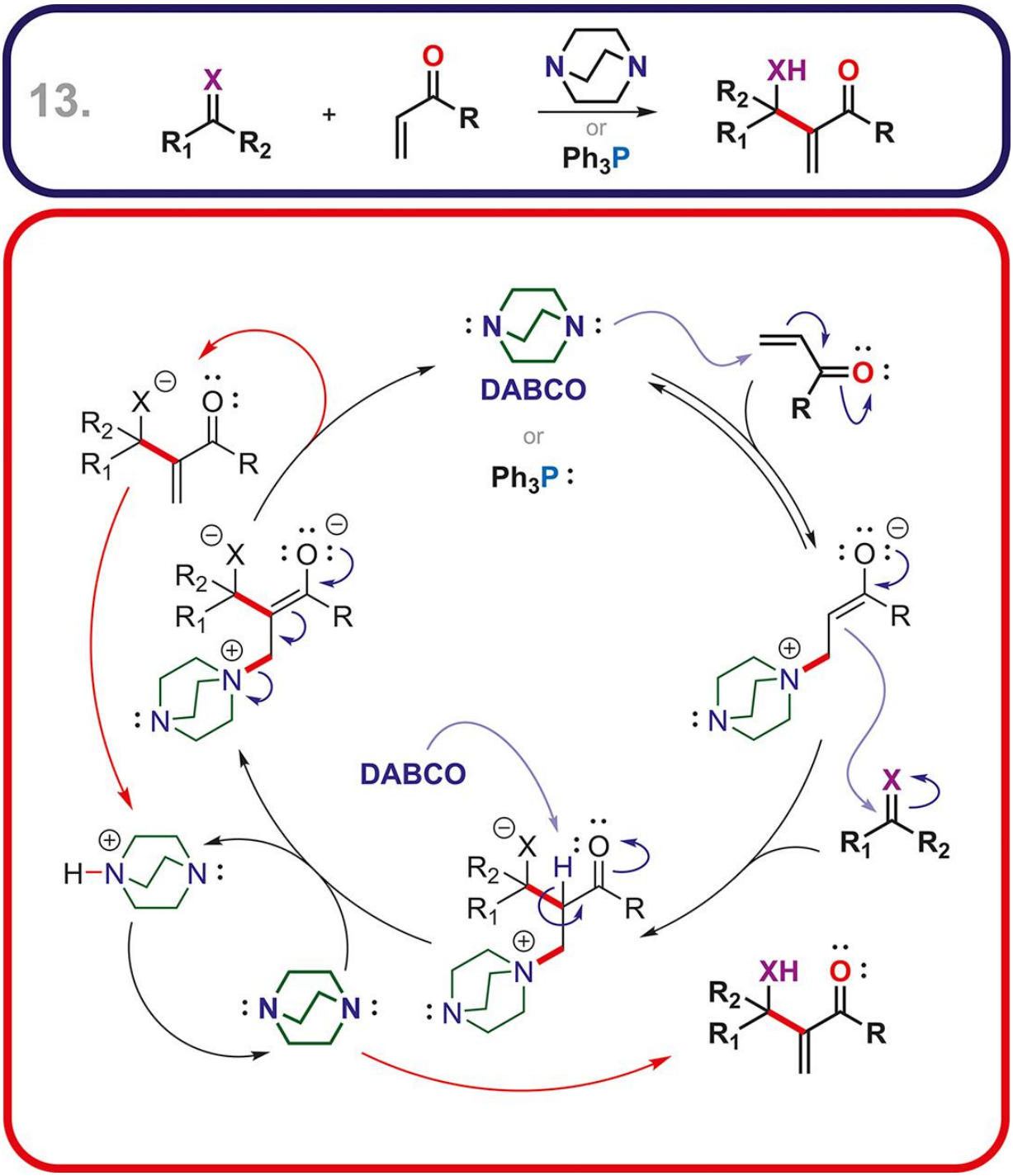


Fig. 13.1: The ***Baylis–Hillman*** *reaction* mechanism.[46].

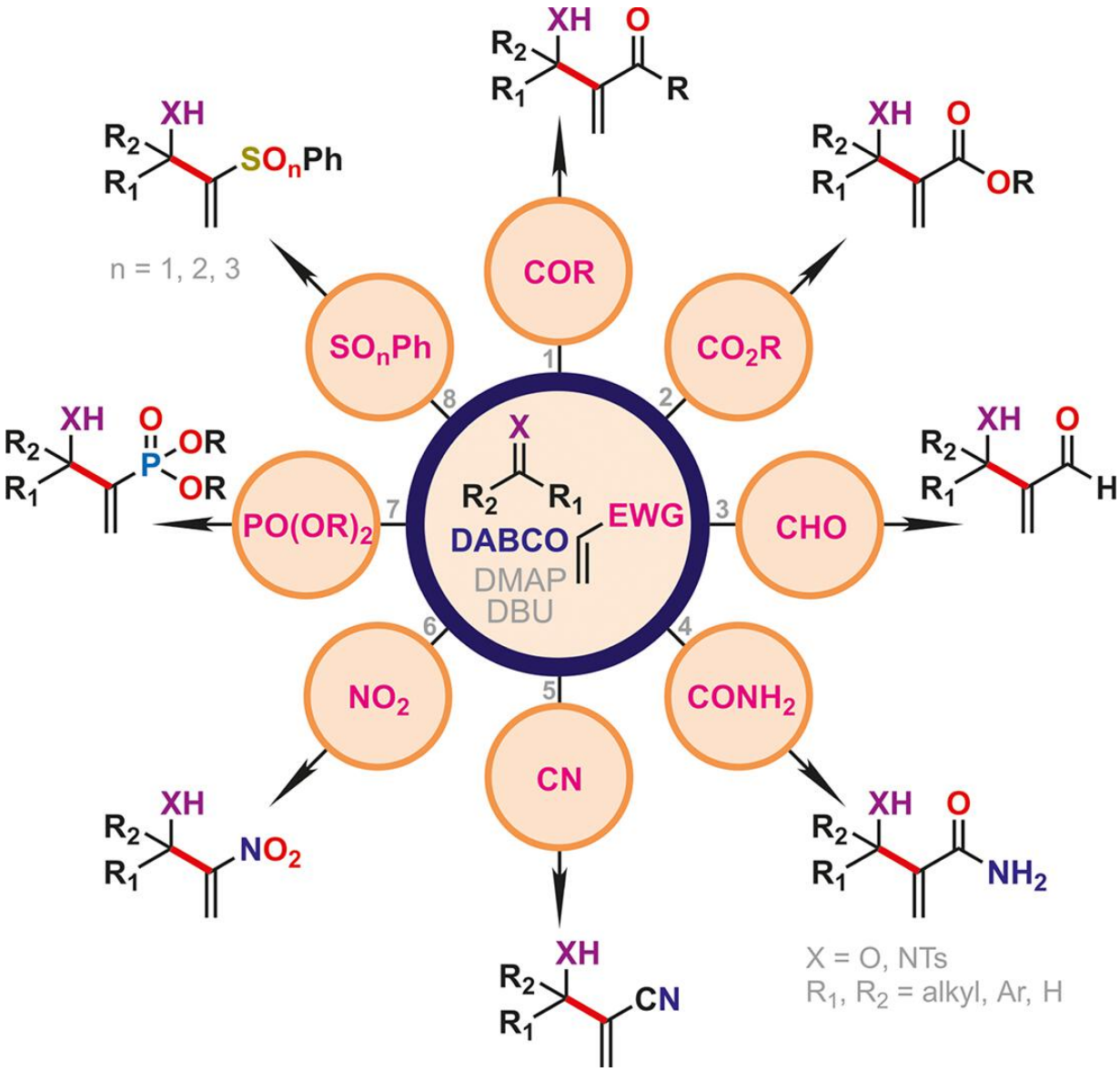


Fig. 13.2: The synthetic versatility of the ***Baylis–Hillman*** *reaction*.[47].

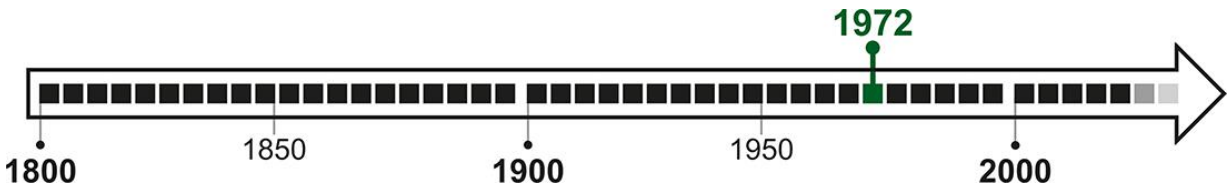


Fig. 13.3: The discovery of the ***Baylis–Hillman*** *reaction*.[48].

14 Beckmann Rearrangement

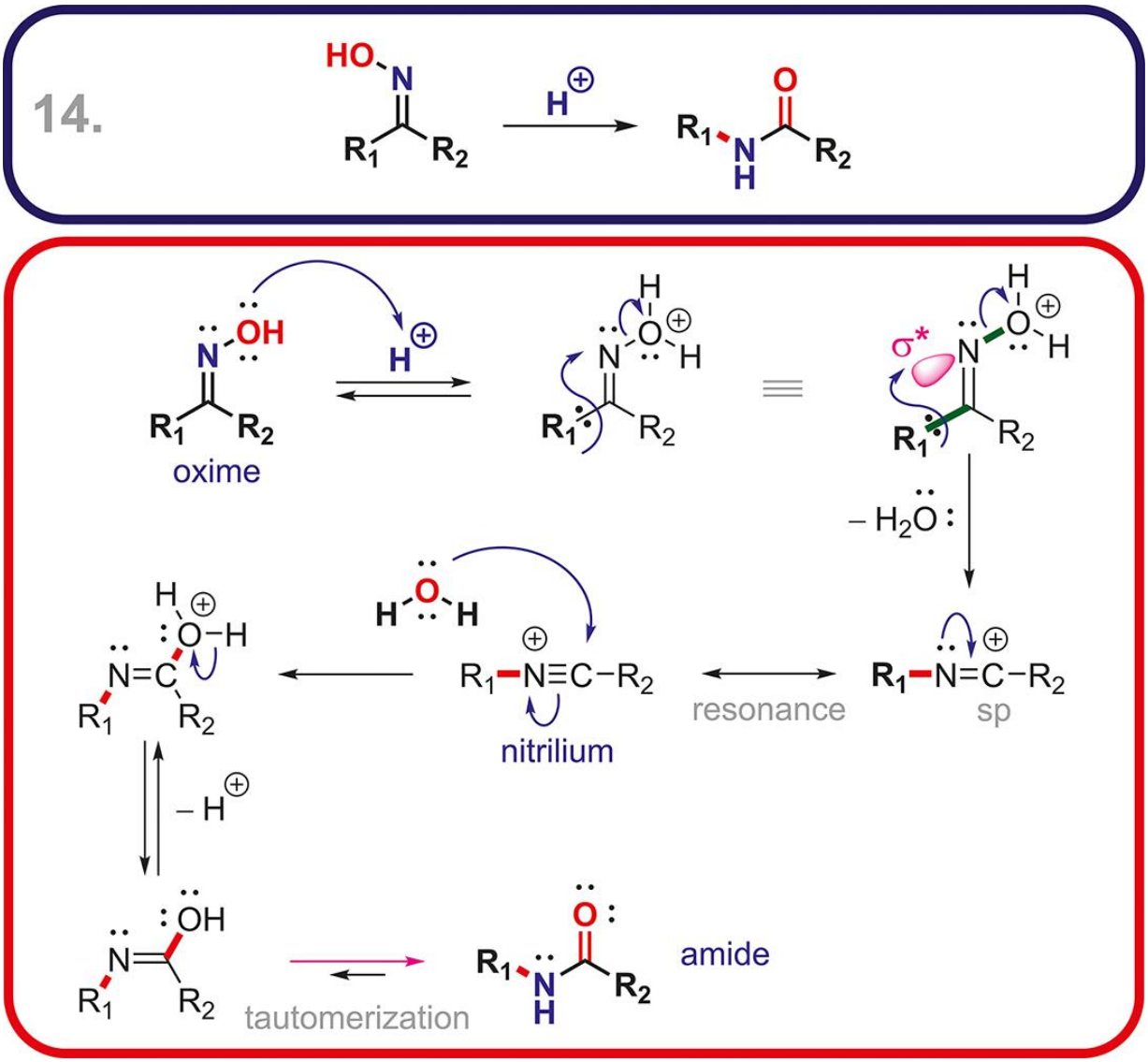


Fig. 14.1: The ***Beckmann*** *rearrangement* mechanism.[49]

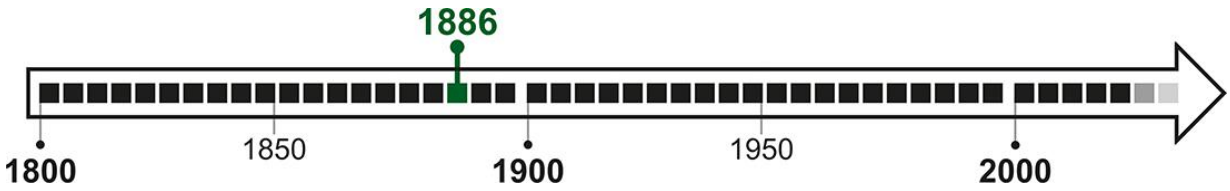


Fig. 14.2: The discovery of the ***Beckmann*** *rearrangement*.[50]

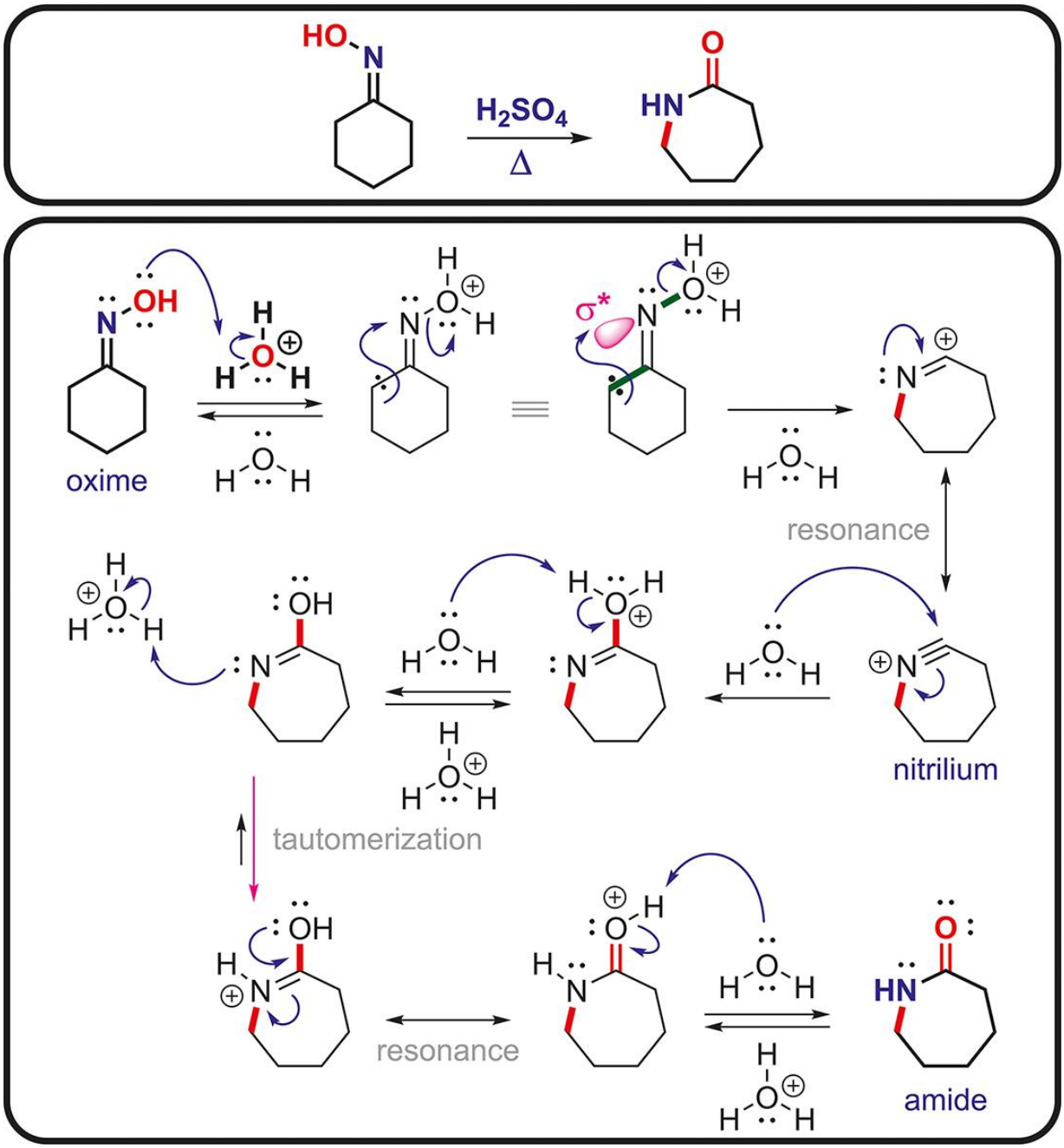


Fig. 14.3: The ***Beckmann*** *rearrangement* mechanism of cyclohexanone oxime.[51]

15 Benzoin Condensation

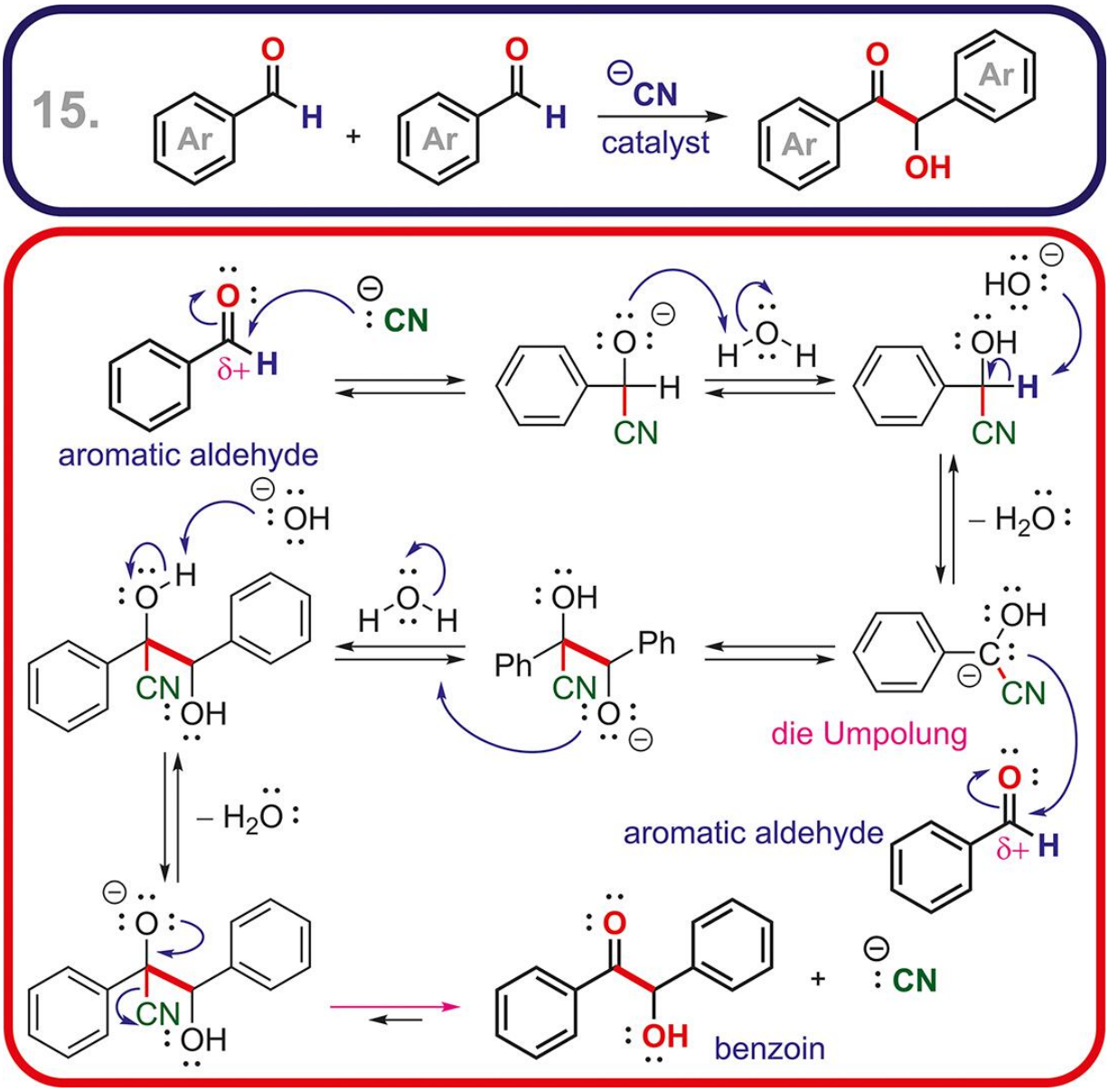


Fig. 15.1: The *benzoin condensation* mechanism.[52]

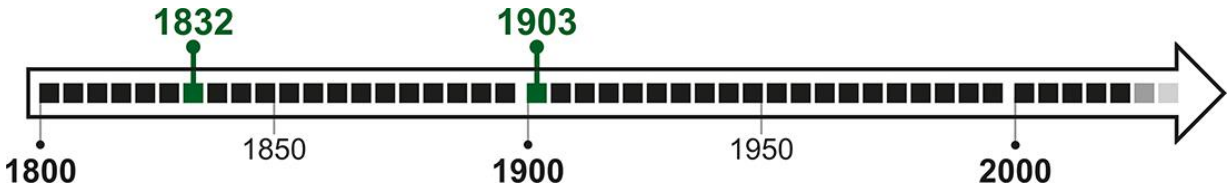


Fig. 15.2: The discovery of the *benzoin condensation*.[53]

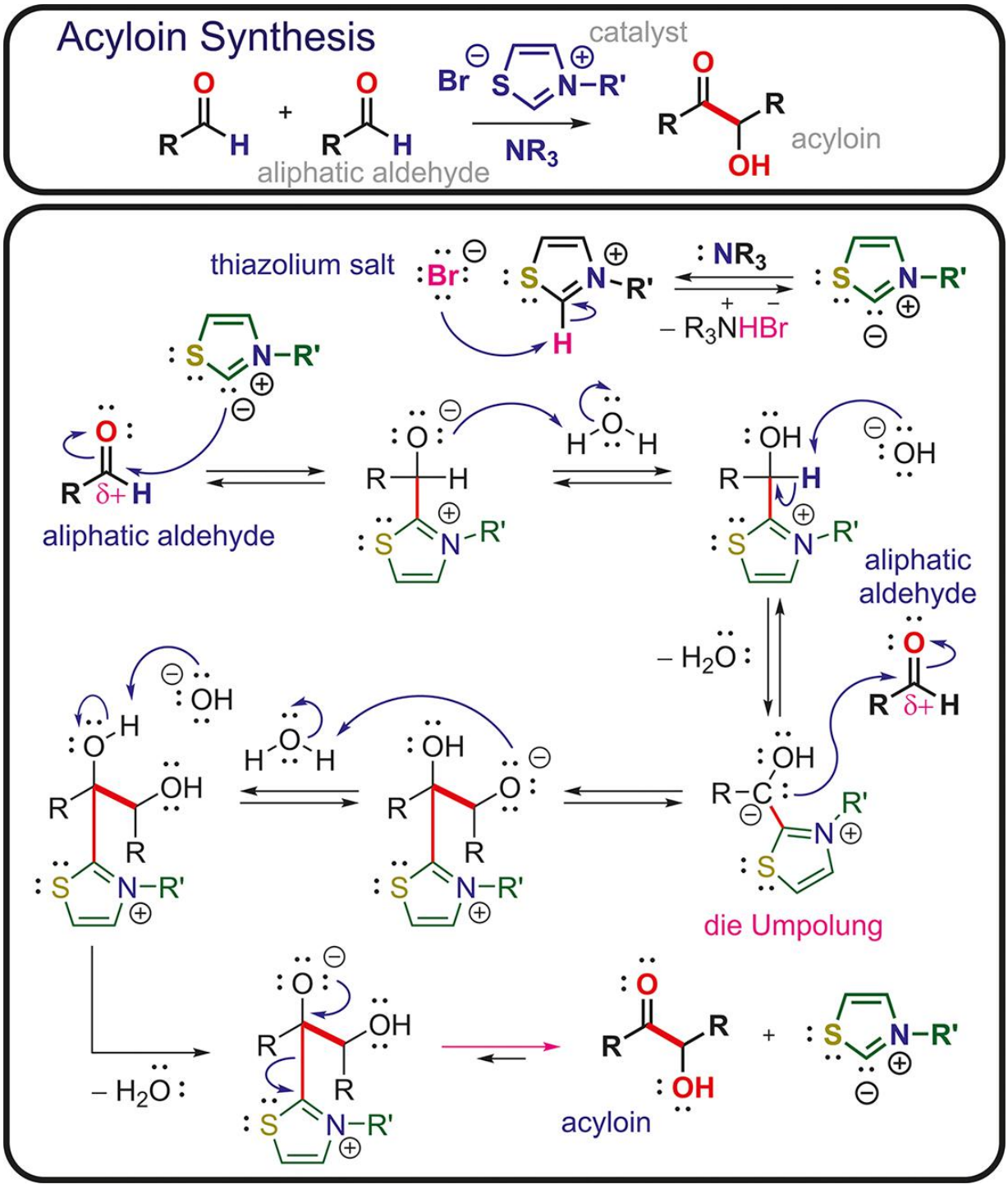


Fig. 15.3: The *acyloin synthesis* mechanism using thiazolium salts.[54]

16 Benzyne Mechanism

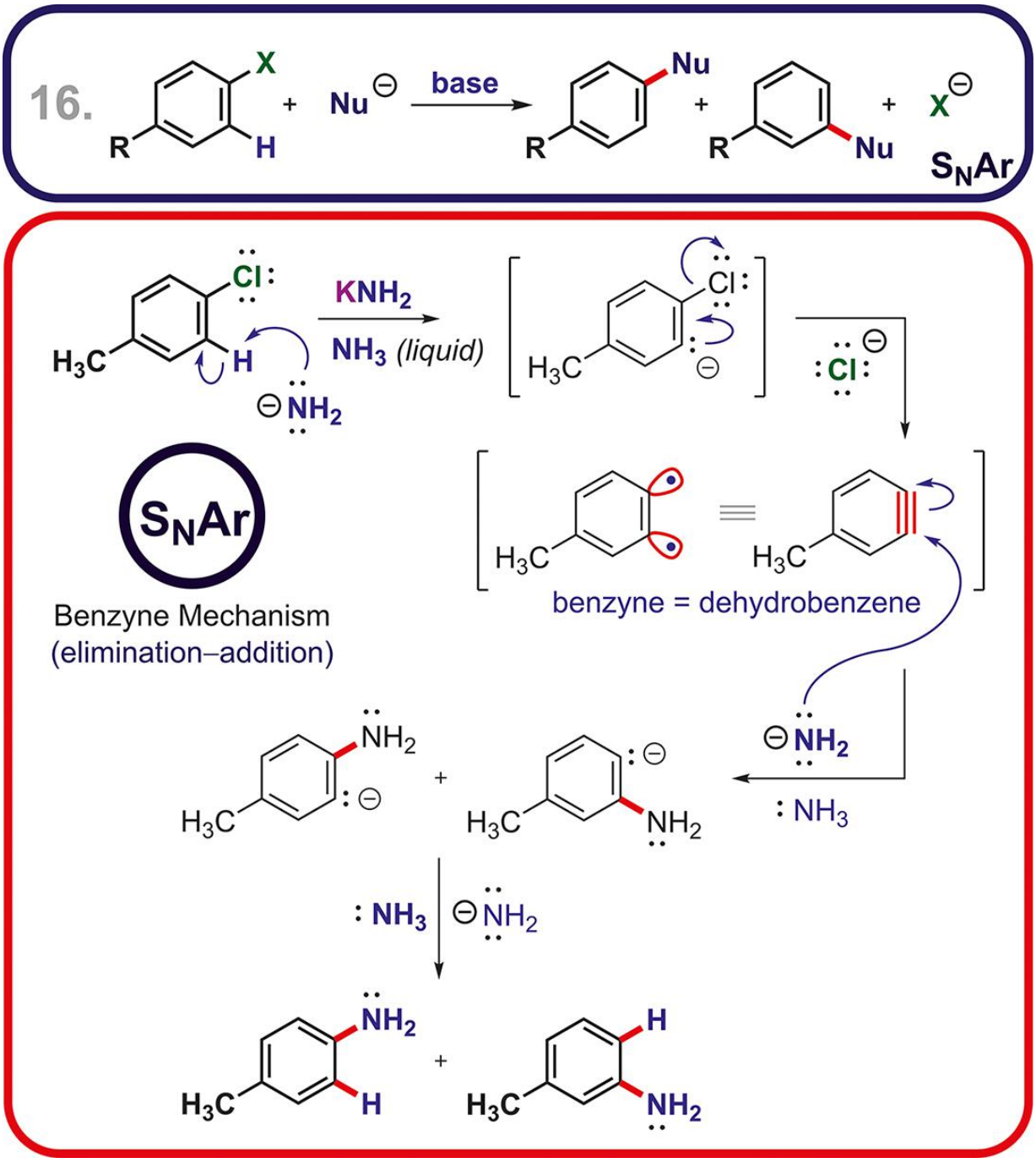


Fig. 16.1: The *benzyne (elimination–addition)* mechanism.[55]

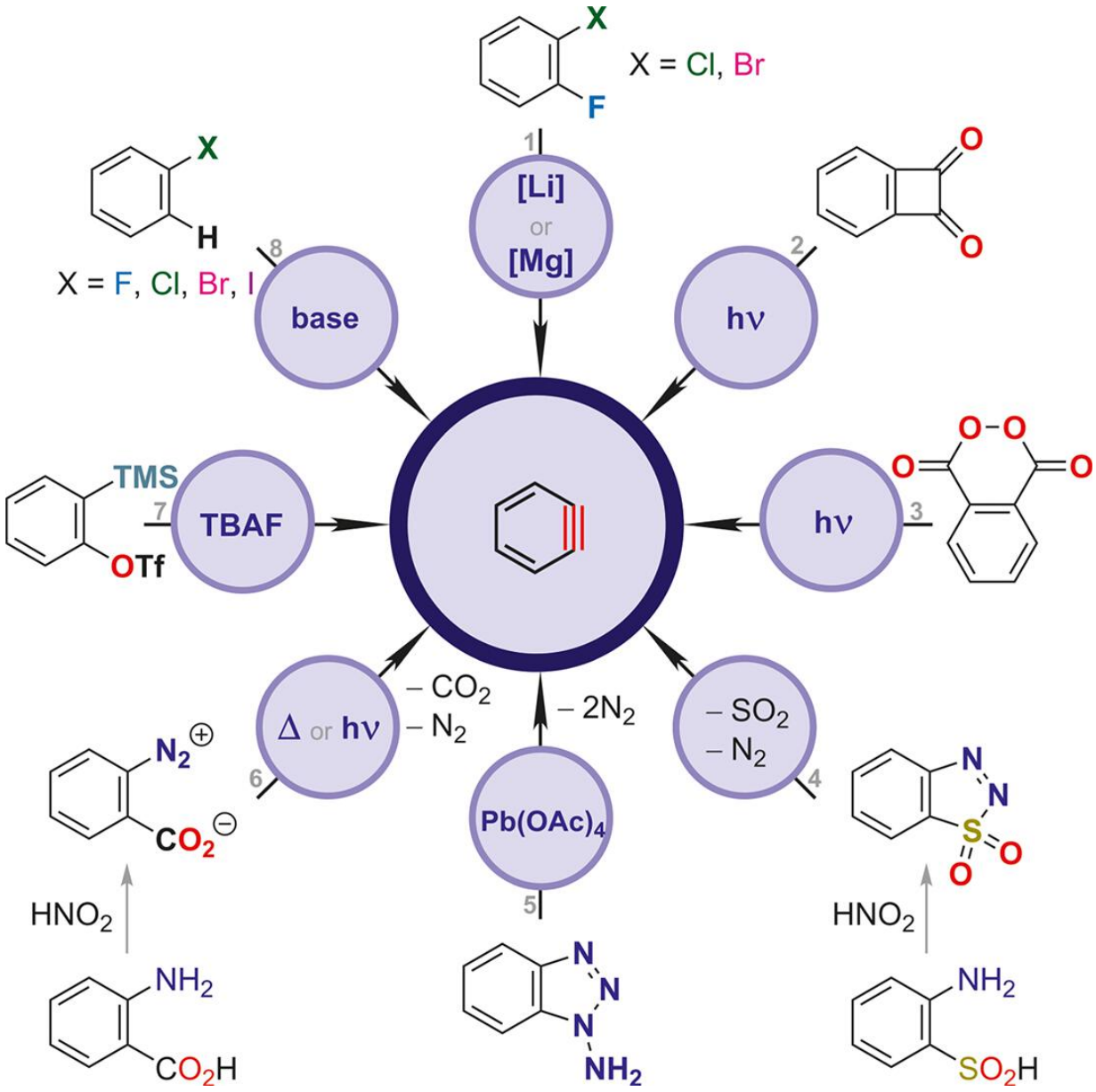


Fig. 16.2: Various synthetic methods leading to the formation of benzyne.[56]

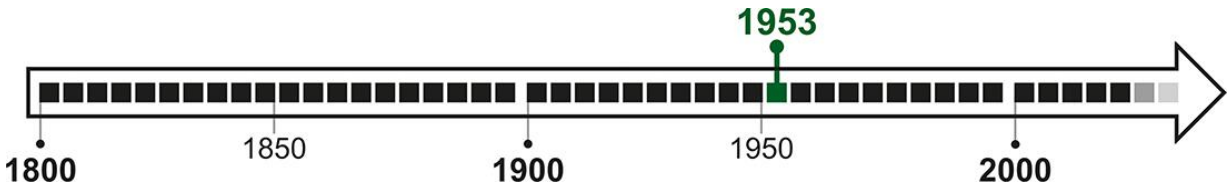


Fig. 16.3: The discovery of the *benzyne* mechanism.[57]

17 Bergman Cyclization

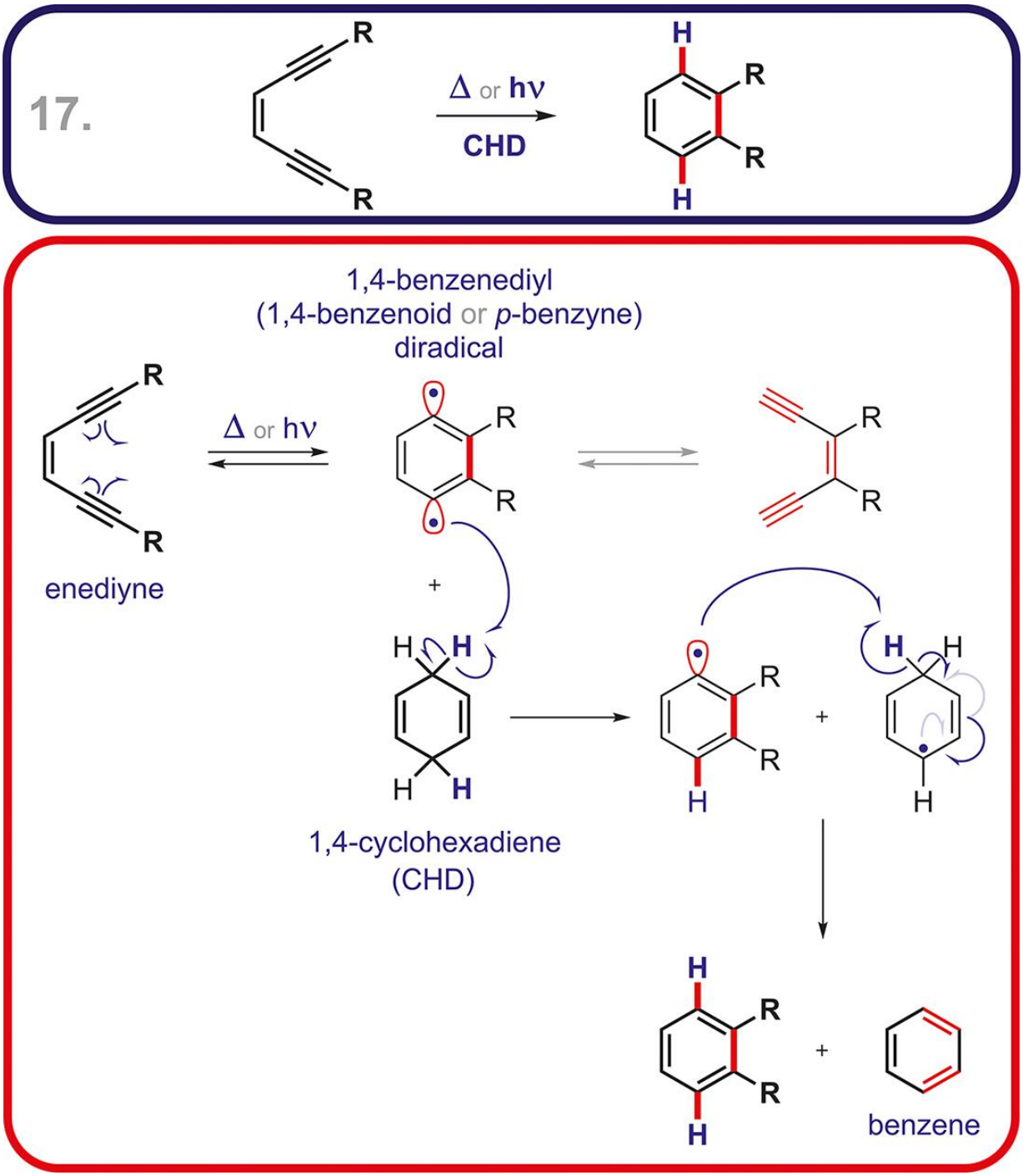


Fig. 17.1: The ***Bergman*** *cyclization* mechanism.[58]

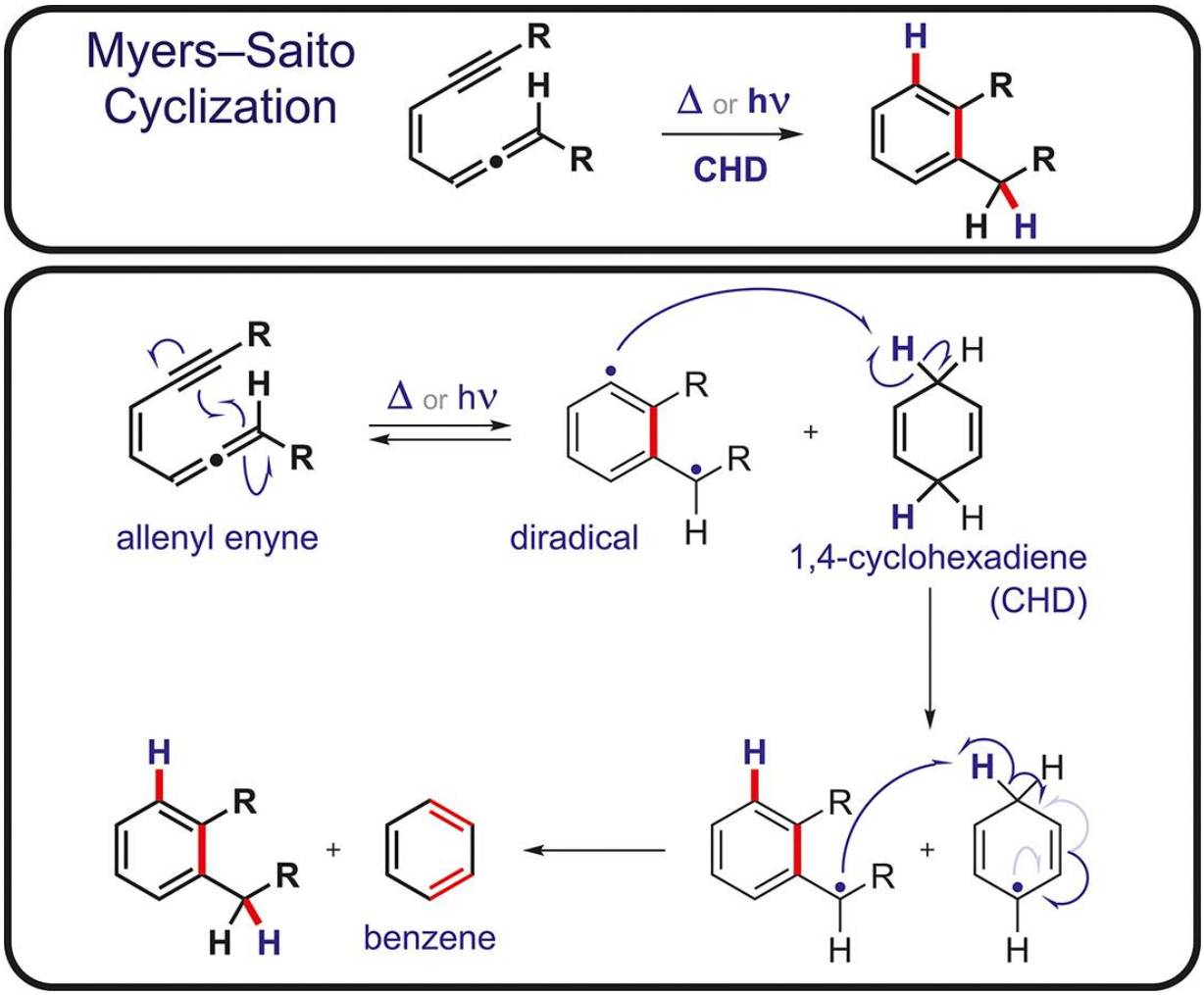


Fig. 17.2: The ***Myers–Saito*** *cyclization* mechanism.[59]

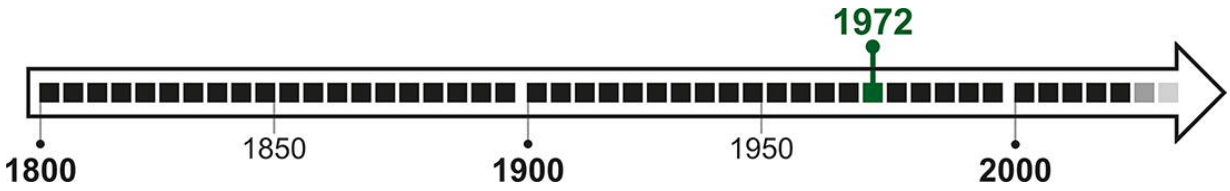


Fig. 17.3: The discovery of the ***Bergman*** *cyclization*.[60]

18 Birch Reduction

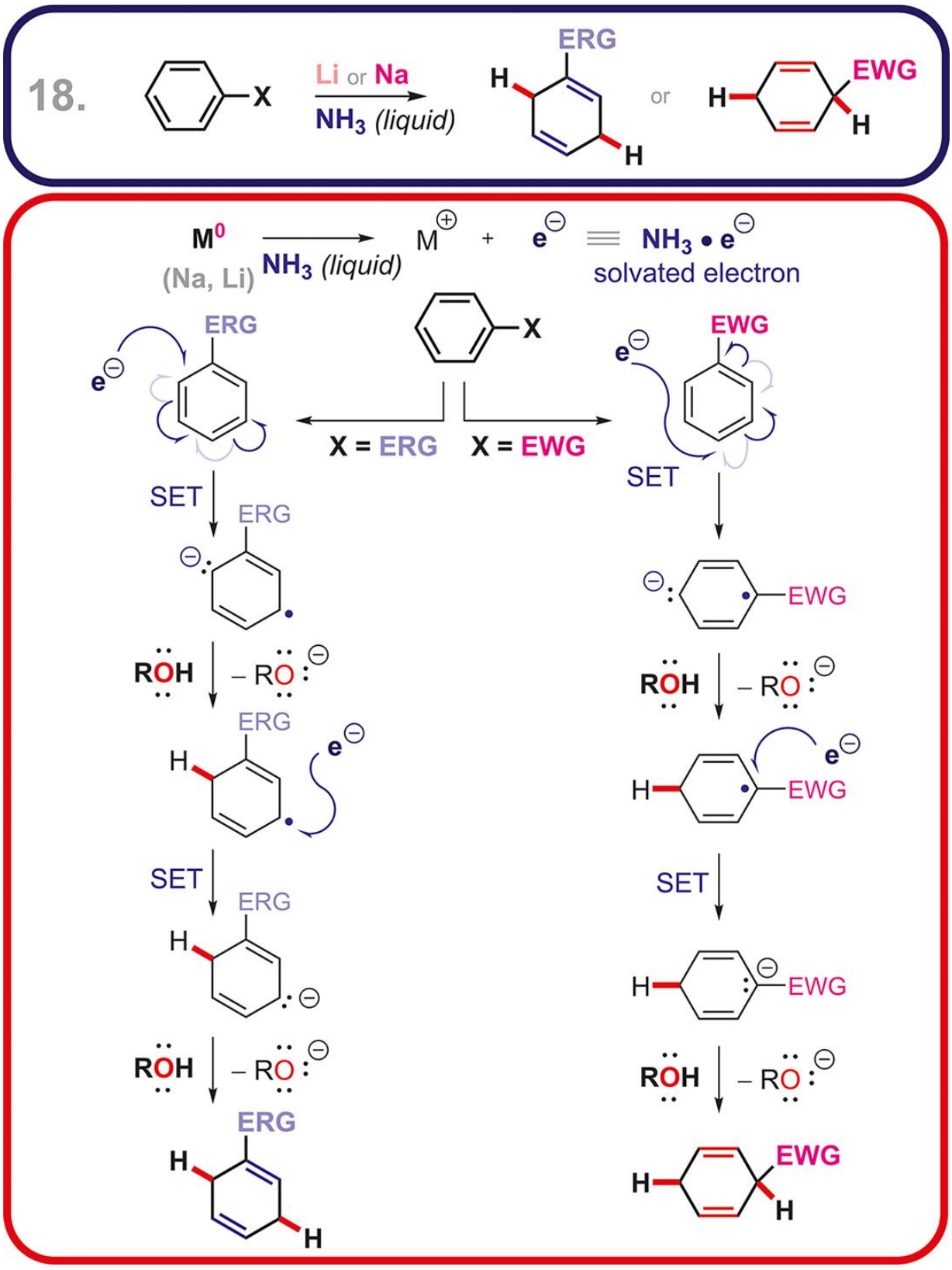


Fig. 18.1: The ***Birch*** *reduction* mechanism.[61].

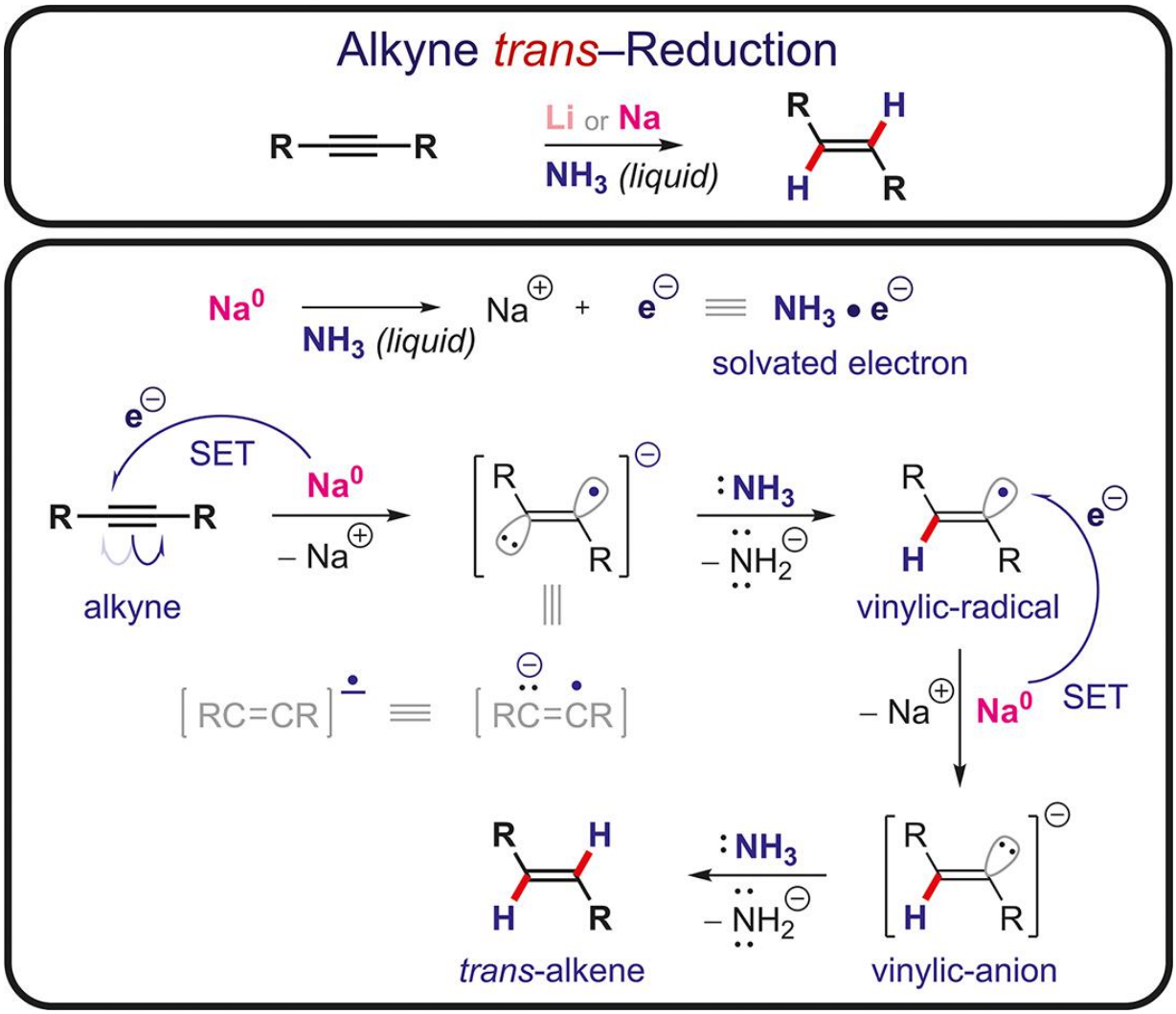


Fig. 18.2: The *alkyne trans-reduction* mechanism.[62].

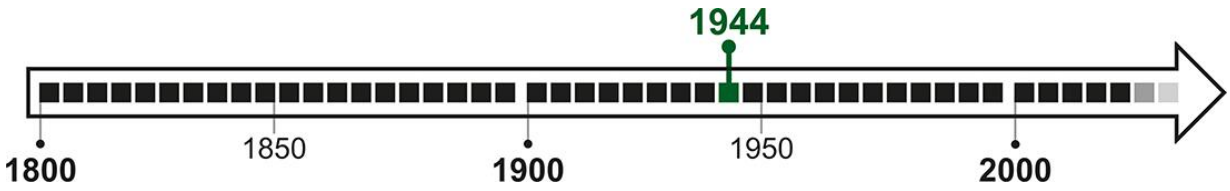


Fig. 18.3: The discovery of the ***Birch*** *reduction*.[63].

19 Bischler–Napieralski Cyclization

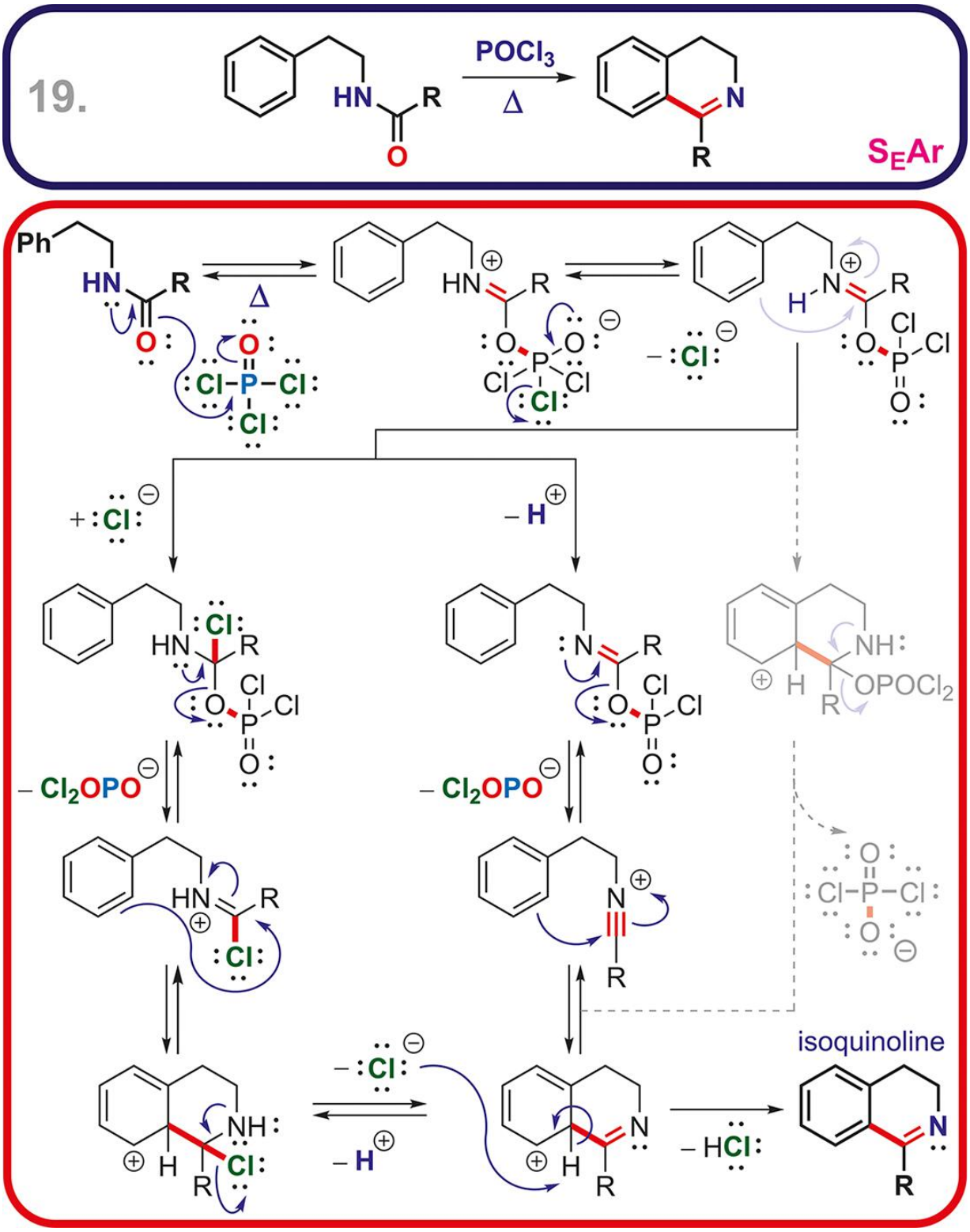


Fig. 19.1: The ***Bischler–Napieralski*** *cyclization* mechanism.[64].

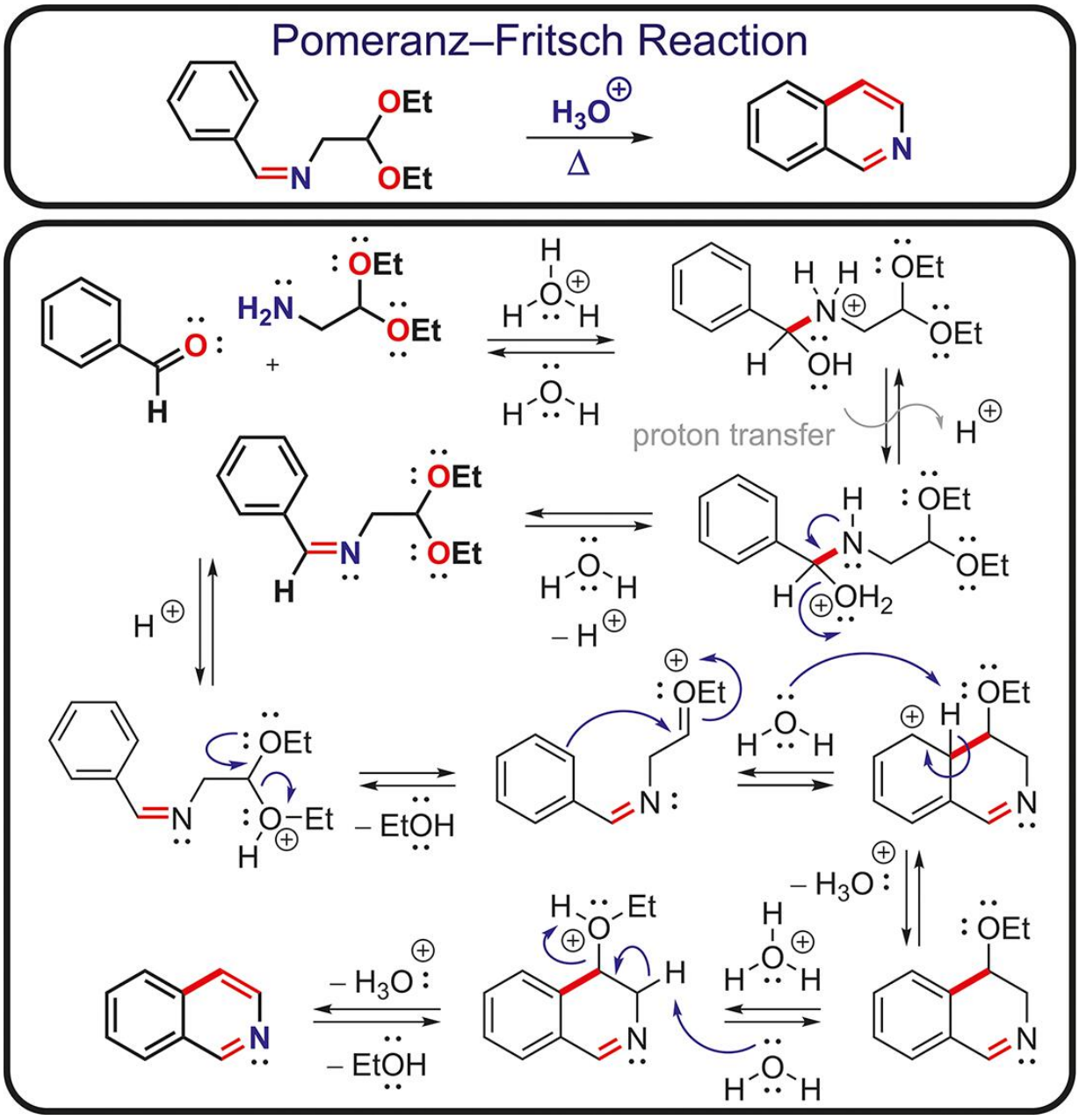


Fig. 19.2: The ***Pomeranz–Fritsch*** *reaction mechanism*.[65].

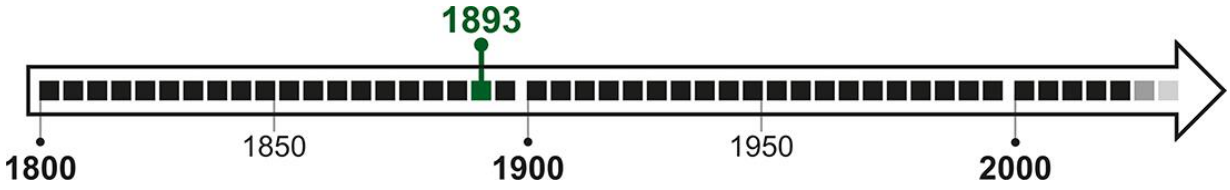


Fig. 19.3: The discovery of the ***Bischler–Napieralski*** *cyclization*.[66].

20 Brown Hydroboration

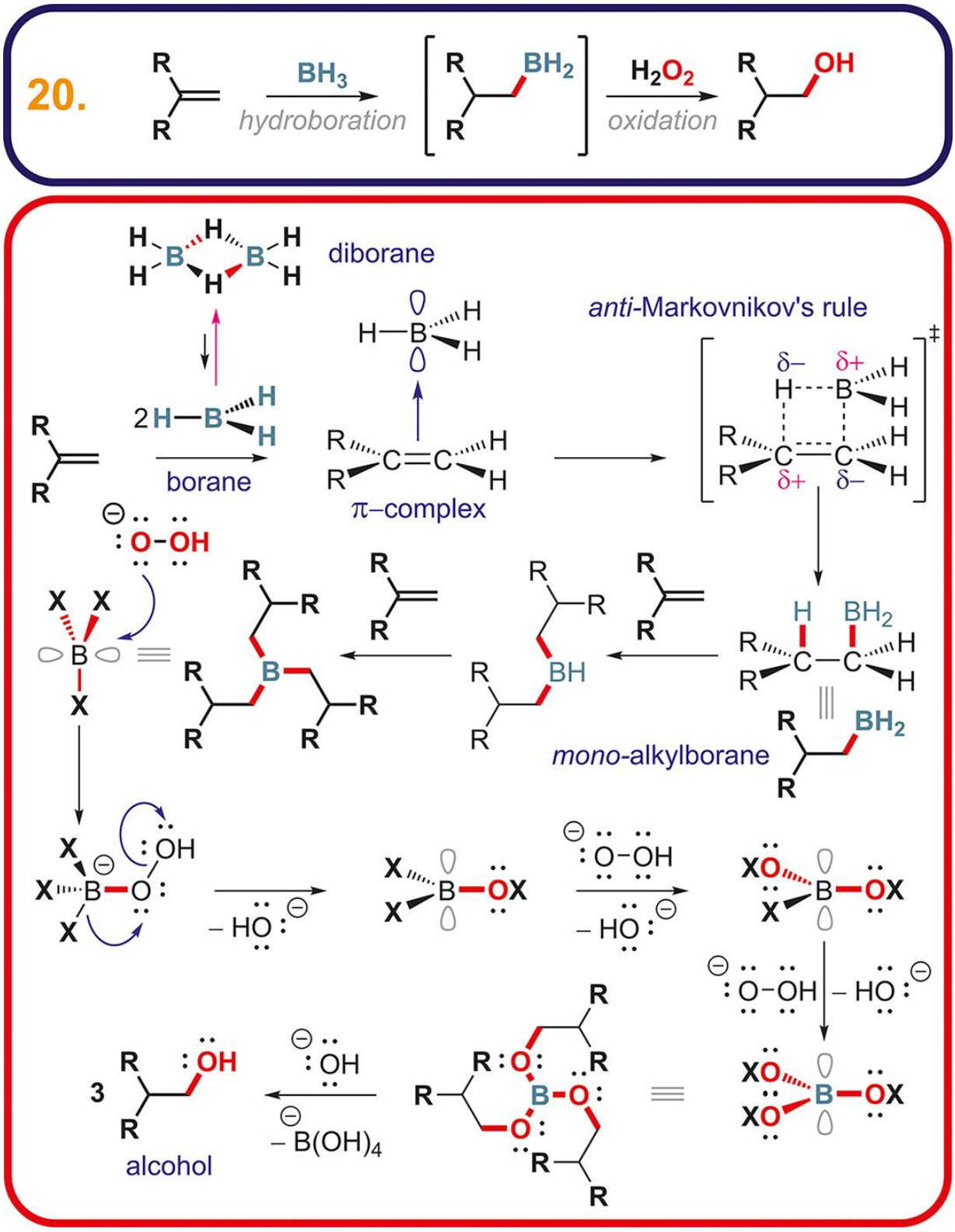


Fig. 20.1: The ***Brown*** *hydroboration* mechanism.[67].

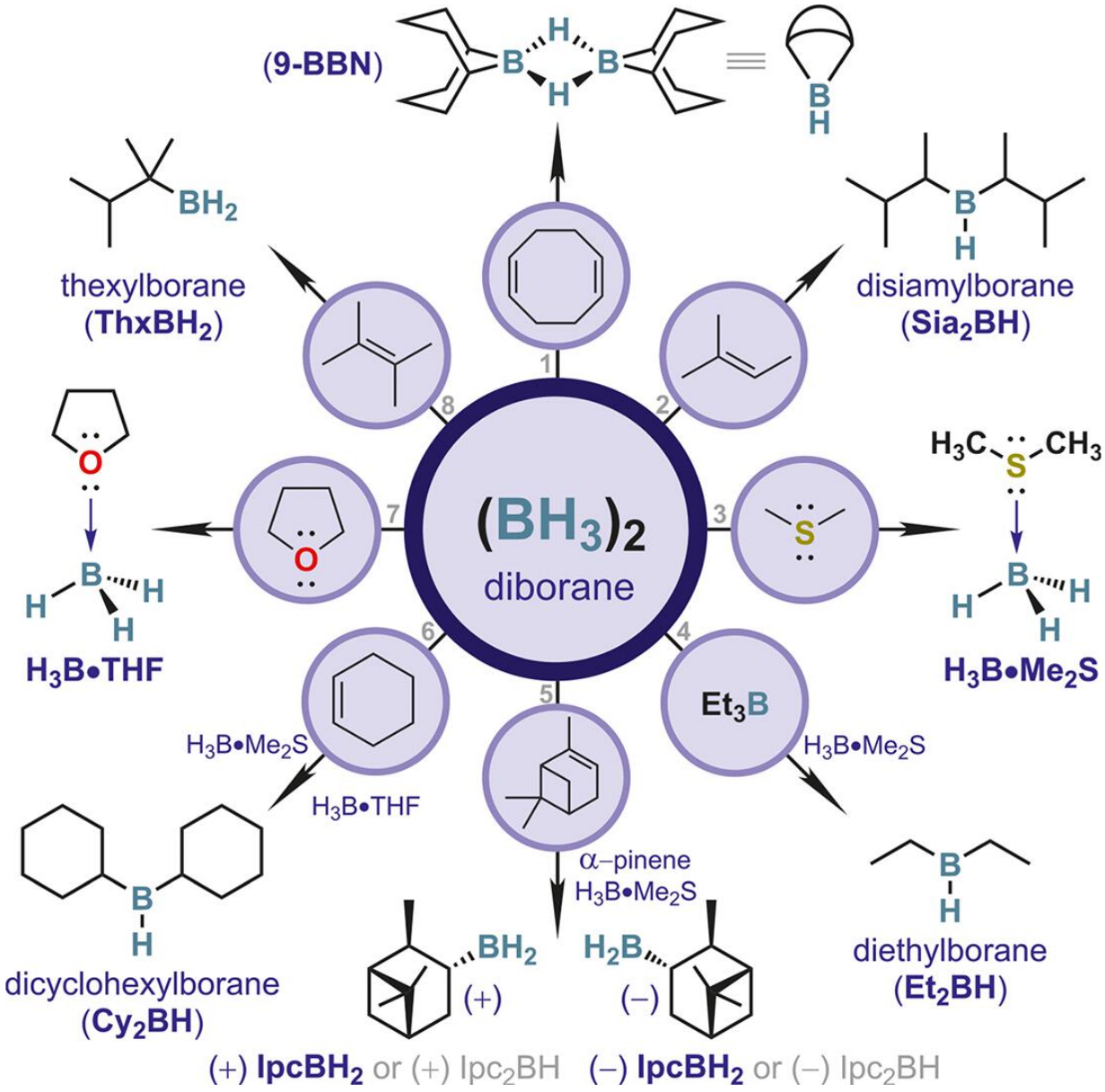


Fig. 20.2: Various borane derivatives formed from diborane.[68]

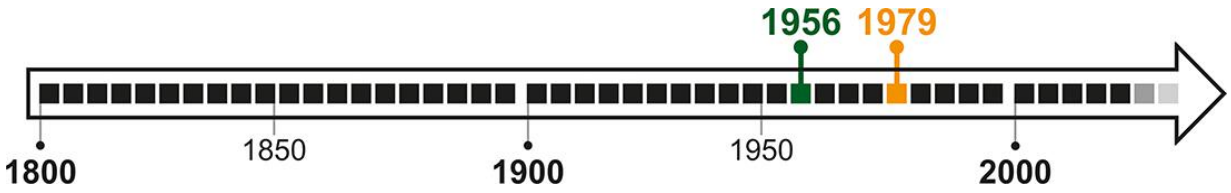


Fig. 20.3: The discovery of the ***Brown*** *hydroboration*.[69]

21 Buchwald–Hartwig Cross-Coupling

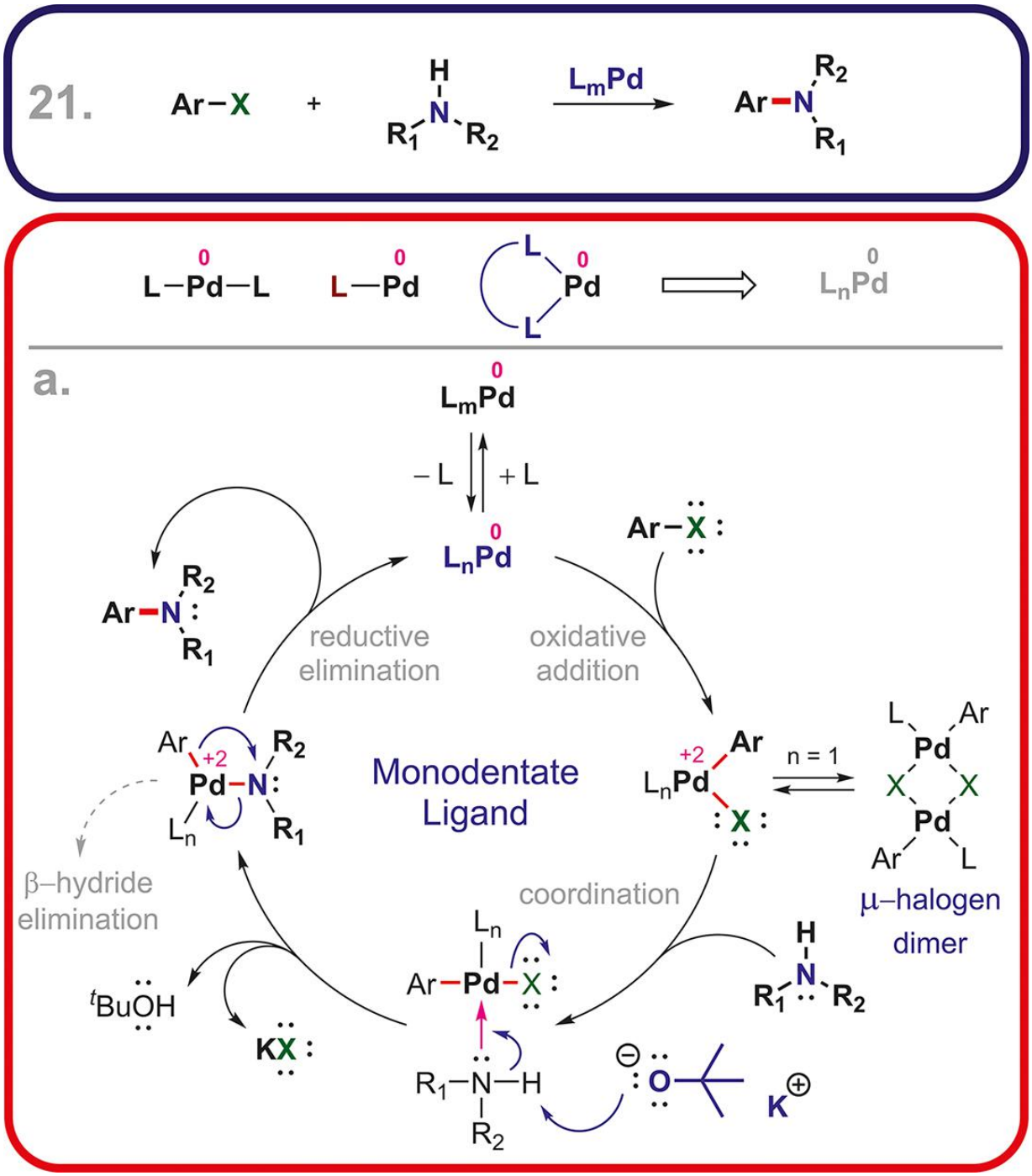


Fig. 21.1: The ***Buchwald–Hartwig*** *cross-coupling* mechanism (monodentate ligand).[70]

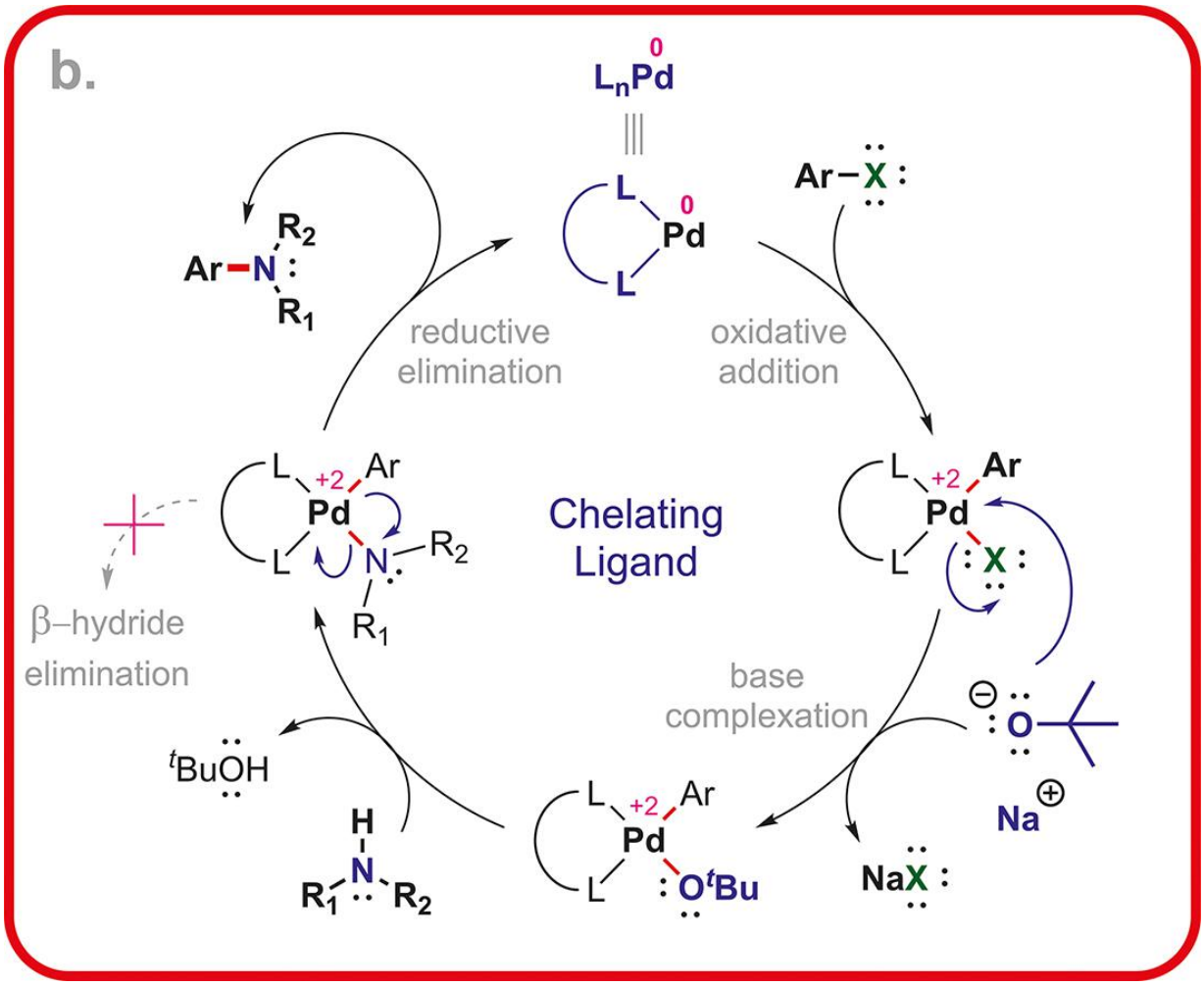


Fig. 21.2: The ***Buchwald–Hartwig*** *cross-coupling* mechanism (chelating ligand).[71]

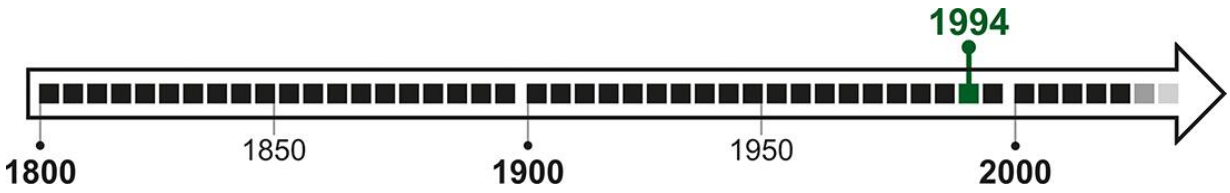


Fig. 21.3: The discovery of the ***Buchwald–Hartwig*** *cross-coupling*.[72]

22 Cannizzaro Reaction

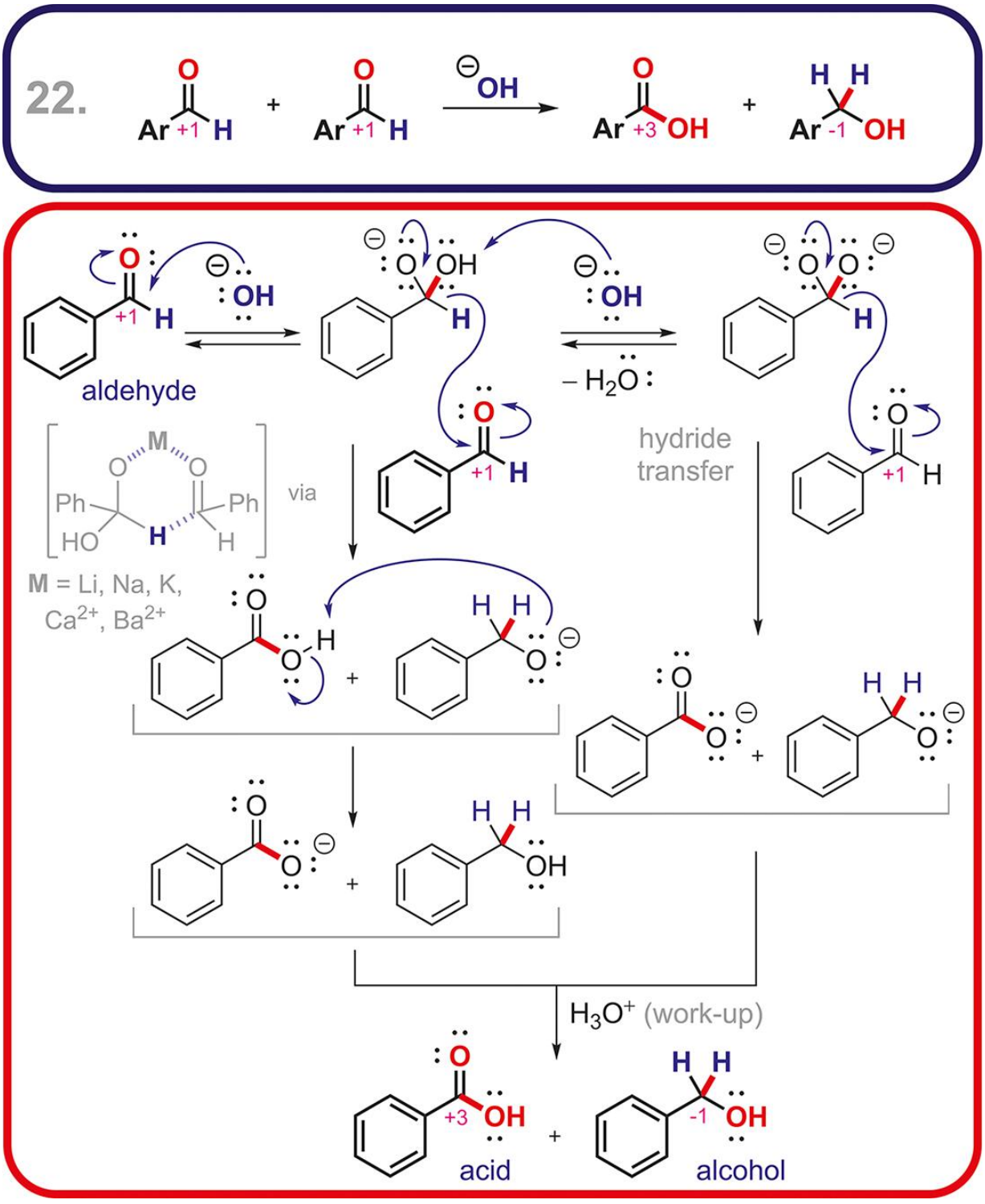


Fig. 22.1: The ***Cannizzaro*** *reaction* mechanism.[73]

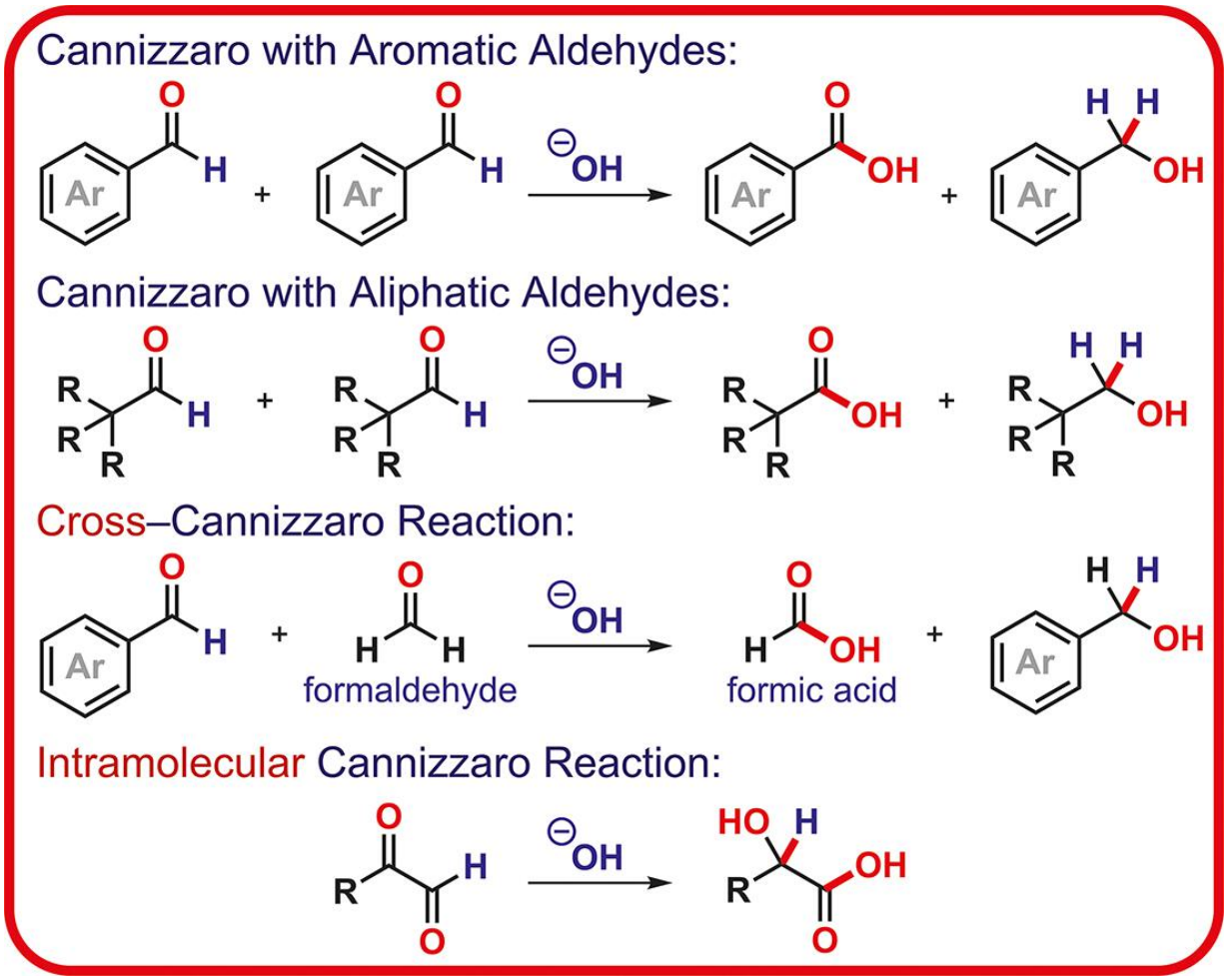


Fig. 22.2: Variations of the ***Cannizzaro*** *reaction*.[74]

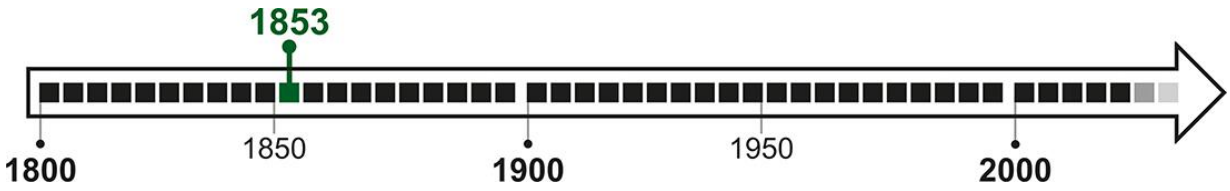


Fig. 22.3: The discovery of the ***Cannizzaro*** *reaction*.[75]

23 Chan–Evans–Lam Cross-Coupling

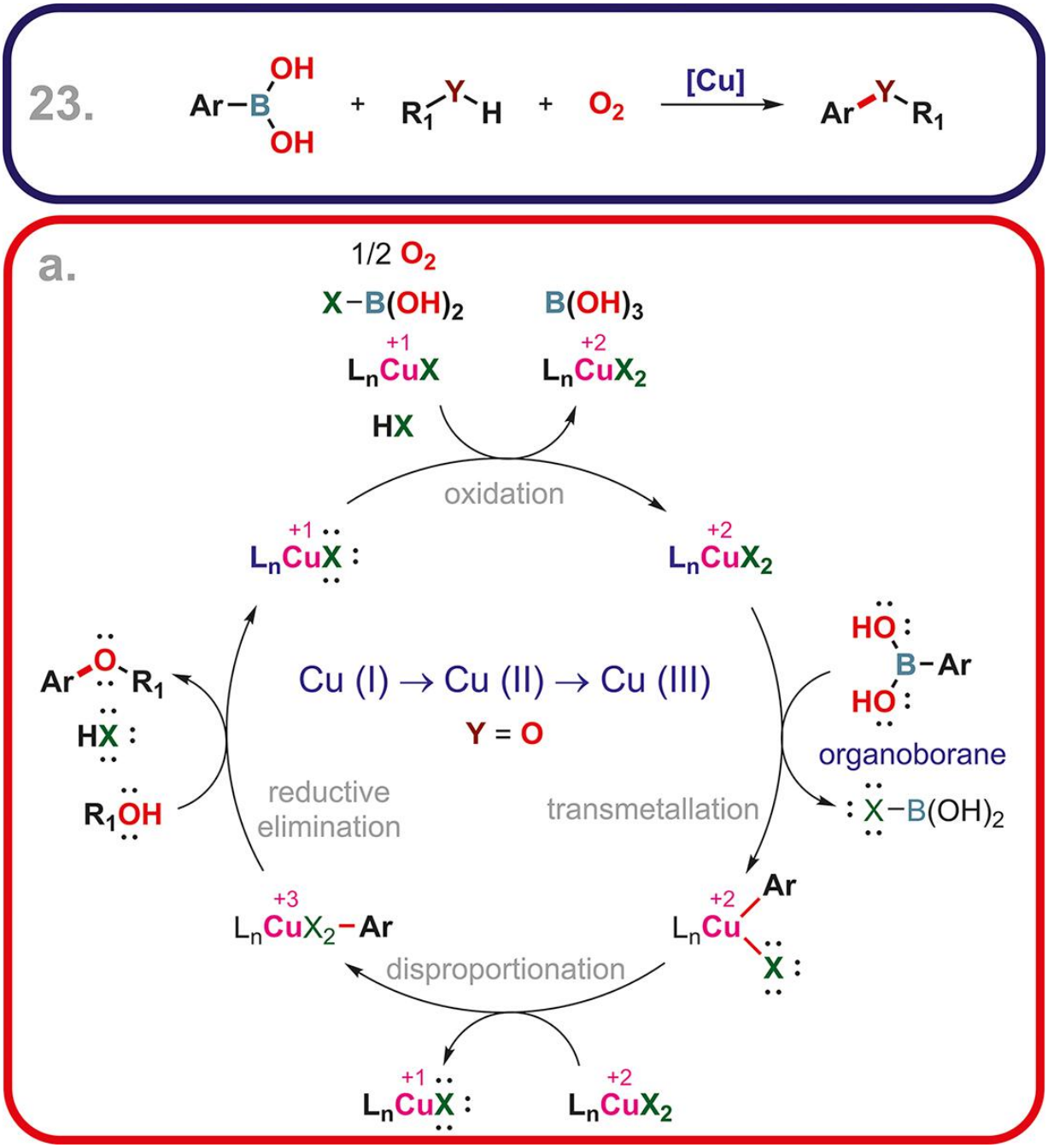


Fig. 23.1: The ***Chan–Evans–Lam*** *cross-coupling* mechanism (Y = O).[76]

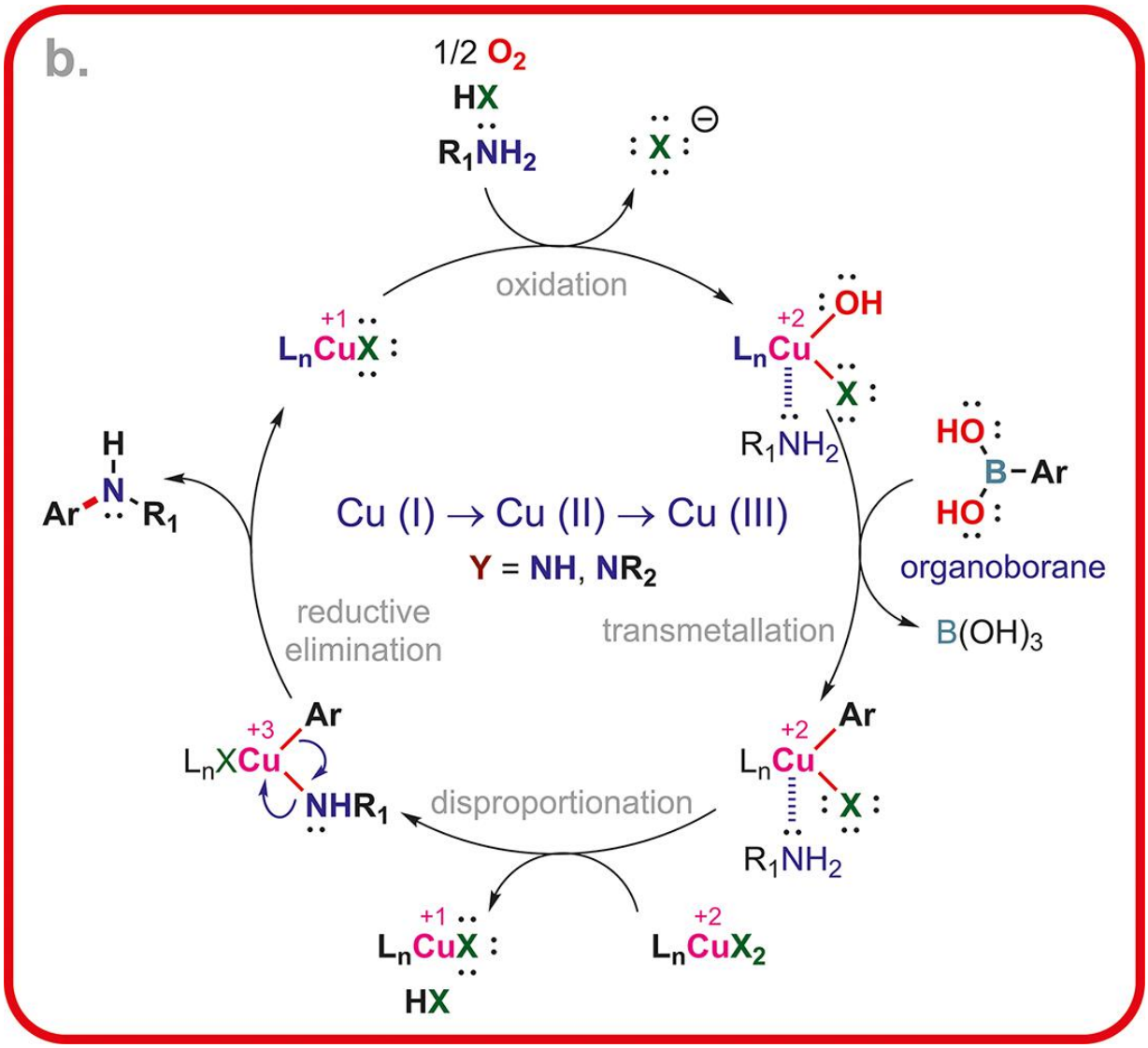


Fig. 23.2: The ***Chan–Evans–Lam*** *cross-coupling* mechanism (Y = NH, NR_2).[77]

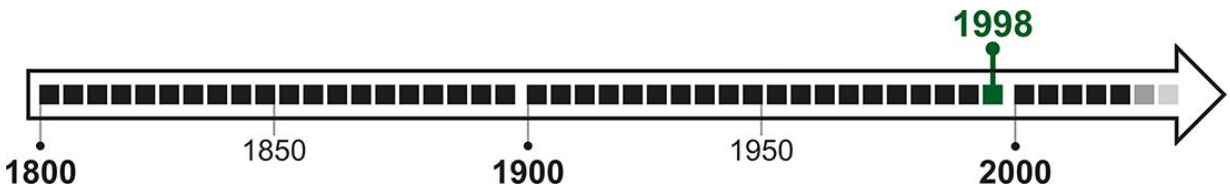


Fig. 23.3: The discovery of the ***Chan–Evans–Lam*** *cross-coupling*.[78]

24 Chichibabin Amination

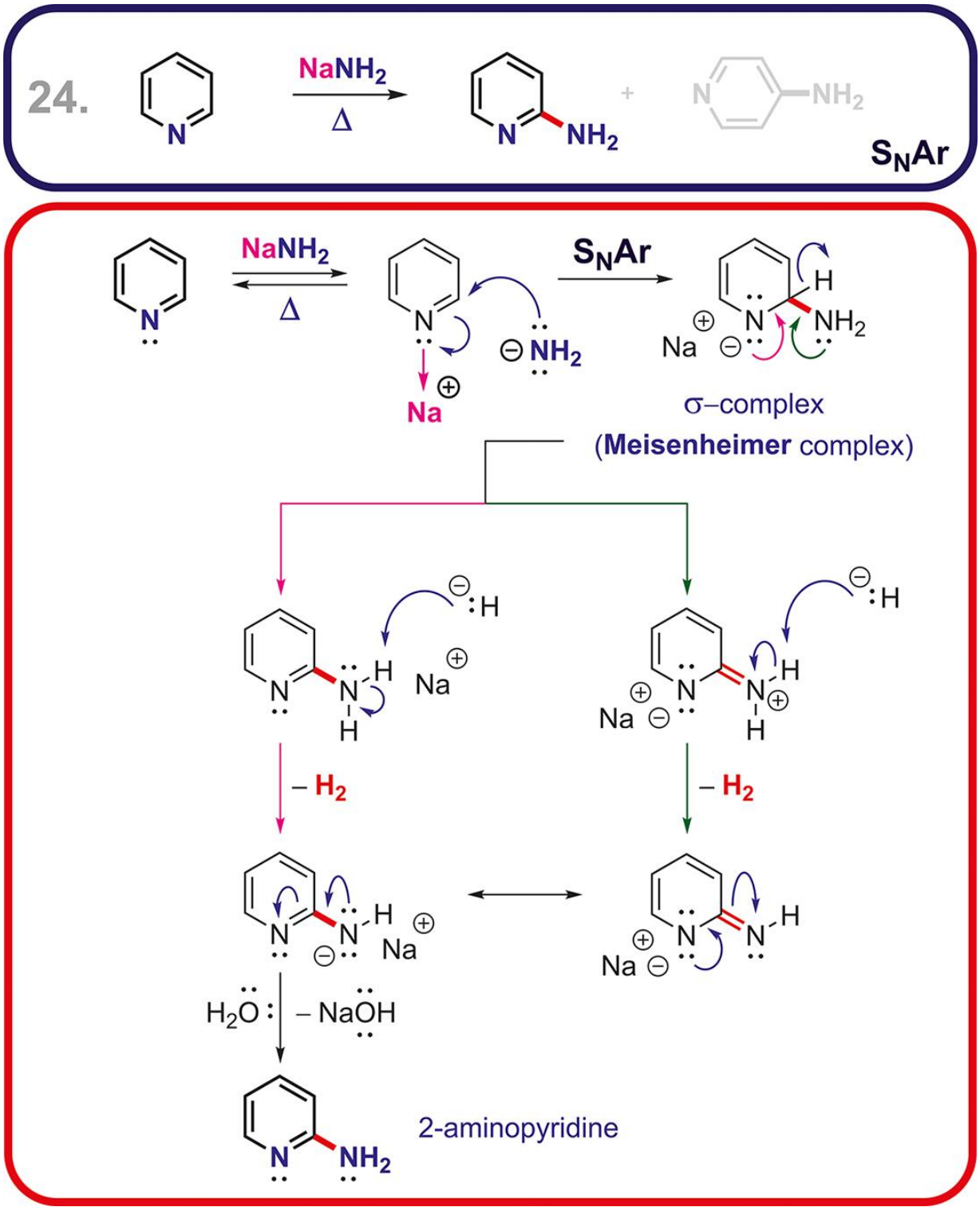


Fig. 24.1: The ***Chichibabin*** *amination* mechanism.[79].

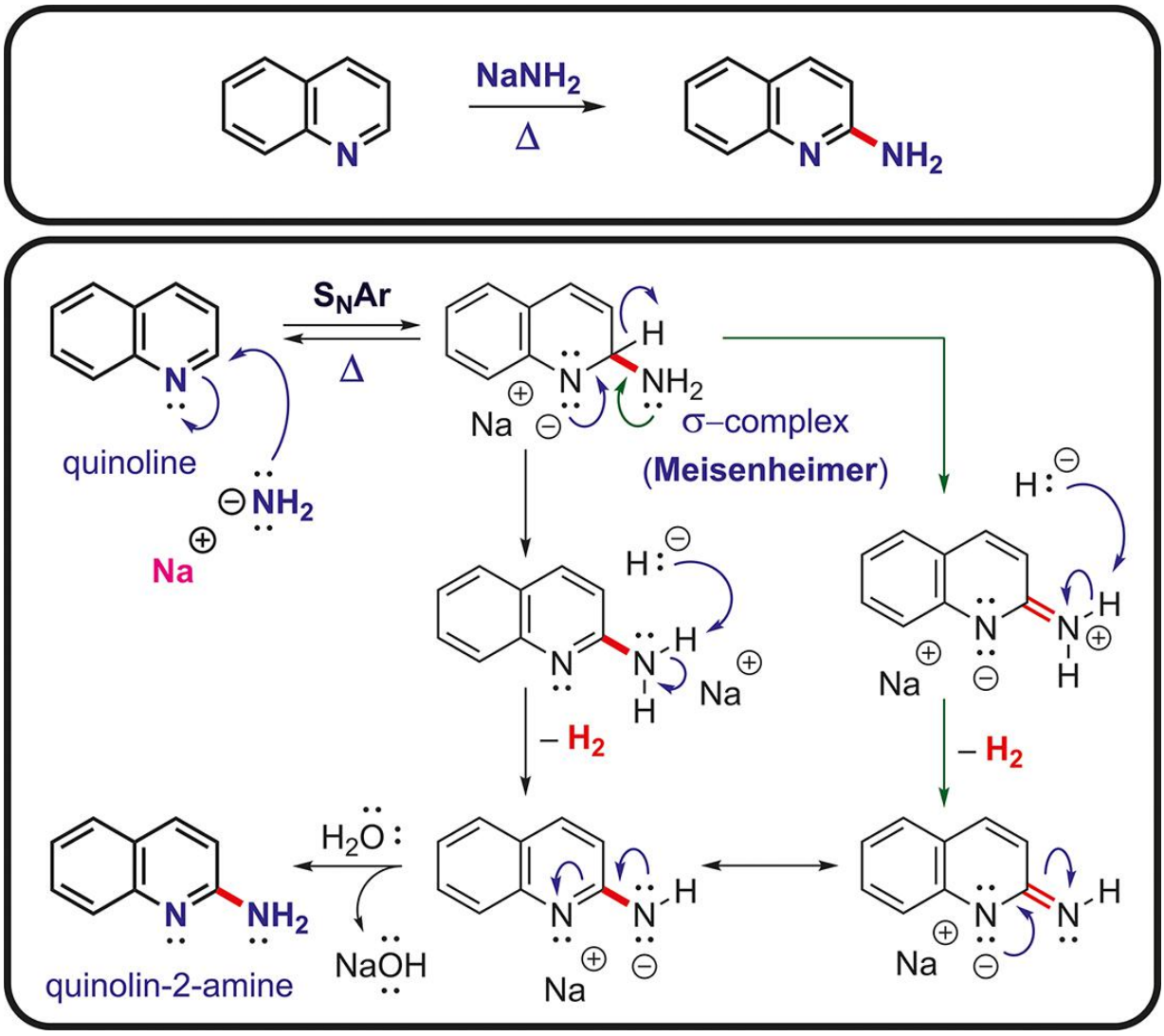


Fig. 24.2: The ***Chichibabin*** *amination* mechanism of quinoline.[80]

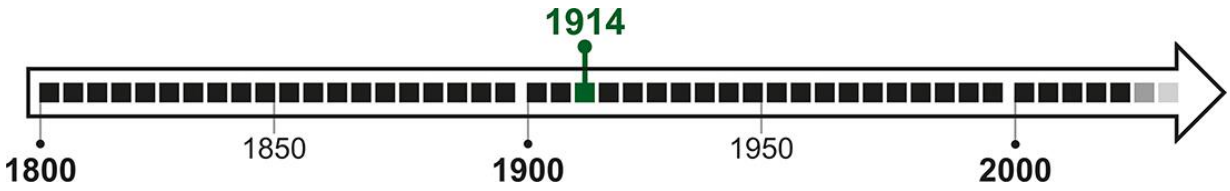


Fig. 24.3: The discovery of the ***Chichibabin*** *amination*.[81]

25 Claisen Condensation

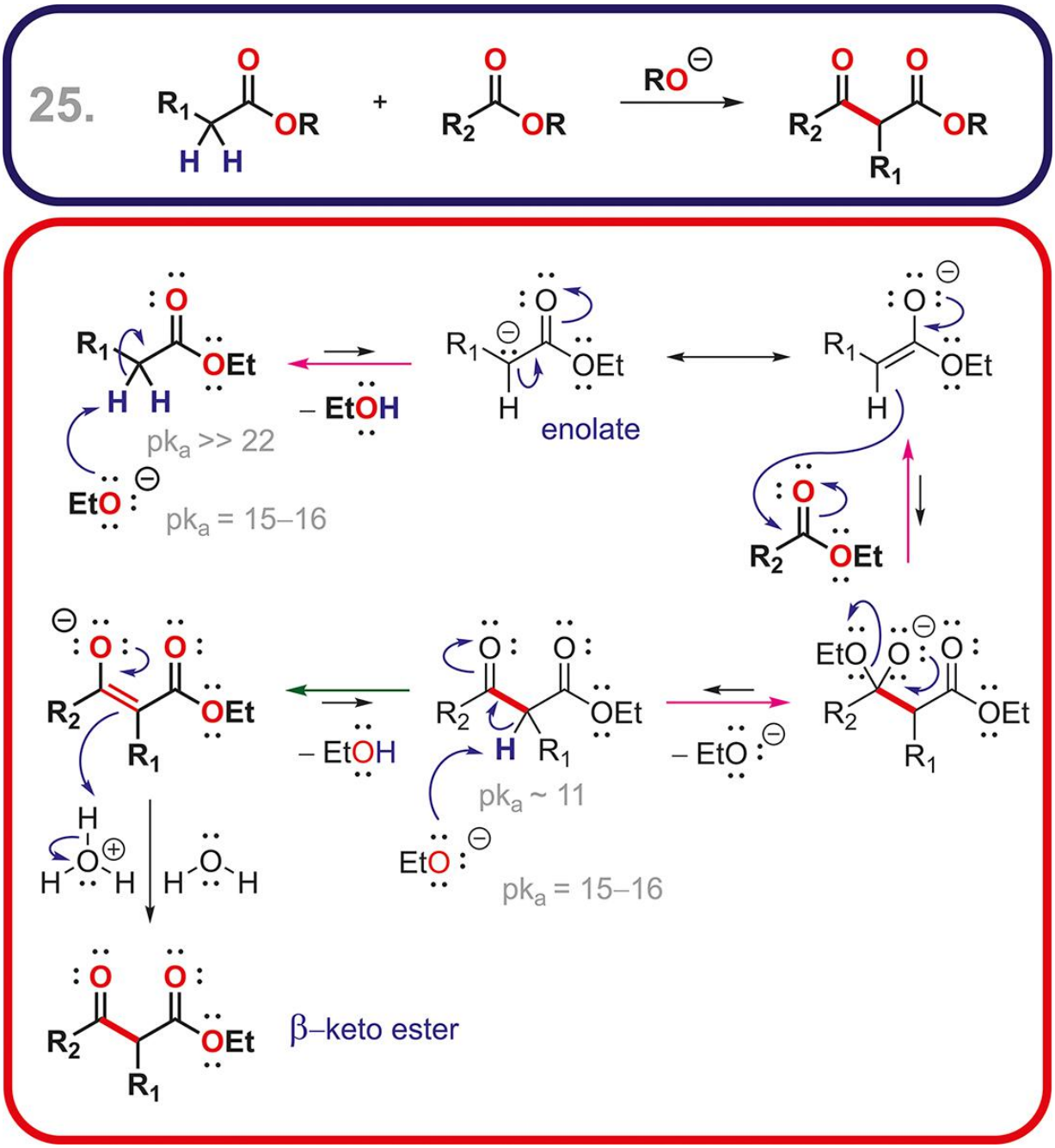


Fig. 25.1: The ***Claisen*** *condensation* mechanism.[82]

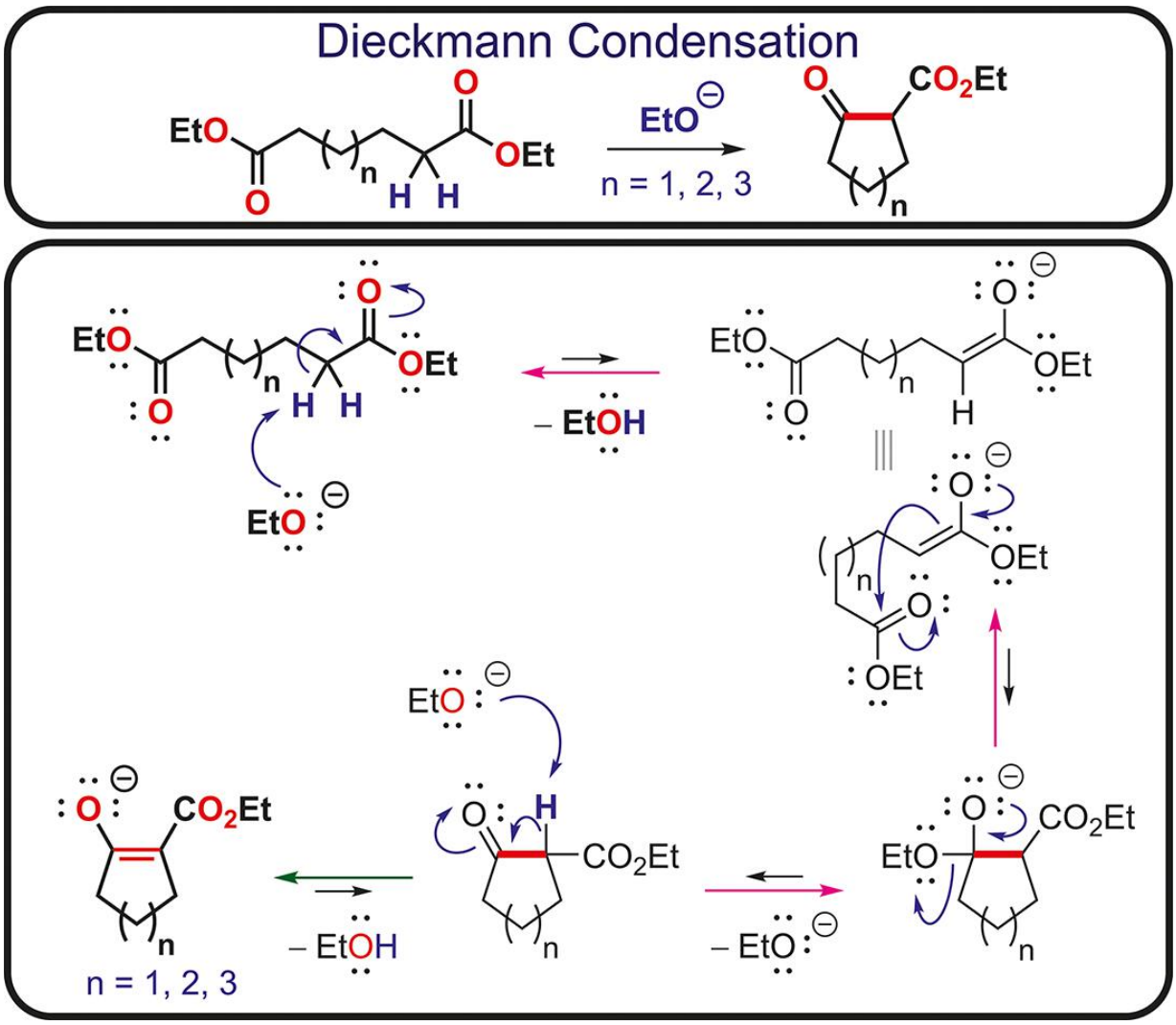


Fig. 25.2: The ***Dieckmann*** *condensation* mechanism.[83]

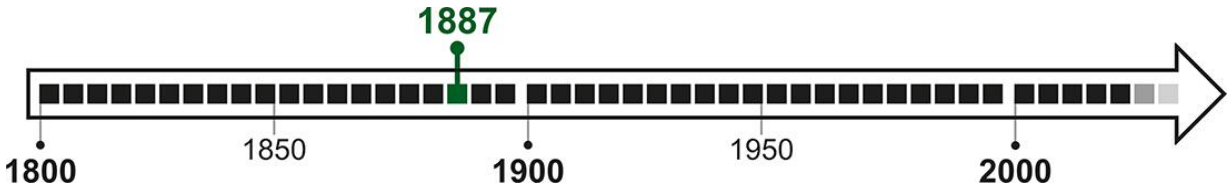


Fig. 25.3: The discovery of the ***Claisen*** *condensation*.[84]

26 Claisen Rearrangement

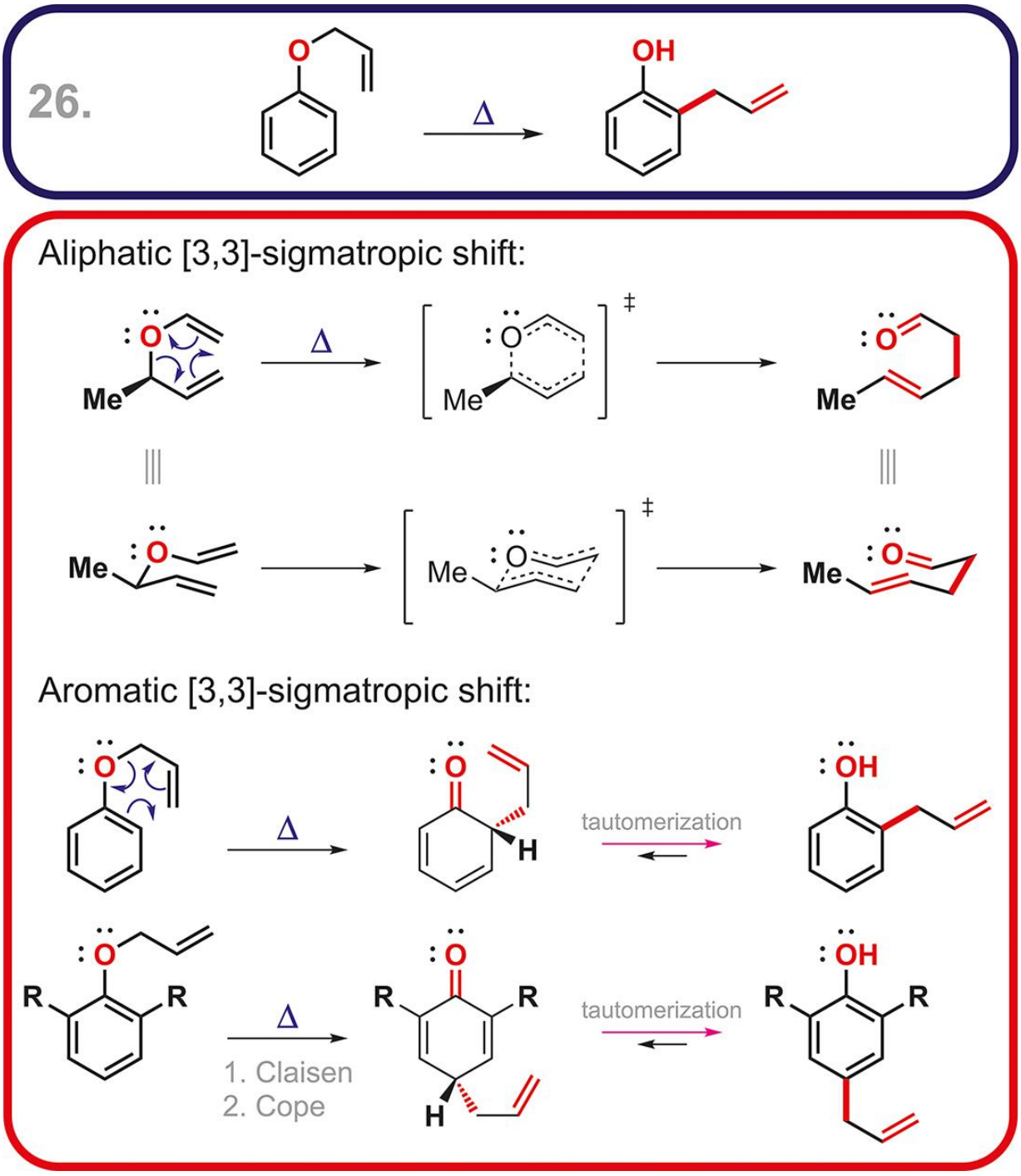


Fig. 26.1: The ***Claisen*** *rearrangement* mechanism.[85]

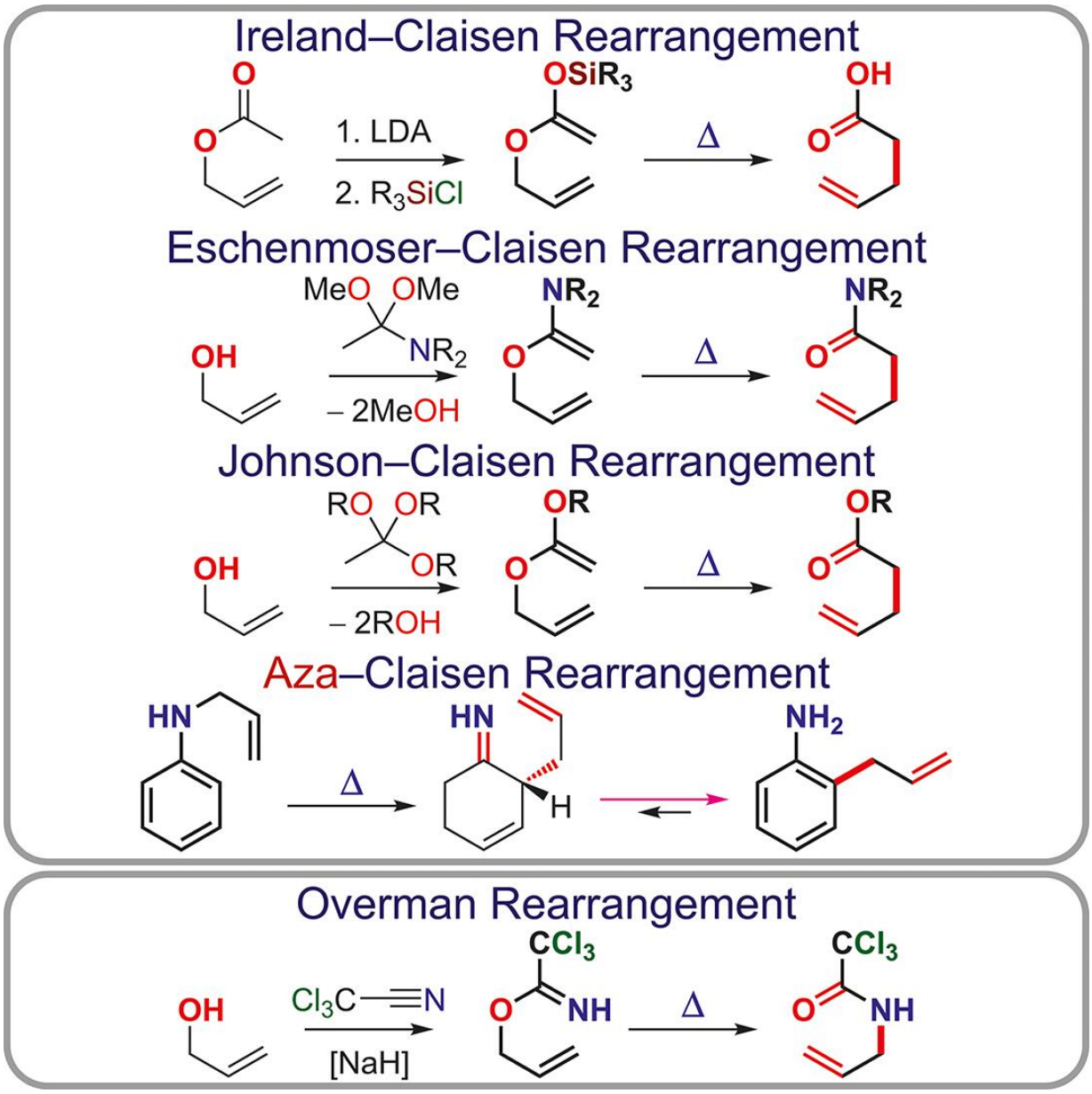


Fig. 26.2: Reactions related to the ***Claisen*** *rearrangement*.[86]

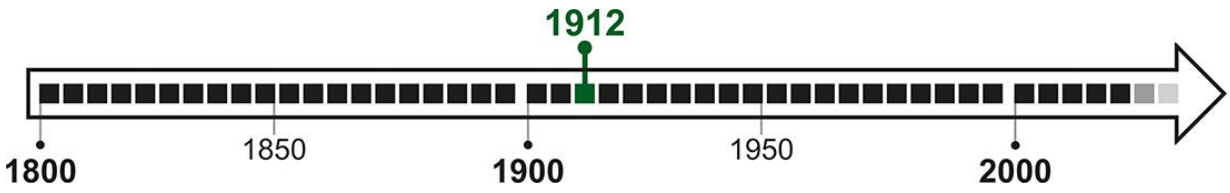


Fig. 26.3: The discovery of the ***Claisen*** *rearrangement*.[87]

27 Cope Elimination

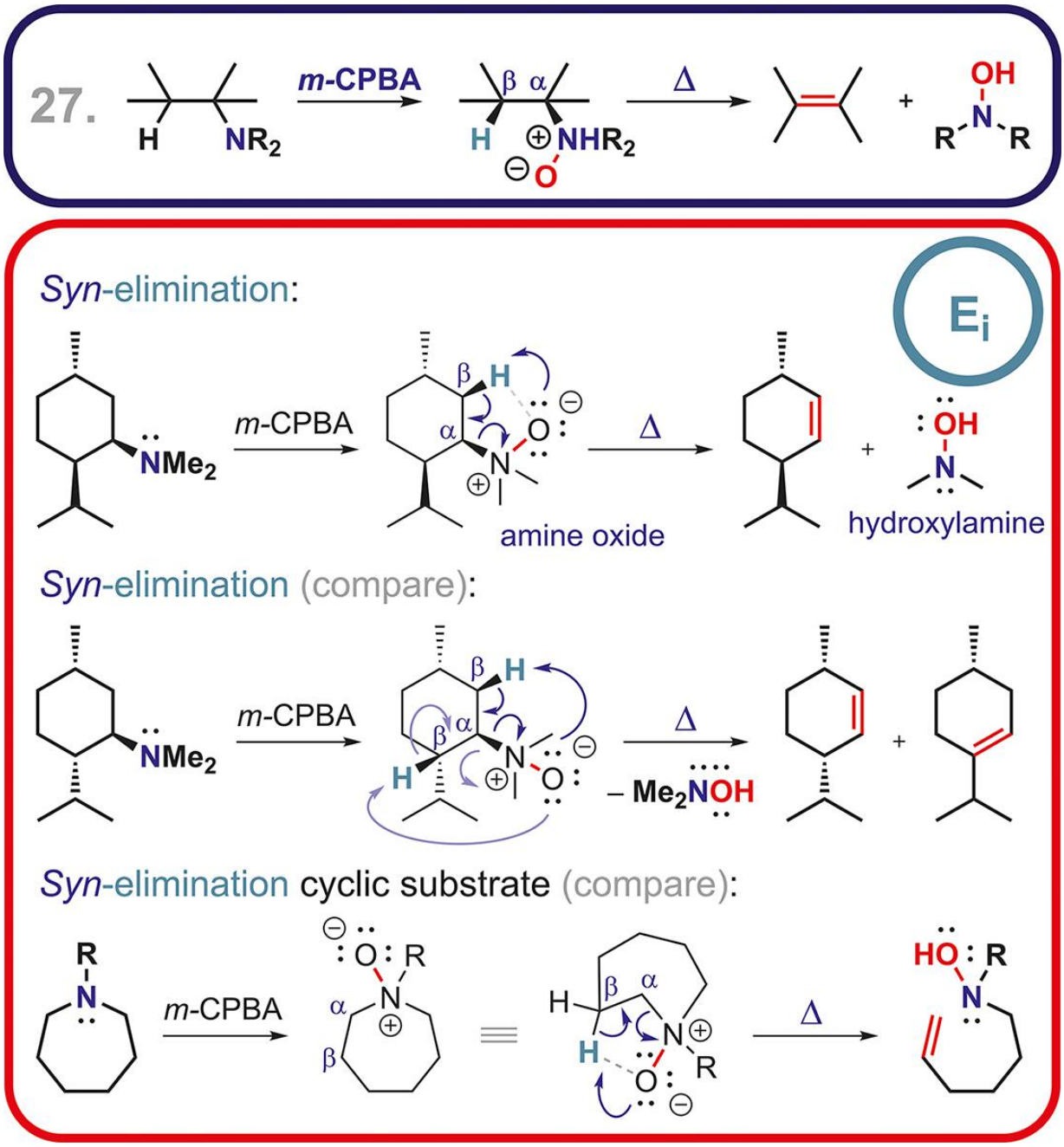


Fig. 27.1: The ***Cope*** *elimination* mechanism.[88]

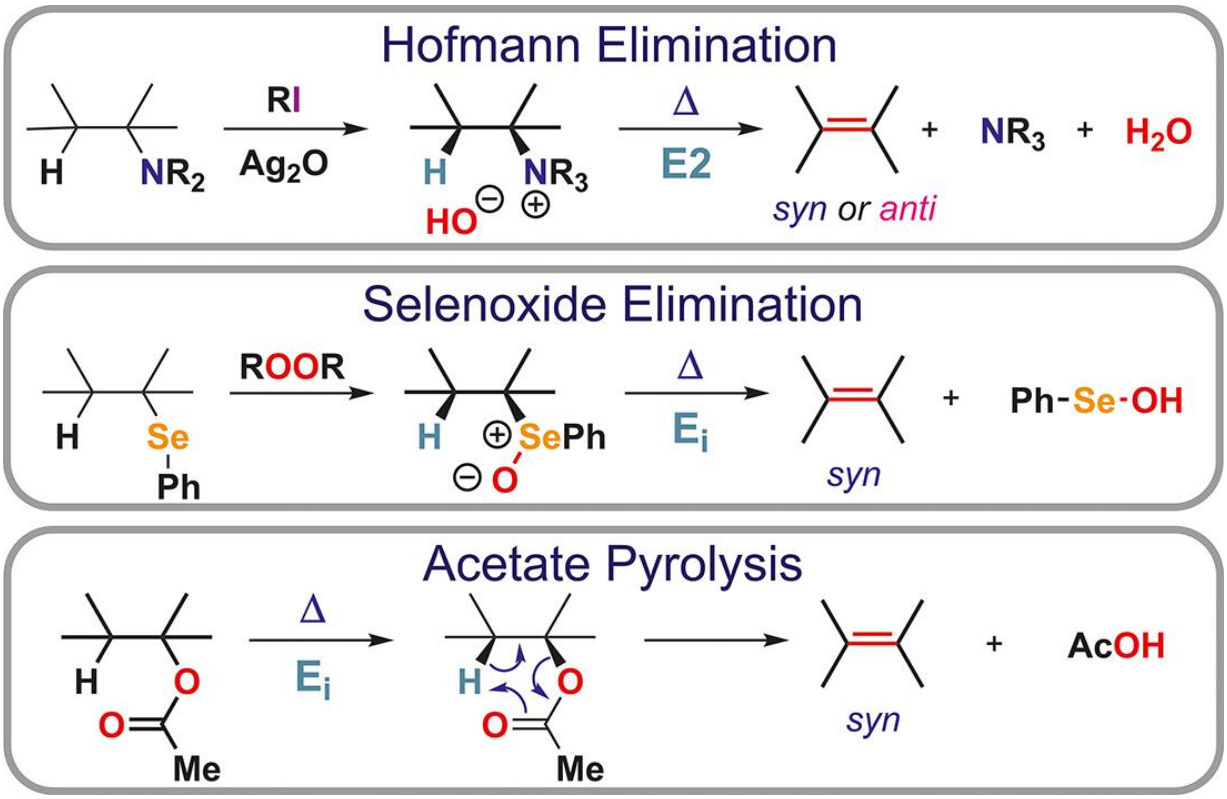


Fig. 27.2: Reactions related to the ***Cope*** *elimination*.[89]

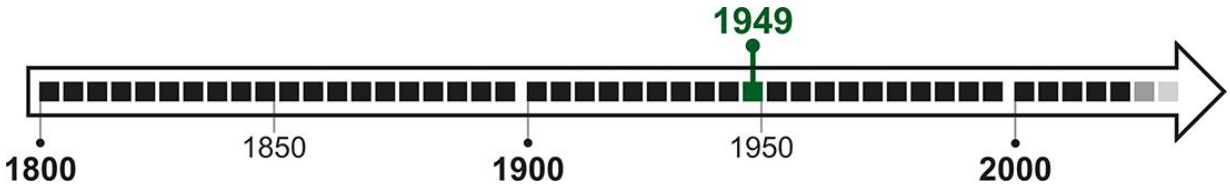


Fig. 27.3: The discovery of the ***Cope*** *elimination*.[90]

28 Cope Rearrangement

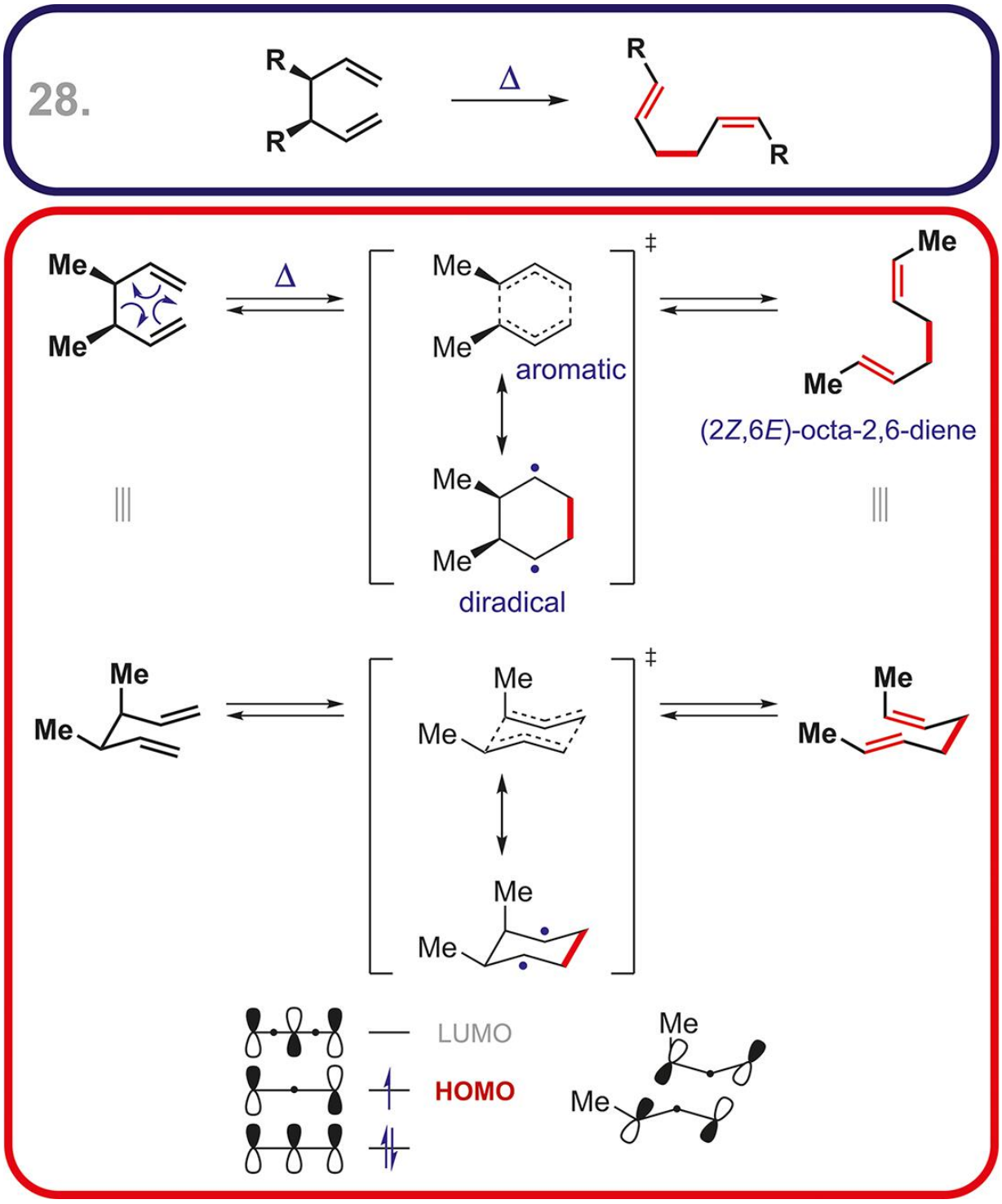


Fig. 28.1: The ***Cope*** *rearrangement* mechanism.[91]

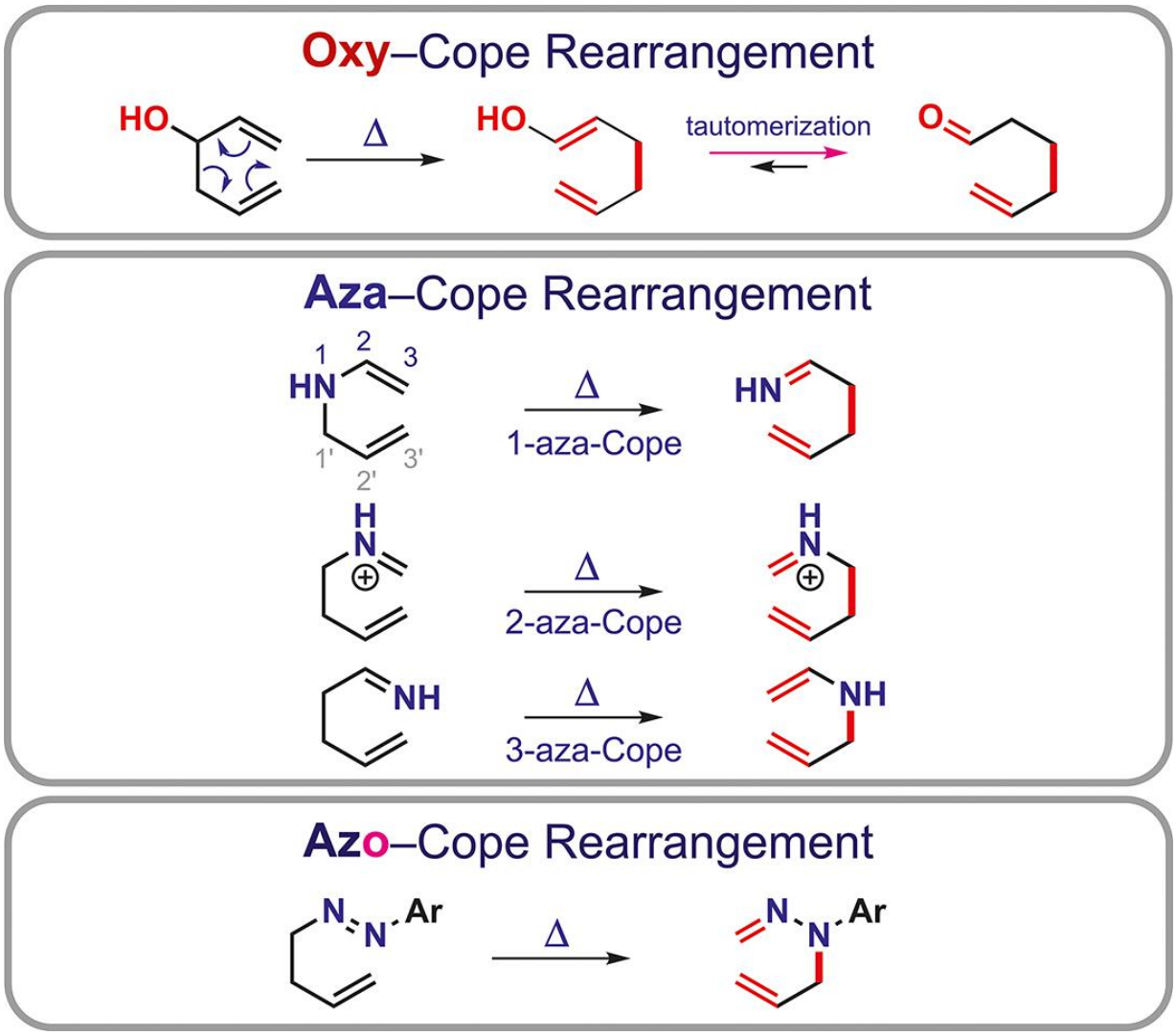


Fig. 28.2: Reactions related to the ***Cope*** *rearrangement*.[92]

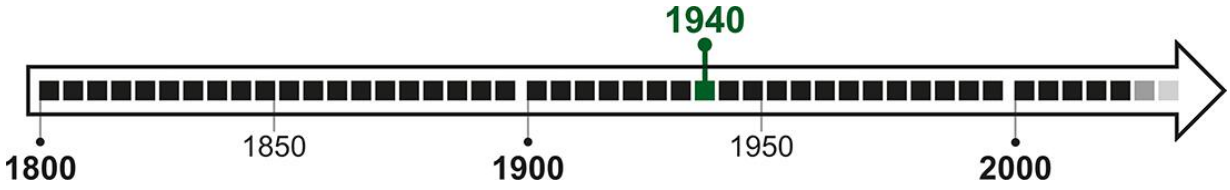


Fig. 28.3: The discovery of the ***Cope*** *rearrangement*.[93]

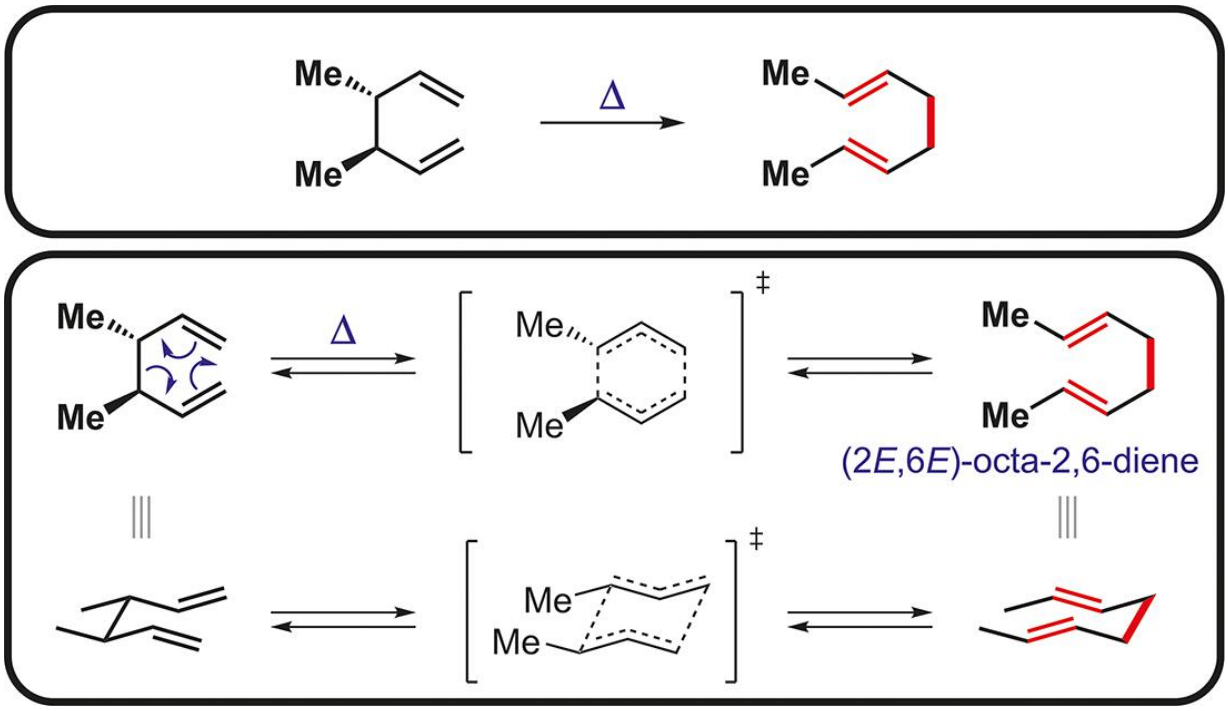


Fig. 28.4: The ***Cope*** *rearrangement* of (3*R*,4*R*)-3,4-dimethylhexa-1,5-diene.[94]

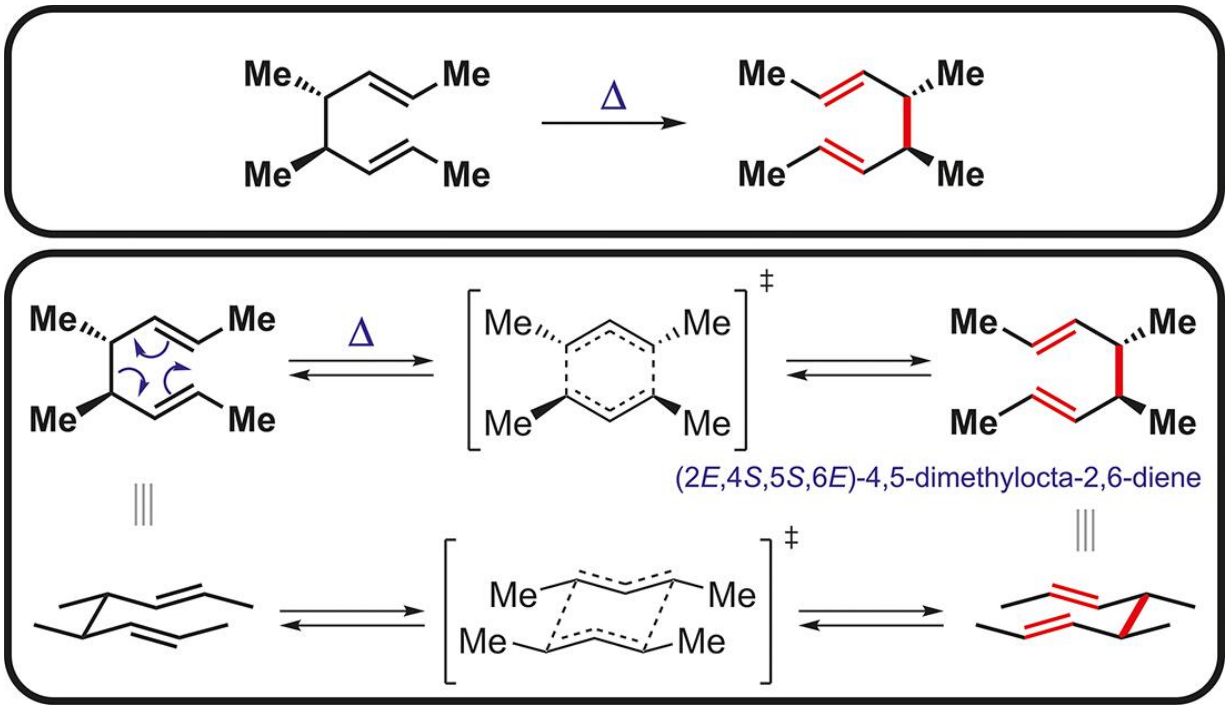


Fig. 28.5: The ***Cope*** *rearrangement* of (2*E*,4*R*,5*R*,6*E*)-4,5-dimethylocta-2,6-diene.[95]

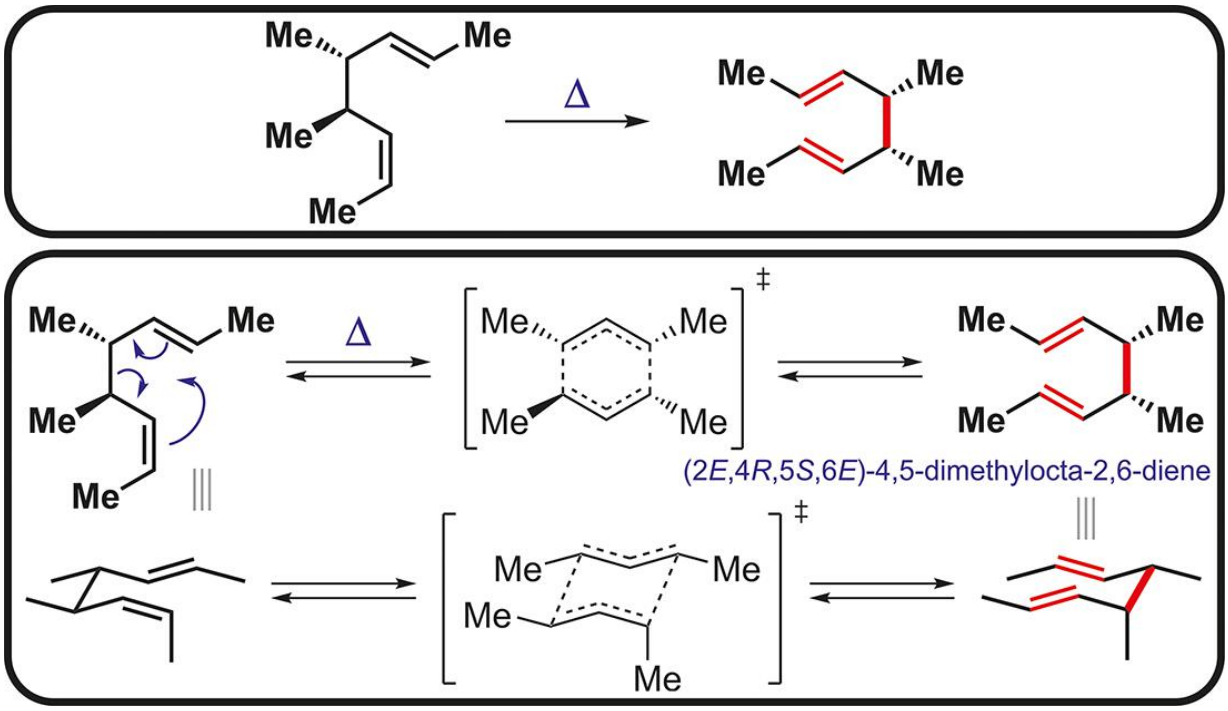


Fig. 28.6: The ***Cope*** *rearrangement* of (2*Z*,4*R*,5*R*,6*E*)-4,5-dimethylocta-2,6-diene.[96]

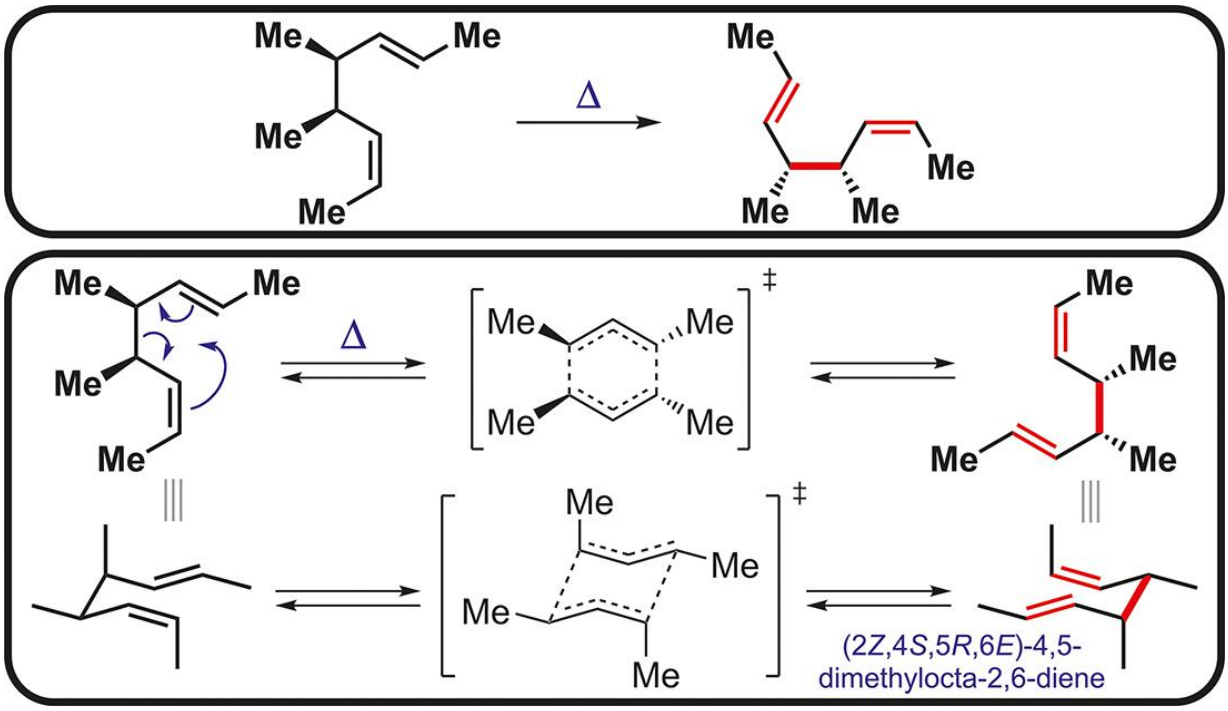


Fig. 28.7: The ***Cope*** *rearrangement* of (2*Z*,4*R*,5*S*,6*E*)-4,5-dimethylocta-2,6-diene.[97]

29 Criegee and Malaprade Oxidation

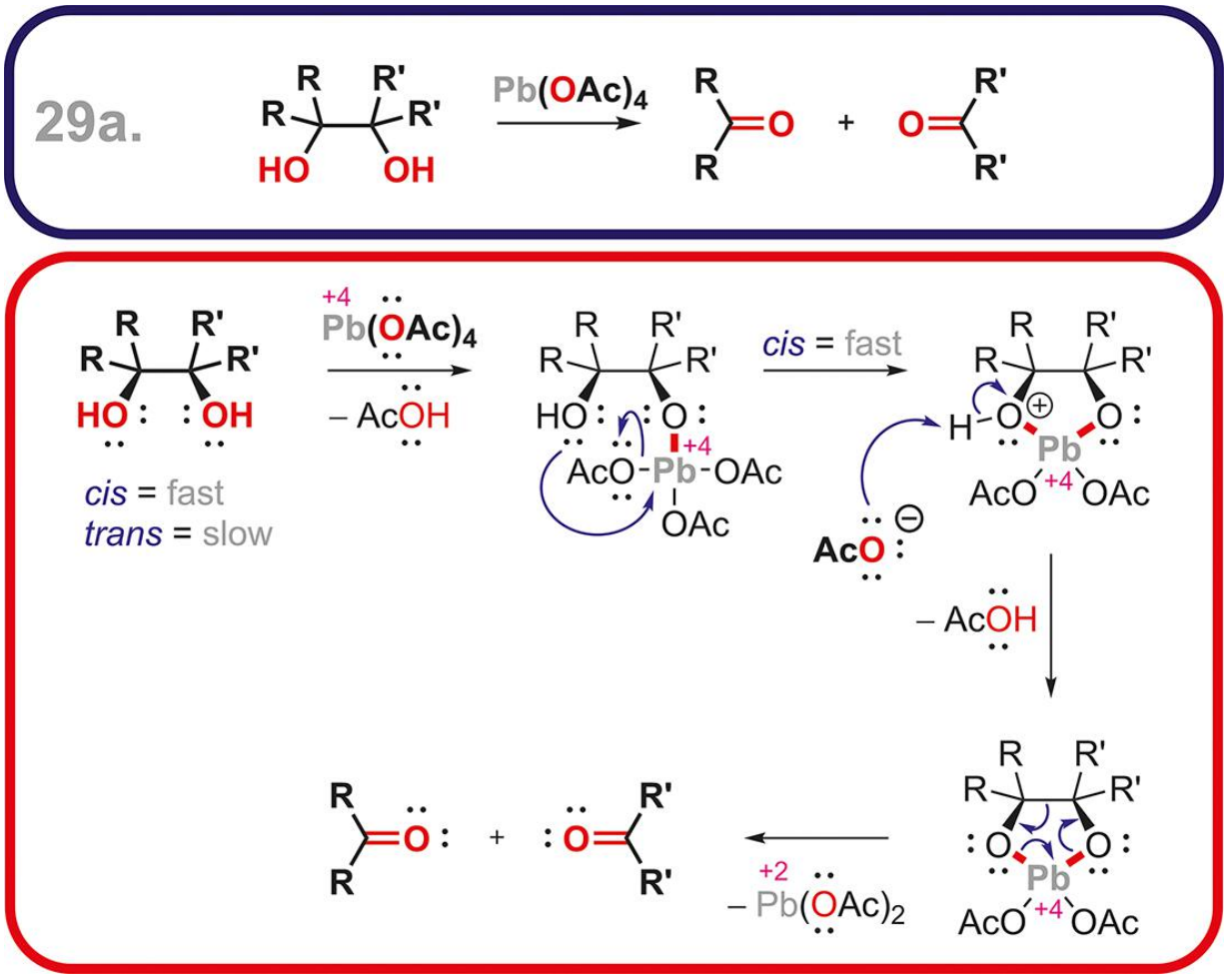


Fig. 29.1: The ***Criegee*** *oxidation* mechanism.[98]

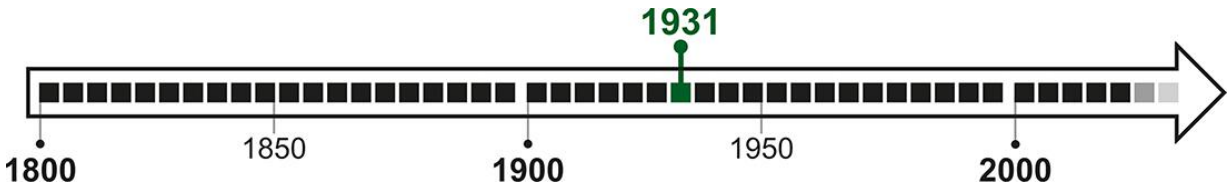


Fig. 29.2: The discovery of the ***Criegee*** *oxidation*.[99]

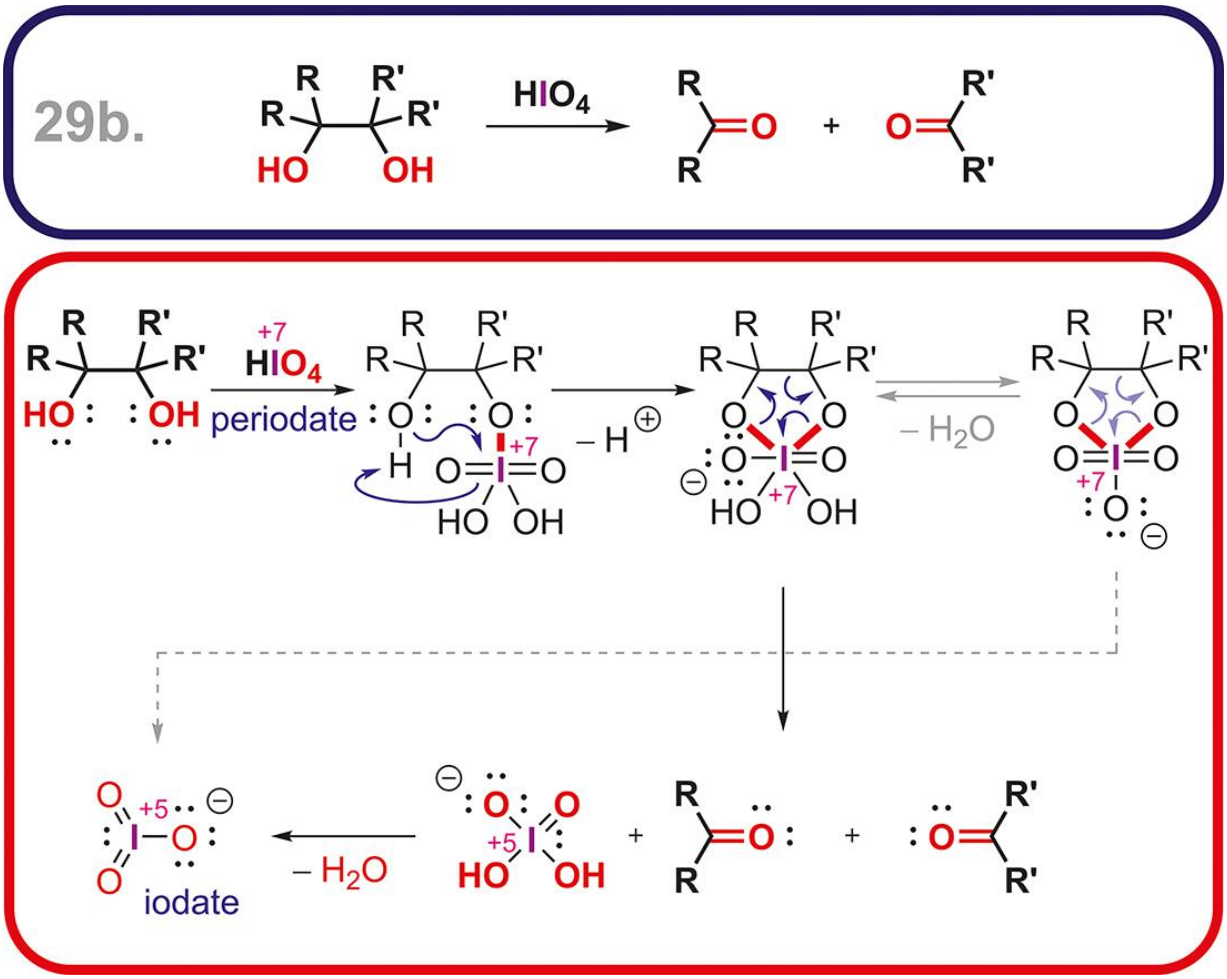


Fig. 29.3: The ***Malaprade*** *oxidation* mechanism.[100]

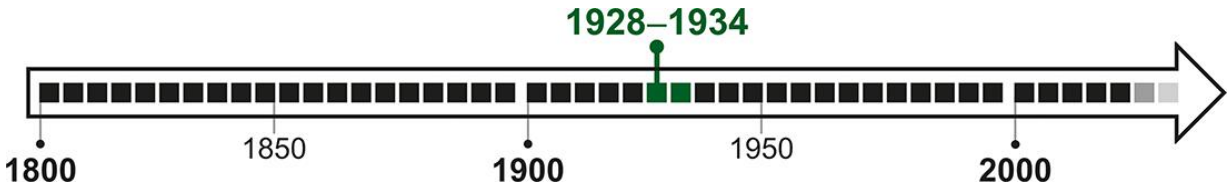


Fig. 29.4: The discovery of the ***Malaprade*** *oxidation*.[101]

30 CuAAC

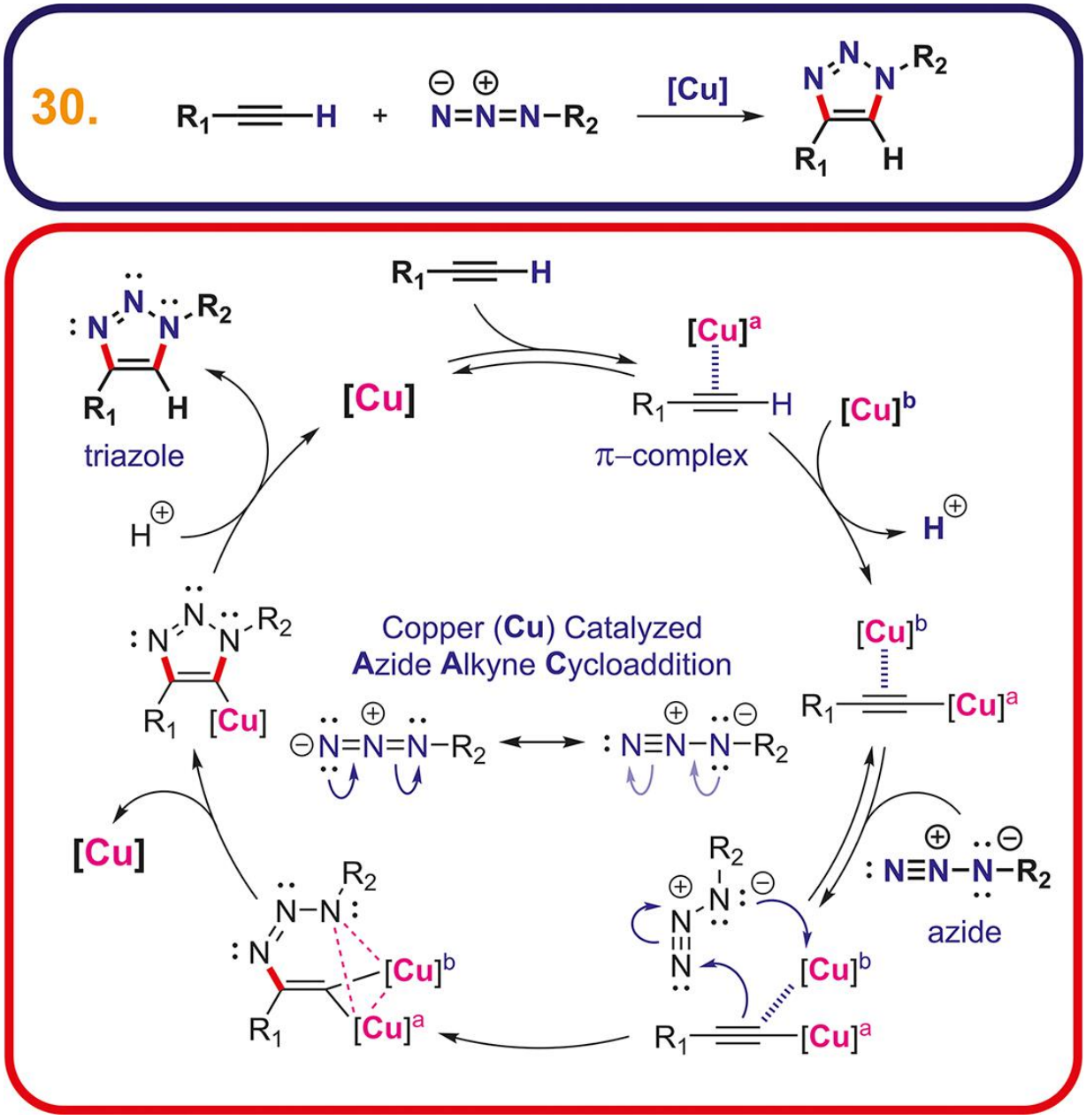


Fig. 30.1: The **CuAAC** mechanism.[102]

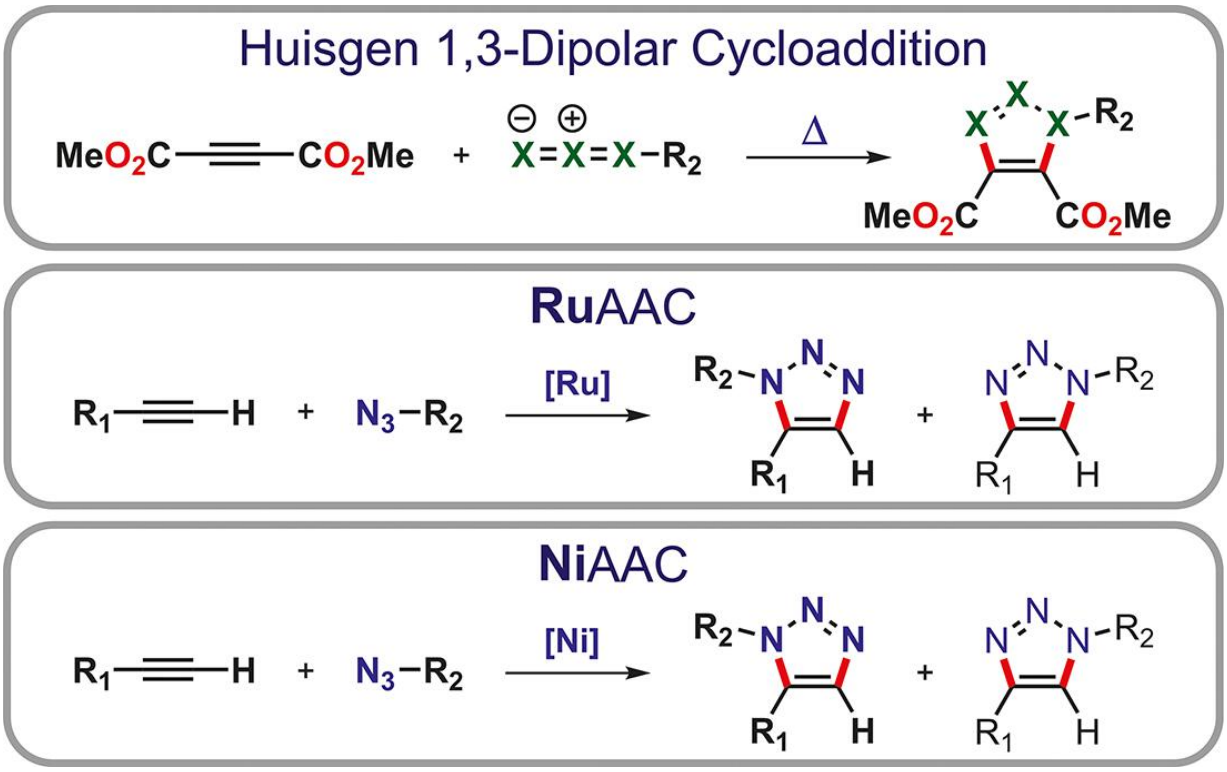


Fig. 30.2: Reactions related to the **CuAAC**.[103]

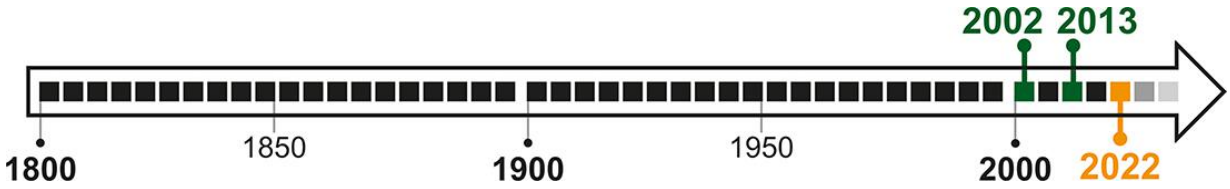


Fig. 30.3: The discovery of the **CuAAC**.[104]

31 Curtius Rearrangement

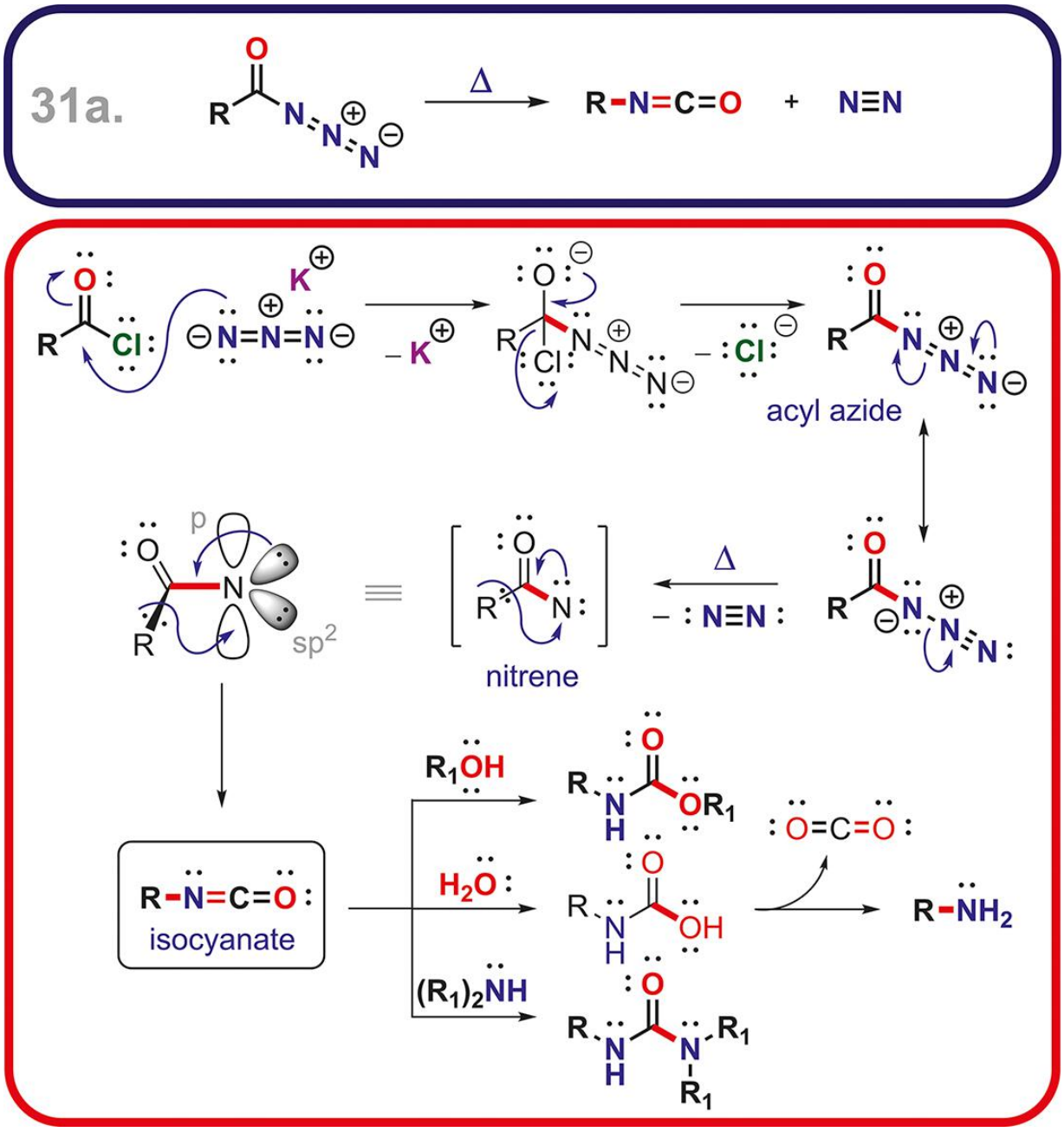


Fig. 31.1: The ***Curtius*** *rearrangement* mechanism.[105]

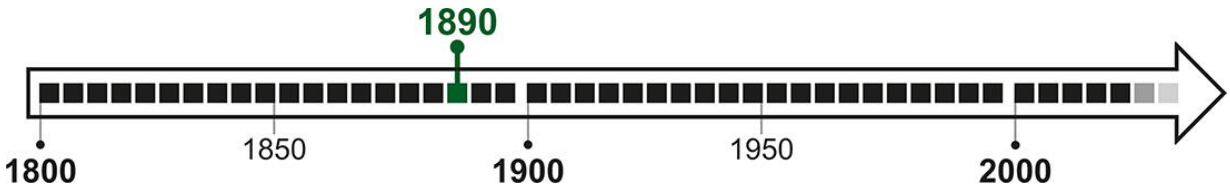


Fig. 31.2: The discovery of the ***Curtius*** *rearrangement*.[106].

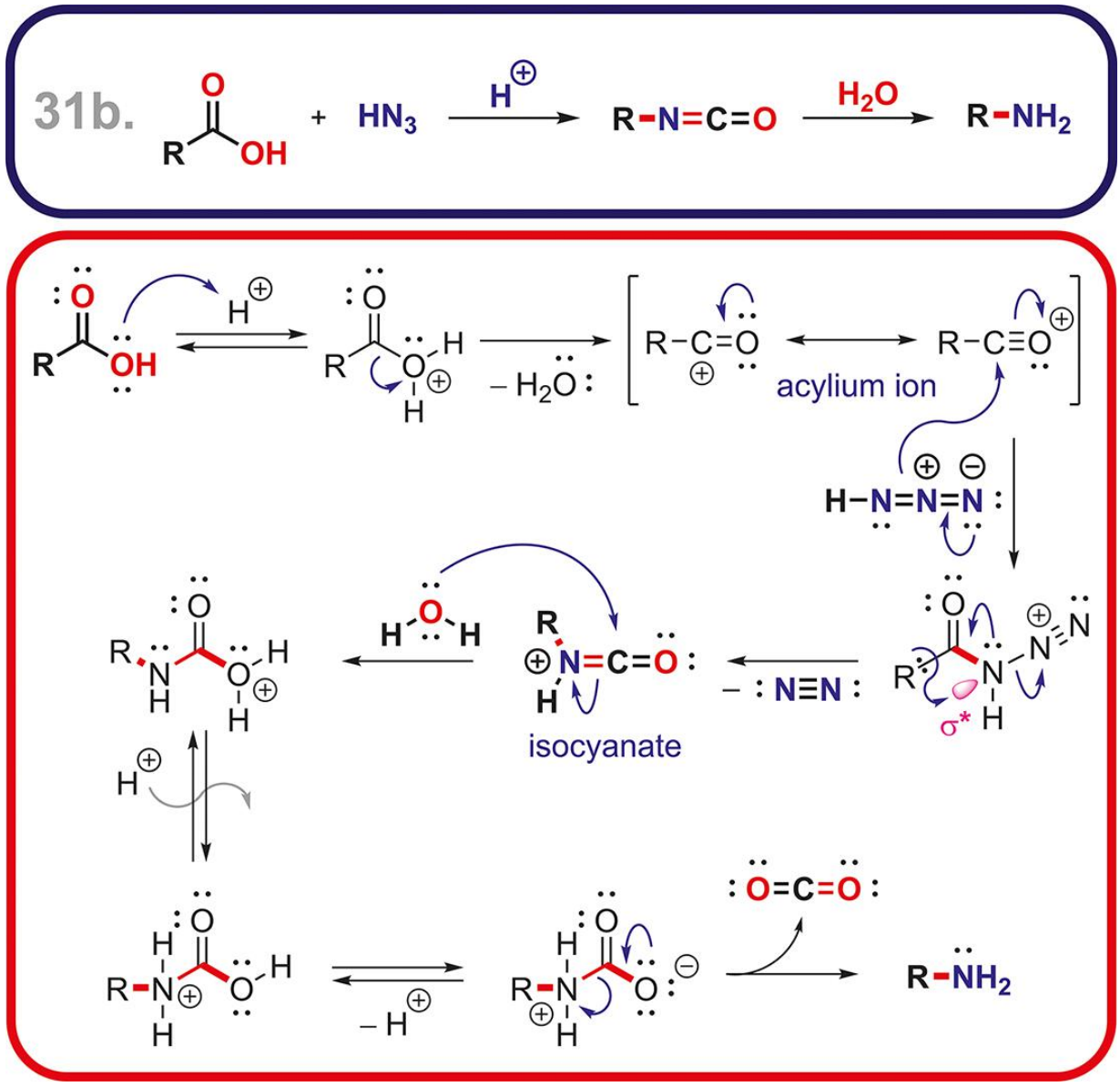


Fig. 31.3: The ***Schmidt*** *reaction* mechanism.[107]

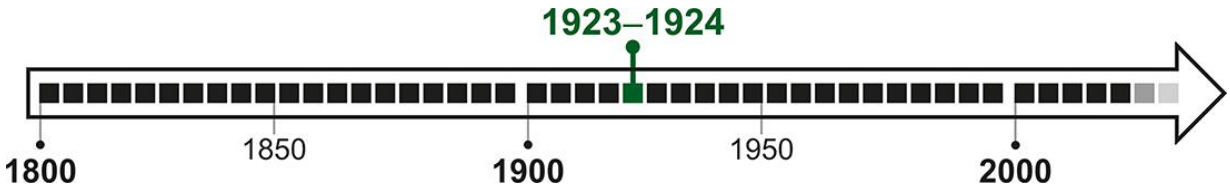


Fig. 31.4: The discovery of the ***Schmidt*** *reaction* mechanism.[108]

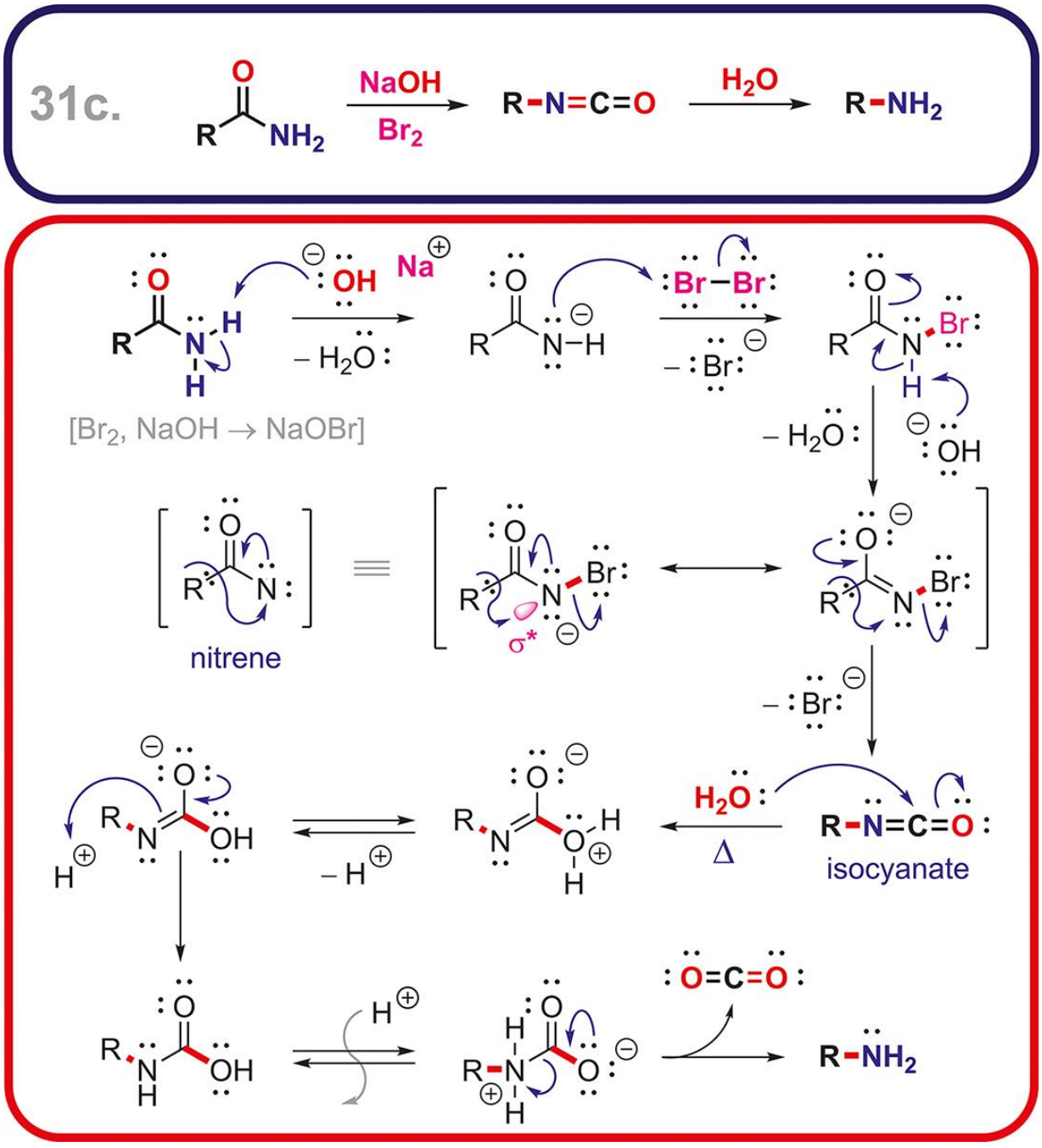


Fig. 31.5: The ***Hofmann*** *rearrangement* mechanism.[109]

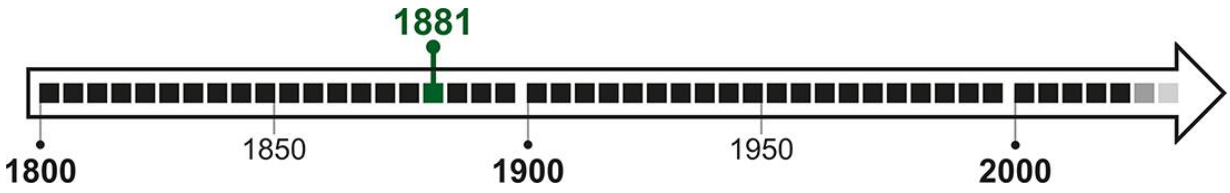


Fig. 31.6: The discovery of the ***Hofmann*** *rearrangement*.[110]

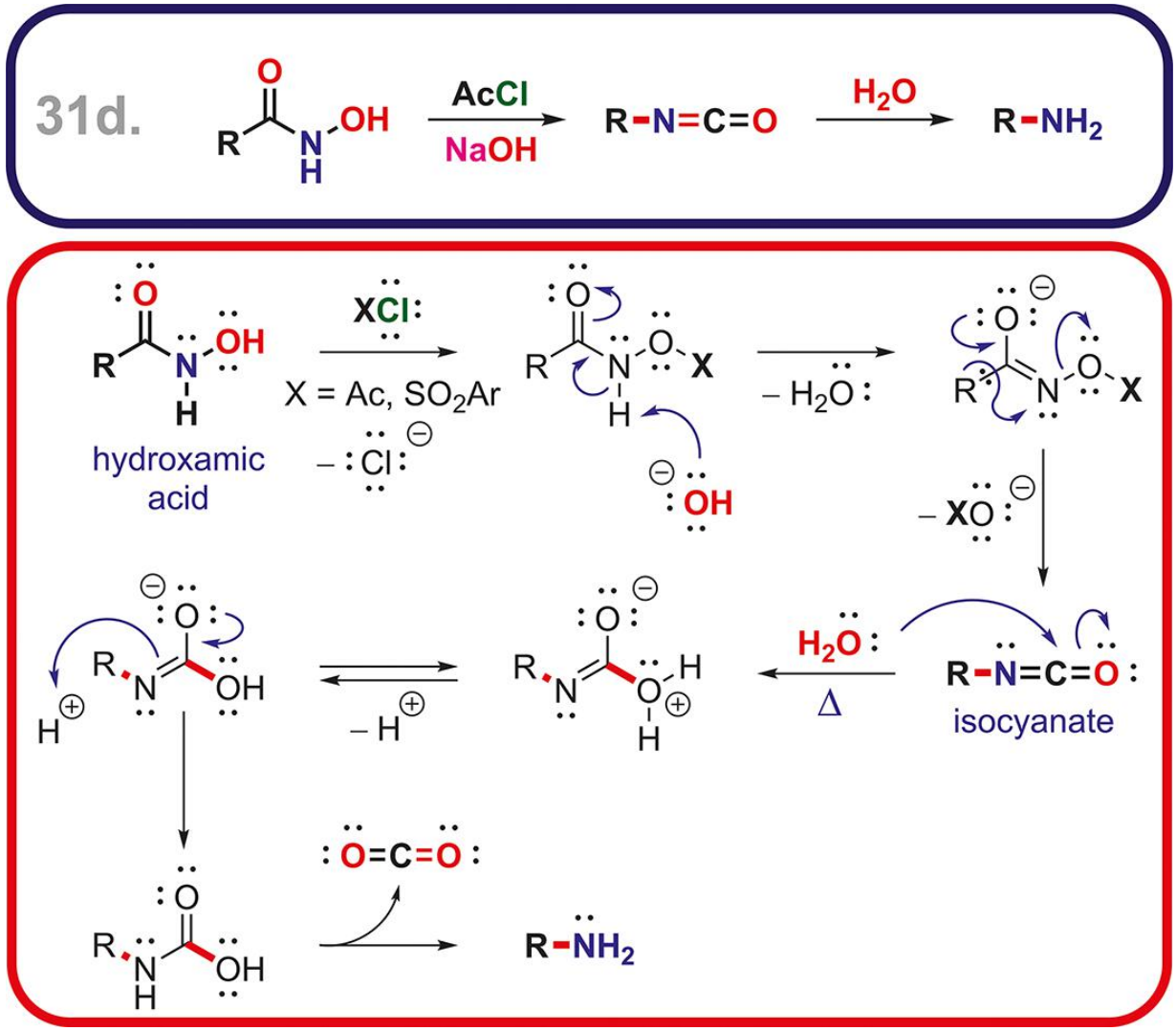


Fig. 31.7: The ***Lossen*** *rearrangement* mechanism.[111]

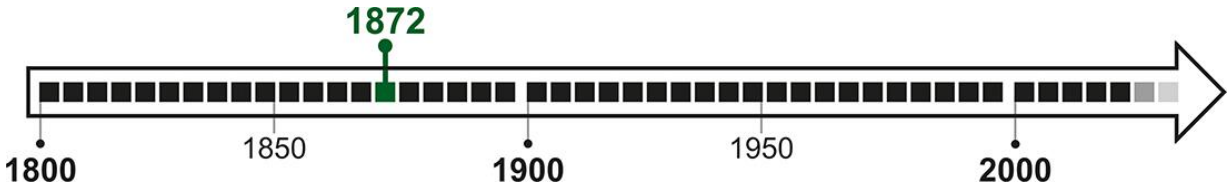


Fig. 31.8: The discovery of the ***Lossen*** *rearrangement*.[112]

32 Darzens Condensation

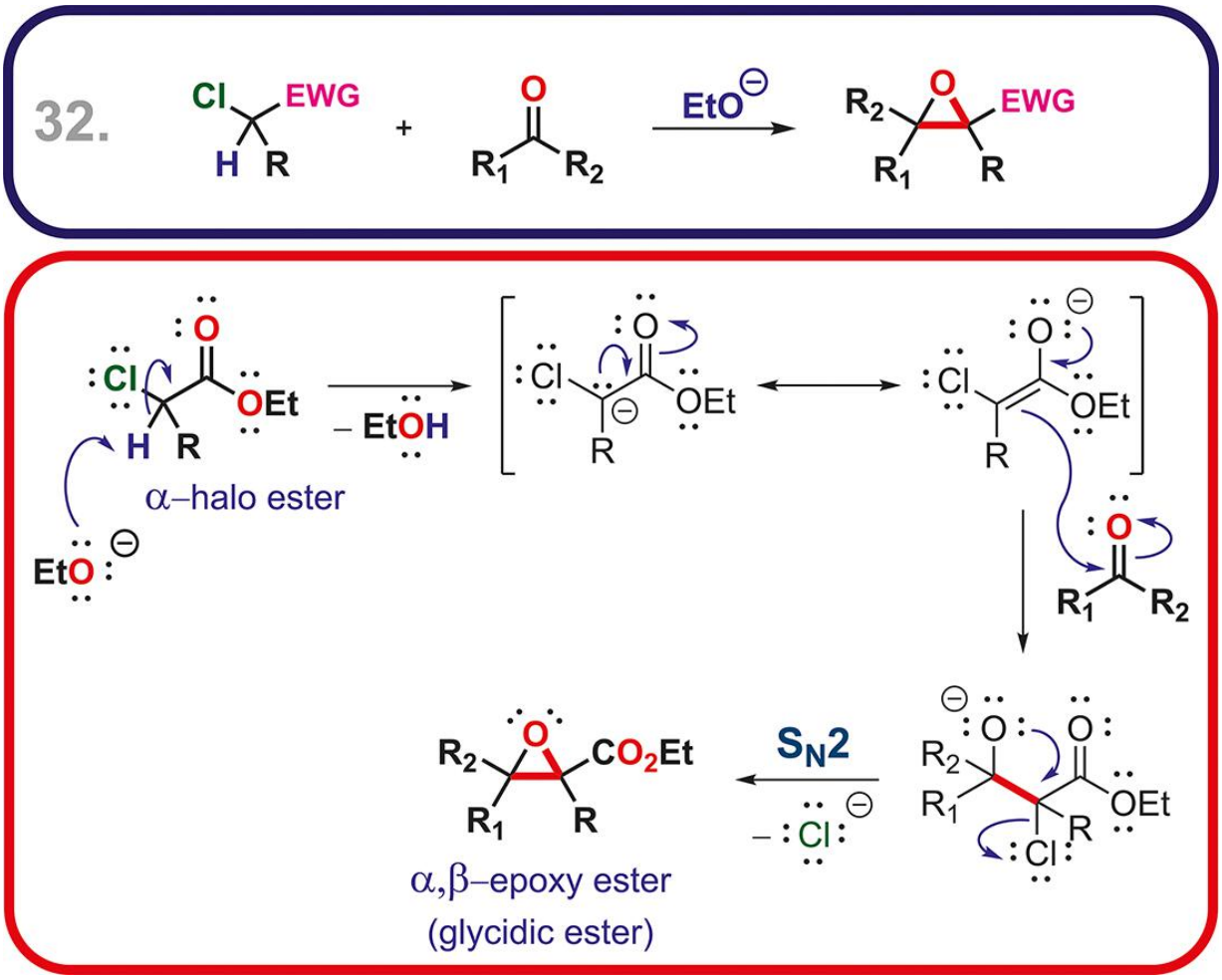


Fig. 32.1: The ***Darzens*** *condensation* mechanism.[113]

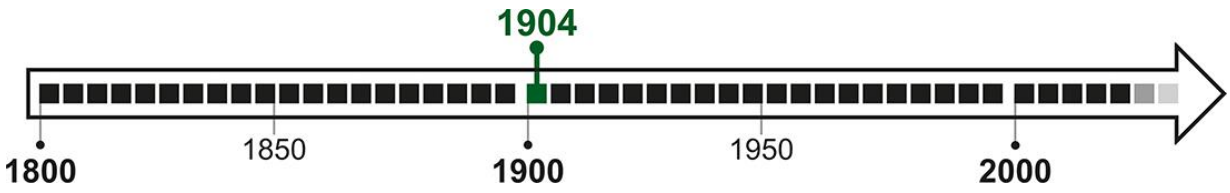


Fig. 32.2: The discovery of the ***Darzens*** *condensation*.[114]

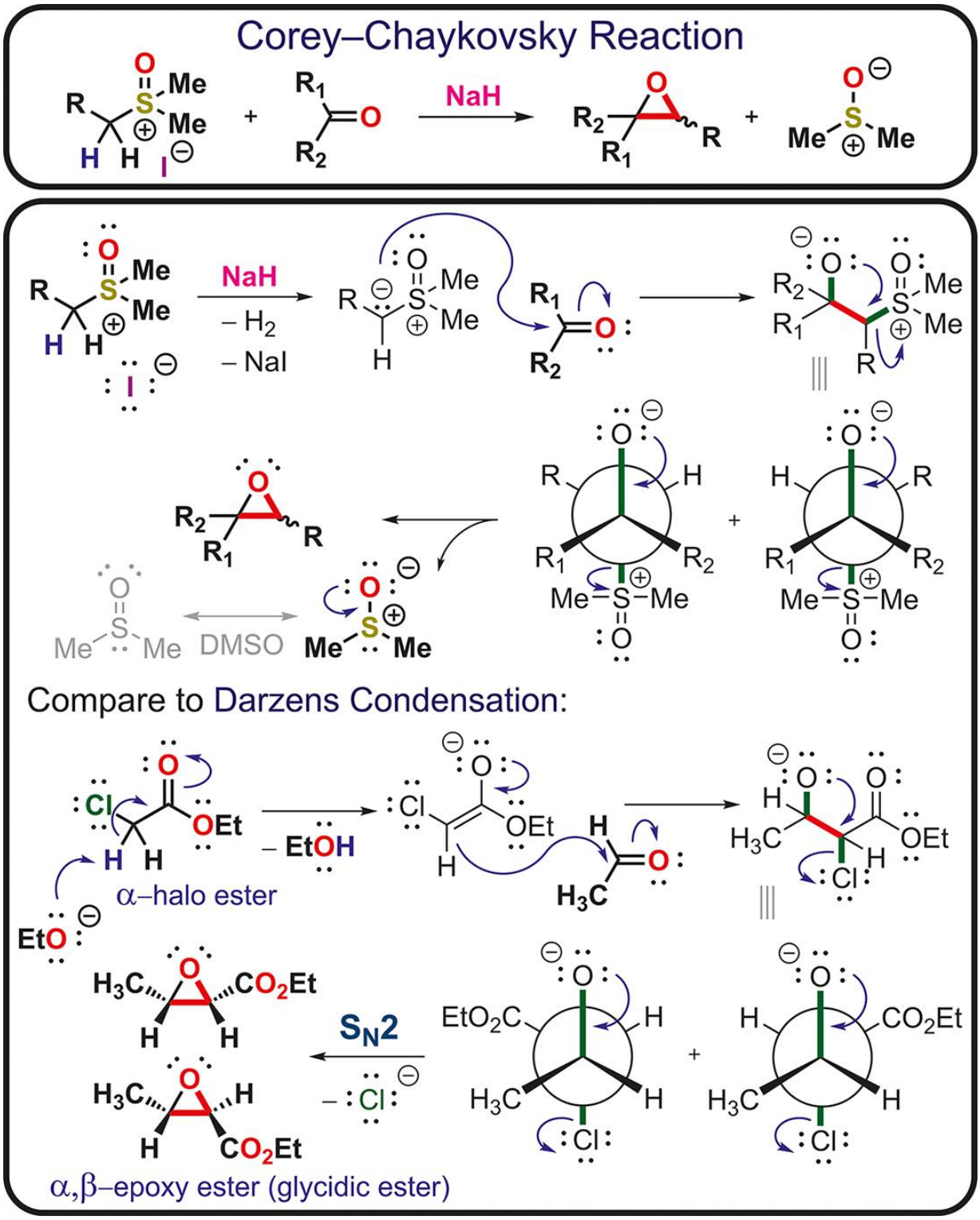


Fig. 32.3: The ***Corey–Chaykovsky*** *reaction* mechanism.[115]

33 Dess–Martin Oxidation

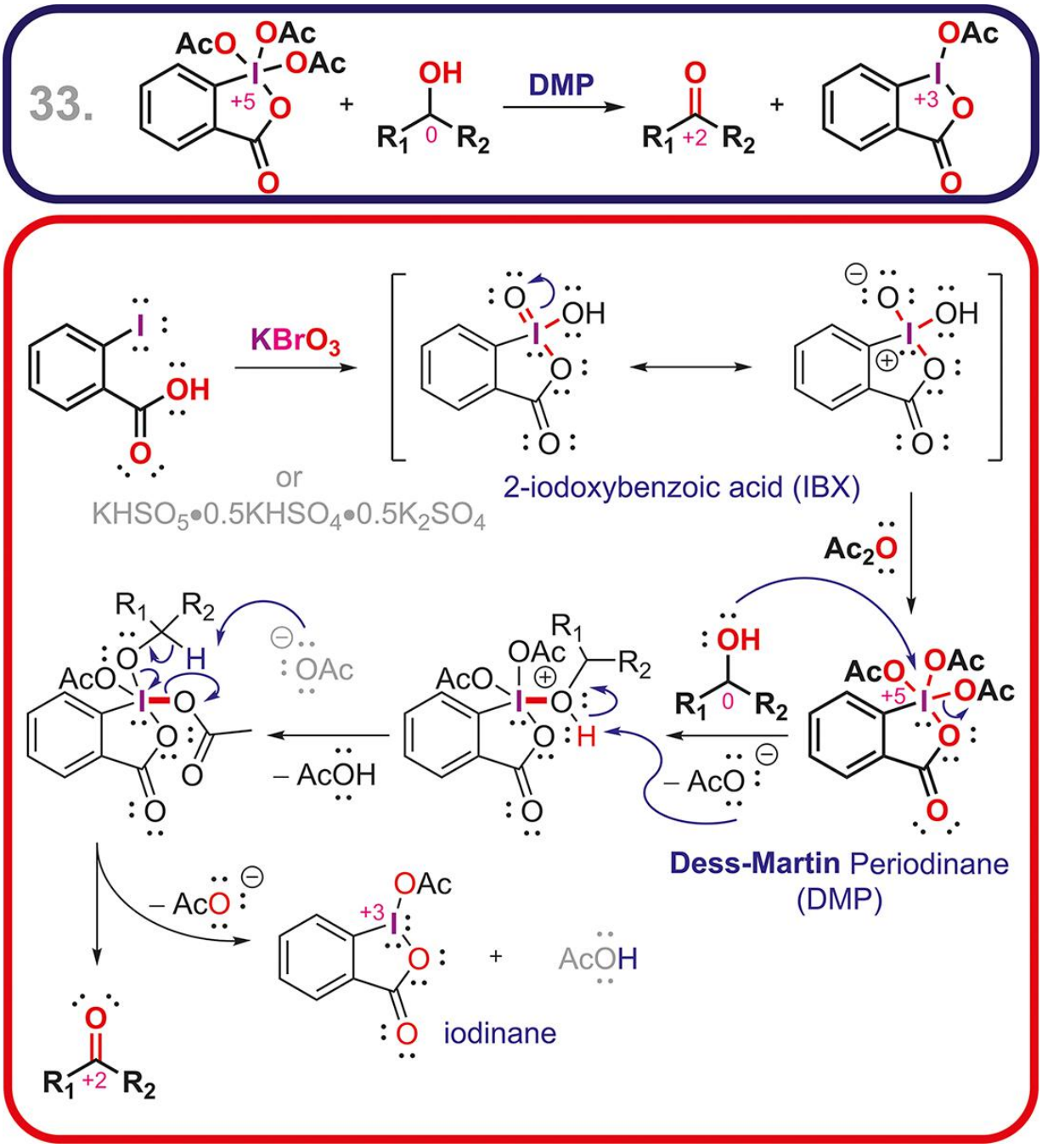


Fig. 33.1: The ***Dess–Martin*** *oxidation* mechanism.[116]

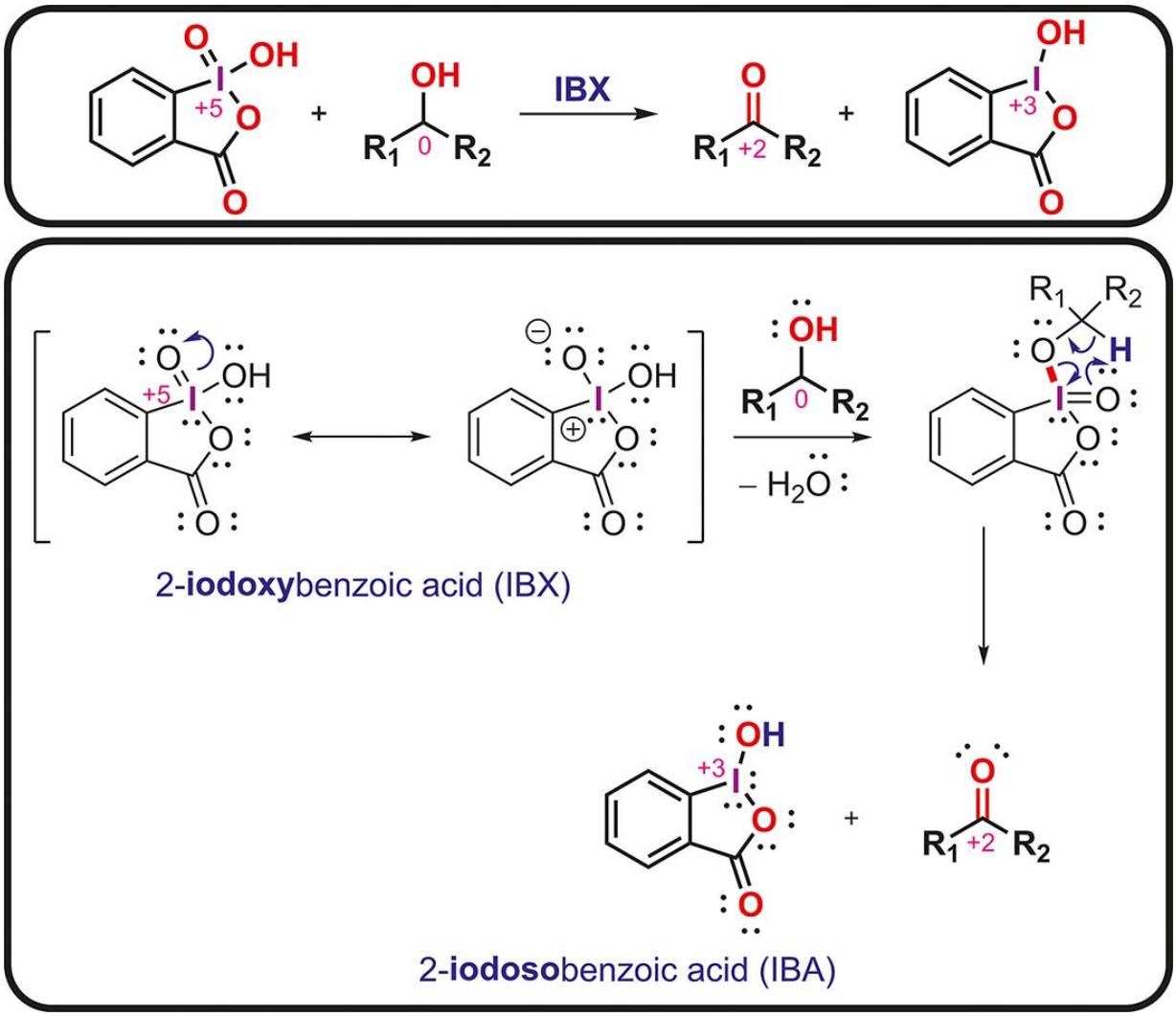


Fig. 33.2: The **IBX** *oxidation* mechanism.[117]

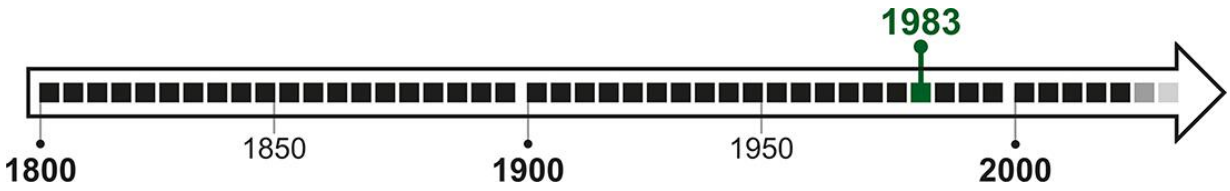


Fig. 33.3: The discovery of the ***Dess–Martin*** *oxidation*.[118]

34 Diazotization (Diazonium Salt)

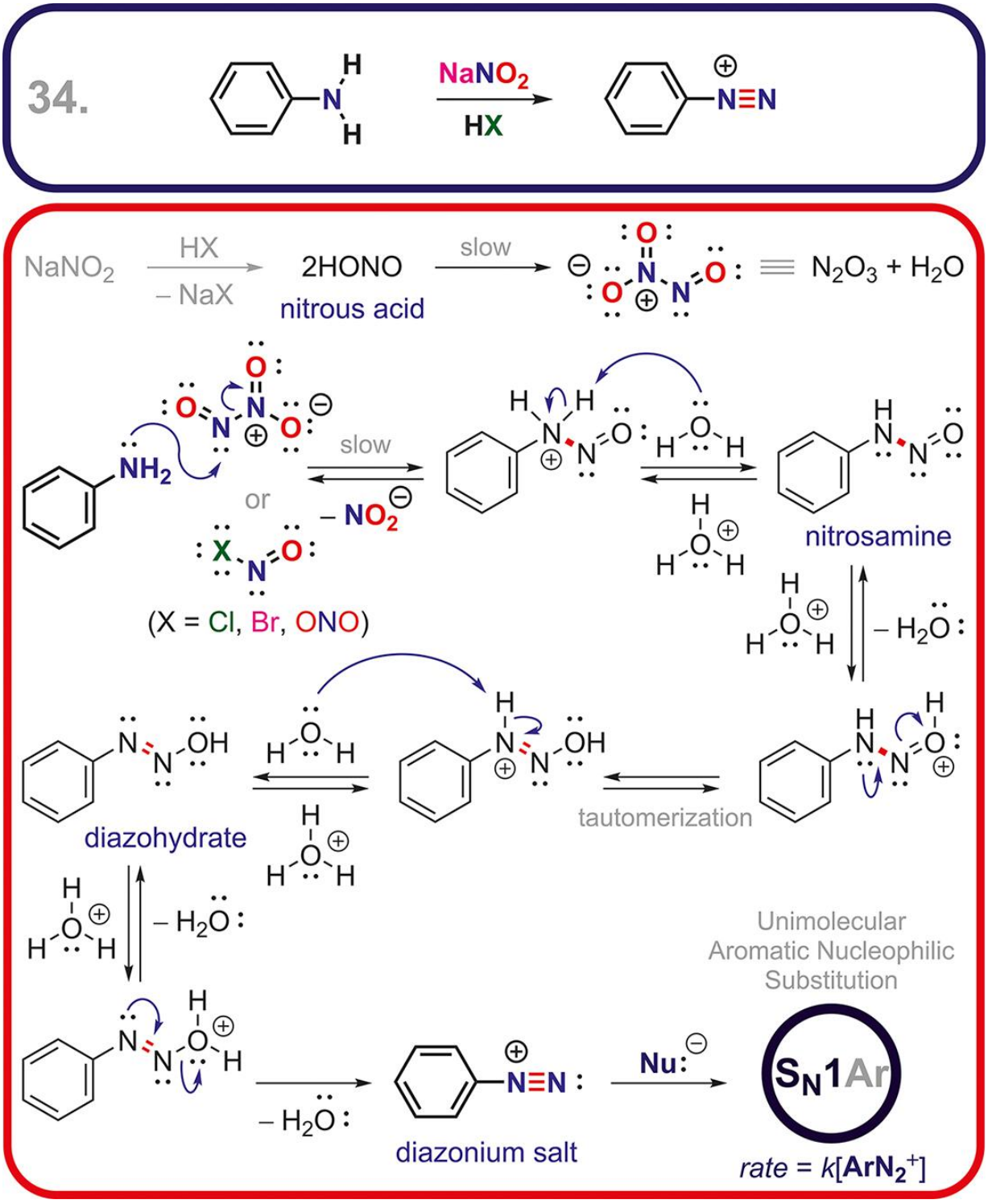


Fig. 34.1: The *diazonium salt formation (diazotization)* mechanism.[119]

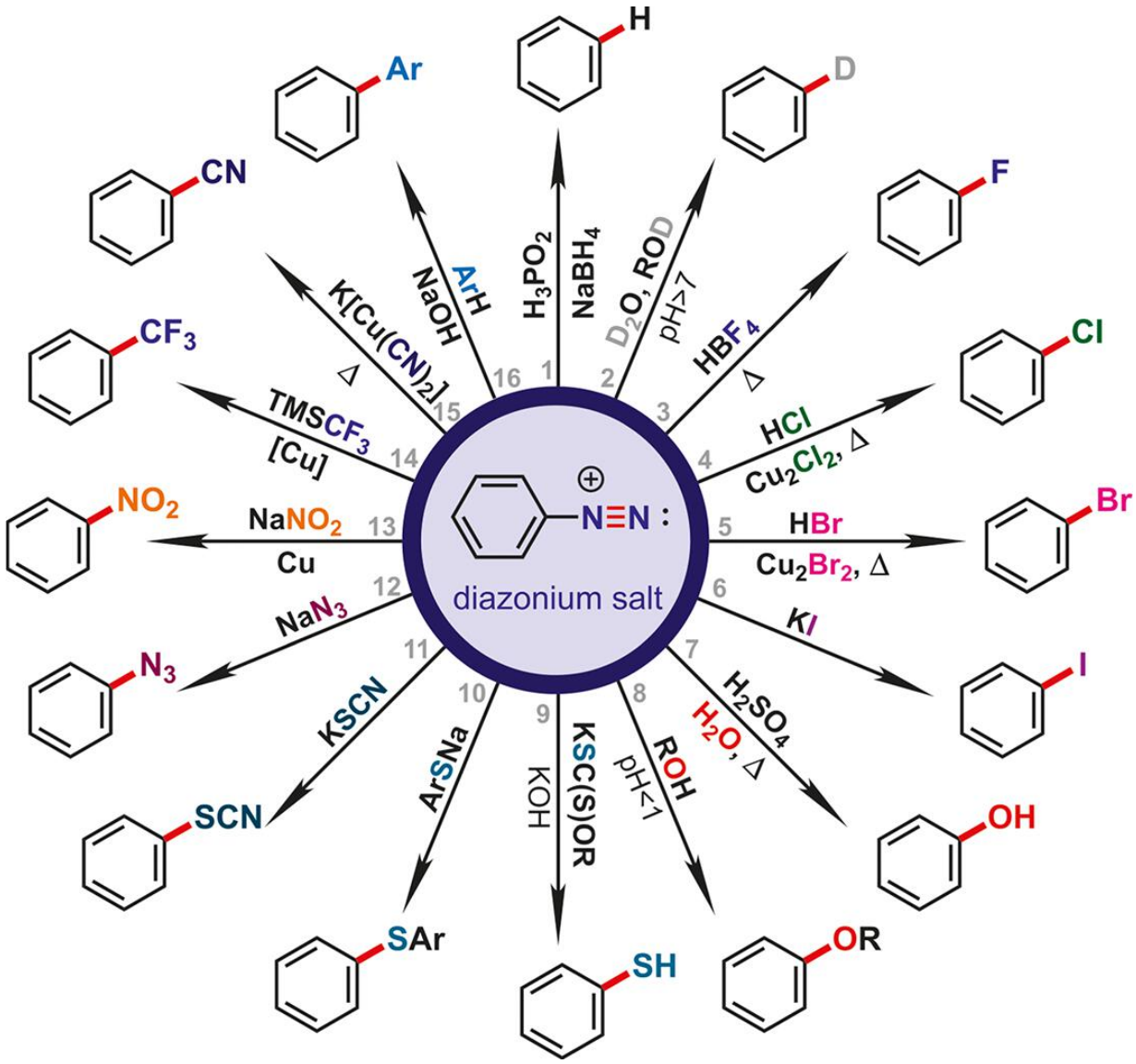


Fig. 34.2: Synthetic versatility of the diazonium salts.[120]

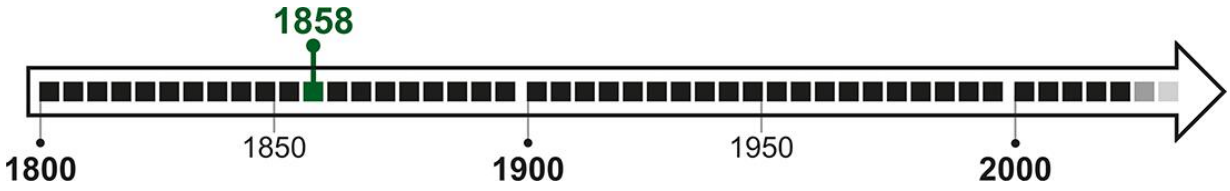


Fig. 34.3: The discovery of the *diazotization reaction*.[121]

35 Diels–Alder Cycloaddition

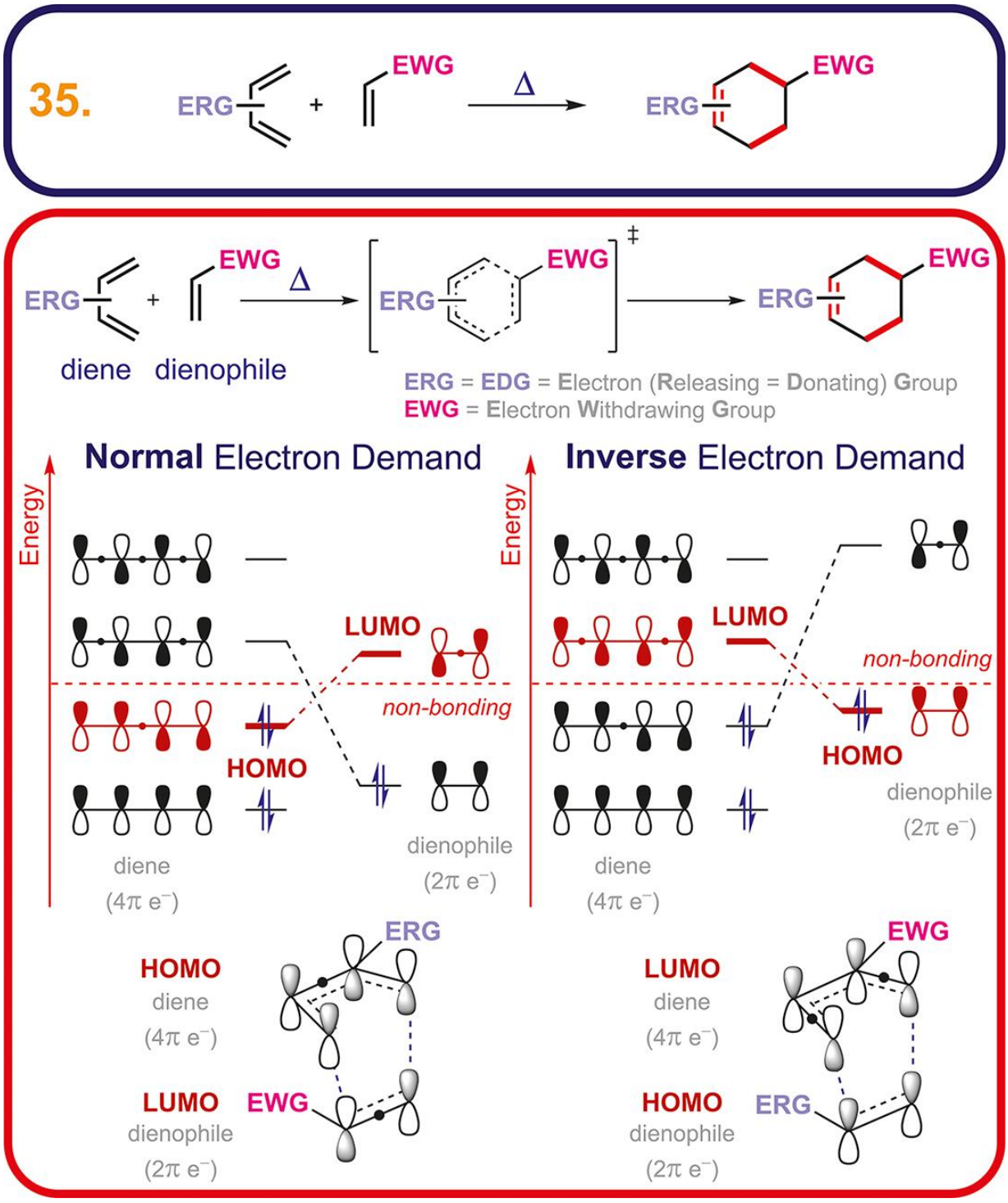


Fig. 35.1: The ***Diels–Alder*** *cycloaddition* mechanism.[122]

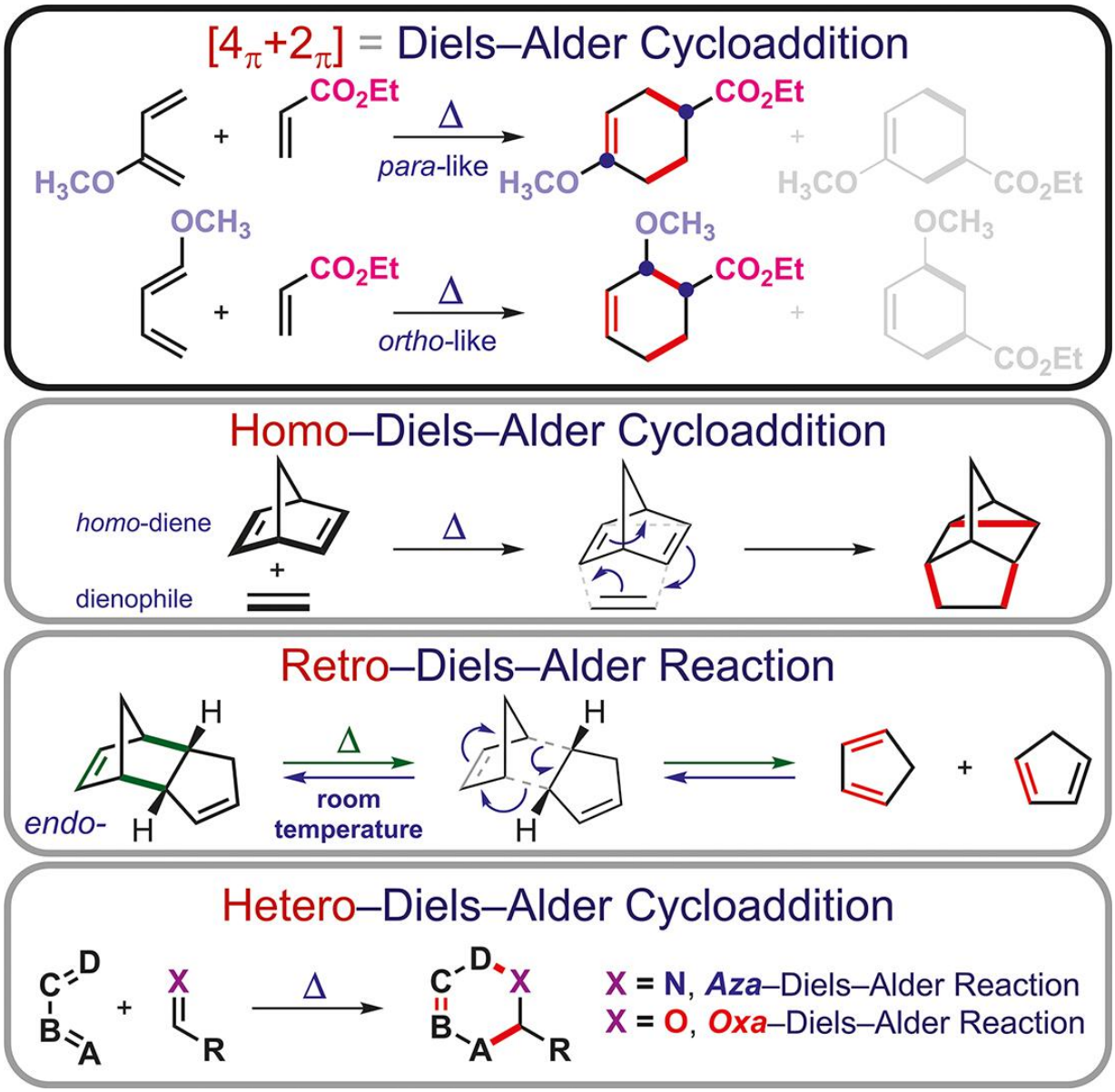


Fig. 35.2: Reactions related to the ***Diels–Alder*** *cycloaddition*.[123]

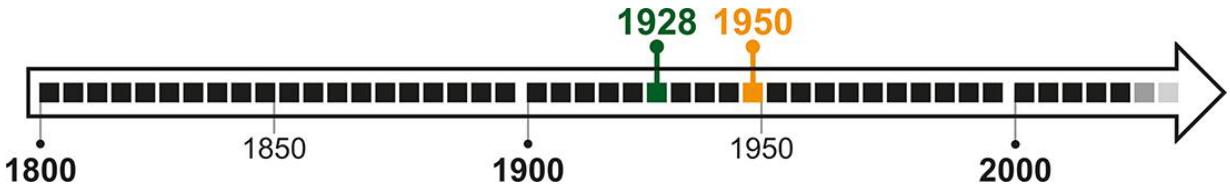


Fig. 35.3: The discovery of the ***Diels–Alder*** *cycloaddition*.[124]

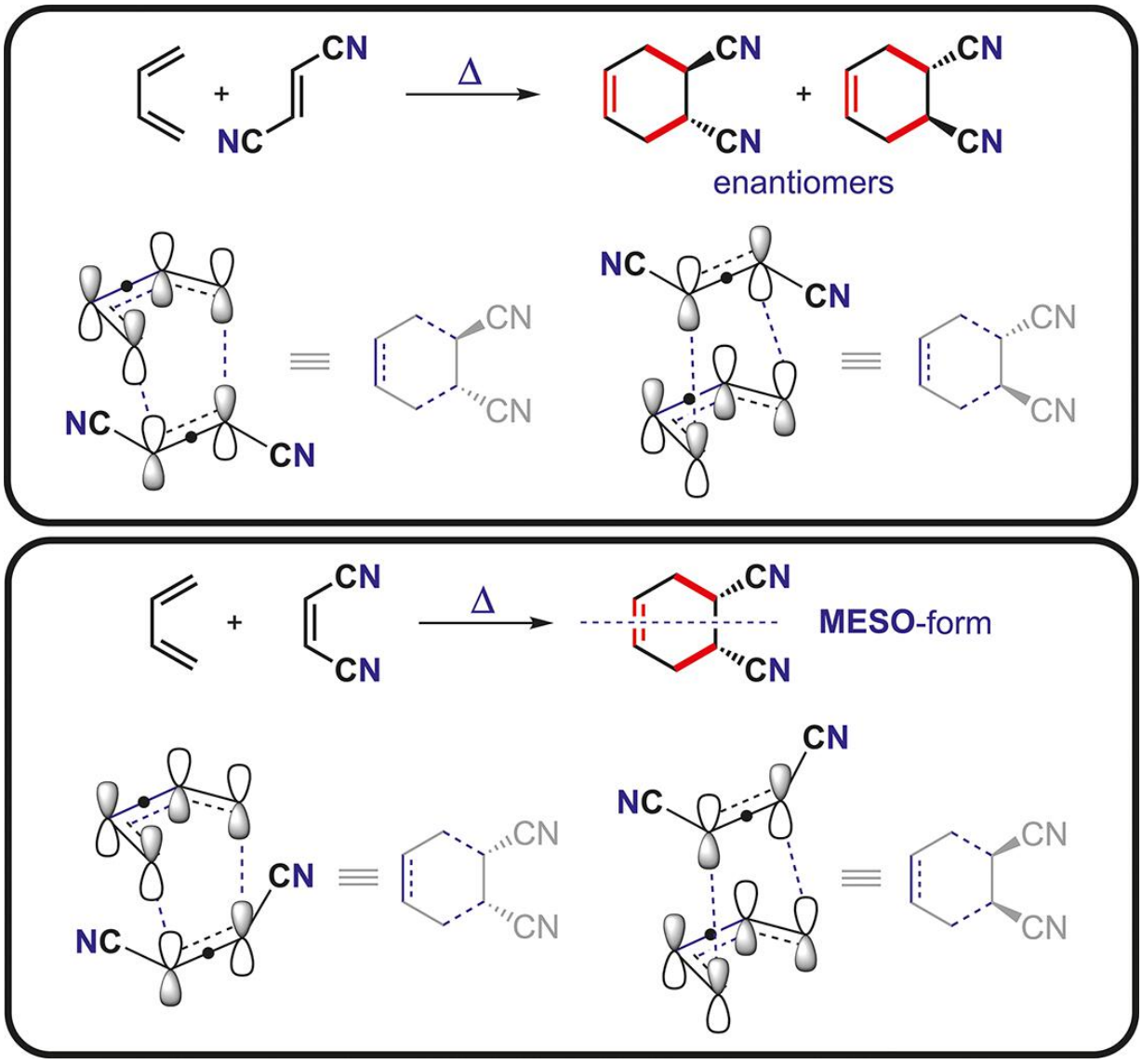


Fig. 35.4: The ***Diels–Alder*** *cycloaddition* using various *dienophiles*.[125]

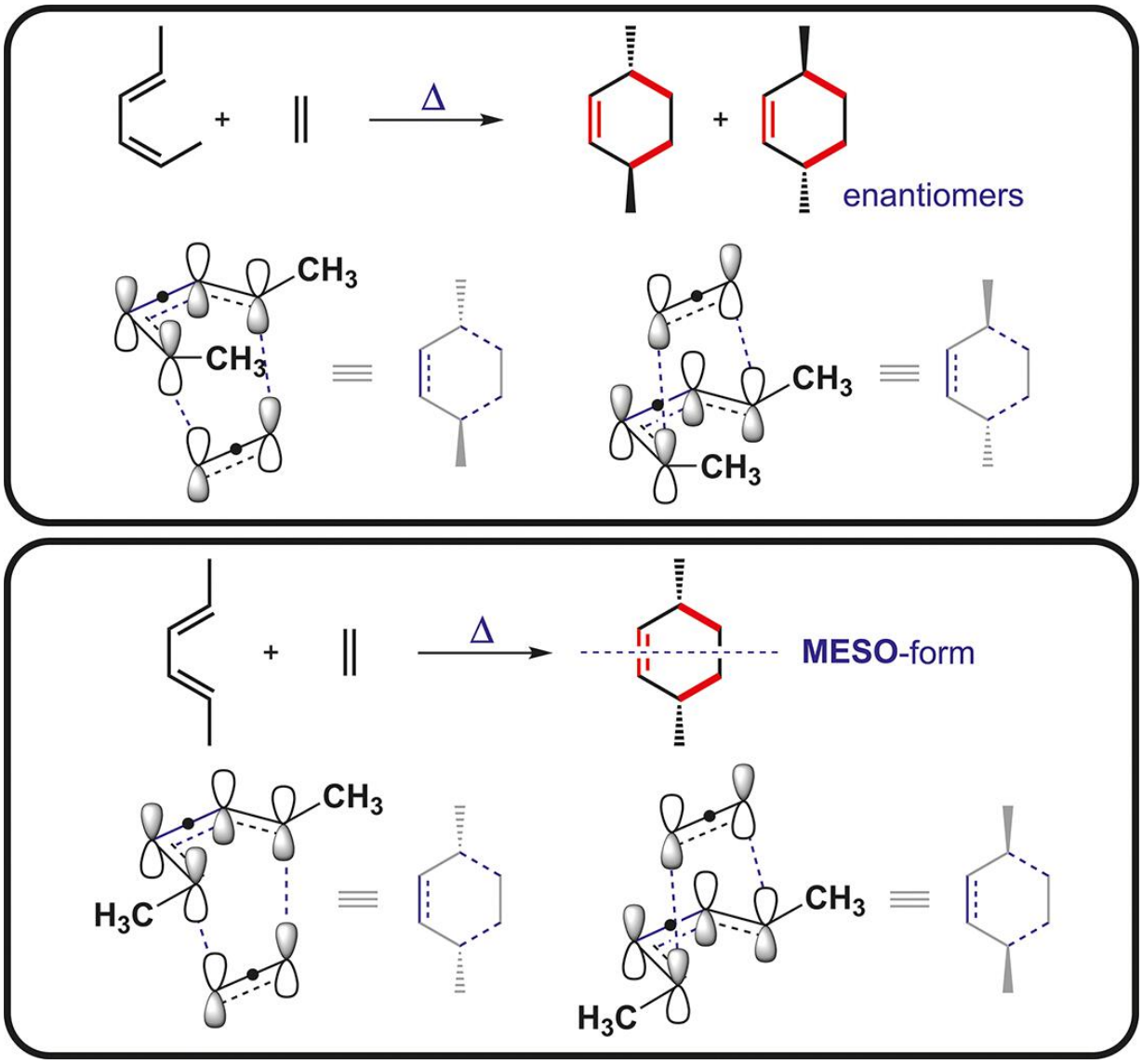


Fig. 35.5: The ***Diels–Alder*** *cycloaddition* using various *dienes*.[126]

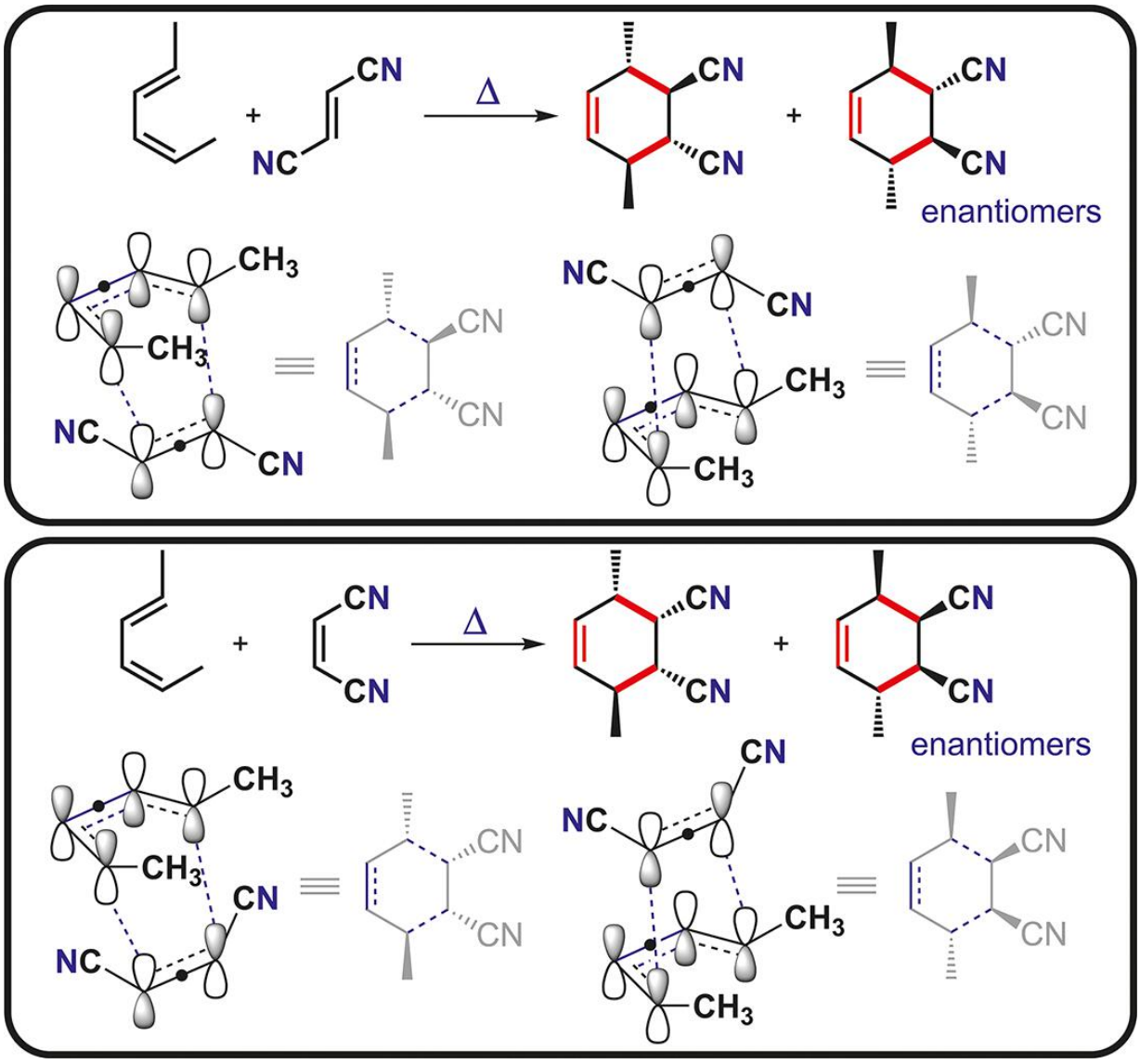


Fig. 35.6: The ***Diels–Alder*** *cycloaddition* using (2*Z*,4*E*)-hexa-2,4-diene and various dienophiles.[127]

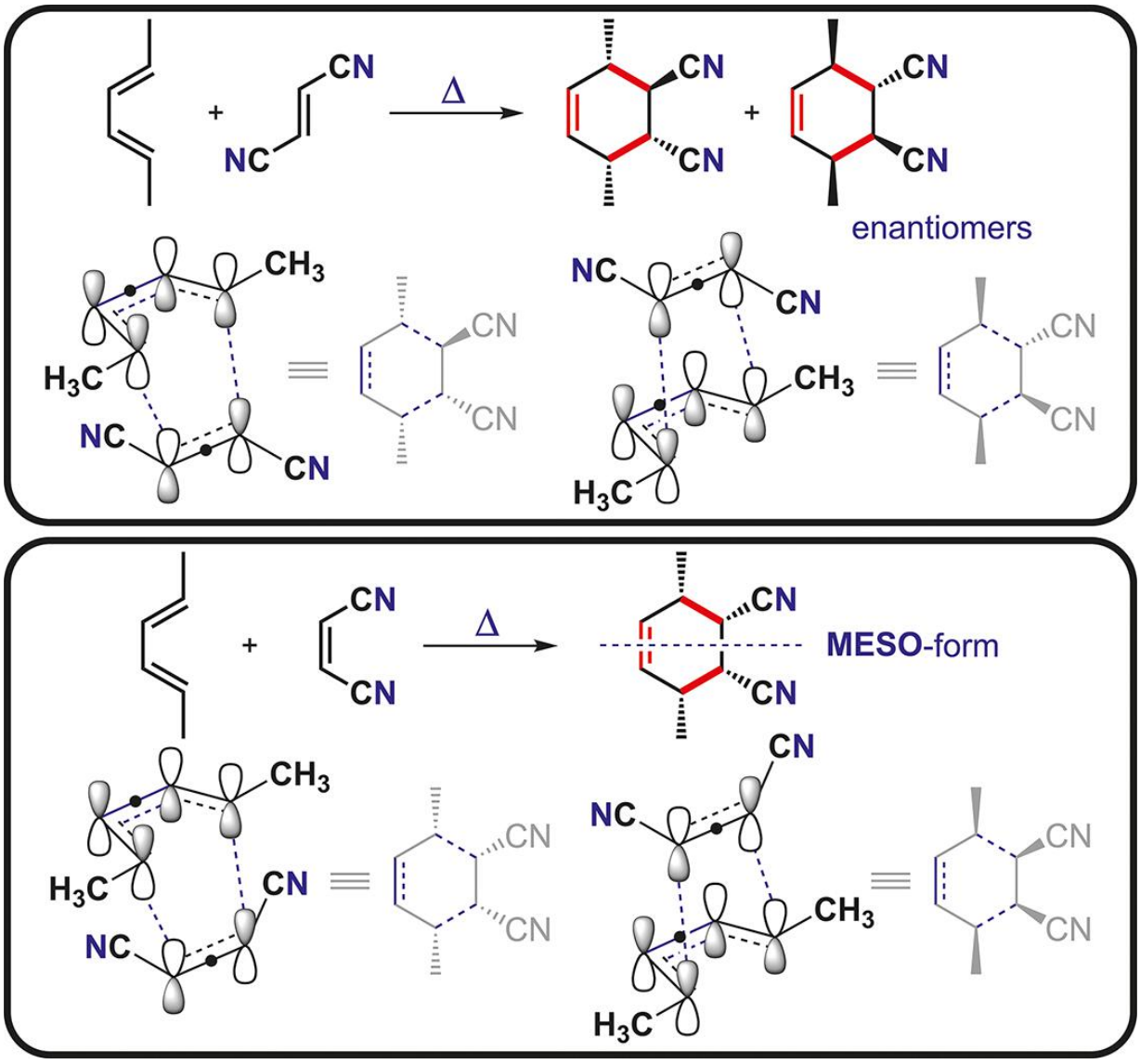


Fig. 35.7: The ***Diels–Alder*** *cycloaddition* using (2*E*,4*E*)-hexa-2,4-diene and various dienophiles.[128]

36 Di-π-Methane Rearrangement

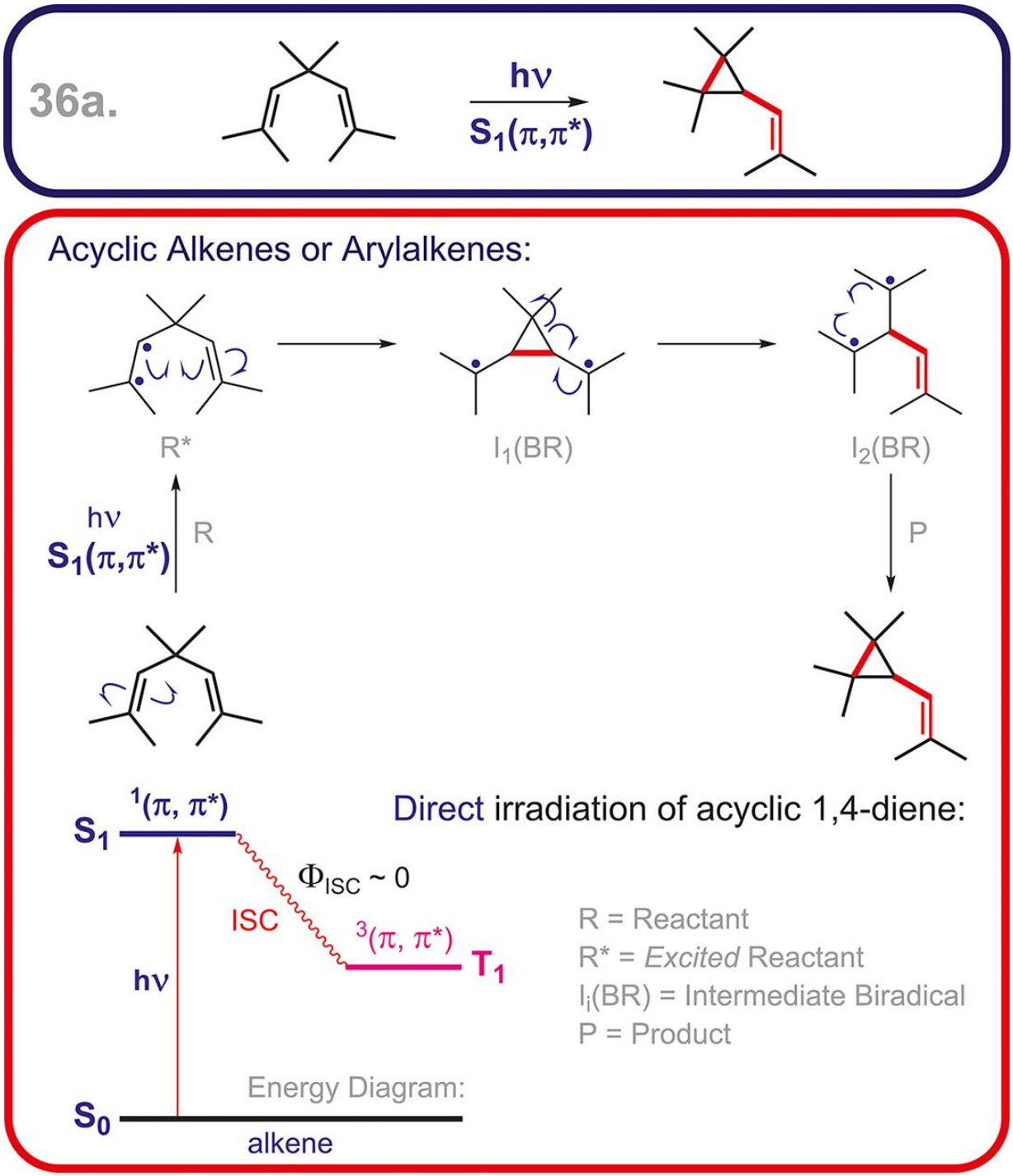


Fig. 36.1: The *di-π-methane rearrangement* mechanism: direct irradiation.[129]

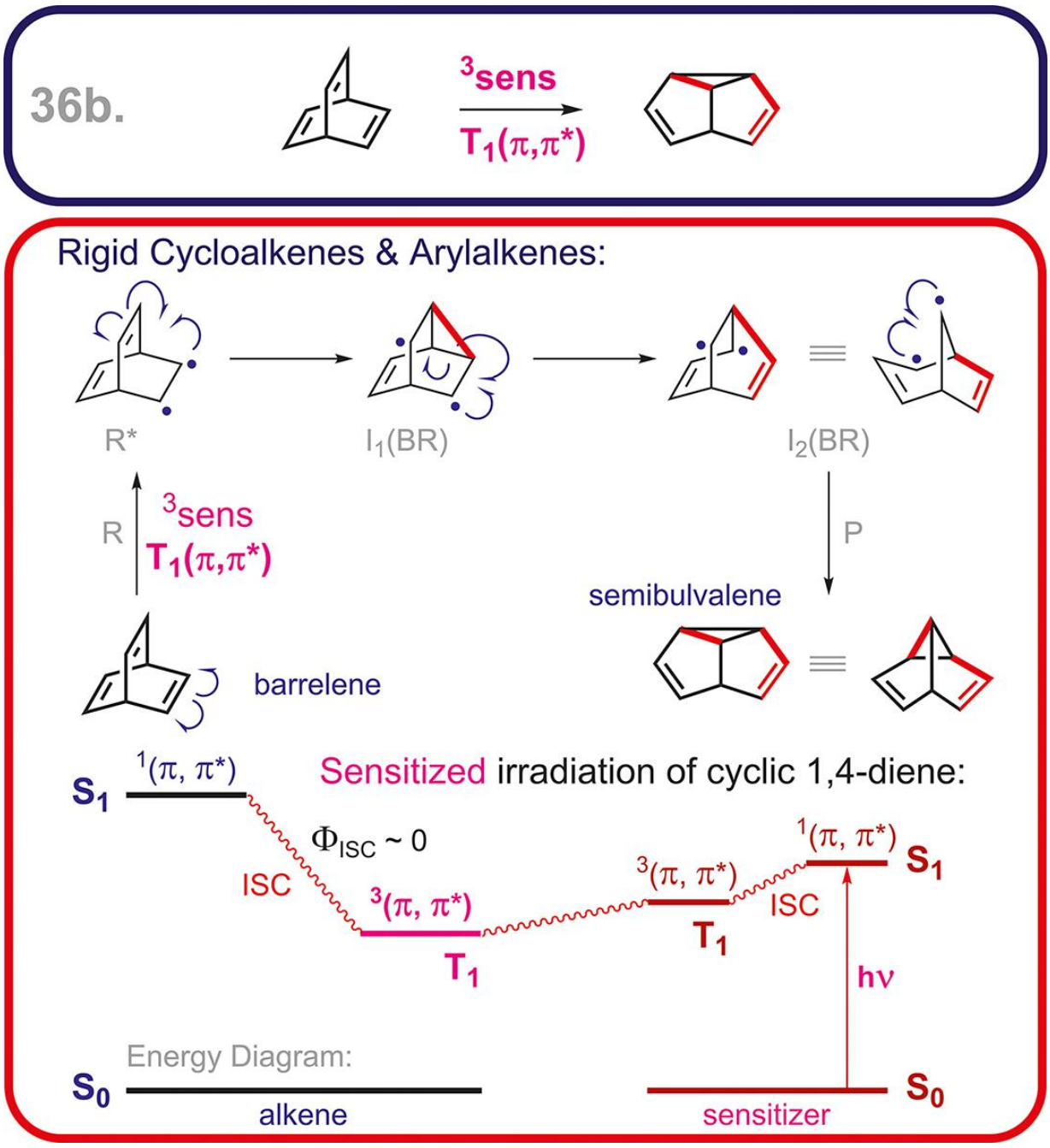


Fig. 36.2: The *di-π-methane rearrangement* mechanism: sensitized irradiation.[130]

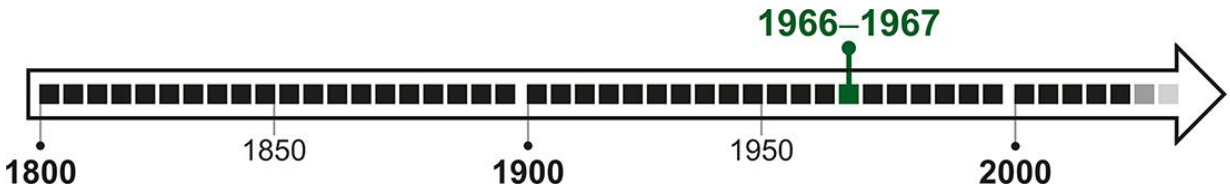


Fig. 36.3: The discovery of the *di-π-methane rearrangement*.[131]

37 Favorskii Rearrangement

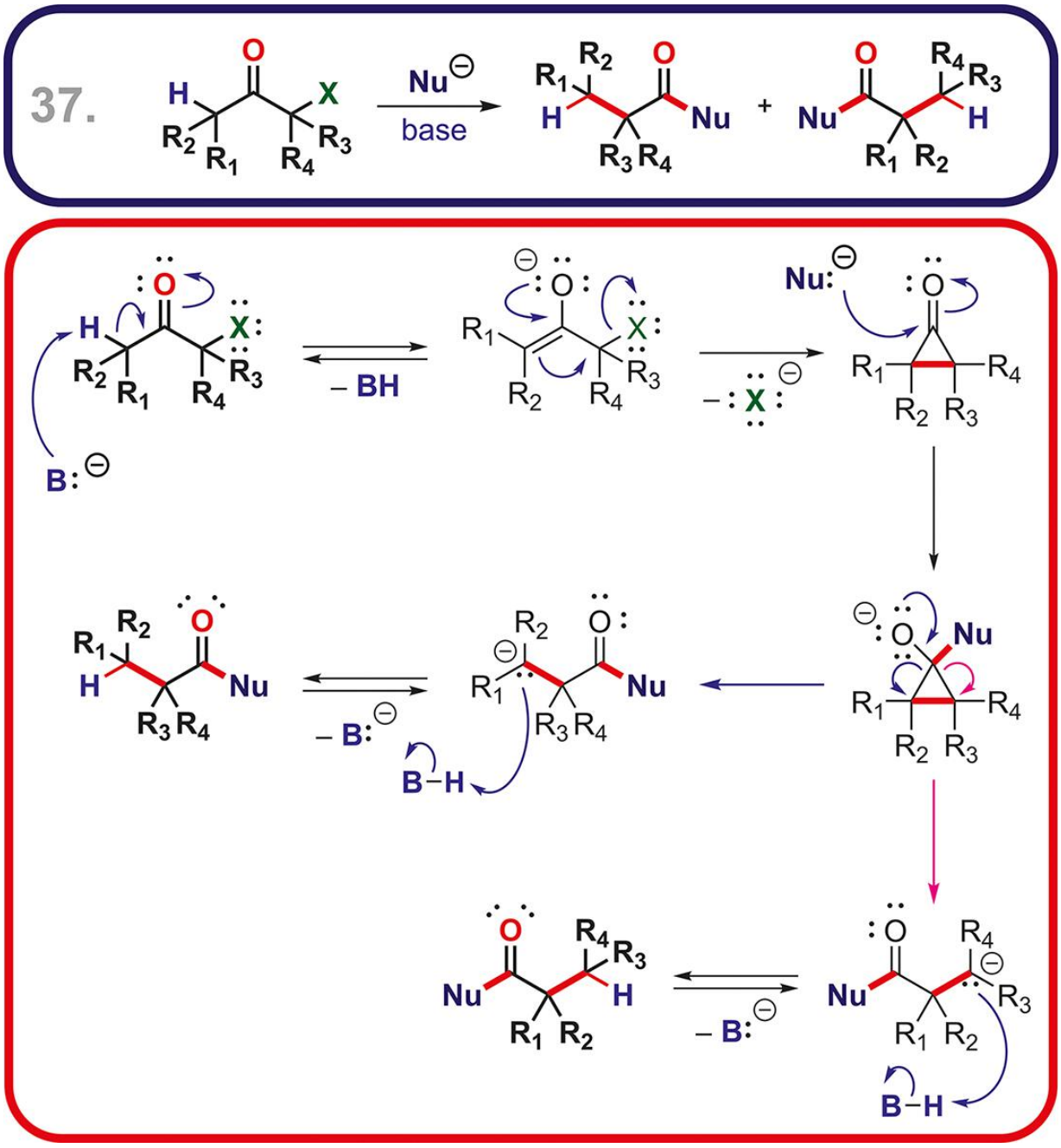


Fig. 37.1: The ***Favorskii*** *rearrangement* mechanism.[132]

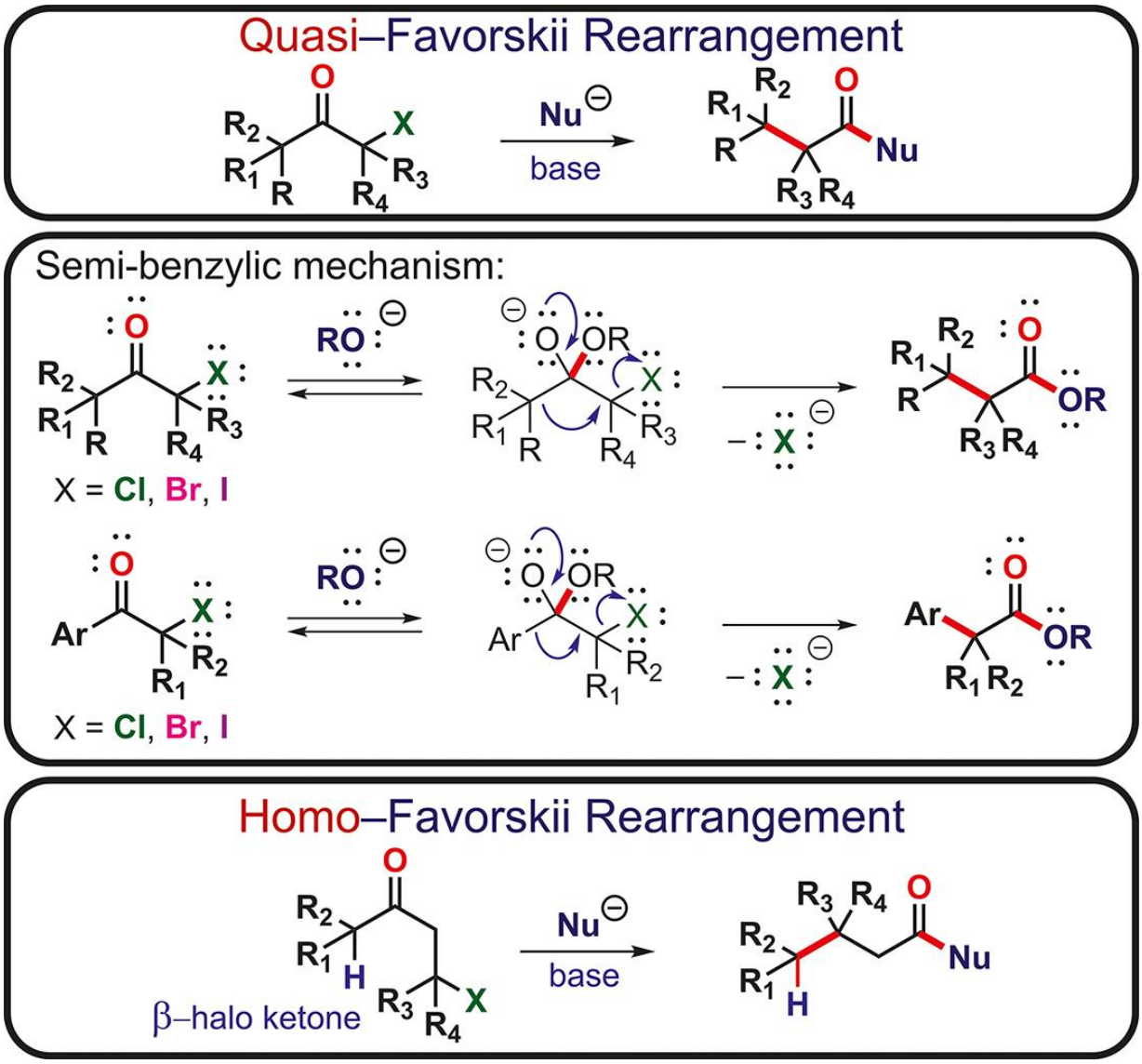


Fig. 37.2: The *quasi-**Favorskii** rearrangement* mechanism and related reactions.[133]

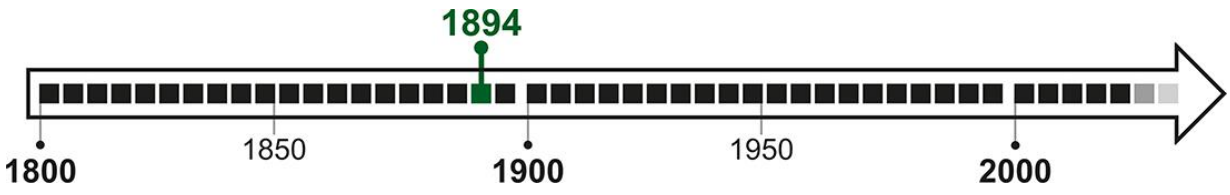


Fig. 37.3: The discovery of the ***Favorskii** rearrangement*.[134]

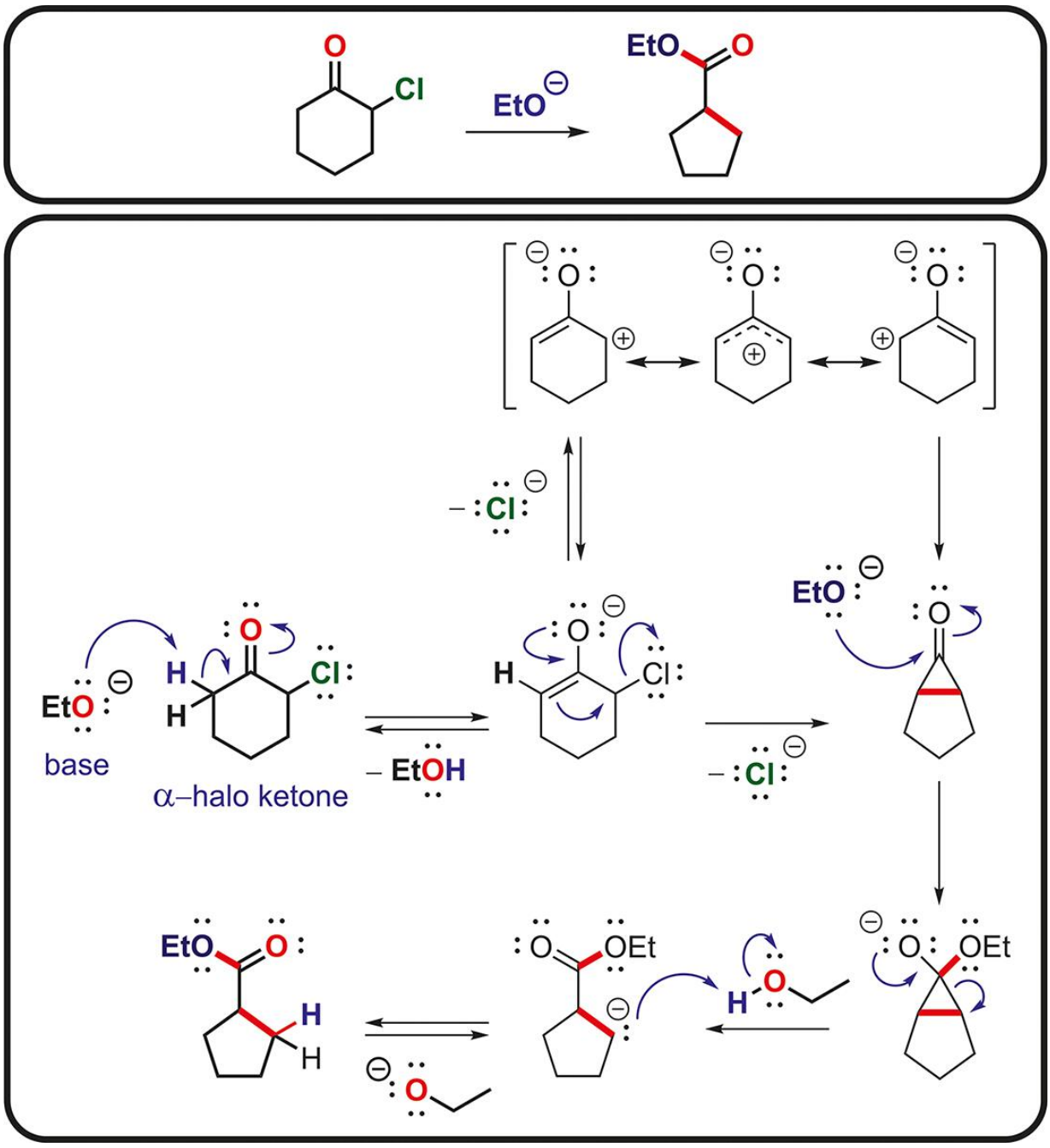


Fig. 37.4: The ***Favorskii*** *rearrangement* mechanism of 2-chlorocyclohexan-1-one.[135]

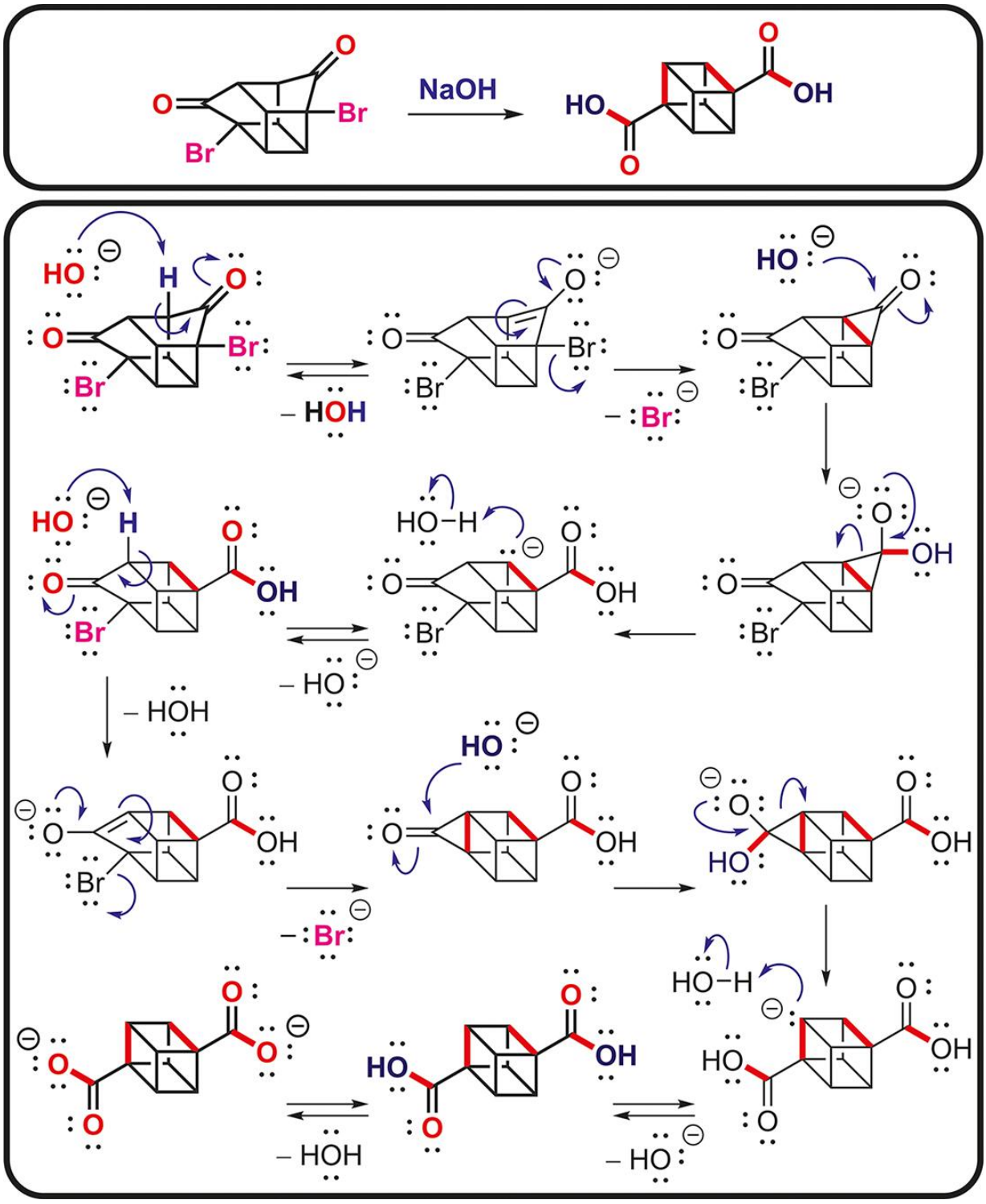
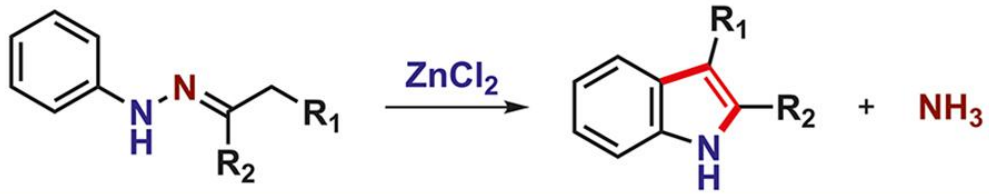


Fig. 37.5: Synthesis of cubane-1,4-dicarboxylic acid.[136]

38 Fischer Indole Synthesis

38.


ZnCl2
NH3

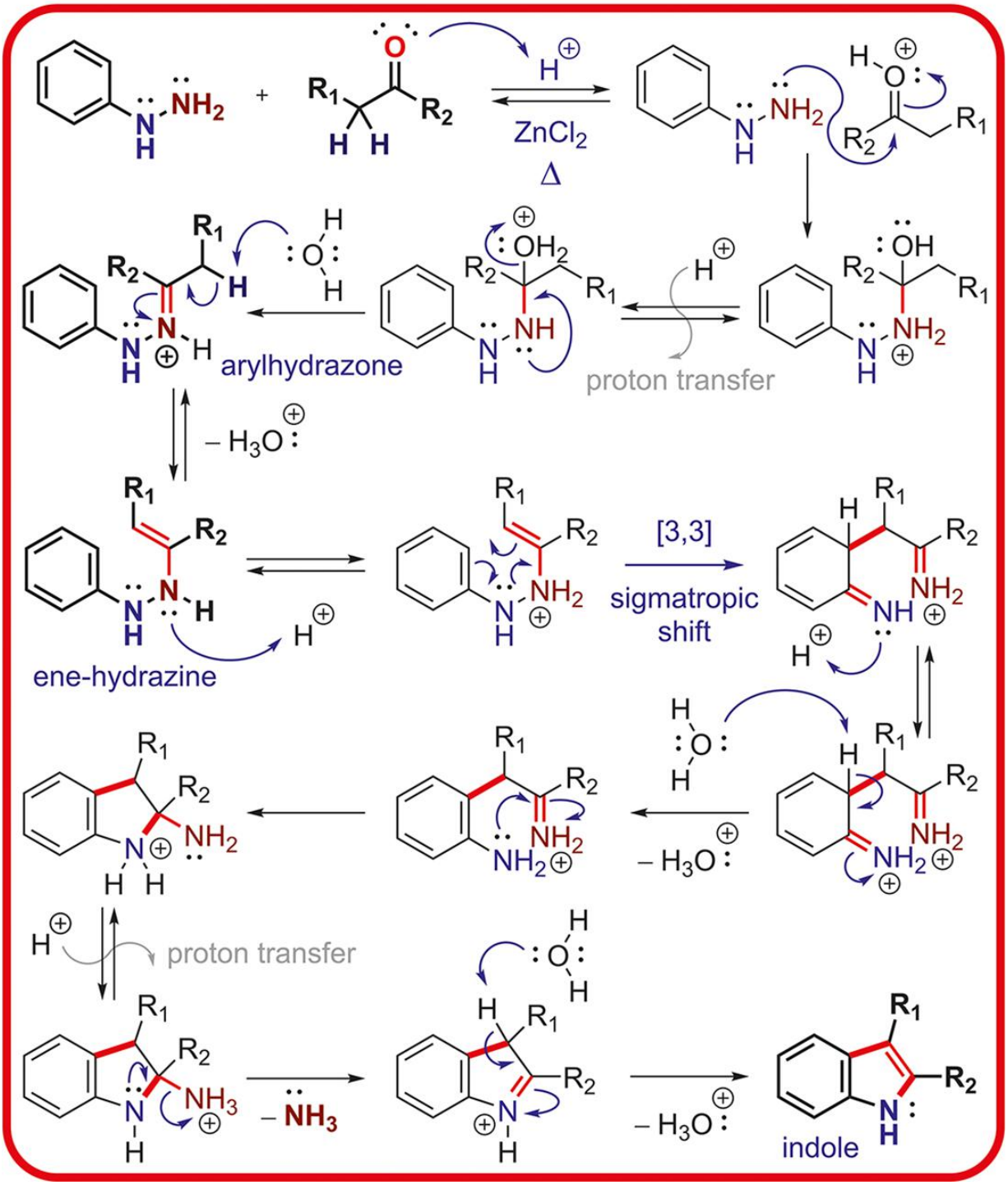

ZnCl2
Δ
arylhydrazone
proton transfer
– H3O
ene-hydrazine
[3,3]
sigmatropic
shift
– H3O
proton transfer
– NH3
– H3O
indole

Fig. 38.1: The ***Fischer*** *indole synthesis* mechanism.[137].

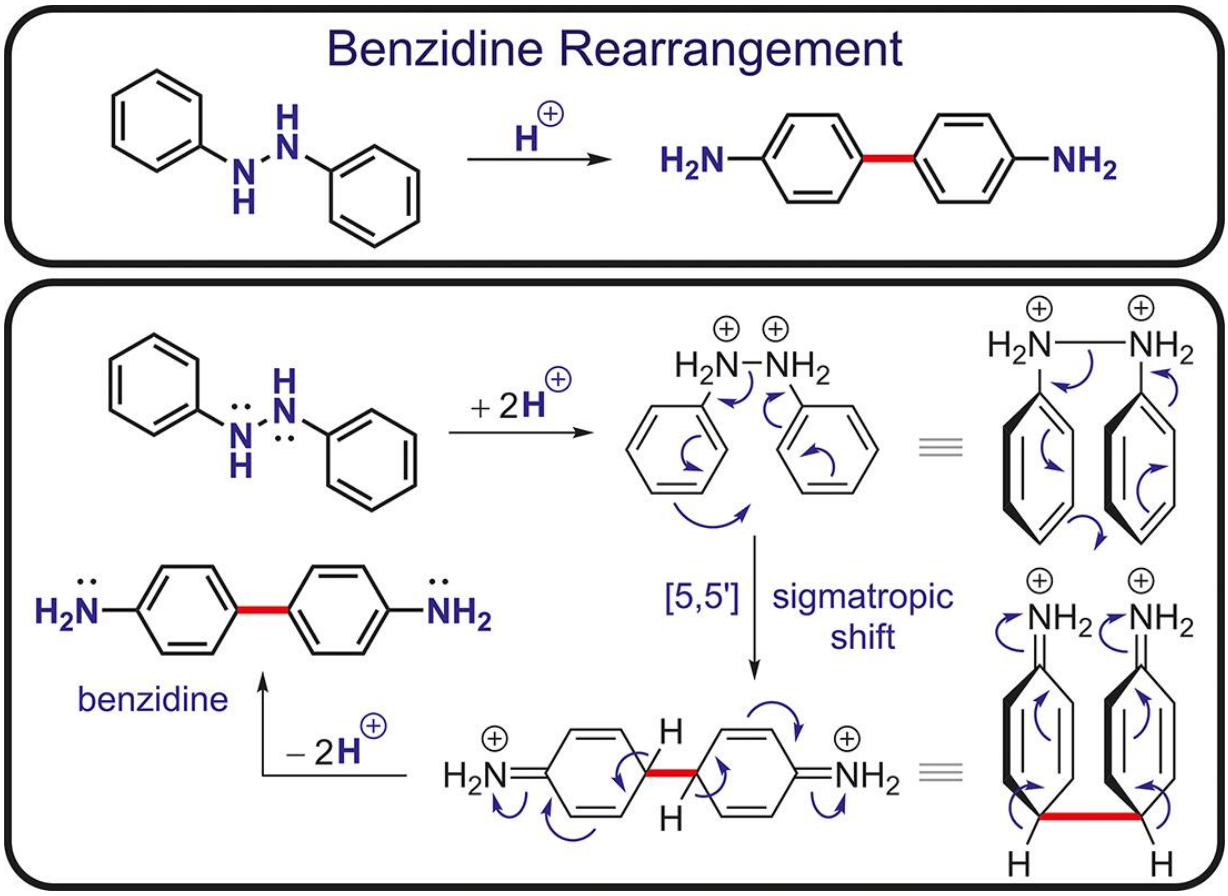


Fig. 38.2: The ***benzidine*** *rearrangement* mechanism.[138]

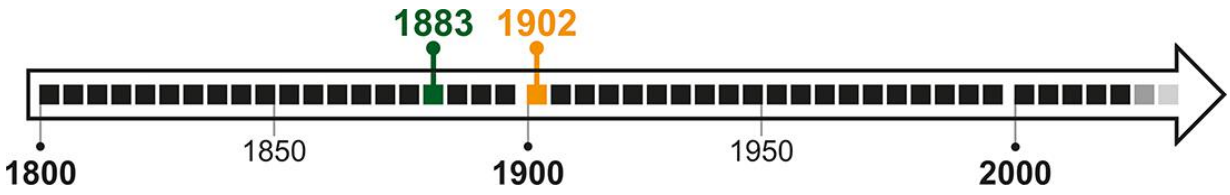


Fig. 38.3: The discovery of the ***Fischer*** *indole synthesis*.[139]

39 Friedel–Crafts Acylation and Alkylation

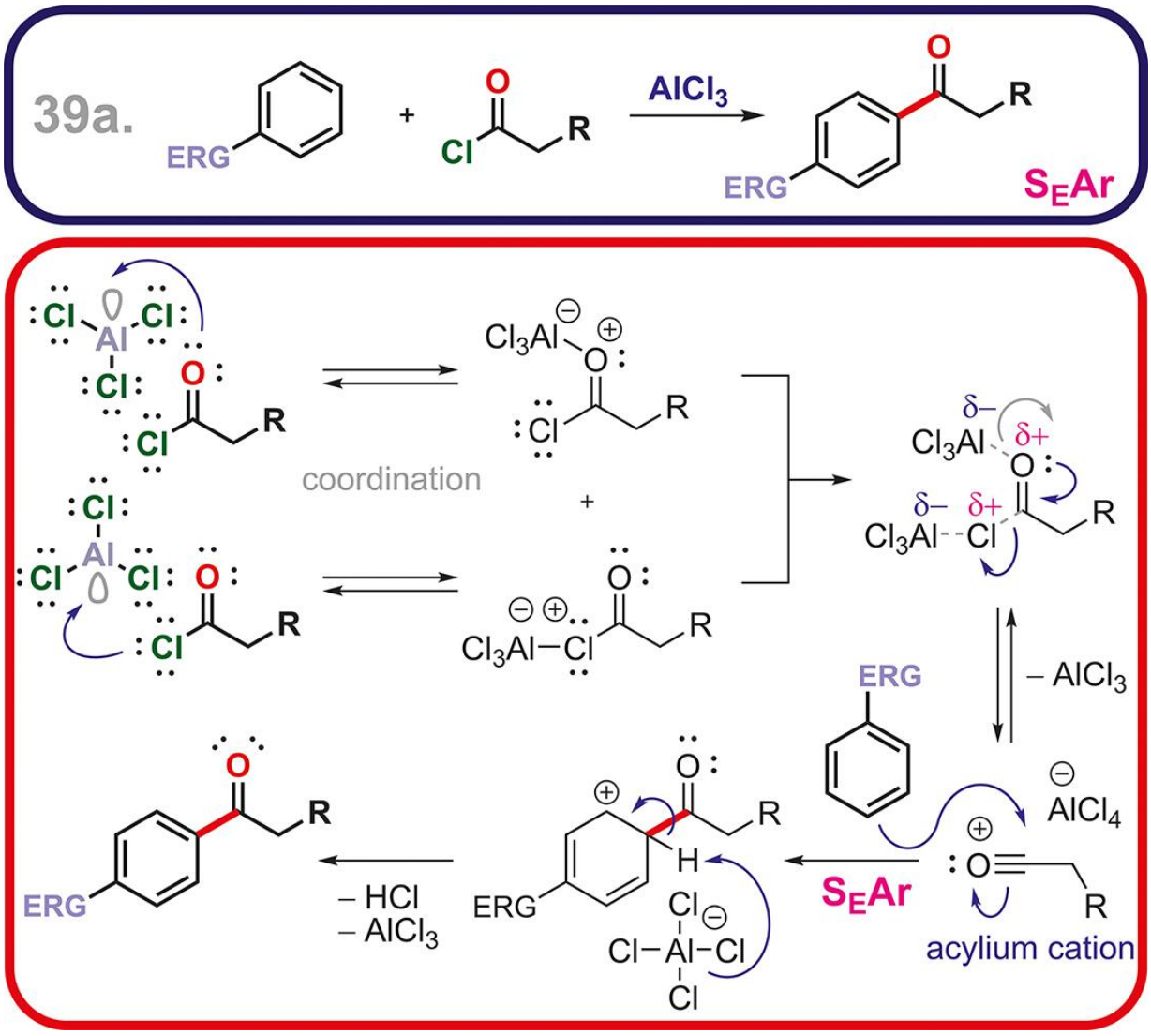


Fig. 39.1: The ***Friedel–Crafts*** *acylation* mechanism.[140]

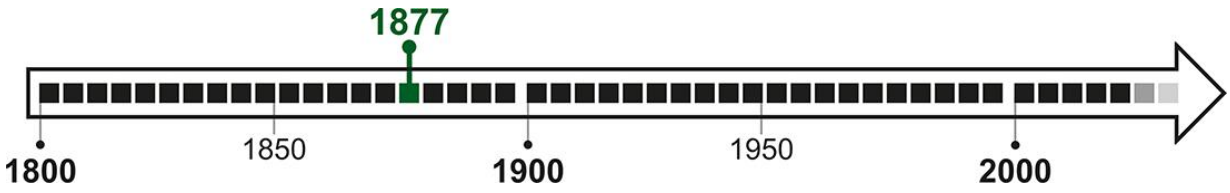


Fig. 39.2: The discovery of the ***Friedel–Crafts*** *acylation*.[141]

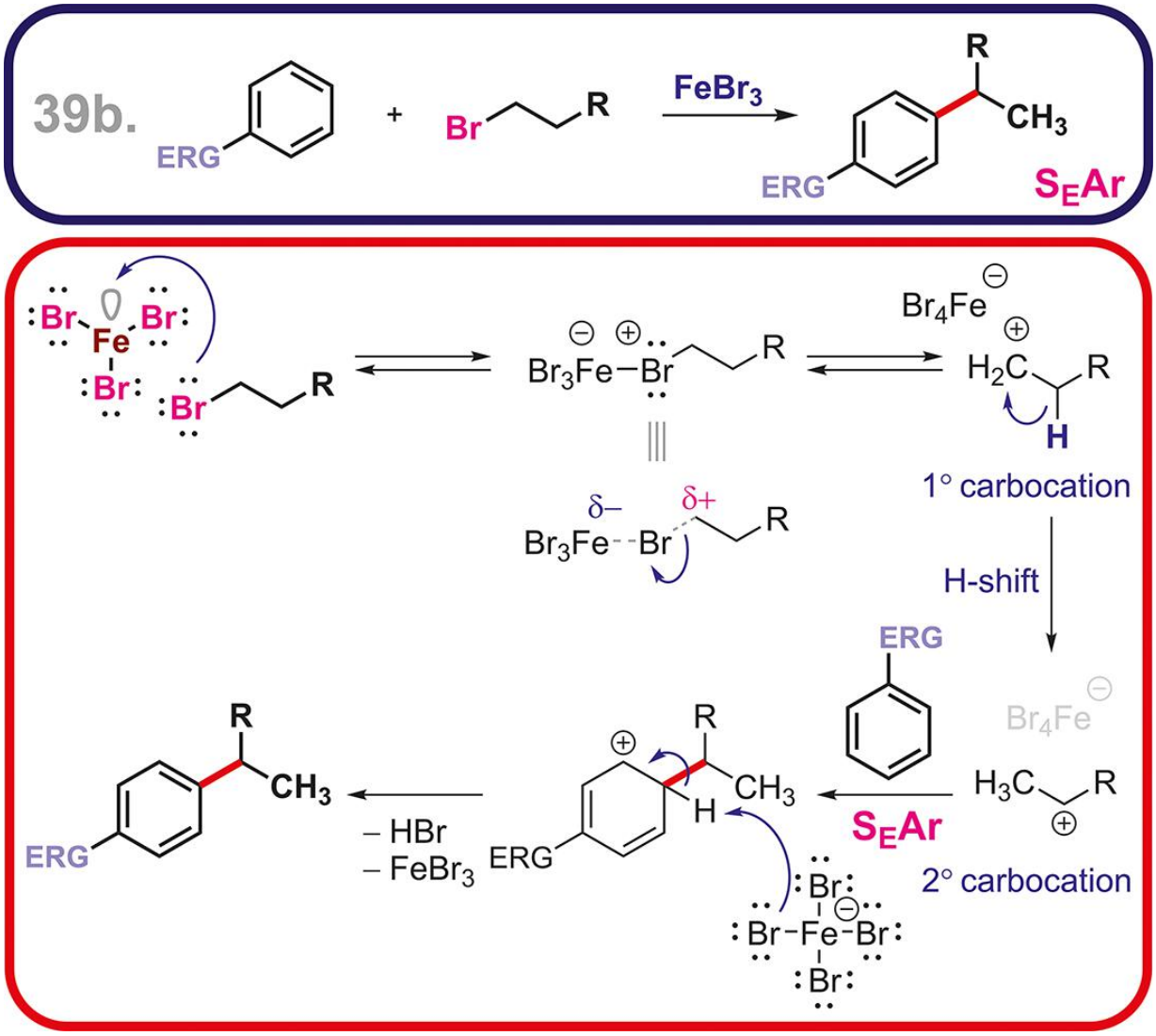


Fig. 39.3: The ***Friedel–Crafts*** *alkylation* mechanism.[142]

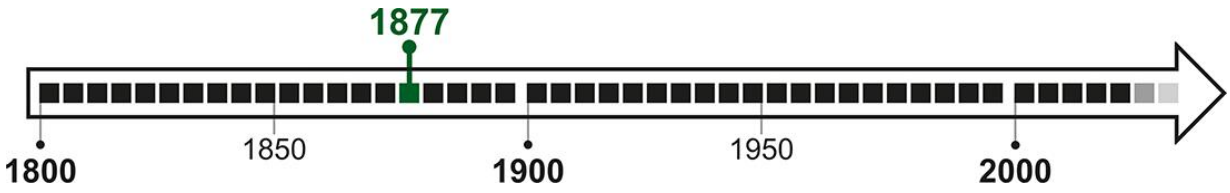


Fig. 39.4: The discovery of the ***Friedel–Crafts*** *alkylation*.[143]

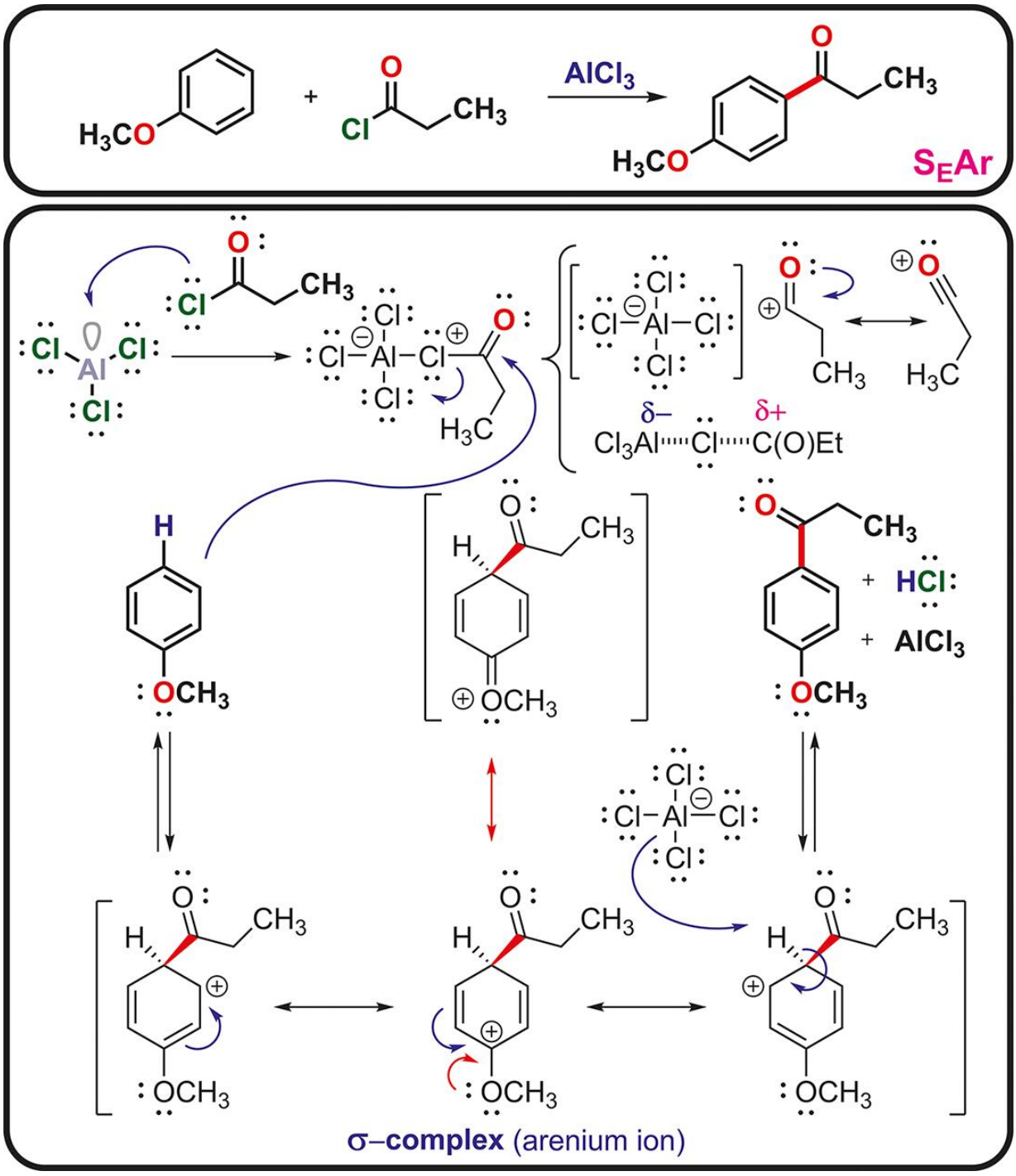


Fig. 39.5: The ***Friedel–Crafts*** *acylation* mechanism of anisole.[144]

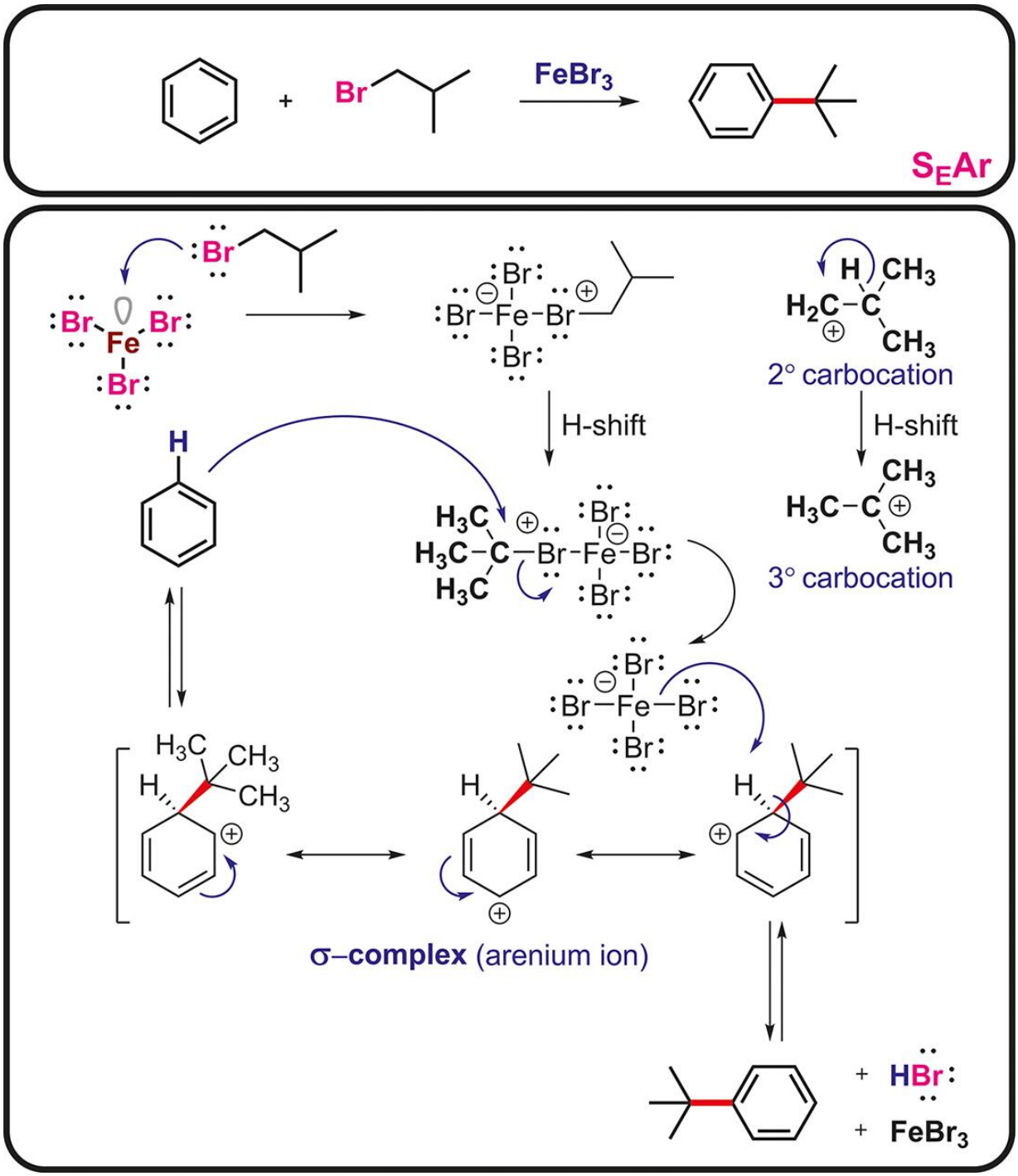


Fig. 39.6: The ***Friedel–Crafts*** *alkylation* mechanism of benzene.[145]

40 Gabriel Synthesis

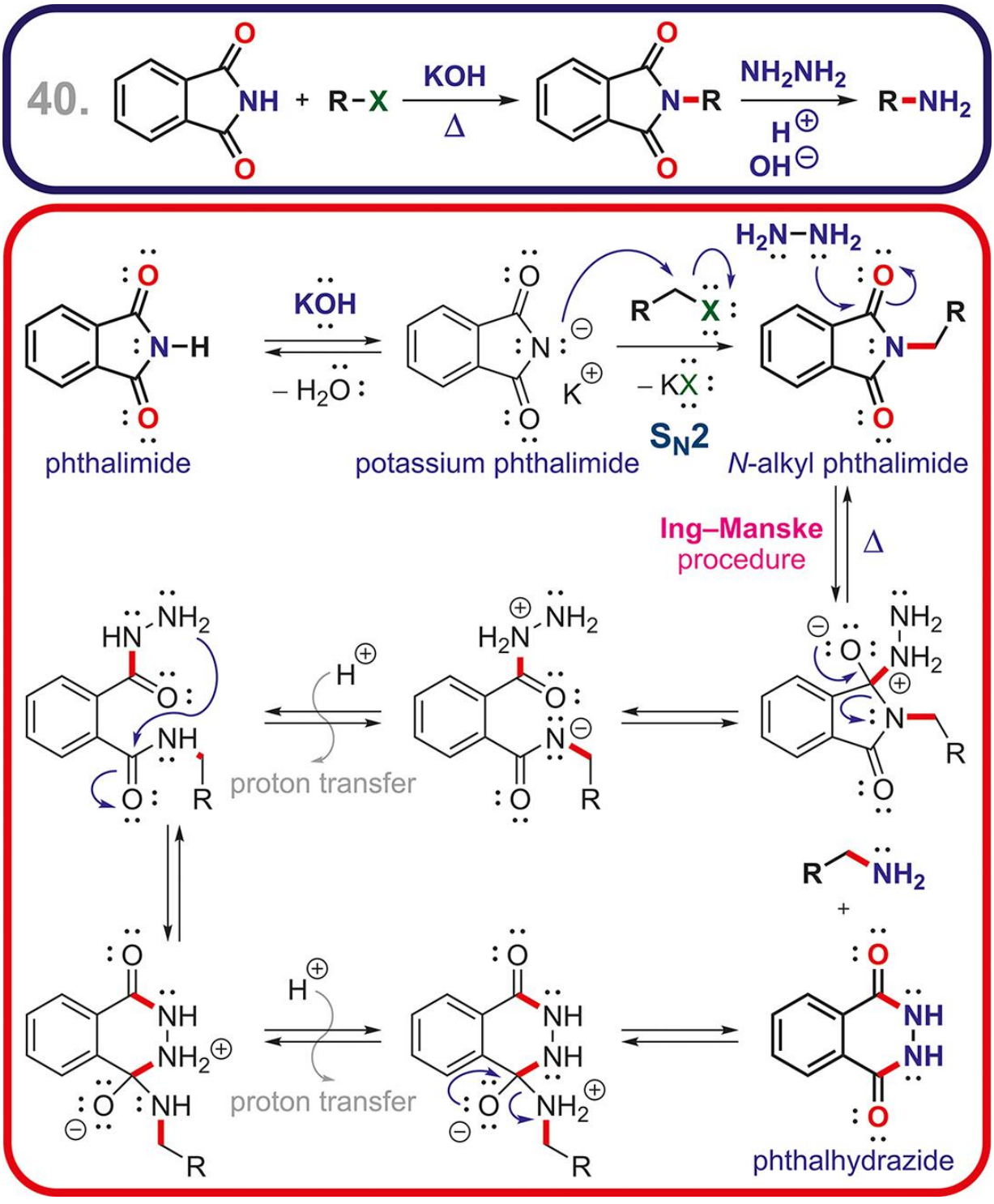


Fig. 40.1: The ***Gabriel*** *synthesis* mechanism.[146].

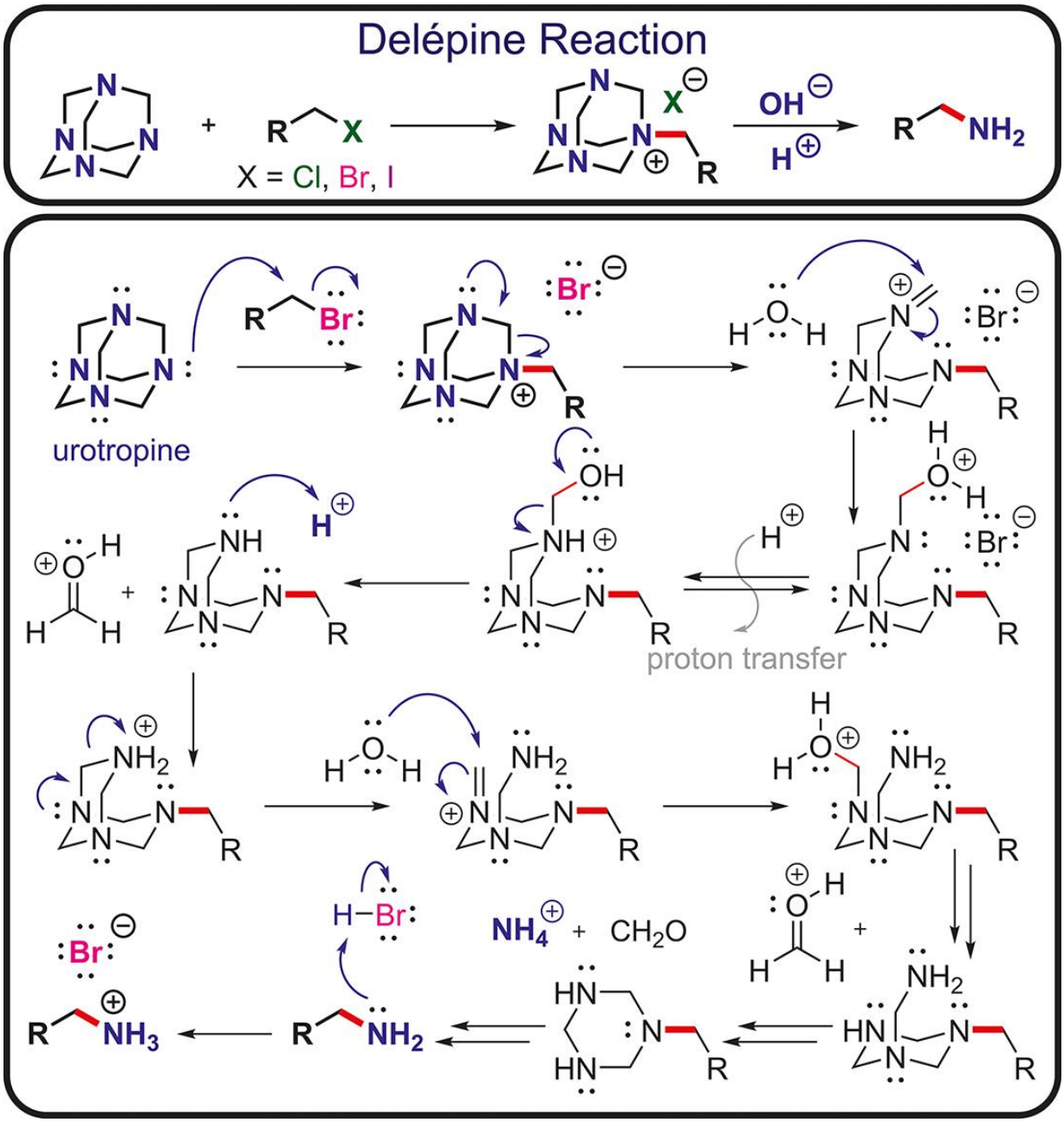


Fig. 40.2: The ***Delépine*** *reaction* mechanism.[147]

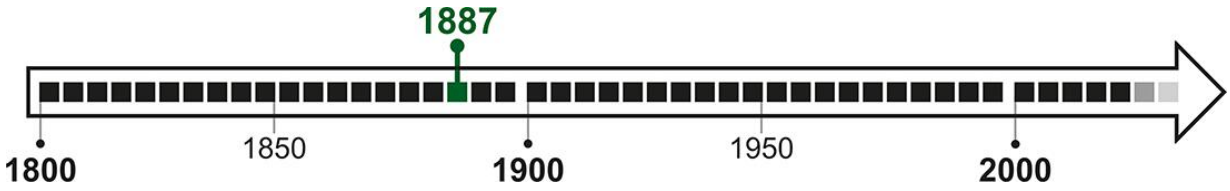


Fig. 40.3: The discovery of the ***Gabriel*** *synthesis*.[148]

41 Gewald Reaction

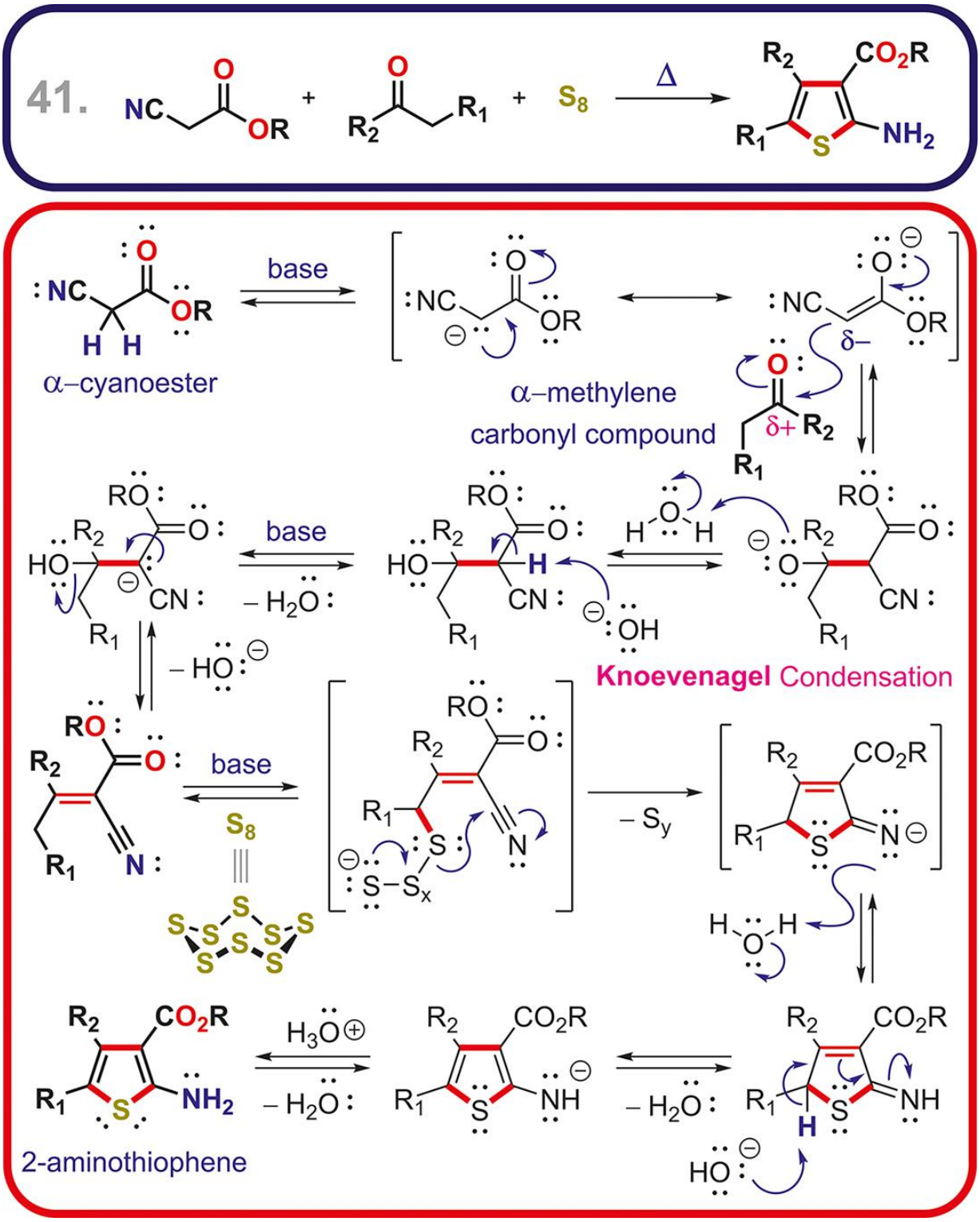


Fig. 41.1: The ***Gewald*** *reaction* mechanism.[149]

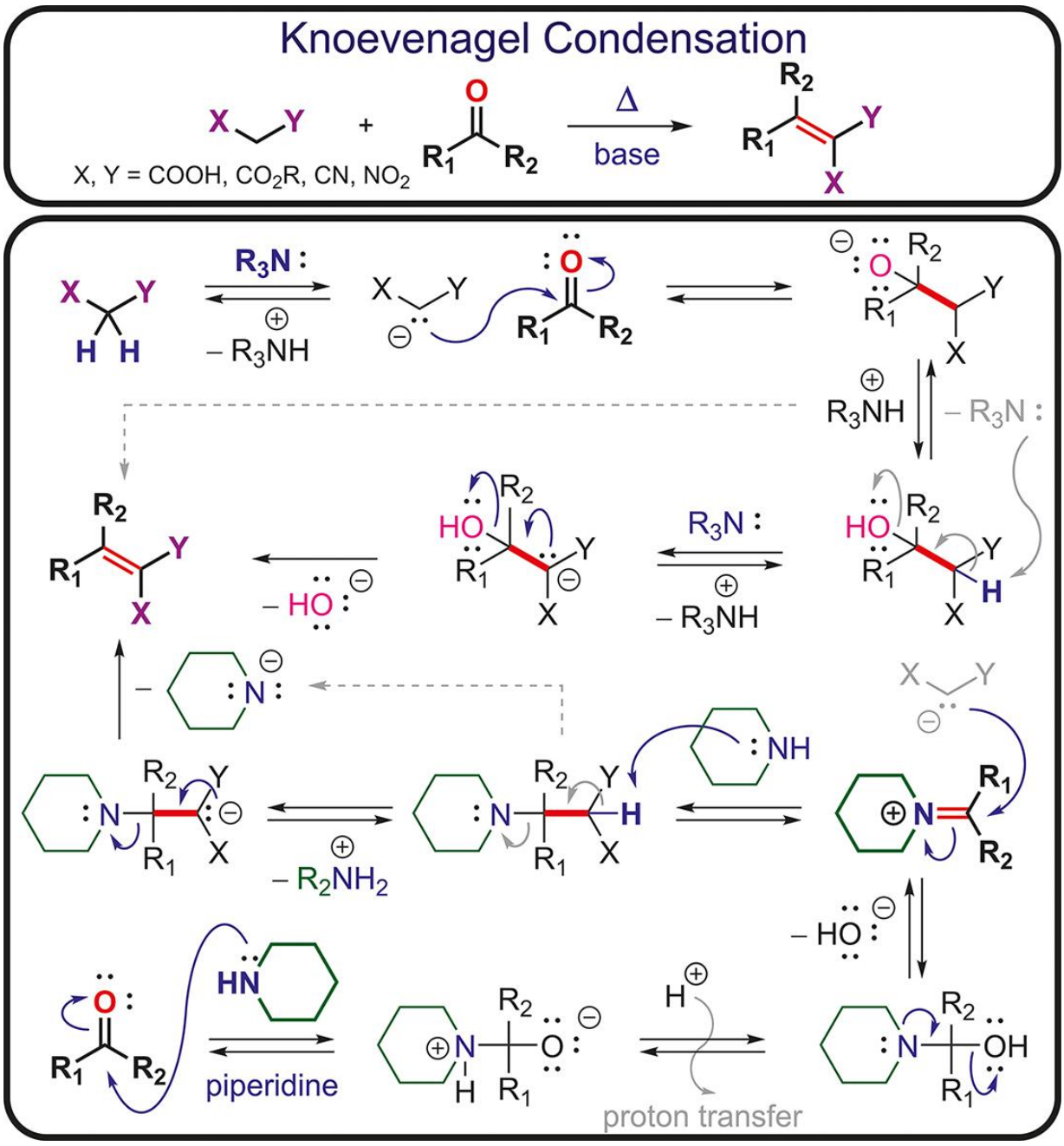


Fig. 41.2: The ***Knoevenagel*** *condensation* mechanism.[150]

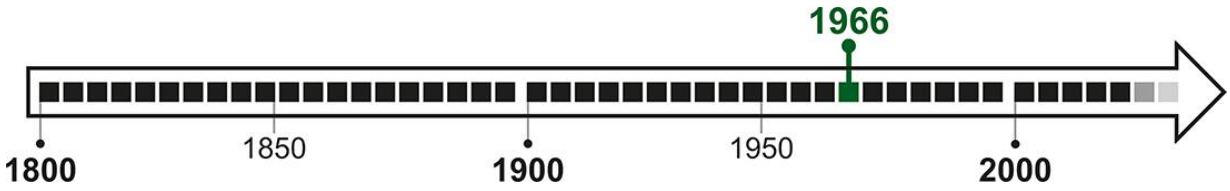


Fig. 41.3: The discovery of the ***Gewald*** *reaction*.[151]

42 Glaser–Eglinton–Hay Coupling

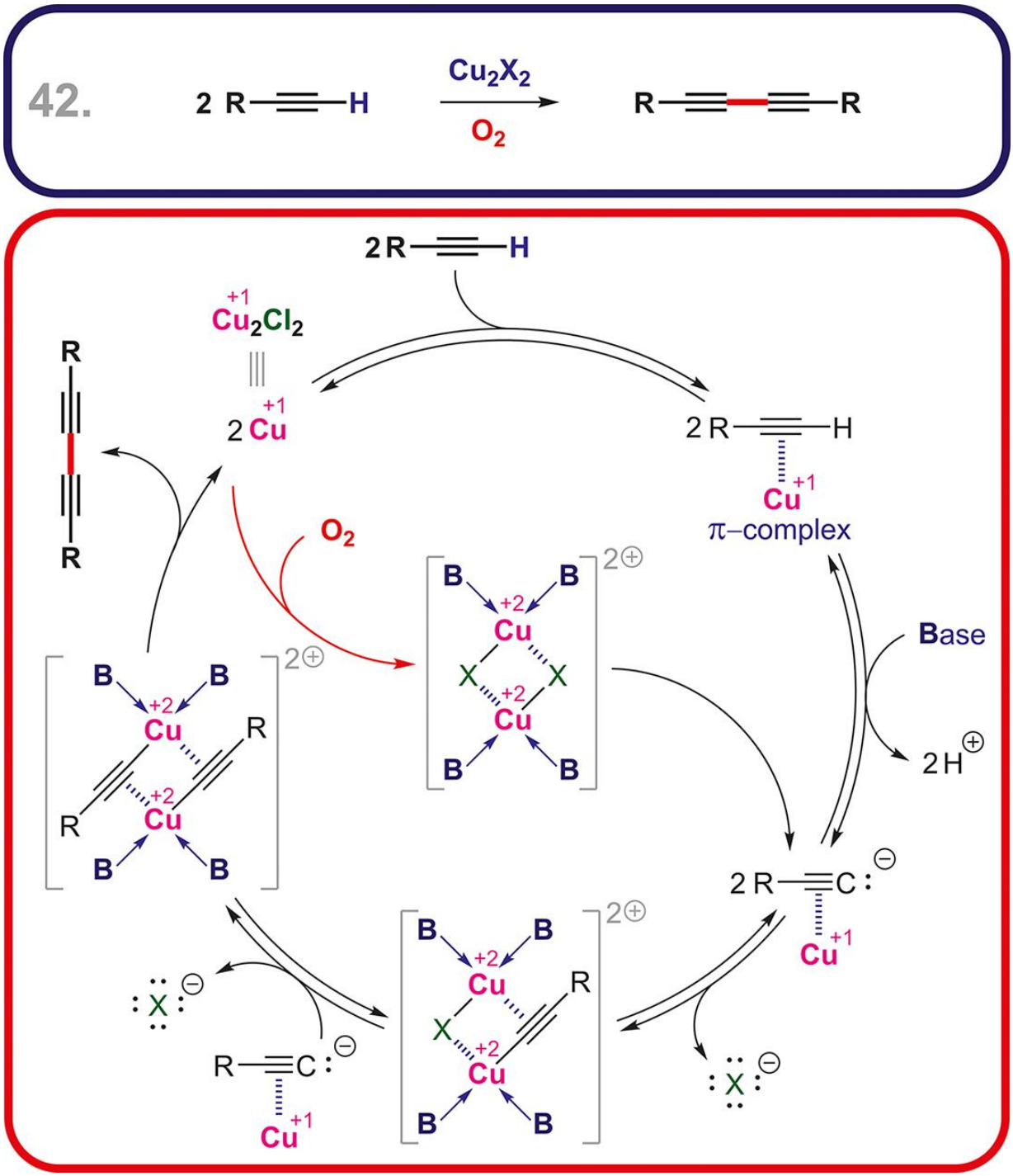


Fig. 42.1: The ***Glaser–Eglinton–Hay*** *coupling* mechanism.[152].

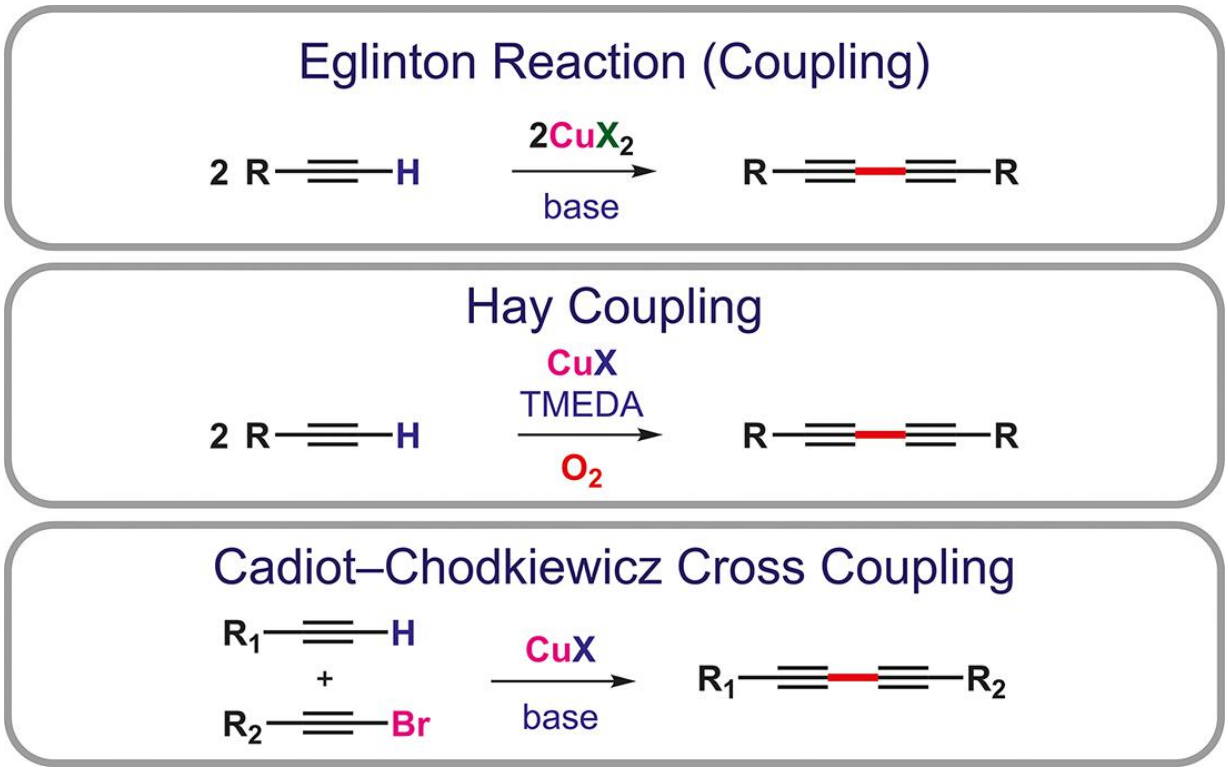


Fig. 42.2: Reactions related to the ***Glaser–Eglinton–Hay*** *coupling*.[153]

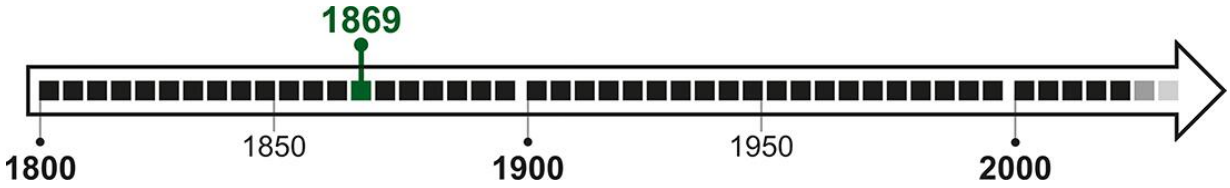


Fig. 42.3: The discovery of the ***Glaser–Eglinton–Hay*** *coupling*.[154]

43 Grignard Reaction

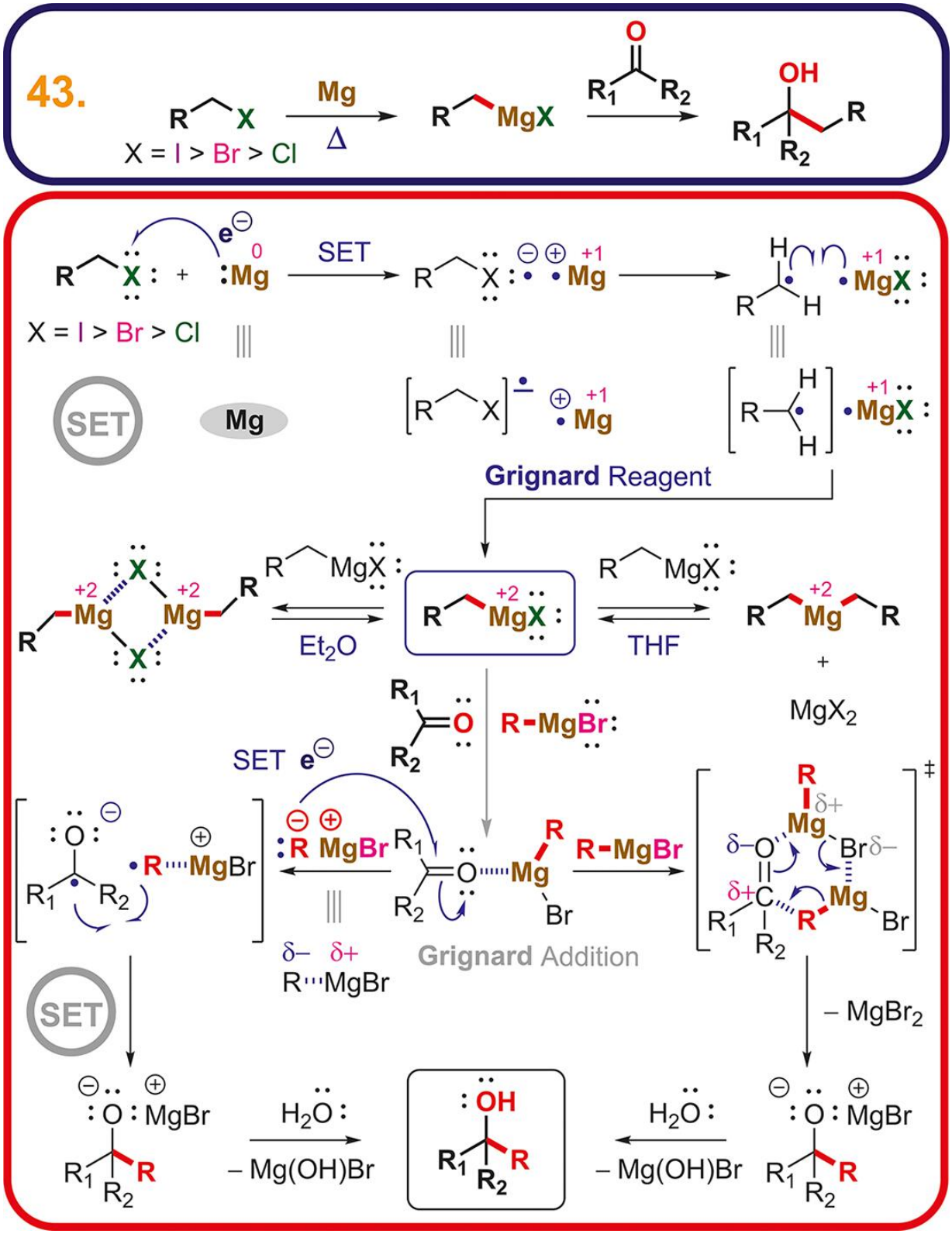


Fig. 43.1: The ***Grignard*** *reaction* mechanism.[155].

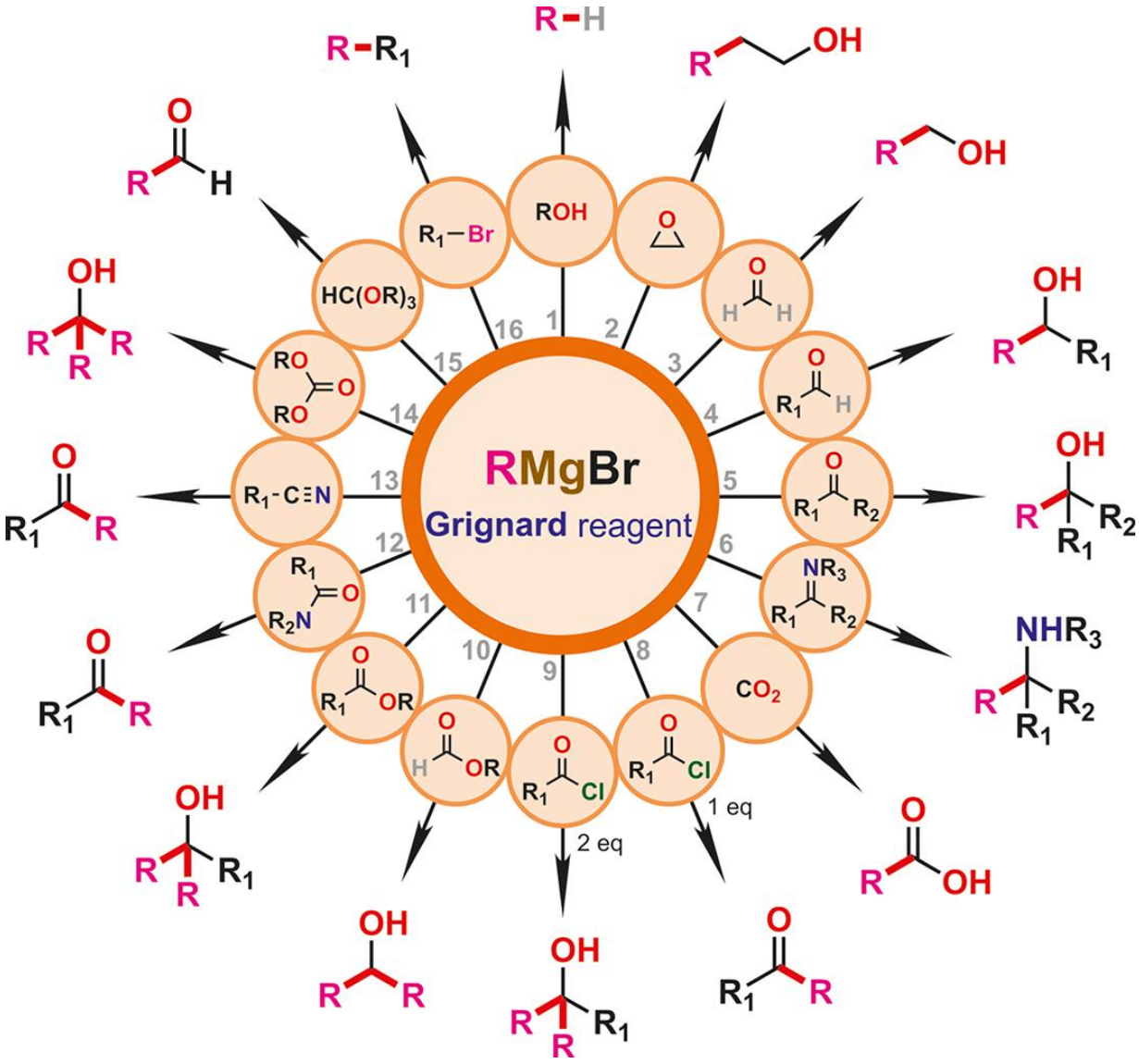


Fig. 43.2: Synthetic versatility of the ***Grignard*** *reagent*.[156]

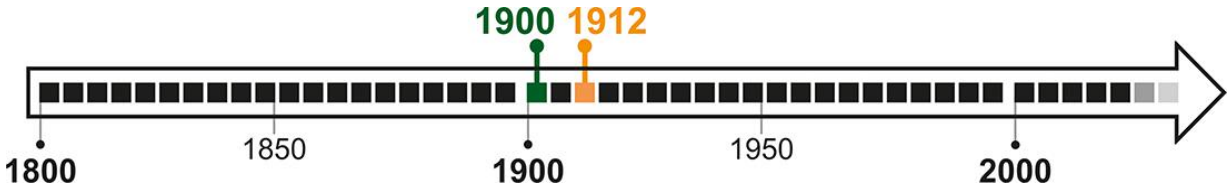


Fig. 43.3: The discovery of the ***Grignard*** *reaction*.[157].

44 Grob Fragmentation

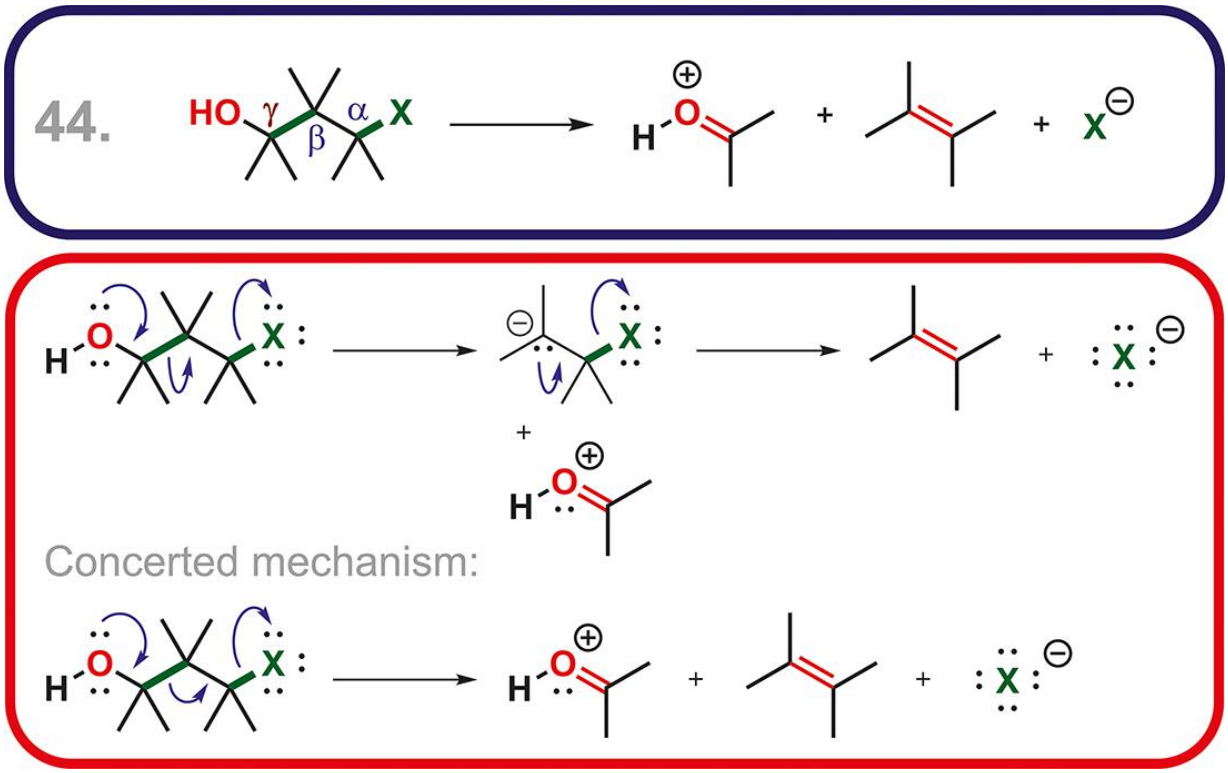


Fig. 44.1: The ***Grob*** *fragmentation* mechanism.[158]

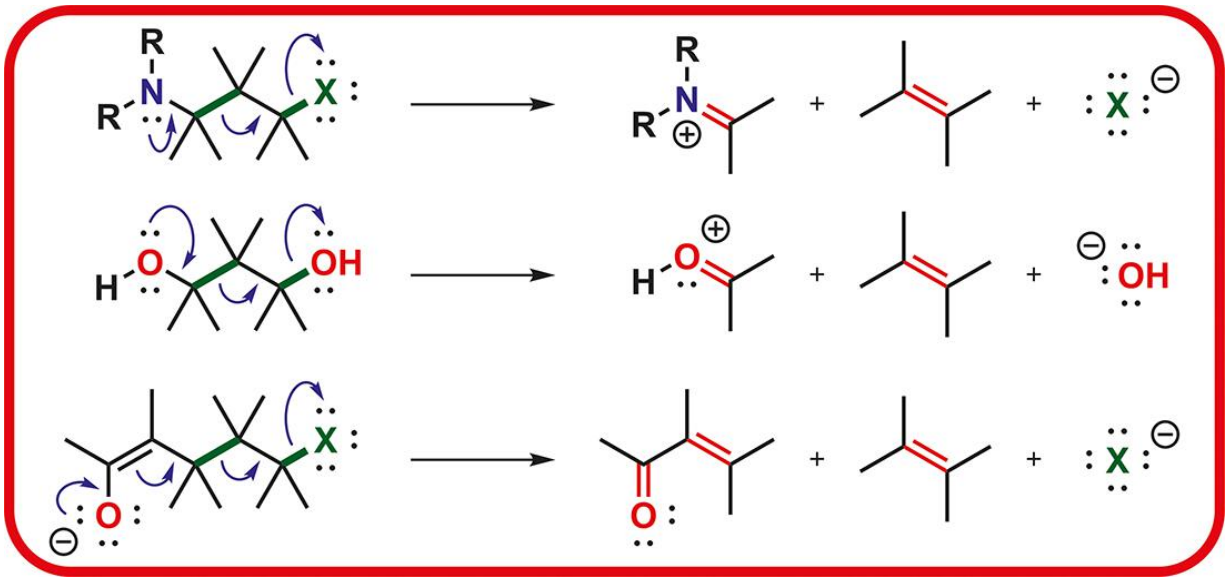


Fig. 44.2: Variations of the ***Grob*** *fragmentation*.[159].

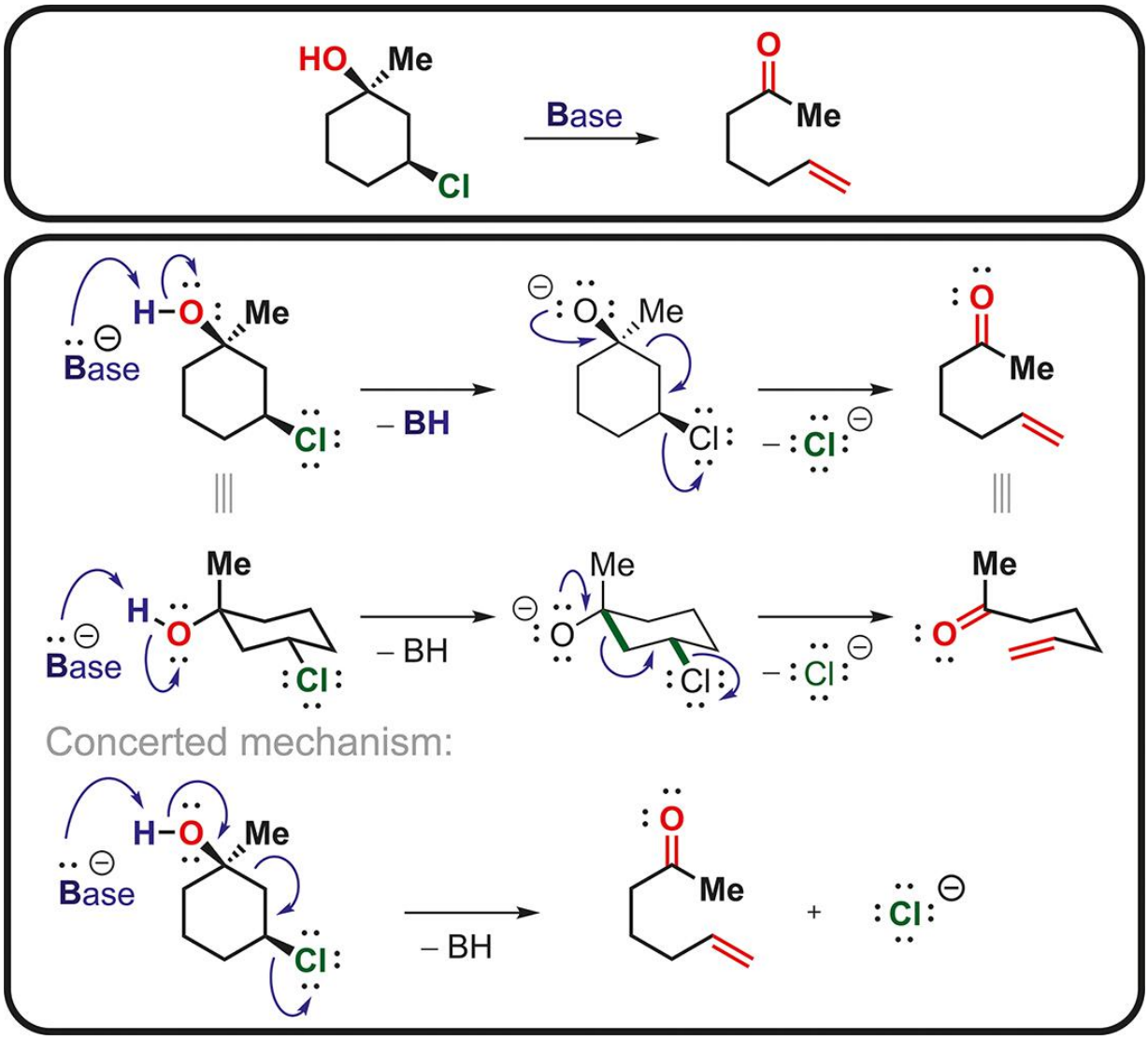


Fig. 44.3: The ***Grob*** *fragmentation* mechanism of (1*R*,3*S*)-3-chloro-1-methylcyclohexan-1-ol.[160]

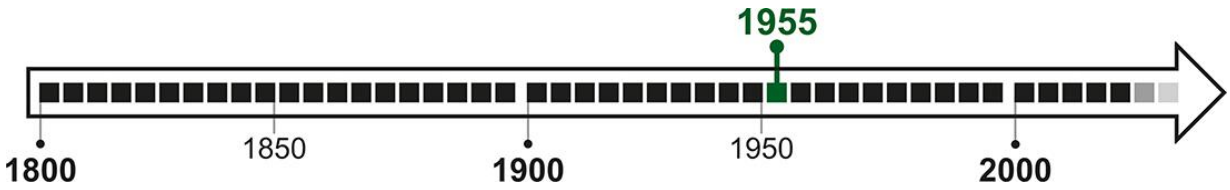


Fig. 44.4: The discovery of the ***Grob*** *fragmentation*.[161]

45 Haloform Reaction

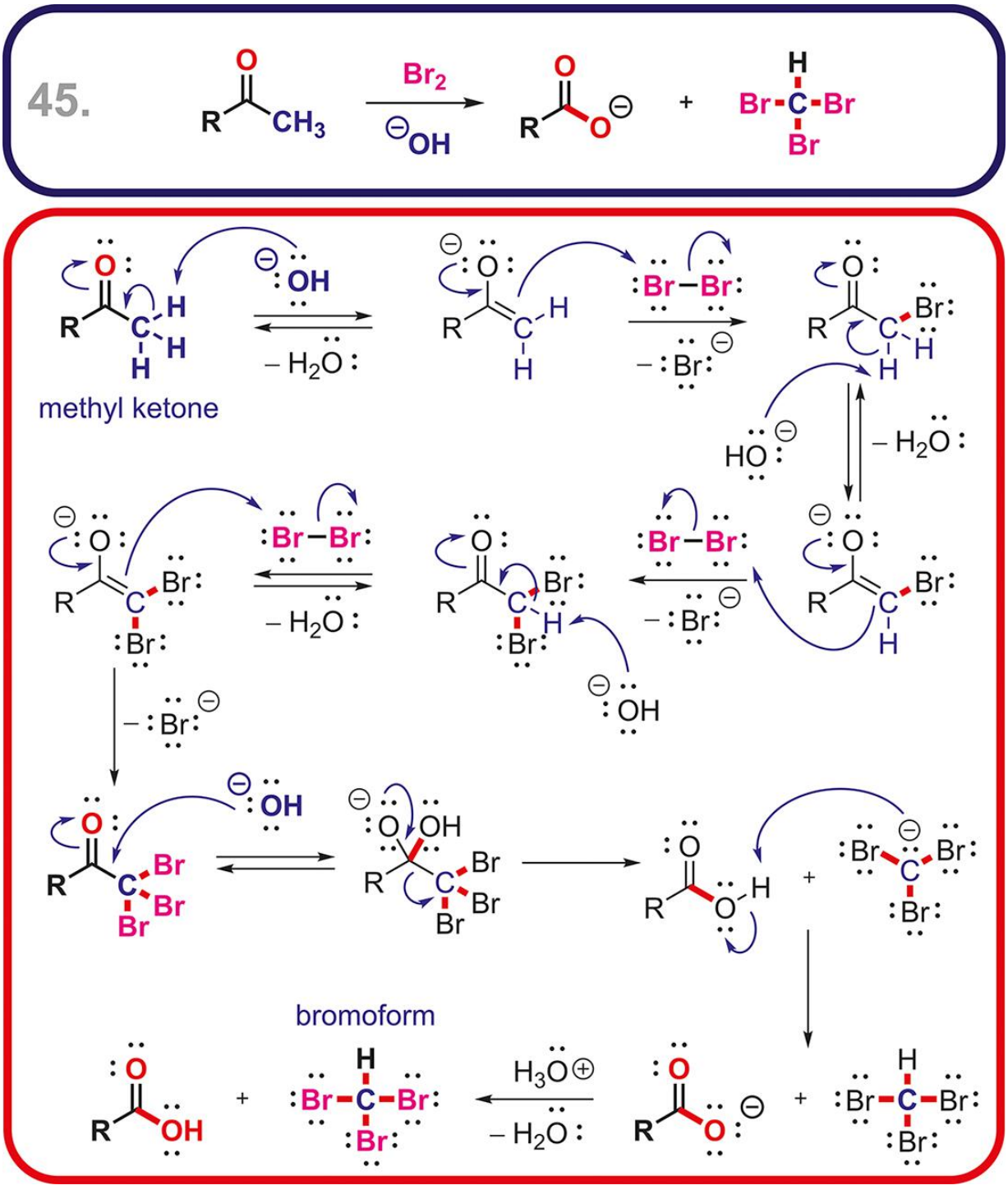


Fig. 45.1: The *haloform reaction* mechanism.[162]

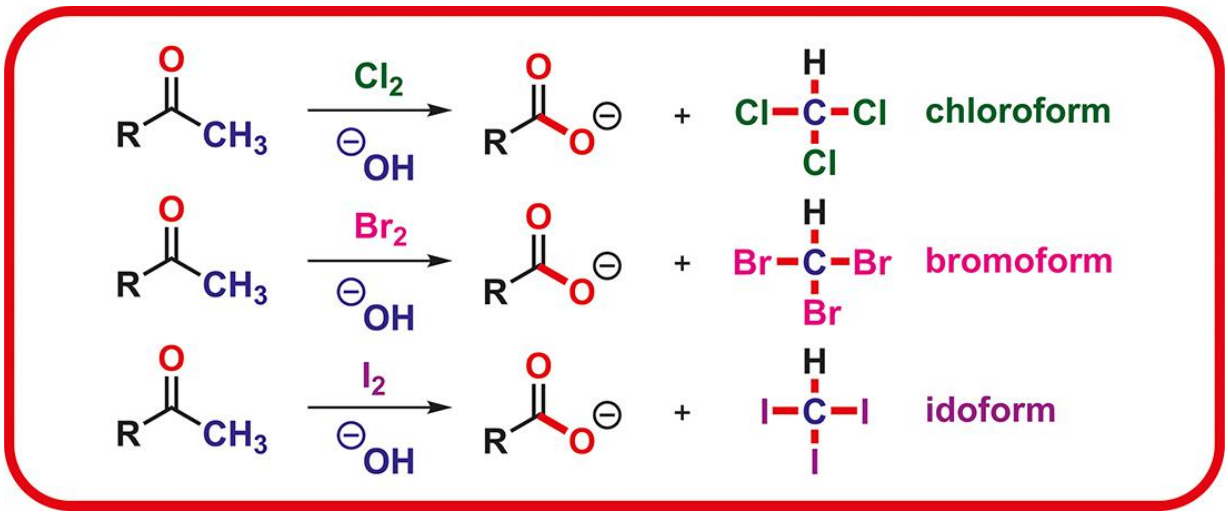


Fig. 45.2: Variations of the *haloform reaction*.[163]

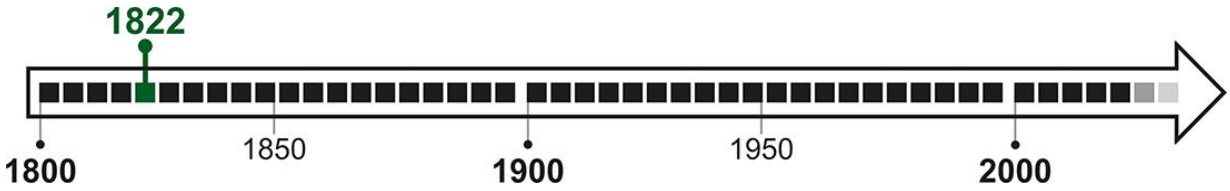


Fig. 45.3: The discovery of the *haloform reaction*.[164]

46 Heck Cross-Coupling

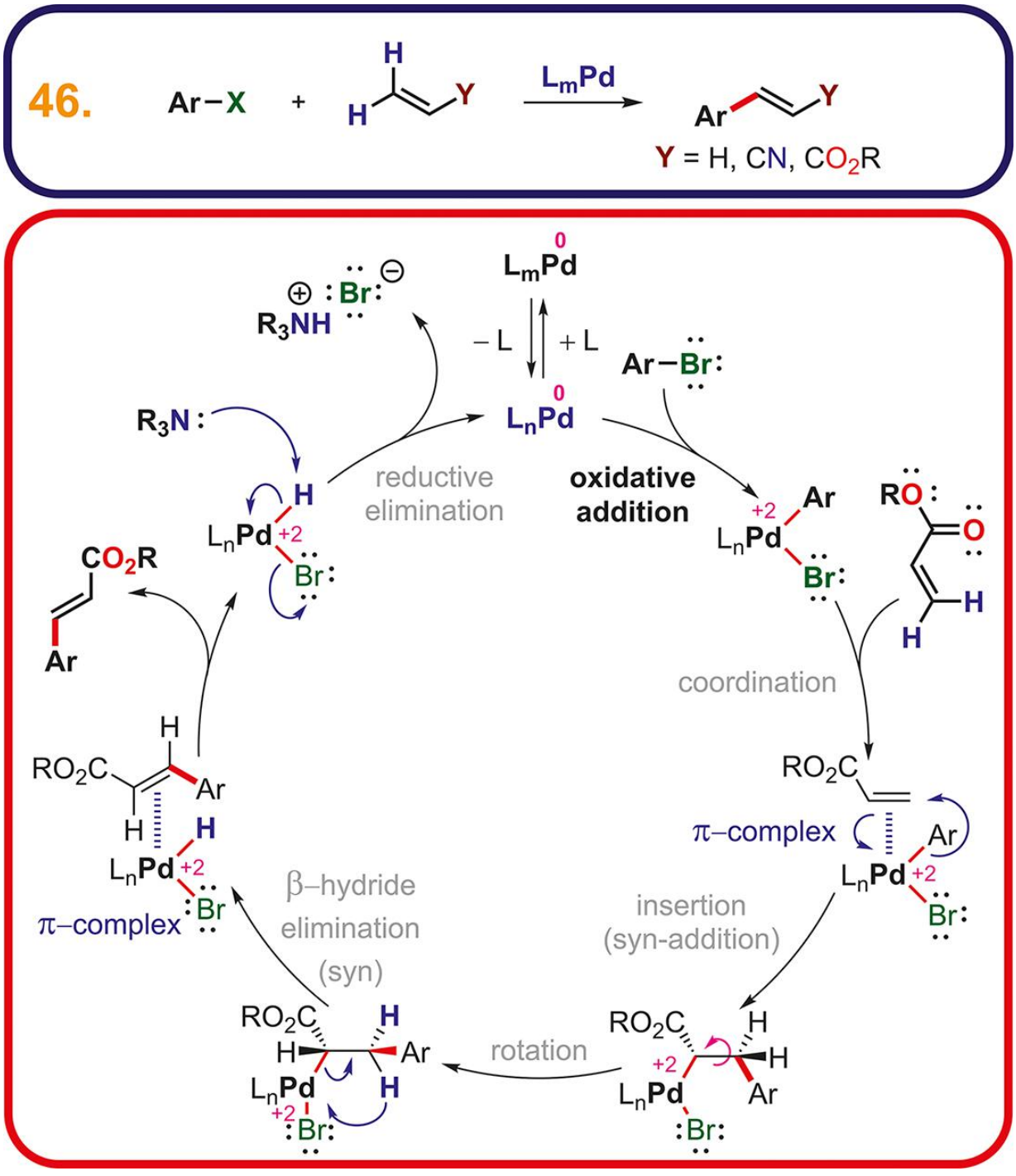


Fig. 46.1: The ***Heck*** *cross-coupling* mechanism.[165]

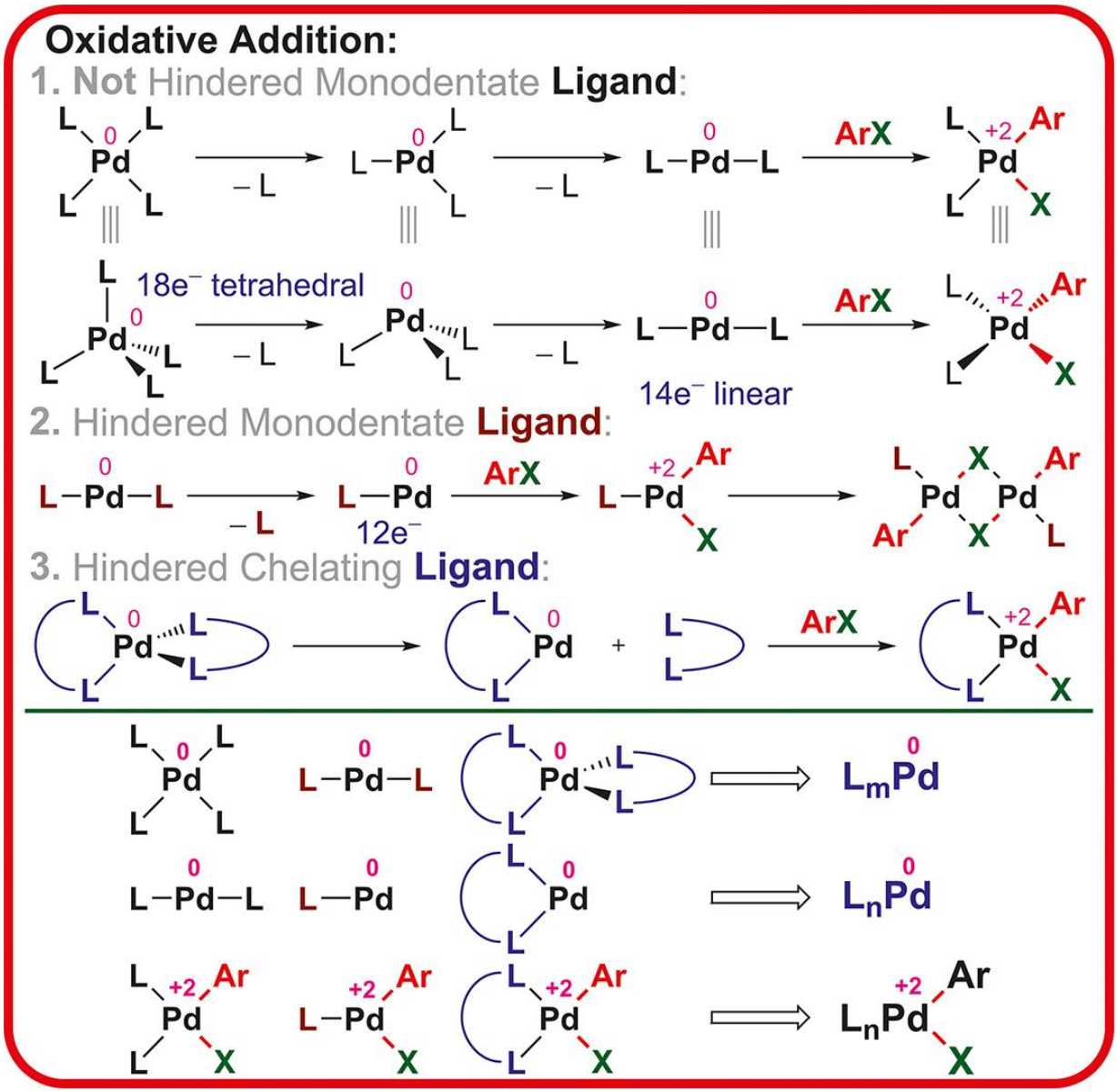


Fig. 46.2: General illustration of the *oxidative addition* step.[166]

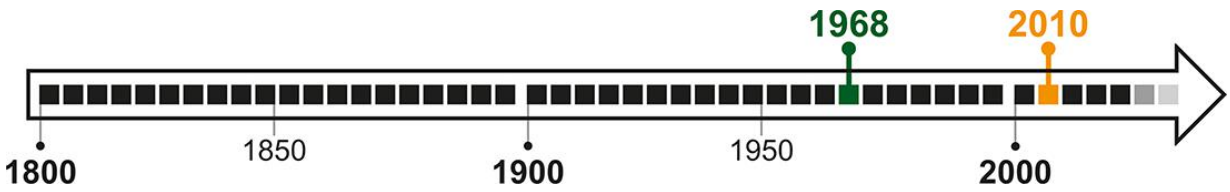


Fig. 46.3: The discovery of the ***Heck*** *cross-coupling*.[167]

47 Hell–Volhard–Zelinsky Reaction

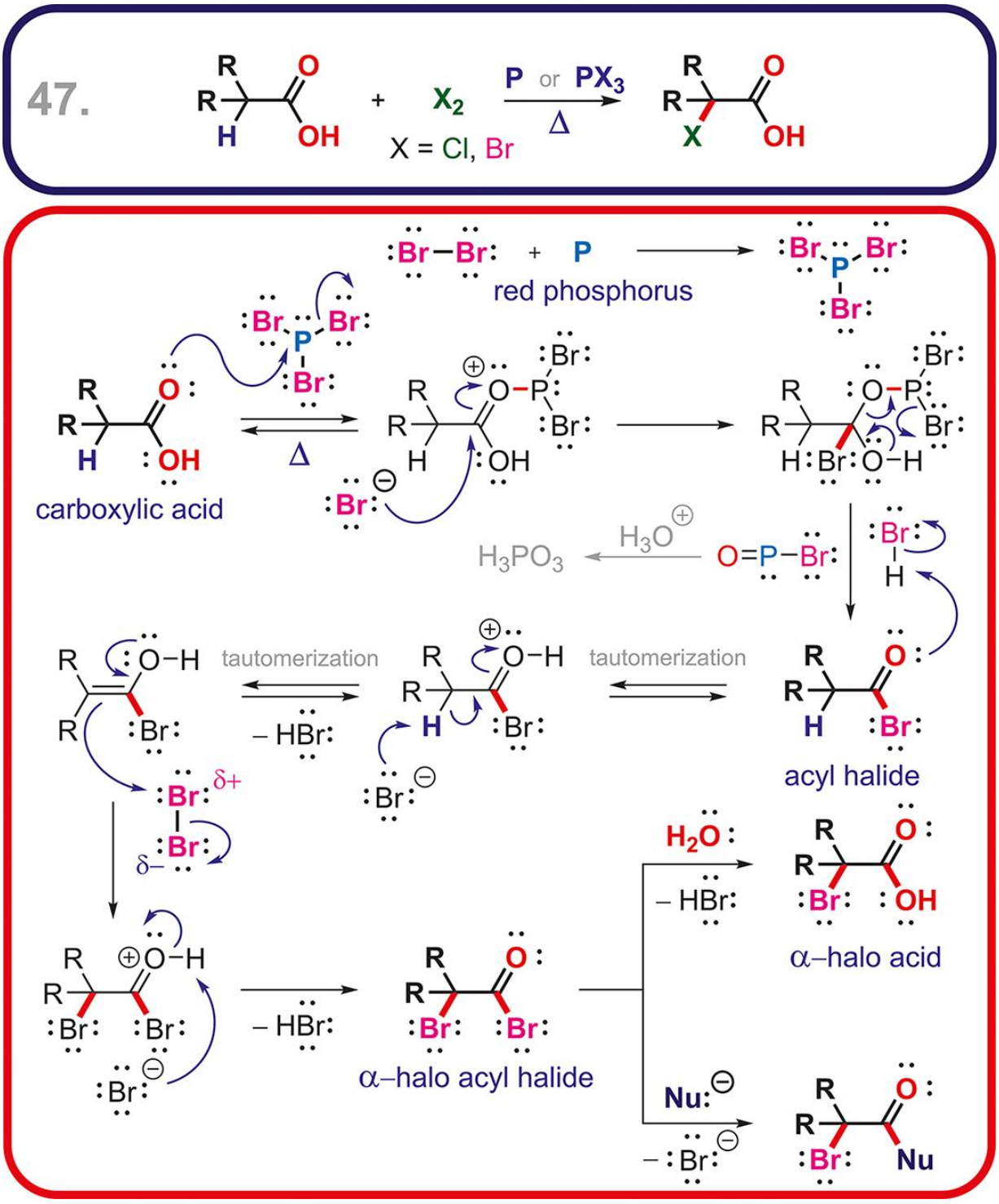


Fig. 47.1: The ***Hell–Volhard–Zelinsky*** *reaction* mechanism.[168]

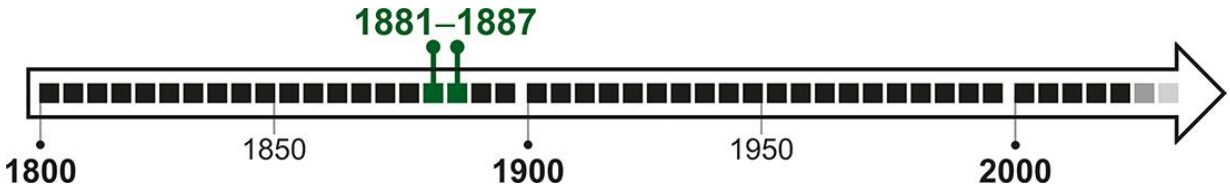


Fig. 47.2: The discovery of the ***Hell–Volhard–Zelinsky*** *reaction*.[169]

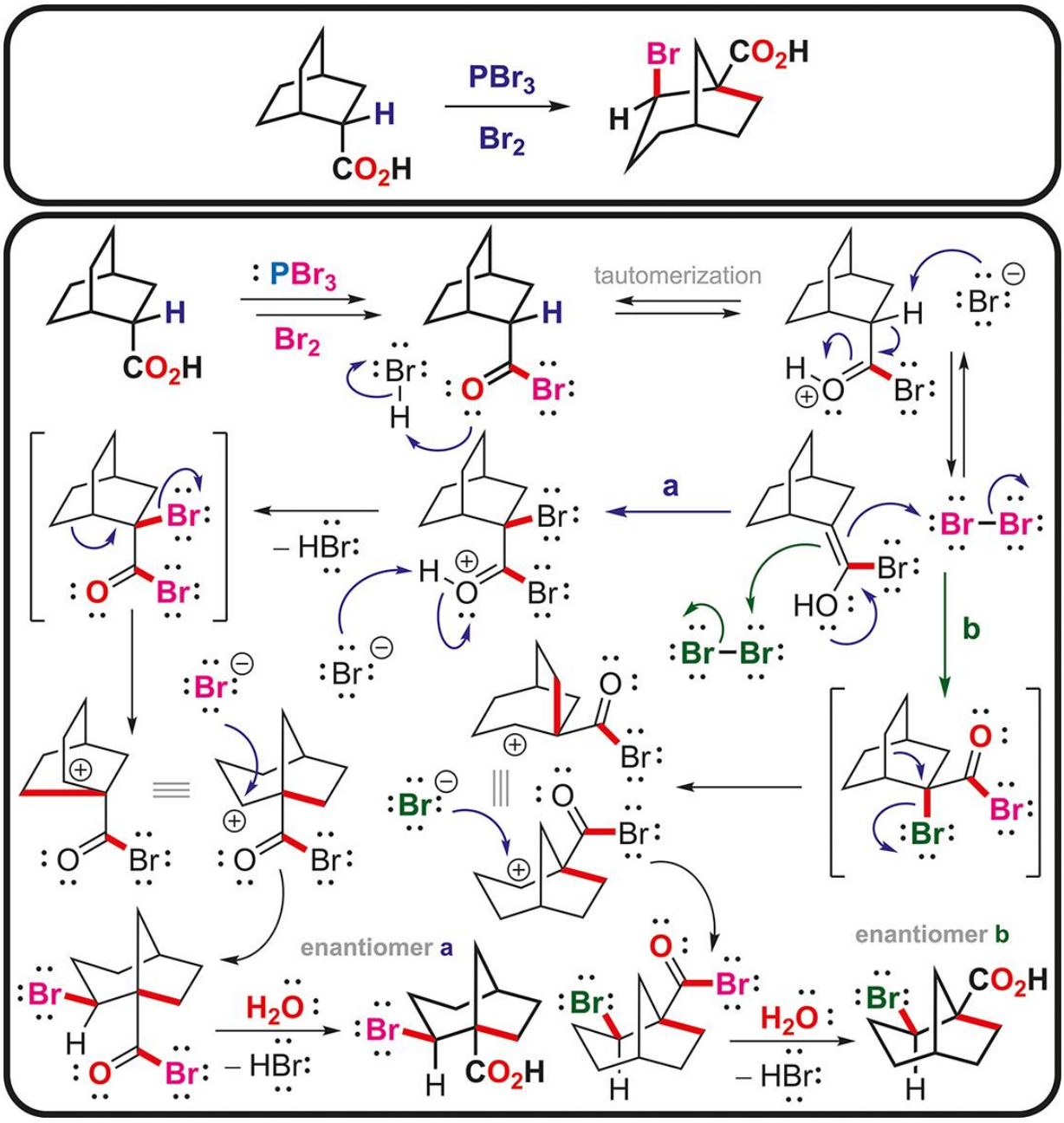


Fig. 47.3: The rearrangement mechanism of bicyclo[2.2.2]octane system.[170]

48 Hiyama Cross-Coupling

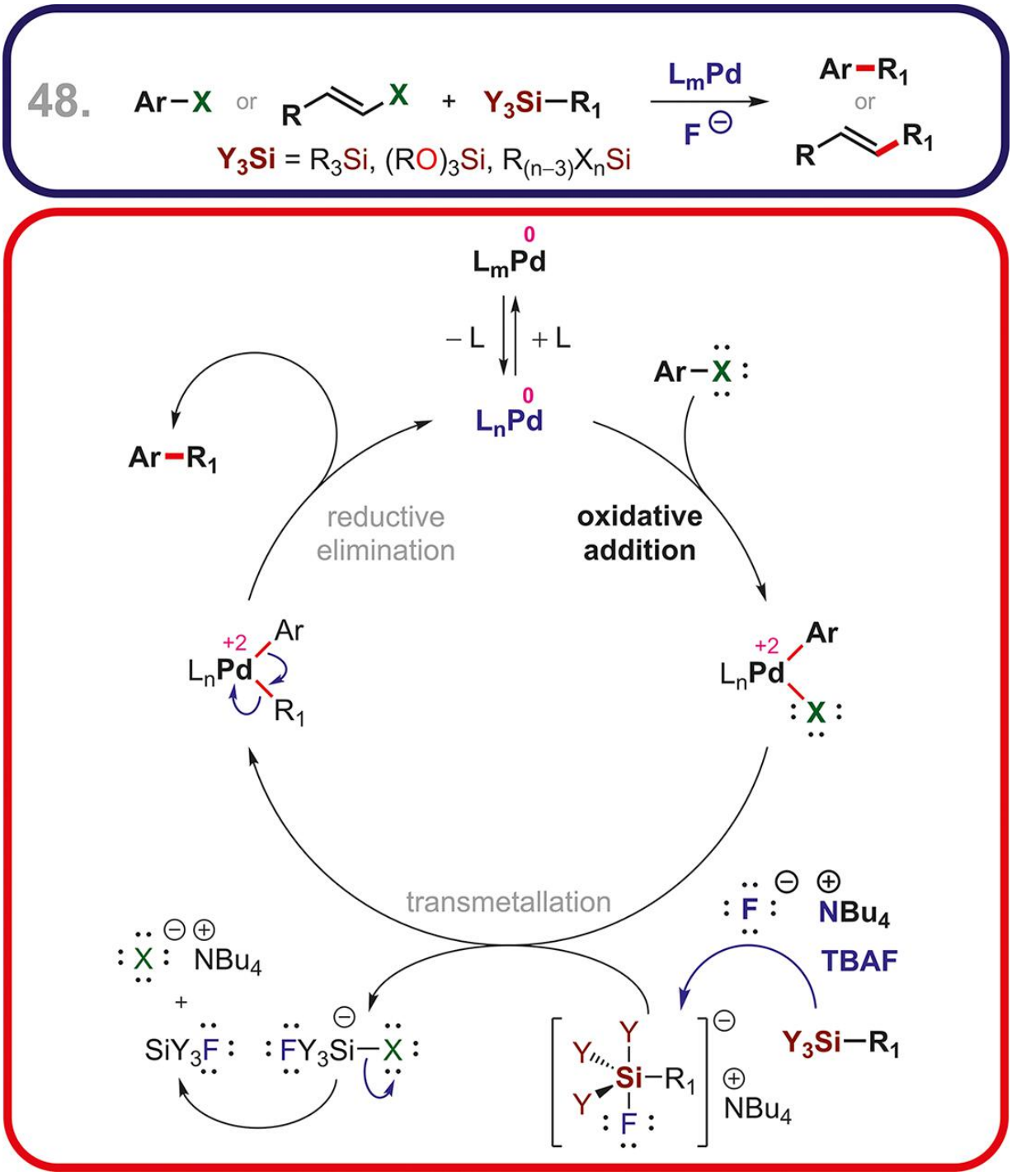


Fig. 48.1: The ***Hiyama*** *cross-coupling* mechanism.[171]

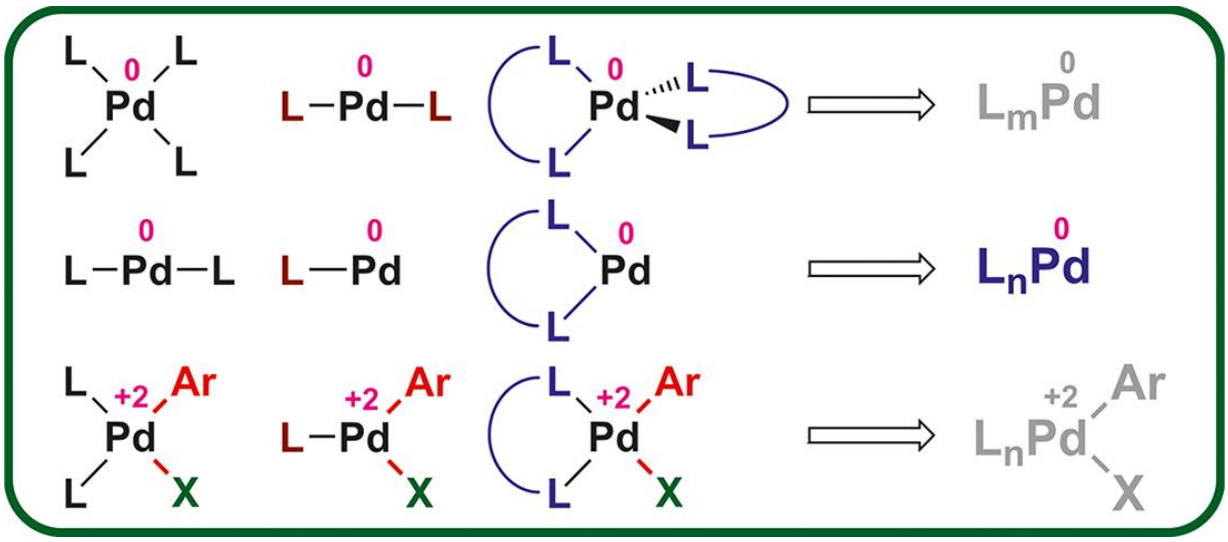


Fig. 48.2: The *oxidative addition* step representation.[172]

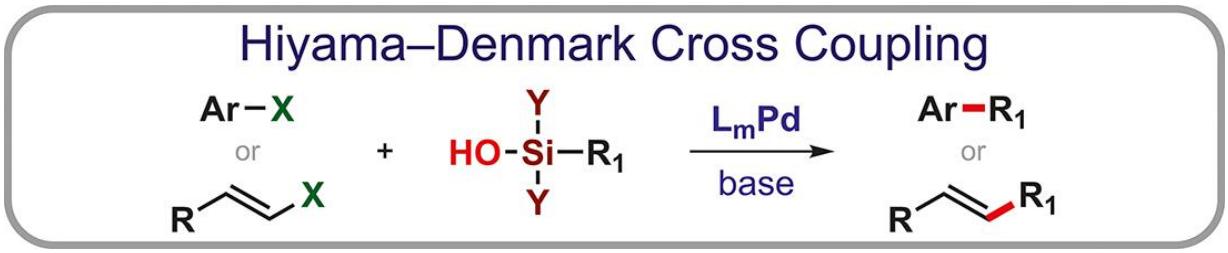


Fig. 48.3: Variations of the ***Hiyama*** *cross-coupling*.[173]

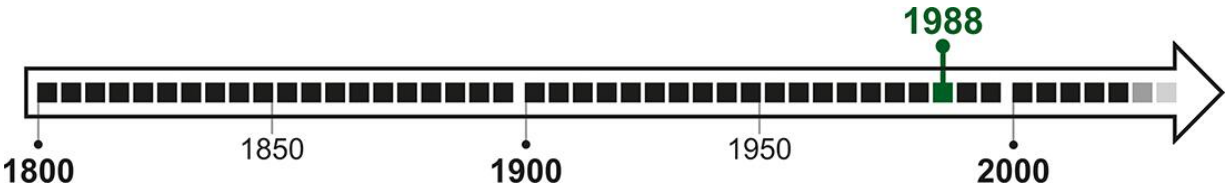


Fig. 48.4: The discovery of the ***Hiyama*** *cross-coupling*.[174]

49 Hofmann Elimination

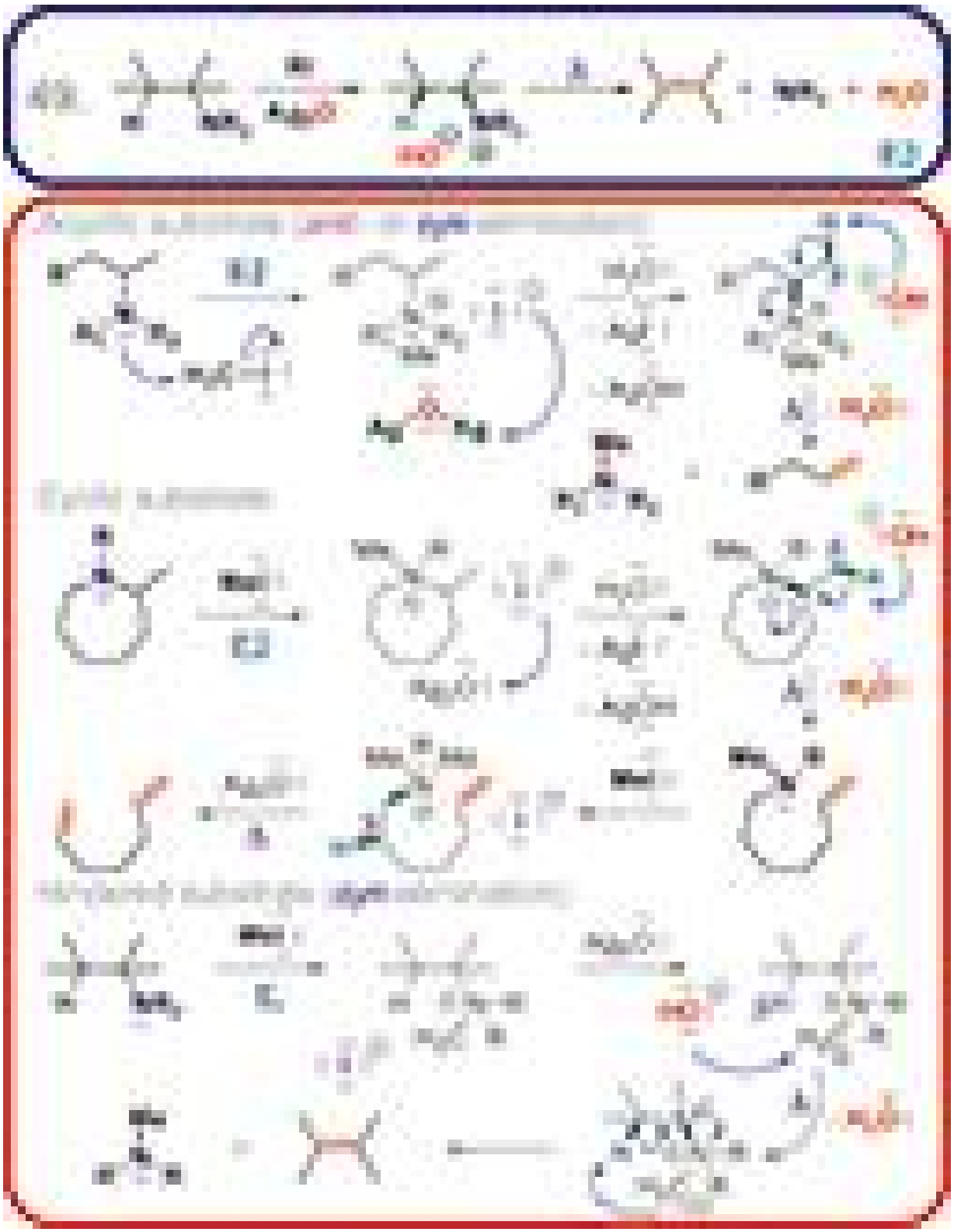


Fig. 49.1: The ***Hofmann*** *elimination* mechanism.[175].

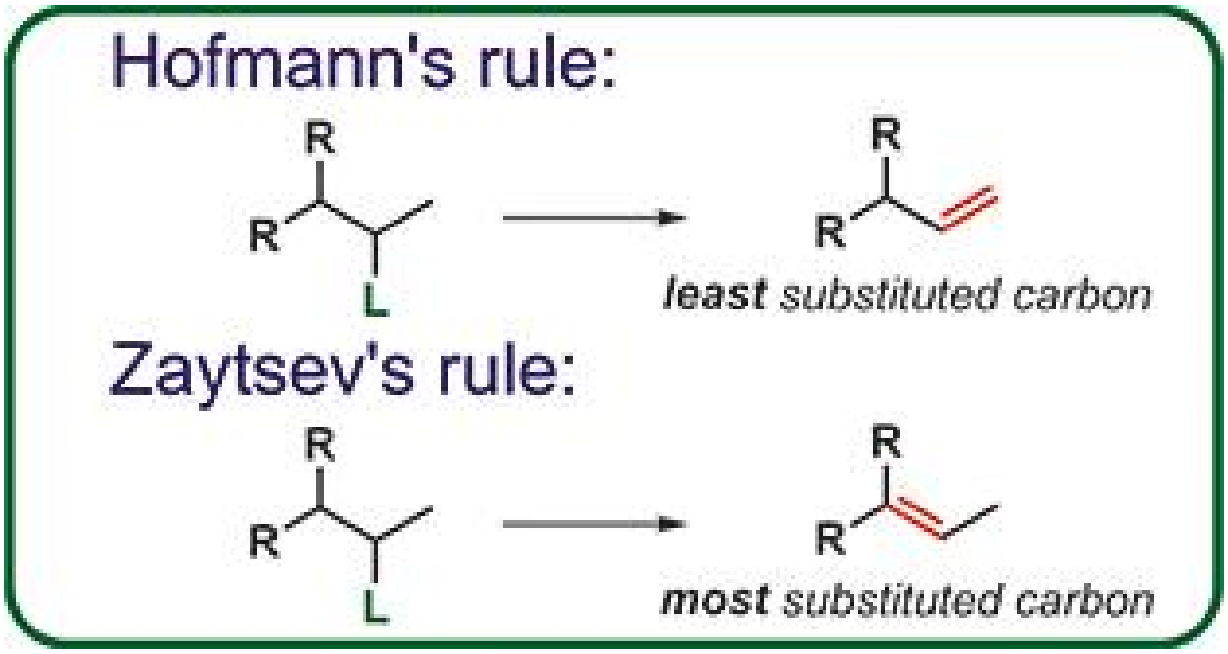


Fig. 49.2: ***Hofmann's*** *rule* and ***Zaytsev's*** *rule*.[176]

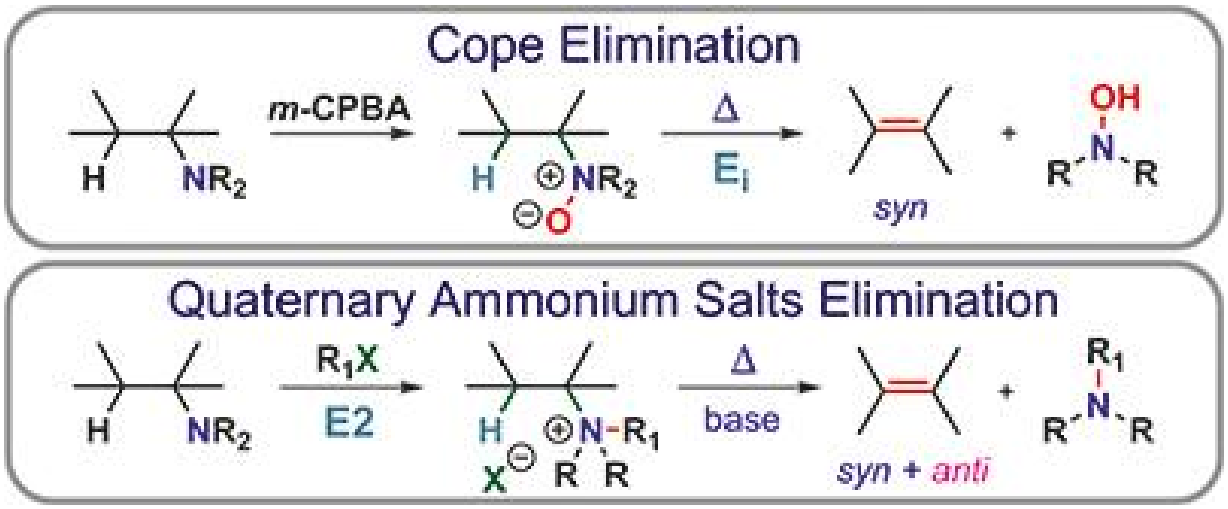


Fig. 49.3: Reactions related to the ***Hofmann*** *elimination*.[177]

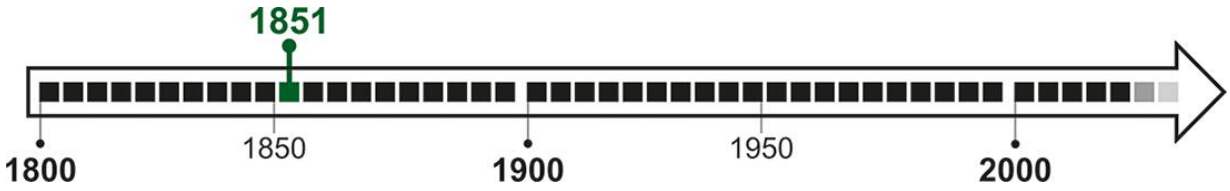


Fig. 49.4: The discovery of the ***Hofmann*** *elimination*.[178]

50 Horner–Wadsworth–Emmons Olefination

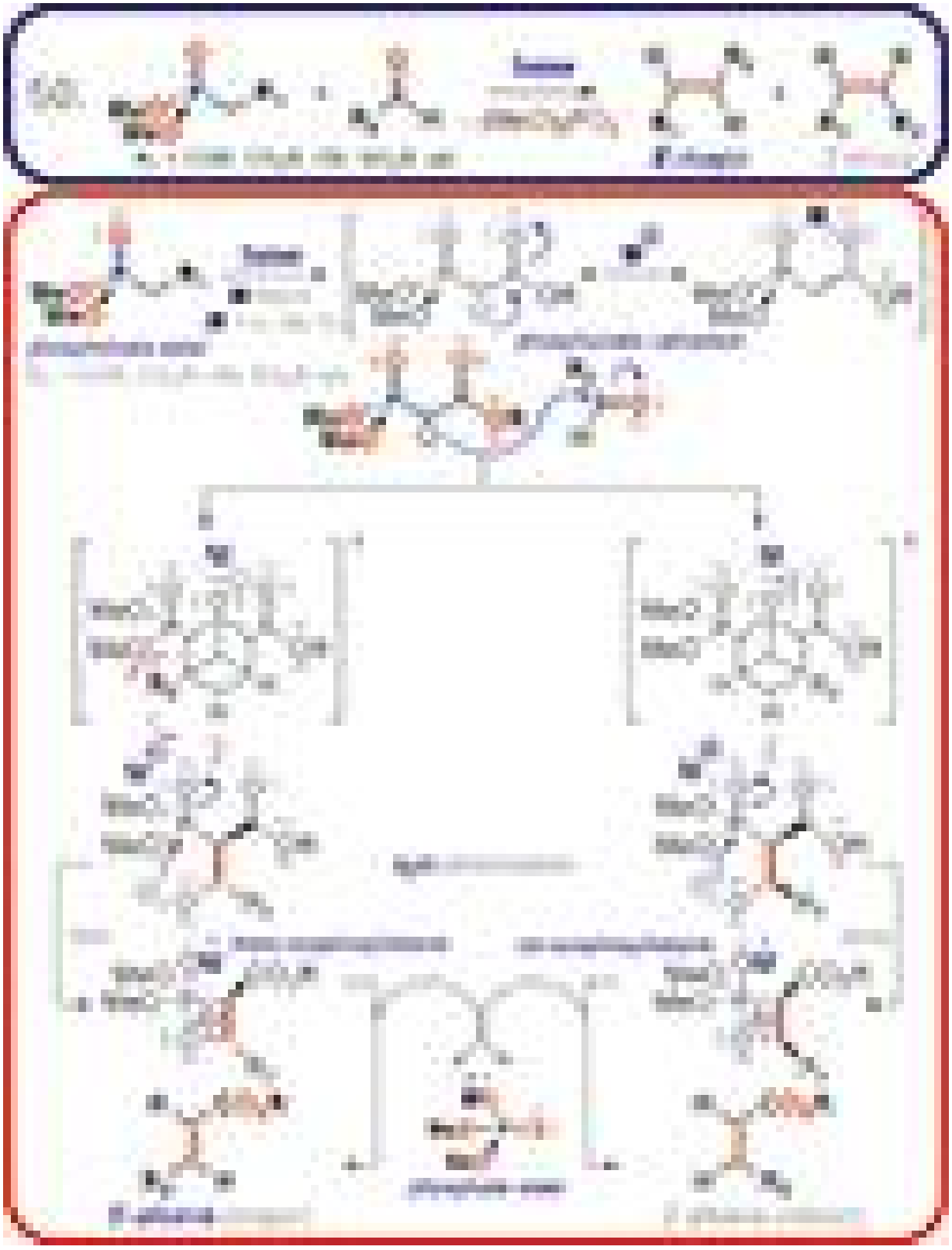


Fig. 50.1: The ***Horner–Wadsworth–Emmons*** *olefination* mechanism.[179].

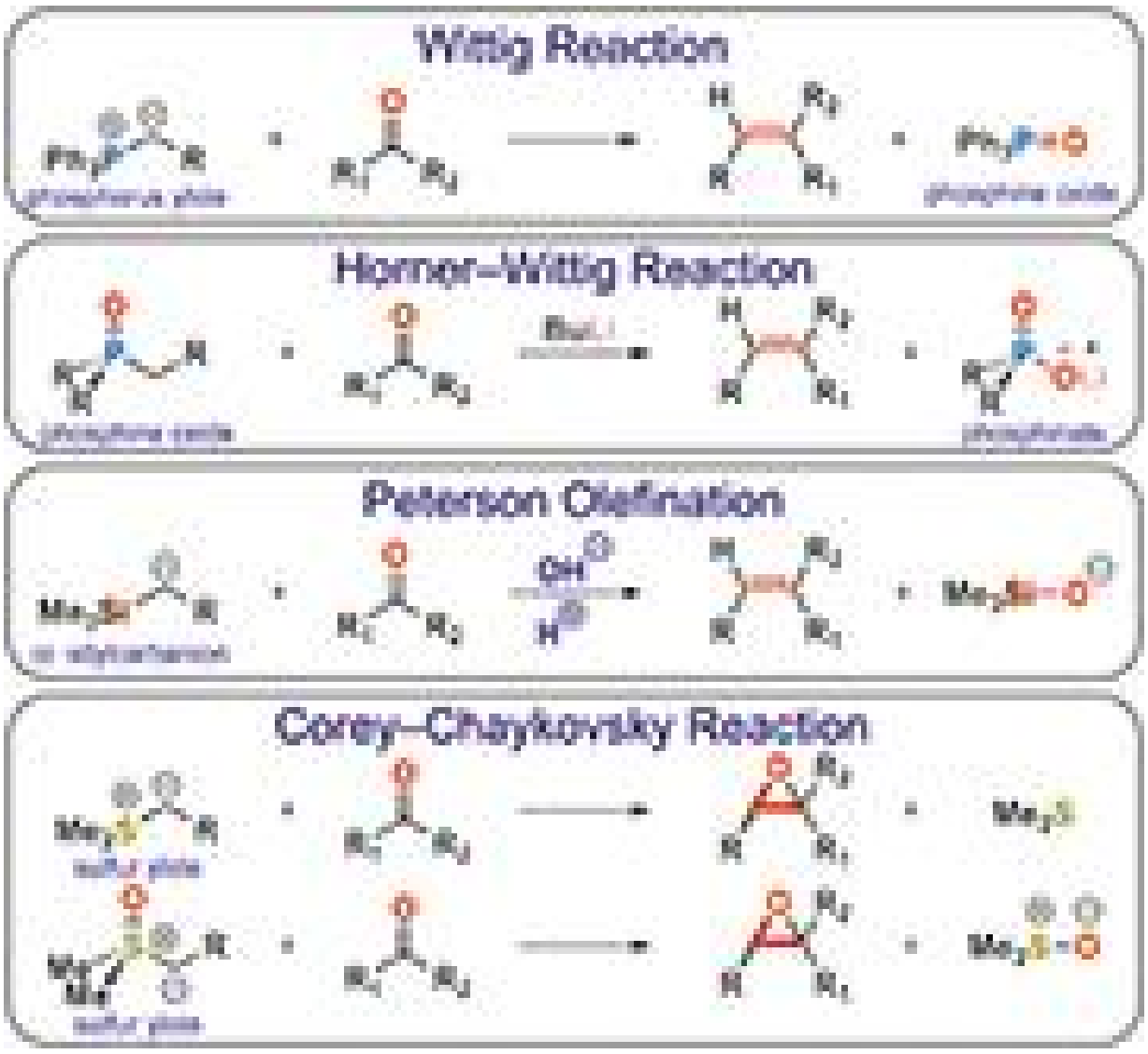


Fig. 50.2: Reactions related to the ***Horner–Wadsworth–Emmons*** *olefination*.[180]

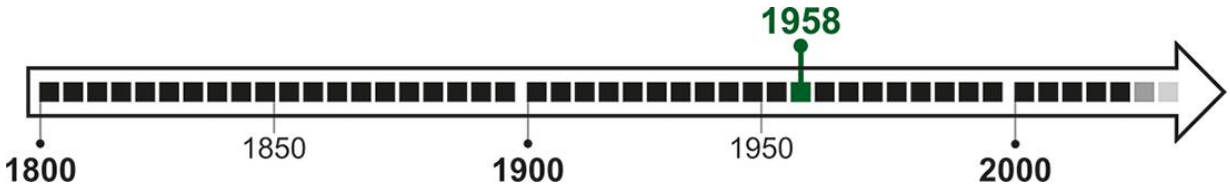


Fig. 50.3: The discovery of the ***Horner–Wadsworth–Emmons*** *olefination*.[181]

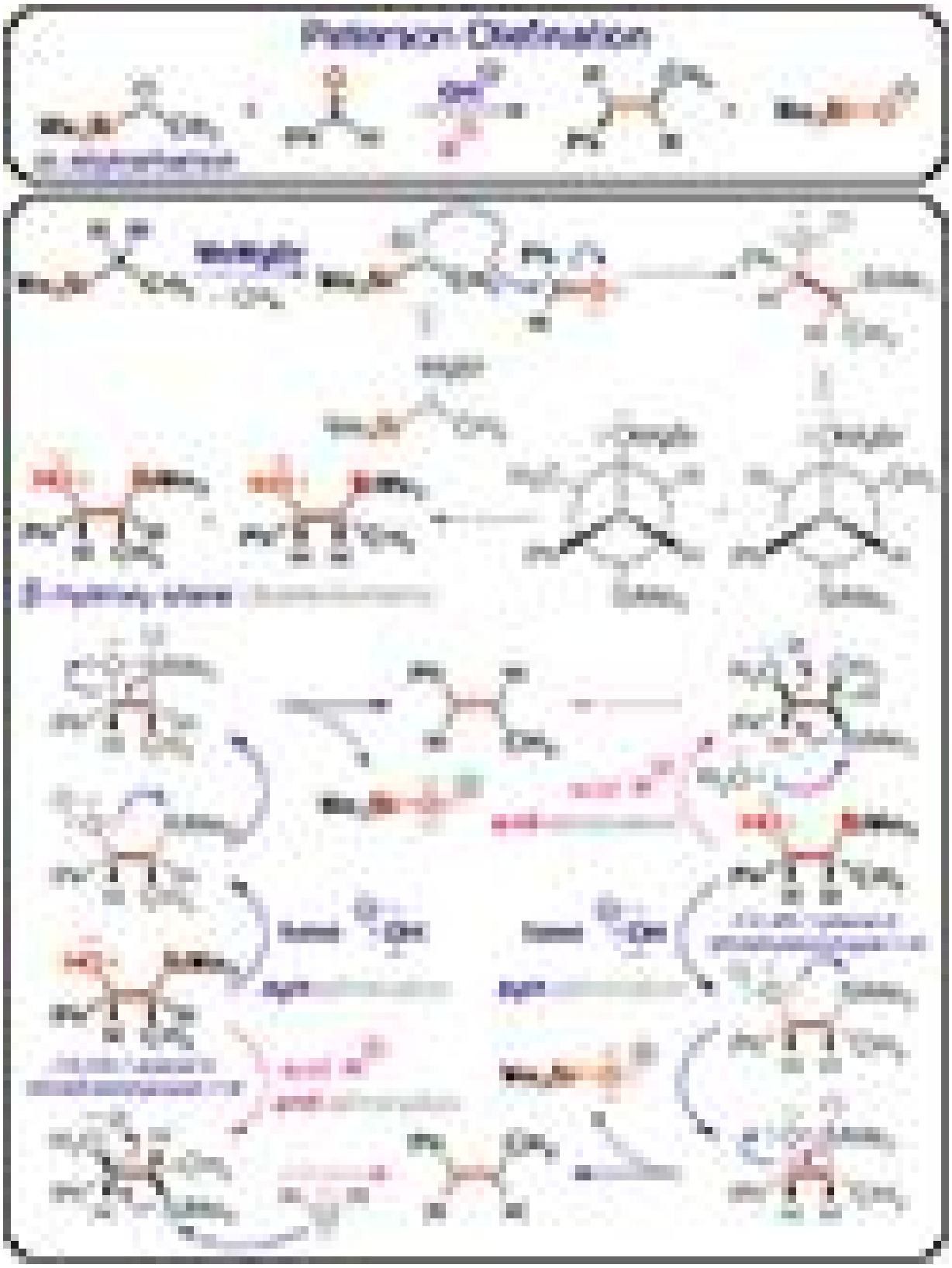


Fig. 50.4: The ***Peterson*** *olefination* mechanism.[182]

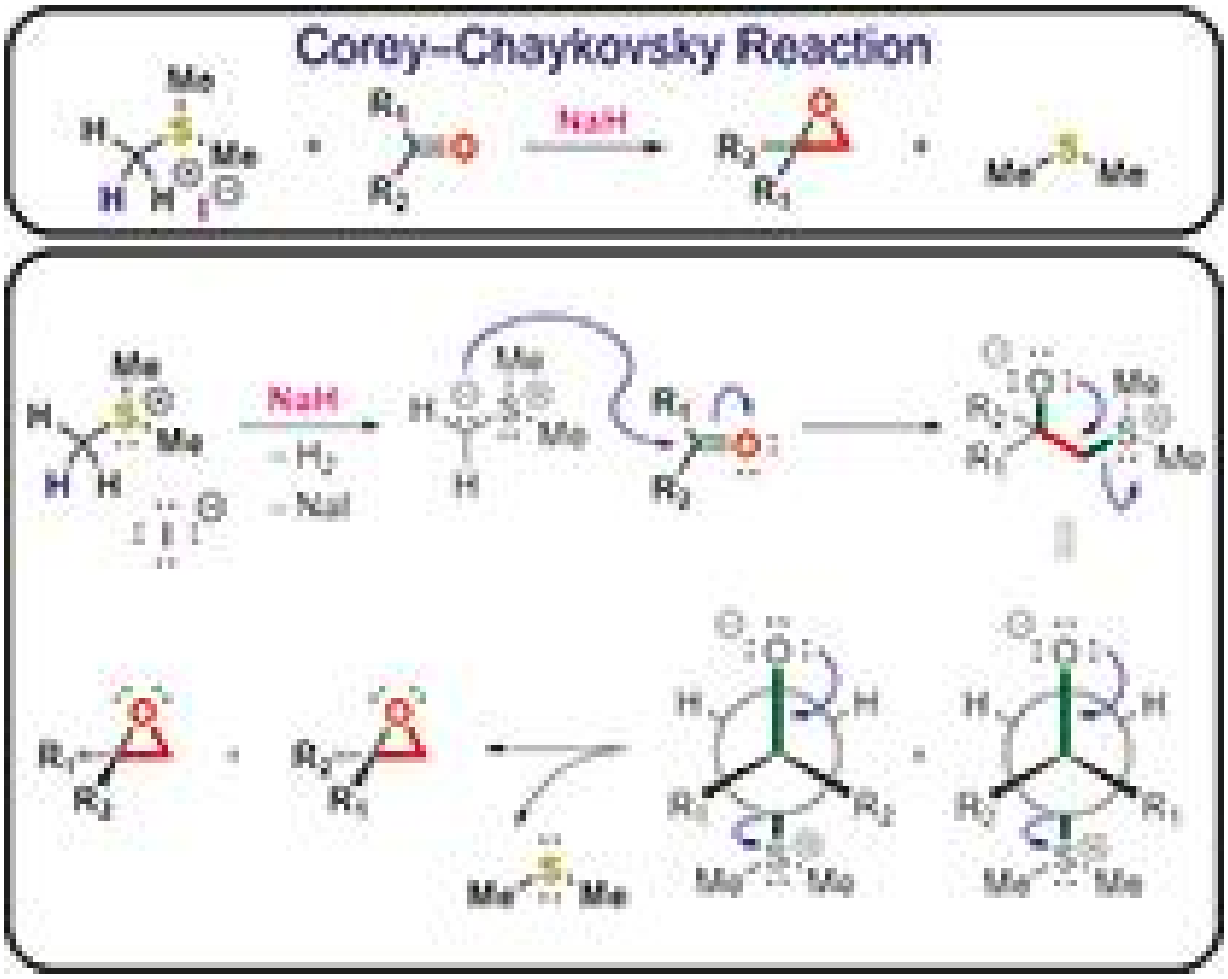


Fig. 50.5: The ***Corey–Chaykovsky*** *reaction* mechanism.[183]

51 Jones Oxidation

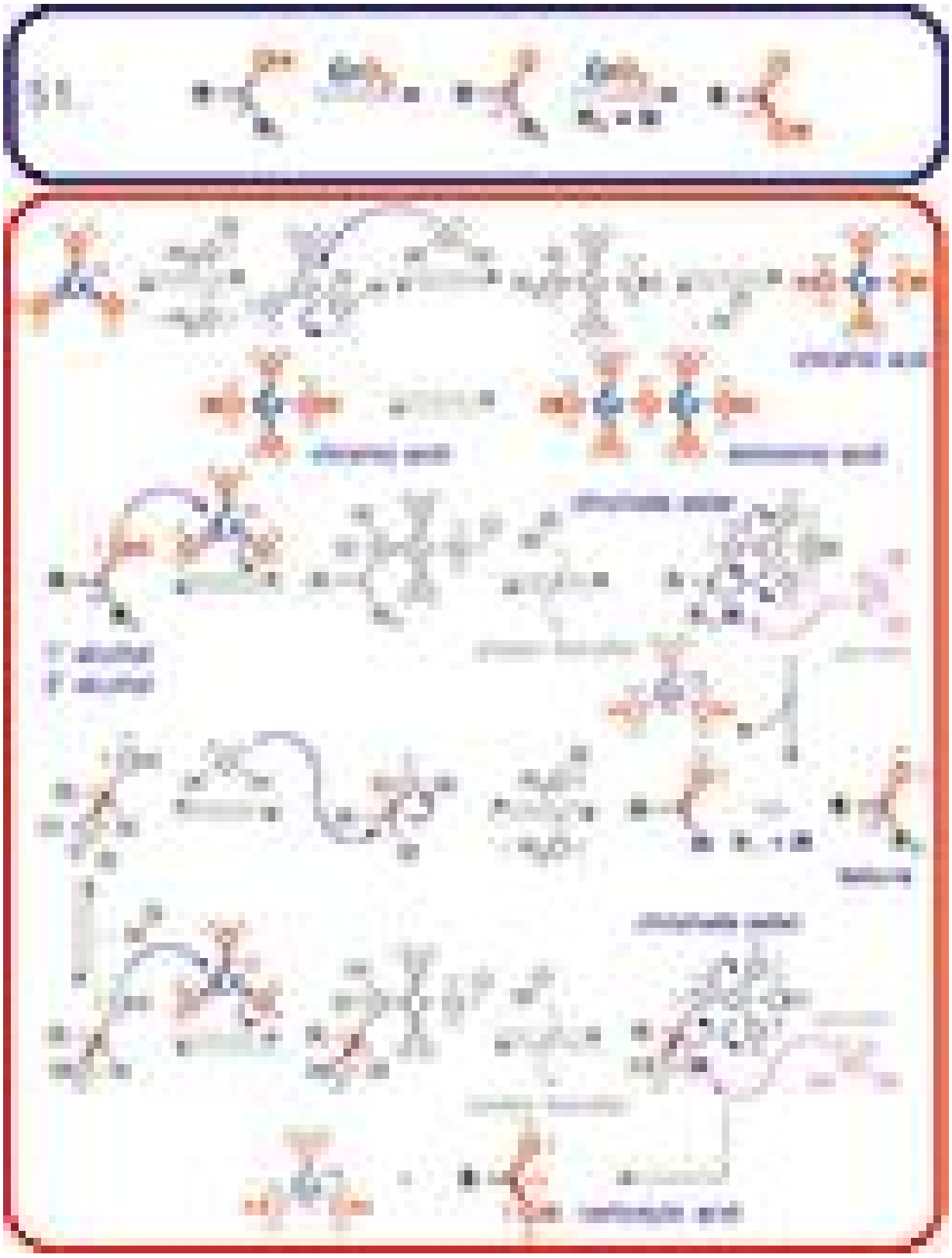


Fig. 51.1: The ***Jones*** *oxidation* mechanism.[184].

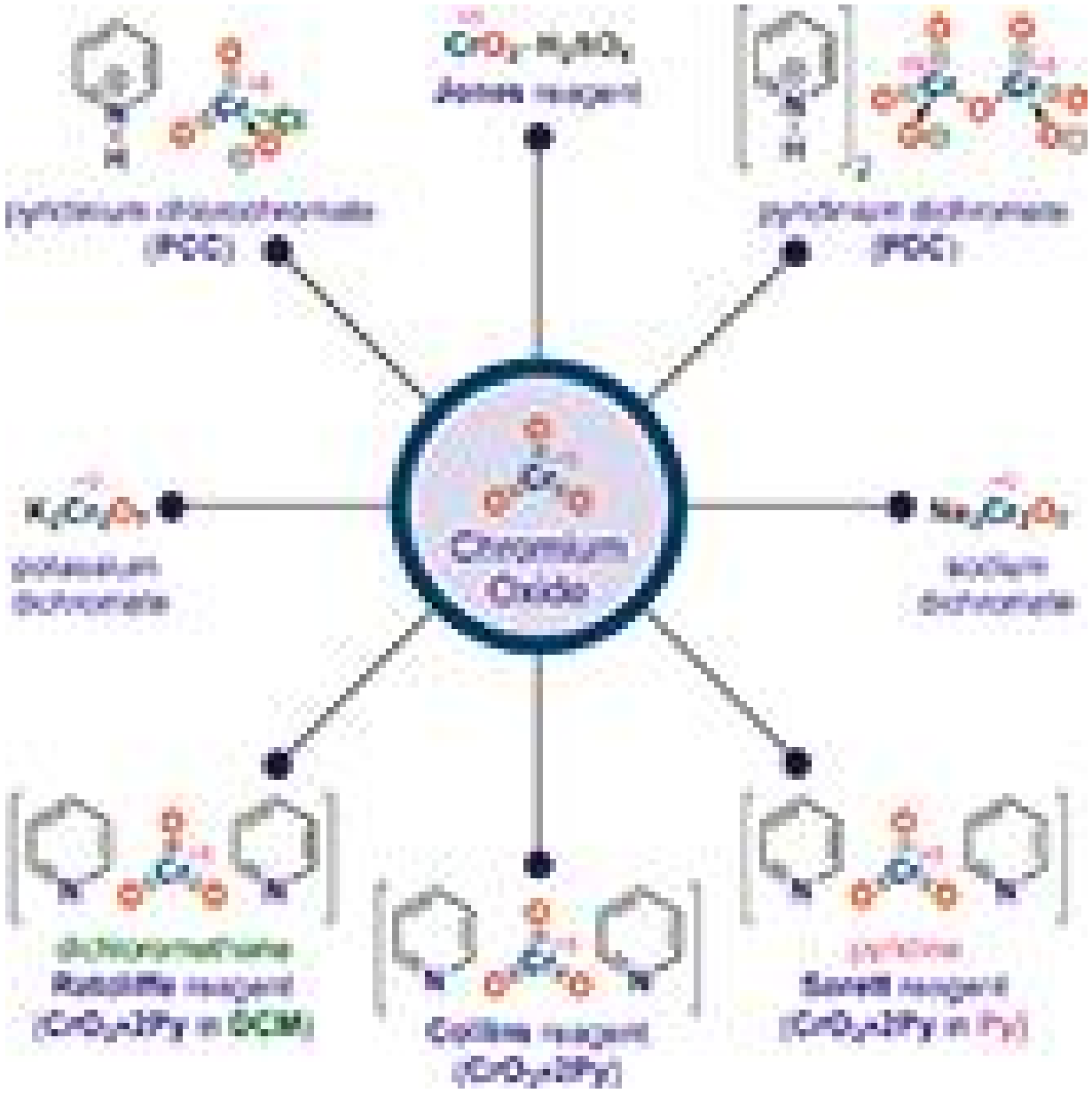


Fig. 51.2: Various oxidizing reagents formed from chromium oxide(VI).[185]

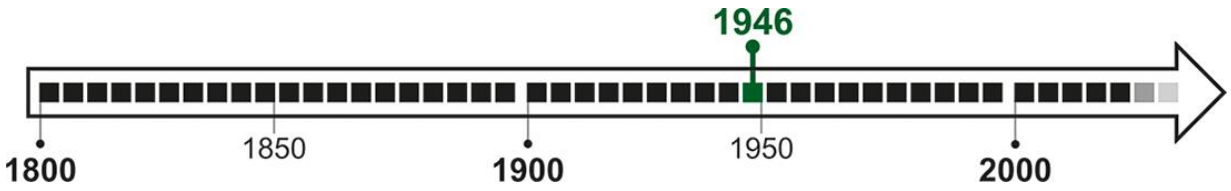


Fig. 51.3: The discovery of the ***Jones*** *oxidation*.[186]

52 Kucherov Reaction

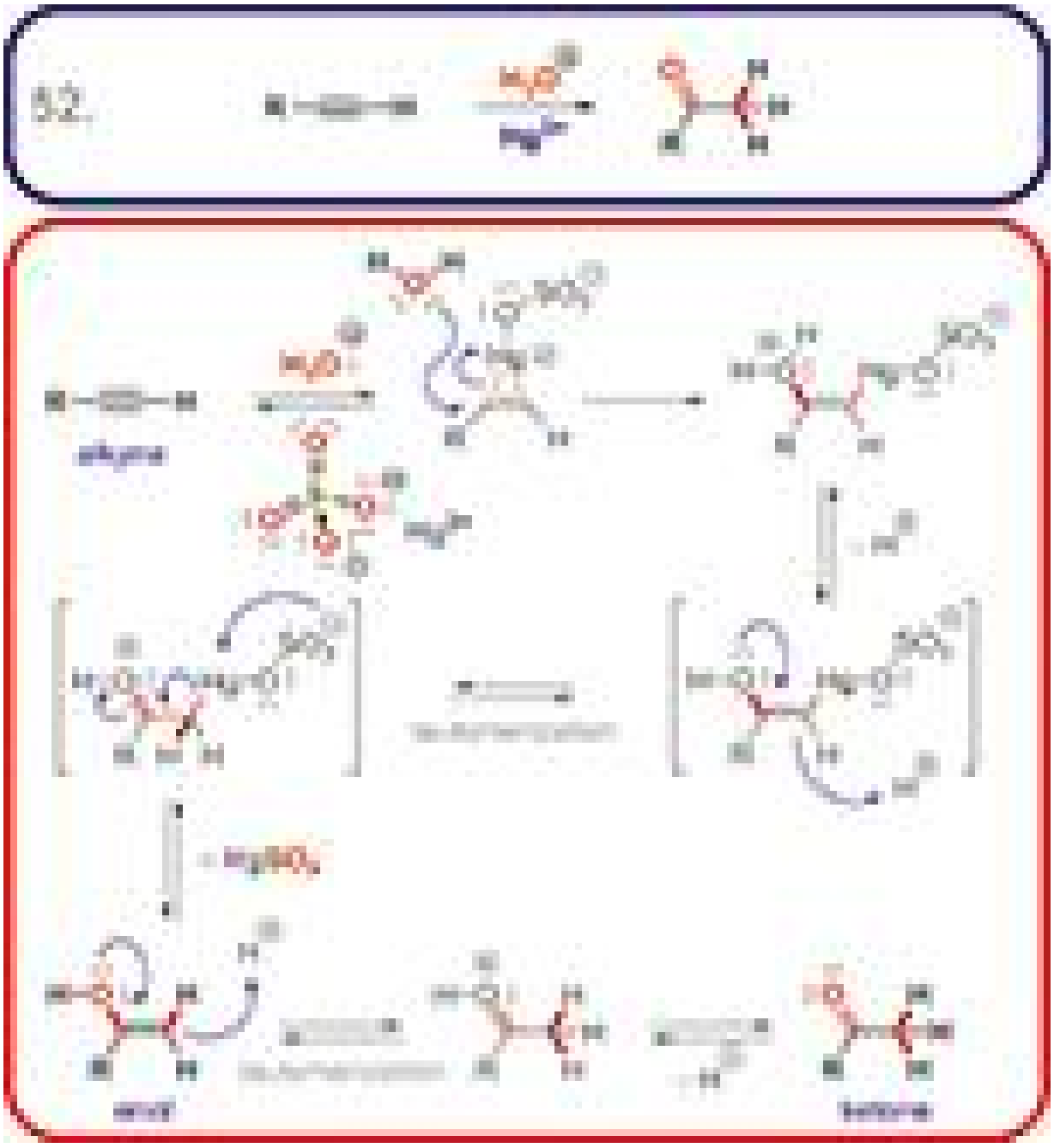


Fig. 52.1: The ***Kucherov*** *reaction* mechanism.[187]

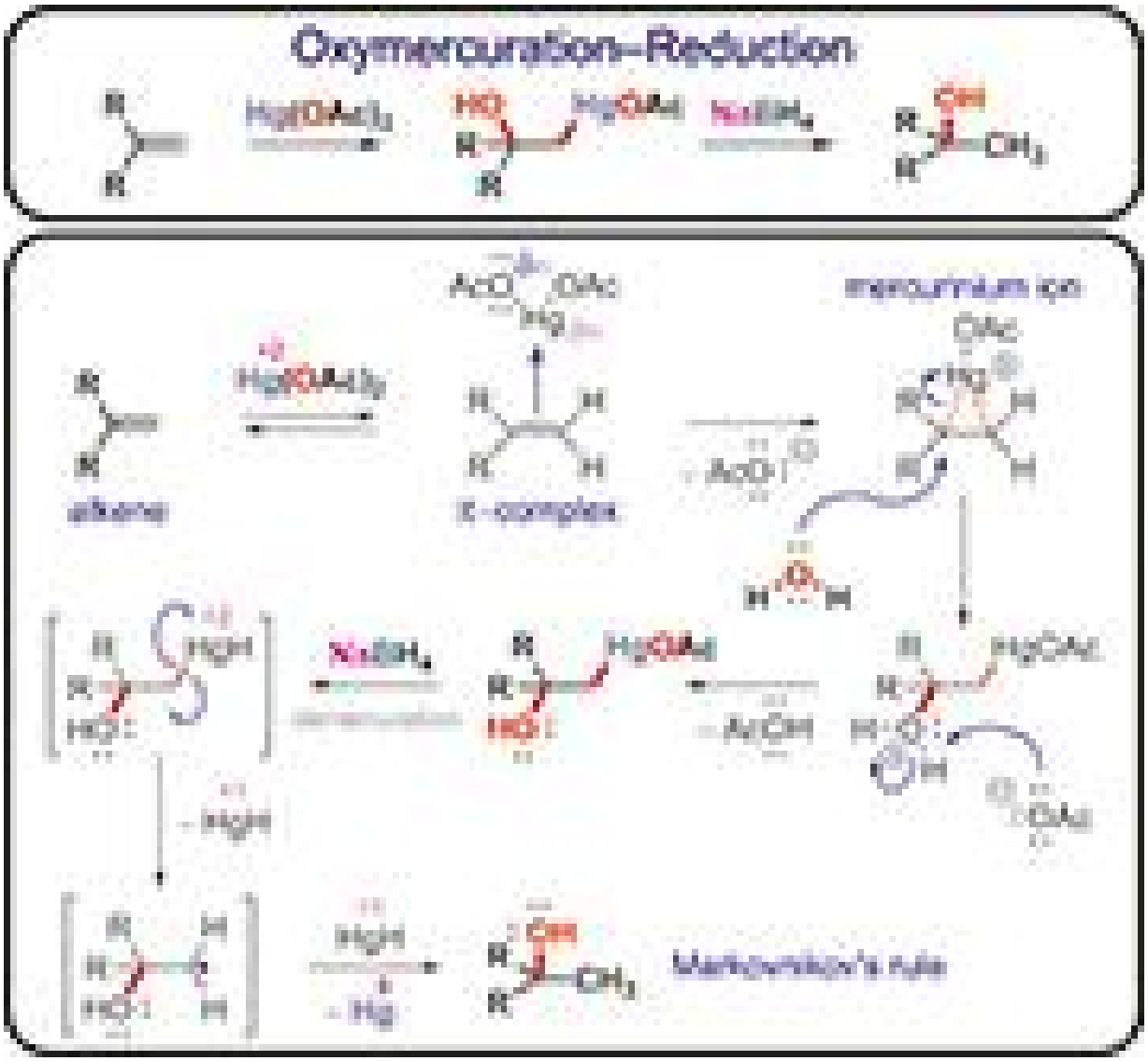


Fig. 52.2: The *oxymercuration reaction* mechanism.[188]

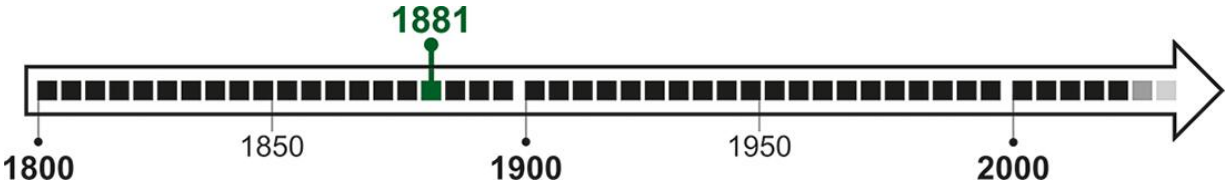


Fig. 52.3: The discovery of the ***Kucherov*** *reaction*.[189]

53 Kumada Cross-Coupling

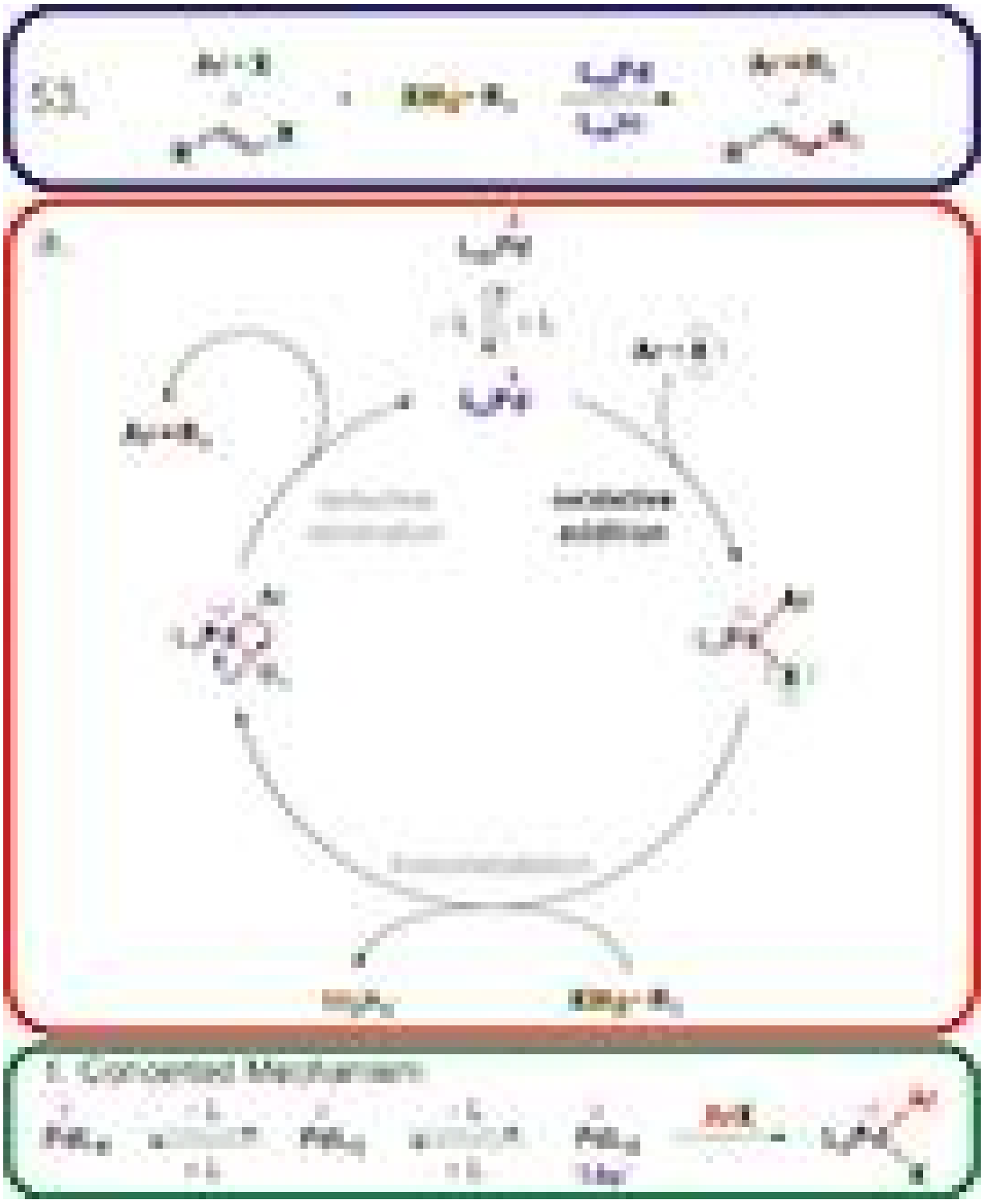


Fig. 53.1: The **Pd**-catalyzed ***Kumada*** *cross-coupling* mechanism.[190]

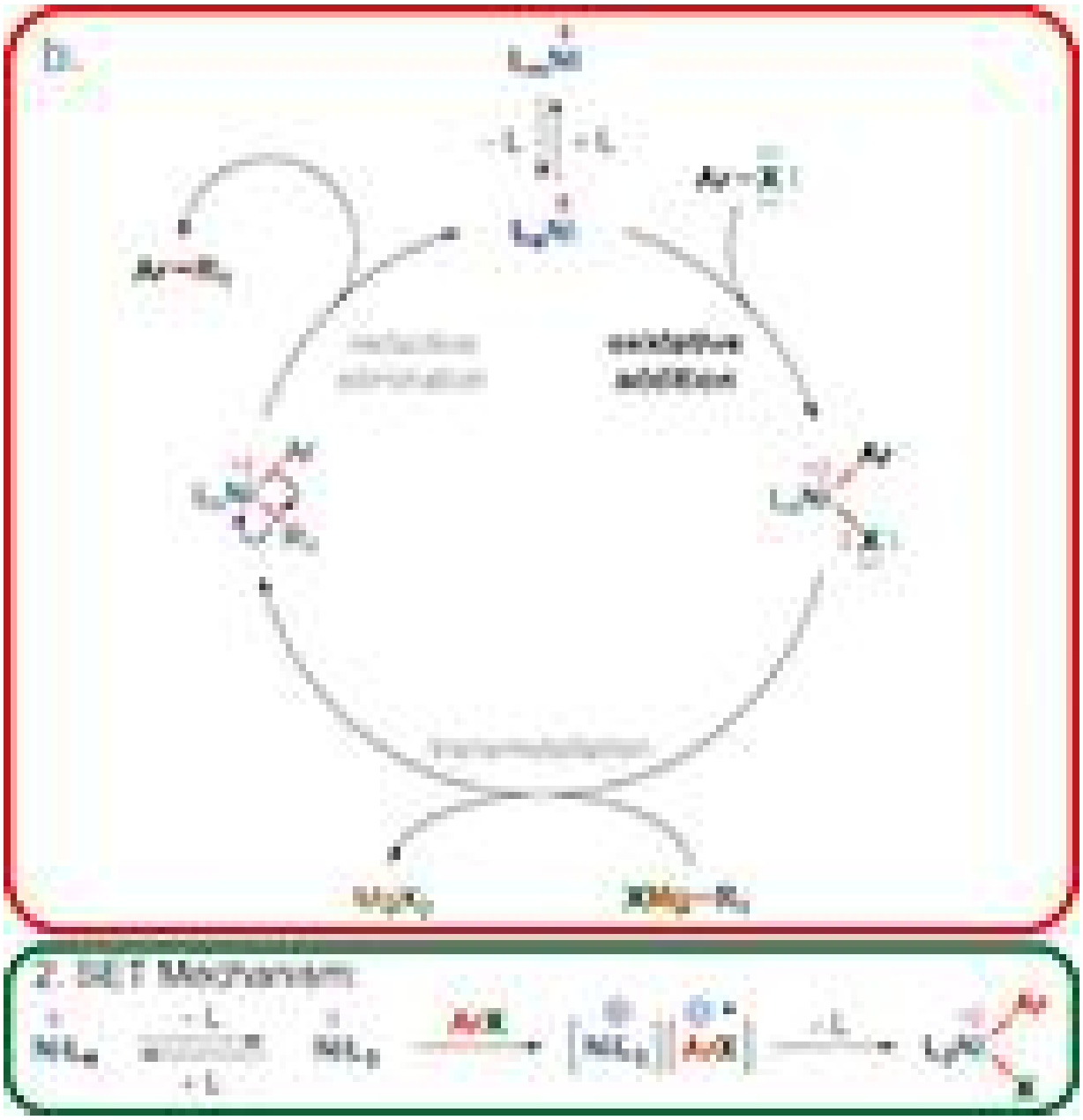


Fig. 53.2: The **Ni**-catalyzed ***Kumada*** *cross-coupling* mechanism.[191]

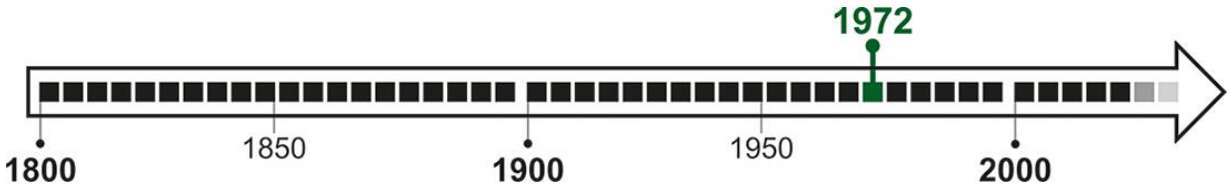


Fig. 53.3: The discovery of the ***Kumada*** *cross-coupling*.[192]

54 Ley–Griffith Oxidation

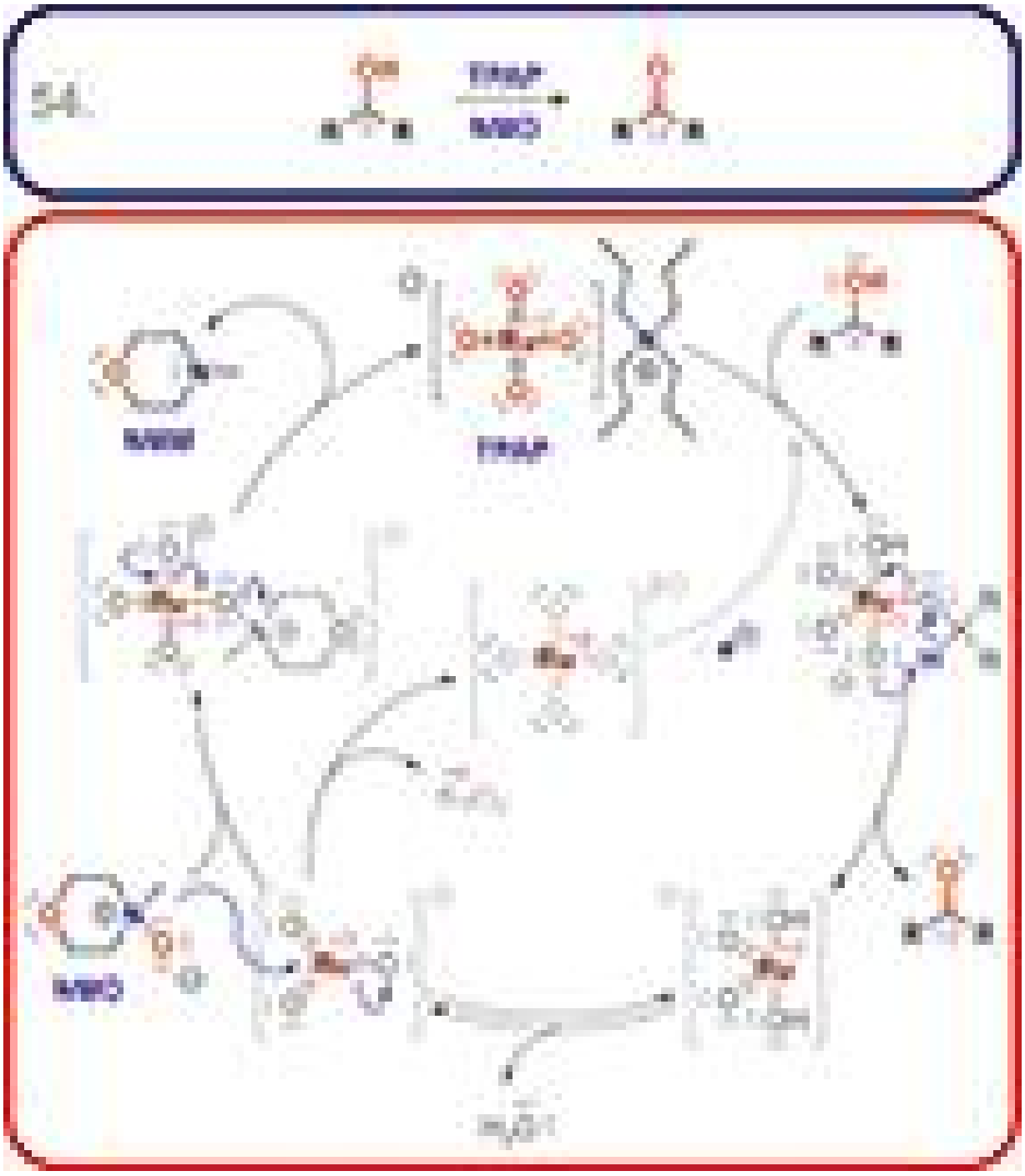


Fig. 54.1: The ***Ley–Griffith*** *oxidation* mechanism.[193]

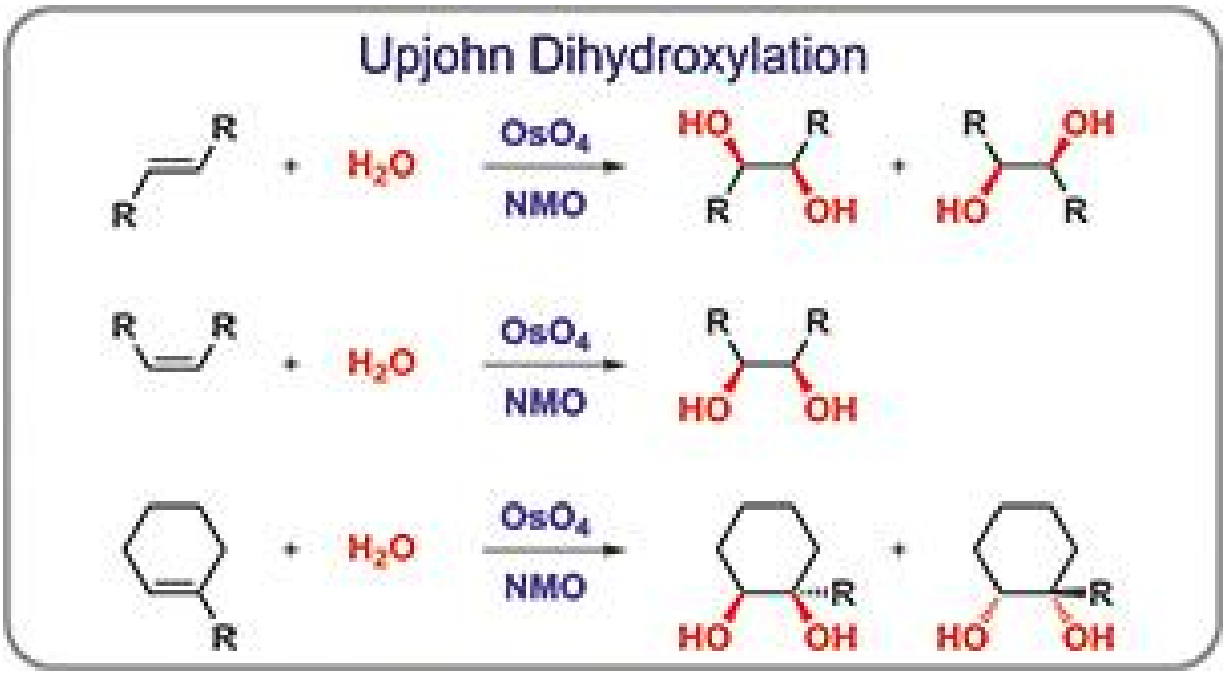


Fig. 54.2: Reactions related to the ***Ley–Griffith*** *oxidation*.[194]

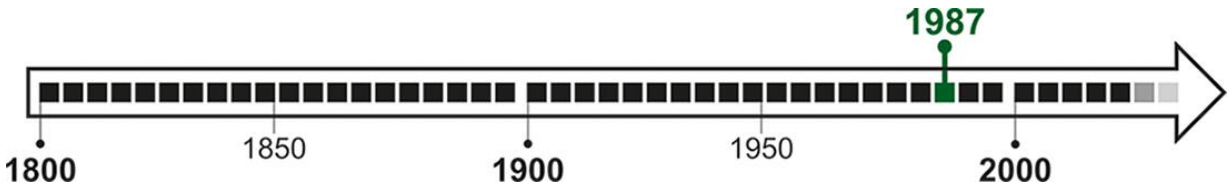


Fig. 54.3: The discovery of the ***Ley–Griffith*** *oxidation*.[195]

55 Liebeskind–Srogl Cross-Coupling

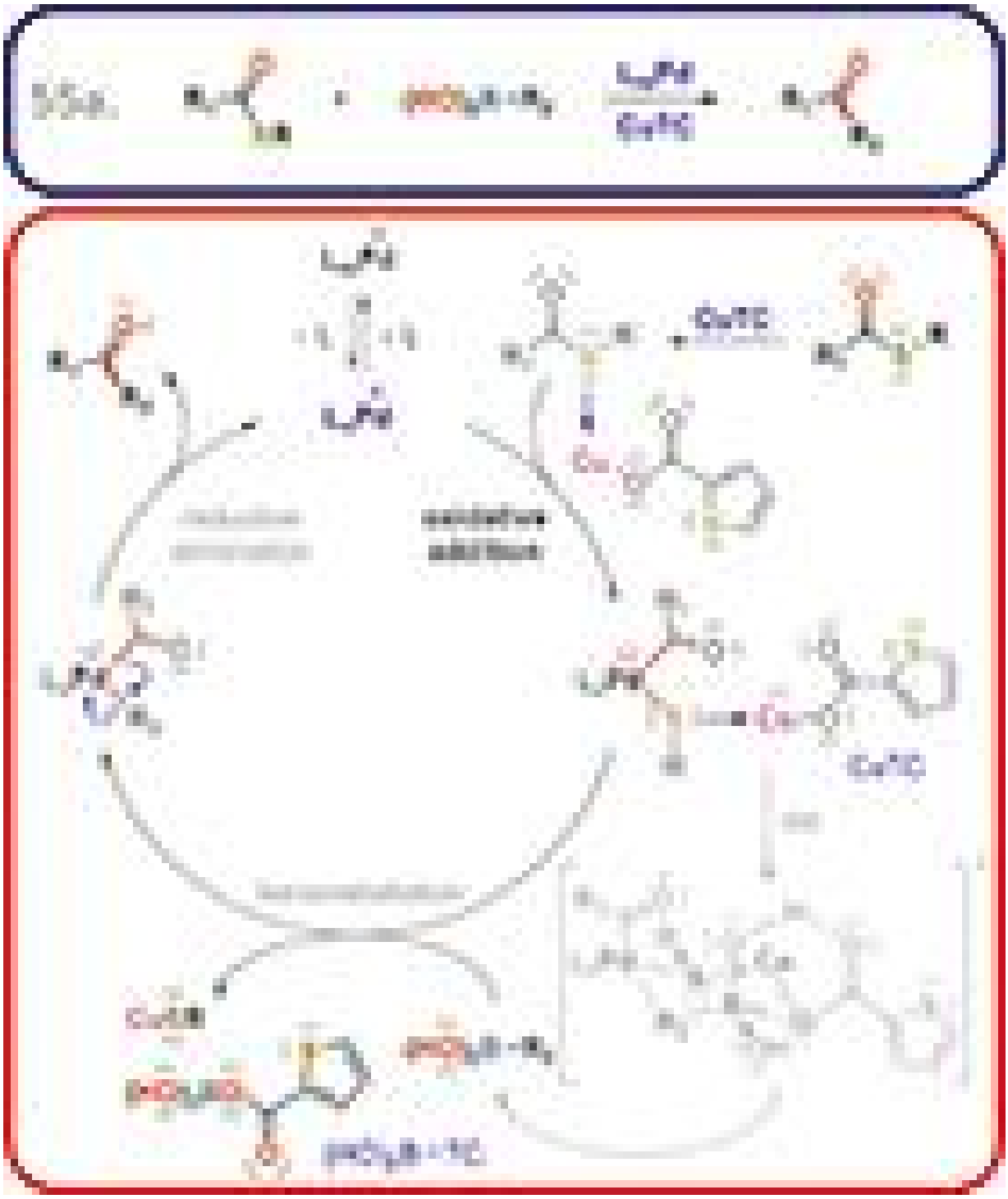


Fig. 55.1: The ***Liebeskind–Srogl*** *cross-coupling* (thioesters) mechanism.[196]

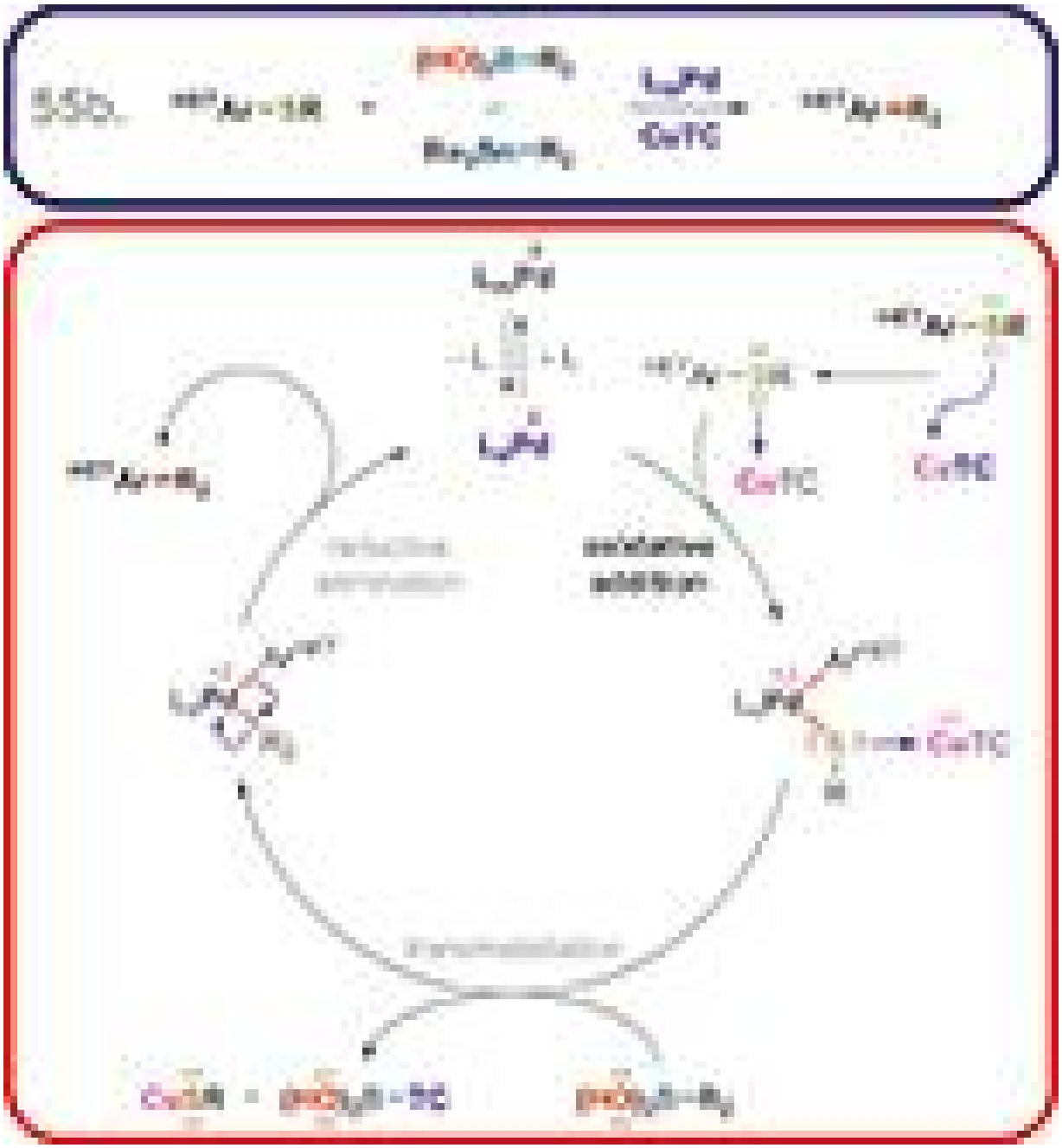


Fig. 55.2: The ***Liebeskind–Srogl*** *cross-coupling* (thioethers) mechanism.[197]

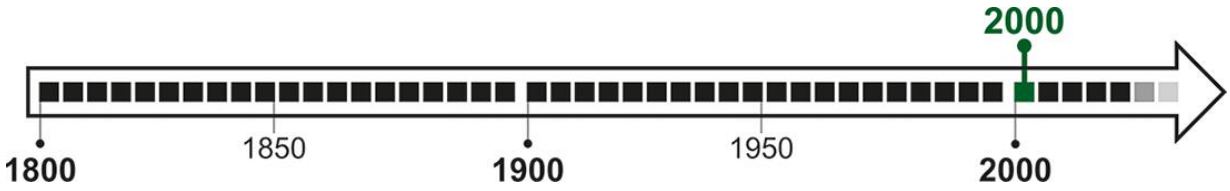


Fig. 55.3: The discovery of the ***Liebeskind–Srogl*** *cross-coupling*.[198]

56 Mannich Reaction

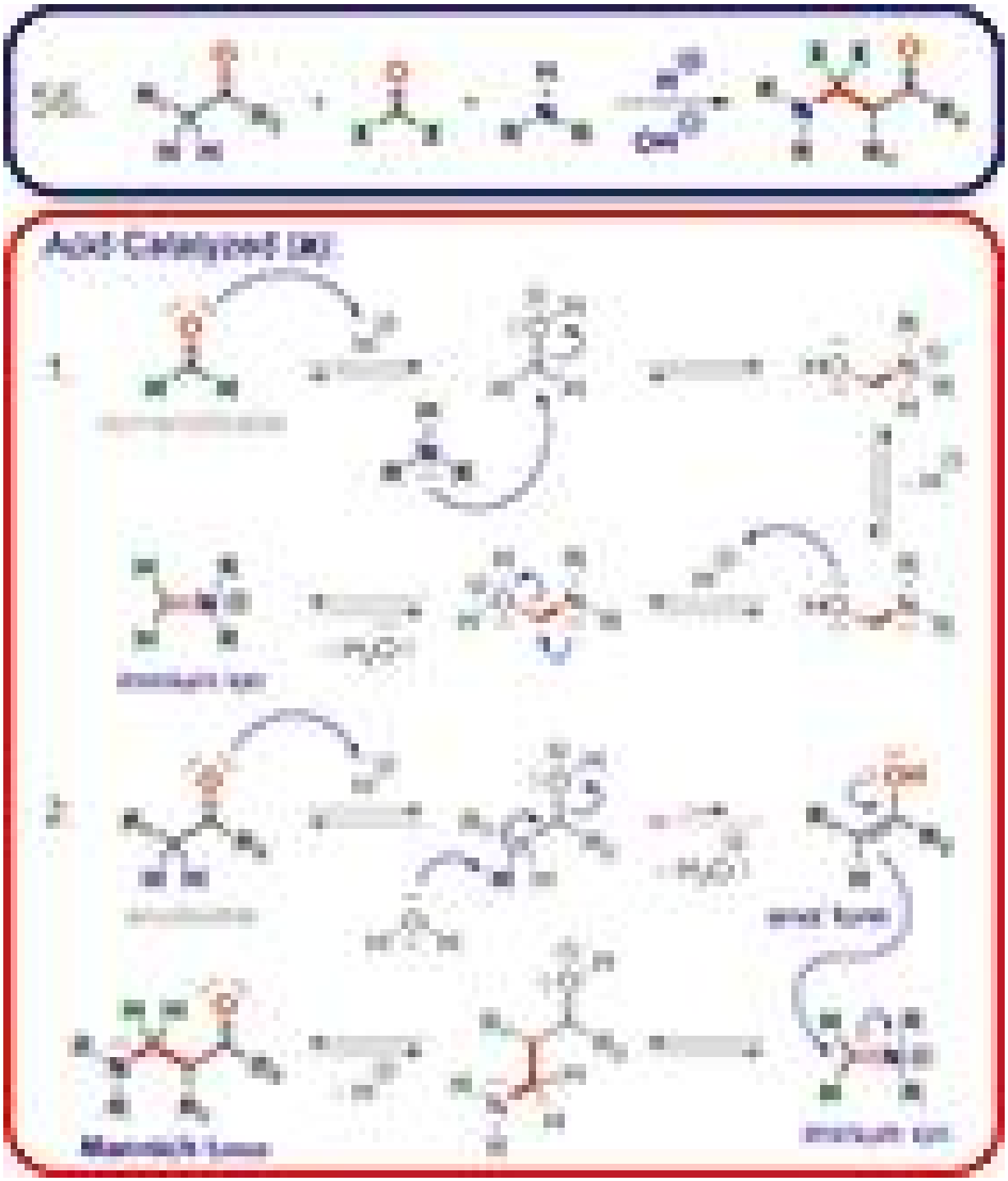


Fig. 56.1: The ***Mannich*** *reaction* mechanism (acid catalyzed).[199]

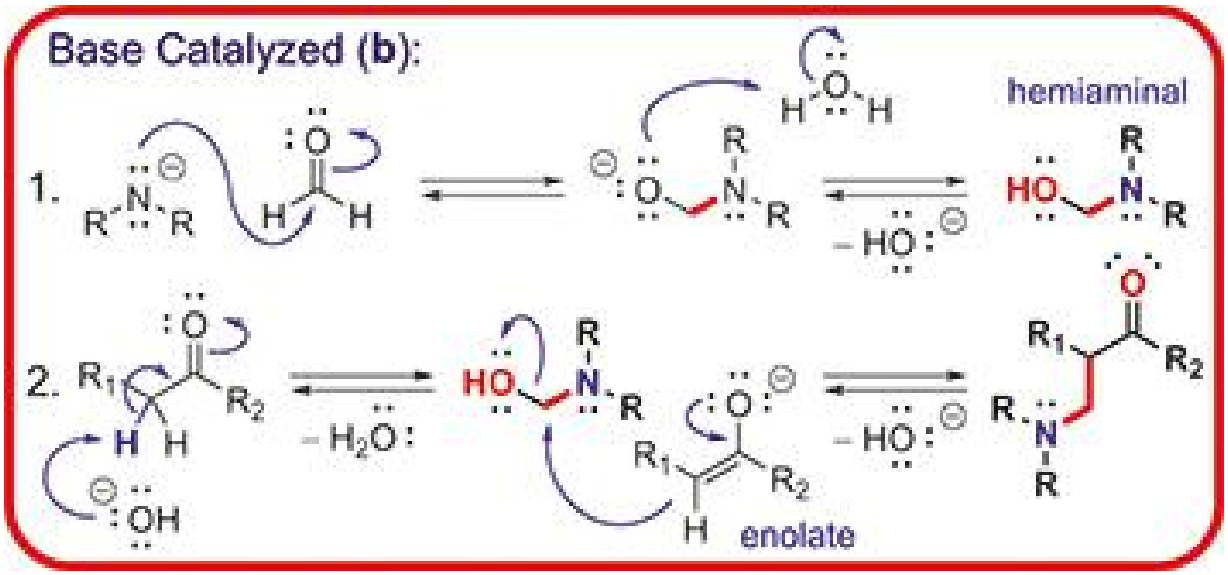


Fig. 56.2: The ***Mannich*** *reaction* mechanism (base catalyzed).[200]

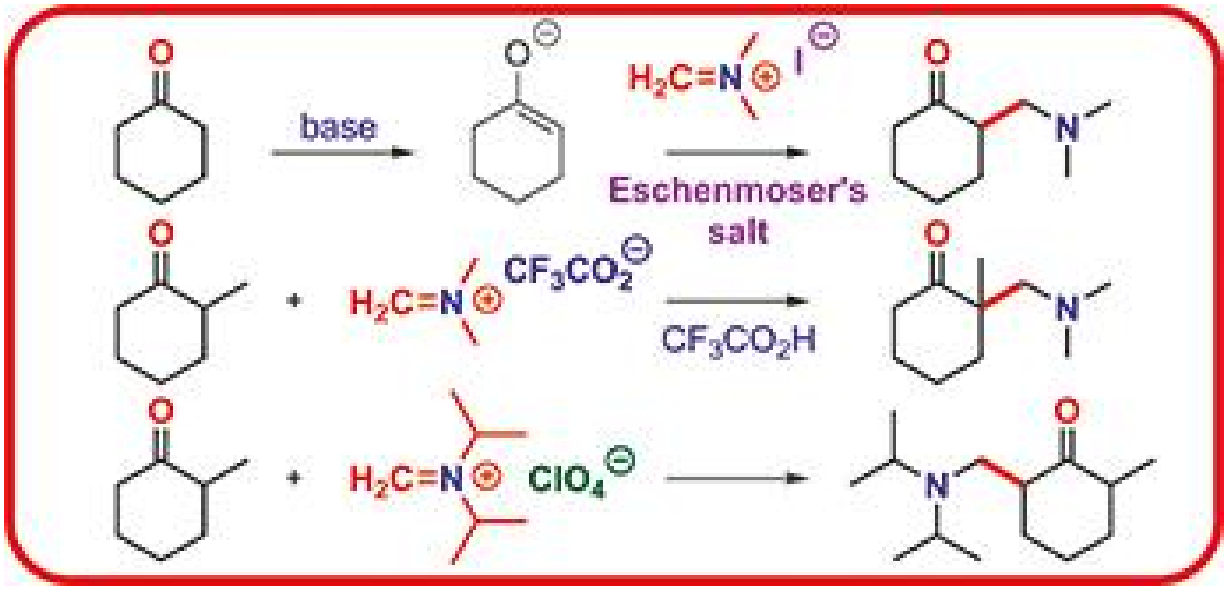


Fig. 56.3: Variations of the ***Mannich*** *reaction*.[201]

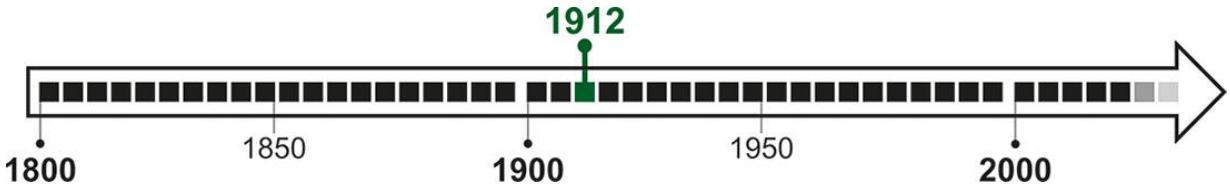


Fig. 56.4: The discovery of the ***Mannich*** *reaction*.[202]

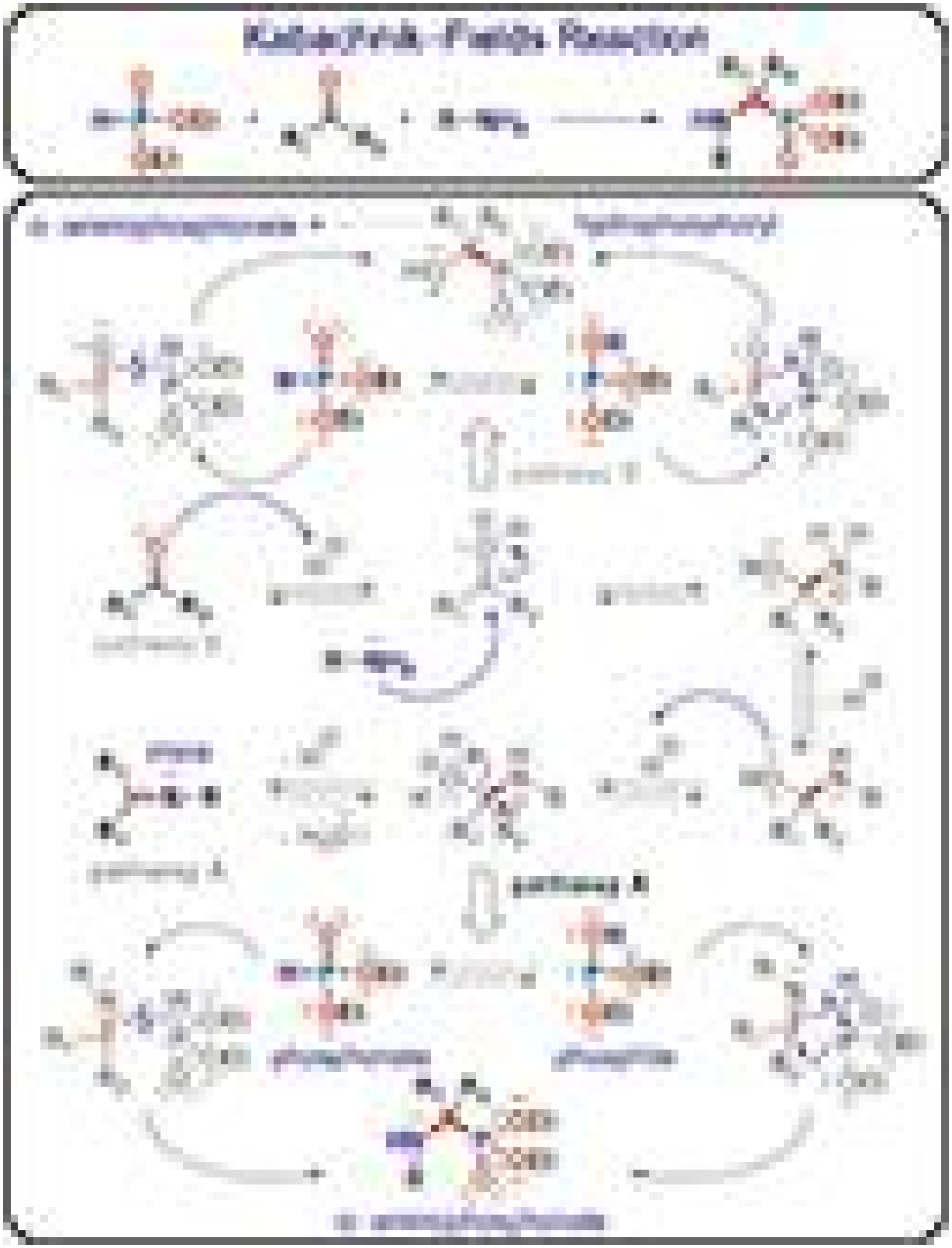


Fig. 56.5: The ***Kabachnik–Fields*** *reaction* mechanism.[203]

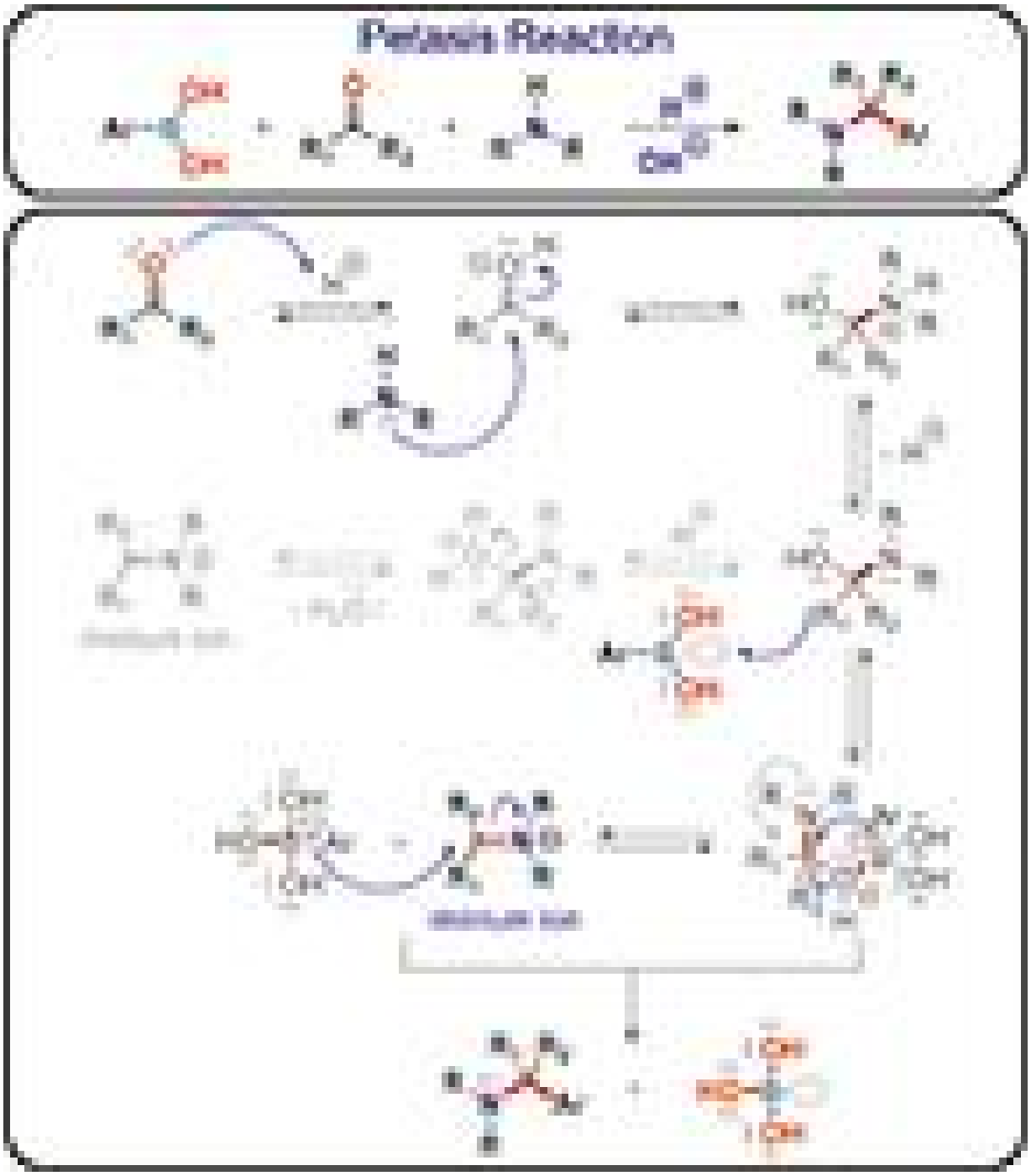


Fig. 56.6: The ***Petasis*** *reaction* mechanism.[204]

57 McMurry Coupling

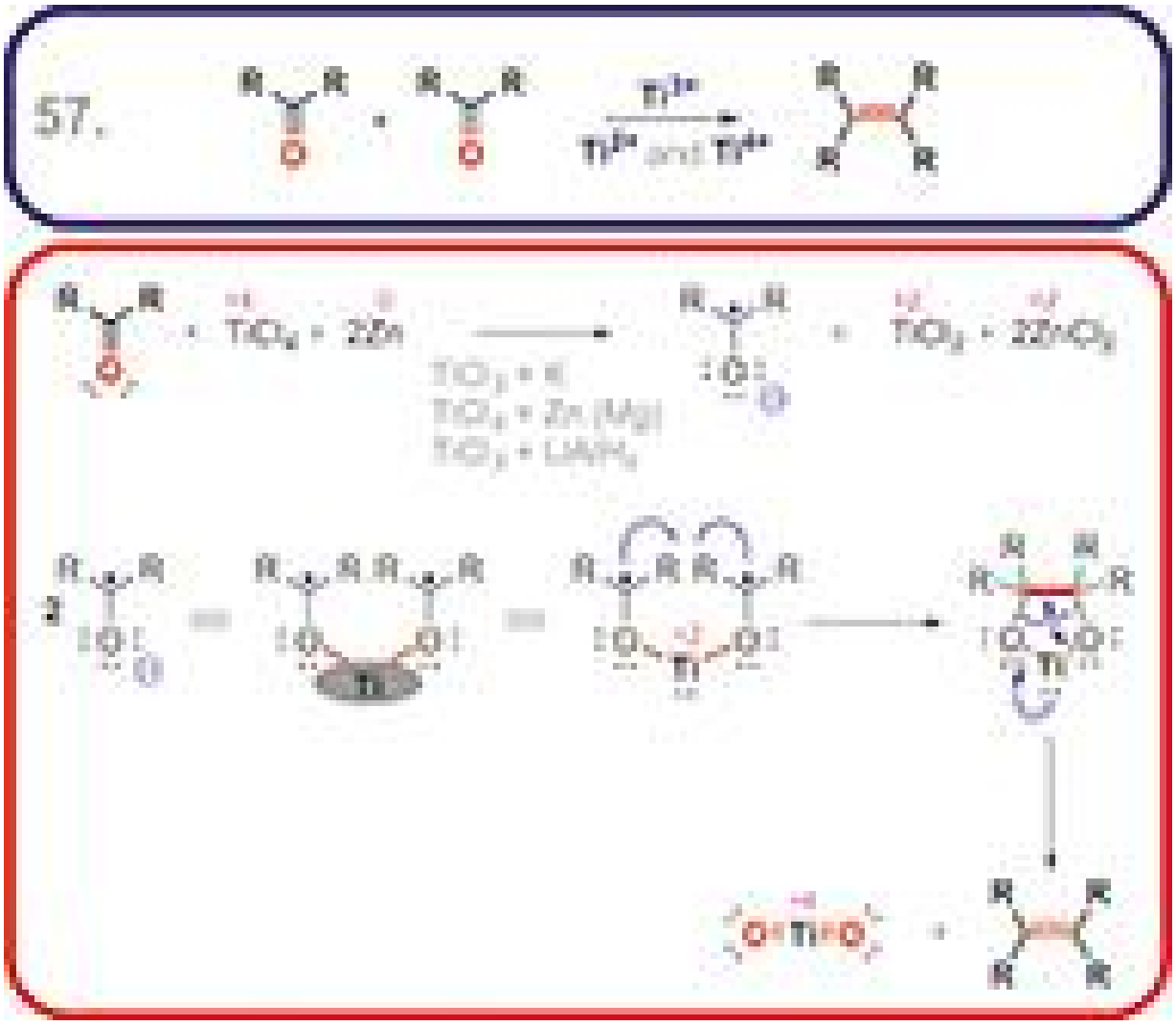


Fig. 57.1: The ***McMurry*** *coupling* mechanism.[205]

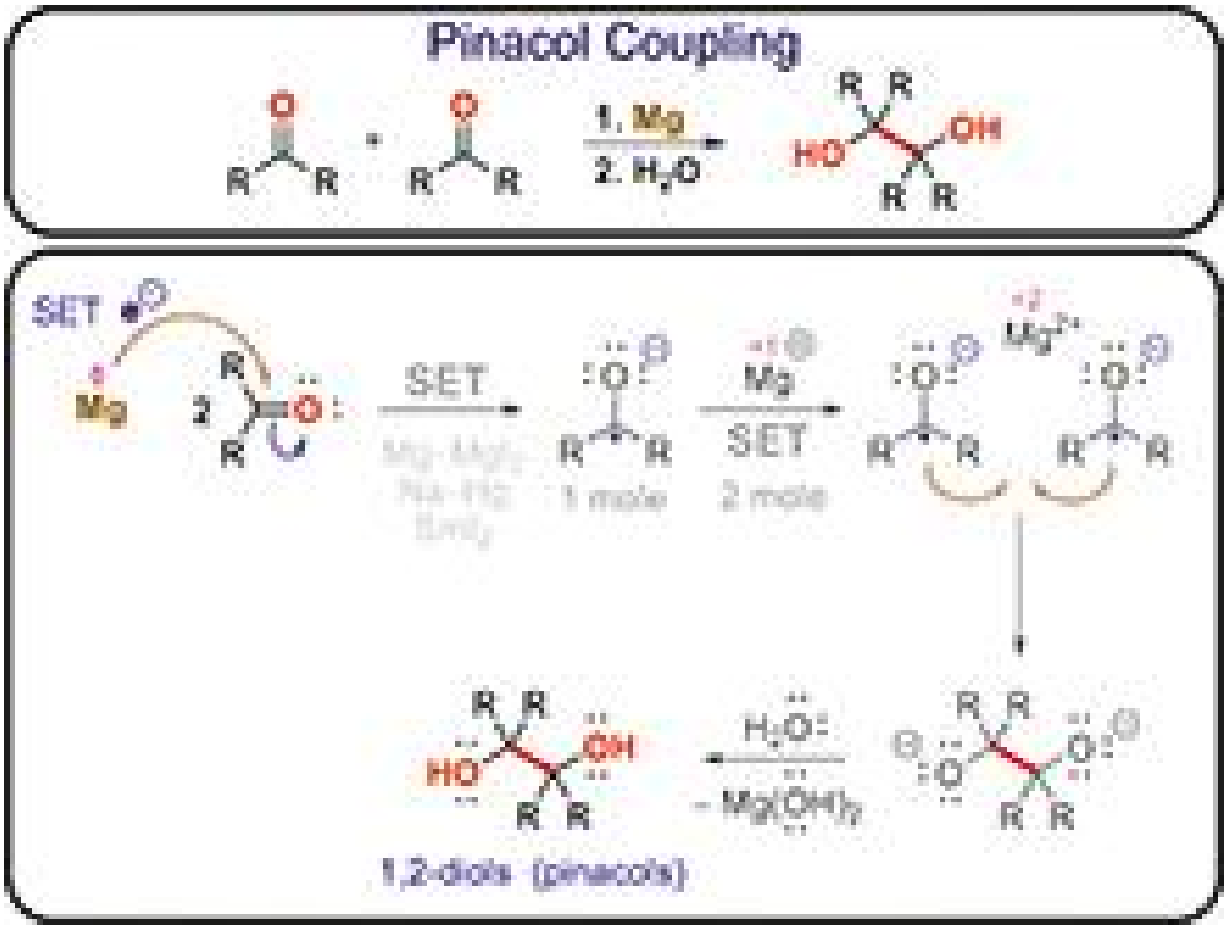


Fig. 57.2: The *pinacol coupling* mechanism.[206]

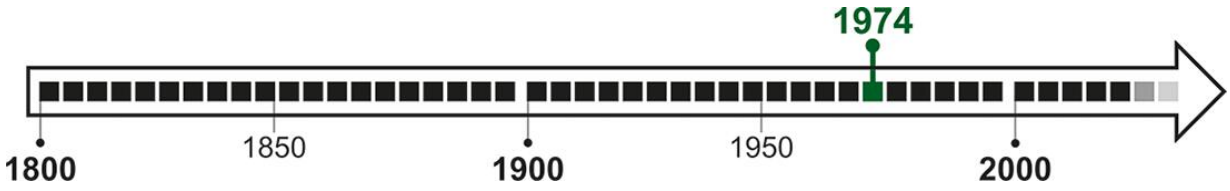


Fig. 57.3: The discovery of the ***McMurry*** *coupling*.[207]

58 Meerwein–Ponndorf–Verley Reduction

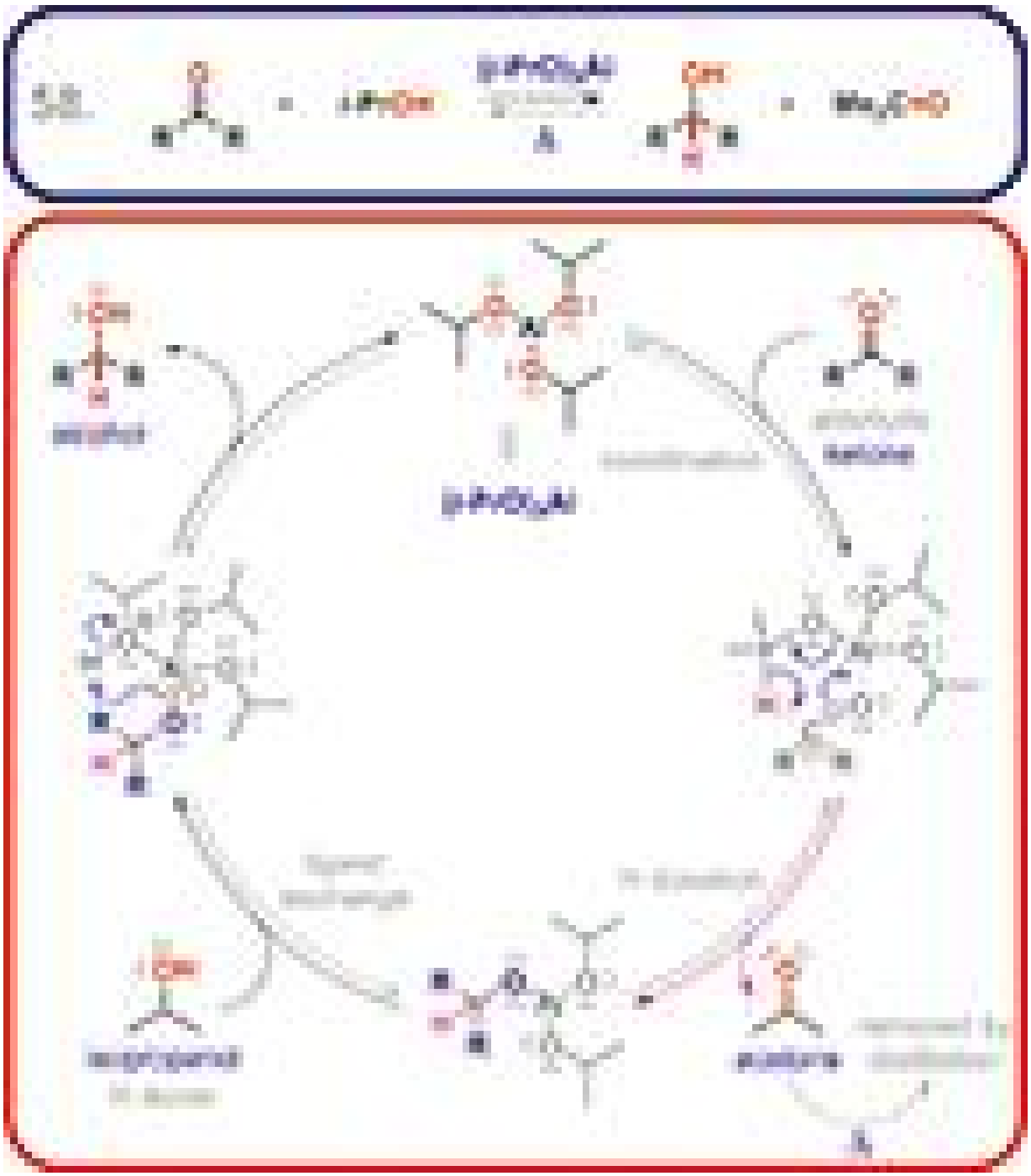


Fig. 58.1: The ***Meerwein–Ponndorf–Verley*** *reaction* mechanism.[208]

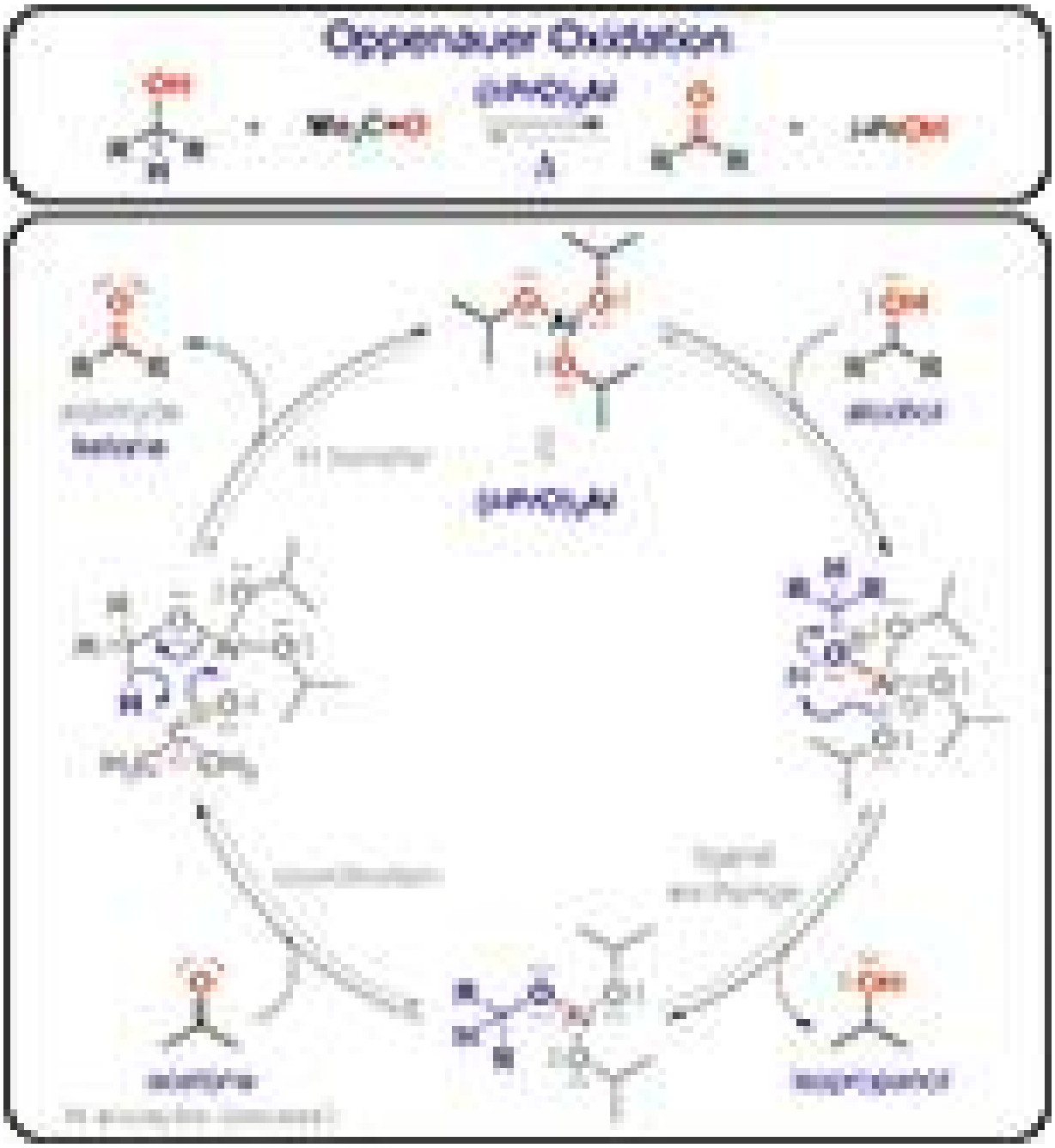


Fig. 58.2: The ***Oppenauer*** *oxidation* mechanism.[209]

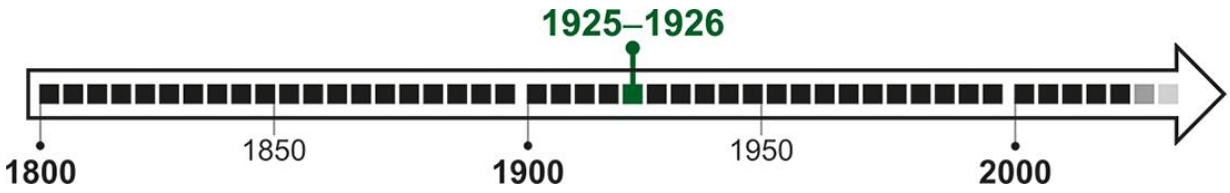


Fig. 58.3: The discovery of the ***Meerwein–Ponndorf–Verley*** *reaction*.[210]

59 Michael Addition

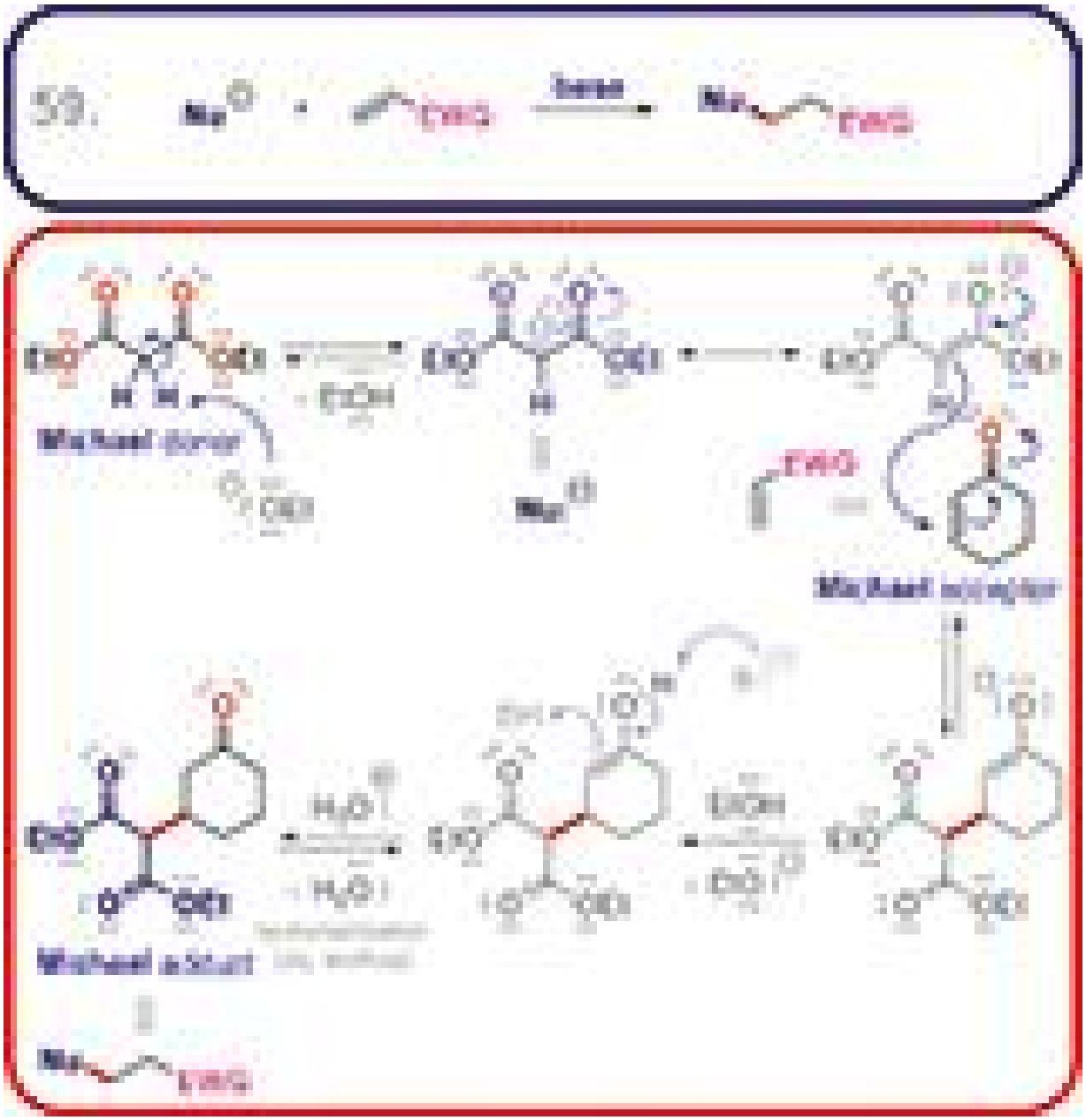


Fig. 59.1: The ***Michael*** *addition* mechanism.[211]

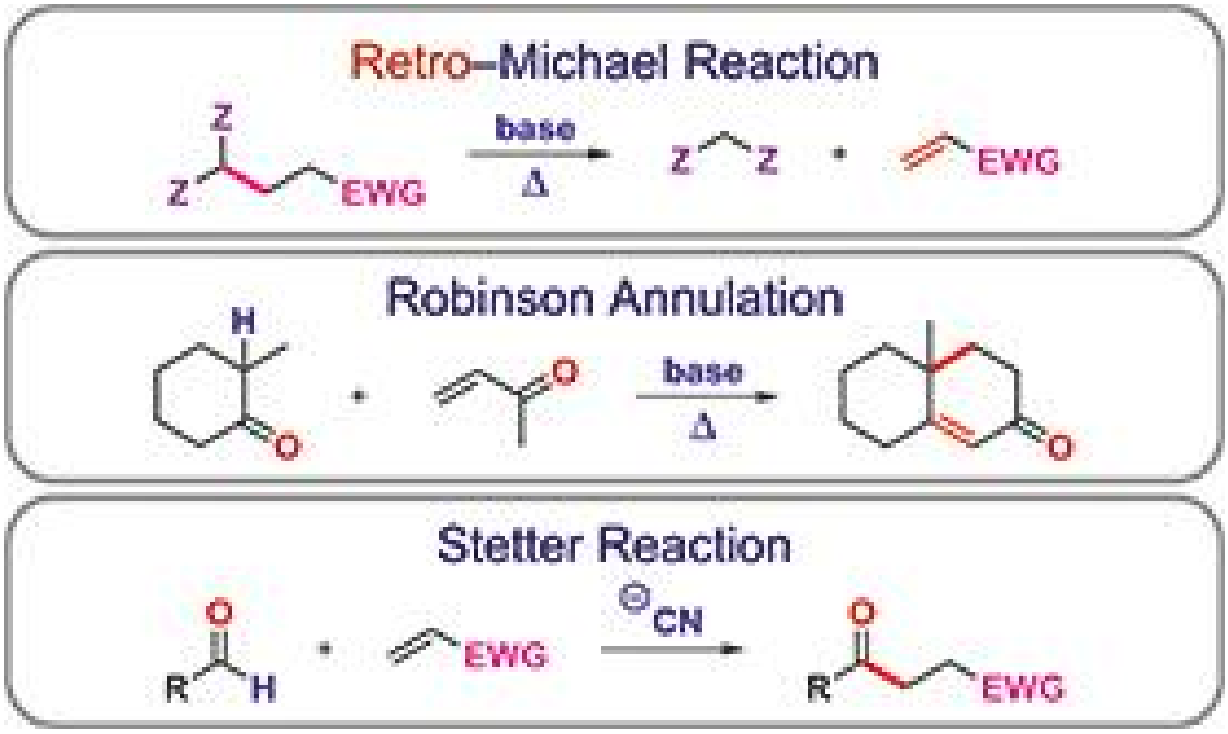


Fig. 59.2: Reactions related to the ***Michael*** *addition*.[212]

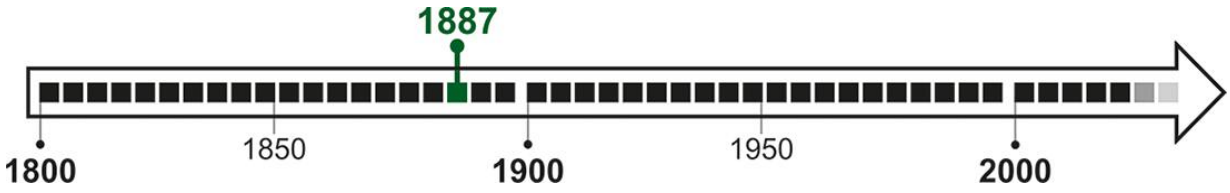


Fig. 59.3: The discovery of the ***Michael*** *addition*.[213]

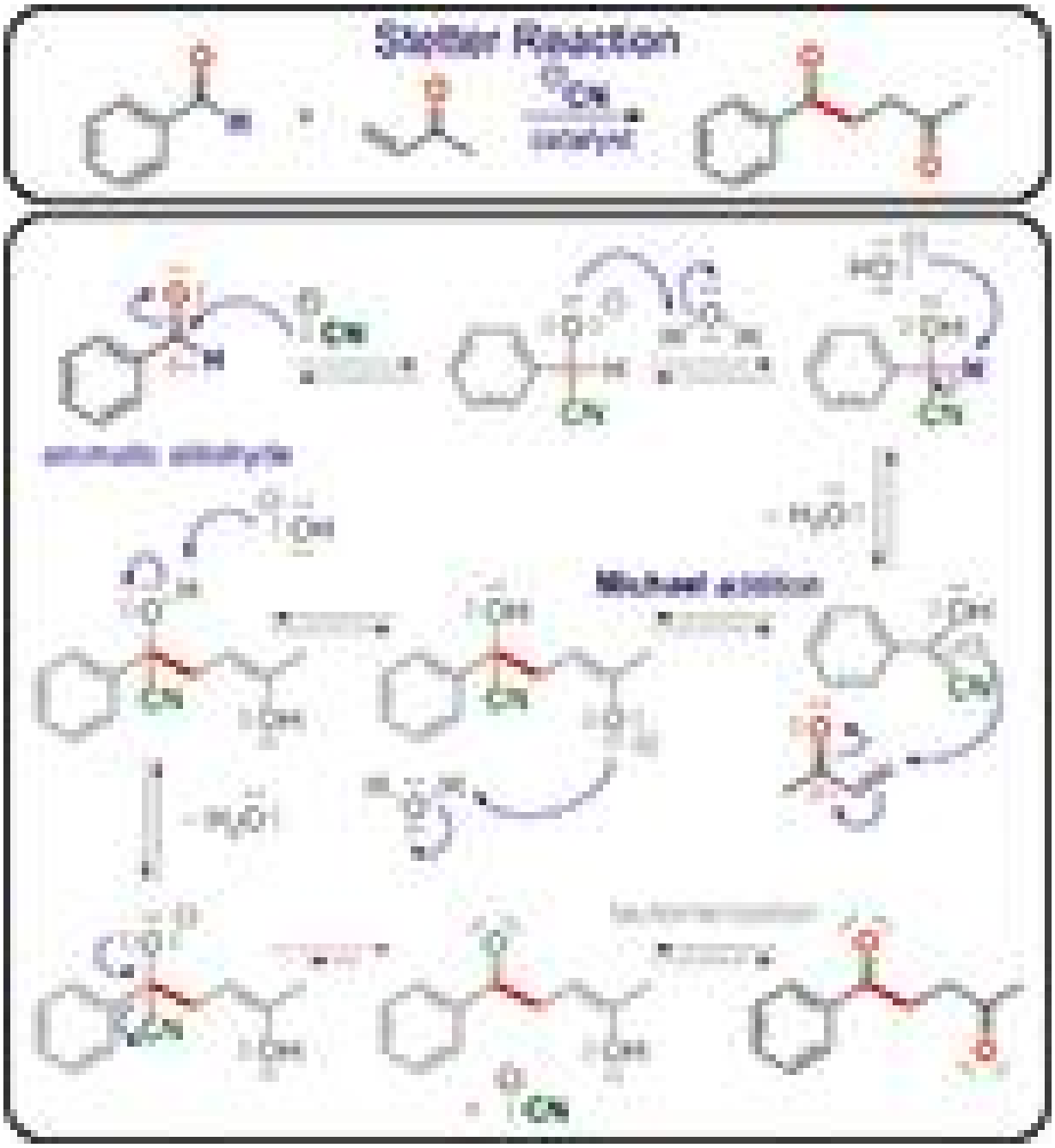


Fig. 59.4: The ***Stetter*** *reaction* mechanism (aromatic aldehyde).[214]

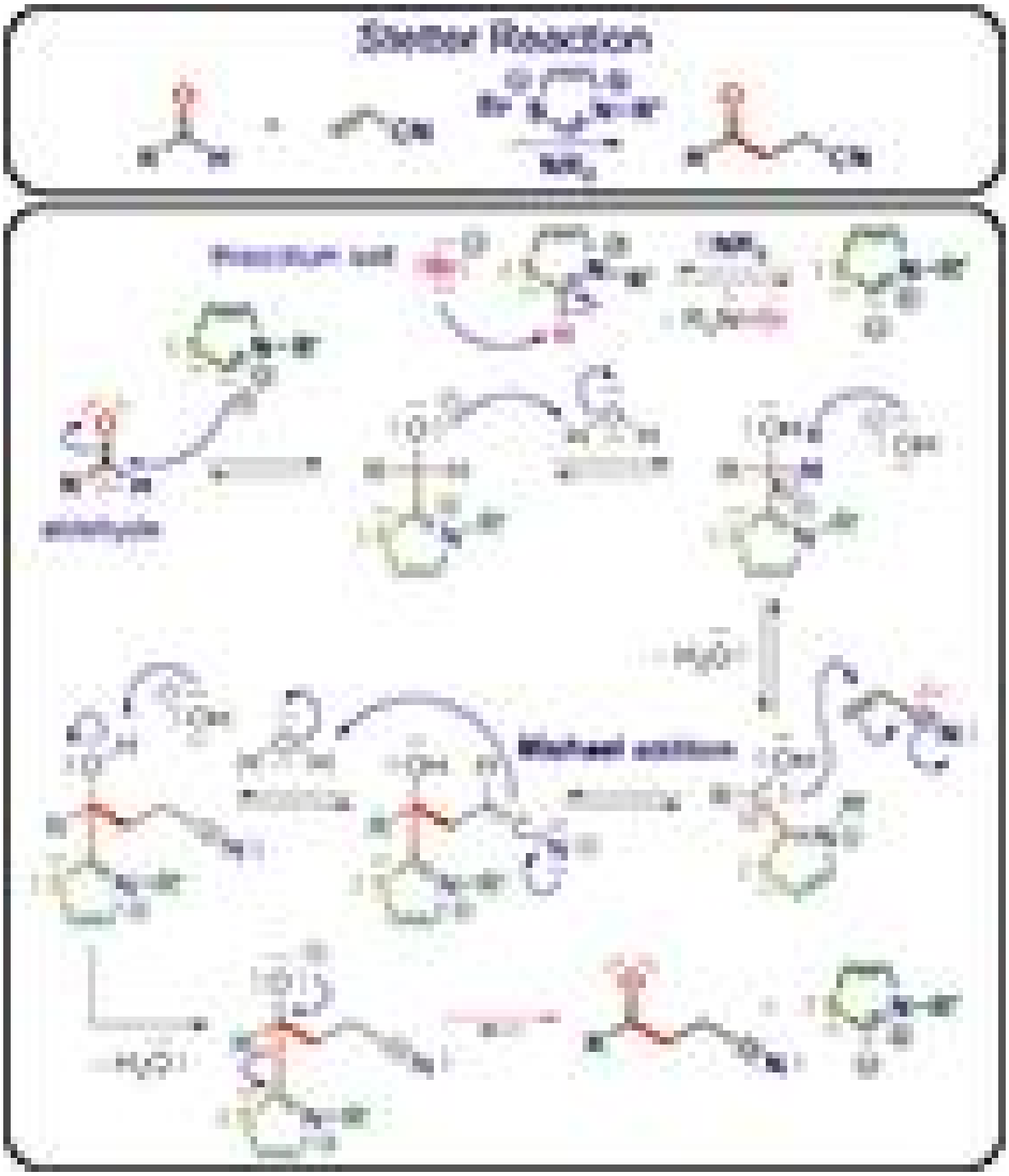


Fig. 59.5: The ***Stetter*** *reaction* mechanism (aliphatic aldehyde).[215]

60 Minisci Reaction

Fig. 60.1: The ***Minisci*** *reaction* mechanism.[216]

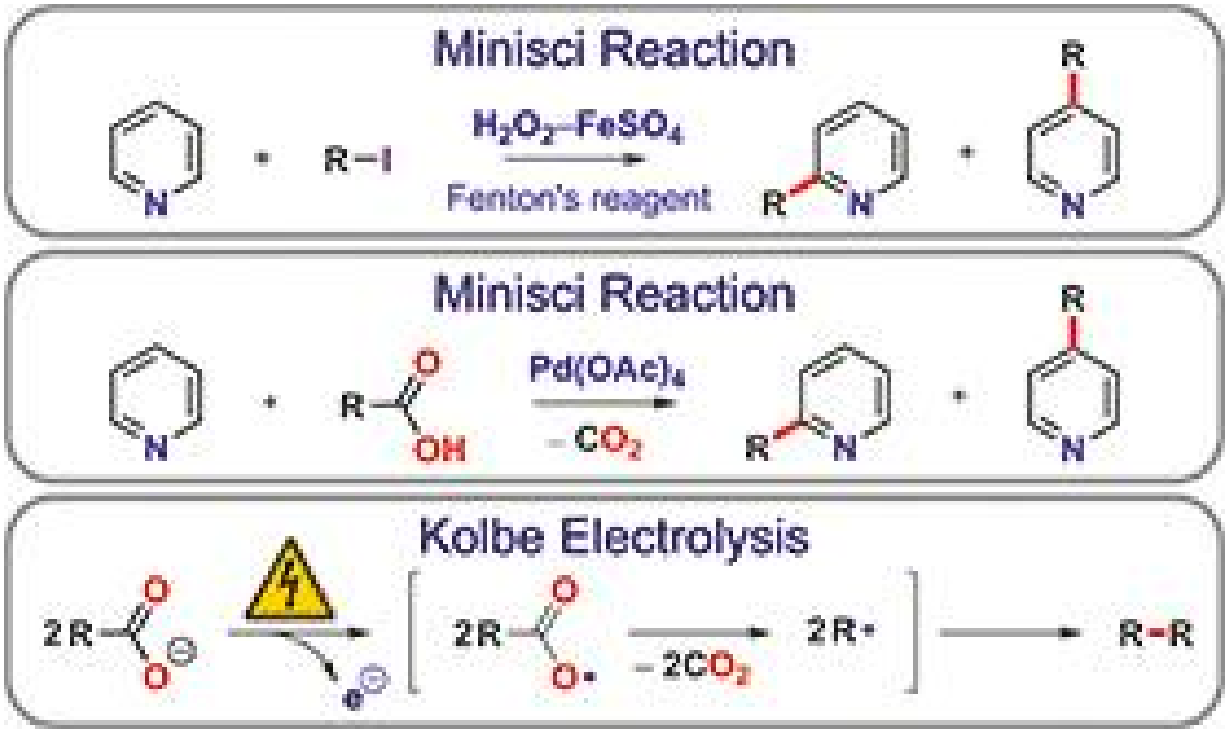


Fig. 60.2: Variations of the ***Minisci*** *reaction*.[217]

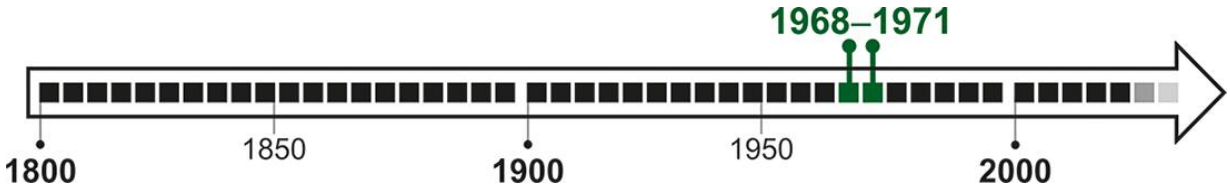


Fig. 60.3: The discovery of the ***Minisci*** *reaction*.[218]

61 Mitsunobu Reaction

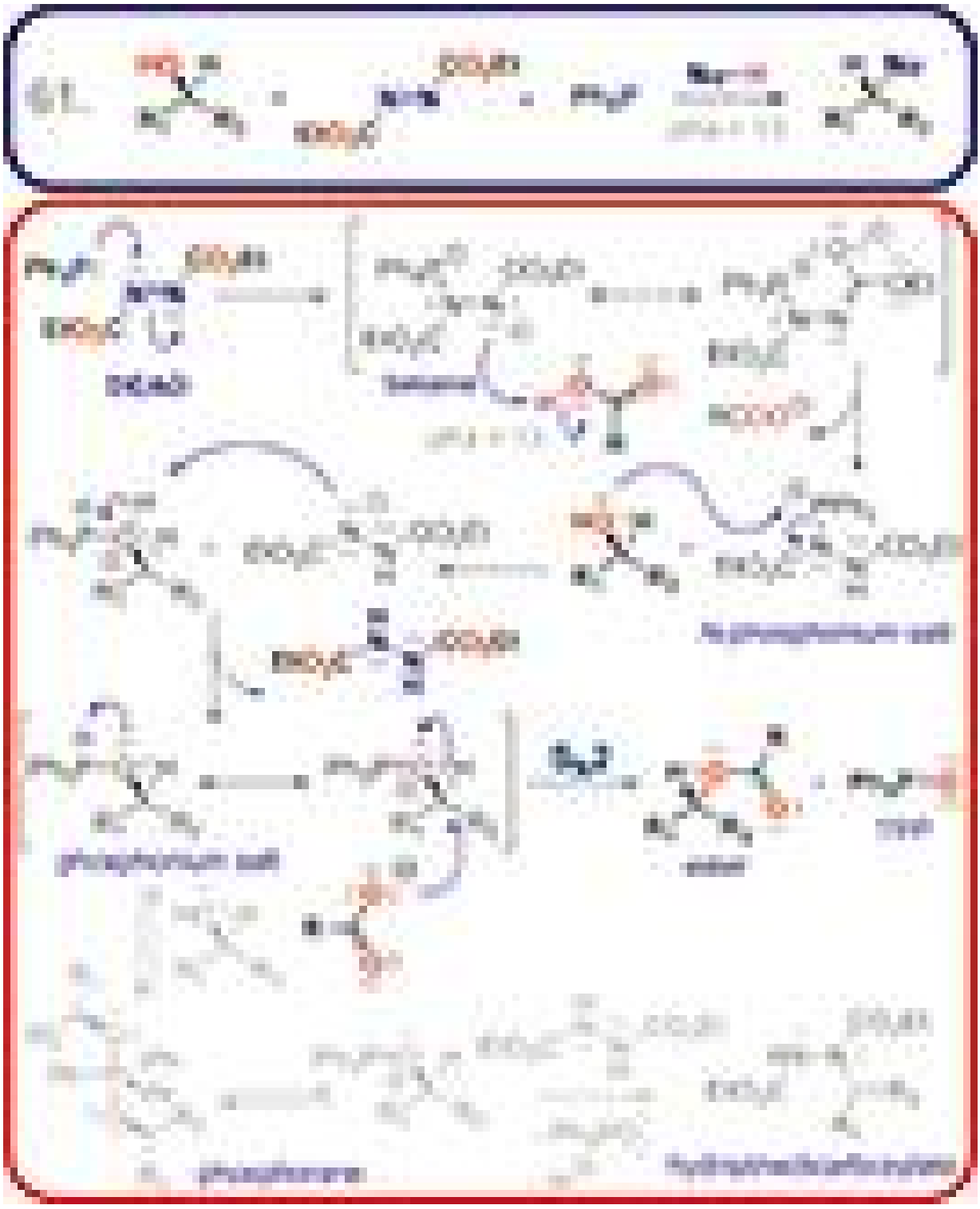


Fig. 61.1: The ***Mitsunobu*** *reaction* mechanism.[219]

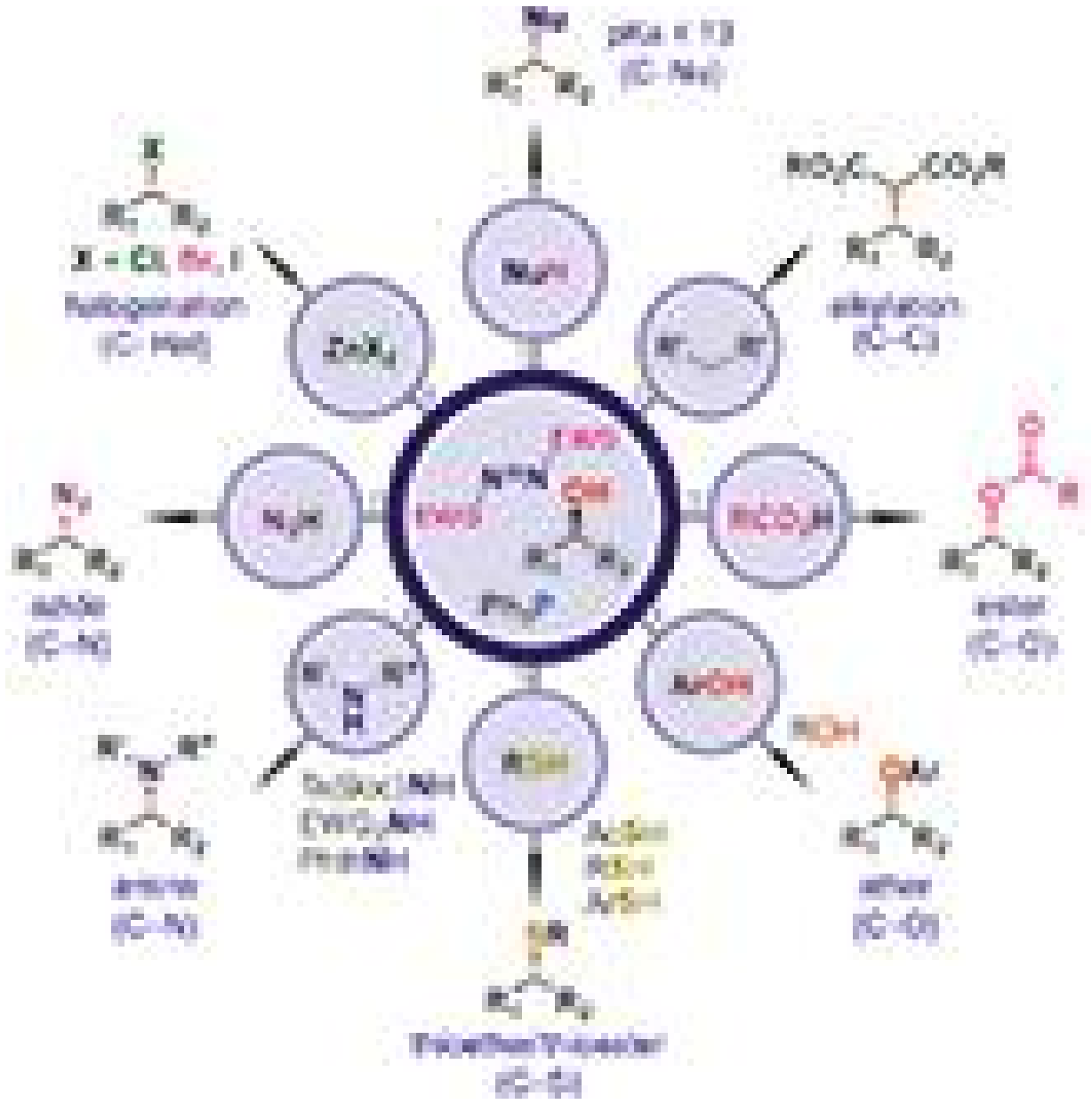


Fig. 61.2: Synthetic versatility of the ***Mitsunobu*** *reaction*.[220]

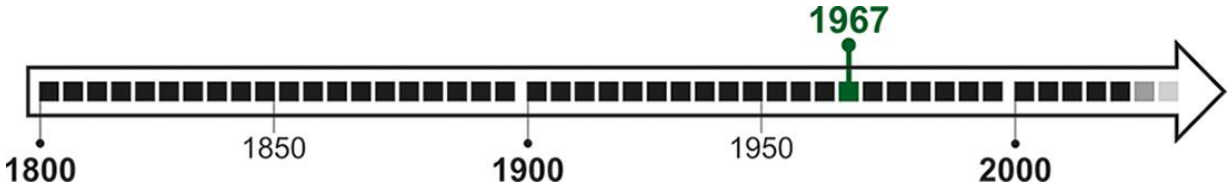


Fig. 61.3: The discovery of the ***Mitsunobu*** *reaction*.[221]

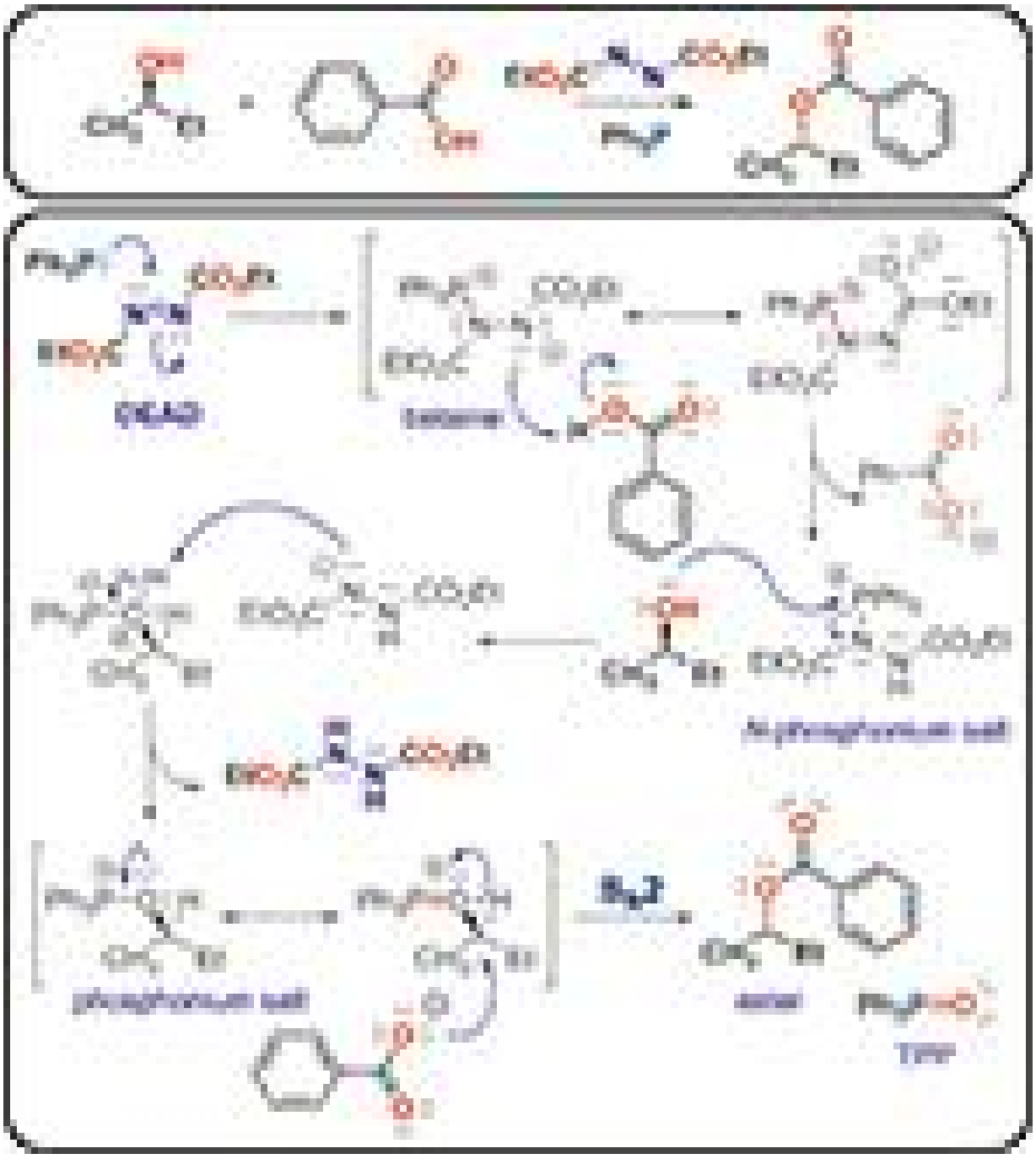


Fig. 61.4: The ***Mitsunobu*** *reaction* mechanism (ester synthesis).[222]

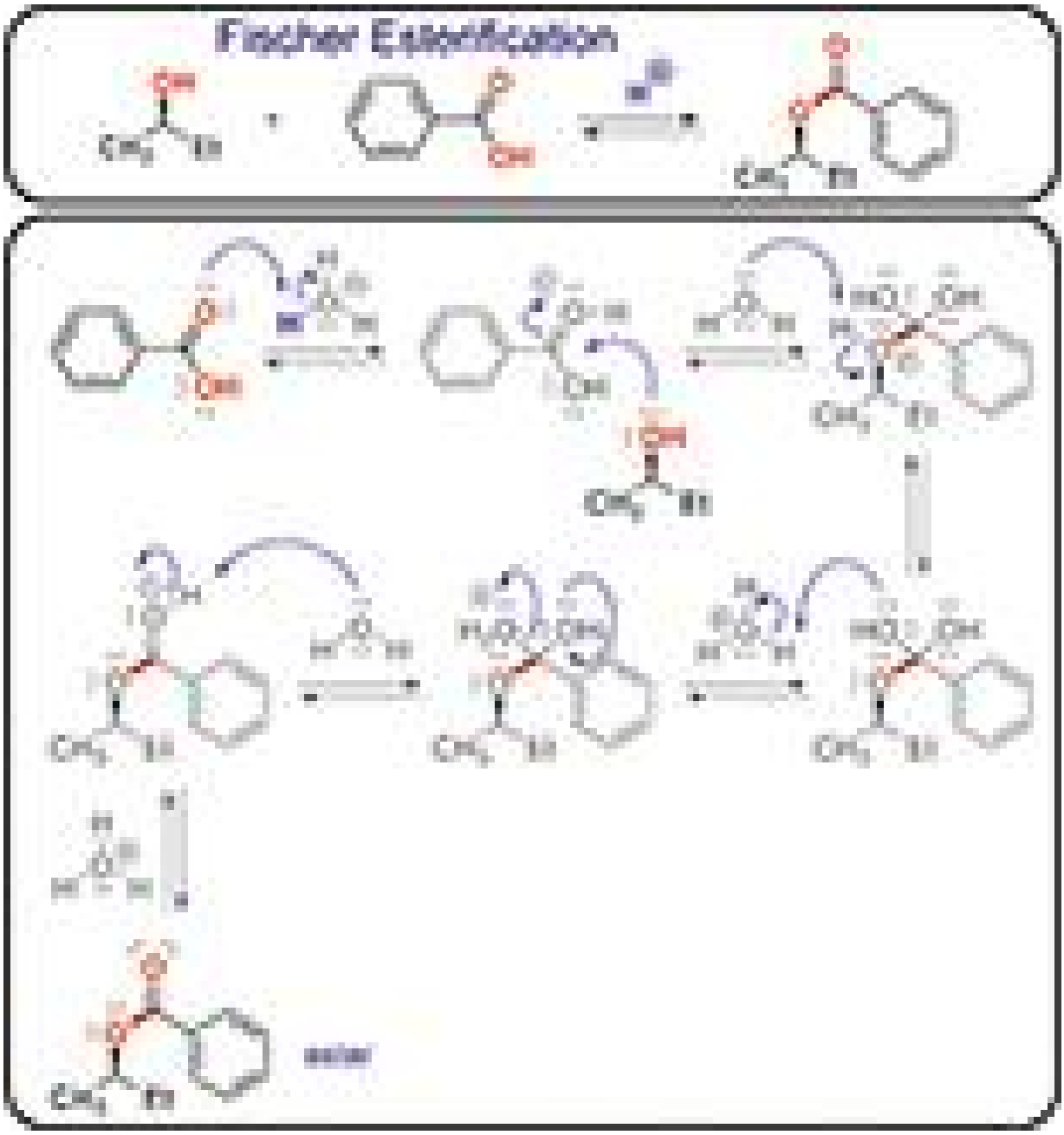


Fig. 61.5: The ***Fischer*** *esterification* mechanism.[223]

62 Miyaura Borylation

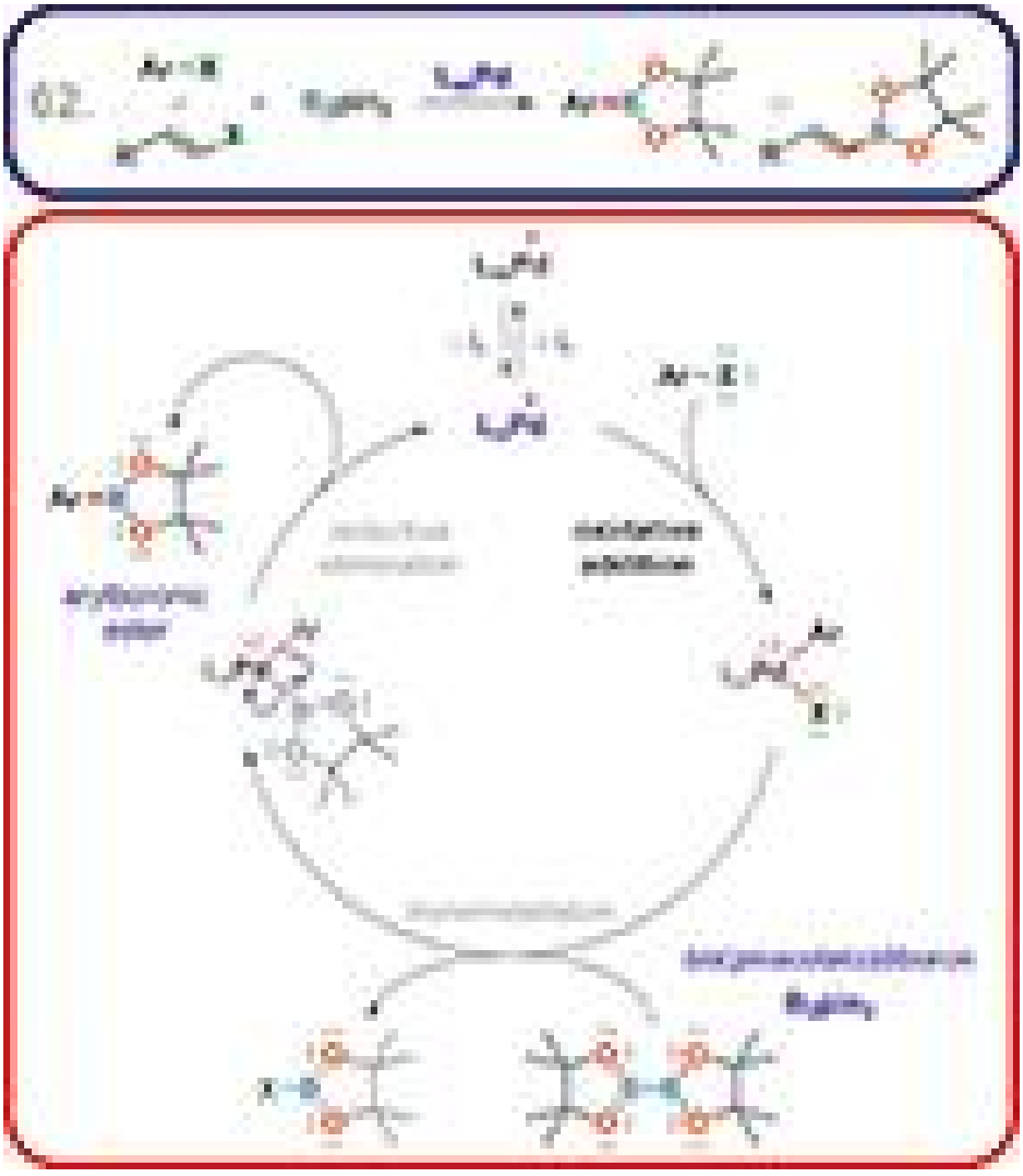


Fig. 62.1: The ***Miyaura*** *borylation* mechanism.[224]

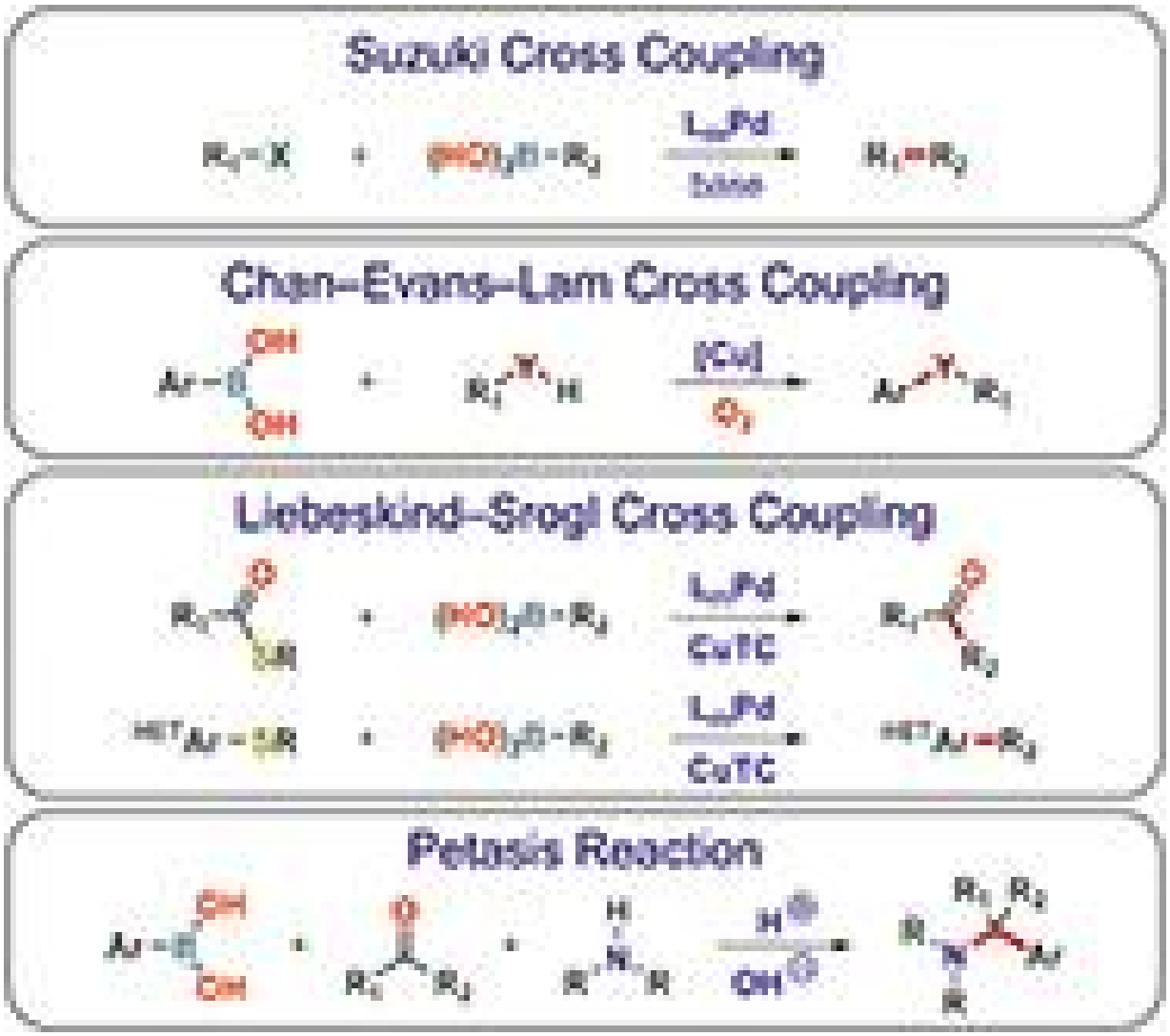


Fig. 62.2: Synthetic application of boronic esters and acids.[225]

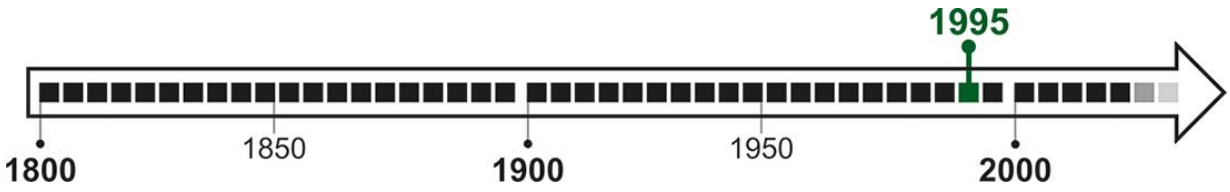


Fig. 62.3: The discovery of the ***Miyaura*** *borylation*.[226]

63 Mukaiyama RedOx Hydration

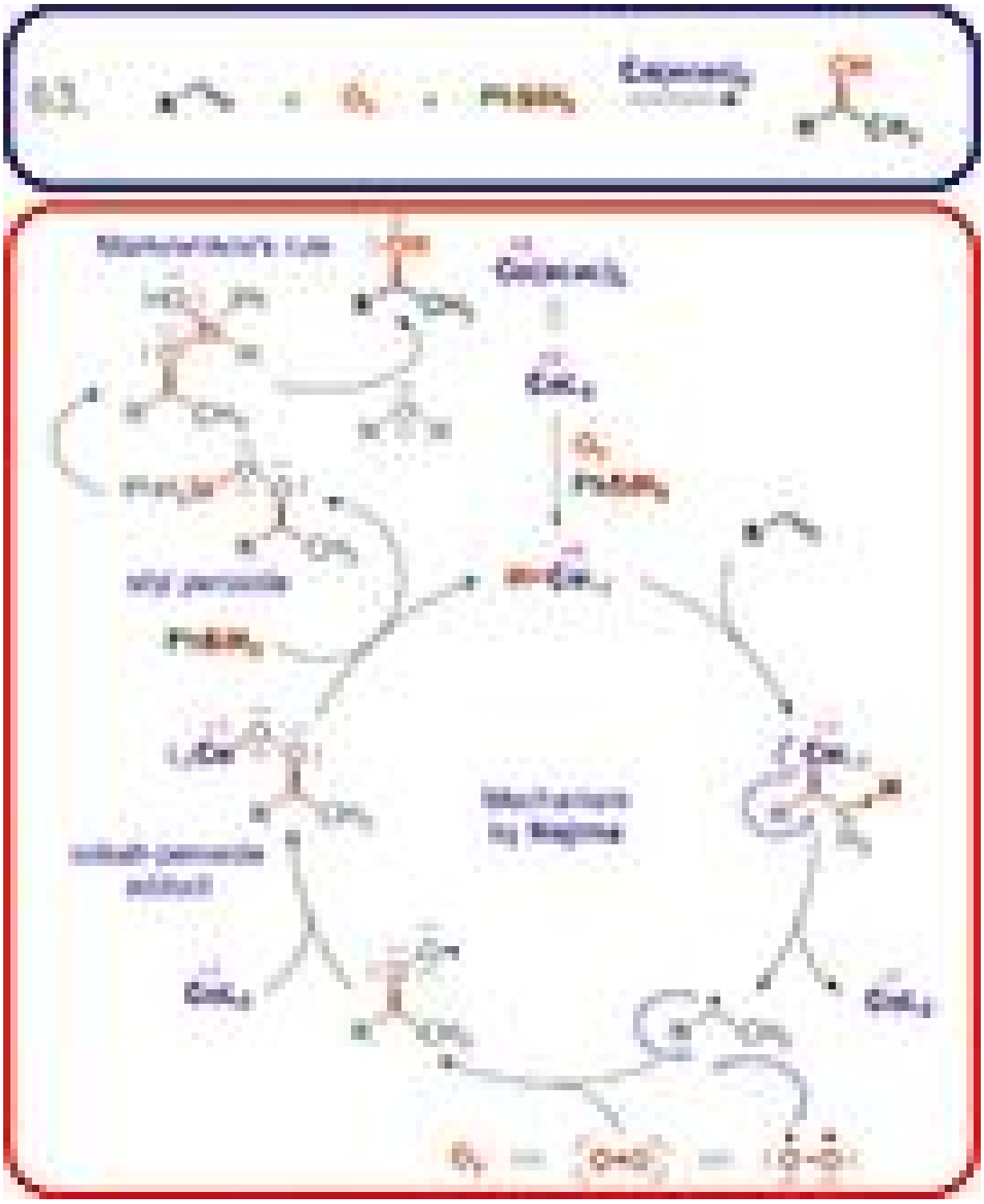


Fig. 63.1: The ***Mukaiyama*** *RedOx hydration* mechanism by **Nojima**.[227]

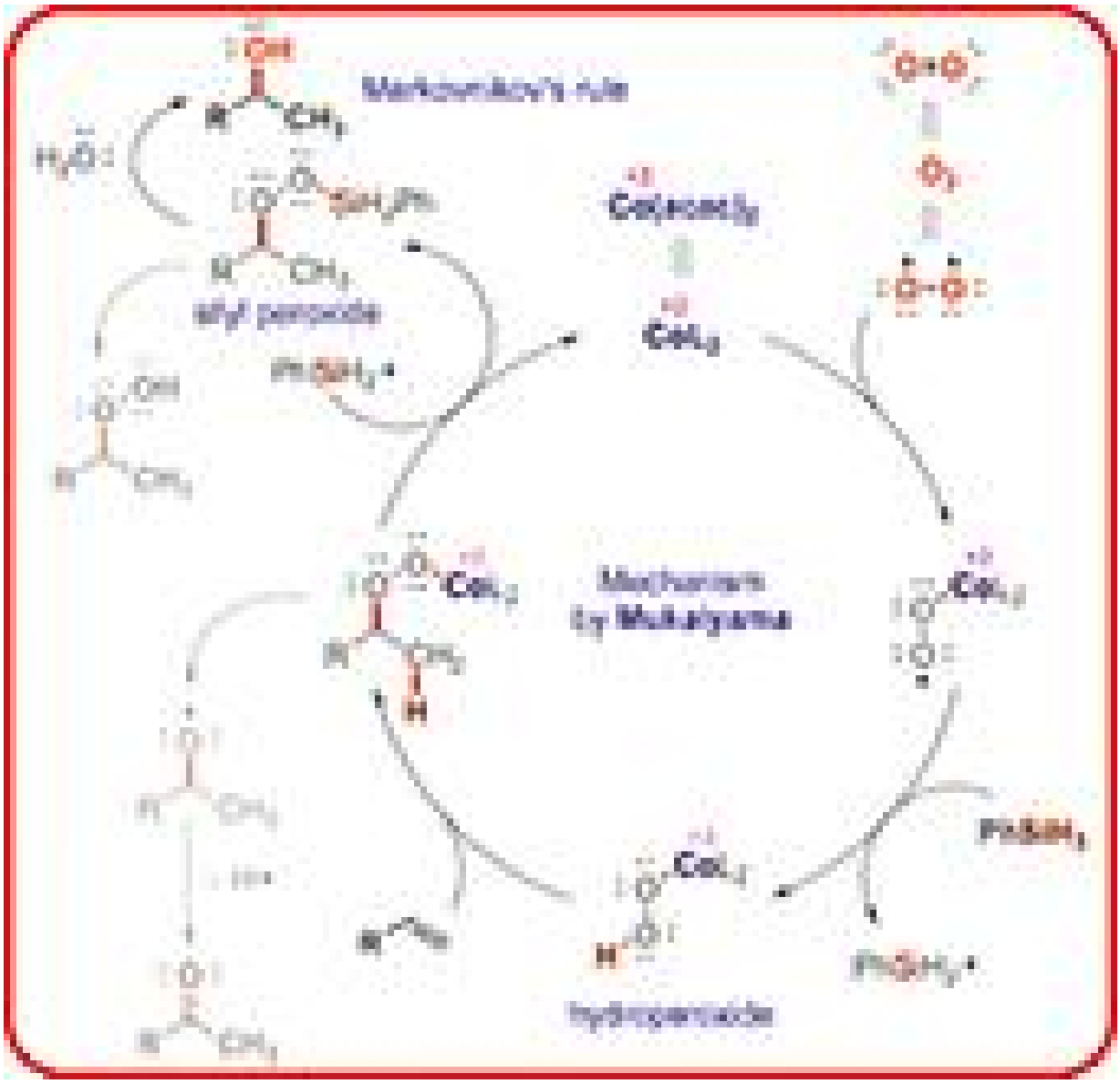


Fig. 63.2: The ***Mukaiyama*** *oxidation–reduction hydration* mechanism by **Mukaiyama**.[228]

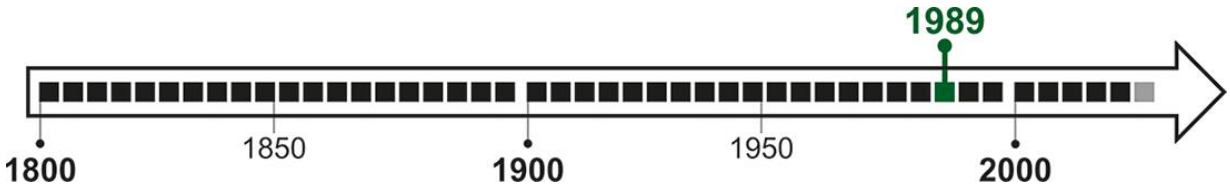


Fig. 63.3: The discovery of the ***Mukaiyama*** *oxidation–reduction hydration*.[229]

64 Nazarov Cyclization

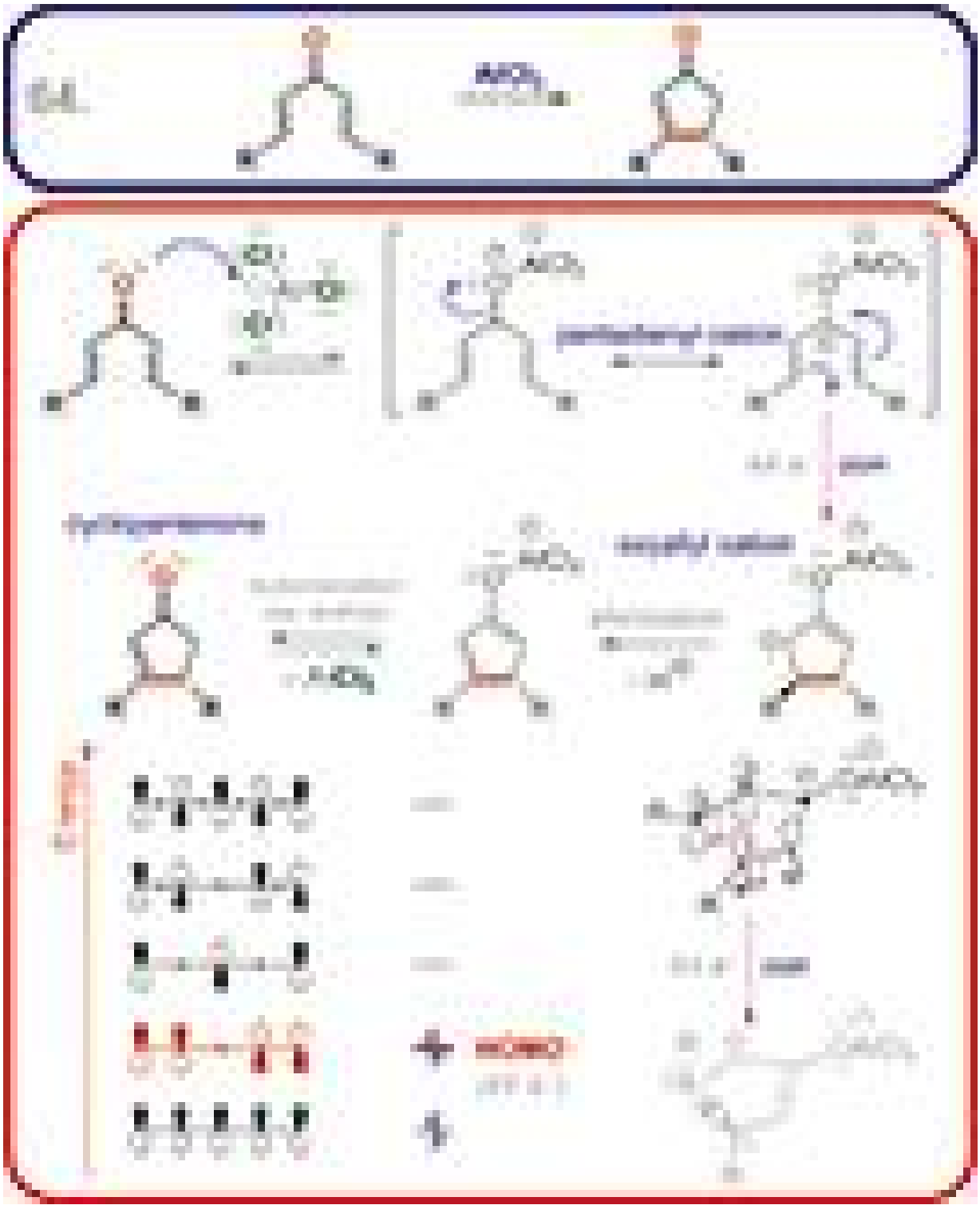


Fig. 64.1: The ***Nazarov*** *cyclization* mechanism.[230]

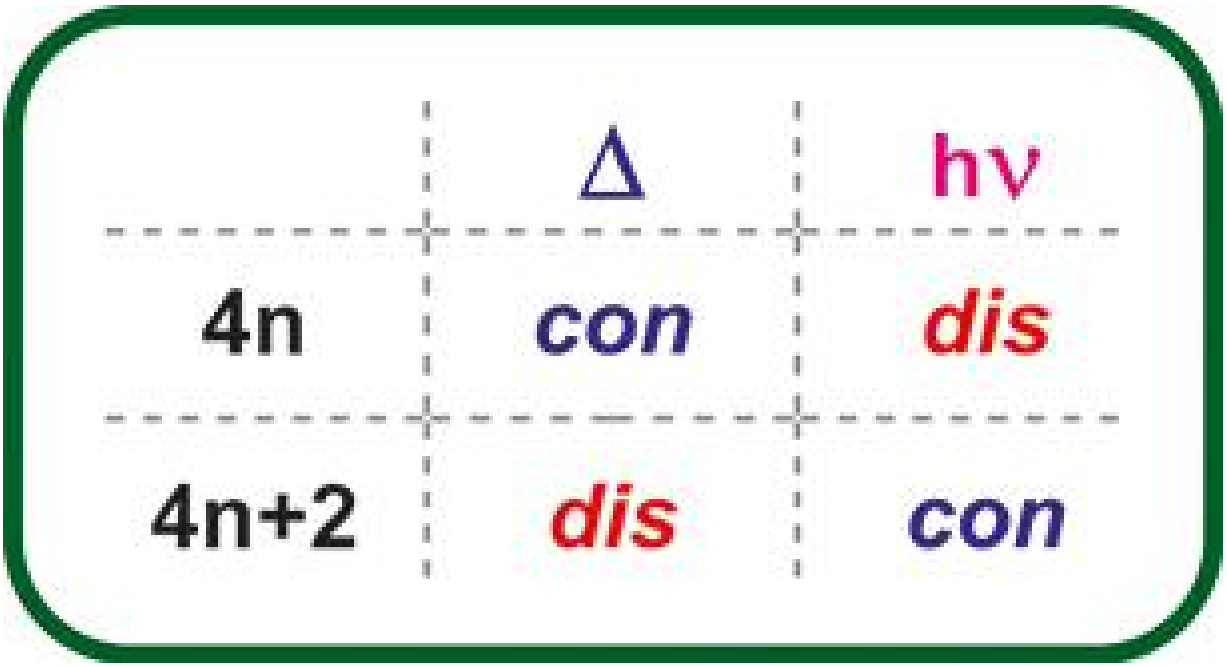


Fig. 64.2: The ***Woodward–Hoffmann*** *rules* (the pericyclic selection rules).[231]

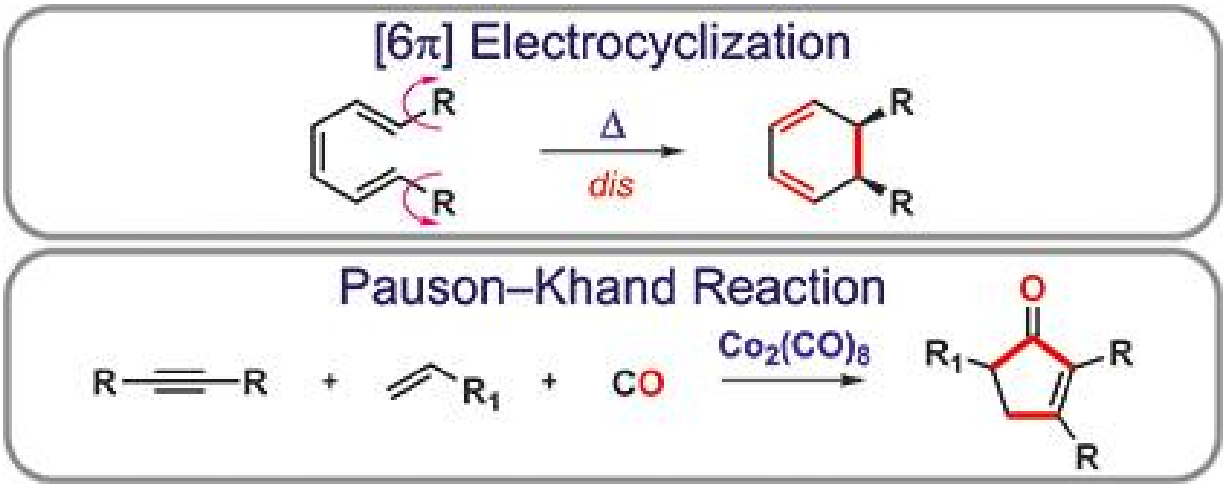


Fig. 64.3: Reactions related to the ***Nazarov*** *cyclization*.[232]

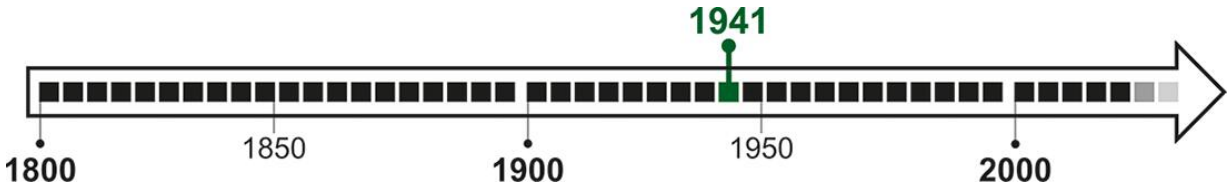


Fig. 64.4: The discovery of the ***Nazarov*** *cyclization*.[233]

65 Nef Reaction

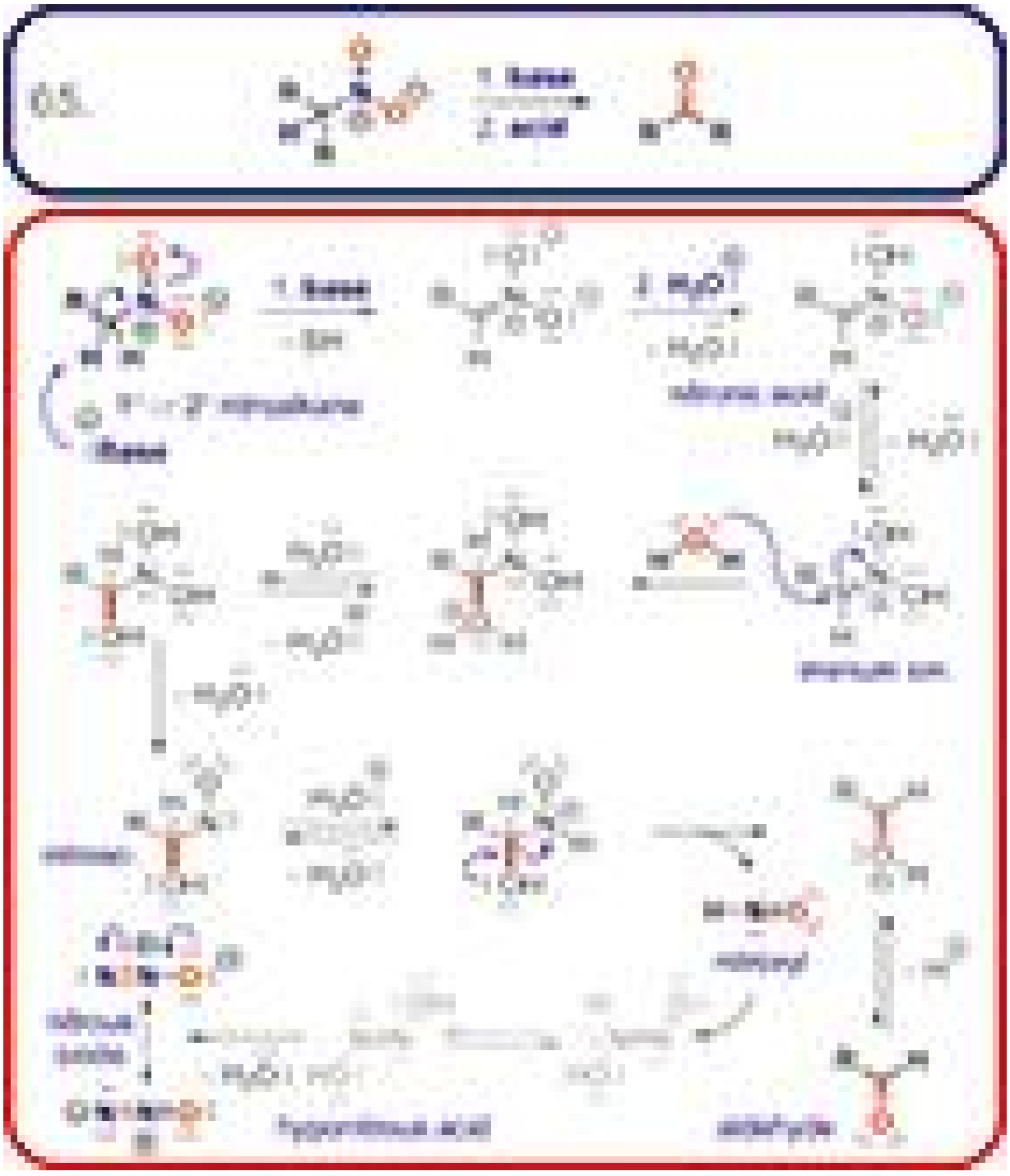


Fig. 65.1: The ***Nef*** *reaction* mechanism (base–acid-catalyzed).[234]

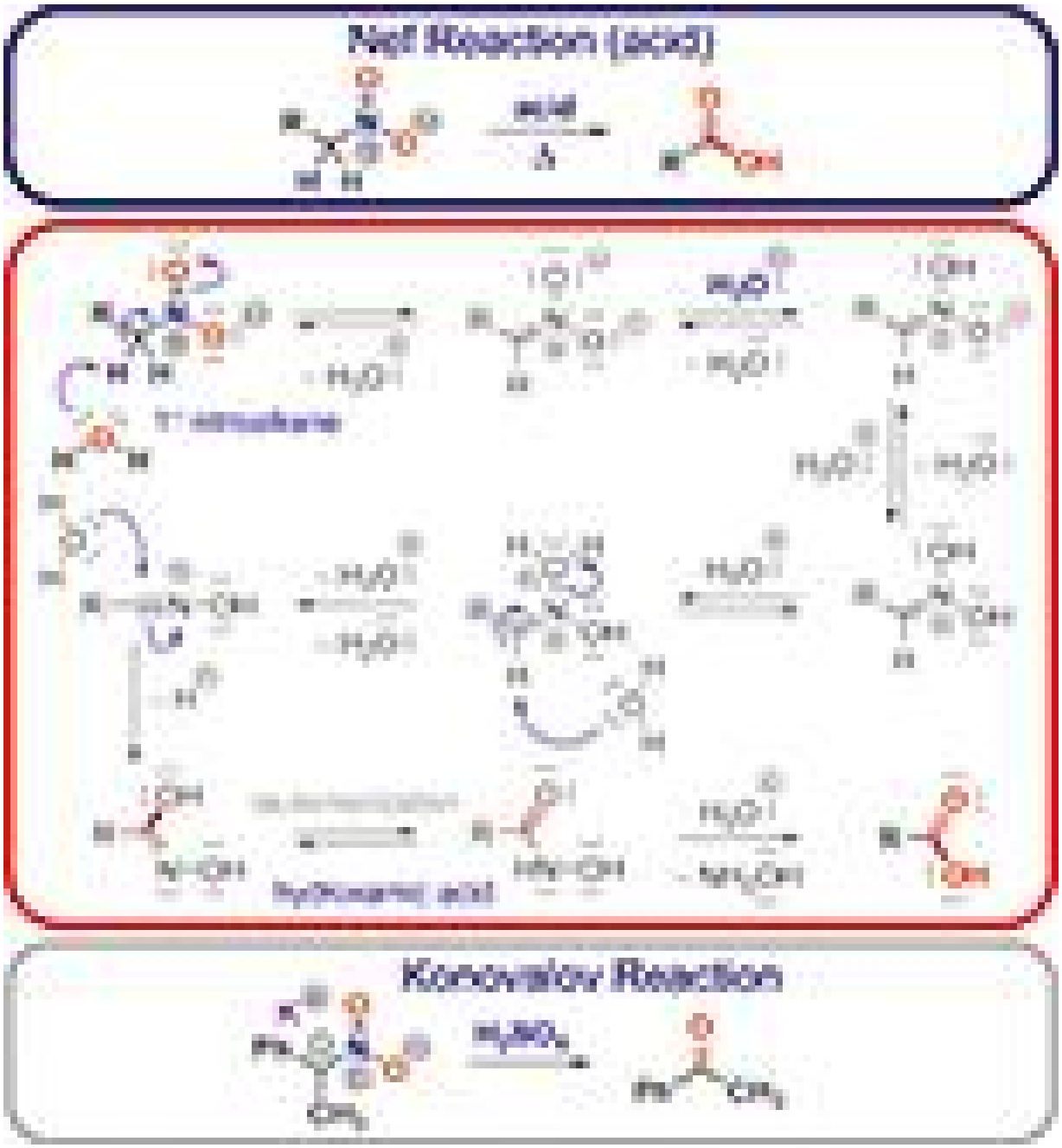


Fig. 65.2: The ***Nef*** *reaction* mechanism (acid-catalyzed).[235]

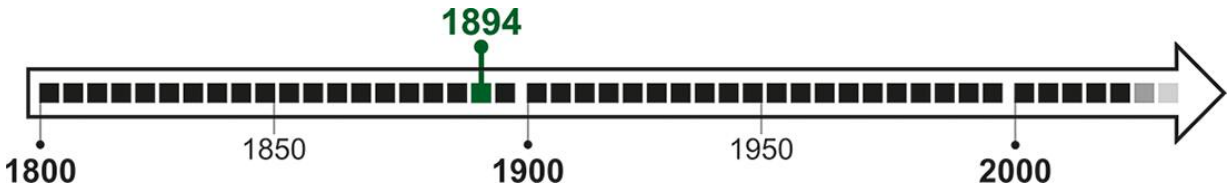


Fig. 65.3: The discovery of the ***Nef*** *reaction*.[236]

66 Negishi Cross-Coupling

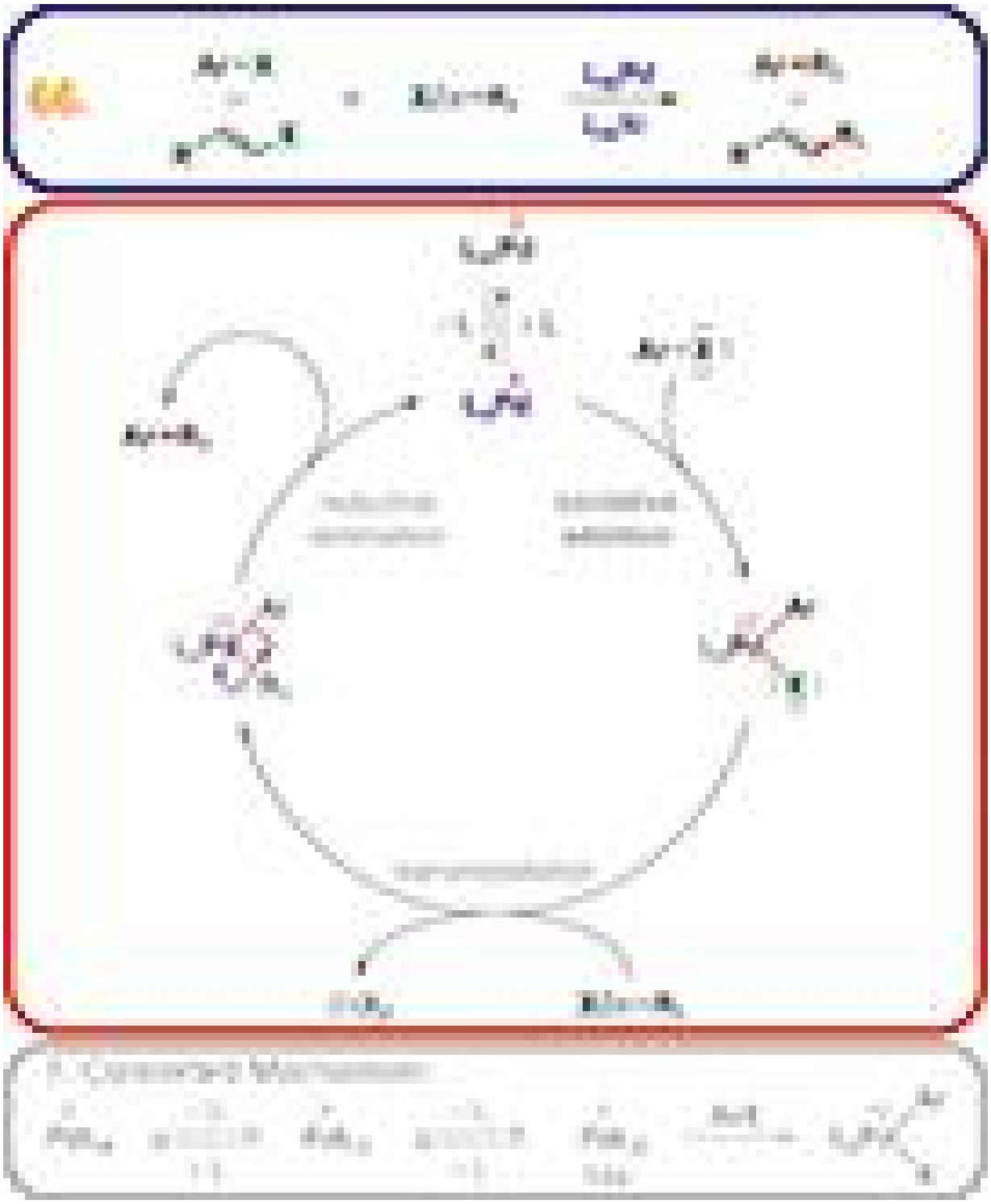


Fig. 66.1: The **Pd**-catalyzed ***Negishi*** *cross-coupling* mechanism.[237]

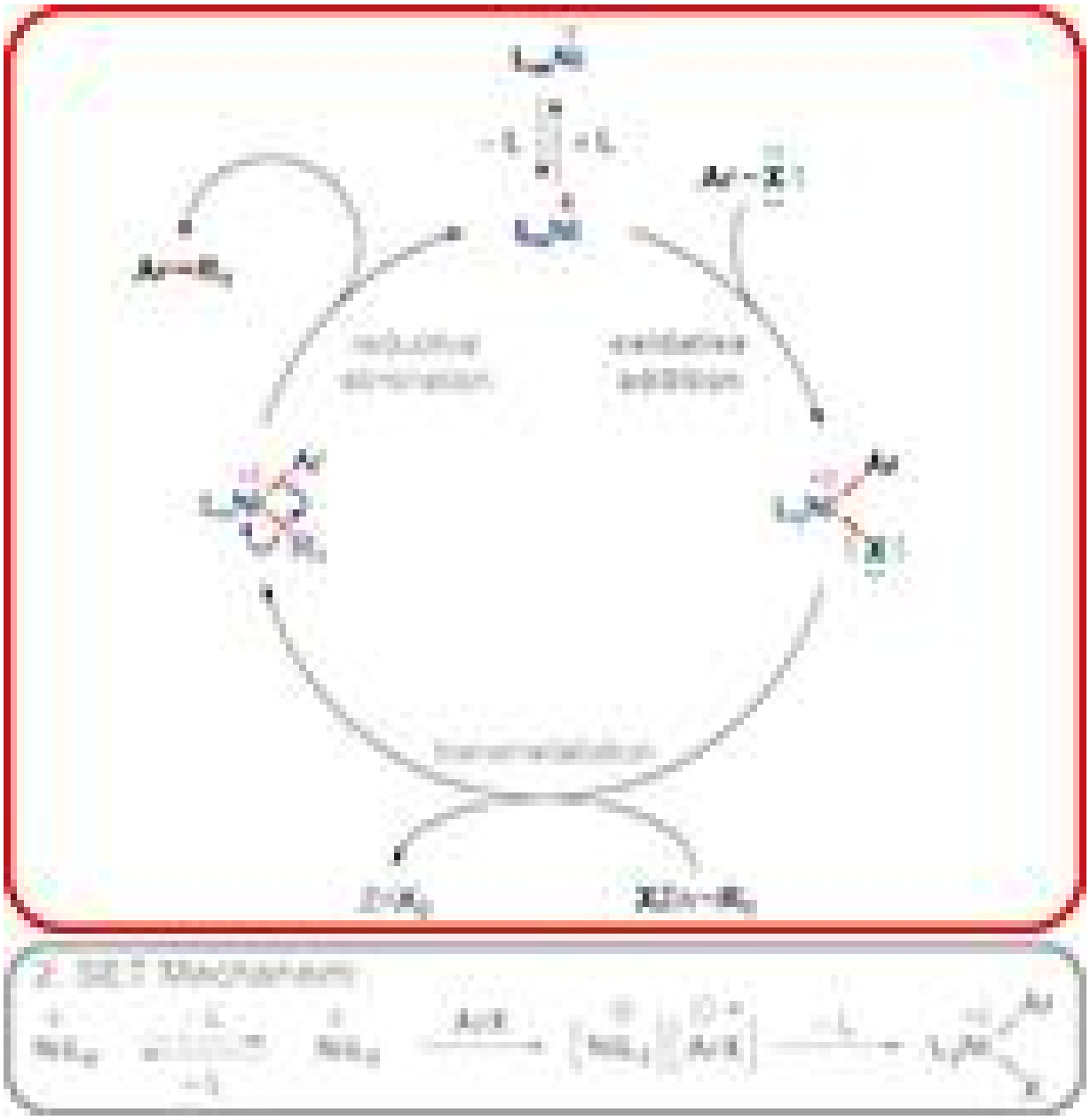


Fig. 66.2: The **Ni**-catalyzed ***Negishi*** *cross-coupling* mechanism.[238]

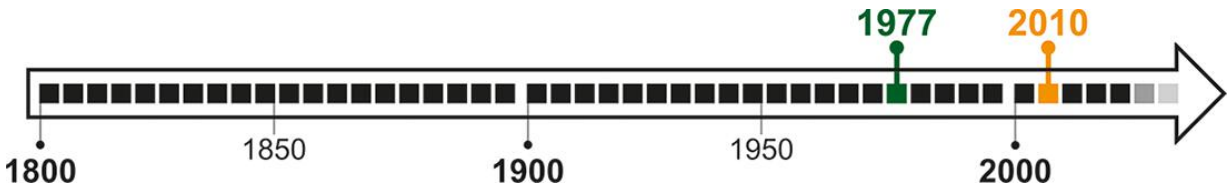


Fig. 66.3: The discovery of the ***Negishi*** *cross-coupling*.[239]

67 Norrish Type I and II Reactions

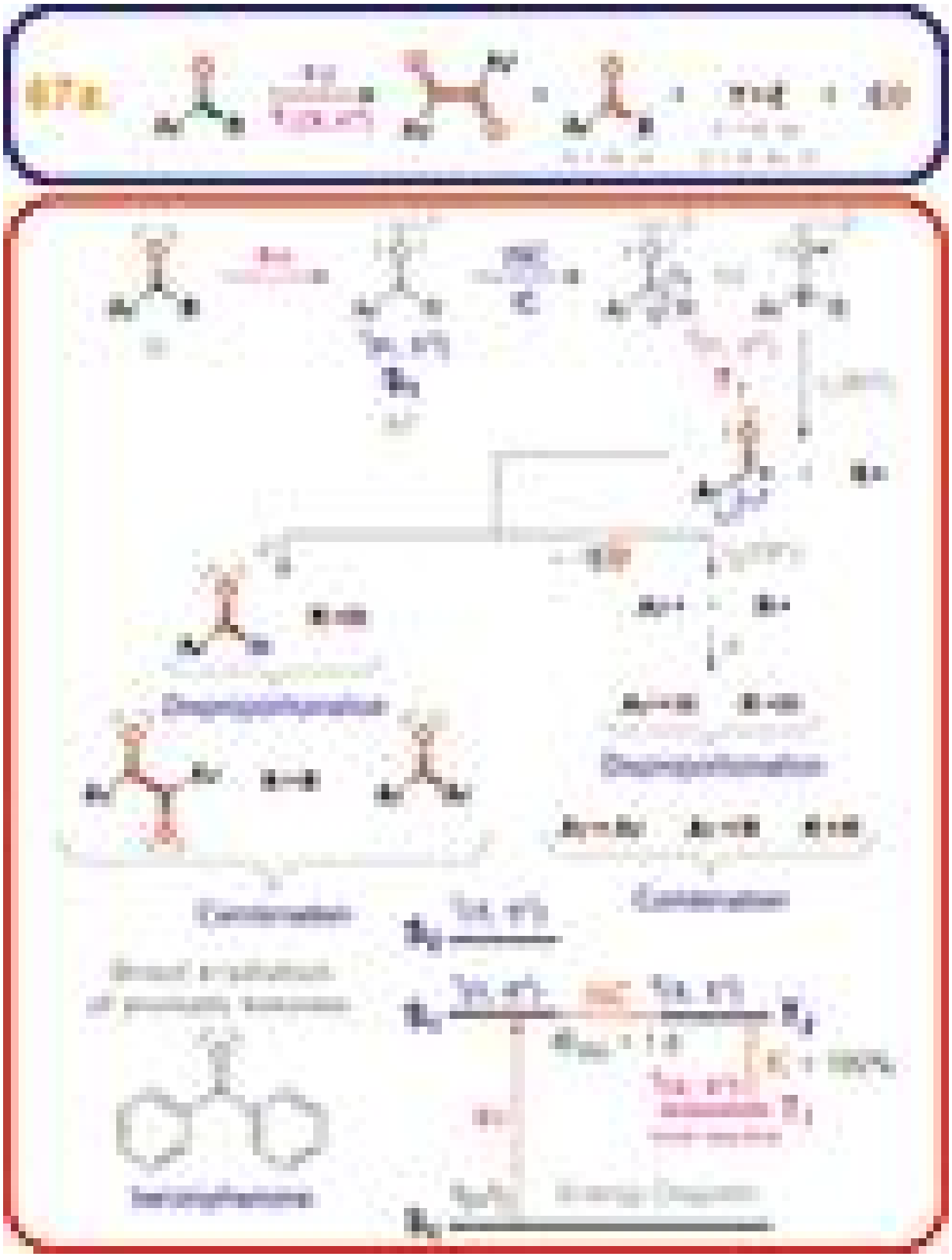


Fig. 67.1: The ***Norrish type I*** *reaction* mechanism.[240].

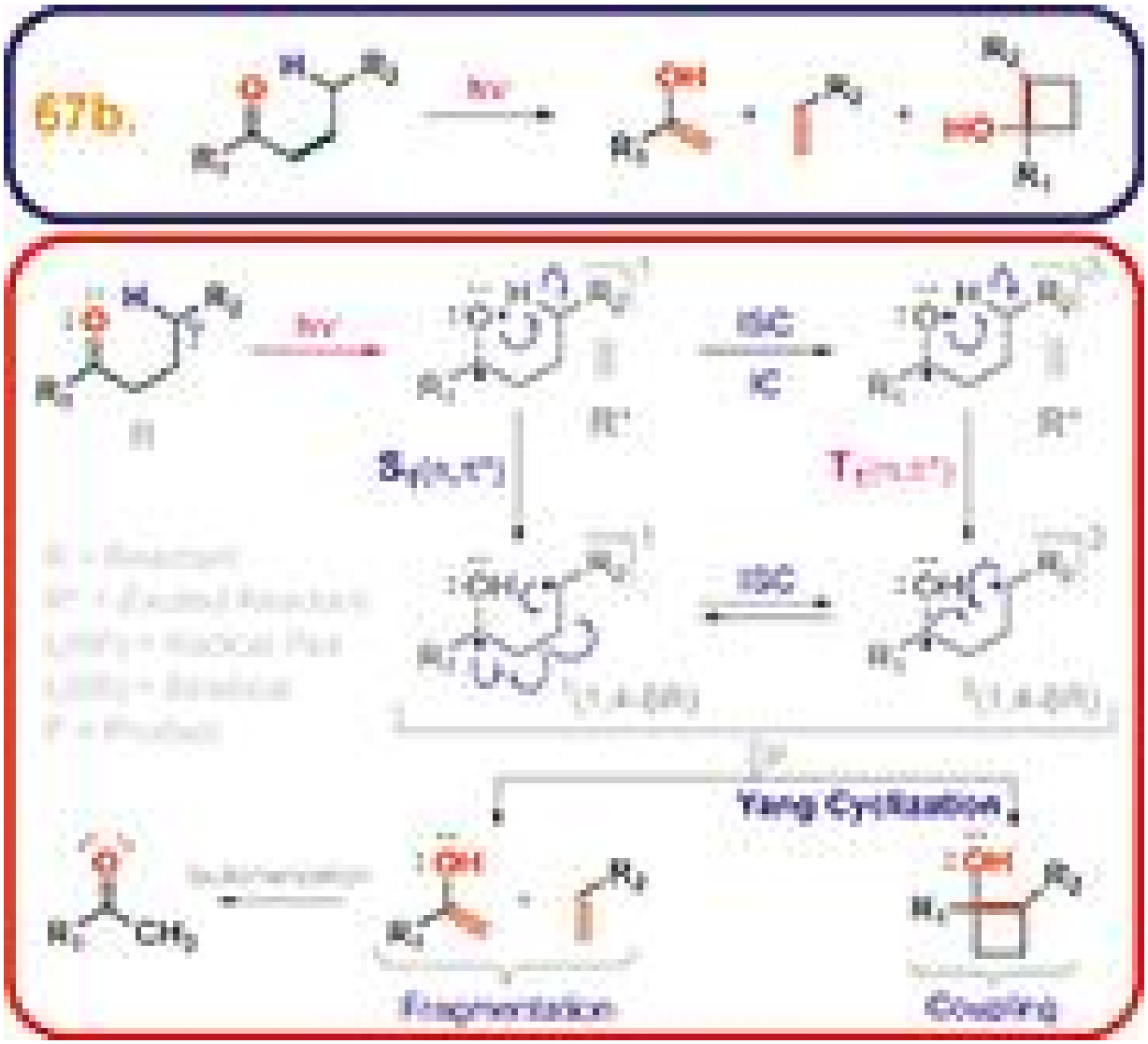


Fig. 67.2: The ***Norrish type II*** *reaction* mechanism.[241]

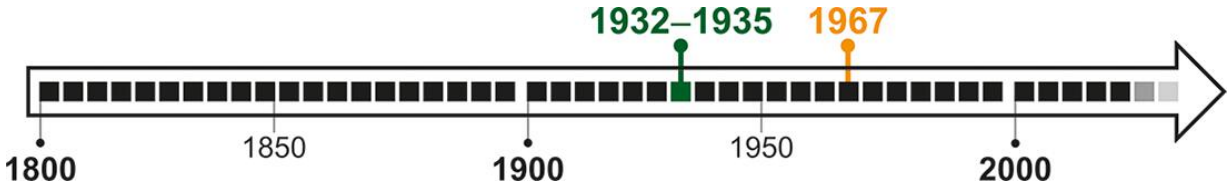


Fig. 67.3: The discovery of the ***Norrish*** *fragmentation*.[242]

68 Olefin (Alkene) Metathesis

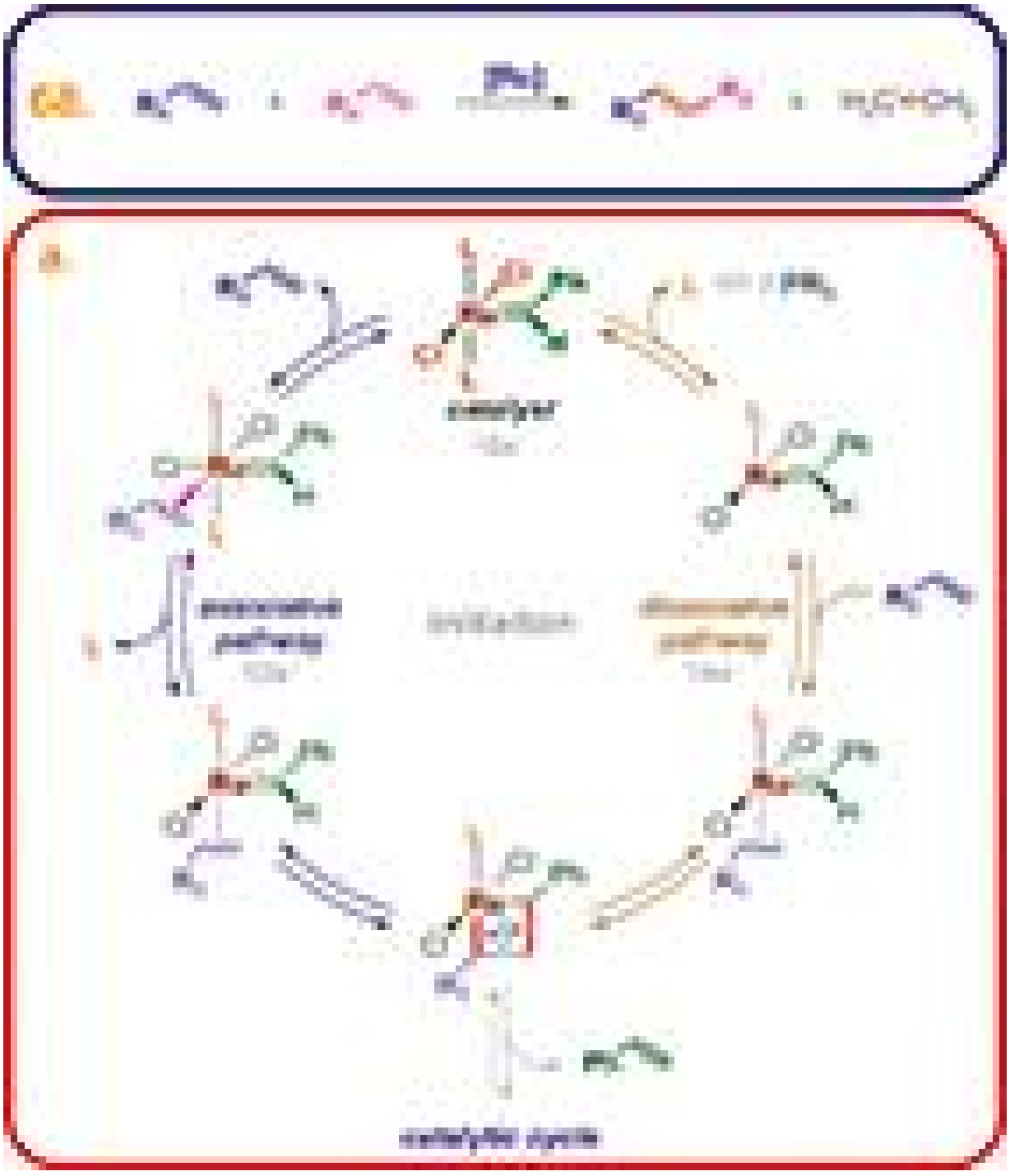


Fig. 68.1: The *olefin (alkene) metathesis* mechanism (initiation).[243]

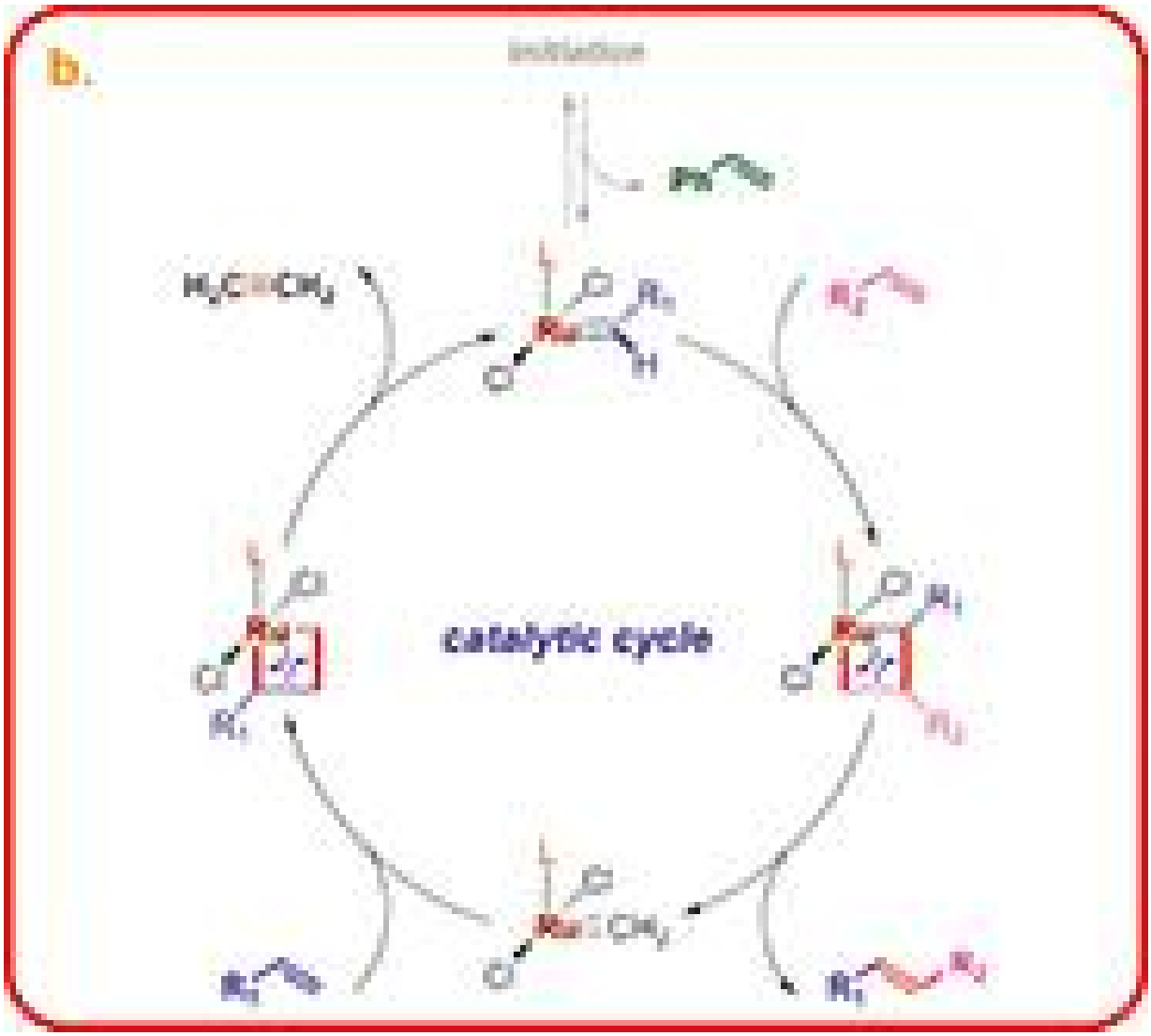


Fig. 68.2: The *olefin (alkene) metathesis* mechanism (catalytic cycle).[244]

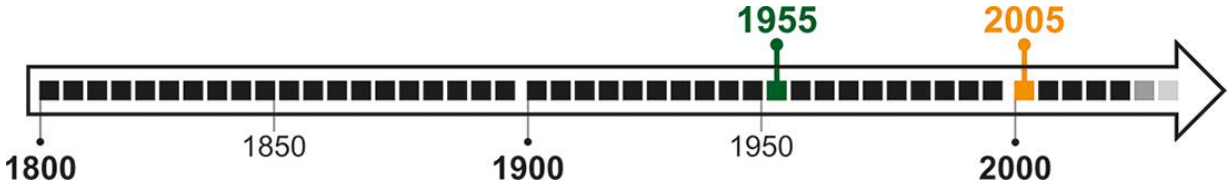


Fig. 68.3: The discovery of the *olefin metathesis*.[245]

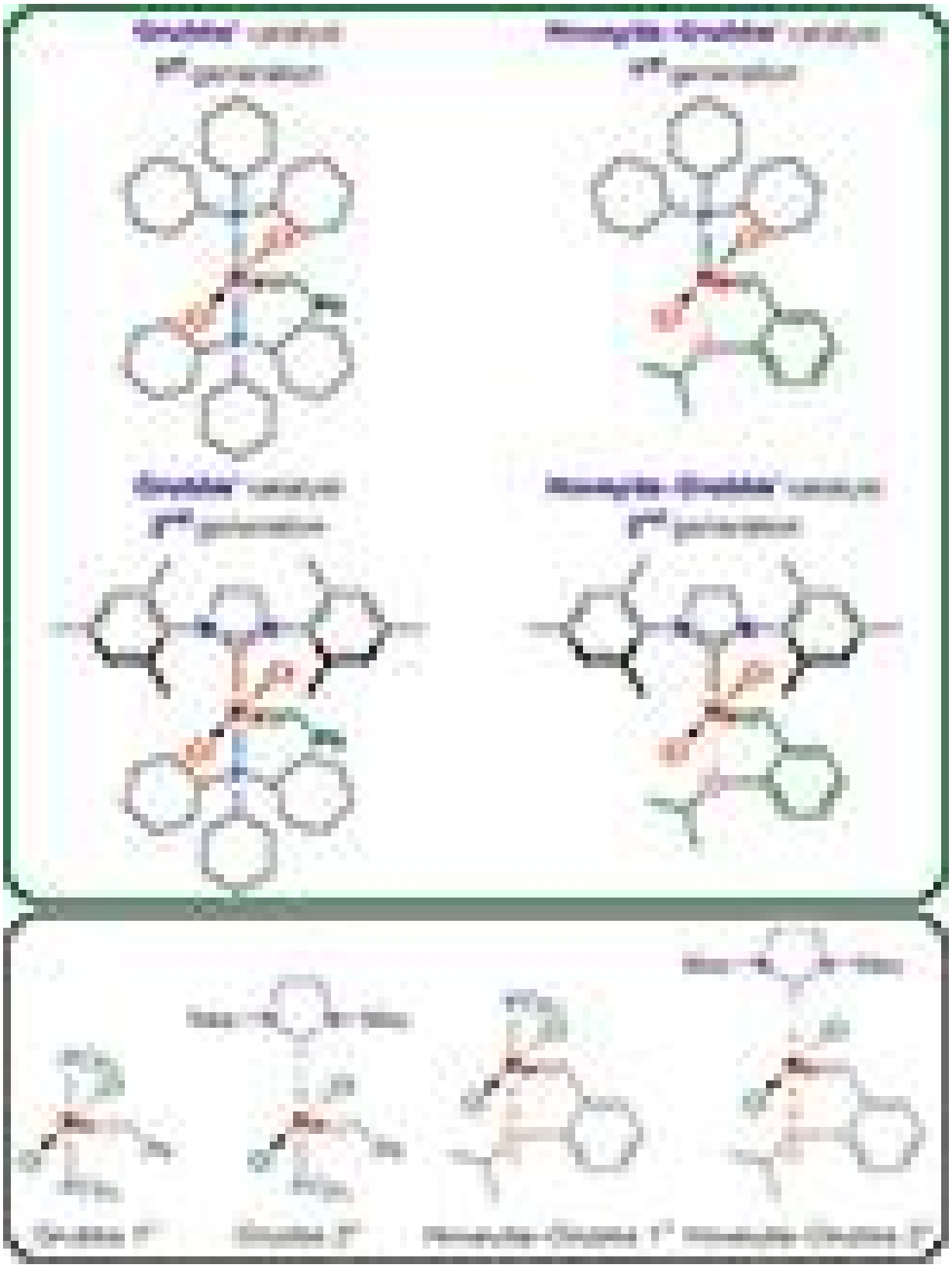


Fig. 68.4: The main *olefin (alkene) metathesis* catalysts.[246]

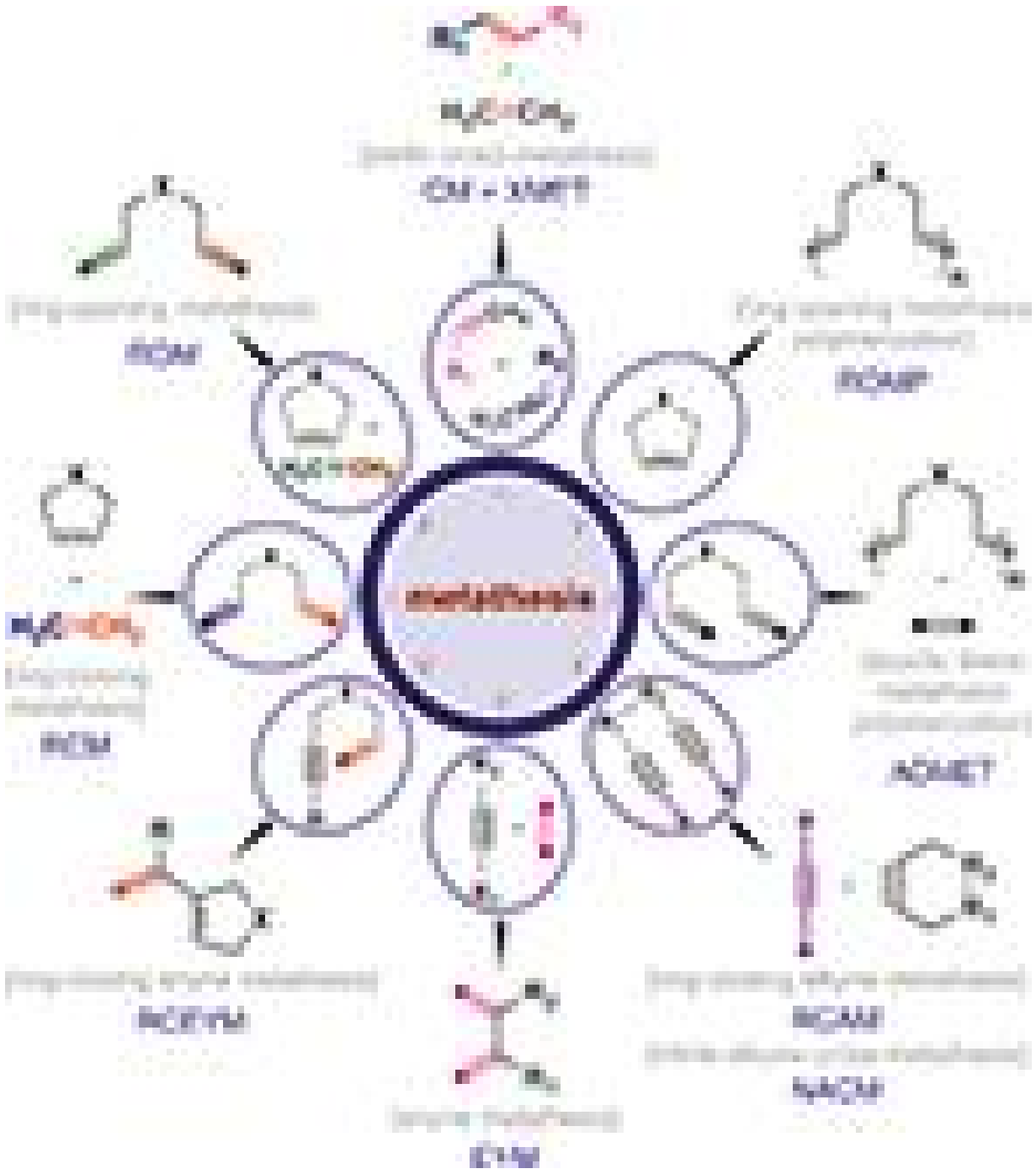


Fig. 68.5: Classification of *metathesis* reactions.[247]

69 Oppenauer Oxidation

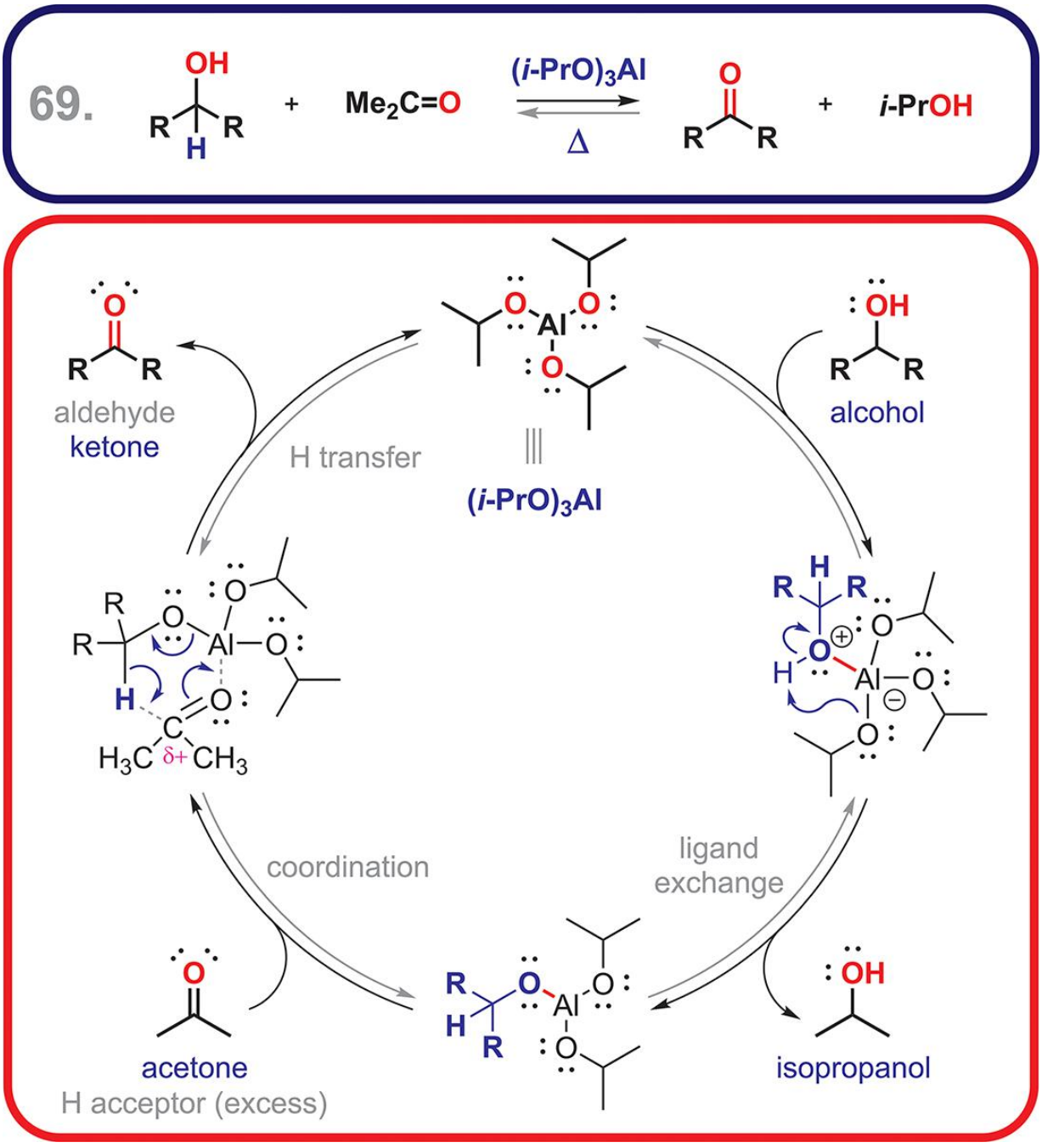


Fig. 69.1: The ***Oppenauer*** *oxidation* mechanism.[248]

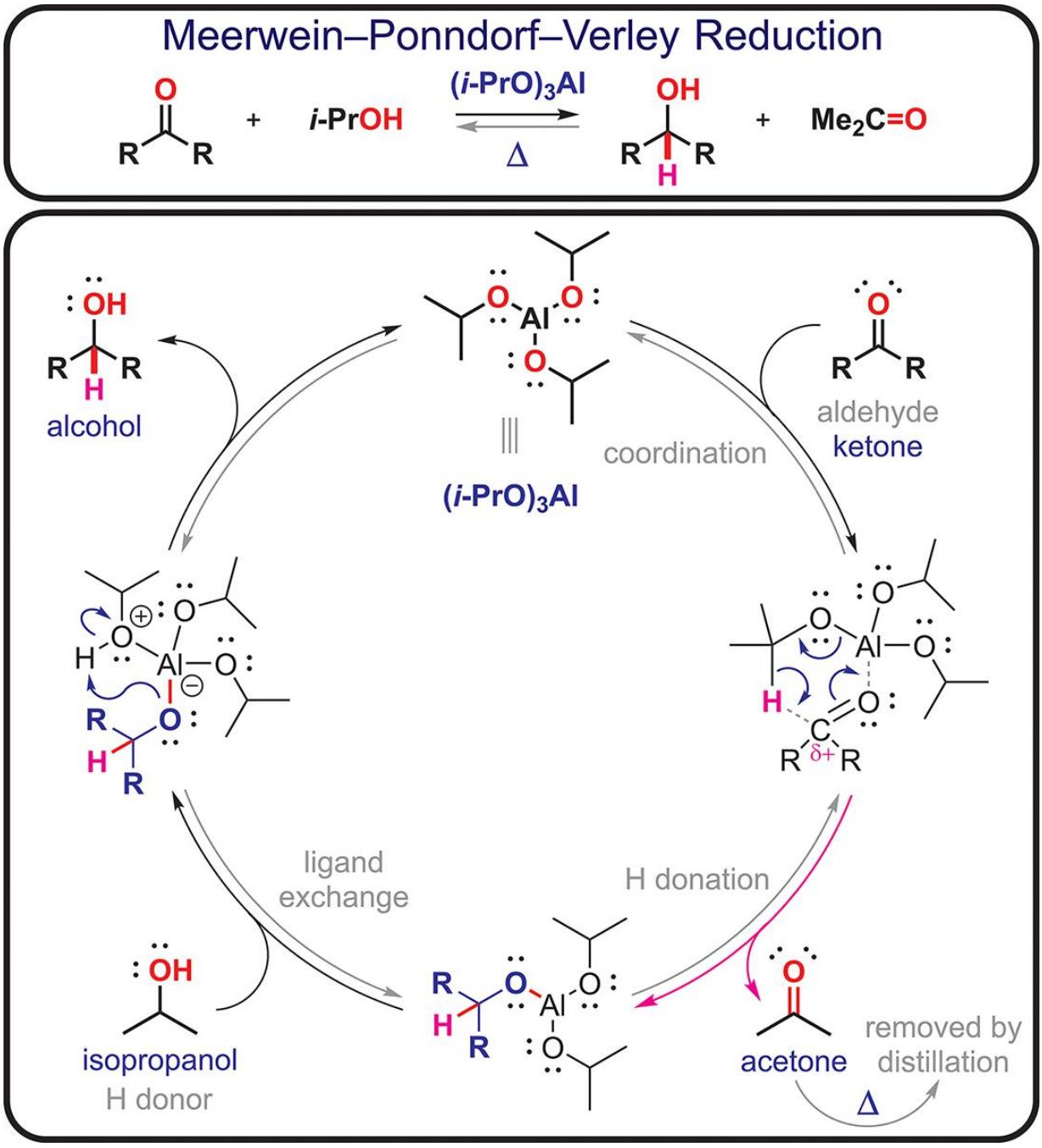


Fig. 69.2: The ***Meerwein–Ponndorf–Verley*** *reaction* mechanism.[249]

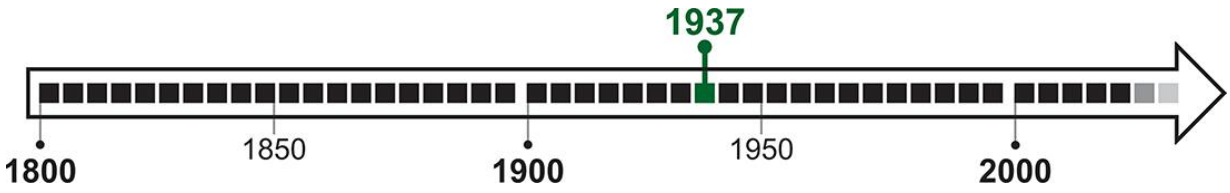


Fig. 69.3: The discovery of the ***Oppenauer*** *oxidation*.[250]

70 Ozonolysis

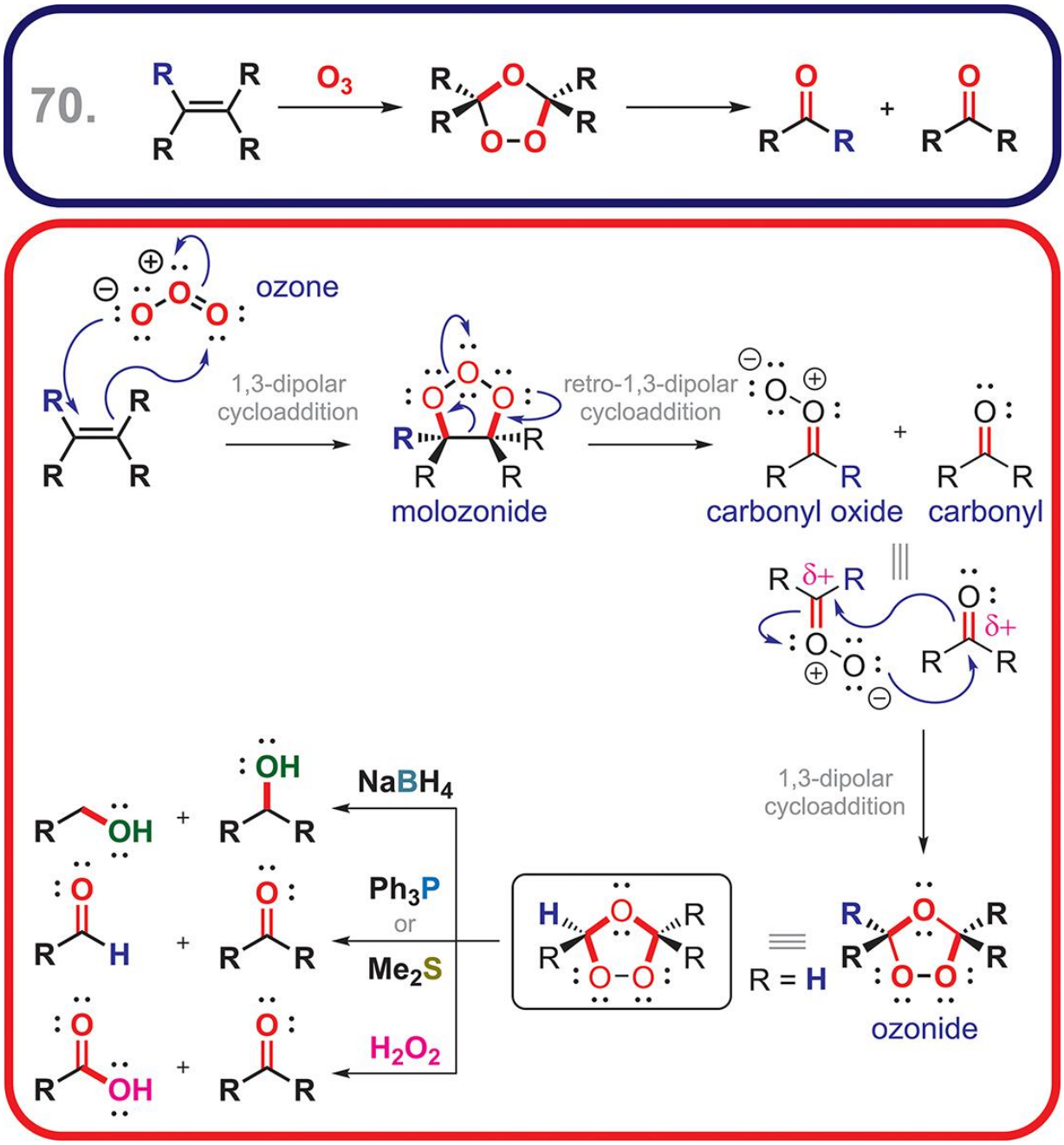


Fig. 70.1: The *ozonolysis* mechanism (the ***Criegee*** mechanism).[251]

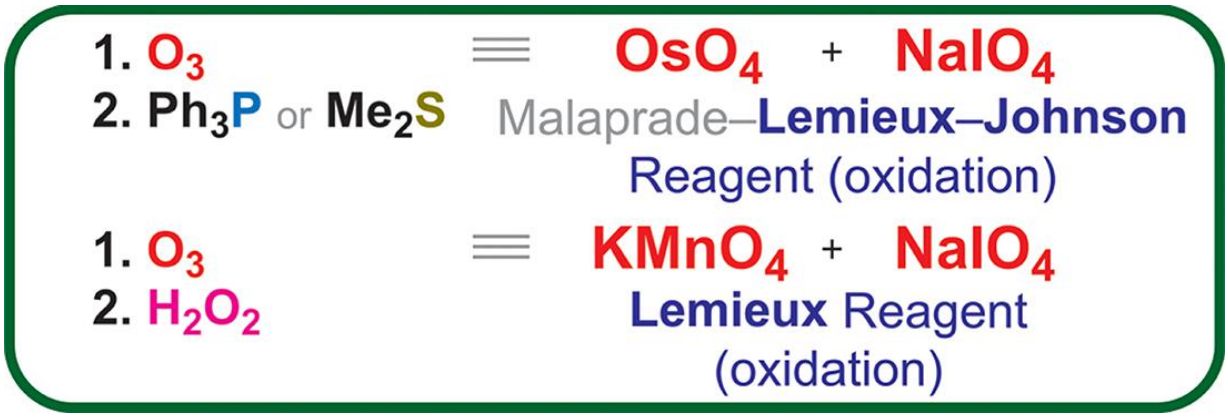


Fig. 70.2: Alternative to the *ozonolysis* reaction conditions.[252]

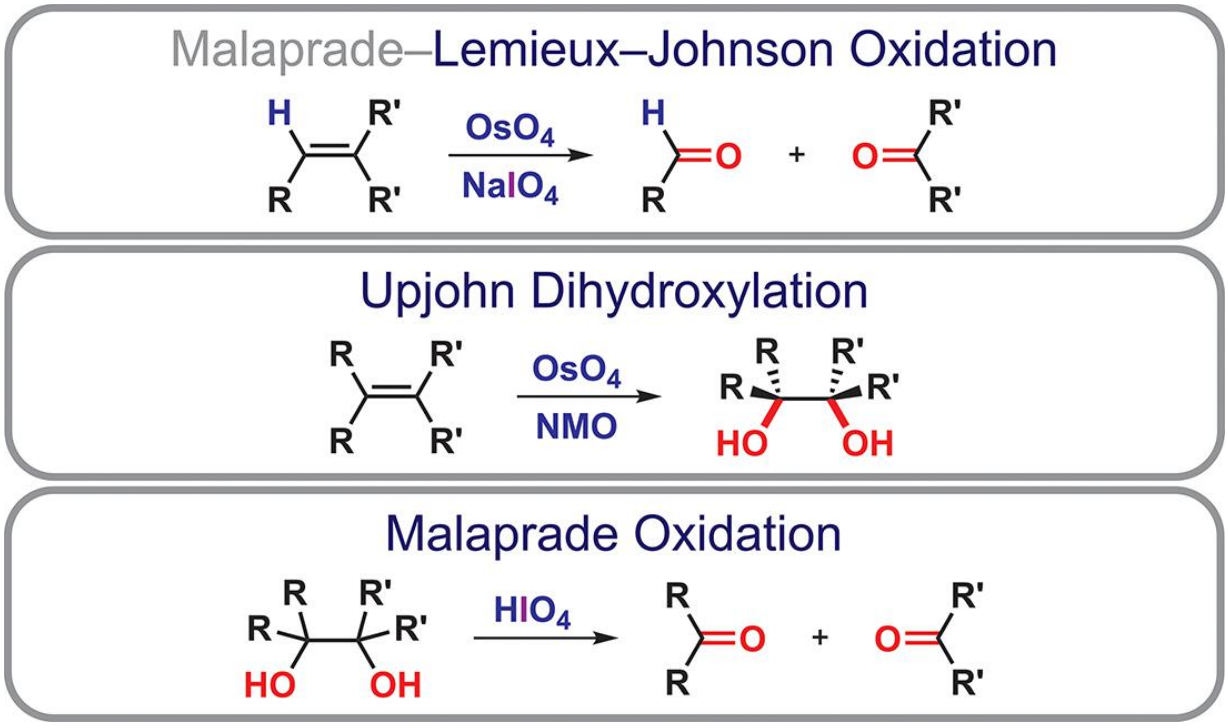


Fig. 70.3: Reactions related to the *ozonolysis*.[253]

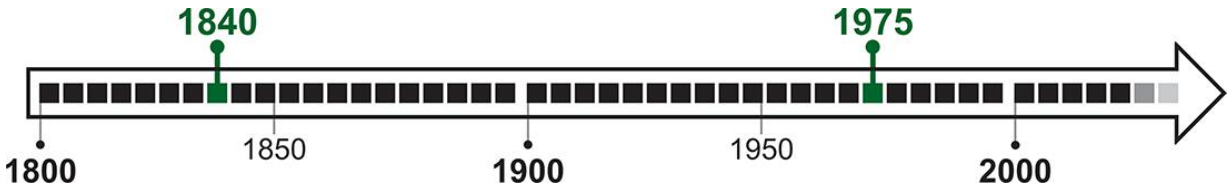


Fig. 70.4: The discovery of the *ozonolysis*.[254]

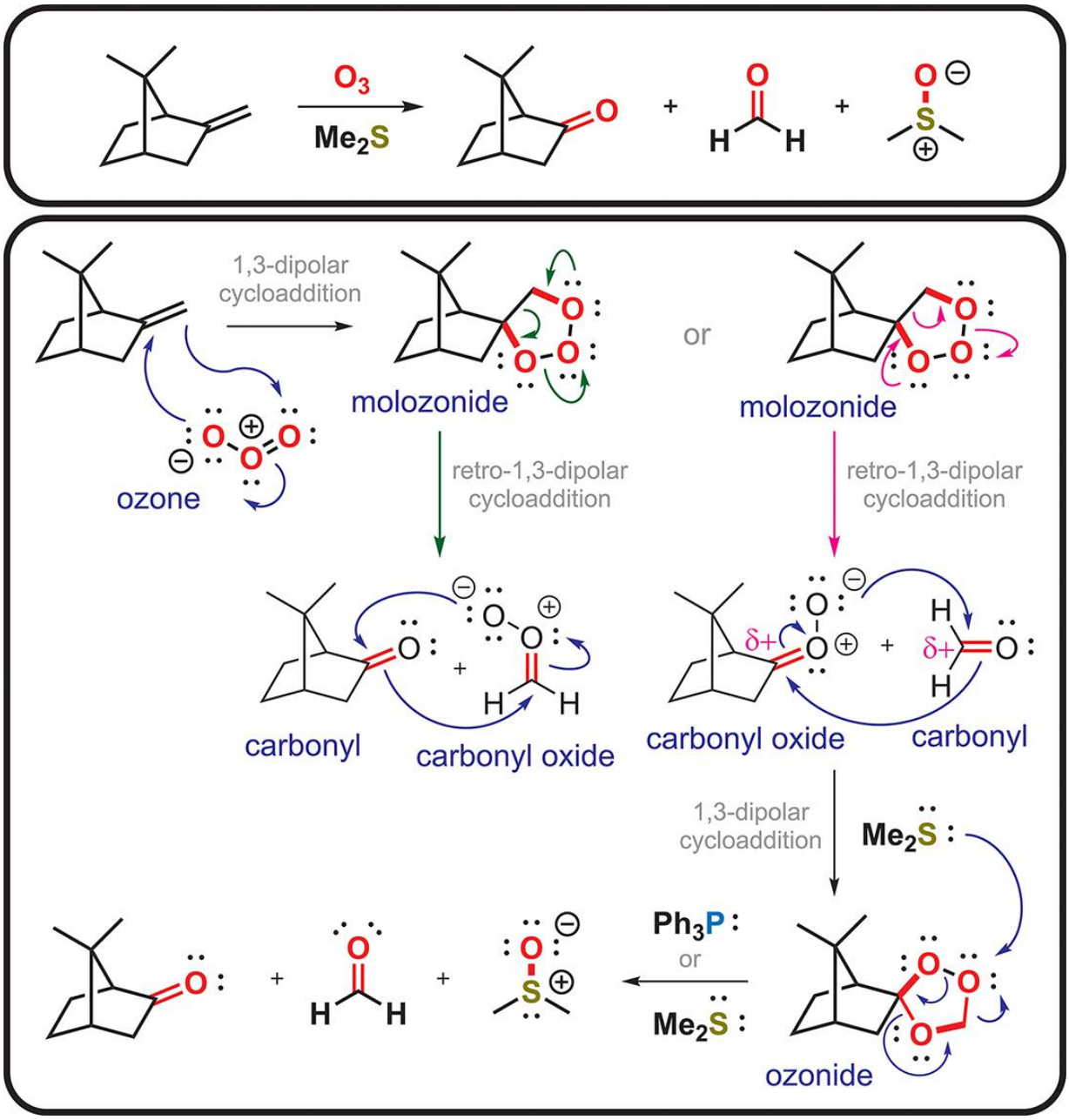


Fig. 70.5: The *ozonolysis* reaction mechanism of (−)-α-fenchene.[255]

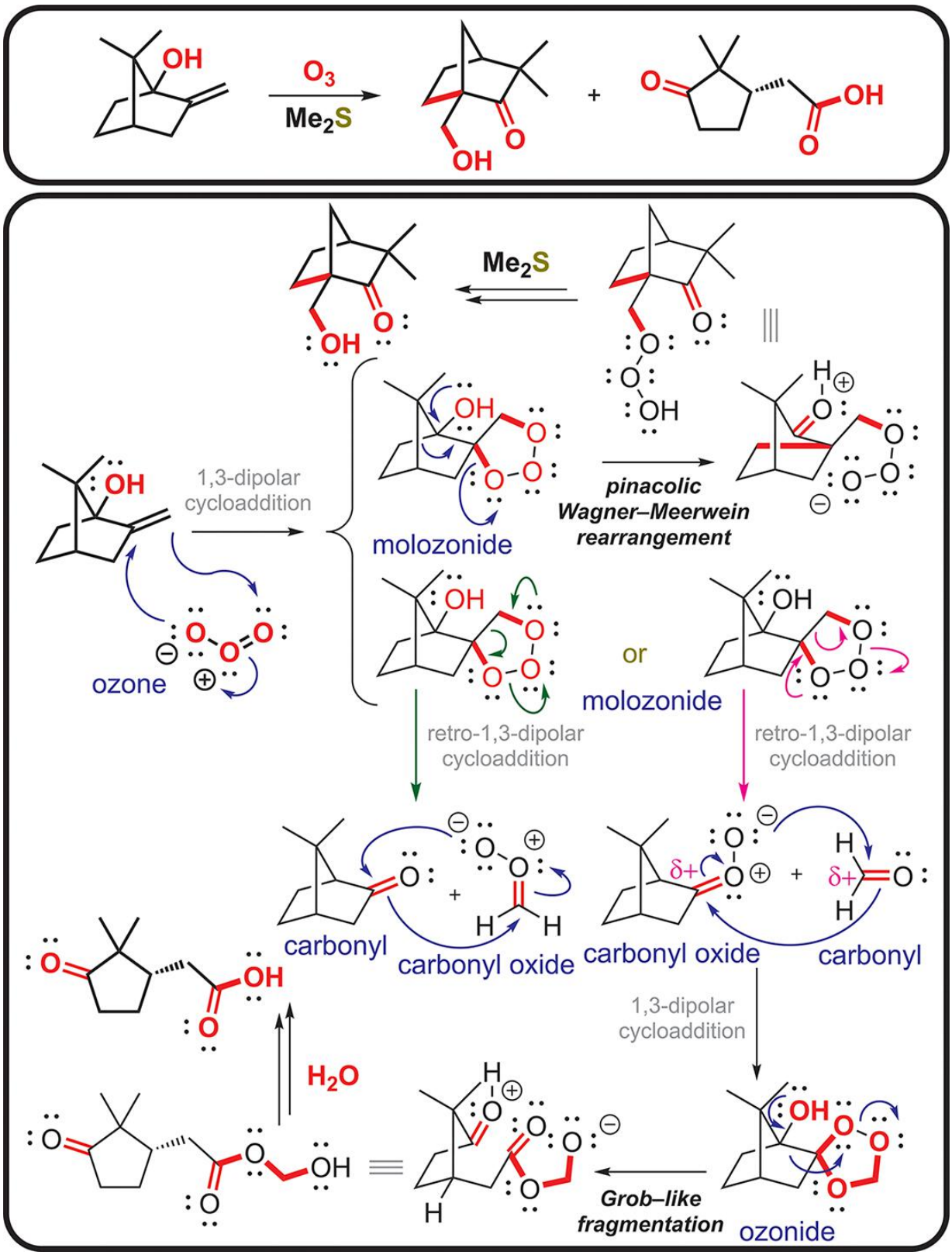

OH
O3
Me2S
OH
O
O
OH
Me2S
OH
O
OH
O
OH
1,3-dipolar
cycloaddition
molozonide
pinacolic
Wagner–Meerwein
rearrangement
ozone
retro-1,3-dipolar
cycloaddition
or
molozonide
retro-1,3-dipolar
cycloaddition
carbonyl
carbonyl oxide
carbonyl oxide
carbonyl
1,3-dipolar
cycloaddition
H2O
Grob–like
fragmentation
ozonide

Fig. 70.6: An anomalous (interrupted) *ozonolysis* reaction mechanism.[256]

71 Paal–Knorr Syntheses

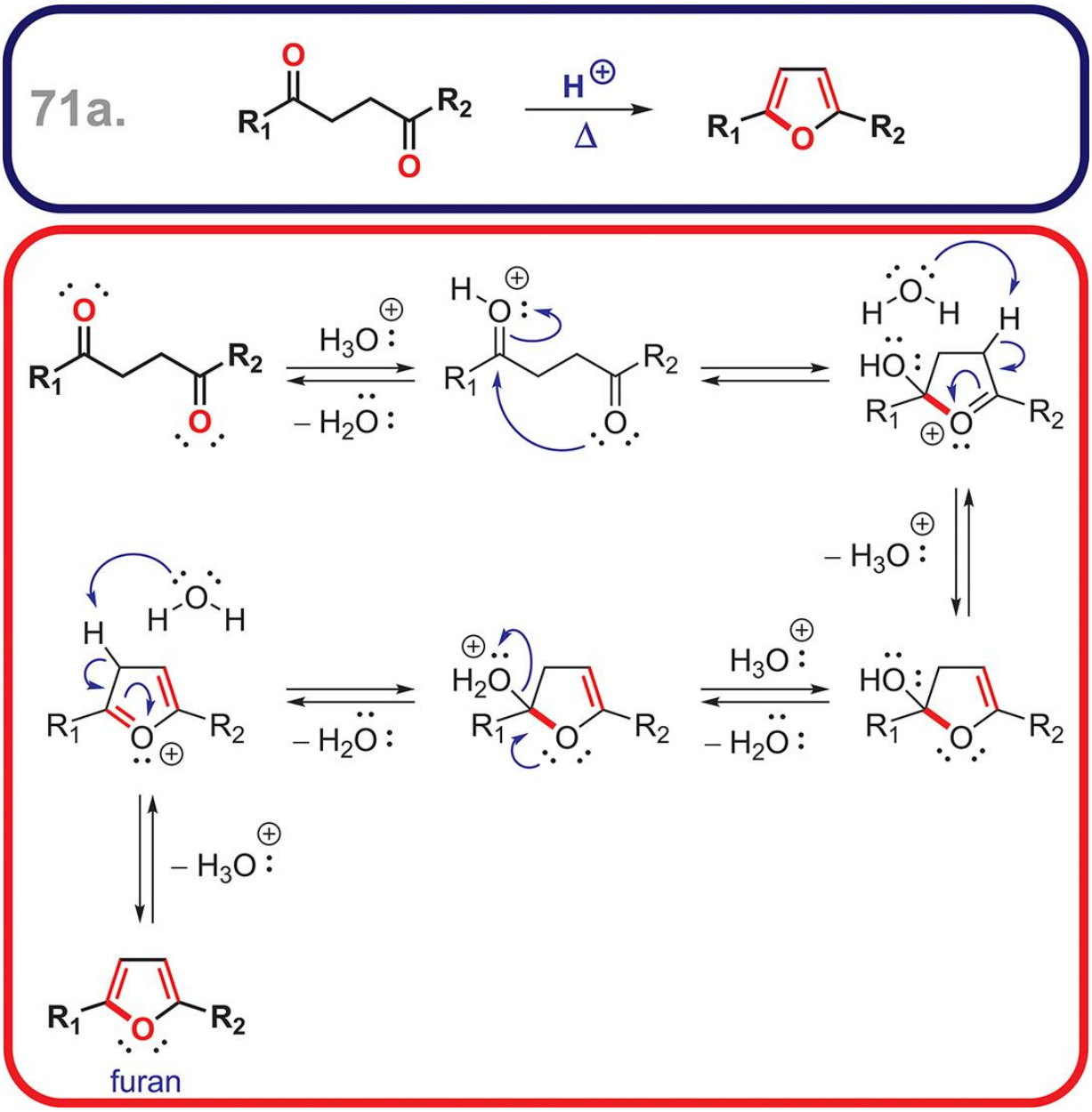


Fig. 71.1: The ***Paal–Knorr*** *furan synthesis* mechanism.[257]

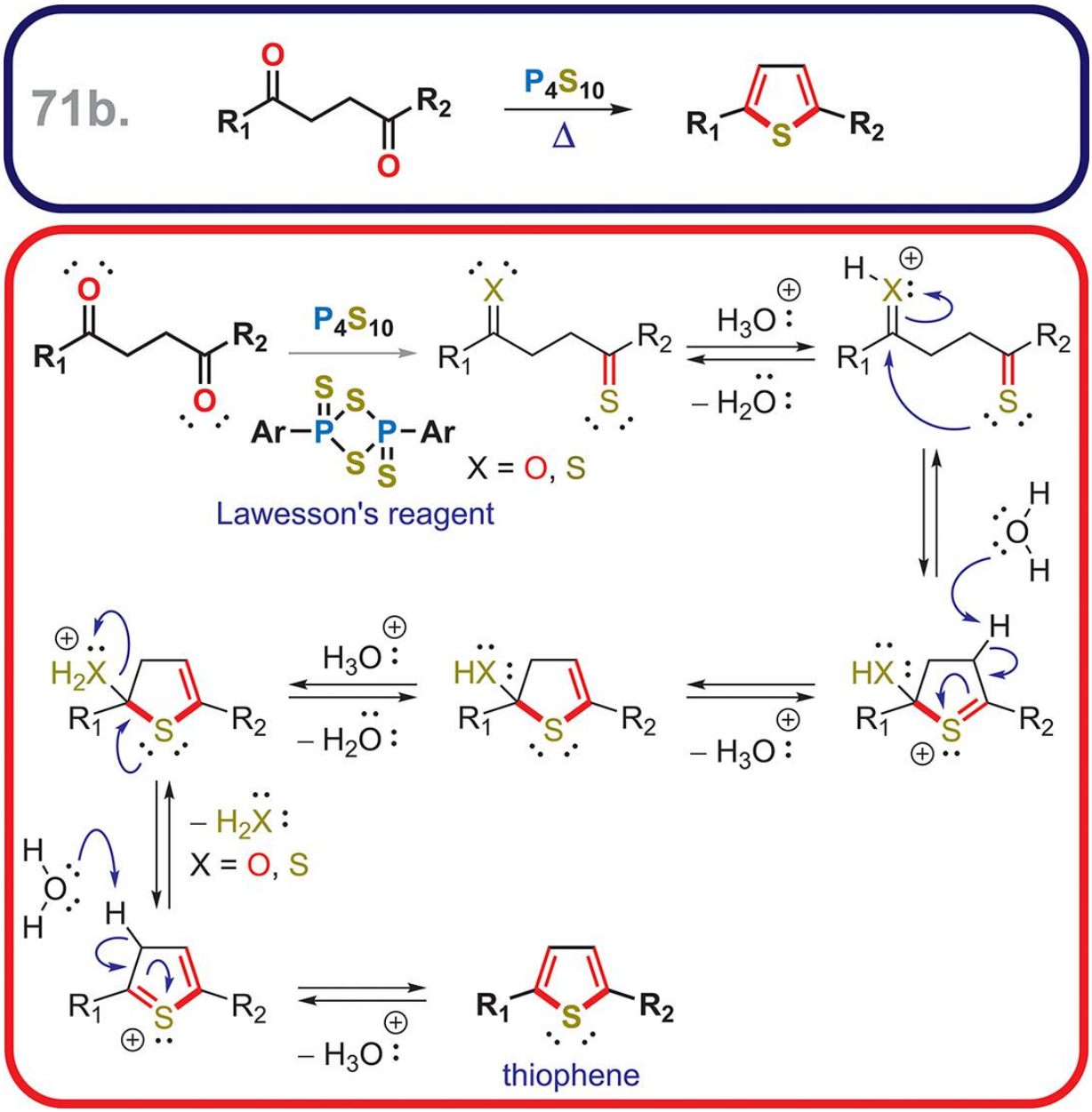


Fig. 71.2: The ***Paal–Knorr*** *thiophene synthesis* mechanism.[258]

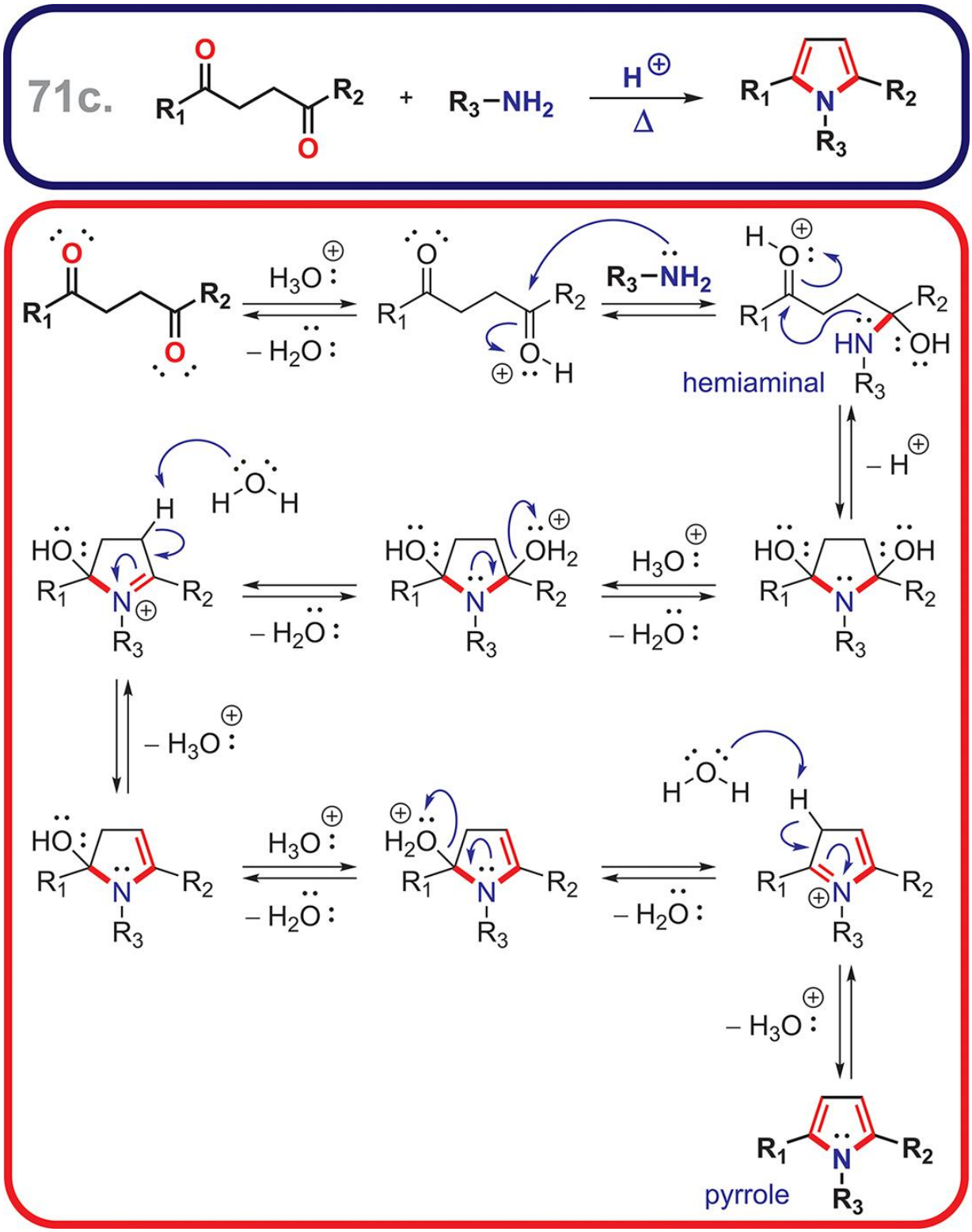


Fig. 71.3: The ***Paal–Knorr*** *pyrrole synthesis* mechanism.[259]

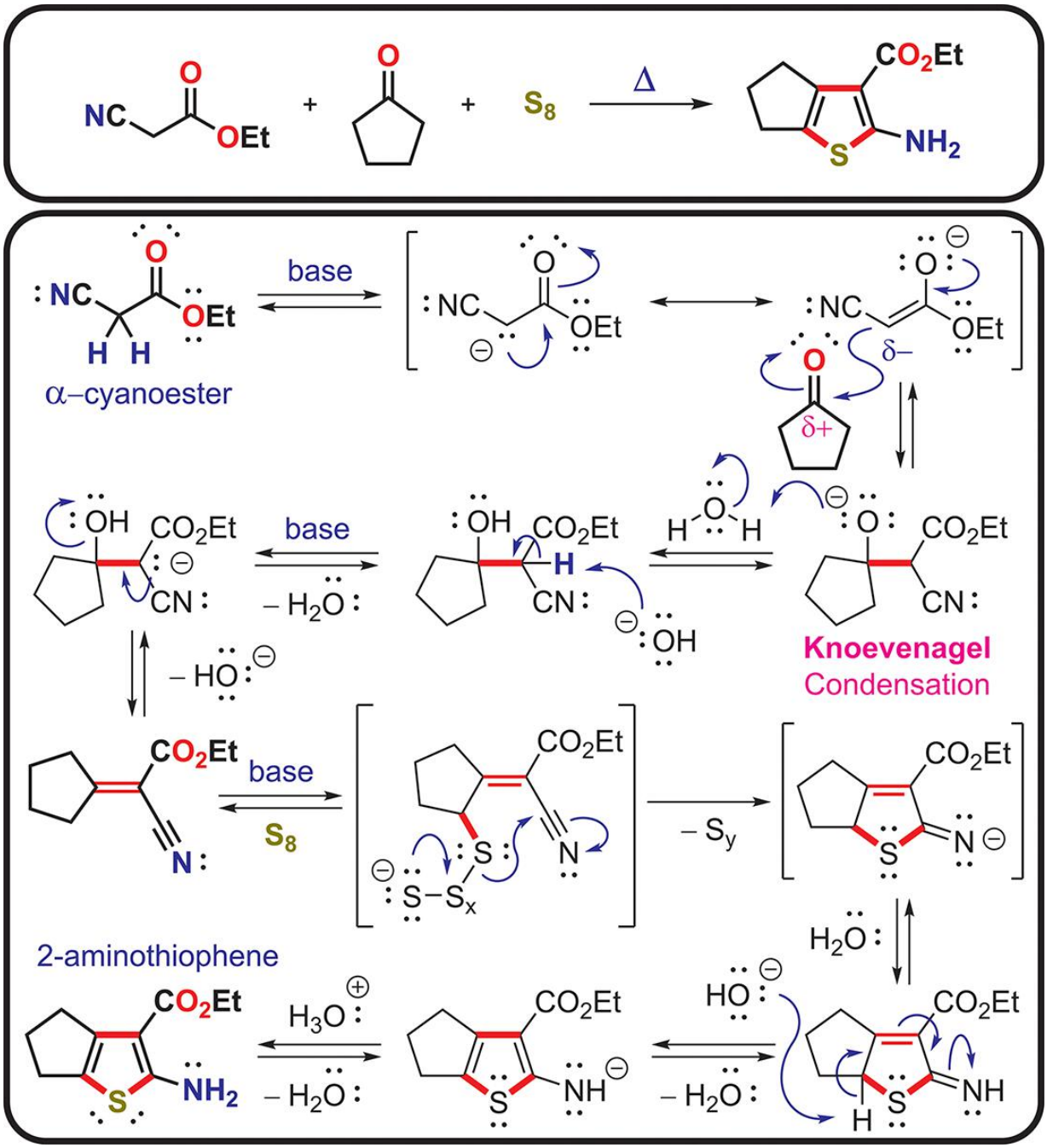


Fig. 71.4: Related to the ***Paal–Knorr*** *synthesis*: the ***Gewald*** *condensation*.[260]

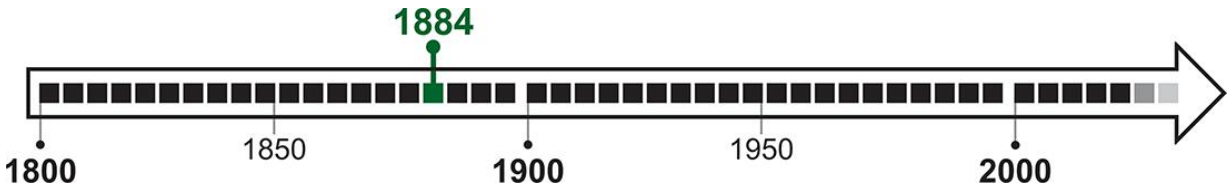


Fig. 71.5: The discovery of the ***Paal–Knorr*** *syntheses*.[261]

72 Paternò–Büchi Reaction

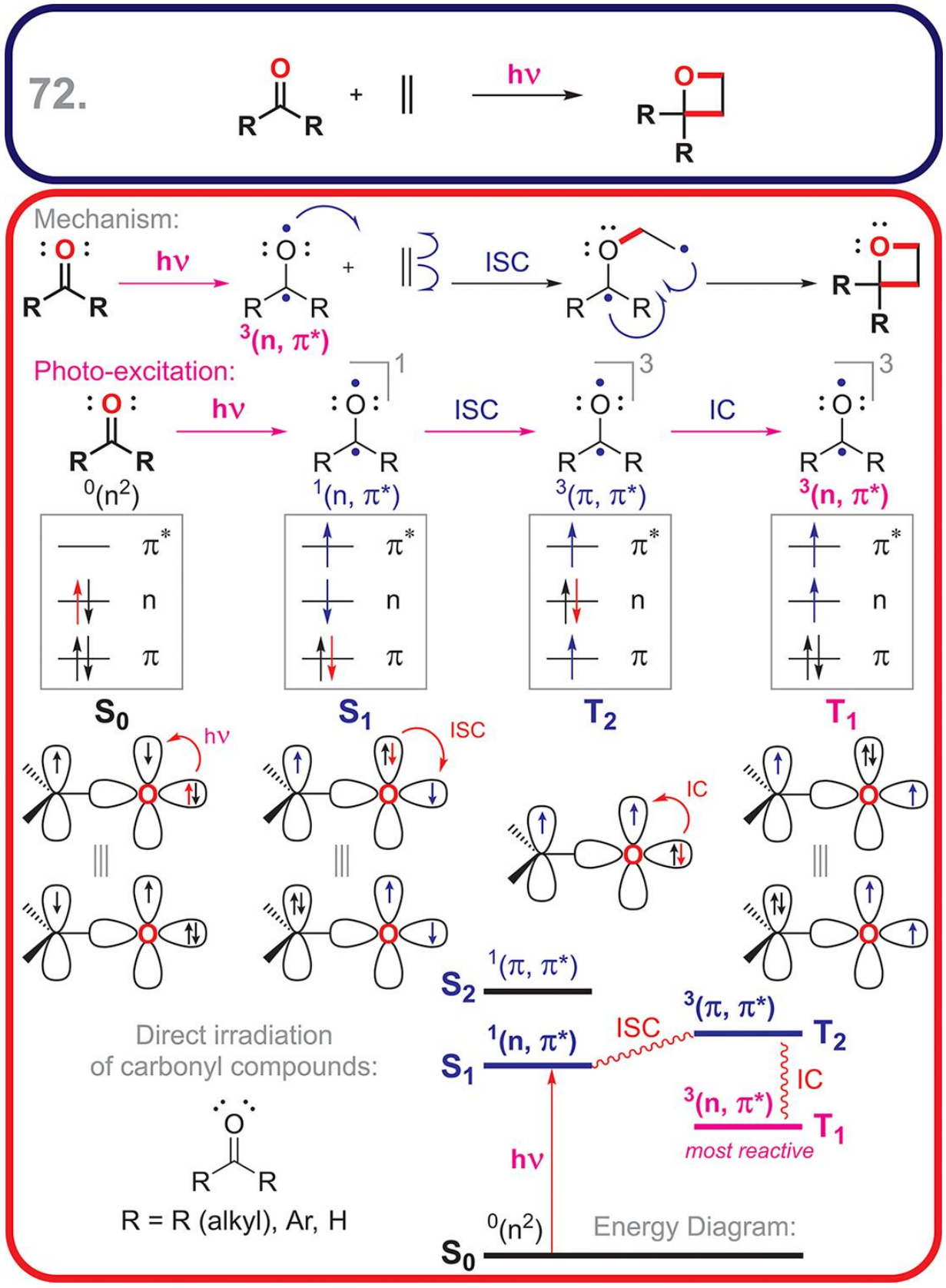

72.
hν
Mechanism:
ISC
$^3(n, \pi^*)$
Photo-excitation:
hν
ISC
IC
$^0(n^2)$
$^1(n, \pi^*)$
$^3(\pi, \pi^*)$
$^3(n, \pi^*)$
π*
n
π
S_0
S_1
T_2
T_1
hν
ISC
IC
S_2 $^1(\pi, \pi^*)$
S_1 $^1(n, \pi^*)$
$^3(\pi, \pi^*)$ T_2
ISC
IC
$^3(n, \pi^*)$ T_1
most reactive
hν
S_0 $^0(n^2)$
Energy Diagram:
Direct irradiation
of carbonyl compounds:
R = R (alkyl), Ar, H

Fig. 72.1: The ***Paternò–Büchi*** *reaction* mechanism.[262].

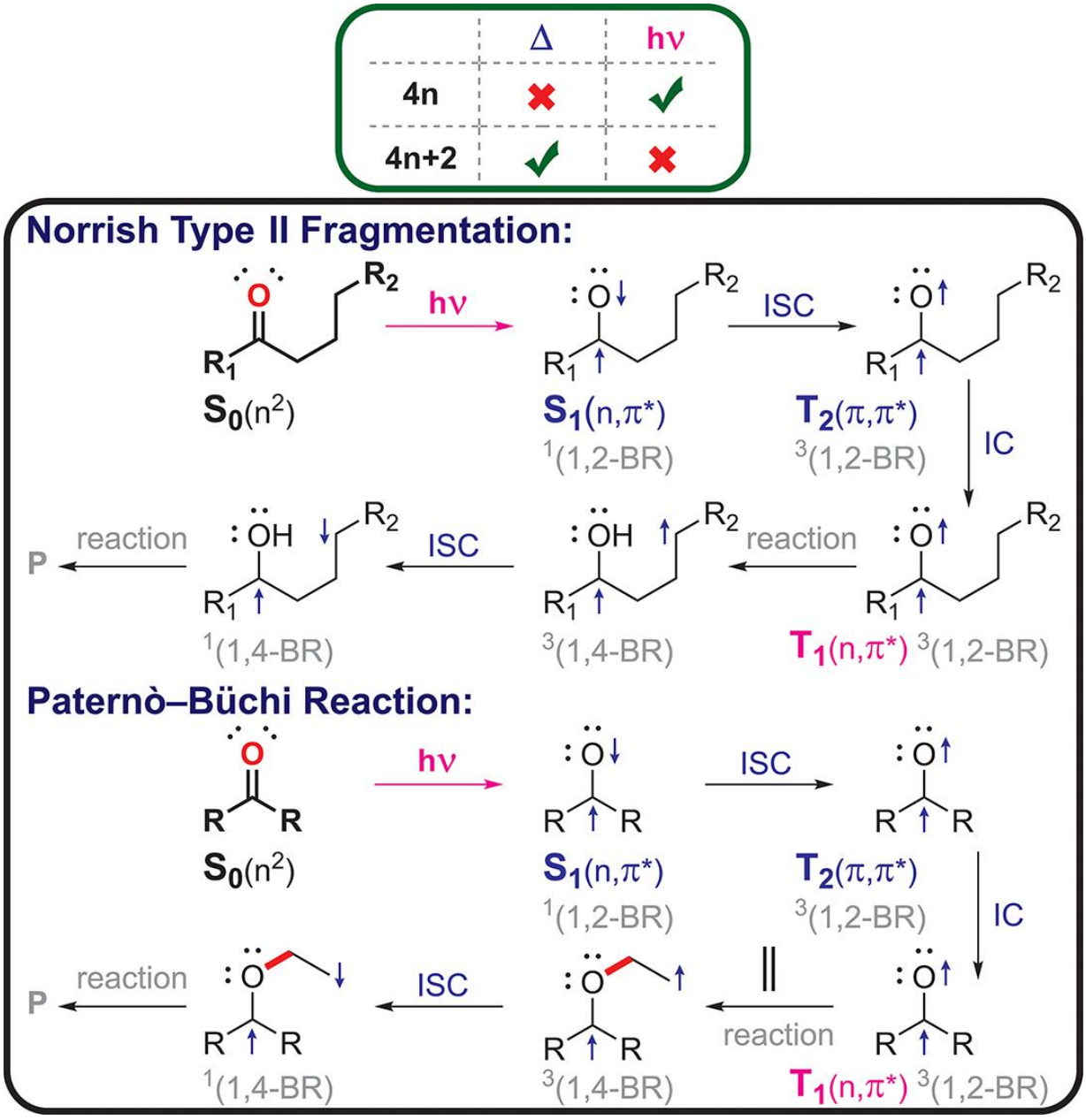


Fig. 72.2: The ***Norrish type II*** *reaction* vs the ***Paternò–Büchi*** *reaction* mechanism.[263]

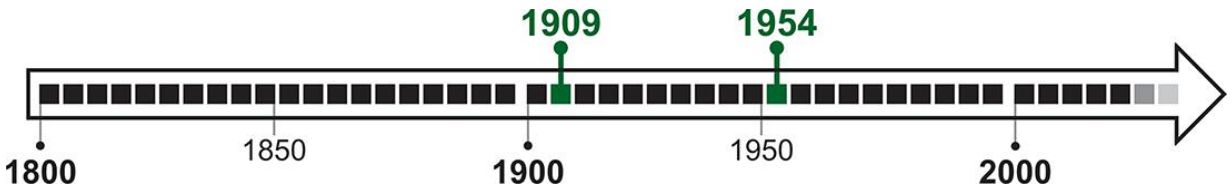


Fig. 72.3: The discovery of the ***Paternò–Büchi*** *reaction*.[264]

73 Pauson–Khand Reaction

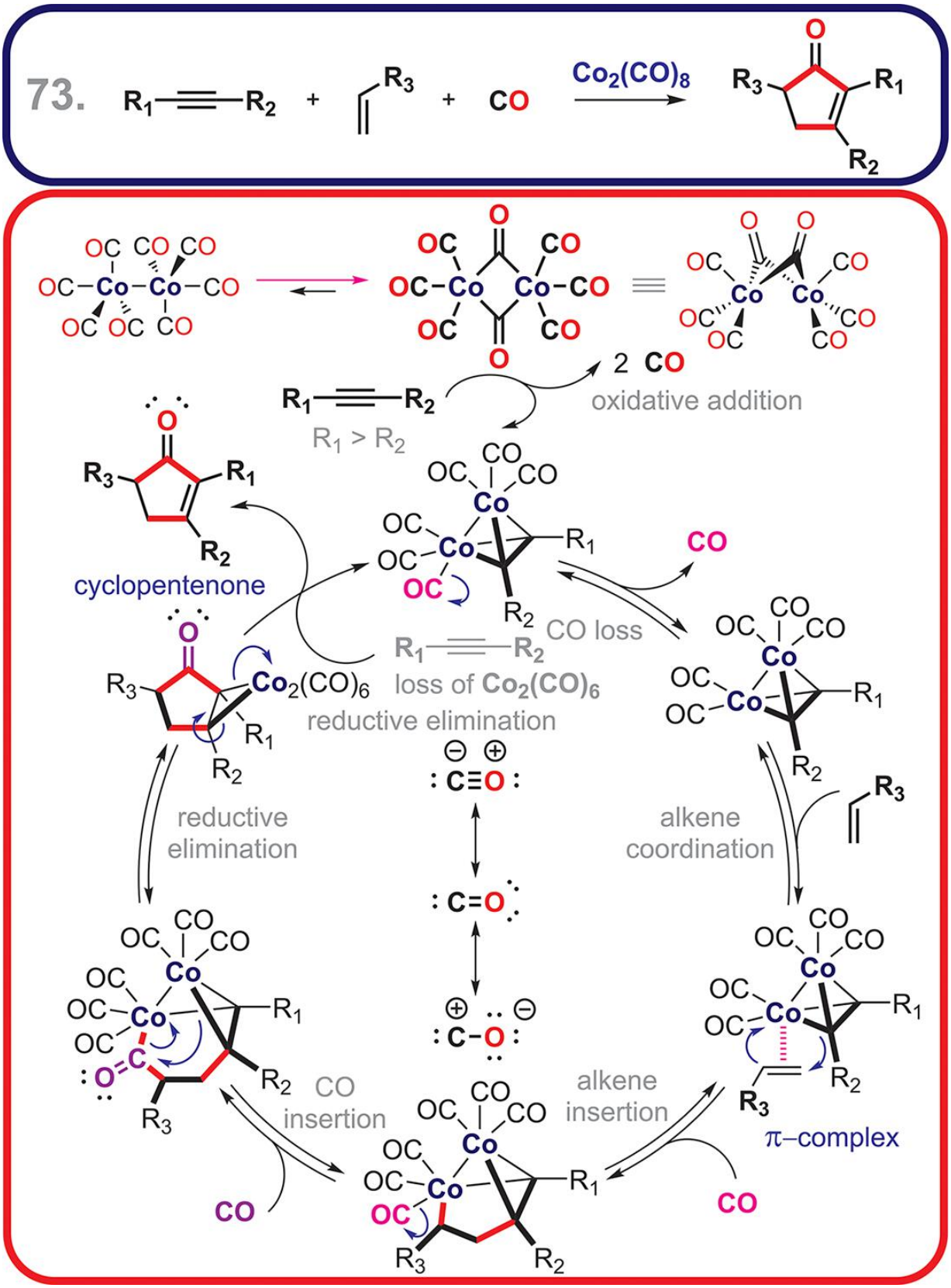

73.
Co2(CO)8
cyclopentenone
2 CO
oxidative addition
R1 > R2
CO loss
loss of Co2(CO)6
reductive elimination
reductive elimination
alkene coordination
CO insertion
alkene insertion
π–complex
CO
CO
CO

Fig. 73.1: The ***Pauson–Khand*** *reaction* mechanism.[265].

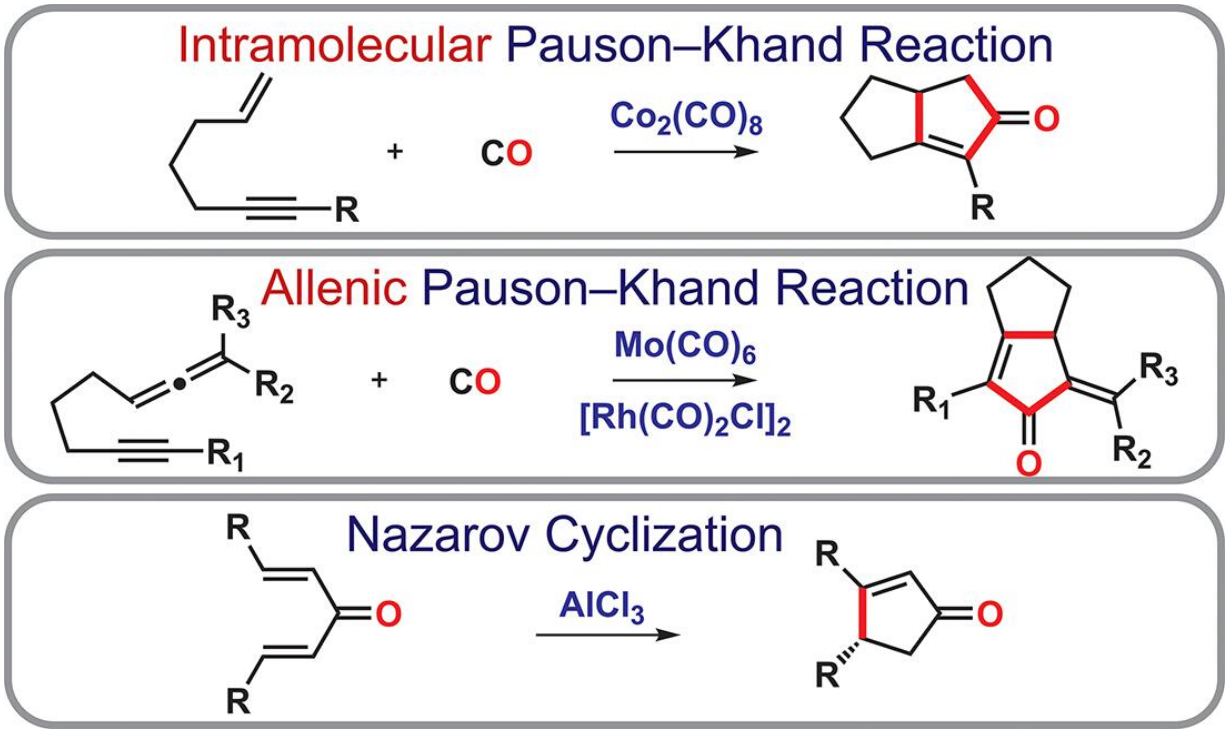


Fig. 73.2: Variations of the ***Pauson–Khand*** *reaction*.[266]

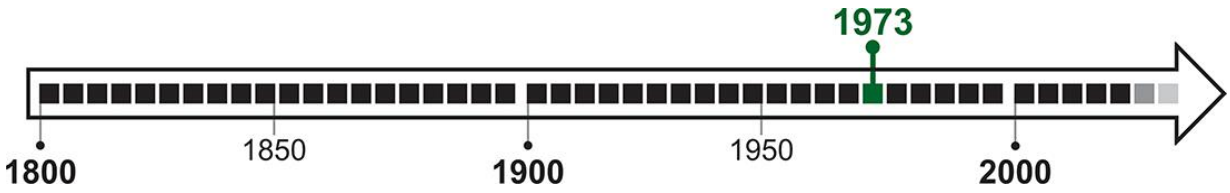


Fig. 73.3: The discovery of the ***Pauson–Khand*** *reaction*.[267]

74 Peptide (Amide) Coupling

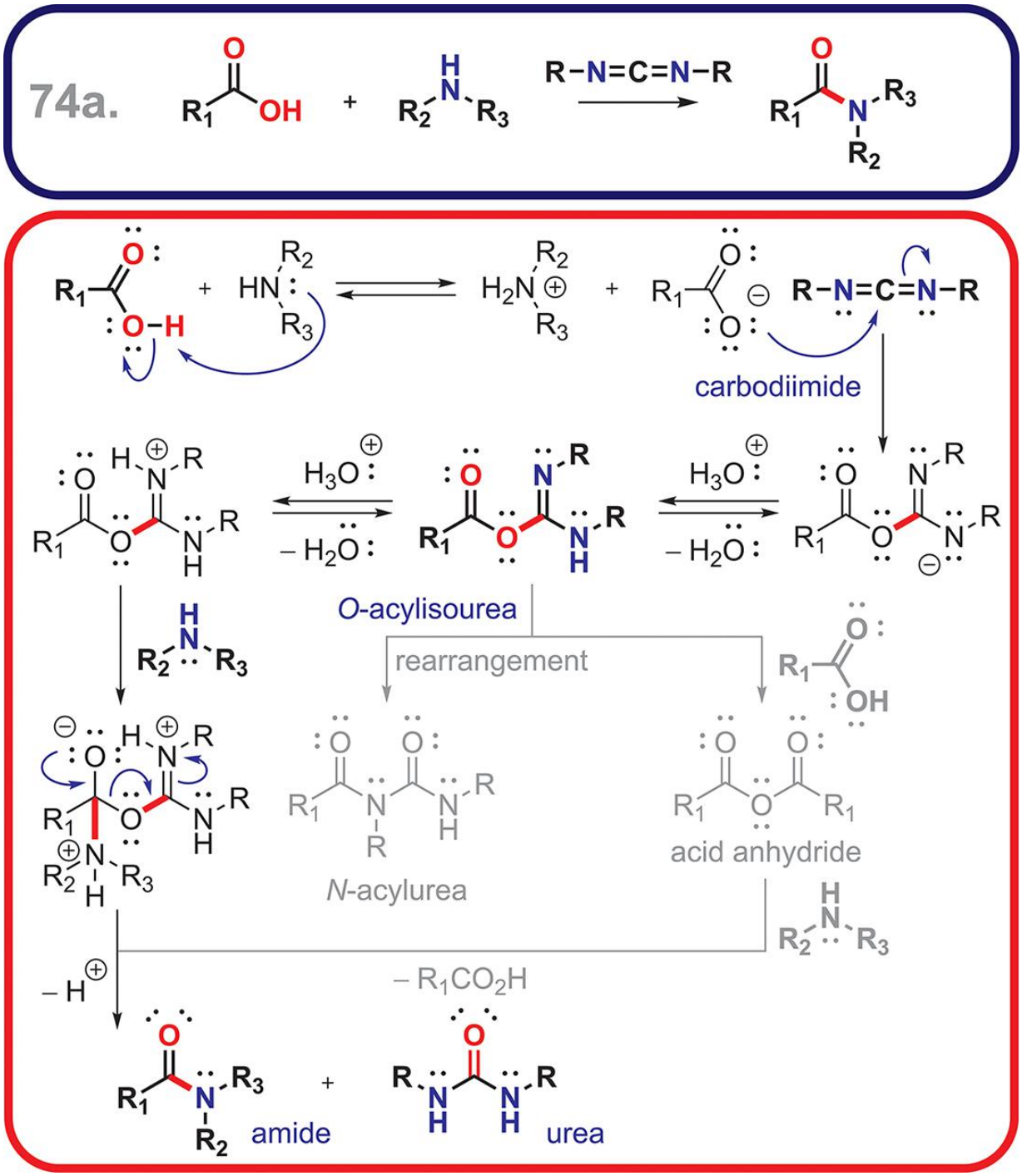


Fig. 74.1: The *peptide (amide) coupling* (DCC) mechanism.[268]

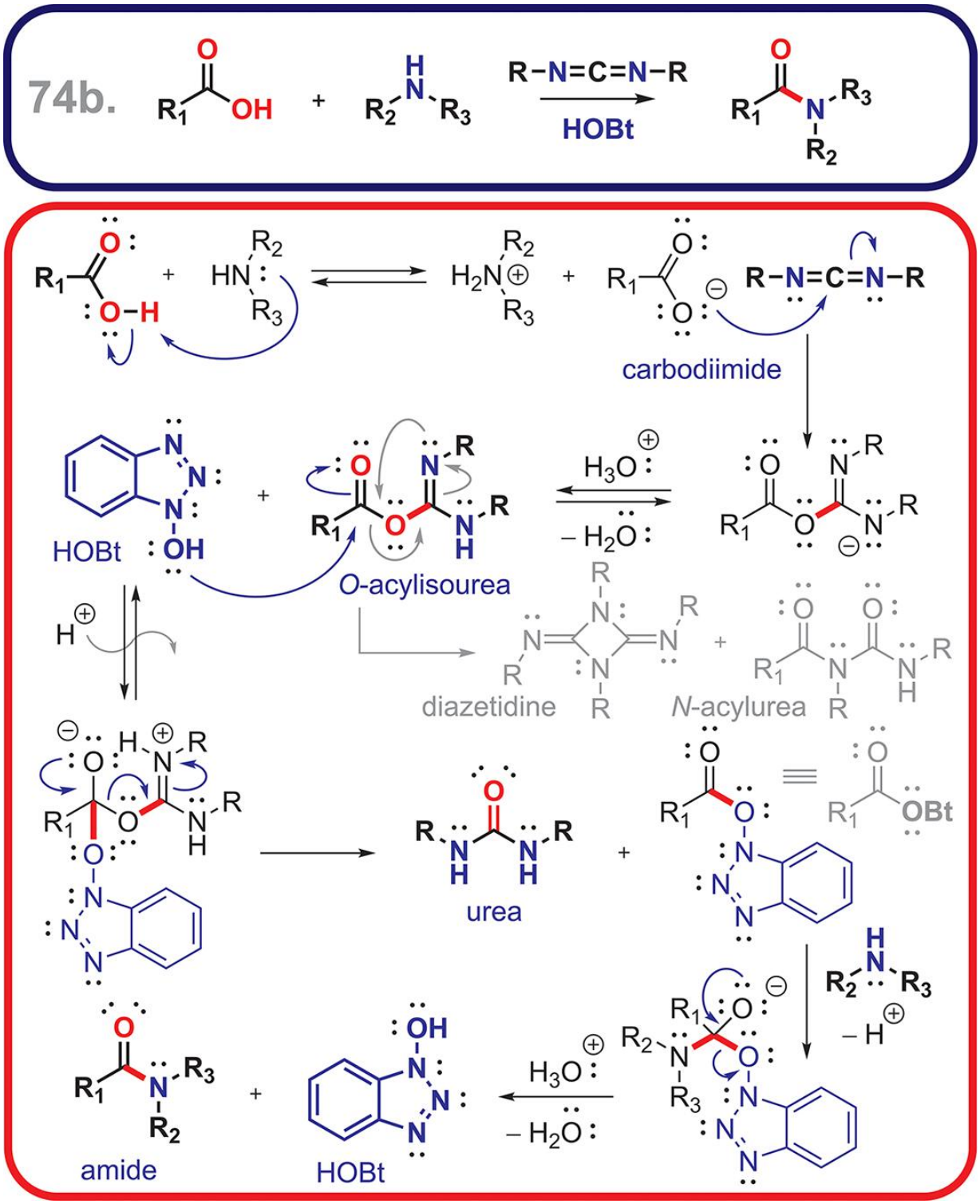


Fig. 74.2: The *peptide (amide) coupling* (DCC + HOBt) mechanism.[269]

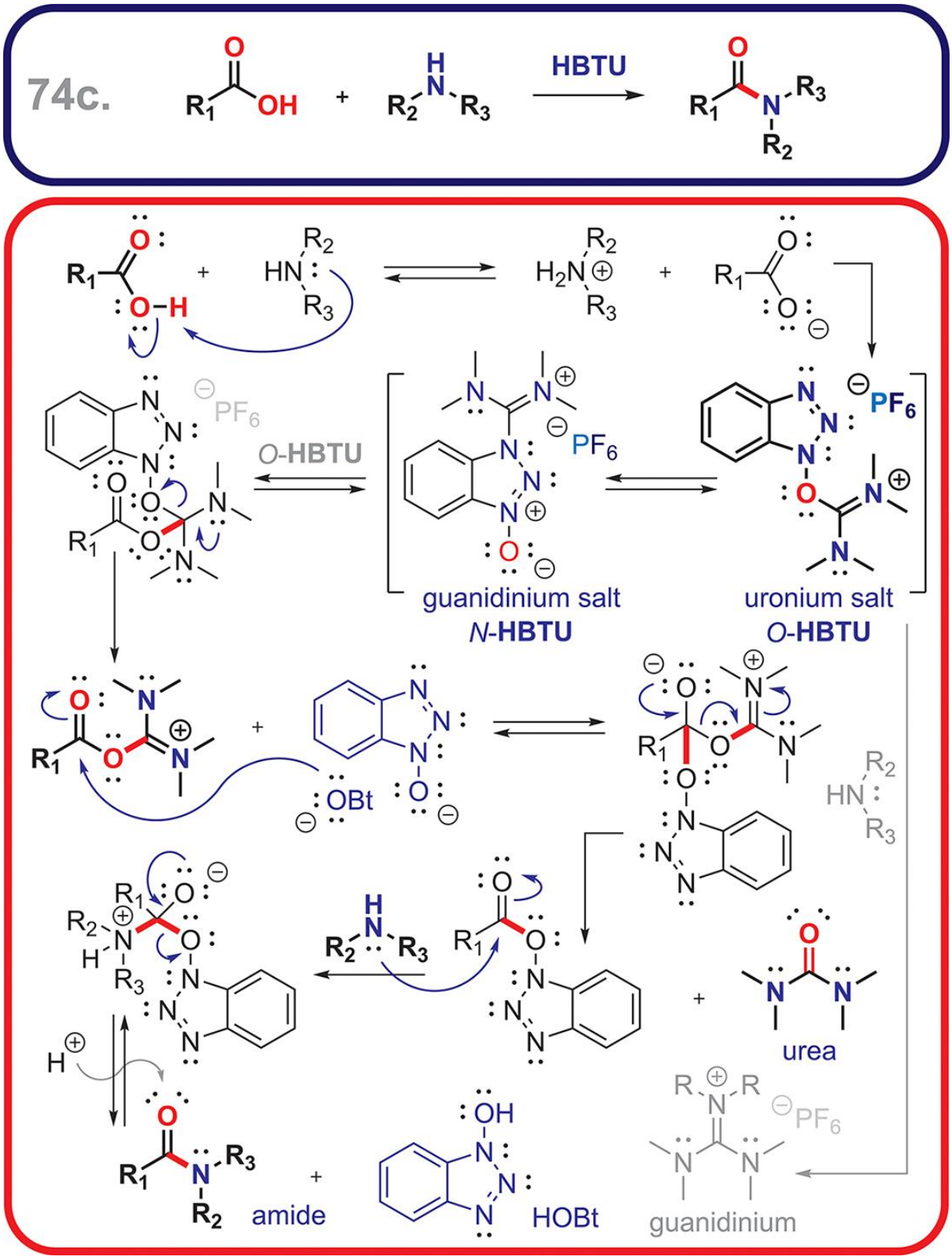


Fig. 74.3: The *peptide (amide) coupling* (HBTU) mechanism.[270]

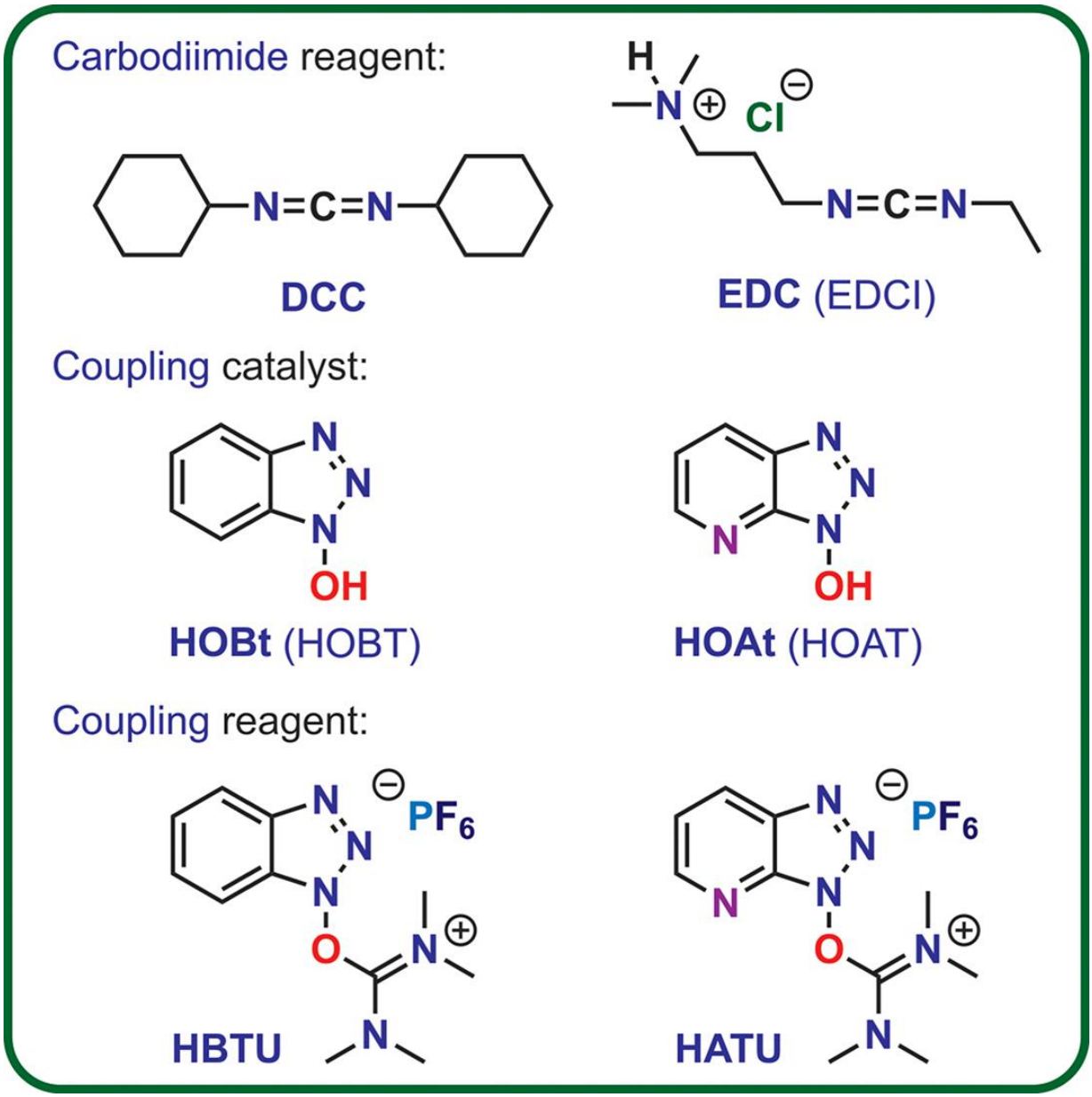


Fig. 74.4: The main *peptide (amide) coupling* reagents and catalysts.[271]

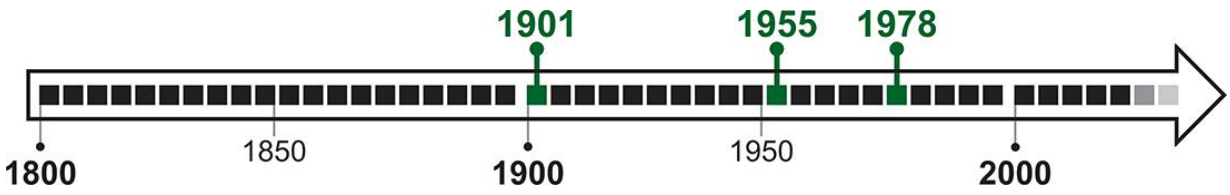


Fig. 74.5: The discovery of the *peptide (amide) coupling*.[272]

75 Pictet–Spengler Reaction

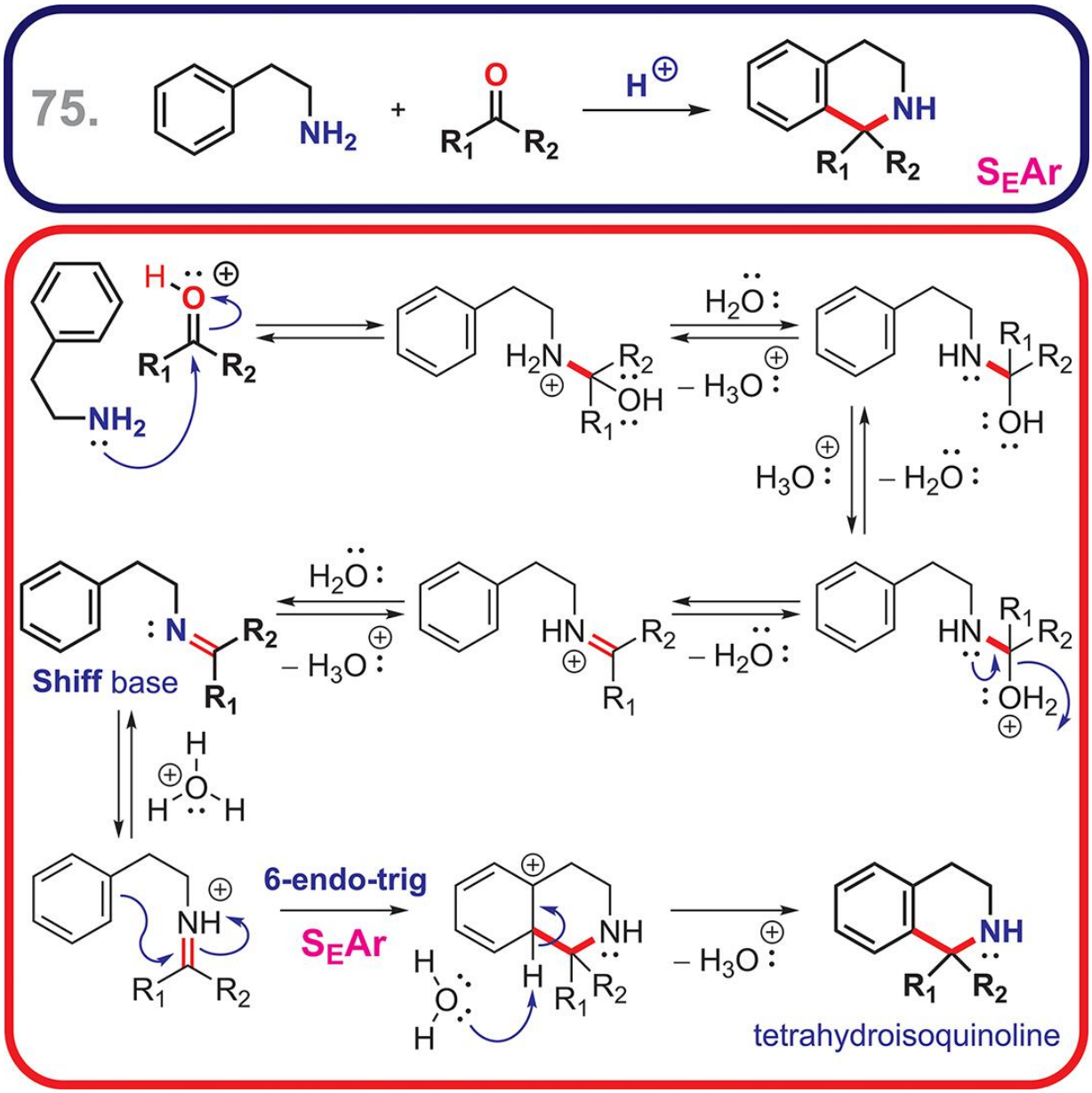


Fig. 75.1: The ***Pictet–Spengler*** *reaction* mechanism.[273]

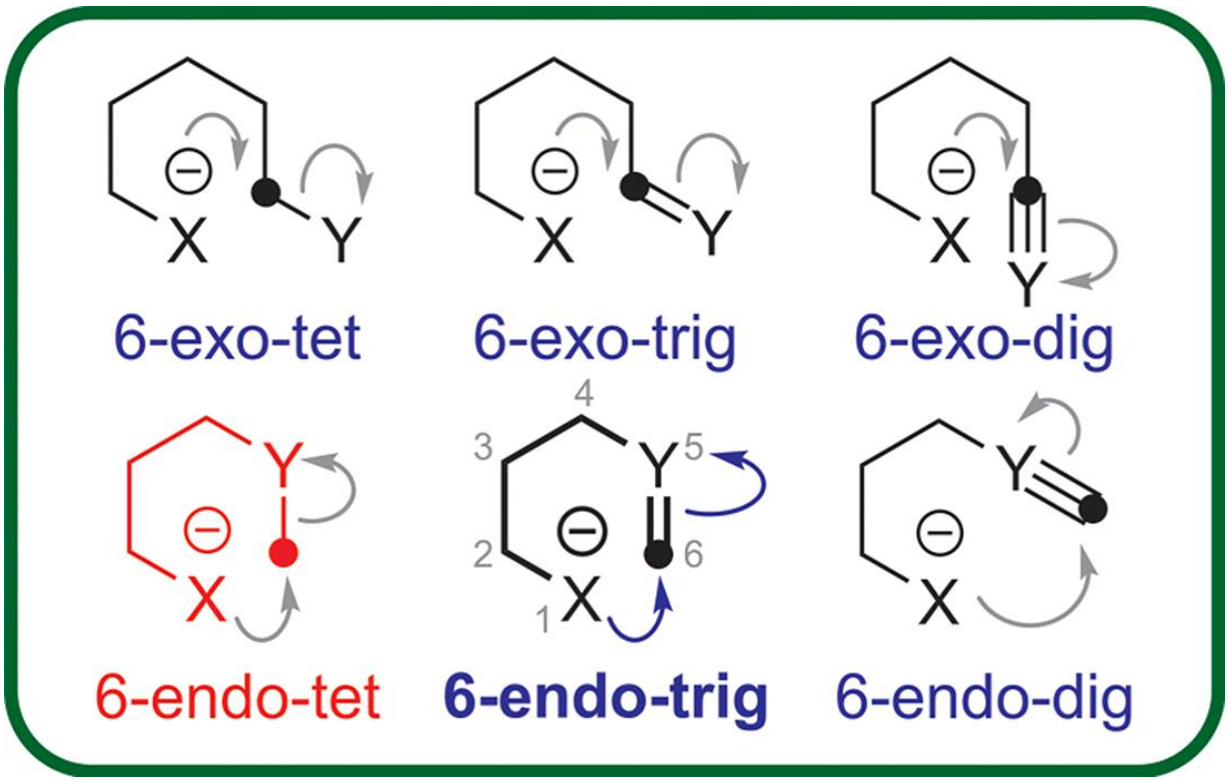


Fig. 75.2: ***Baldwin's*** *rules*.[274]

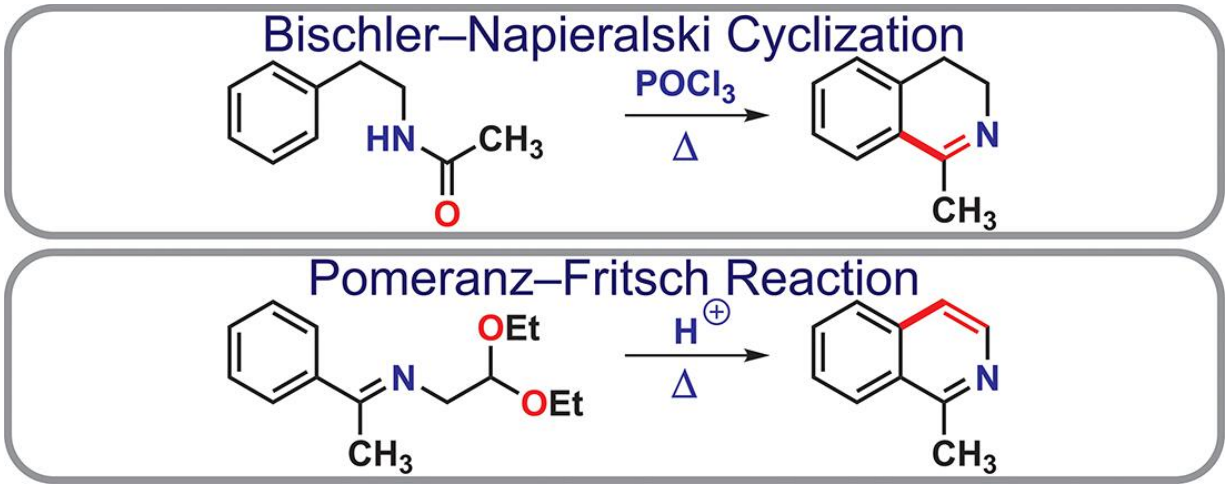


Fig. 75.3: Reactions related to the ***Pictet–Spengler*** *reaction*.[275]

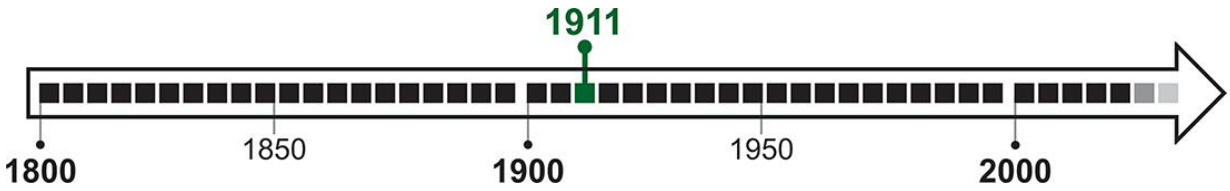


Fig. 75.4: The discovery of the ***Pictet–Spengler*** *reaction*.[276]

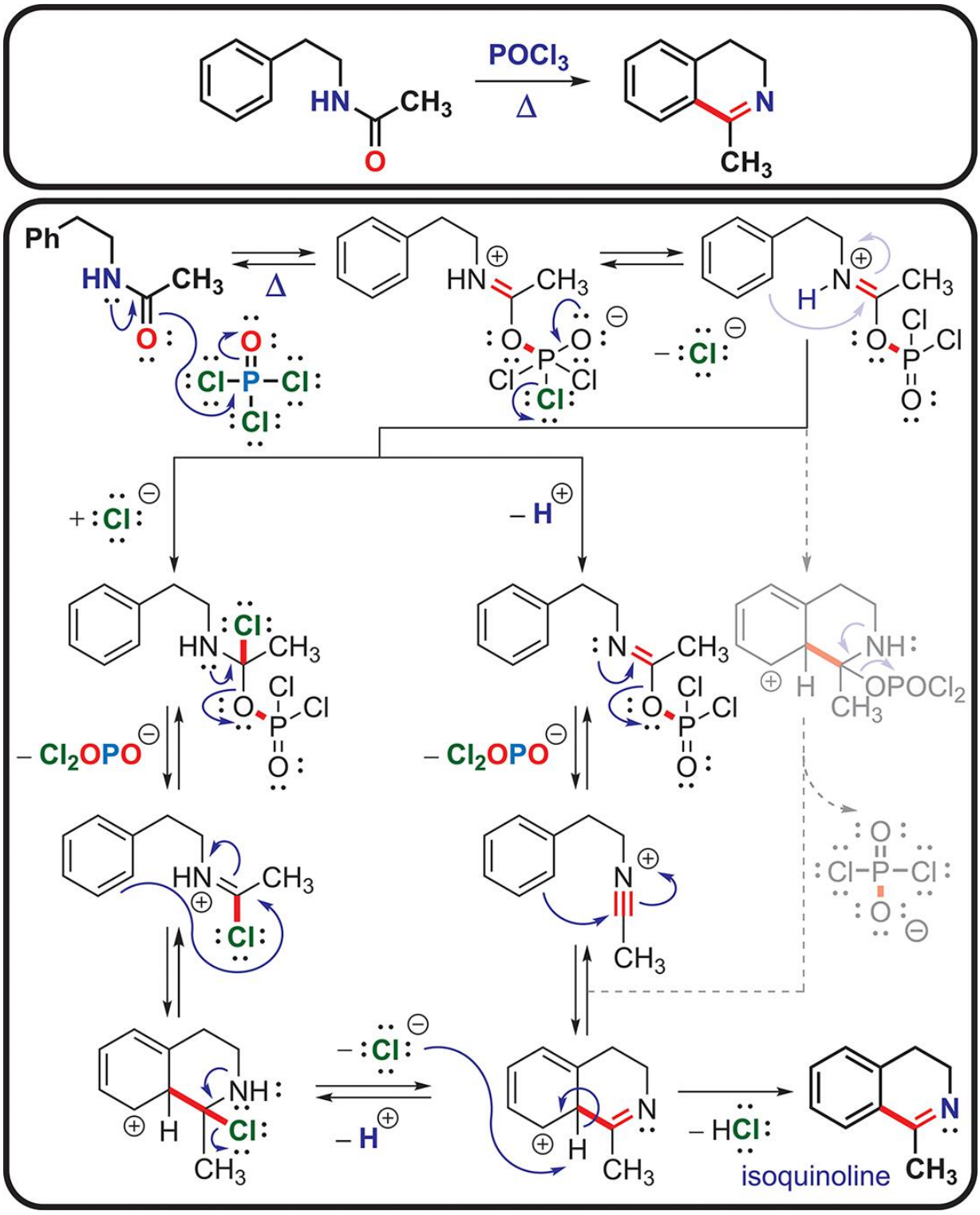


Fig. 75.5: The ***Bischler–Napieralski*** *cyclization* mechanism of *N*-phenethylacetamide.[277]

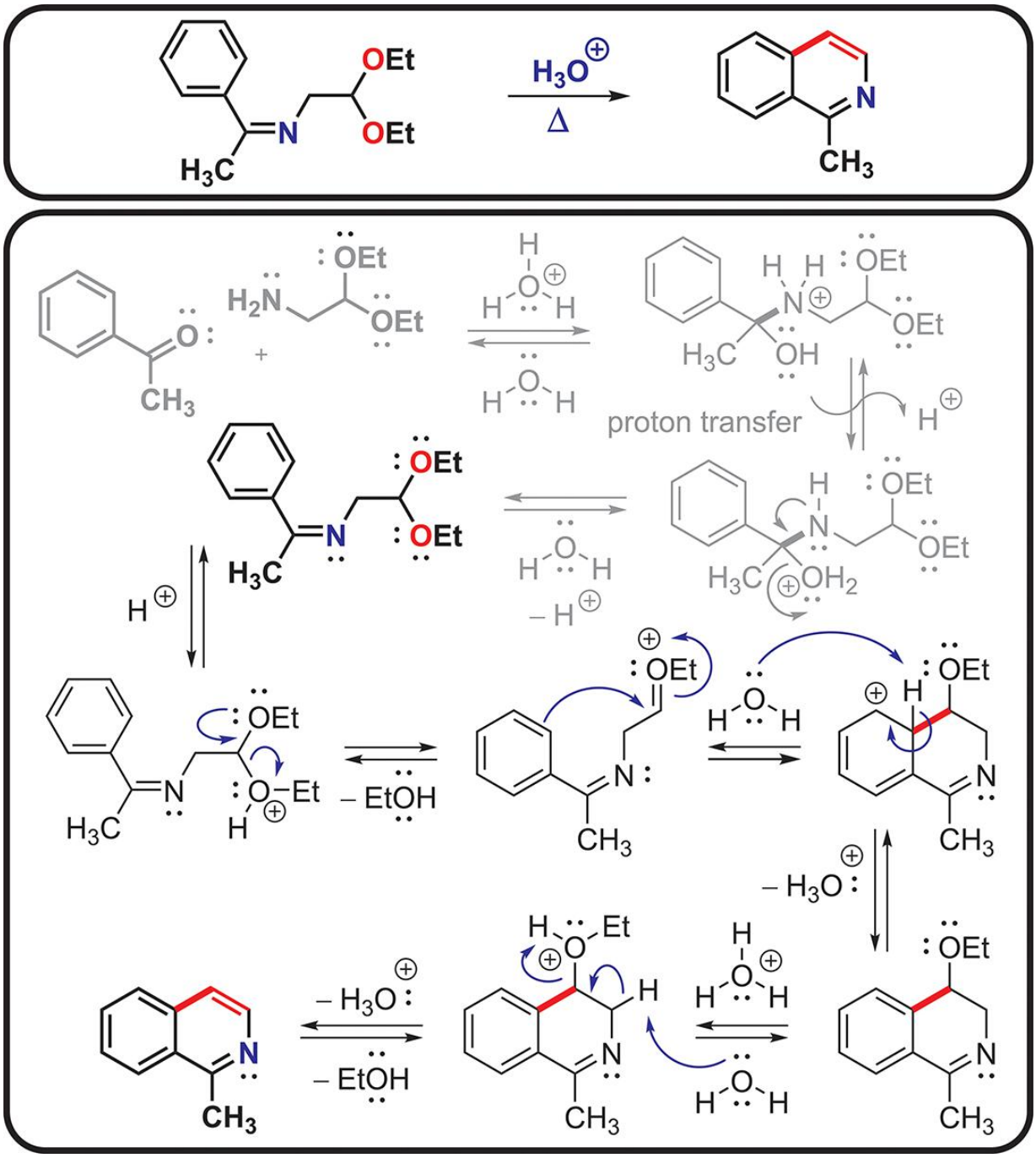


Fig. 75.6: The ***Pomeranz–Fritsch*** *reaction* mechanism.[278]

76 Pinacol–Pinacolone Rearrangement

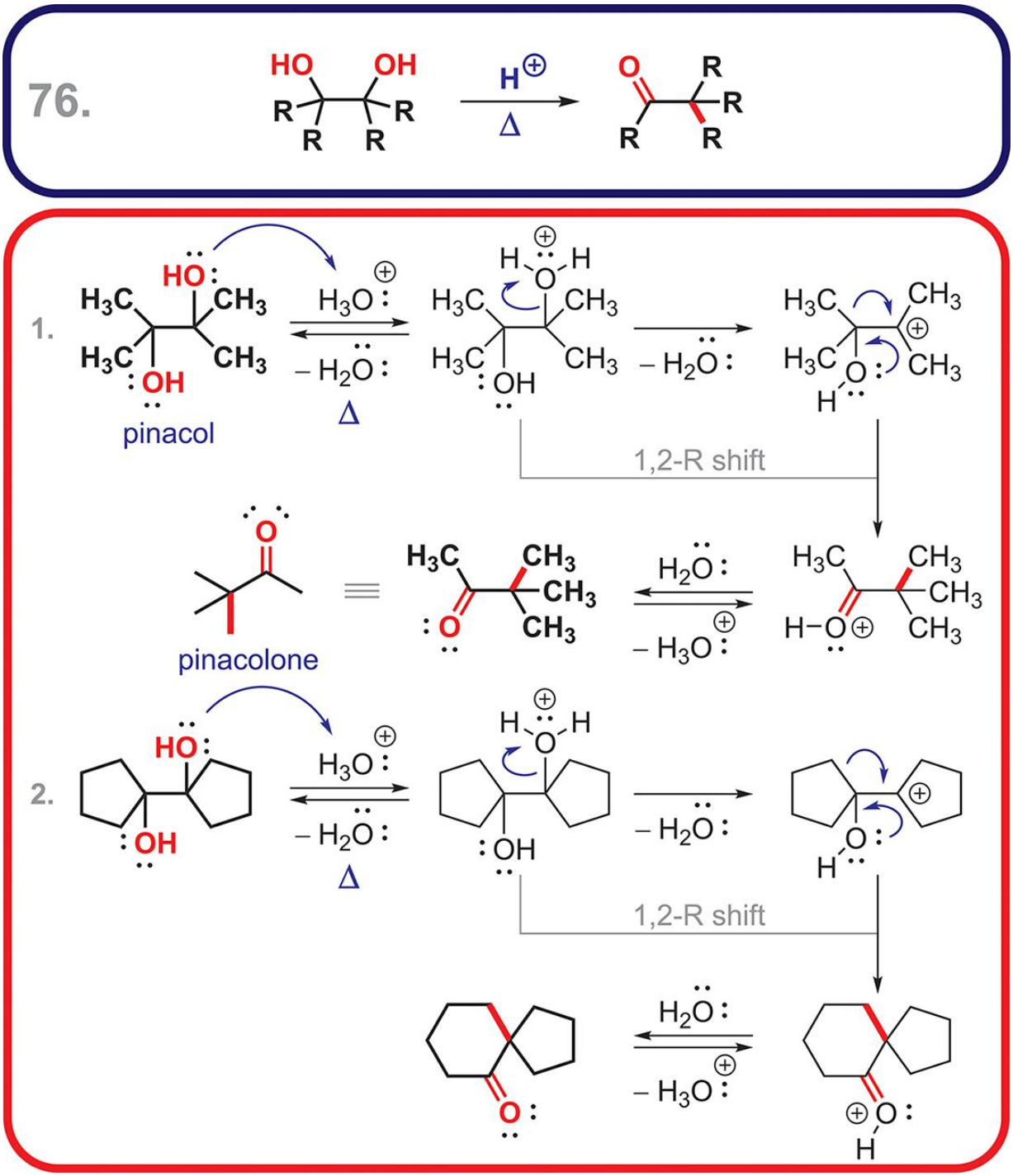


Fig. 76.1: The *pinacol–pinacolone rearrangement* mechanism.[279]

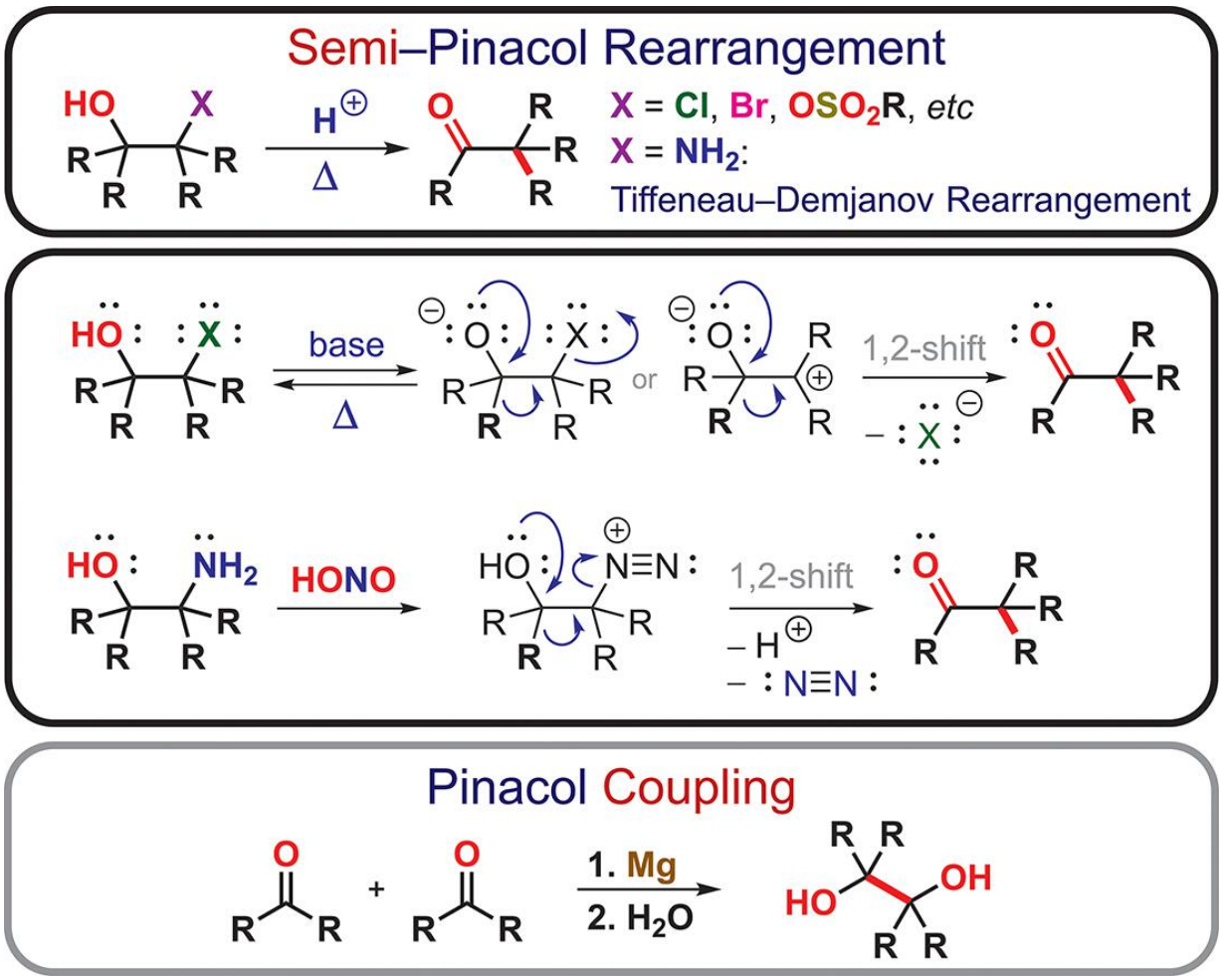


Fig. 76.2: The *semi-pinacol rearrangement* mechanism.[280]

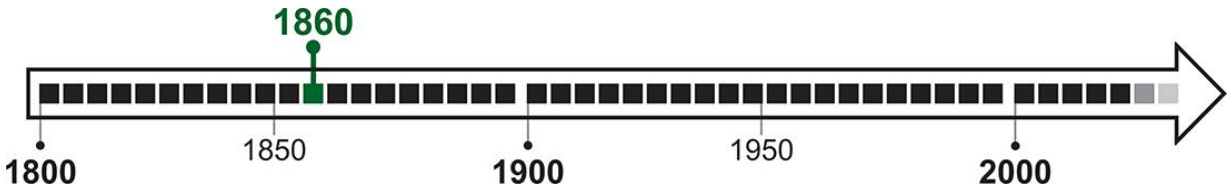


Fig. 76.3: The discovery of the *pinacol–pinacolone rearrangement*.[281]

77 Polonovski Reaction

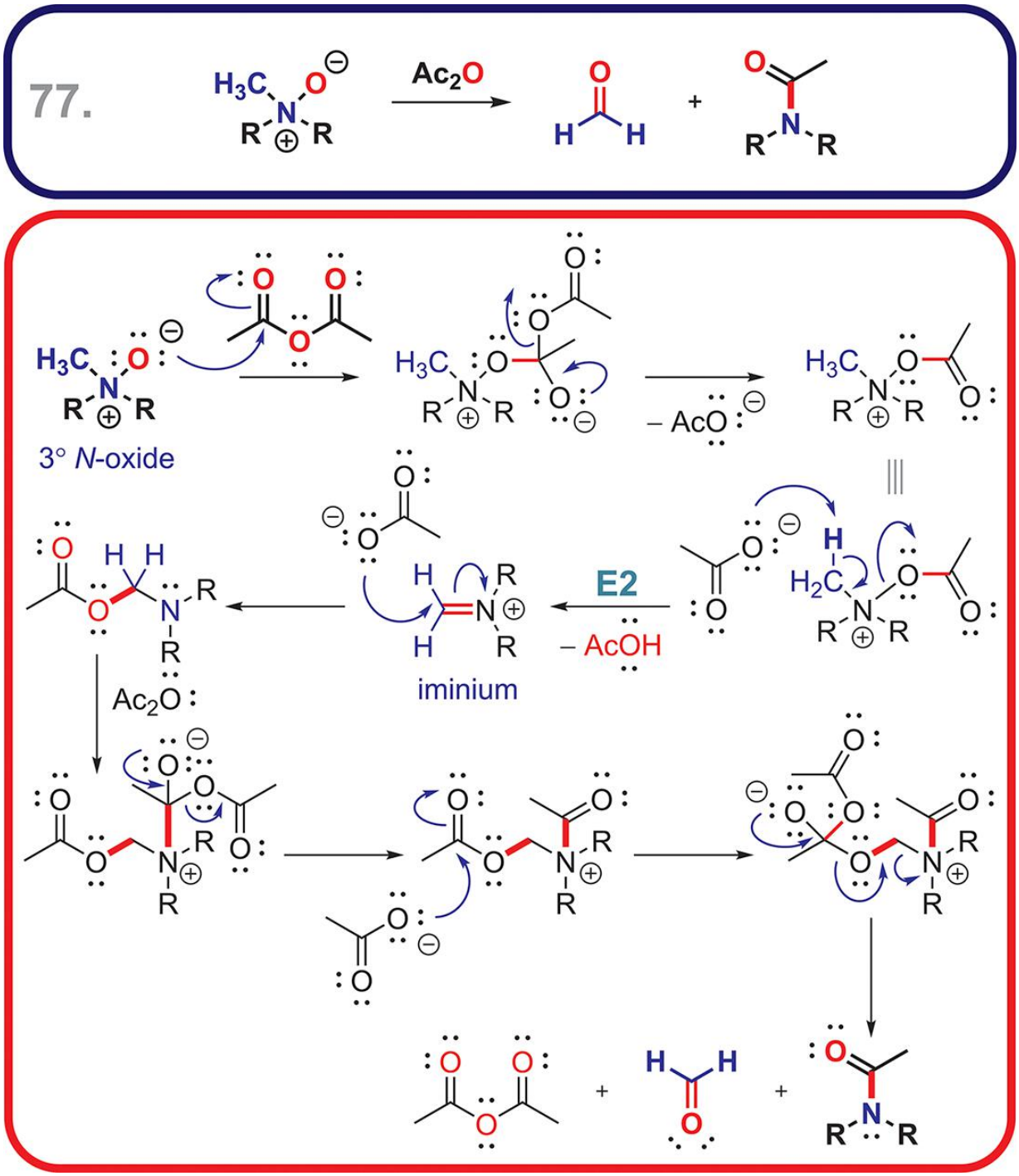


Fig. 77.1: The ***Polonovski*** *reaction* mechanism.[282]

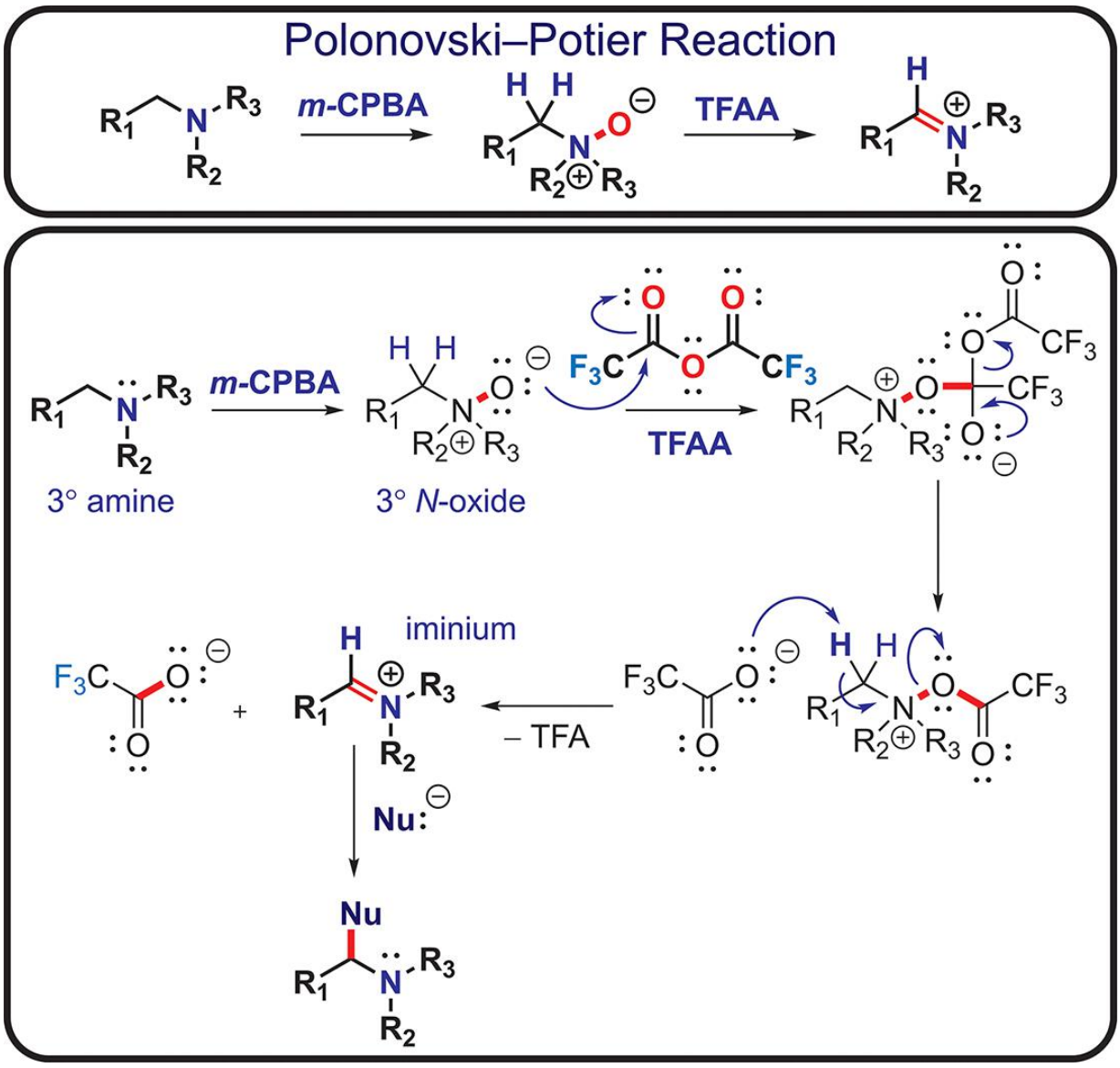


Fig. 77.2: The ***Polonovski–Potier*** *reaction* mechanism.[283]

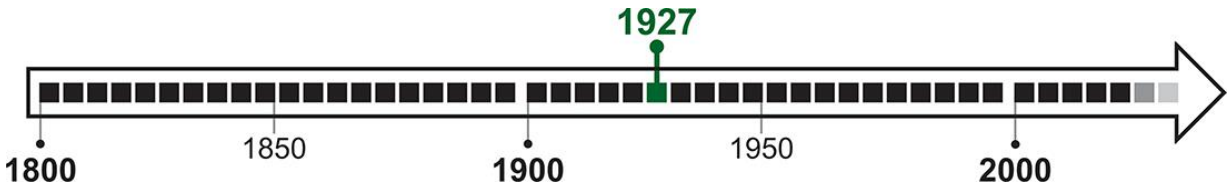


Fig. 77.3: The discovery of the ***Polonovski*** *reaction*.[284]

78 Prilezhaev Epoxidation

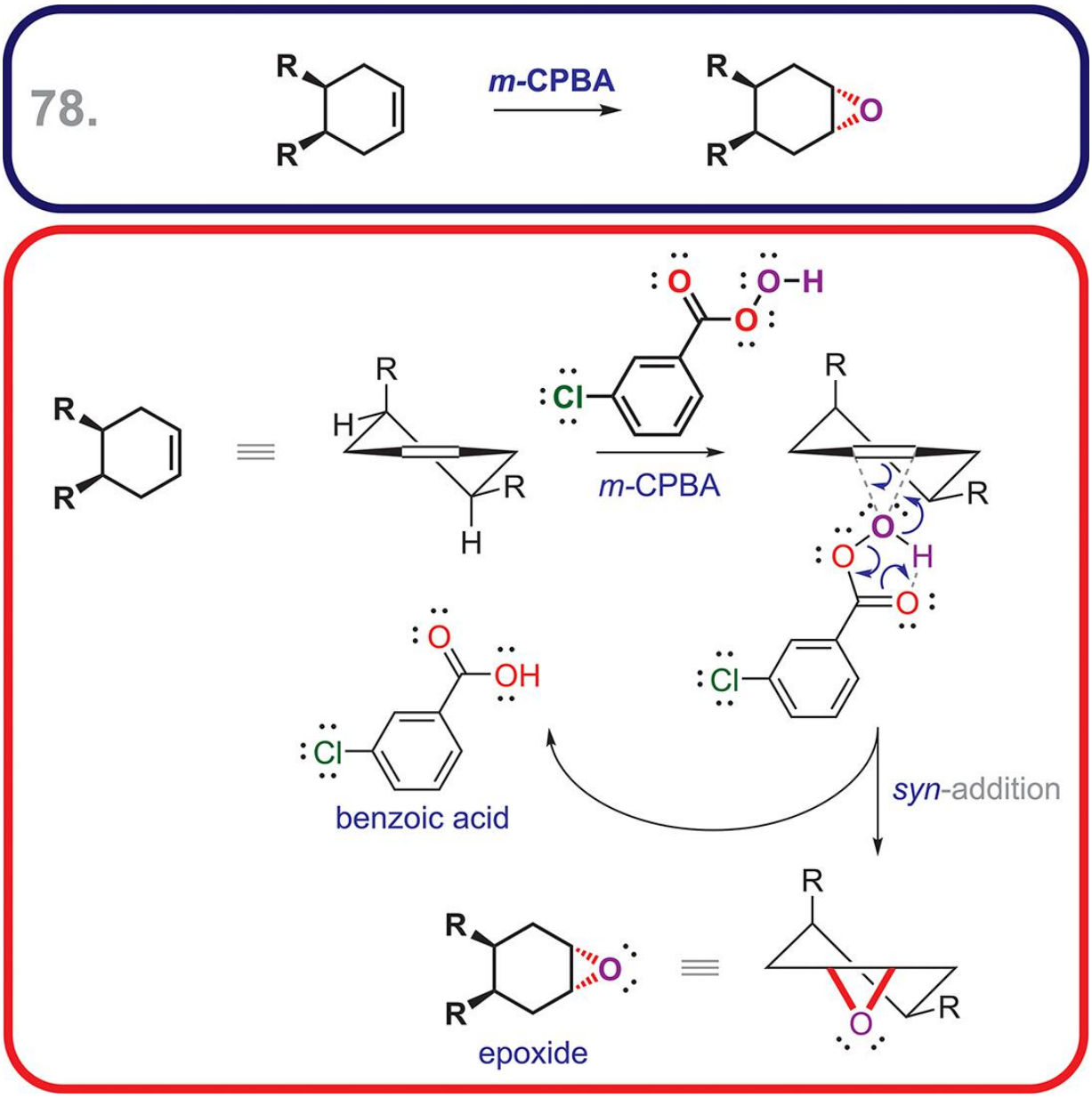


Fig. 78.1: The ***Prilezhaev*** *epoxidation* mechanism.[285]

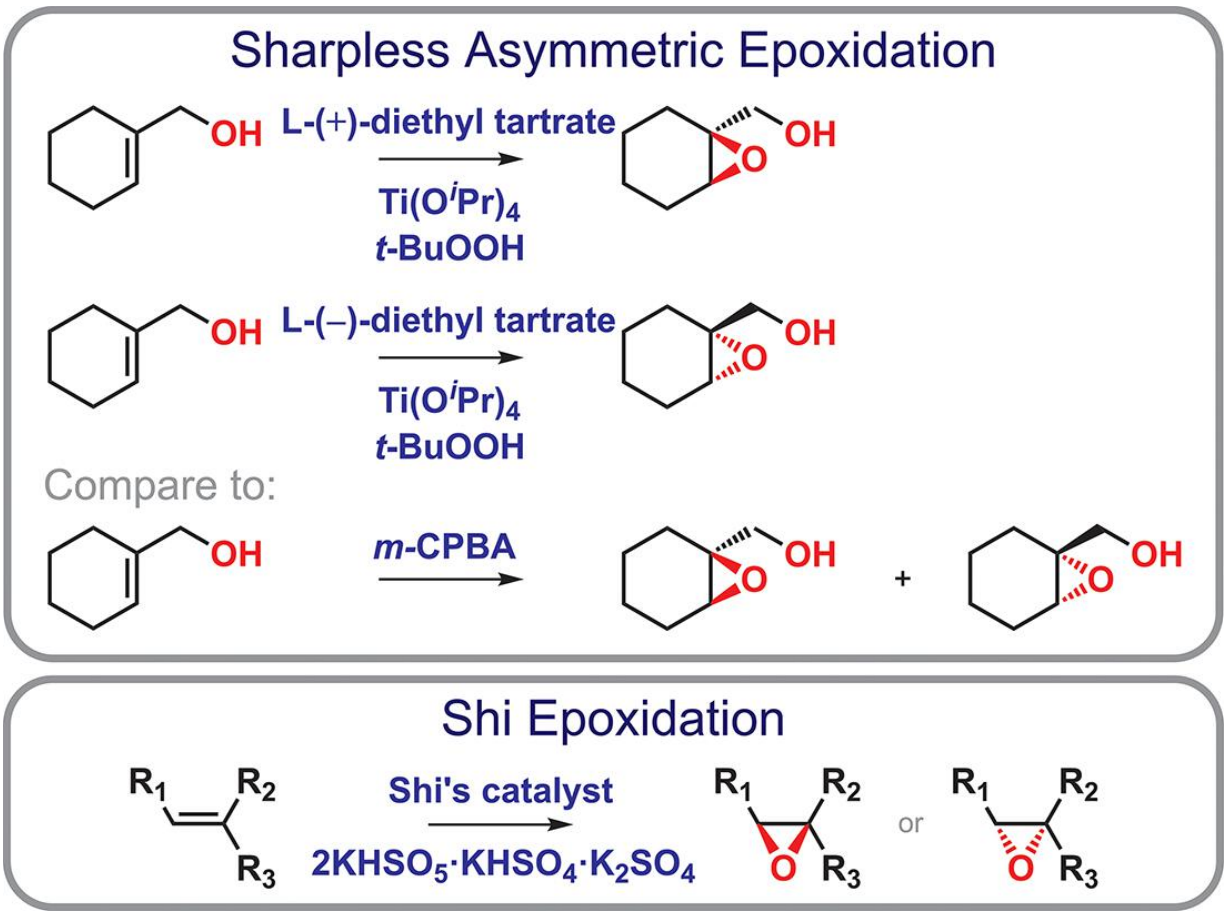


Fig. 78.2: Reactions related to the ***Prilezhaev*** *epoxidation*.[286]

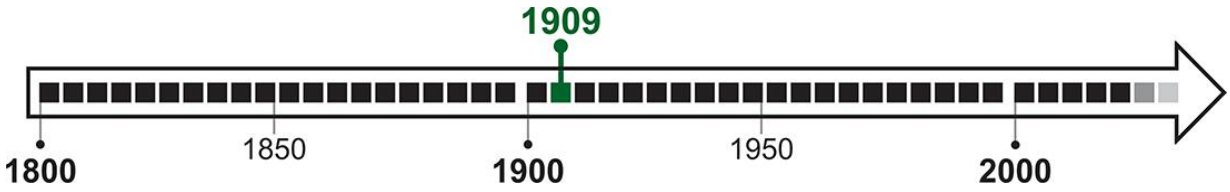


Fig. 78.3: The discovery of the ***Prilezhaev*** *epoxidation*.[287]

79 Prins Reaction

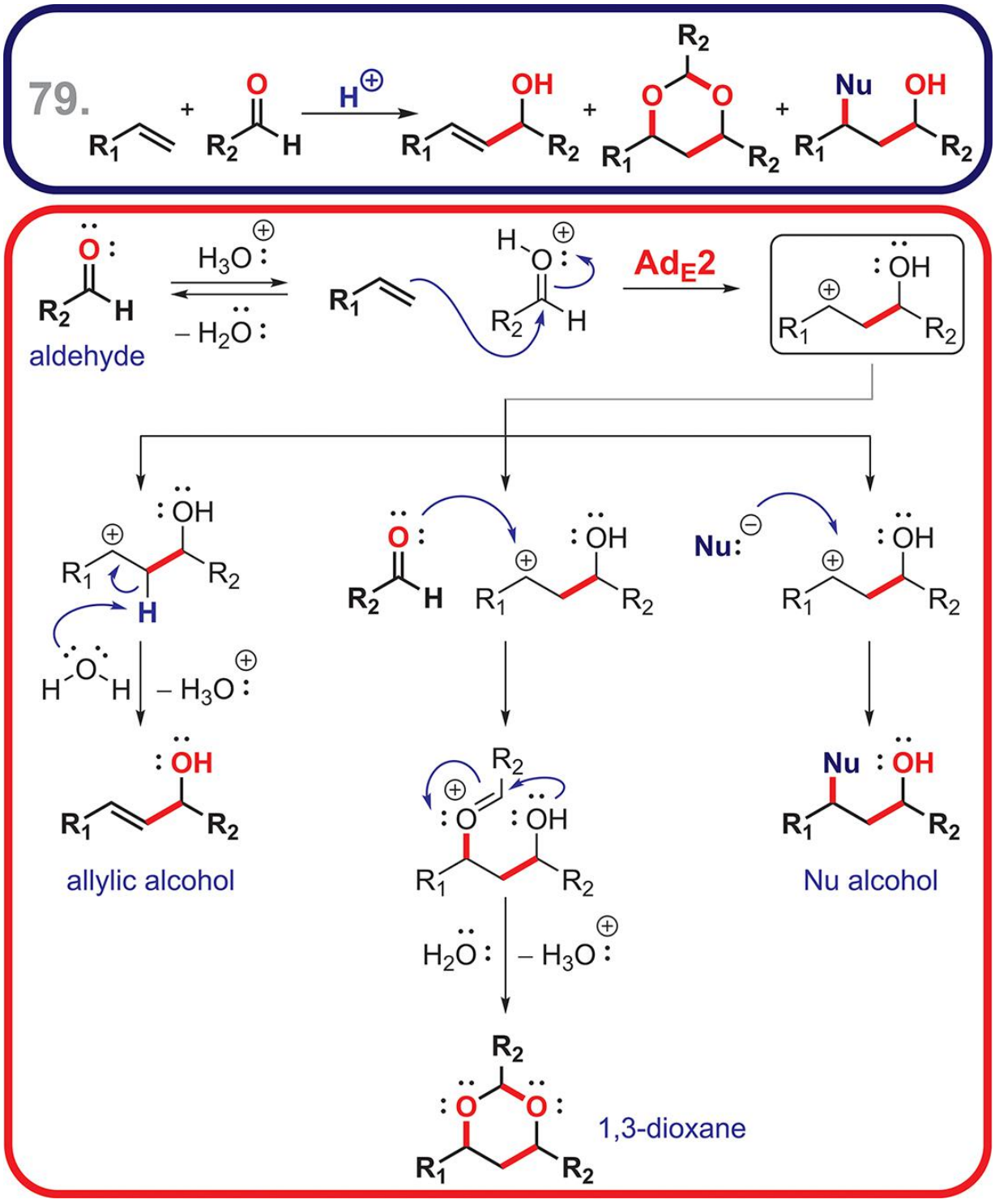


Fig. 79.1: The ***Prins*** *reaction* mechanism.[288]

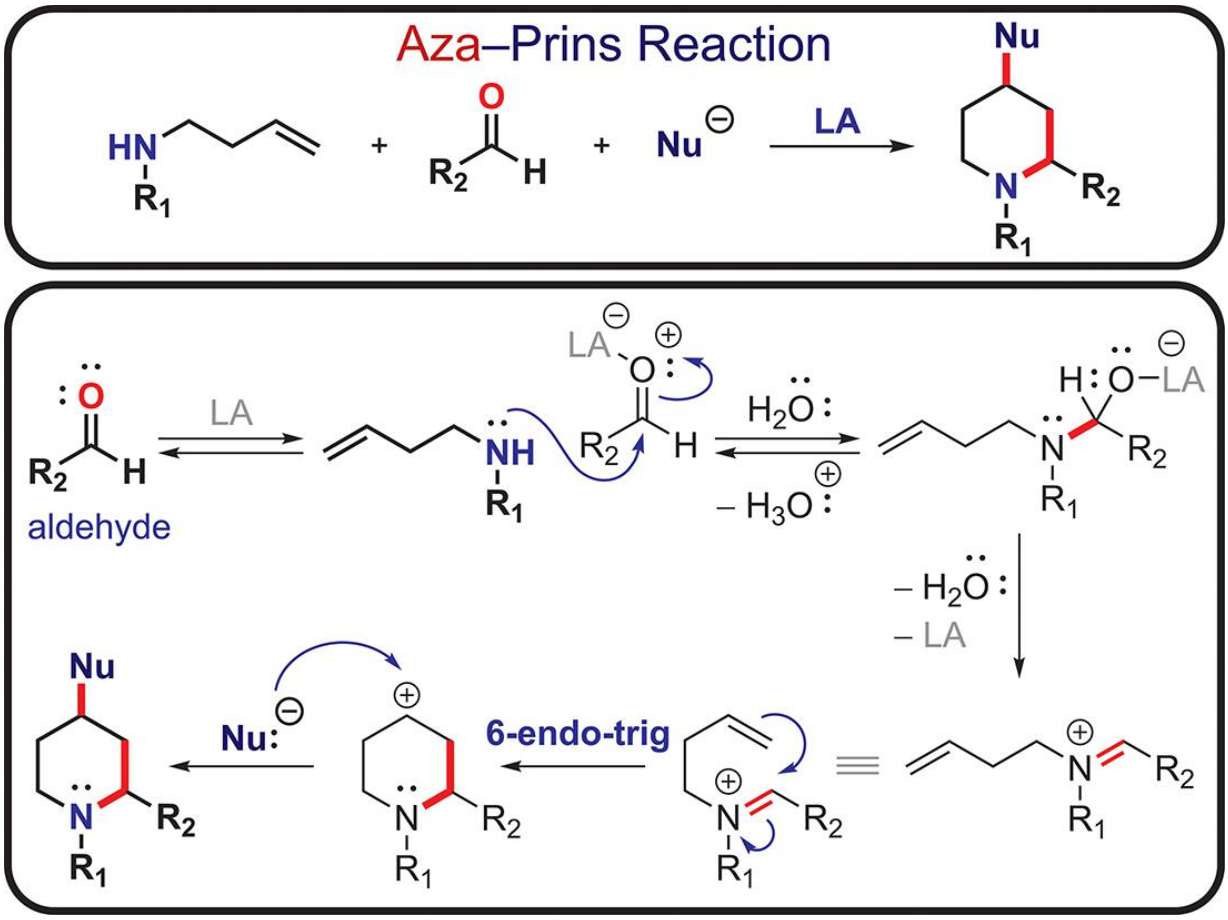


Fig. 79.2: The *aza-**Prins** reaction* mechanism.[289]

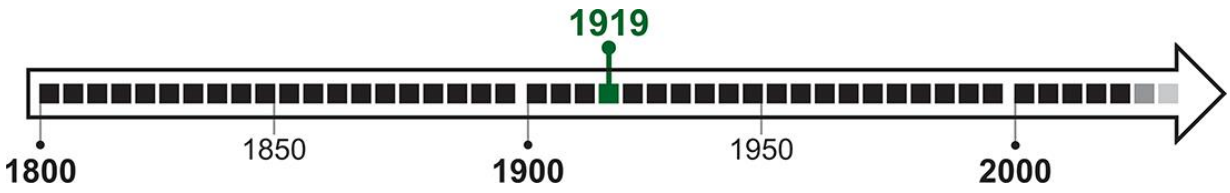


Fig. 79.3: The discovery of the ***Prins** reaction*.[290]

80 Pummerer Rearrangement

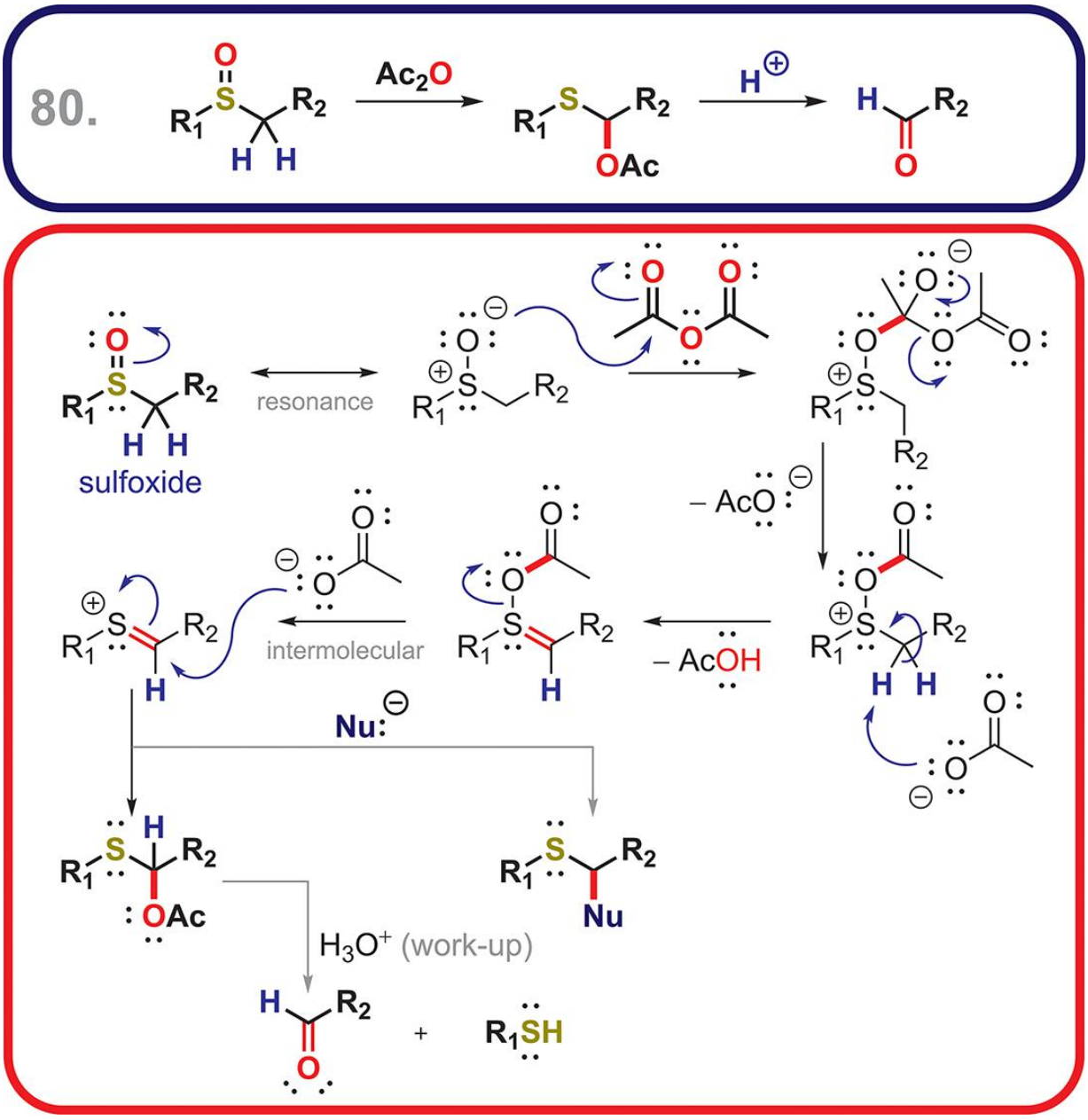


Fig. 80.1: The ***Pummerer*** *rearrangement* mechanism.[291]

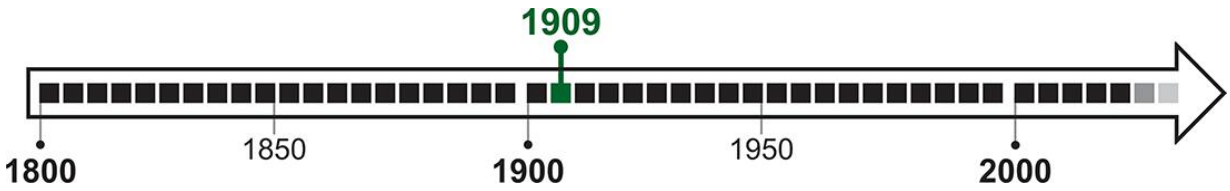


Fig. 80.2: The discovery of the ***Pummerer*** *rearrangement*.[292]

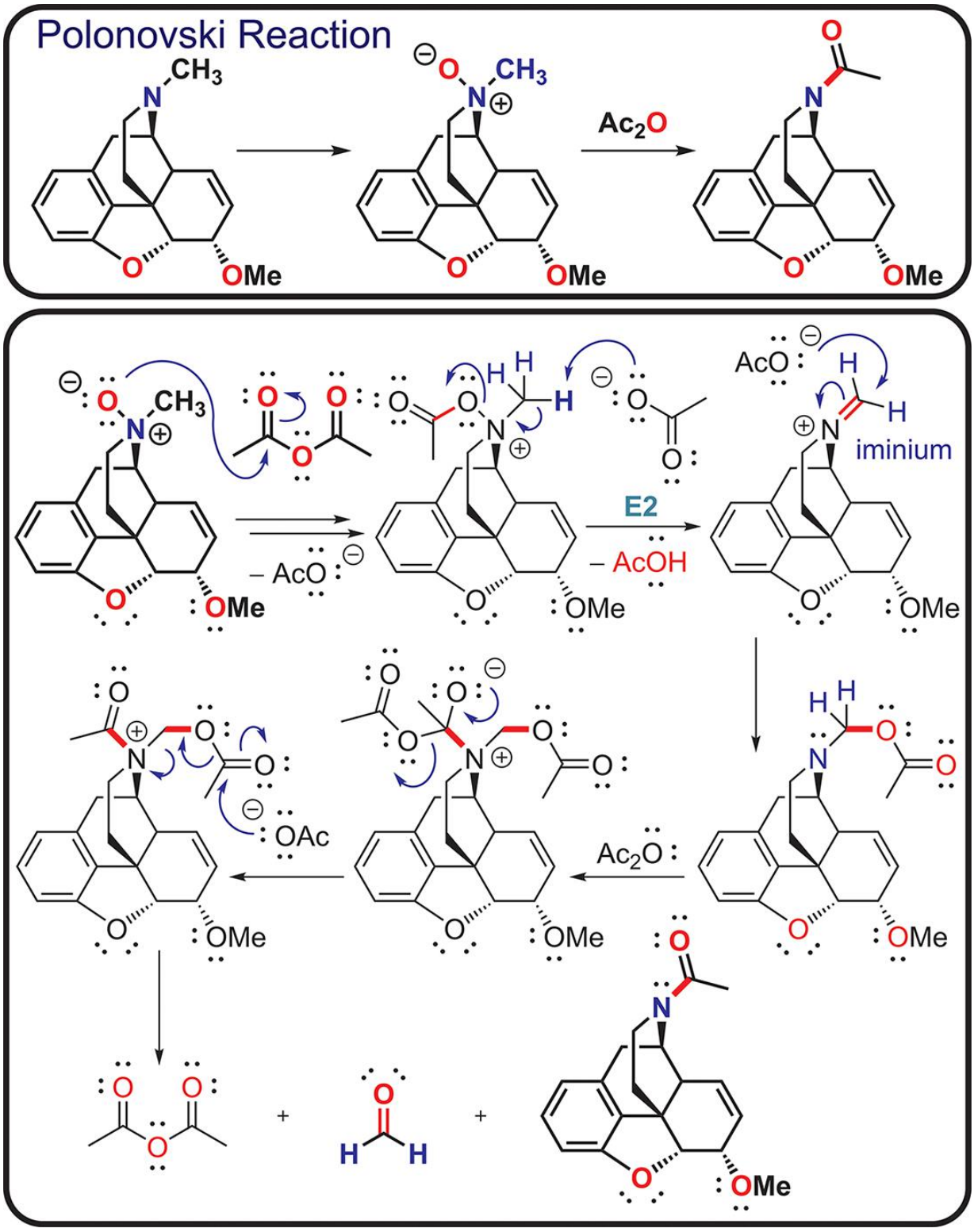


Fig. 80.3: The ***Polonovski*** *reaction* mechanism (*N*-demethylation).[293]

81 Ramberg–Bäcklund Rearrangement

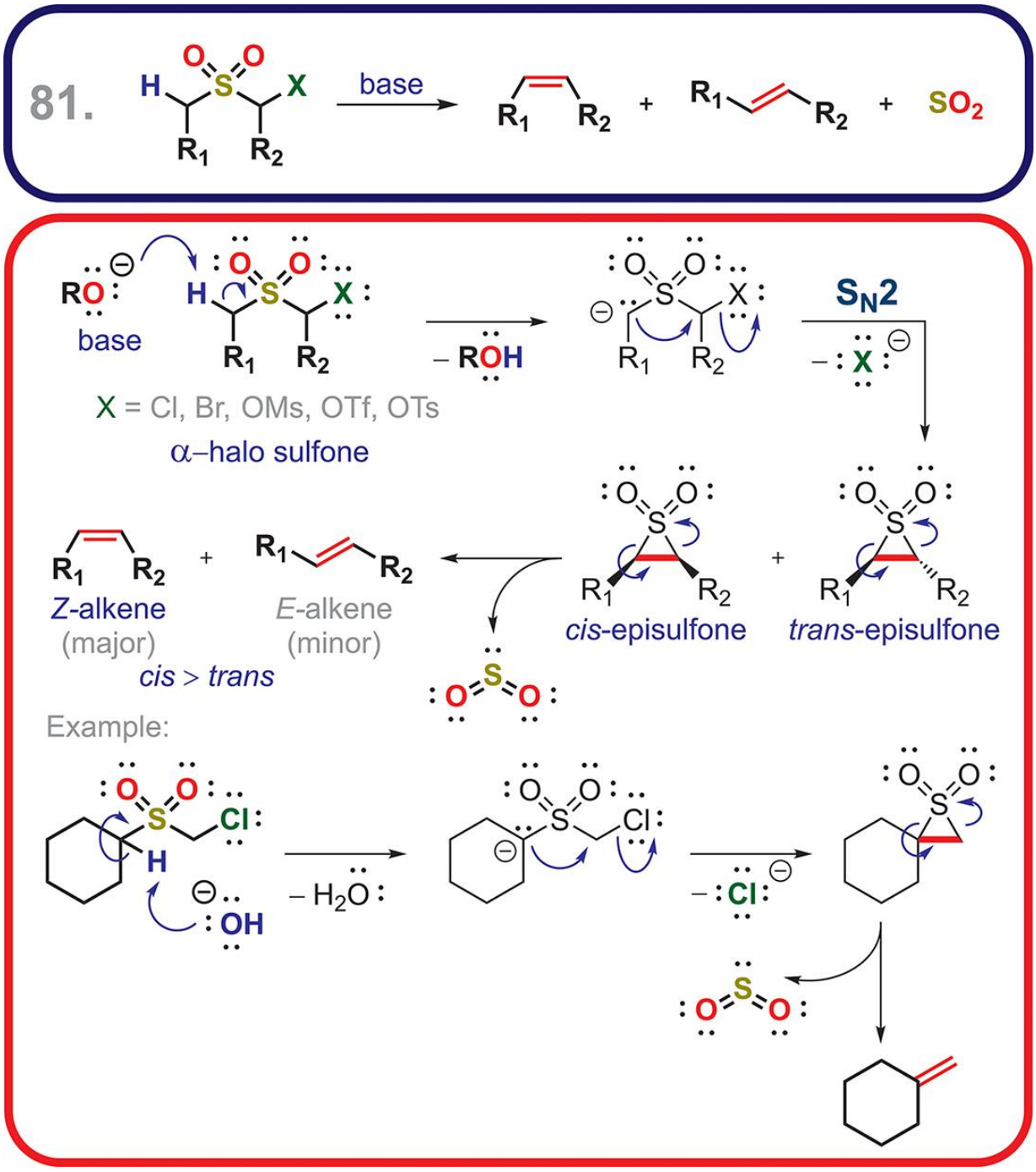


Fig. 81.1: The ***Ramberg–Bäcklund*** *rearrangement* mechanism.[294]

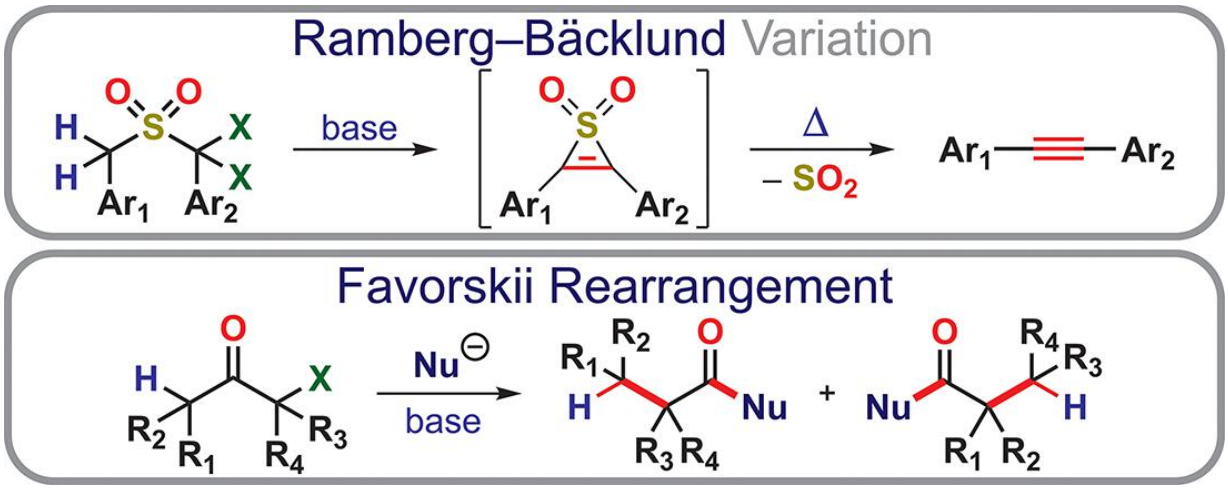


Fig. 81.2: Reactions related to the ***Ramberg–Bäcklund*** *rearrangement*.[295]

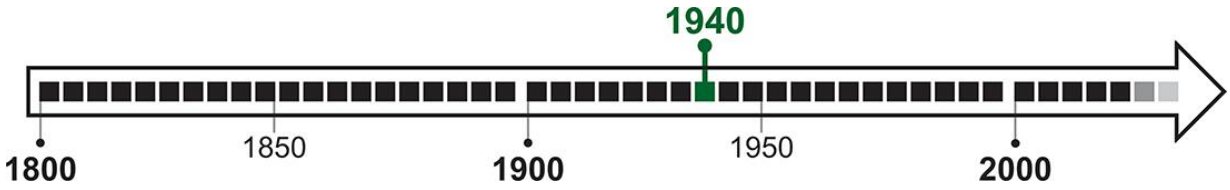


Fig. 81.3: The discovery of the ***Ramberg–Bäcklund*** *rearrangement*.[296]

82 Reformatsky Reaction

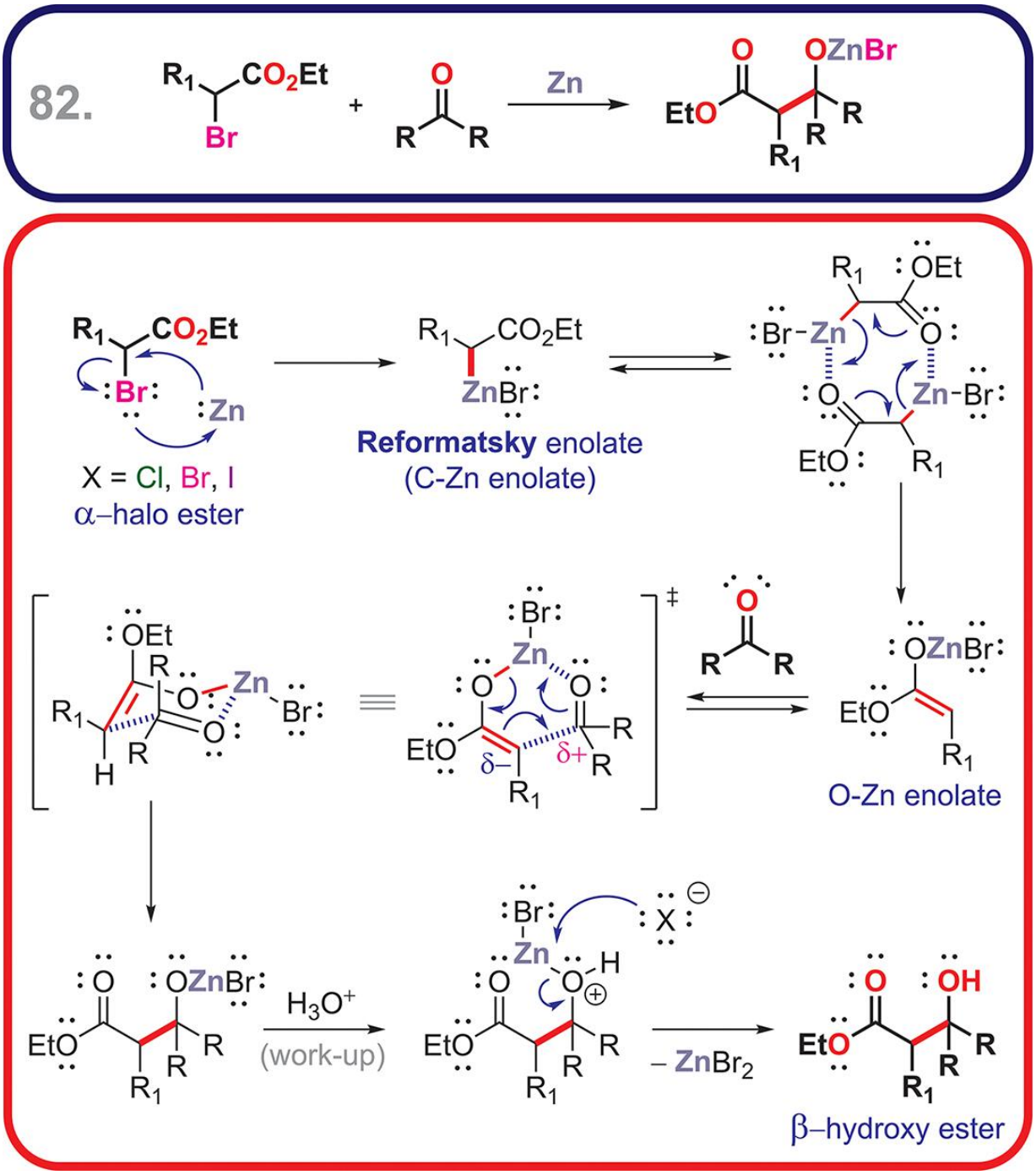


Fig. 82.1: The ***Reformatsky*** *reaction* mechanism.[297]

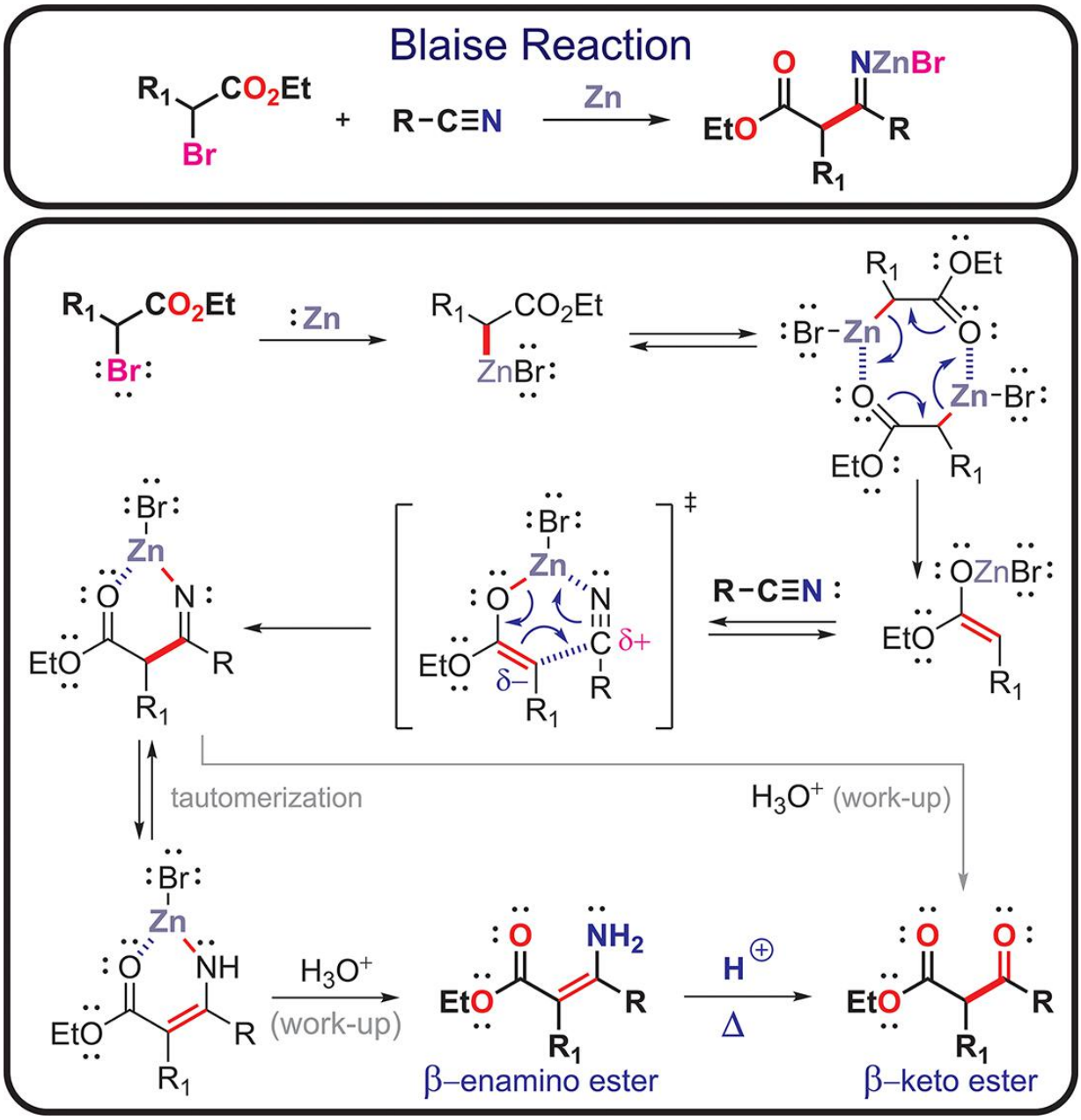


Fig. 82.2: The ***Blaise*** *reaction* mechanism.[298]

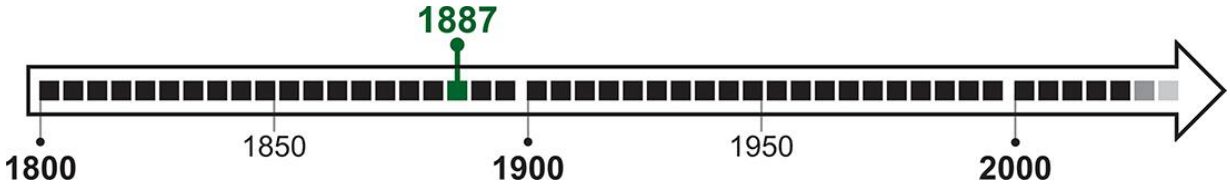


Fig. 82.3: The discovery of the ***Reformatsky*** *reaction*.[299]

83 Robinson Annulation

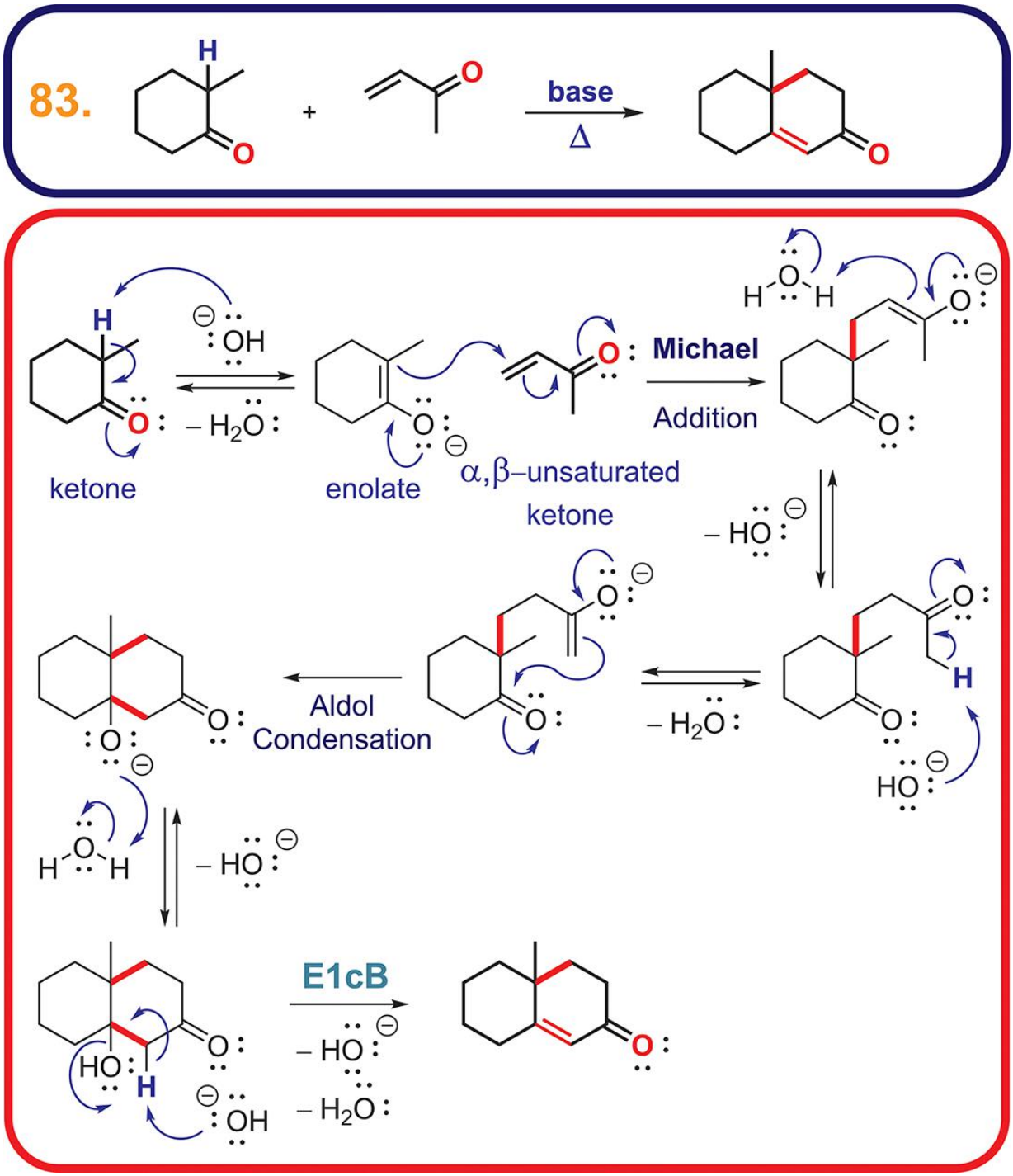


Fig. 83.1: The ***Robinson*** *annulation* mechanism.[300]

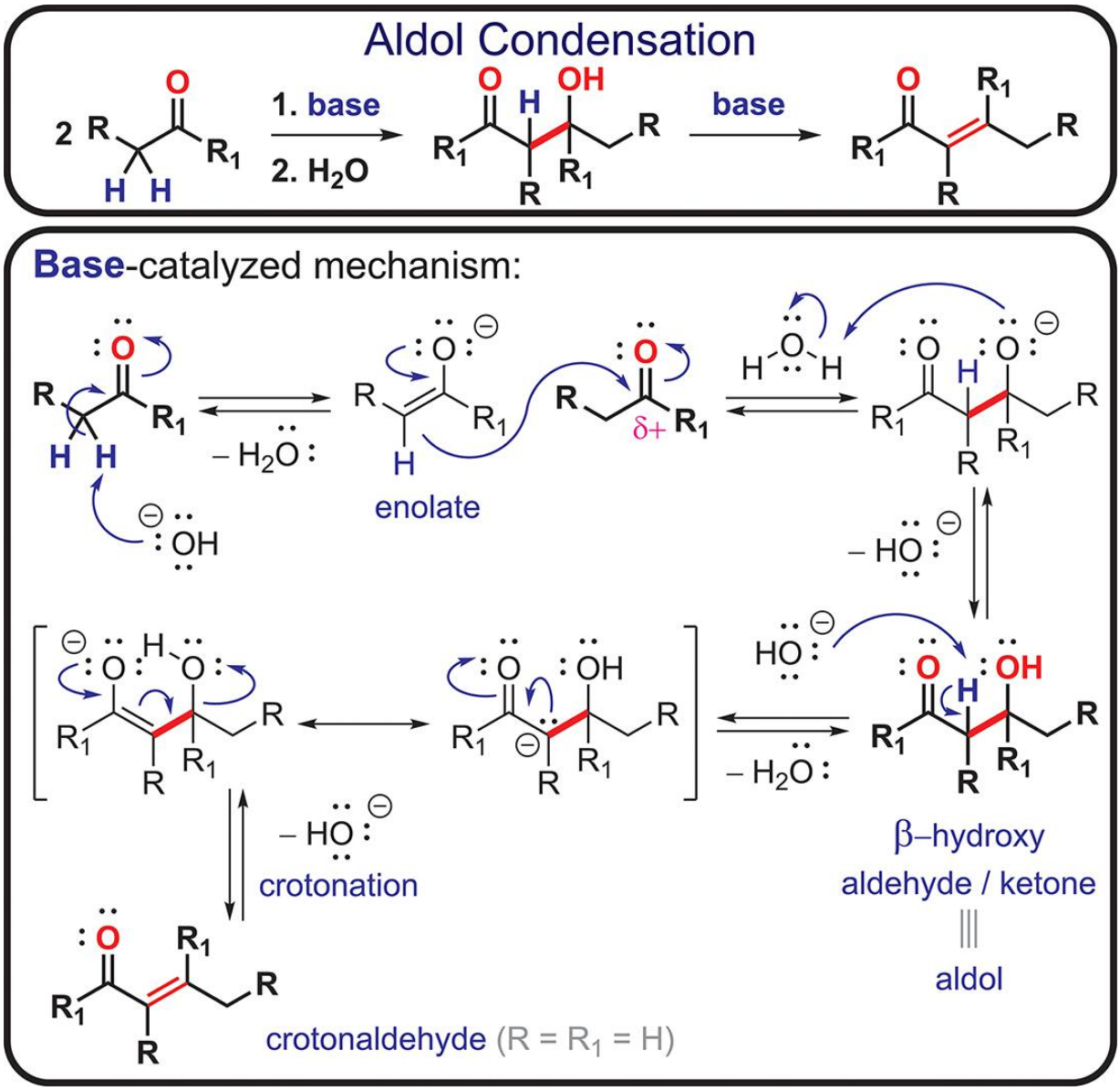


Fig. 83.2: The *aldol condensation* mechanism.[301]

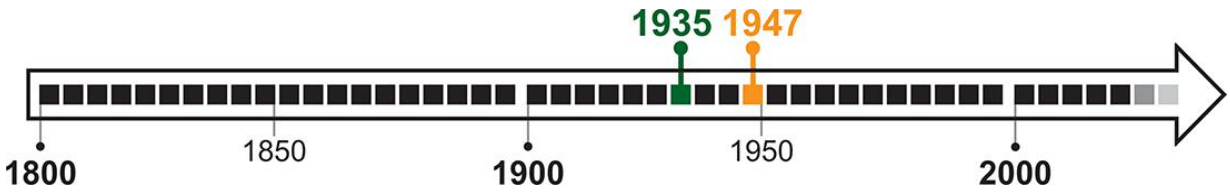


Fig. 83.3: The discovery of the ***Robinson*** *annulation*.[302]

84 Shapiro Reaction

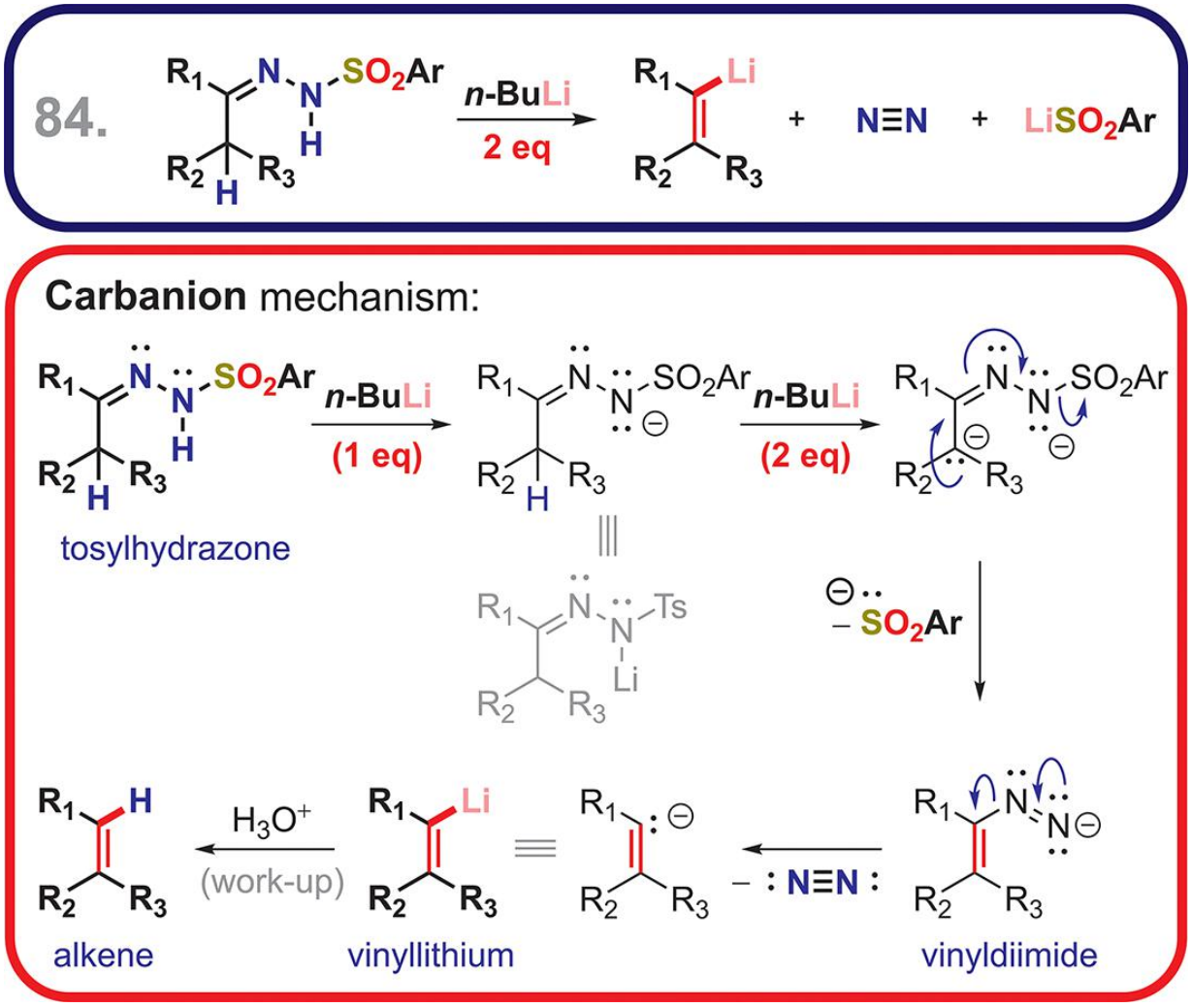


Fig. 84.1: The ***Shapiro*** *reaction* mechanism.[303]

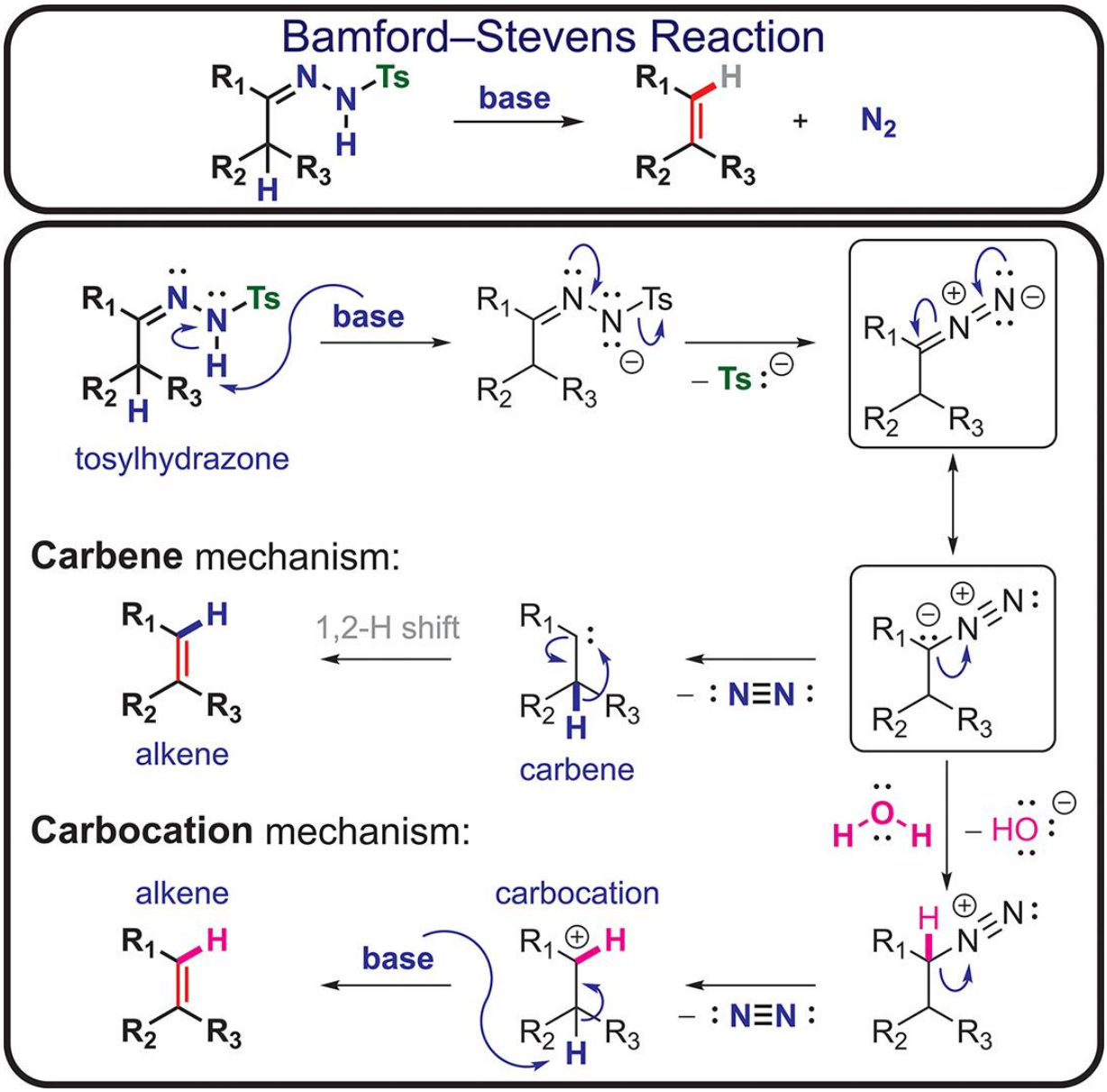


Fig. 84.2: The ***Bamford–Stevens*** *reaction* mechanism.[304]

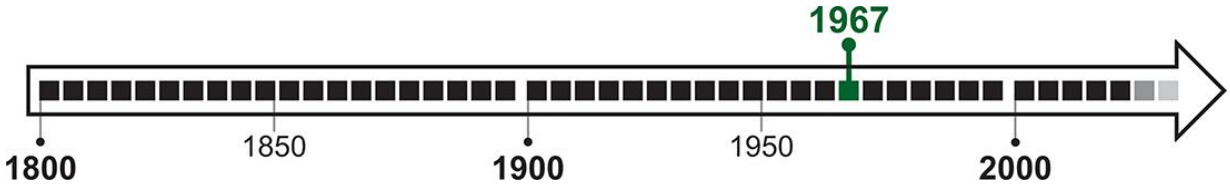


Fig. 84.3: The discovery of the ***Shapiro*** *reaction*.[305]

85 Sonogashira Cross-Coupling

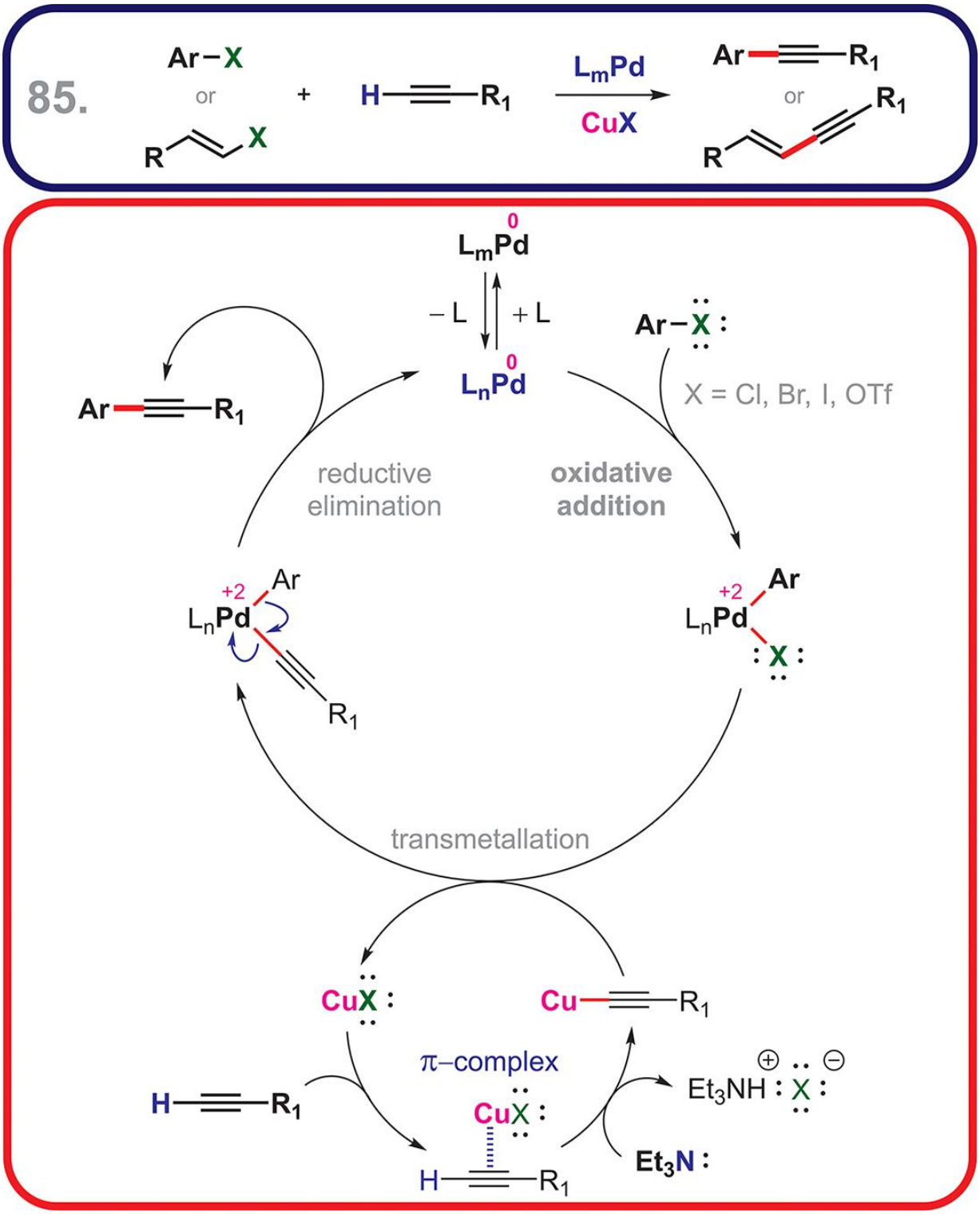


Fig. 85.1: The ***Sonogashira*** *cross-coupling* mechanism.[306]

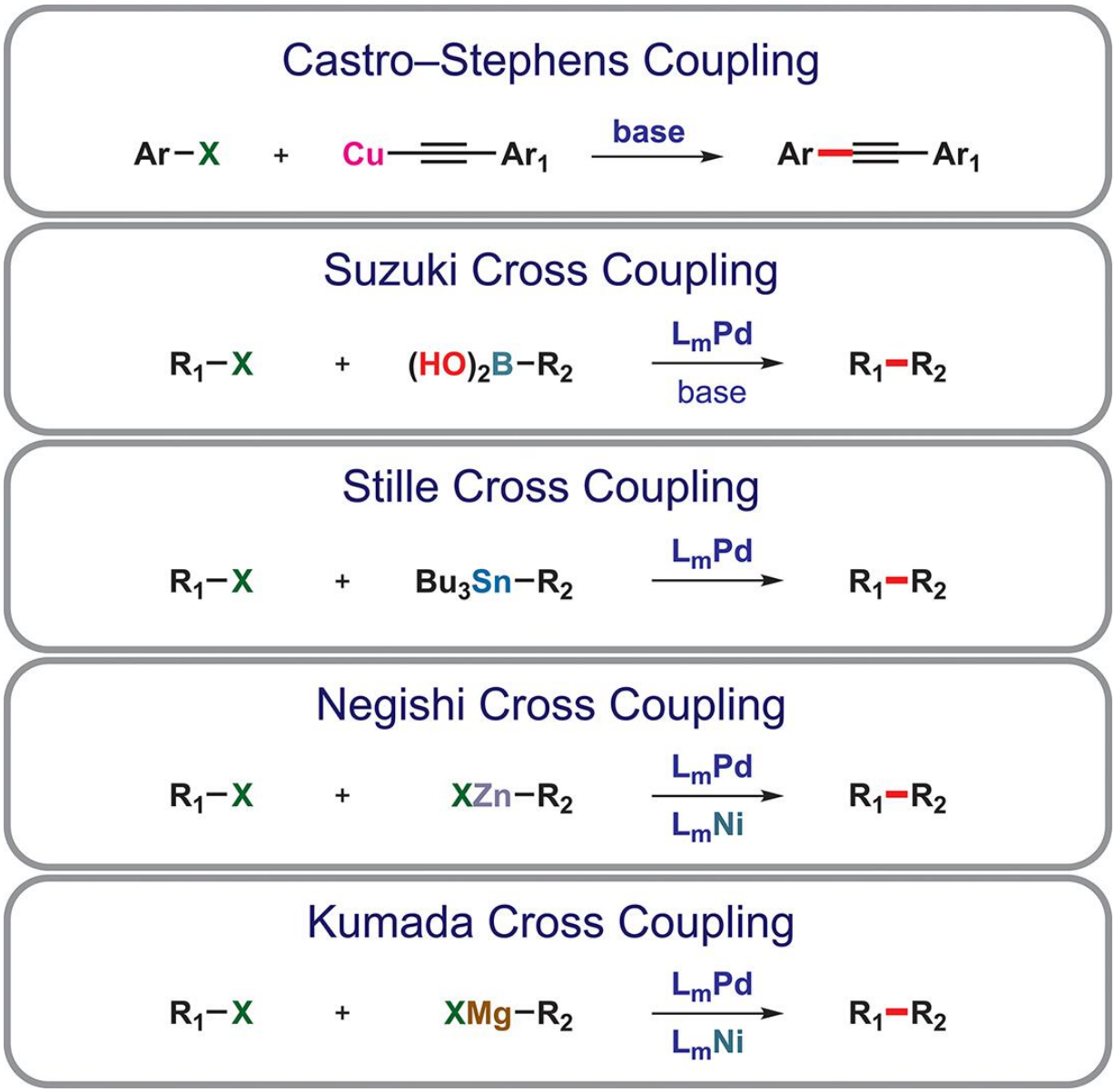


Fig. 85.2: Reactions related to the ***Sonogashira*** *cross-coupling*.[307]

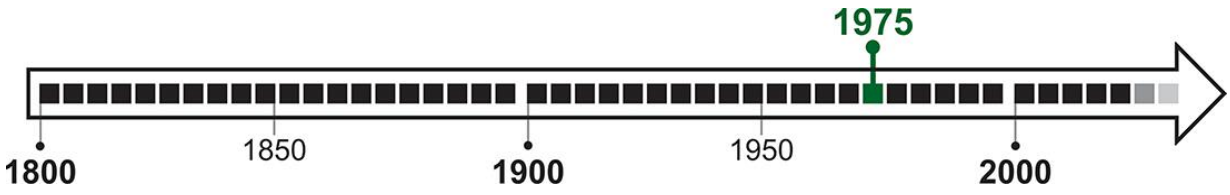


Fig. 85.3: The discovery of the ***Sonogashira*** *cross-coupling*.[308]

86 Staudinger Reaction

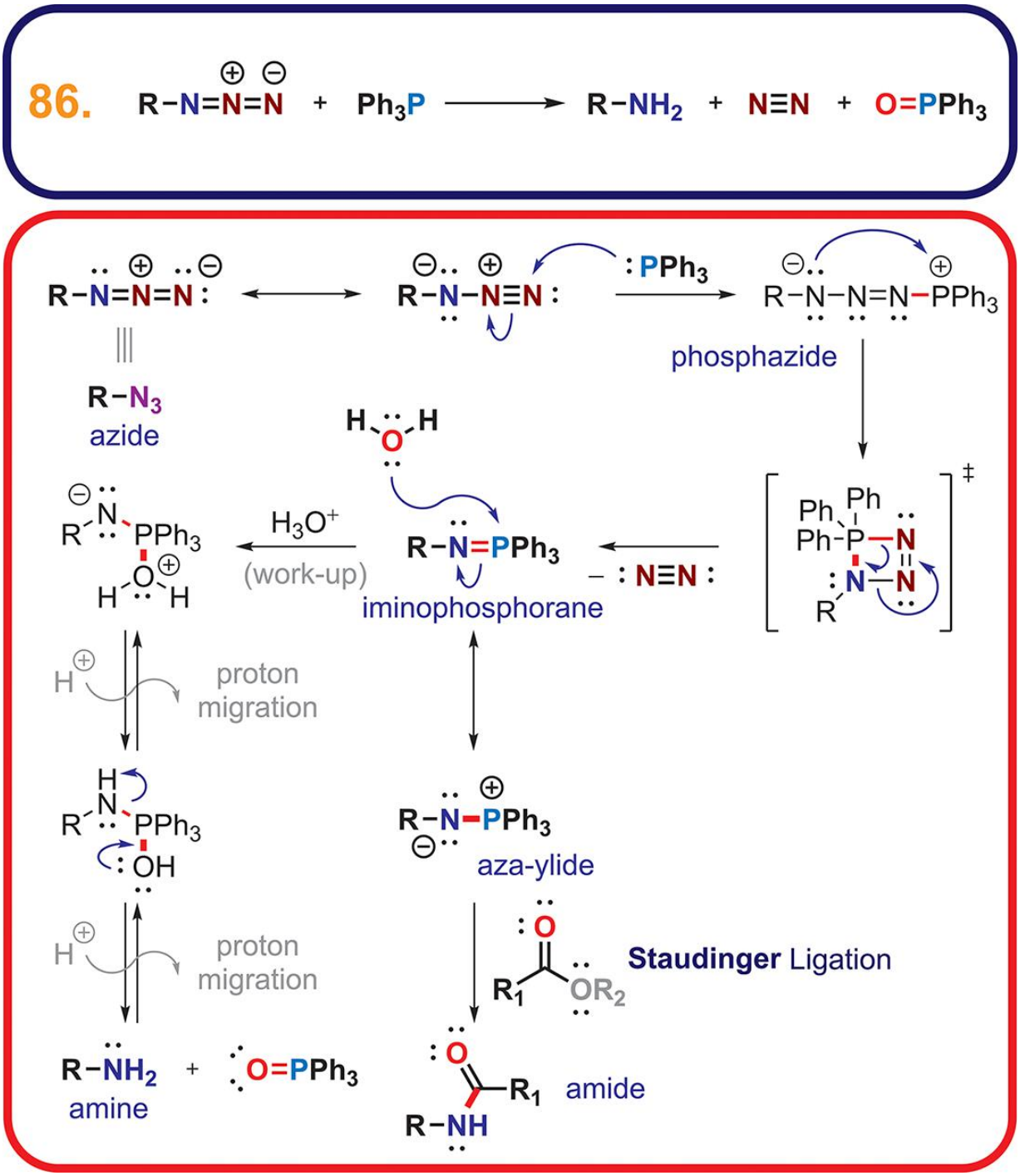


Fig. 86.1: The ***Staudinger*** *reaction* mechanism.[309]

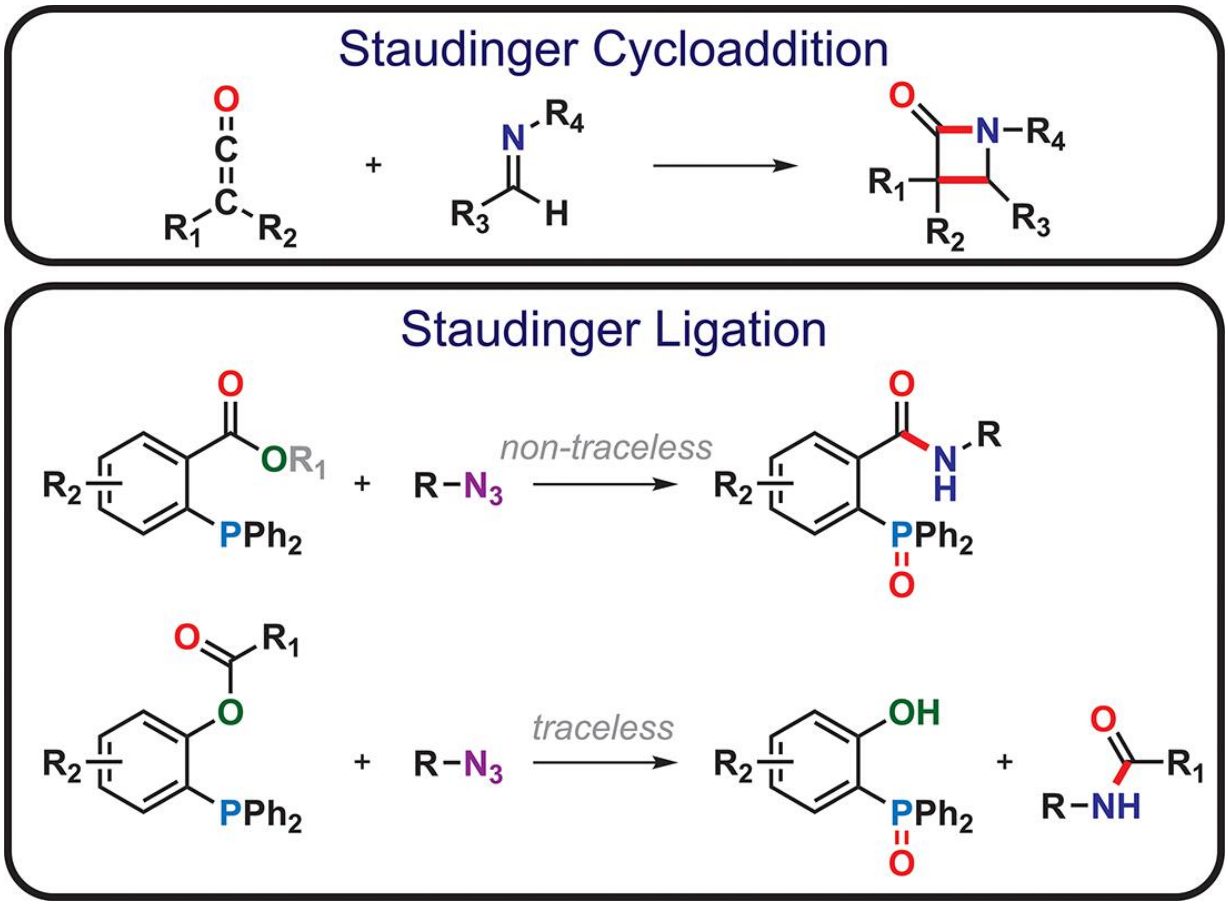


Fig. 86.2: The ***Staudinger*** *cycloaddition* and *ligation*.[310]

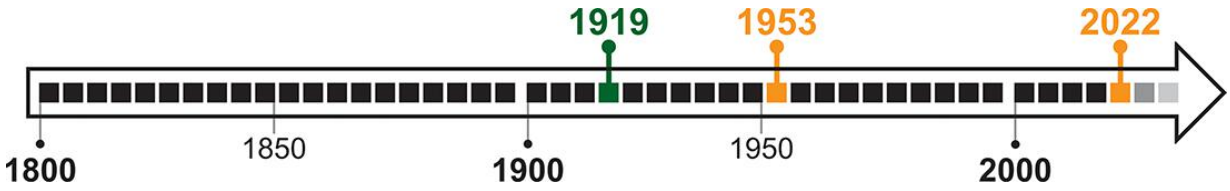


Fig. 86.3: The discovery of the ***Staudinger*** *reaction*.[311]

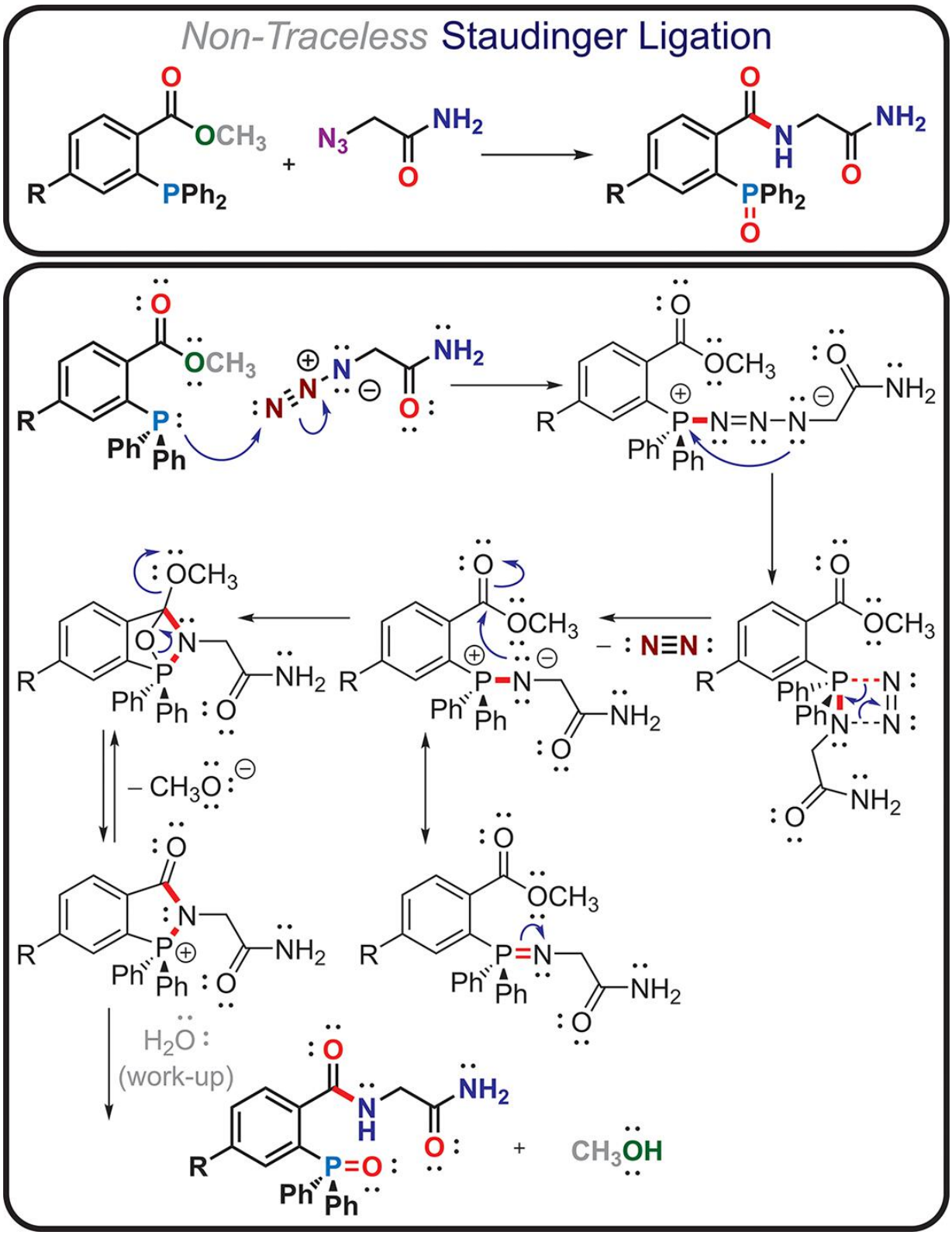


Fig. 86.4: The *non-traceless* ***Staudinger*** *ligation* mechanism.[312]

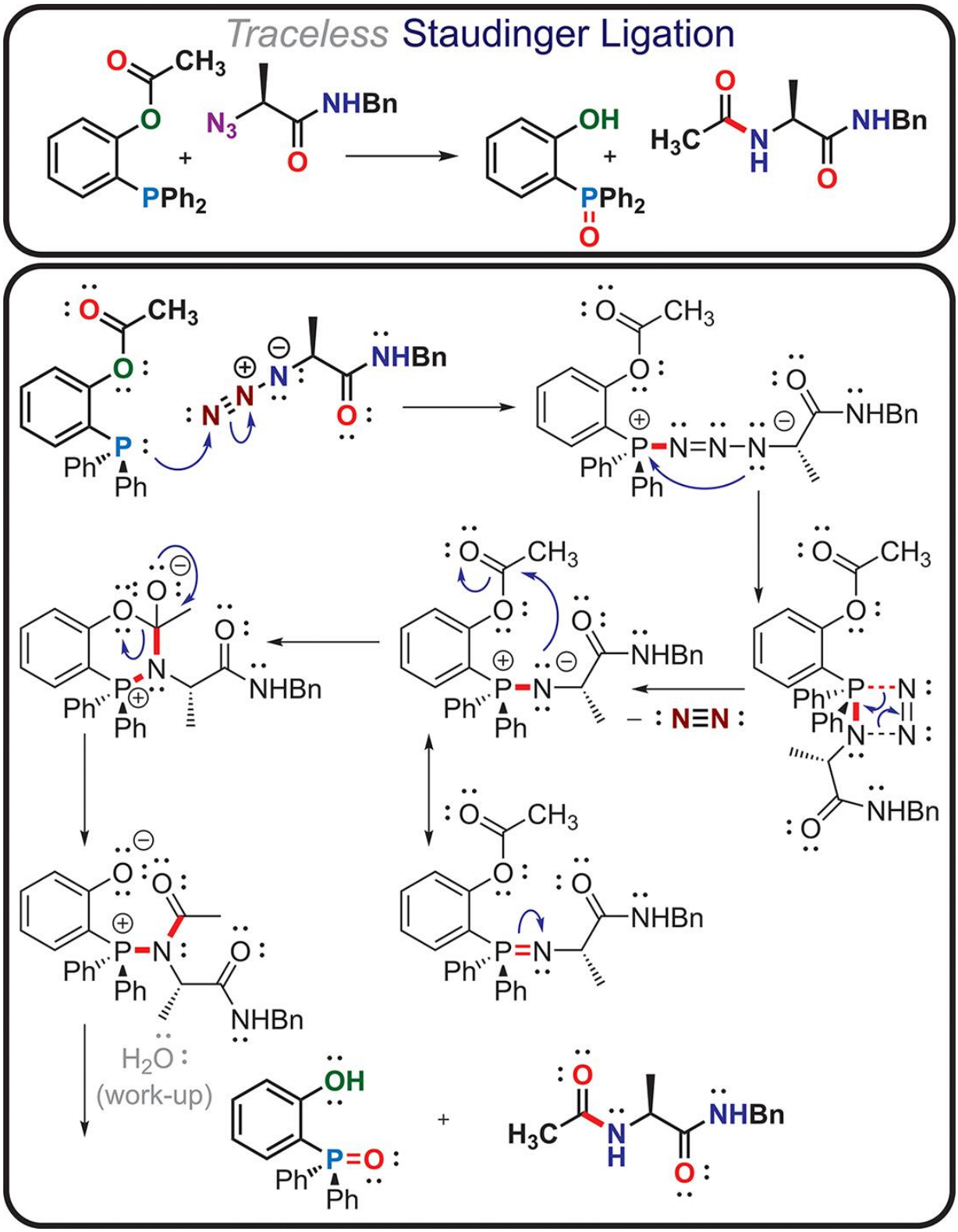


Fig. 86.5: The *traceless* ***Staudinger*** *ligation* mechanism.[313]

87 Steglich Esterification

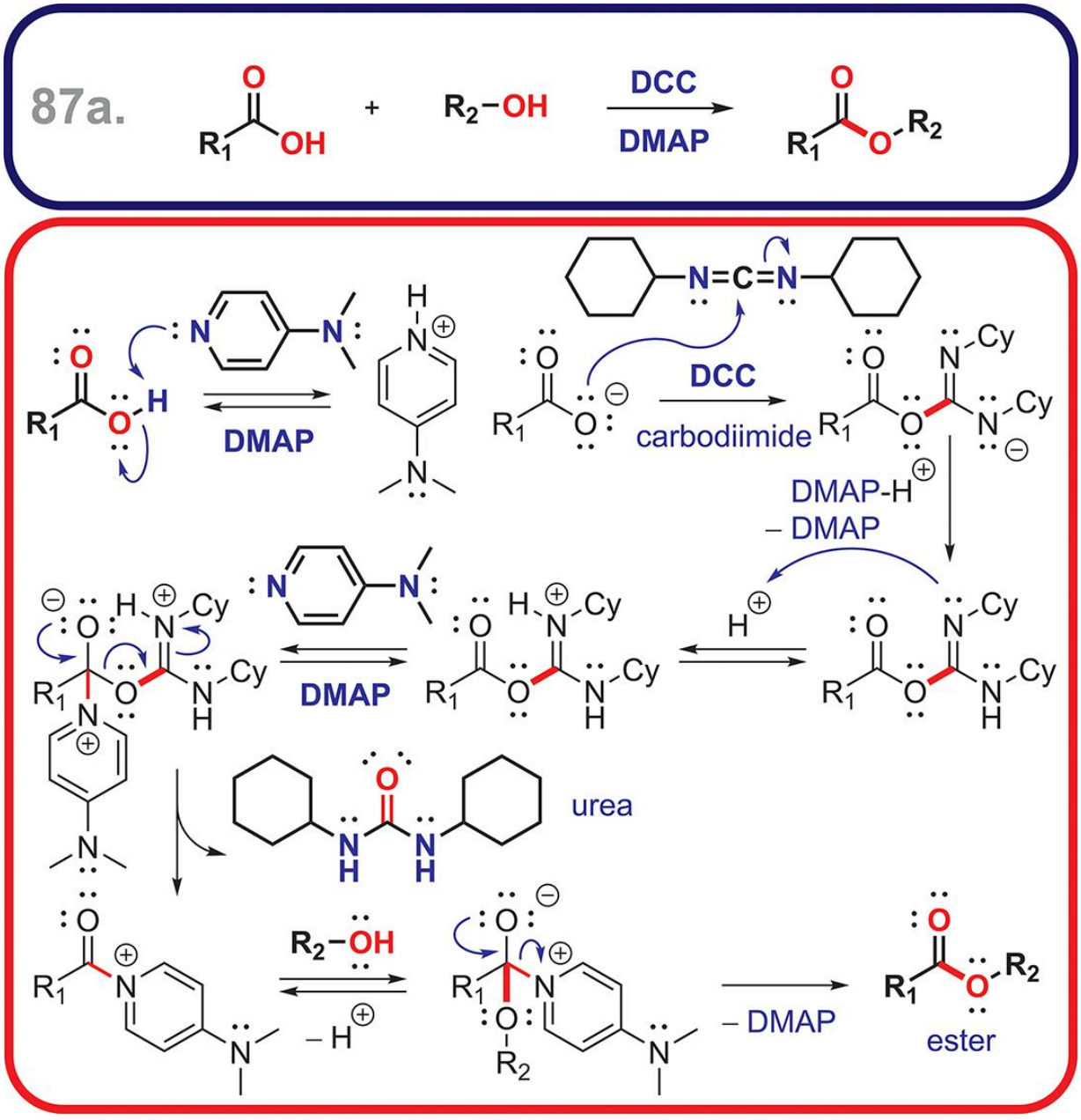


Fig. 87.1: The ***Steglich*** *esterification* mechanism (DCC + DMAP).[314].

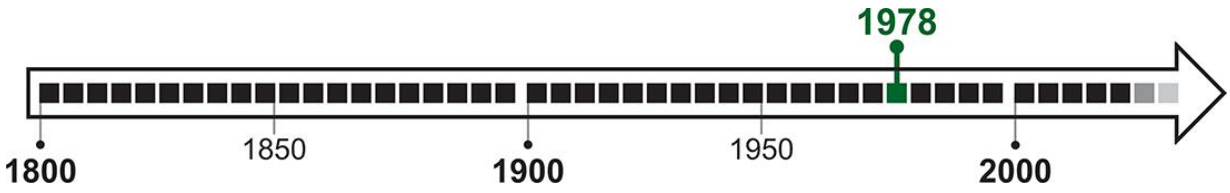


Fig. 87.2: The discovery of the ***Steglich*** *esterification*.[315].

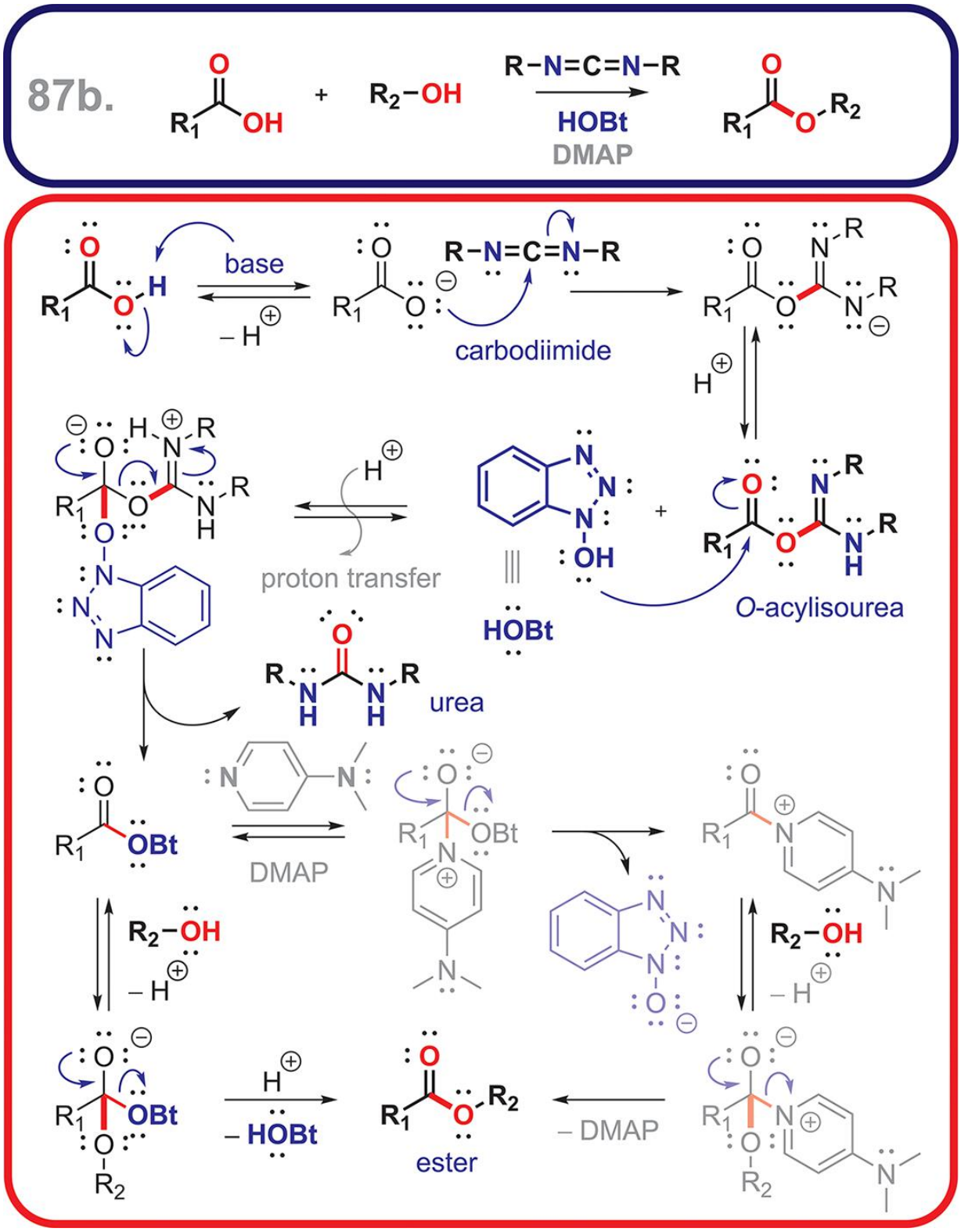


Fig. 87.3: The ***Steglich*** *esterification* mechanism (DCC + HOBt + DMAP).[316].

88 Stille Cross-Coupling

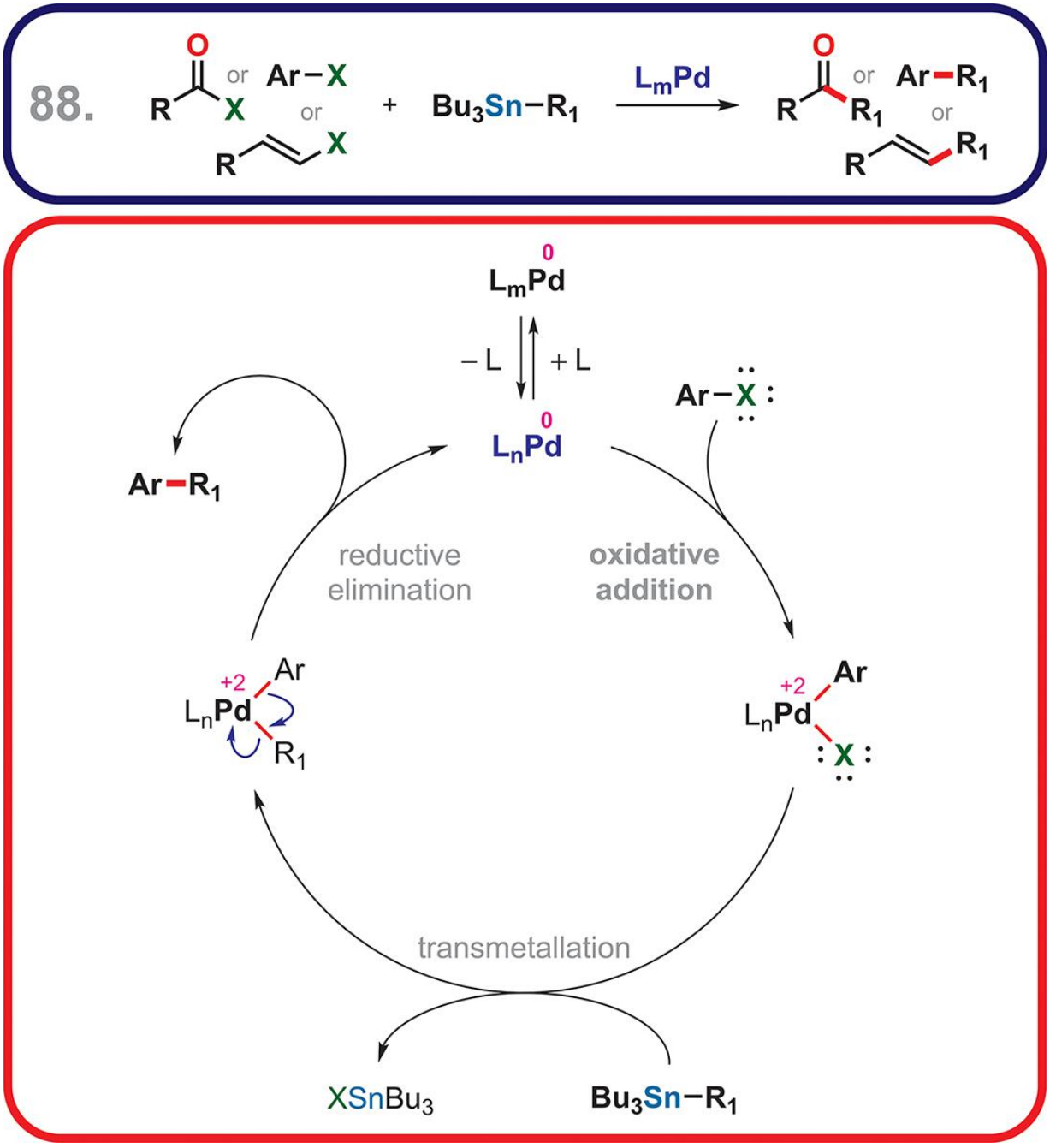


Fig. 88.1: The ***Stille*** *cross-coupling* mechanism.[317]

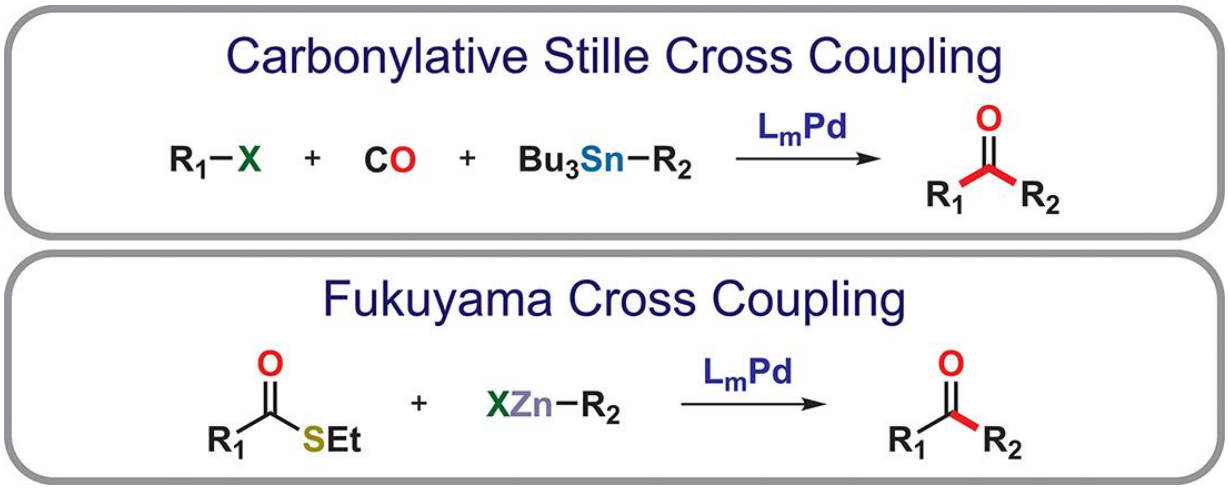


Fig. 88.2: Reactions related to the ***Stille*** *cross-coupling*.[318]

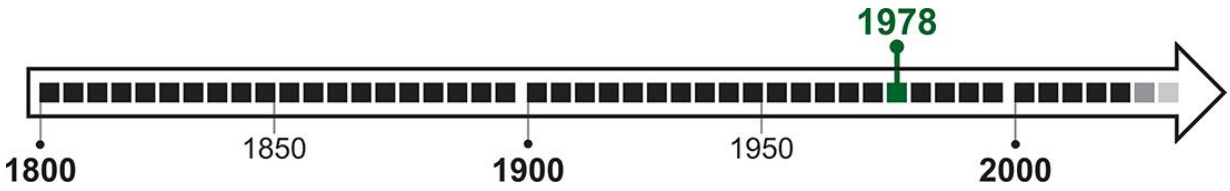


Fig. 88.3: The discovery of the ***Stille*** *cross-coupling*.[319]

89 Suzuki Cross-Coupling

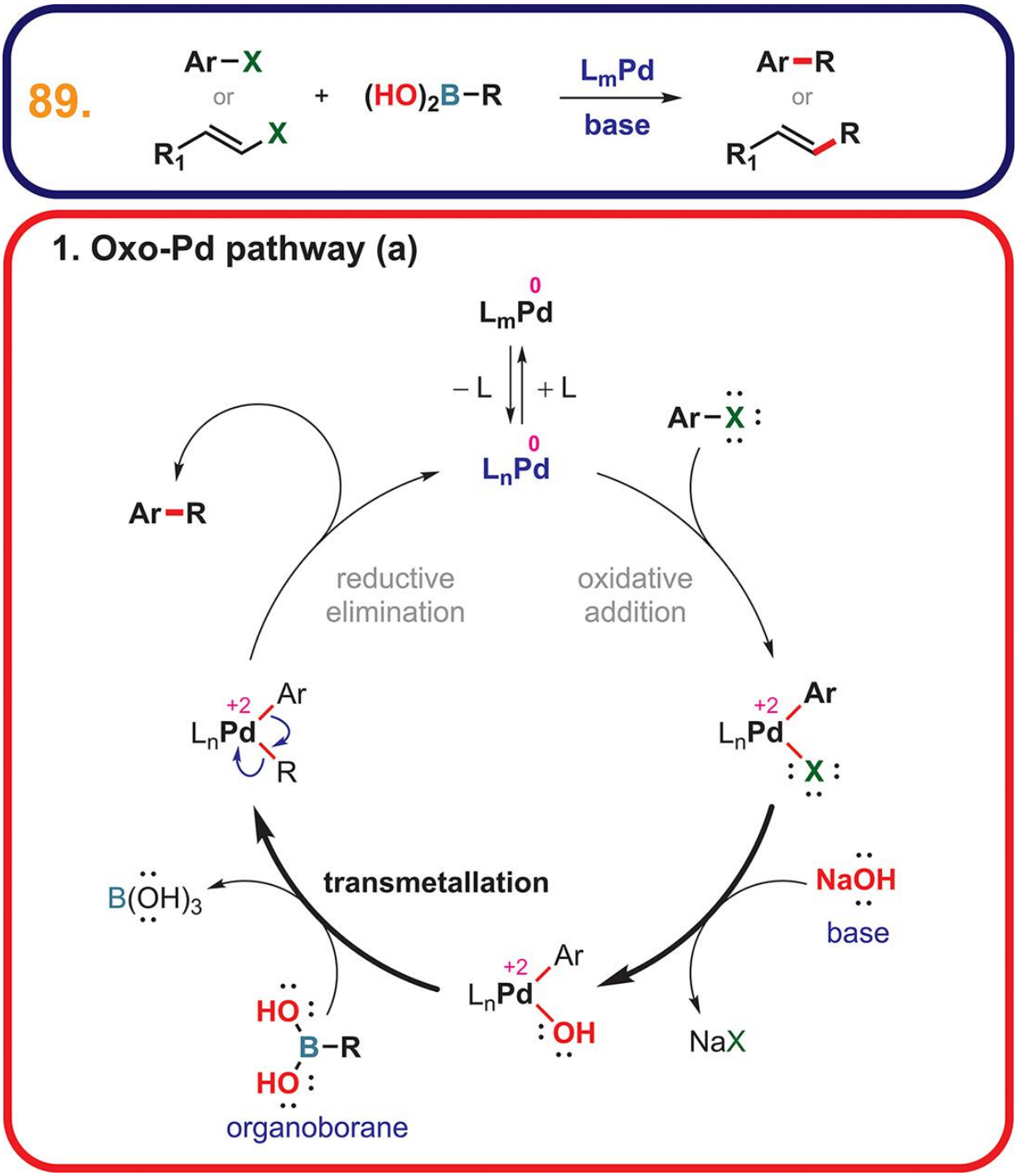


Fig. 89.1: The ***Suzuki*** *cross-coupling* mechanism (oxo-**Pd** pathway (**a**)).[320]

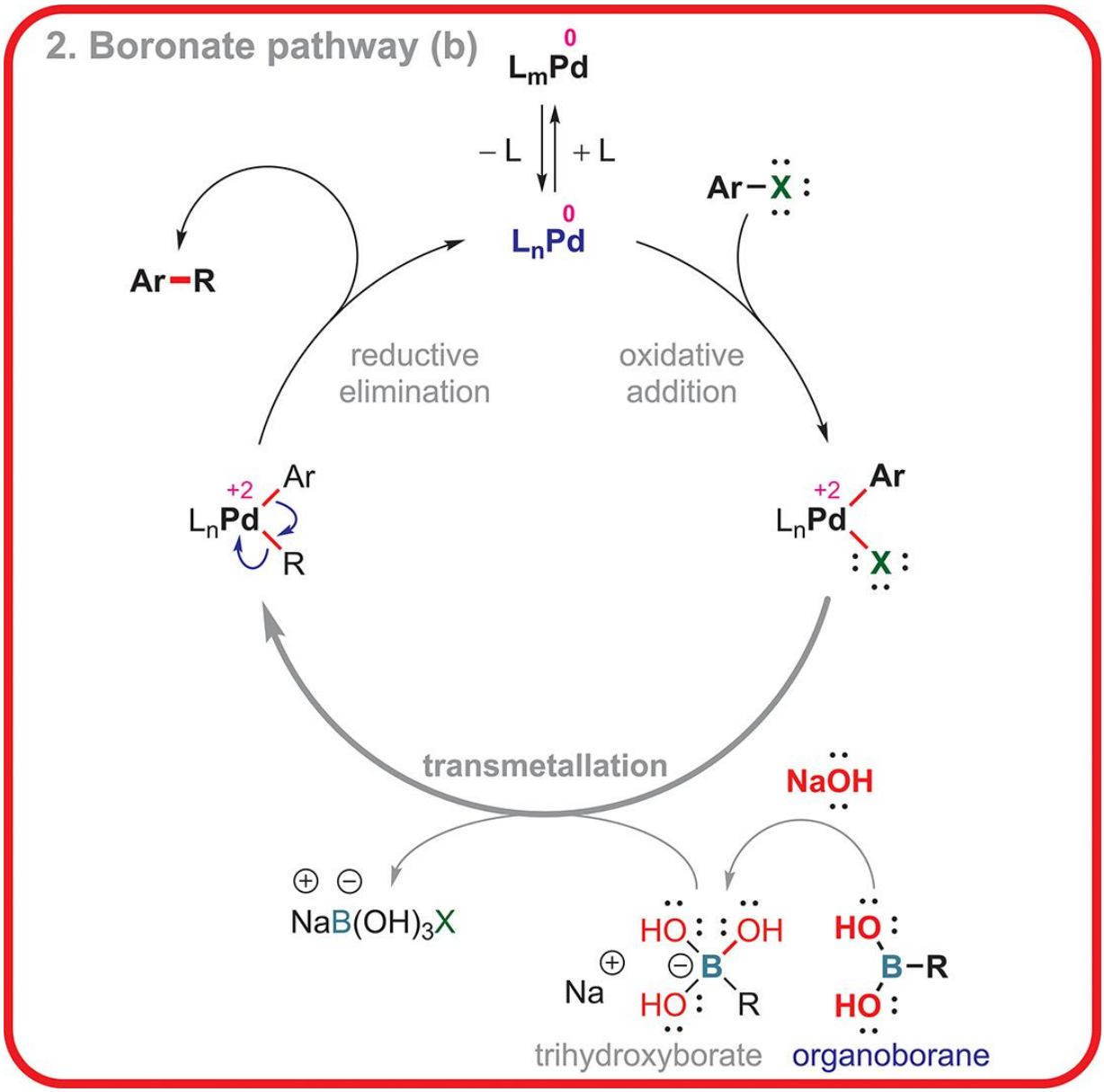


Fig. 89.2: The ***Suzuki*** *cross-coupling* mechanism (boronate pathway (**b**)).[321]

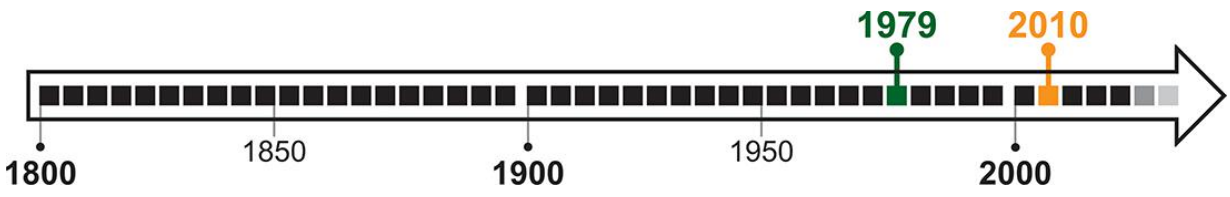


Fig. 89.3: The discovery of the ***Suzuki*** *cross-coupling*.[322]

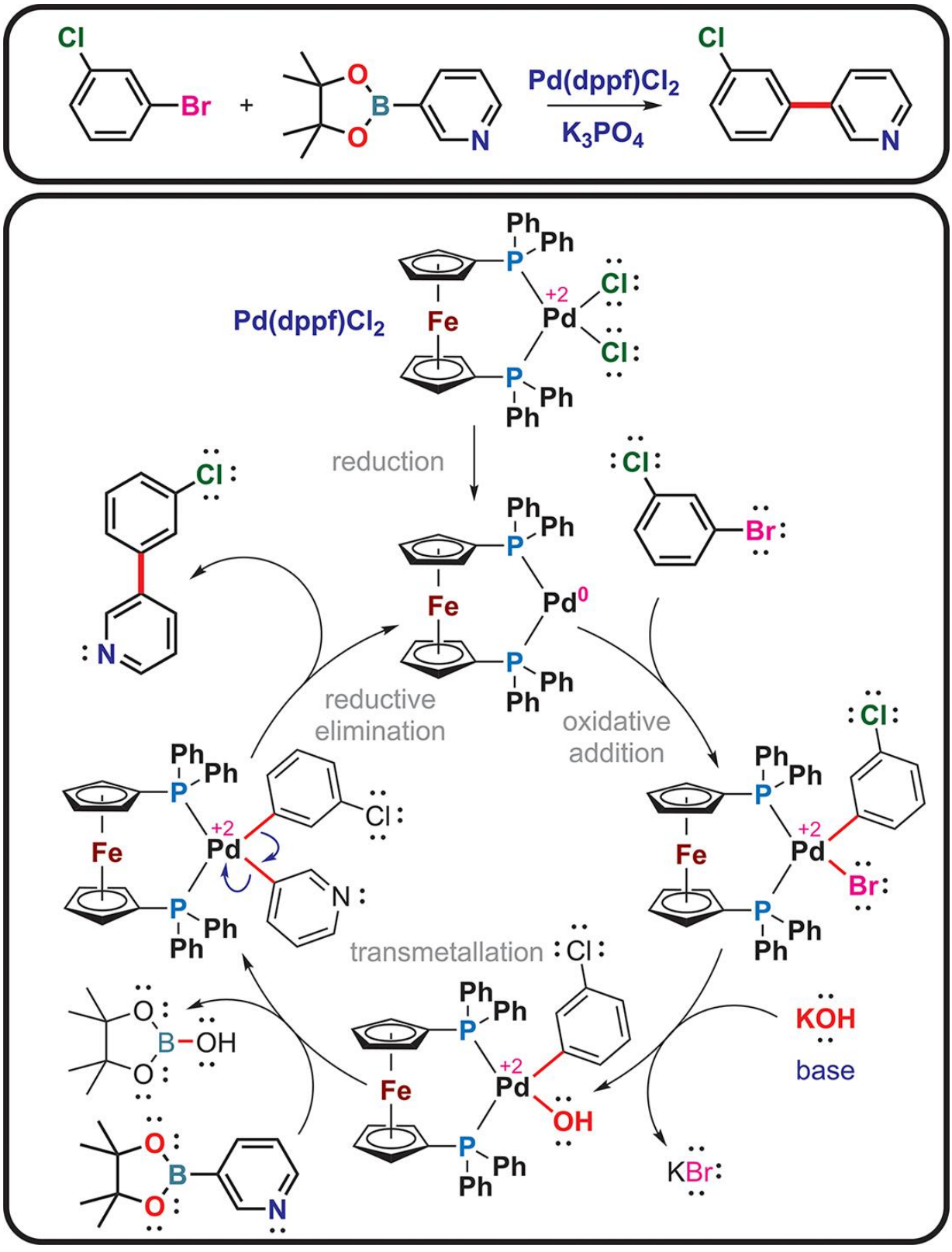

Cl
Br
+
O
B
O
N
Pd(dppf)Cl2
K3PO4
Cl
N
Pd(dppf)Cl2
Ph
Ph
P
Fe
+2
Pd
Cl
Cl
P
Ph
Ph
reduction
Cl
N
Cl
Br
Fe
Pd0
P
Ph
Ph
reductive
elimination
oxidative
addition
Cl
Ph
Ph
P
Fe
+2
Pd
Cl
P
Ph
Ph
N
Cl
Ph
Ph
P
Fe
+2
Pd
Br
P
Ph
Ph
transmetallation
Cl
O
B
OH
O
Ph
Ph
P
Fe
+2
Pd
OH
P
Ph
Ph
KOH
base
O
B
O
N
KBr

Fig. 89.4: The ***Suzuki*** *cross-coupling* mechanism catalyzed by **Pd(dppf)Cl_2**.[323]

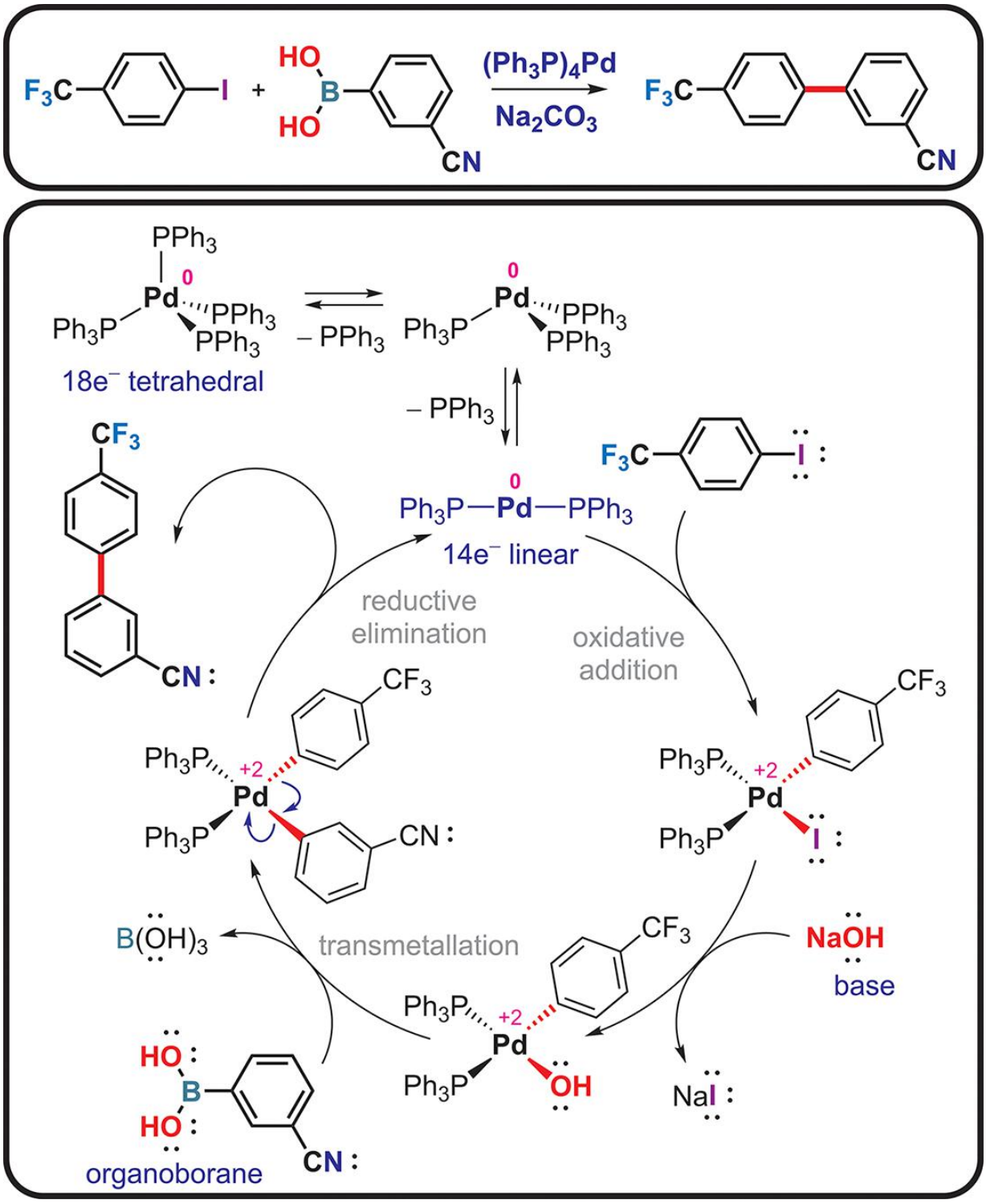


Fig. 89.5: The ***Suzuki*** *cross-coupling* mechanism catalyzed by **$Pd(PPh_3)_4$**.[324]

90 Swern Oxidation

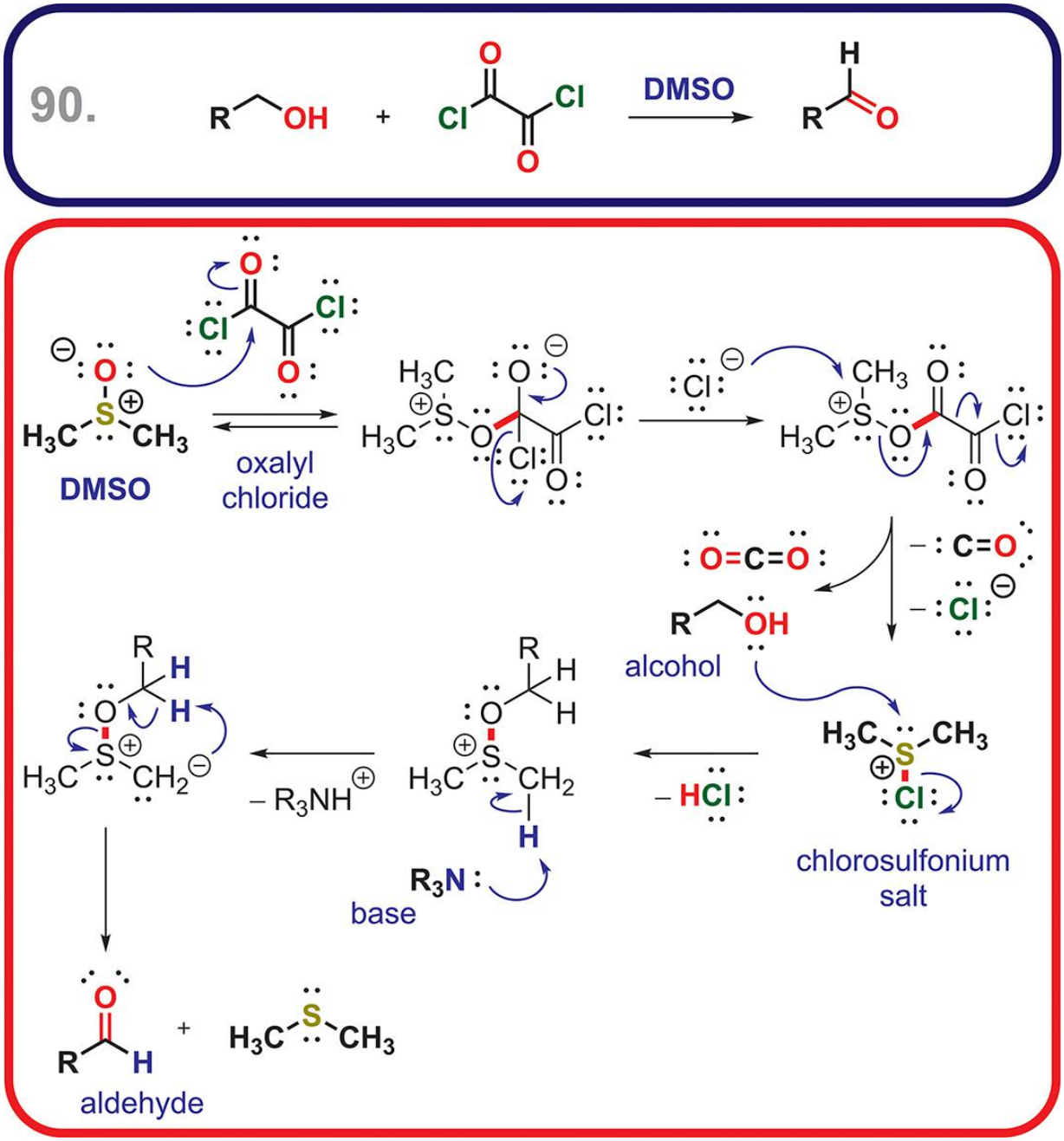


Fig. 90.1: The ***Swern*** *oxidation* mechanism.[325]

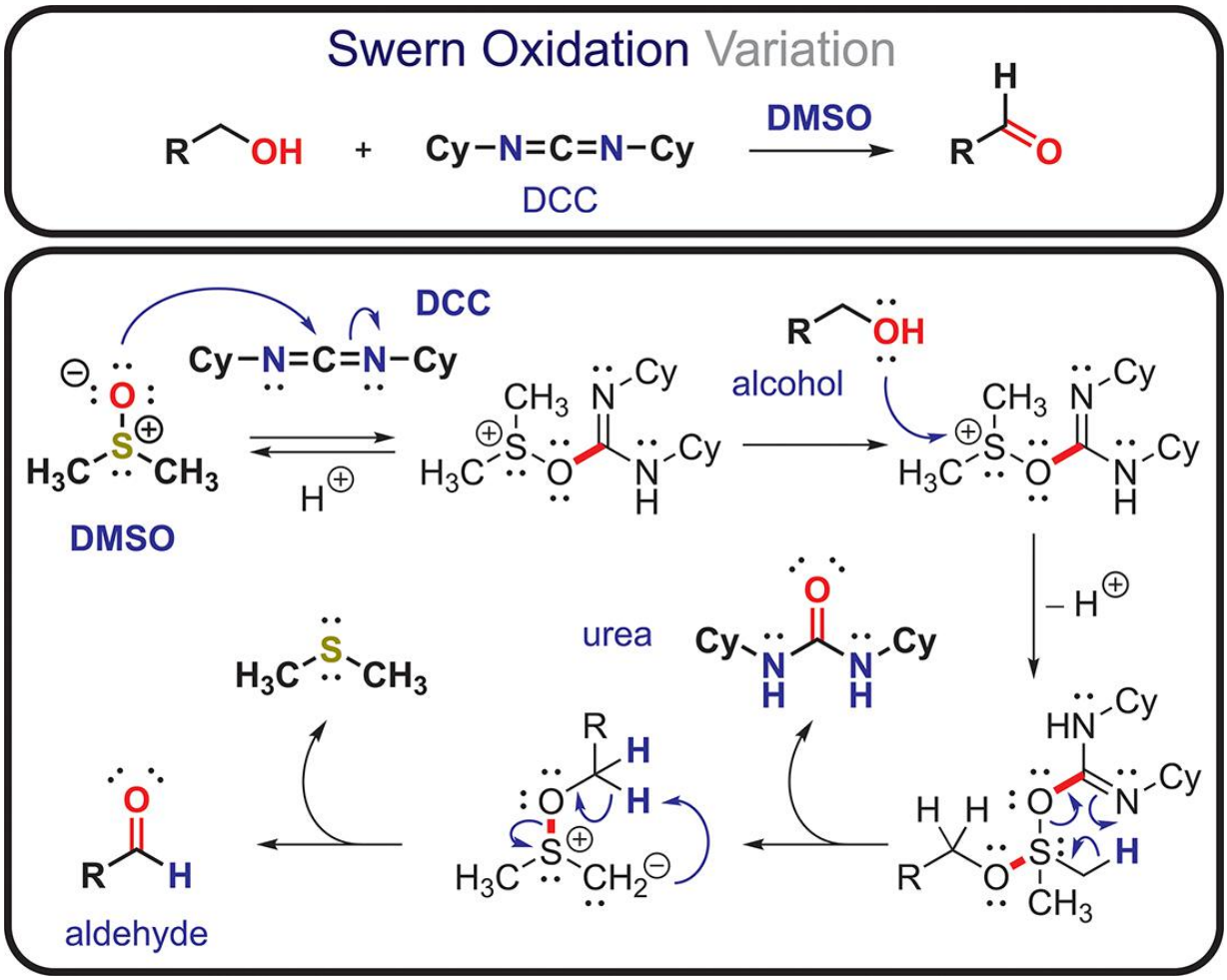


Fig. 90.2: The ***Swern*** *oxidation* variation mechanism (DCC + DMSO).[326]

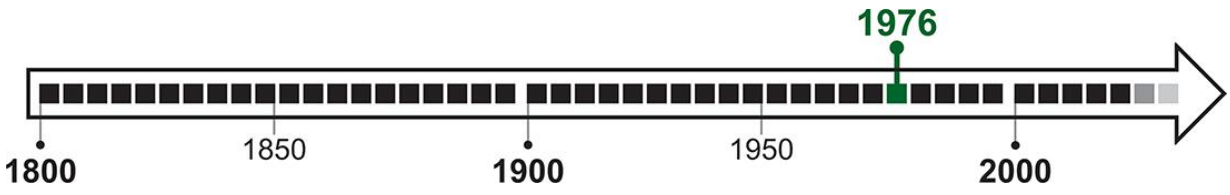


Fig. 90.3: The discovery of the ***Swern*** *oxidation*.[327]

91 Ugi Reaction

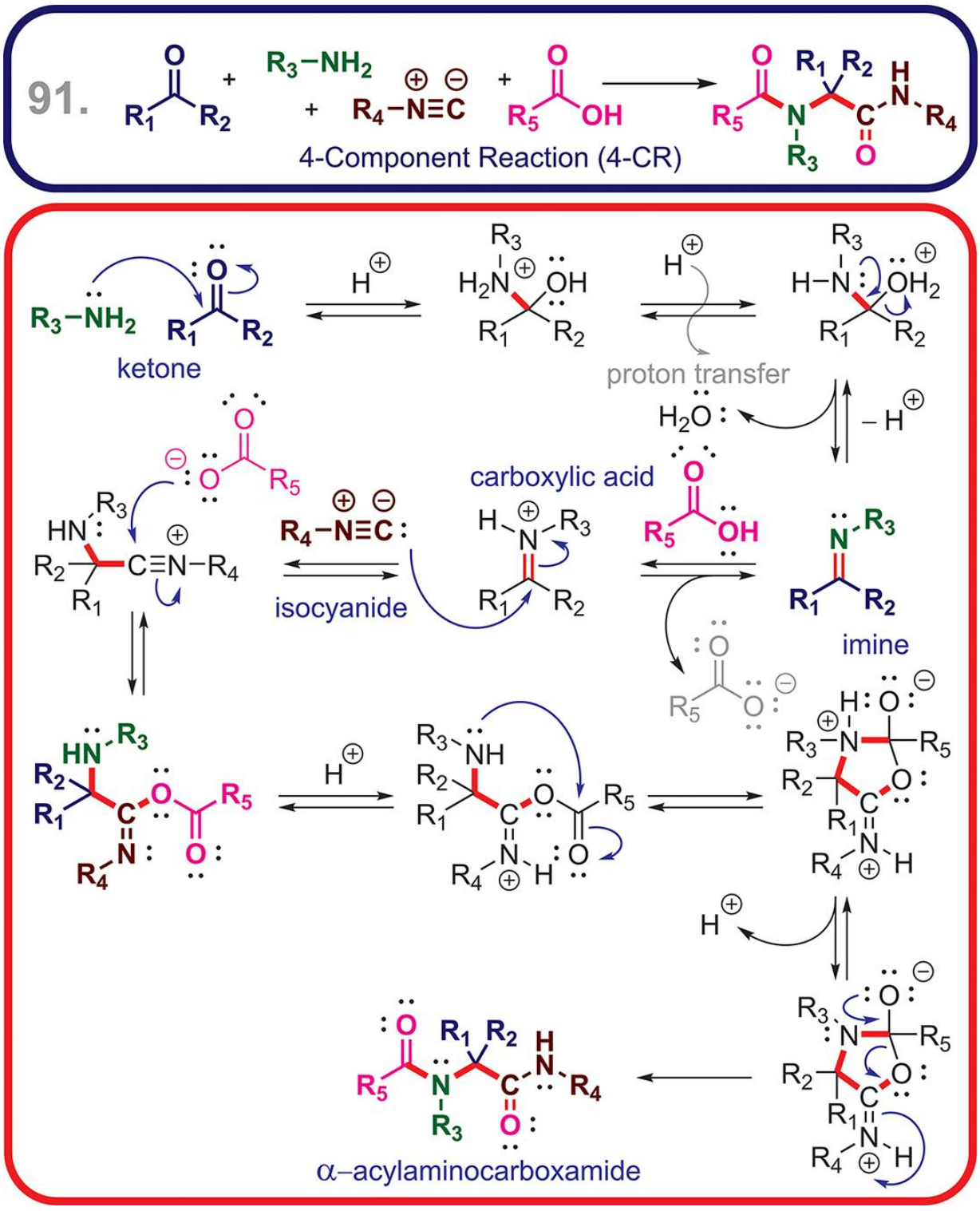


Fig. 91.1: The ***Ugi*** *reaction* mechanism.[328]

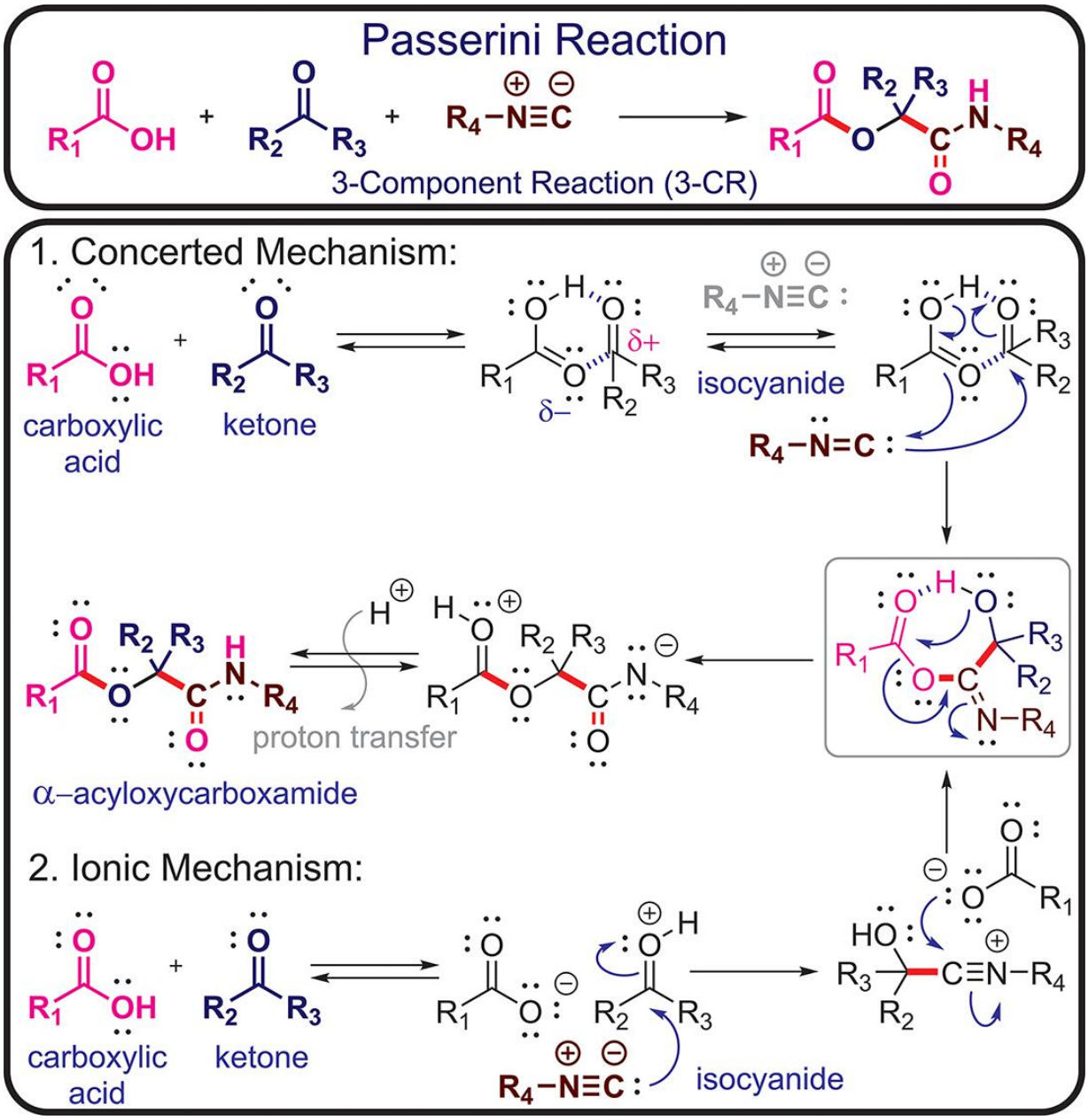


Fig. 91.2: The ***Passerini*** *reaction* mechanism.[329]

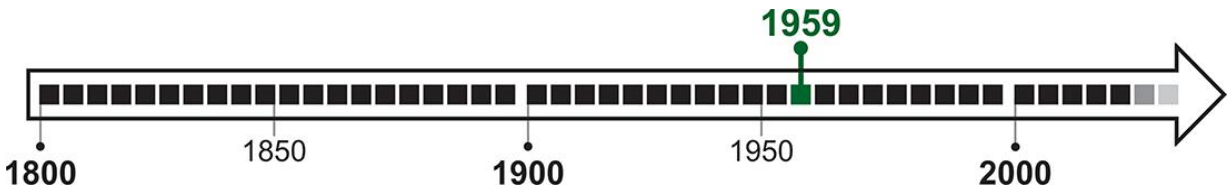


Fig. 91.3: The discovery of the ***Ugi*** *reaction*.[330]

92 Ullmann Aryl–Aryl Coupling

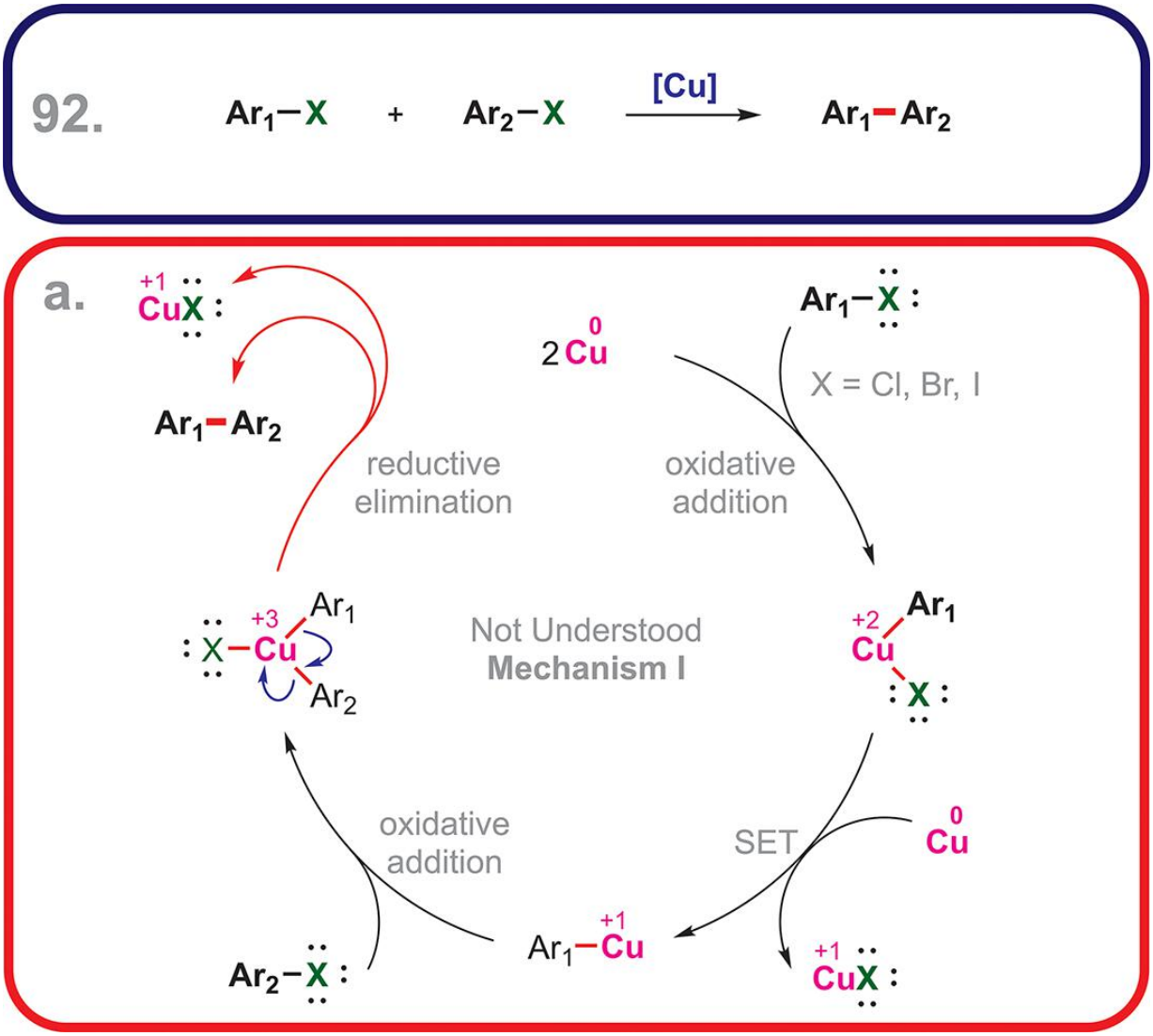


Fig. 92.1: The ***Ullmann*** *aryl–aryl coupling* mechanism I.[331]

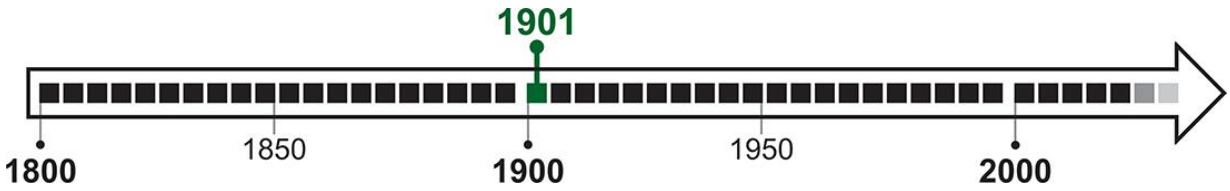


Fig. 92.2: The discovery of the ***Ullmann*** *aryl–aryl coupling*.[332]

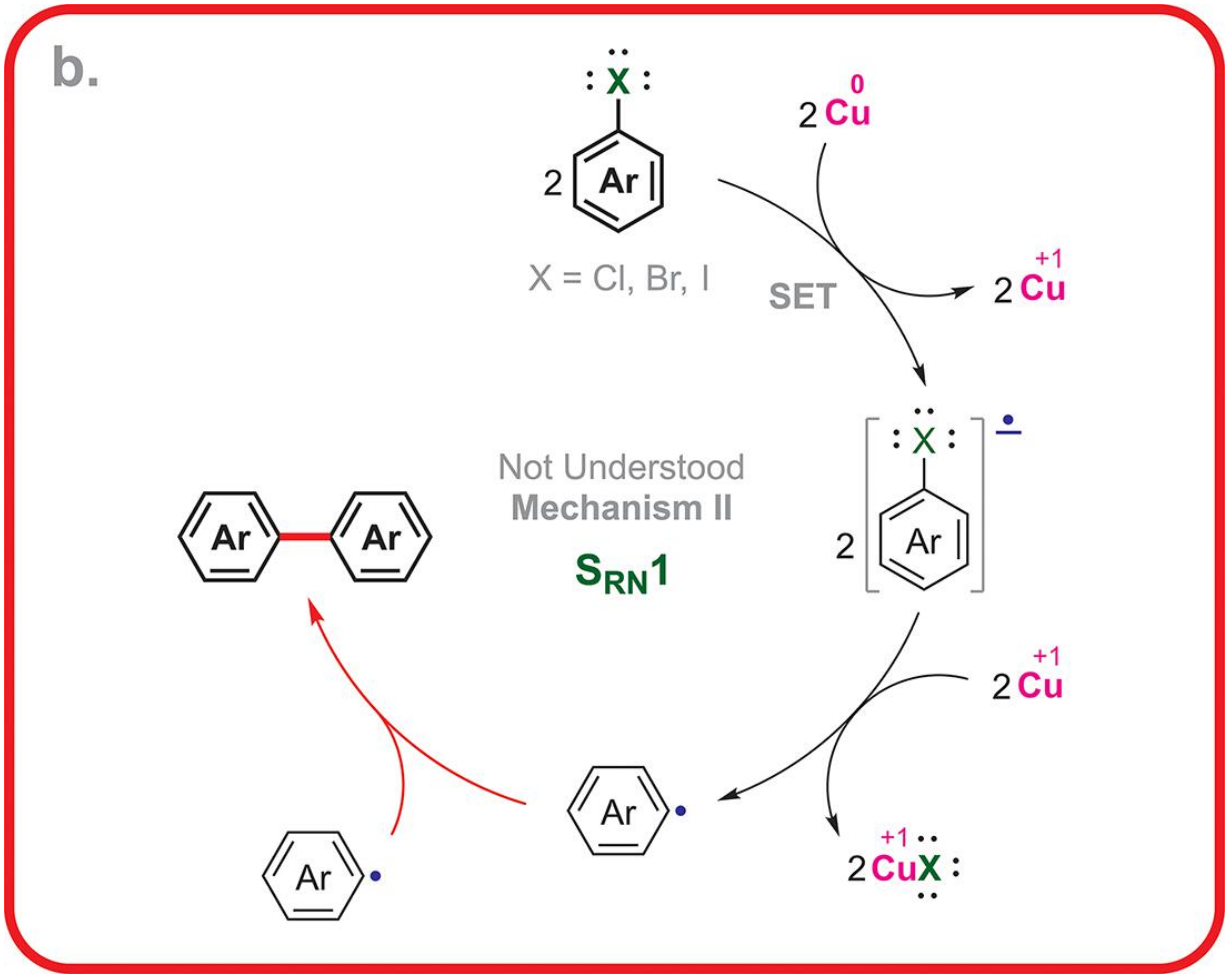


Fig. 92.3: The ***Ullmann*** *aryl–aryl coupling* mechanism II.[333]

Fig. 92.4: The ***Ullmann*** *biaryl ether and amine coupling*.[334]

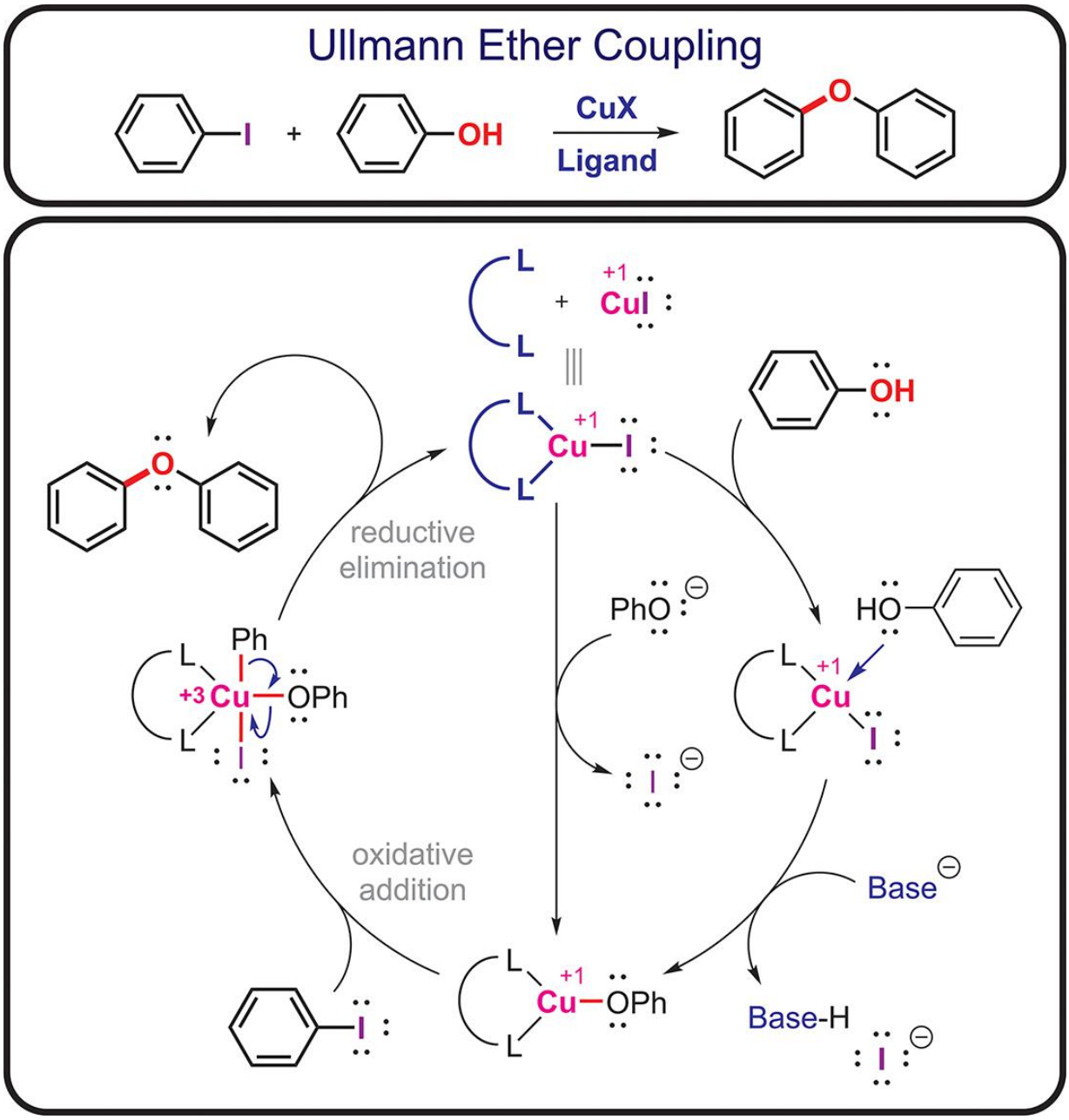


Fig. 92.5: The ***Ullmann*** *biaryl ether coupling* mechanism (neutral ligand).[335]

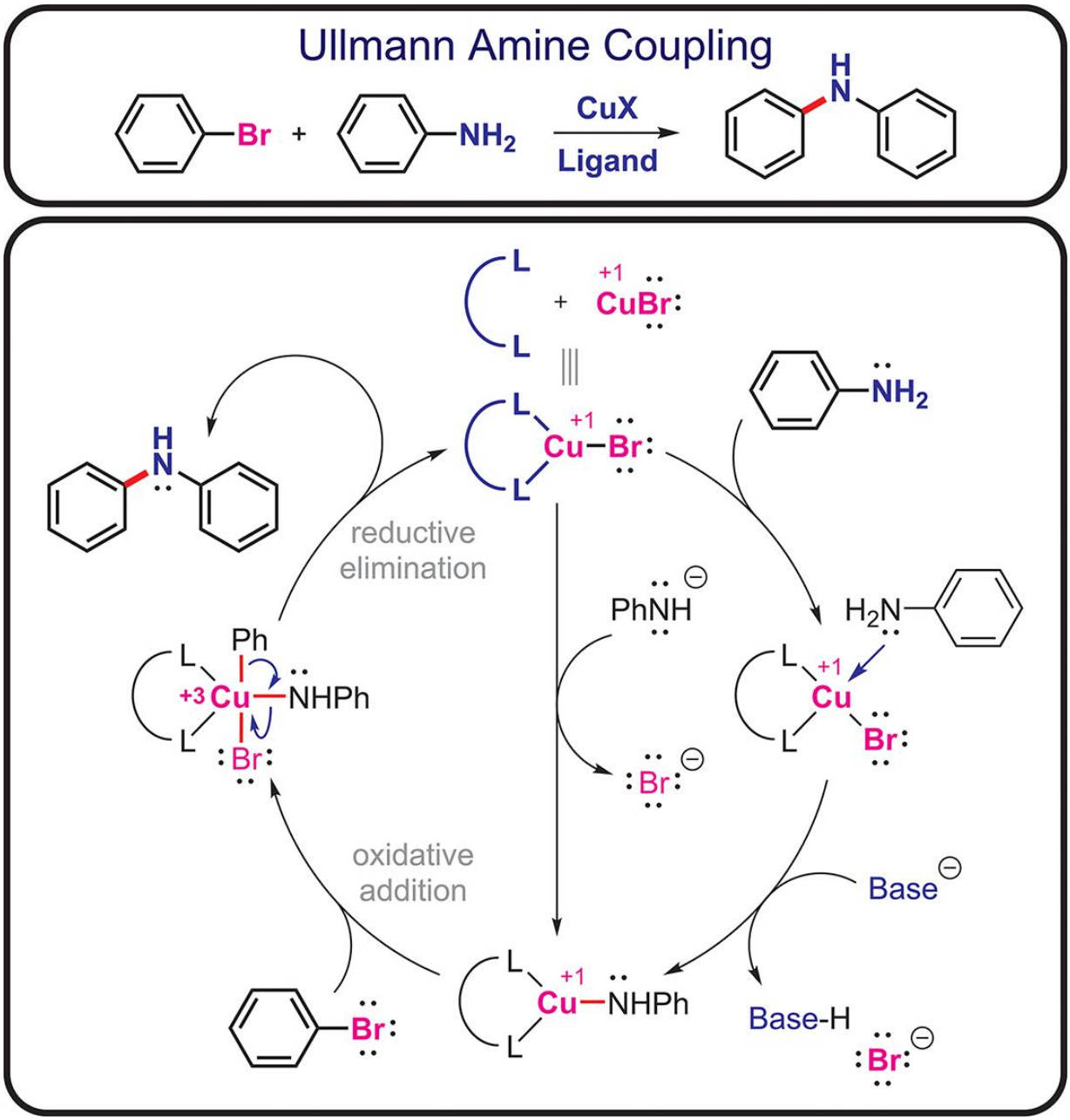


Fig. 92.6: The ***Ullmann*** *biaryl amine coupling* mechanism (neutral ligand).[336]

93 Upjohn Dihydroxylation

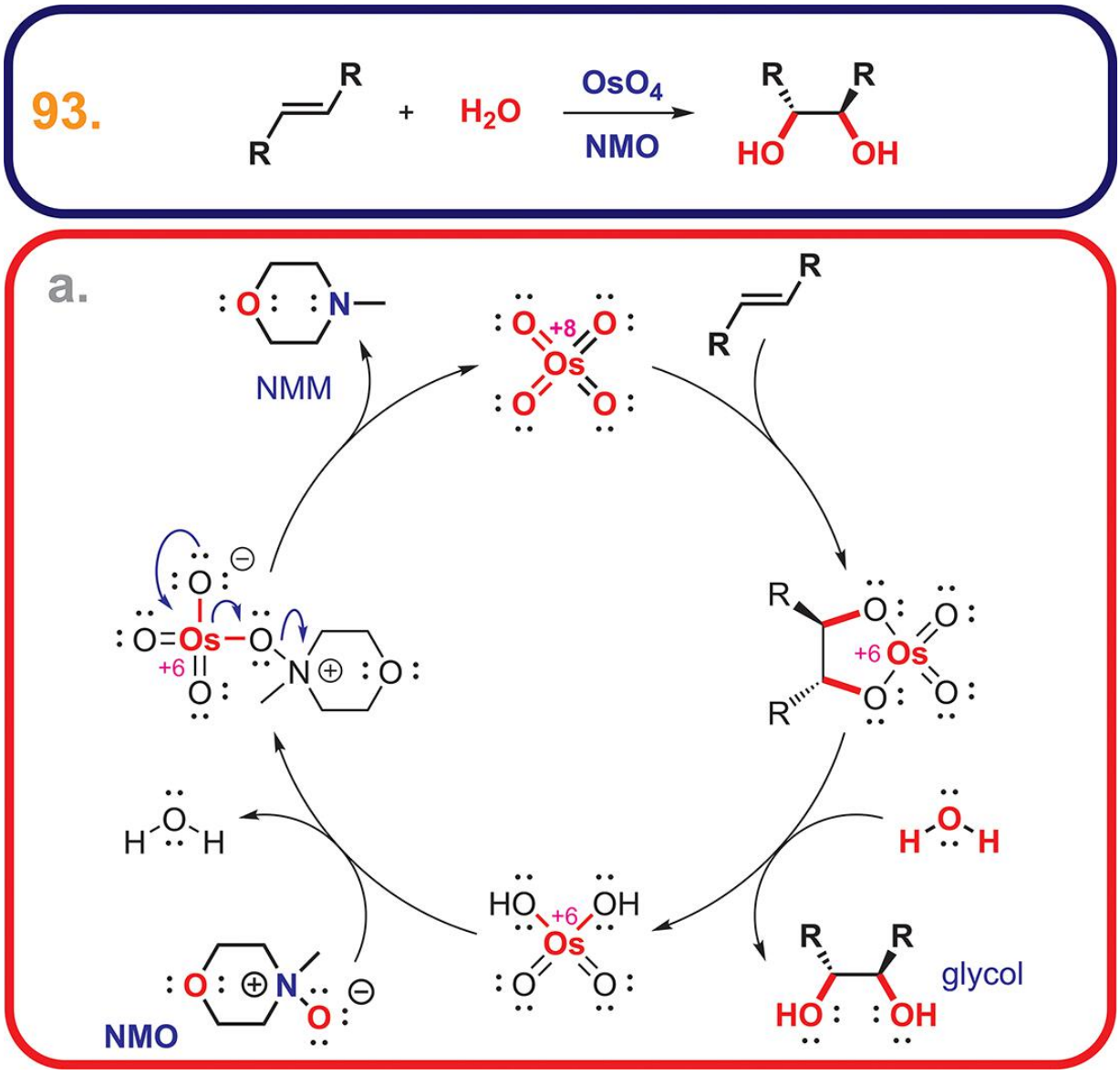


Fig. 93.1: The ***Upjohn*** *dihydroxylation* mechanism (a).[337]

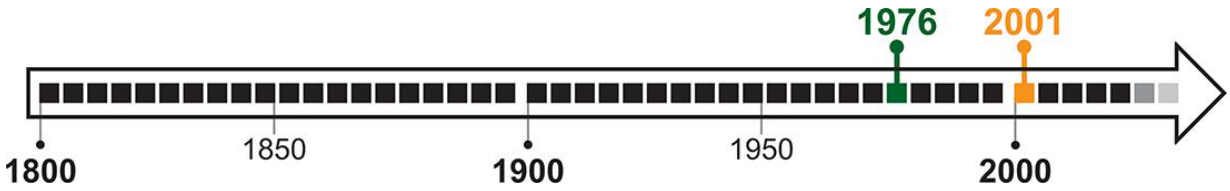


Fig. 93.2: The discovery of the ***Upjohn*** *dihydroxylation*.[338]

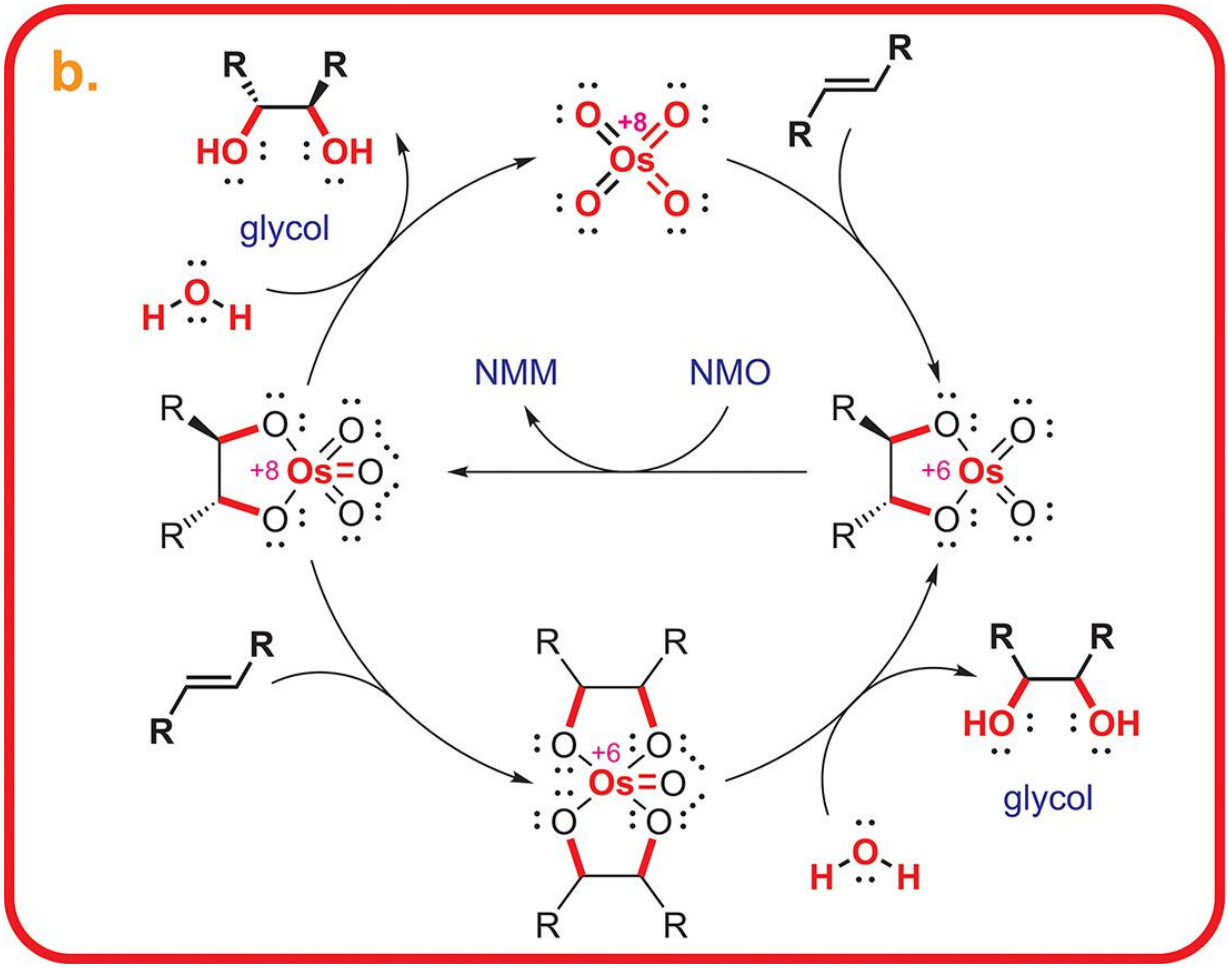


Fig. 93.3: The ***Upjohn*** *dihydroxylation* mechanism (b).[339]

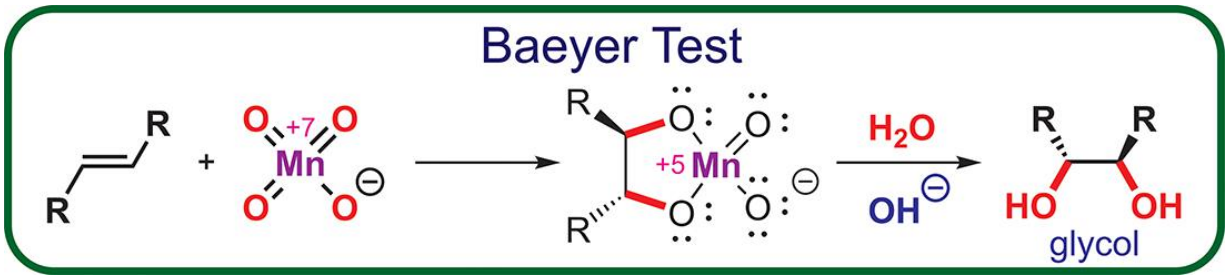


Fig. 93.4: The ***Baeyer*** *test*.[340]

94 Vilsmeier–Haack Reaction

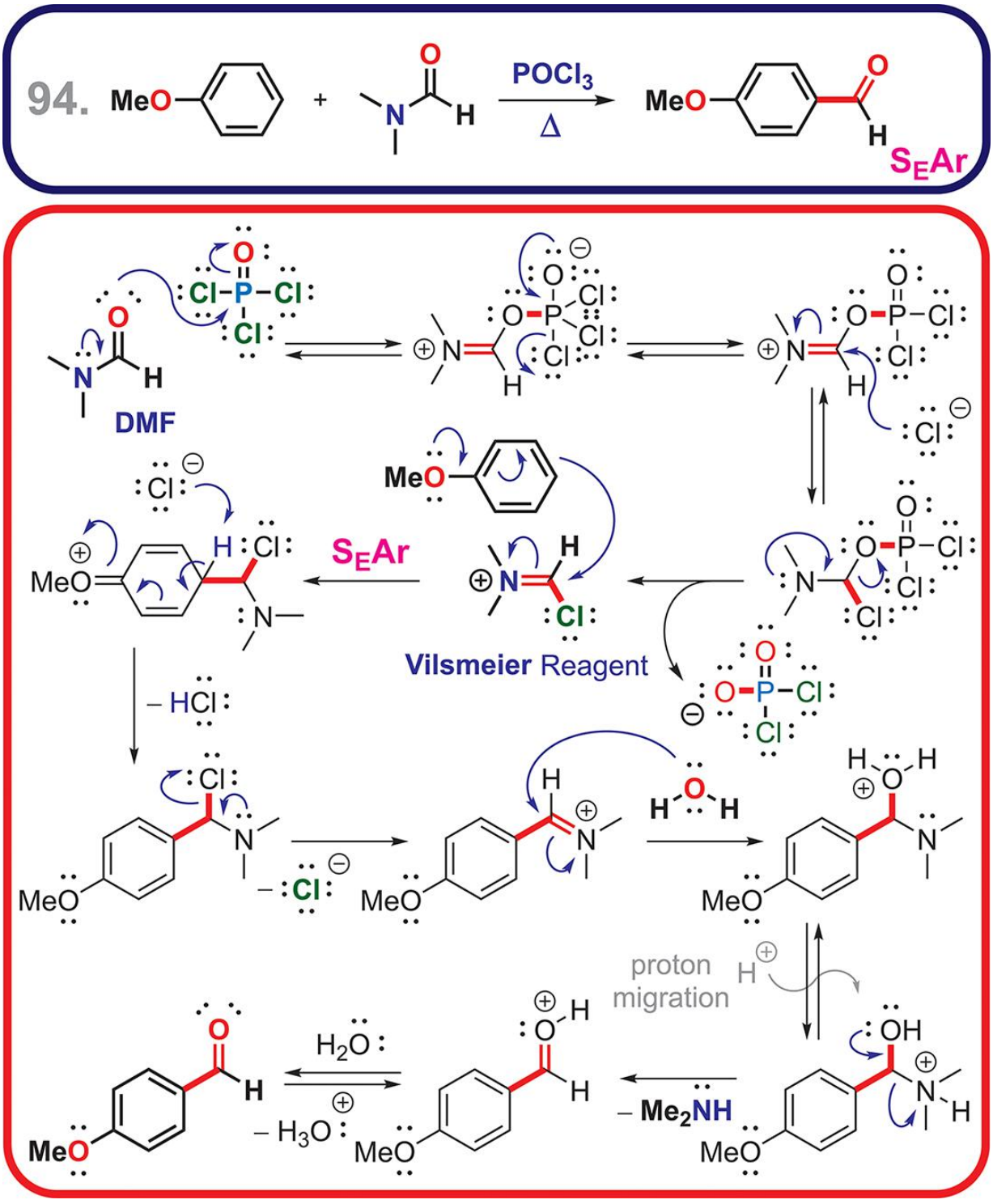


Fig. 94.1: The ***Vilsmeier–Haack*** *reaction* mechanism.[341]

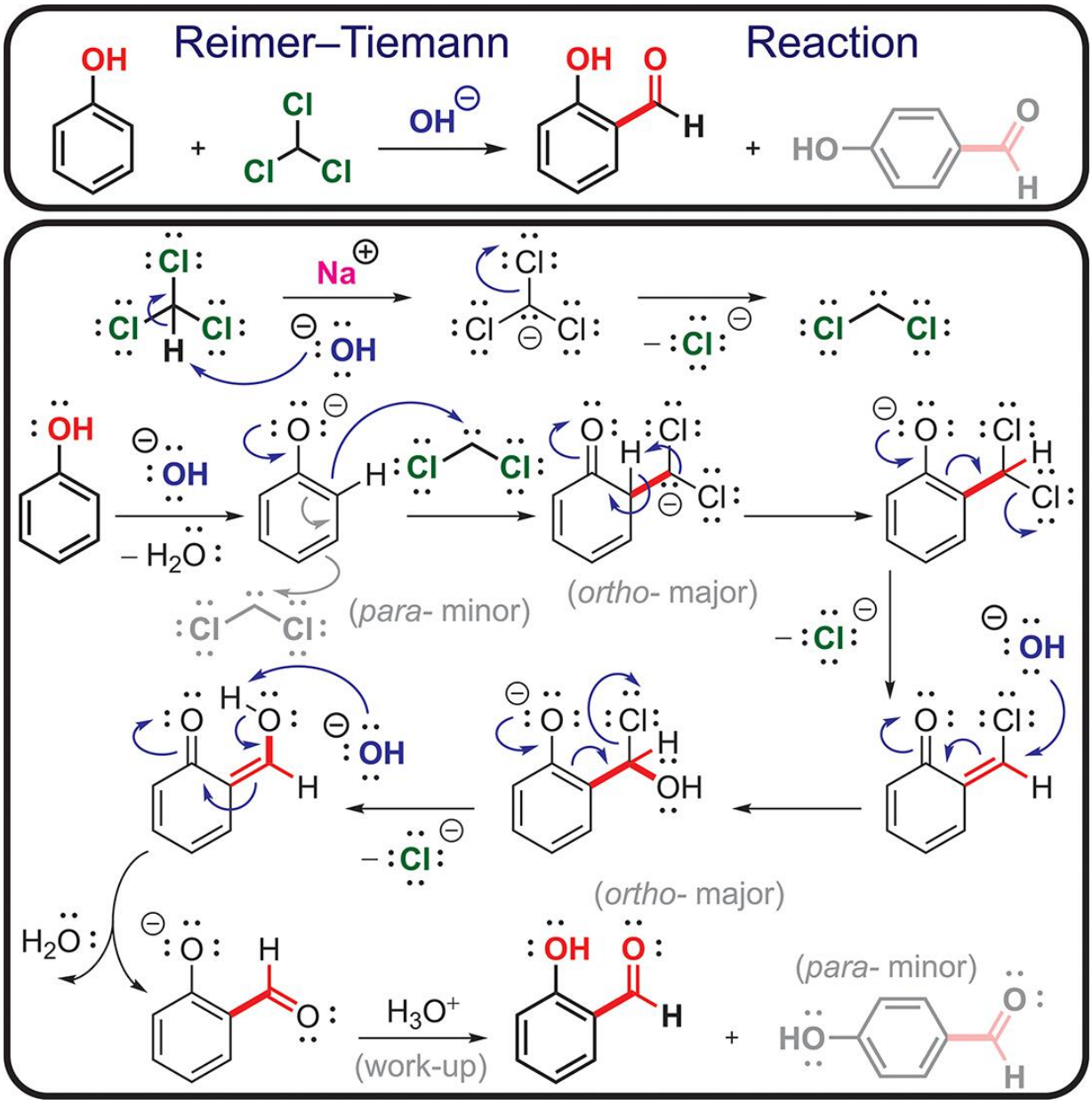


Fig. 94.2: The ***Reimer–Tiemann*** *reaction* mechanism.[342]

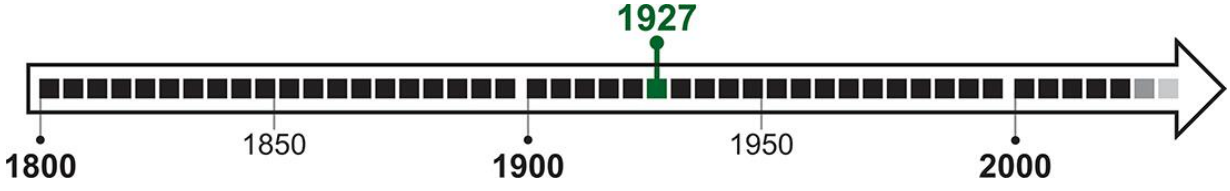


Fig. 94.3: The discovery of the ***Vilsmeier–Haack*** *reaction*.[343]

95 Wacker Oxidation

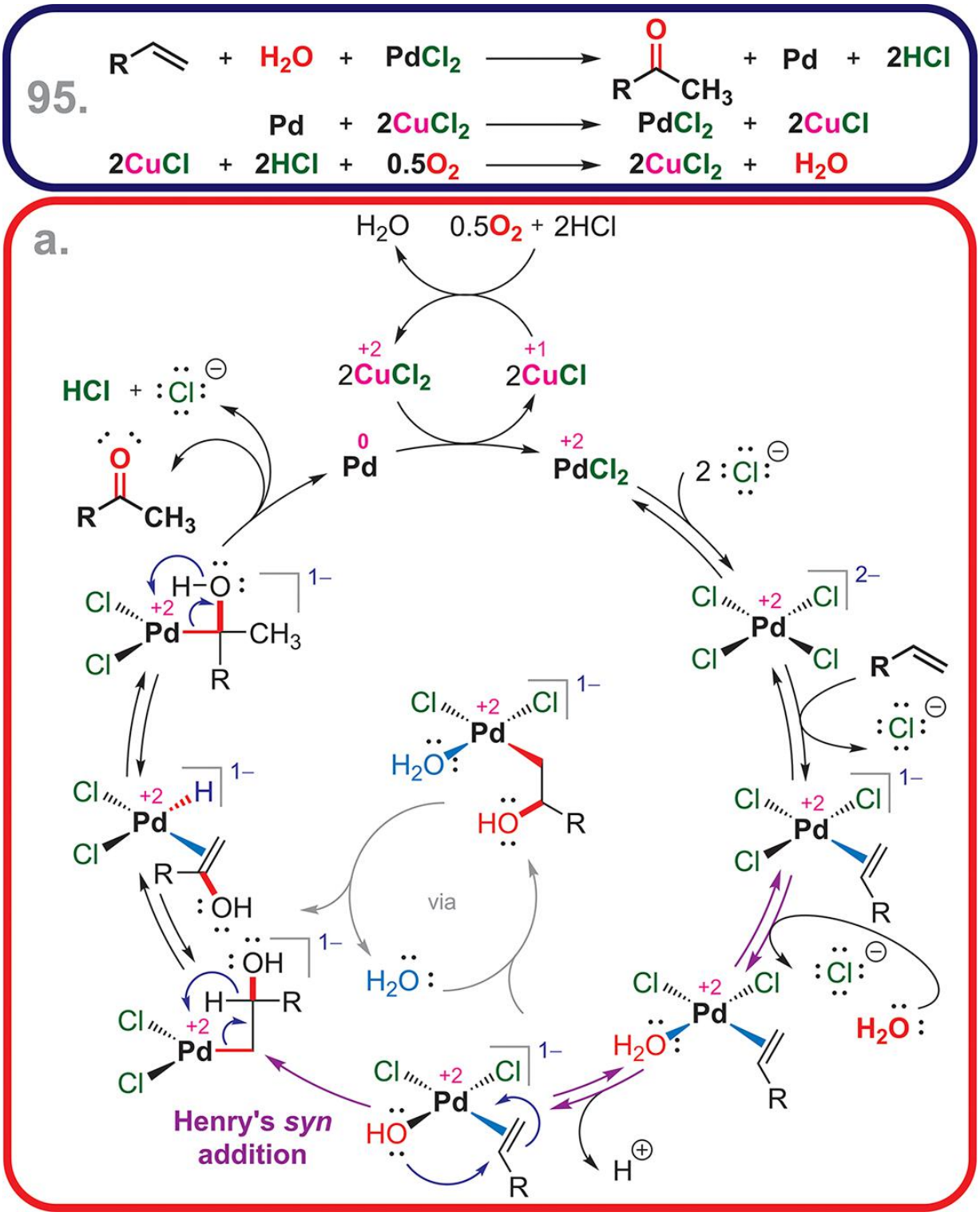


Fig. 95.1: The ***Wacker*** *oxidation* mechanism (a).[344]

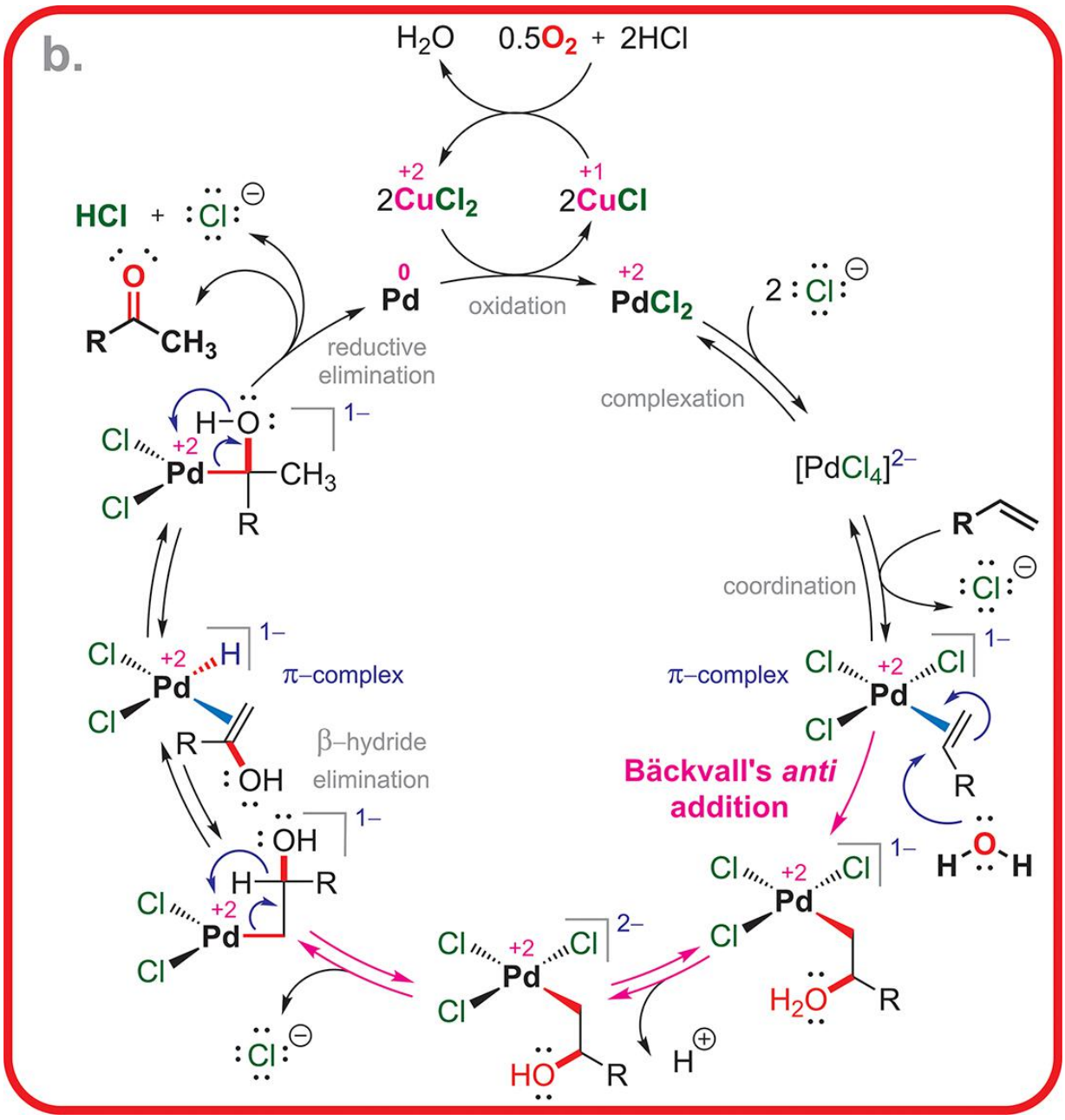


Fig. 95.2: The ***Wacker*** *oxidation* mechanism (b).[345]

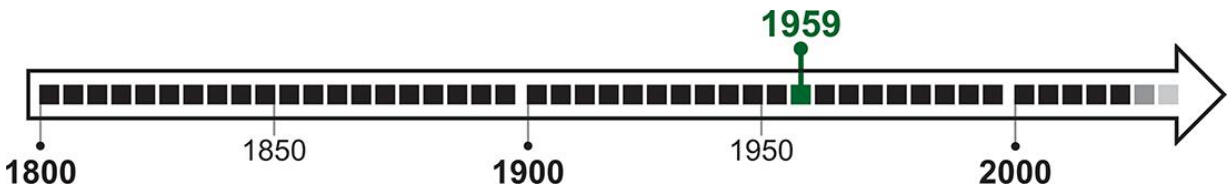


Fig. 95.3: The discovery of the ***Wacker*** *oxidation*.[346]

96 Wagner–Meerwein Rearrangement

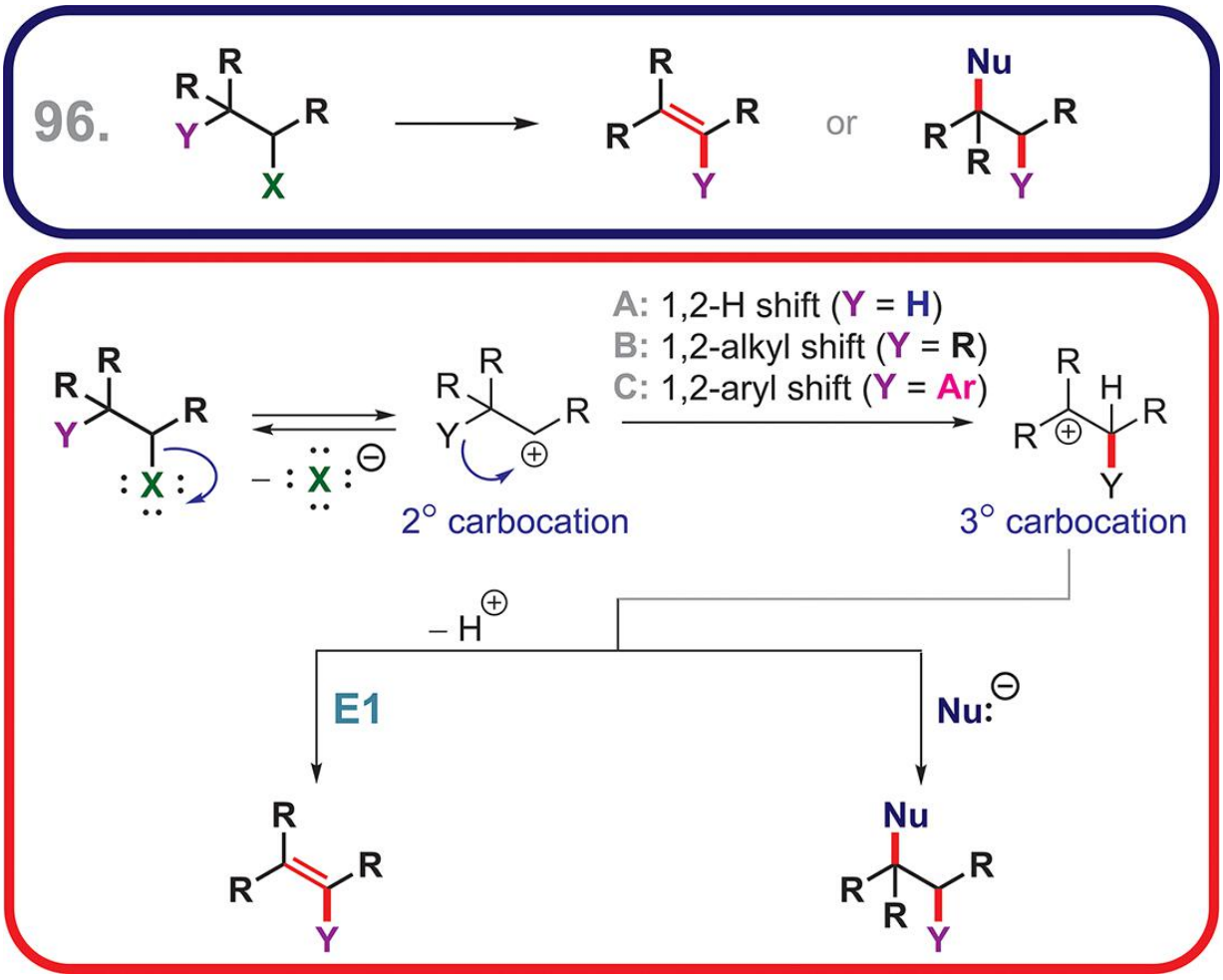


Fig. 96.1: The *general* ***Wagner–Meerwein*** *rearrangement* mechanism.[347]

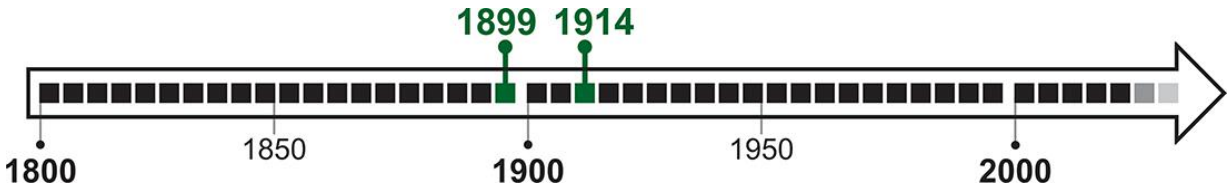


Fig. 96.2: The discovery of the ***Wagner–Meerwein*** *rearrangement*.[348]

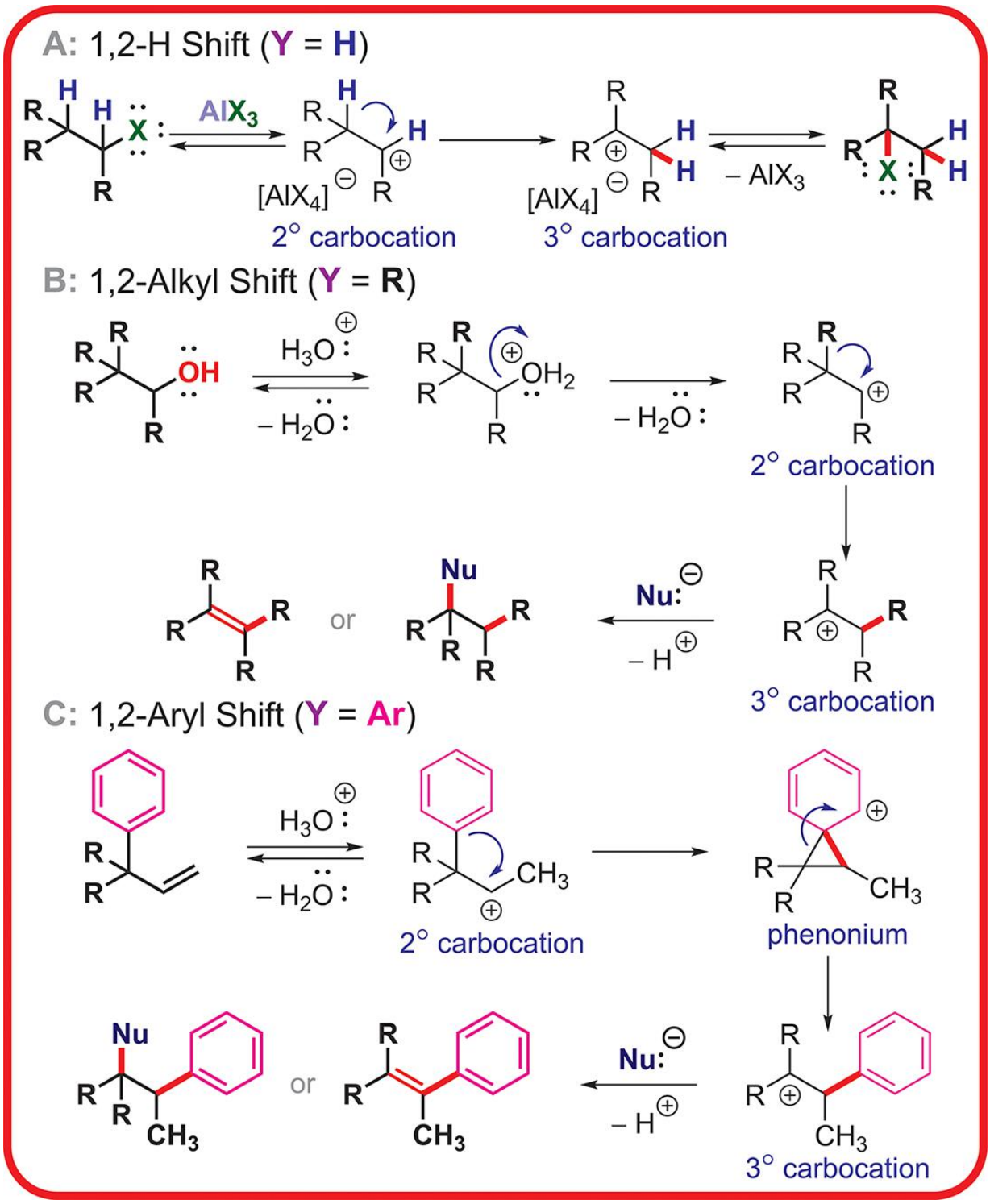


Fig. 96.3: The ***Wagner–Meerwein*** *rearrangement* mechanism (A, B, and C).[349]

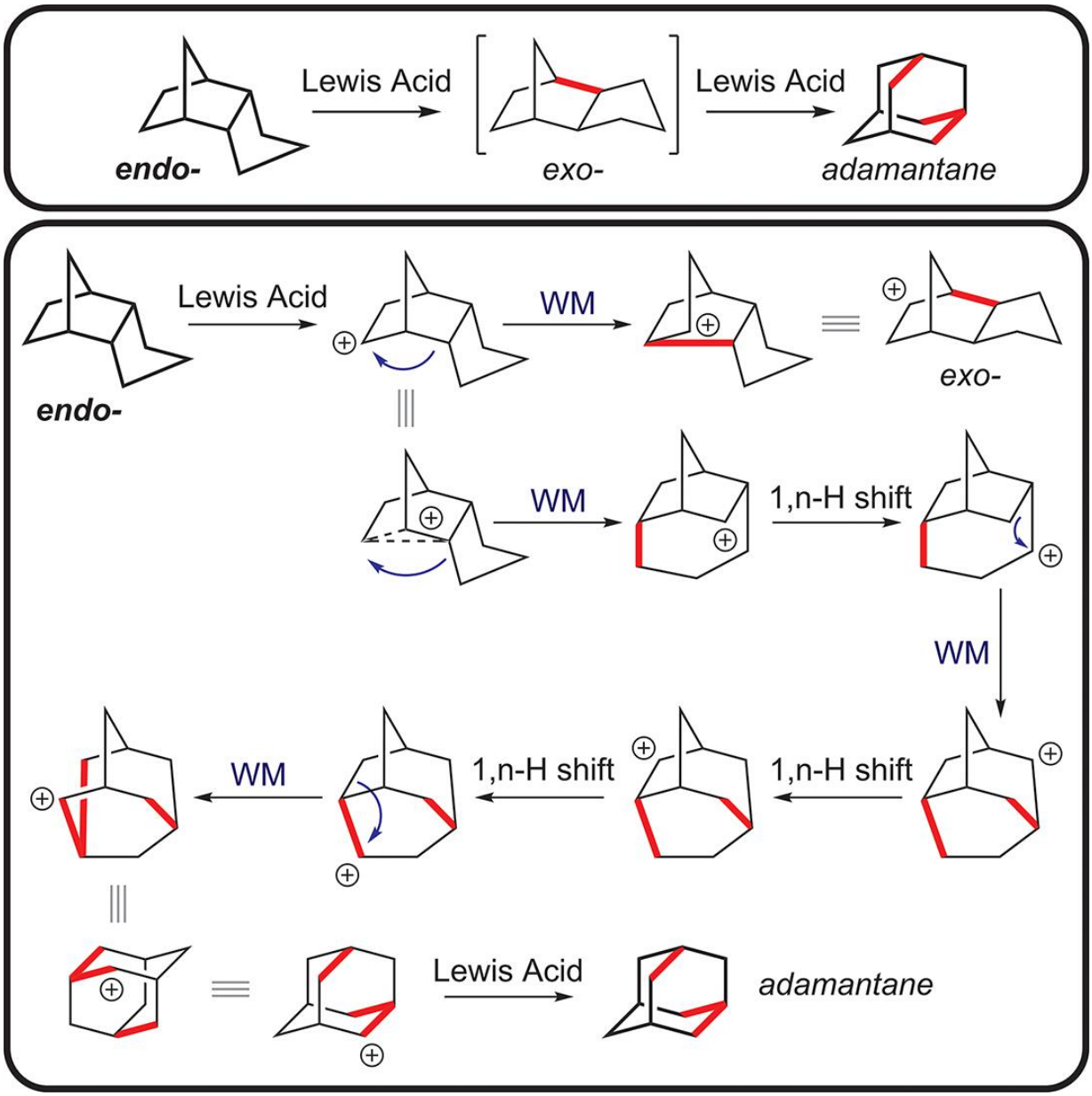


Fig. 96.4: A possible mechanism of ***adamantane*** rearrangement (pathway A).[350]

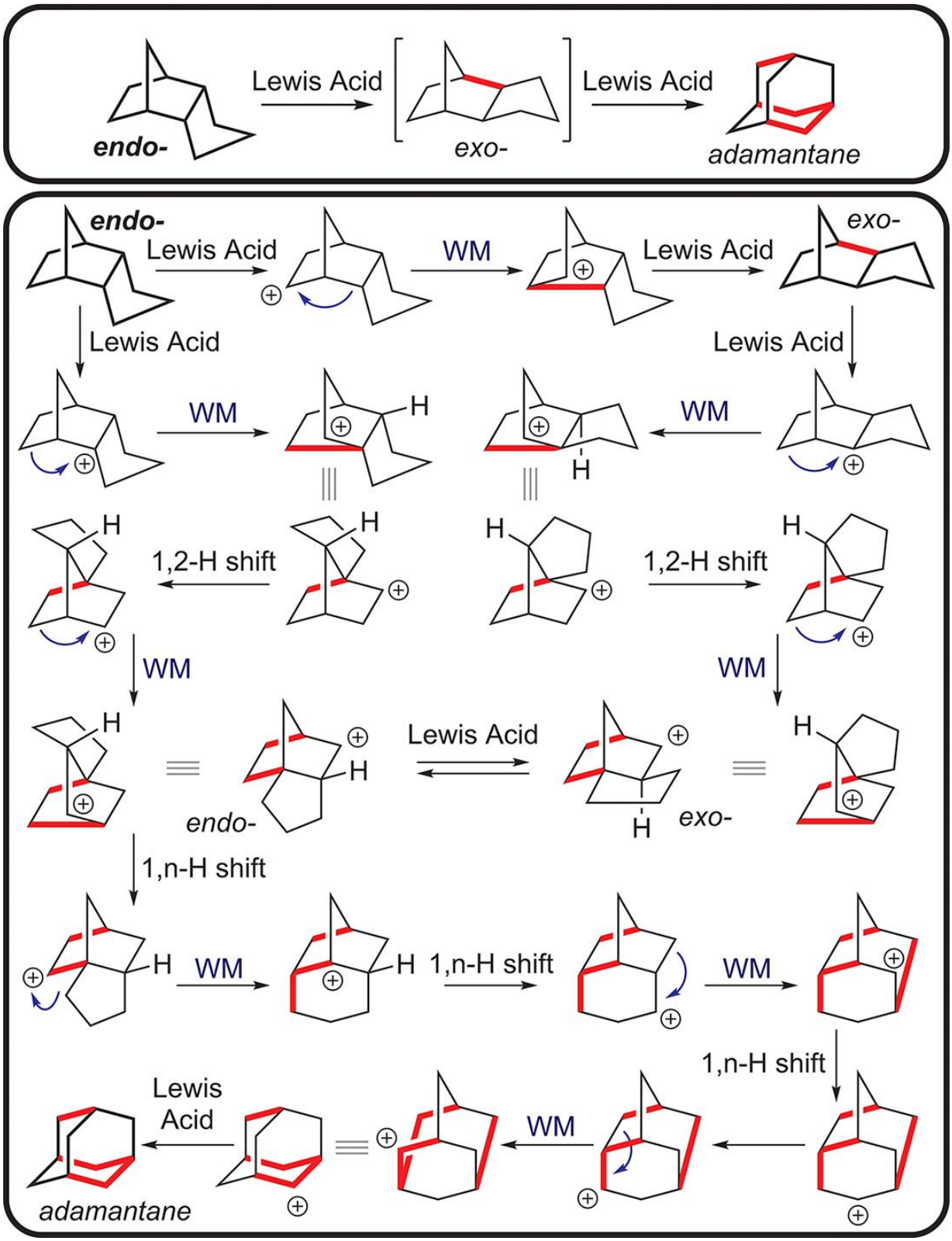

endo-
Lewis Acid
exo-
Lewis Acid
adamantane
endo-
Lewis Acid
WM
Lewis Acid
exo-
Lewis Acid
Lewis Acid
WM
WM
H
H
1,2-H shift
1,2-H shift
WM
WM
Lewis Acid
endo-
exo-
1,n-H shift
WM
1,n-H shift
WM
1,n-H shift
Lewis Acid
WM
adamantane

Fig. 96.5: A possible mechanism of ***adamantane*** rearrangement (pathway B).[351]

97 Weinreb Ketone Synthesis

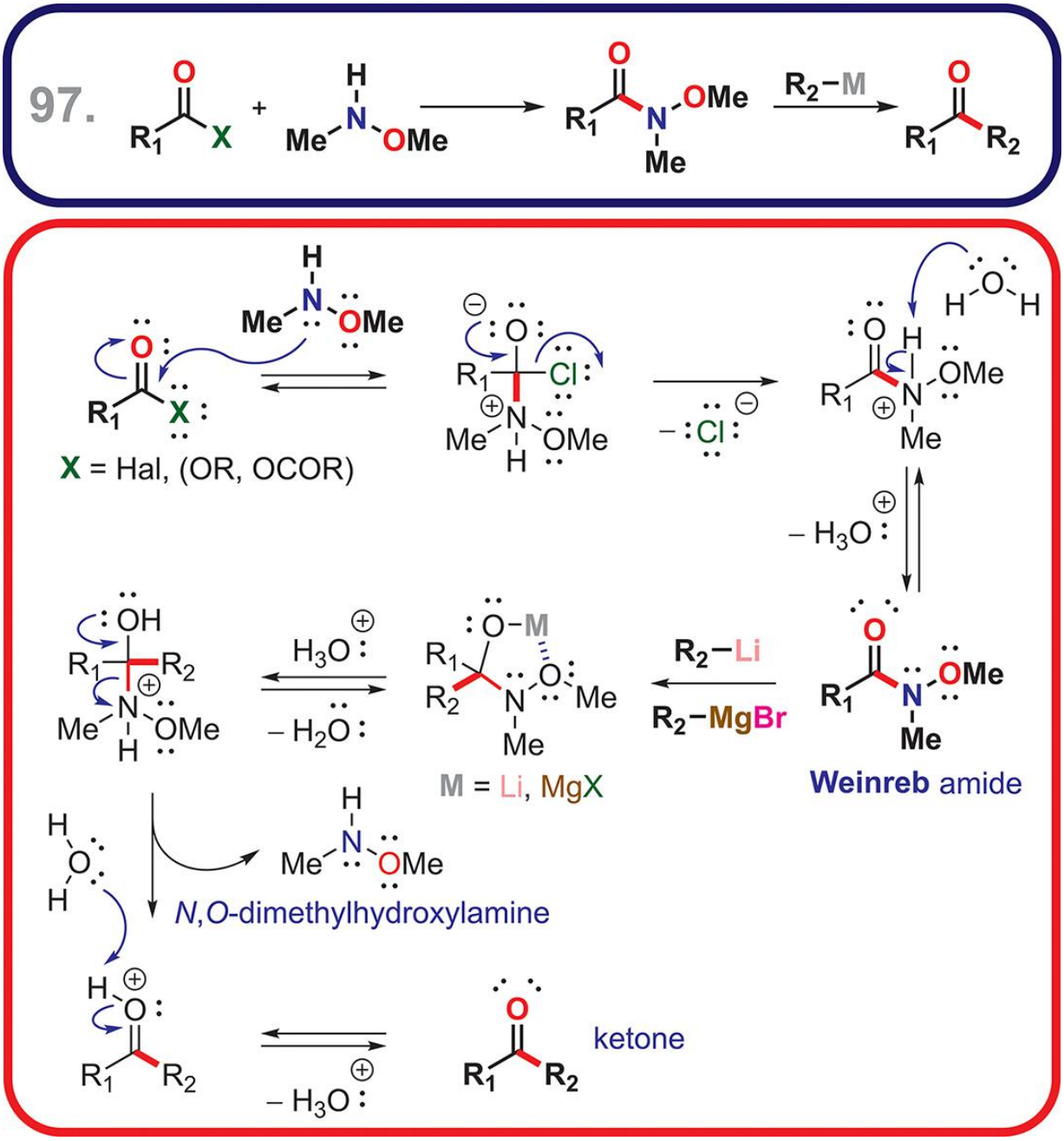


Fig. 97.1: The ***Weinreb*** *ketone synthesis* mechanism.[352]

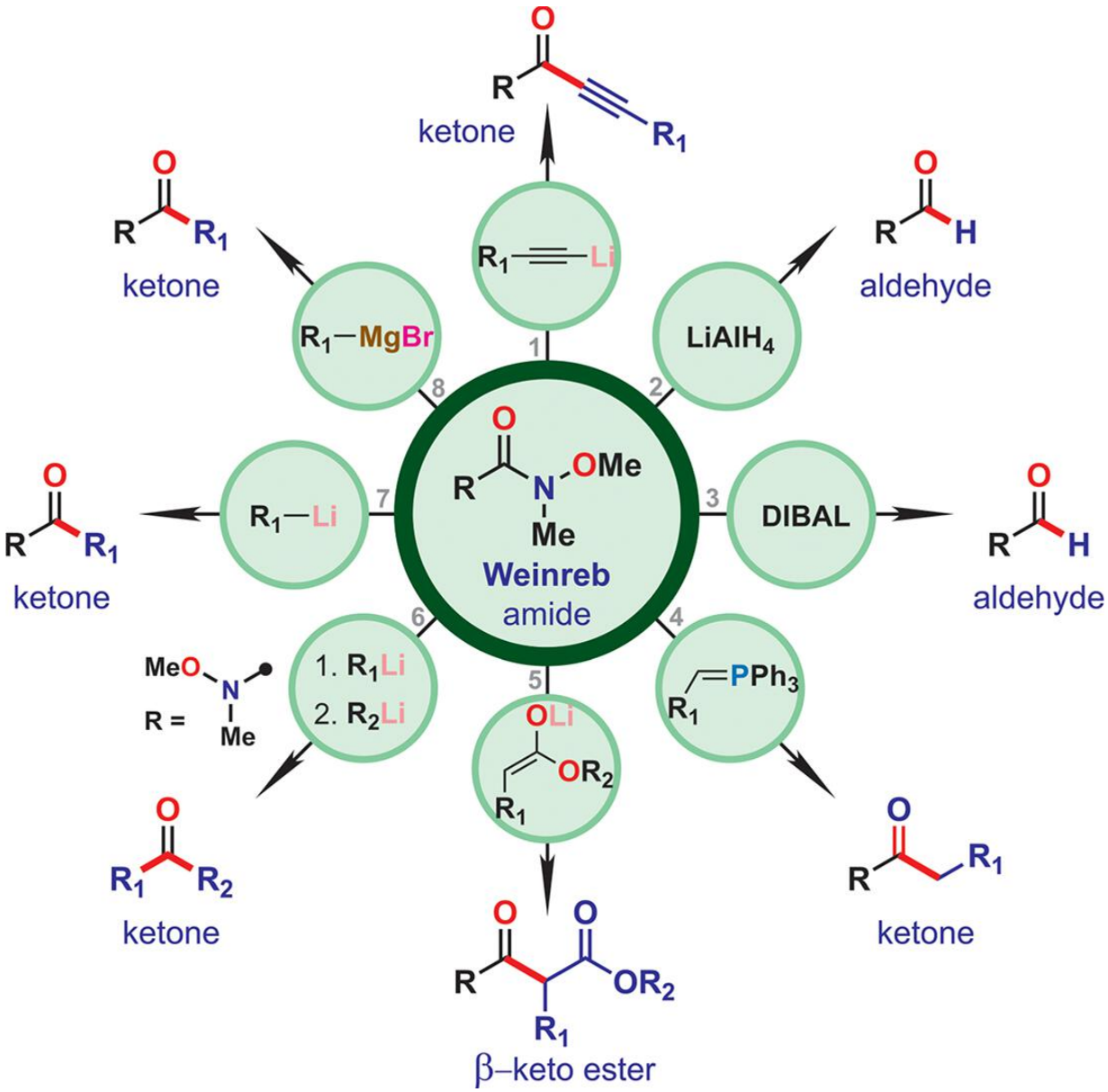


Fig. 97.2: Synthetic versatility of the ***Weinreb*** *amide*.[353]

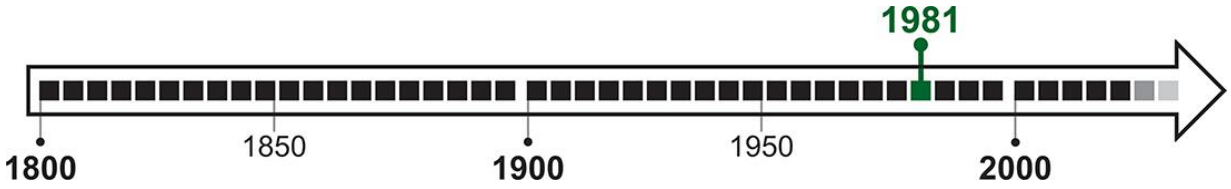


Fig. 97.3: The discovery of the ***Weinreb*** *ketone synthesis*.[354]

98 Wittig Reaction

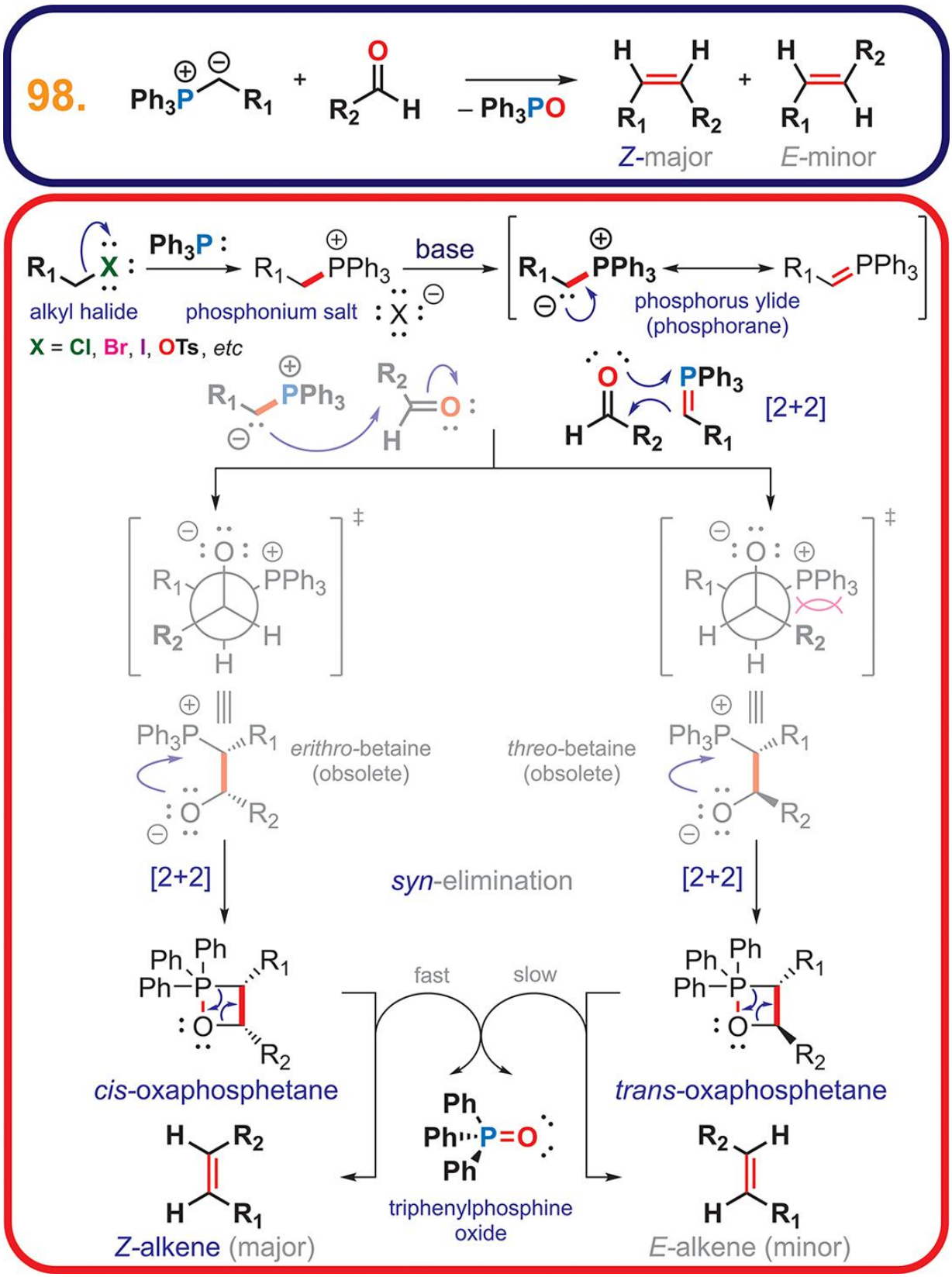

98.
Ph3P
R1
R2
H
– Ph3PO
Z-major
E-minor
alkyl halide
phosphonium salt
base
phosphorus ylide
(phosphorane)
X = Cl, Br, I, OTs, etc
[2+2]
erithro-betaine
(obsolete)
threo-betaine
(obsolete)
syn-elimination
fast
slow
cis-oxaphosphetane
trans-oxaphosphetane
triphenylphosphine
oxide
Z-alkene (major)
E-alkene (minor)

Fig. 98.1: The ***Wittig*** *reaction* mechanism.[355].

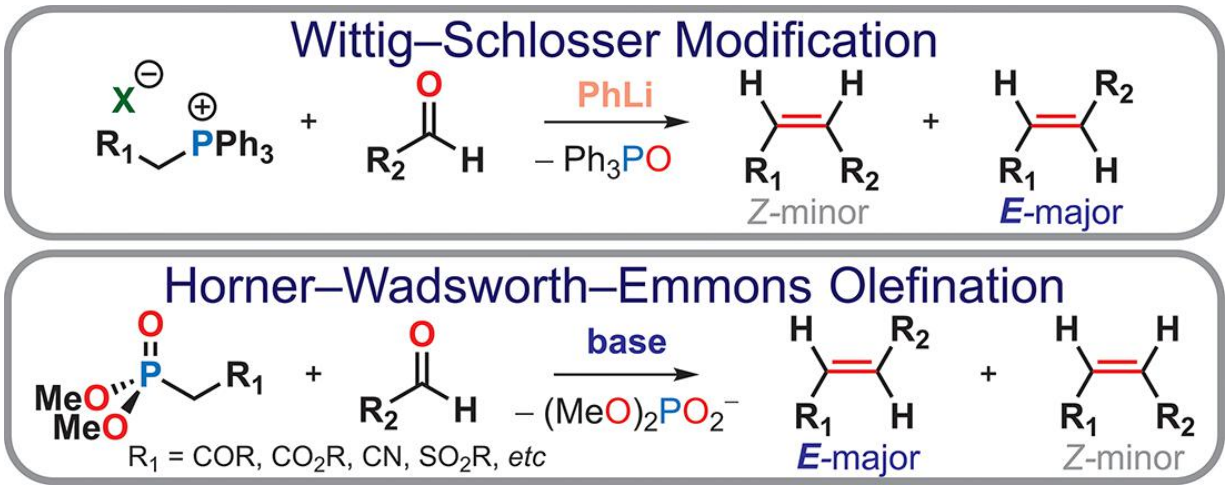


Fig. 98.2: Reactions related to the ***Wittig*** *reaction*.[356]

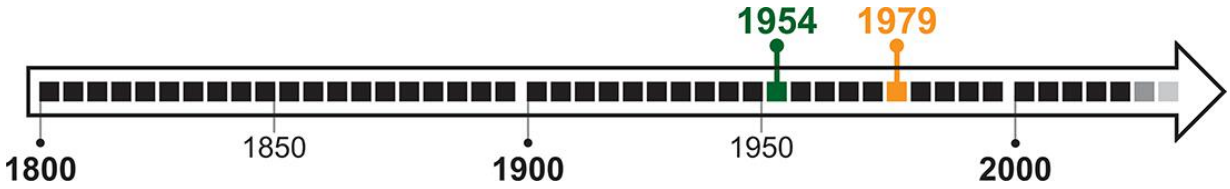


Fig. 98.3: The discovery of the ***Wittig*** *reaction*.[357]

99 Wohl–Ziegler Reaction

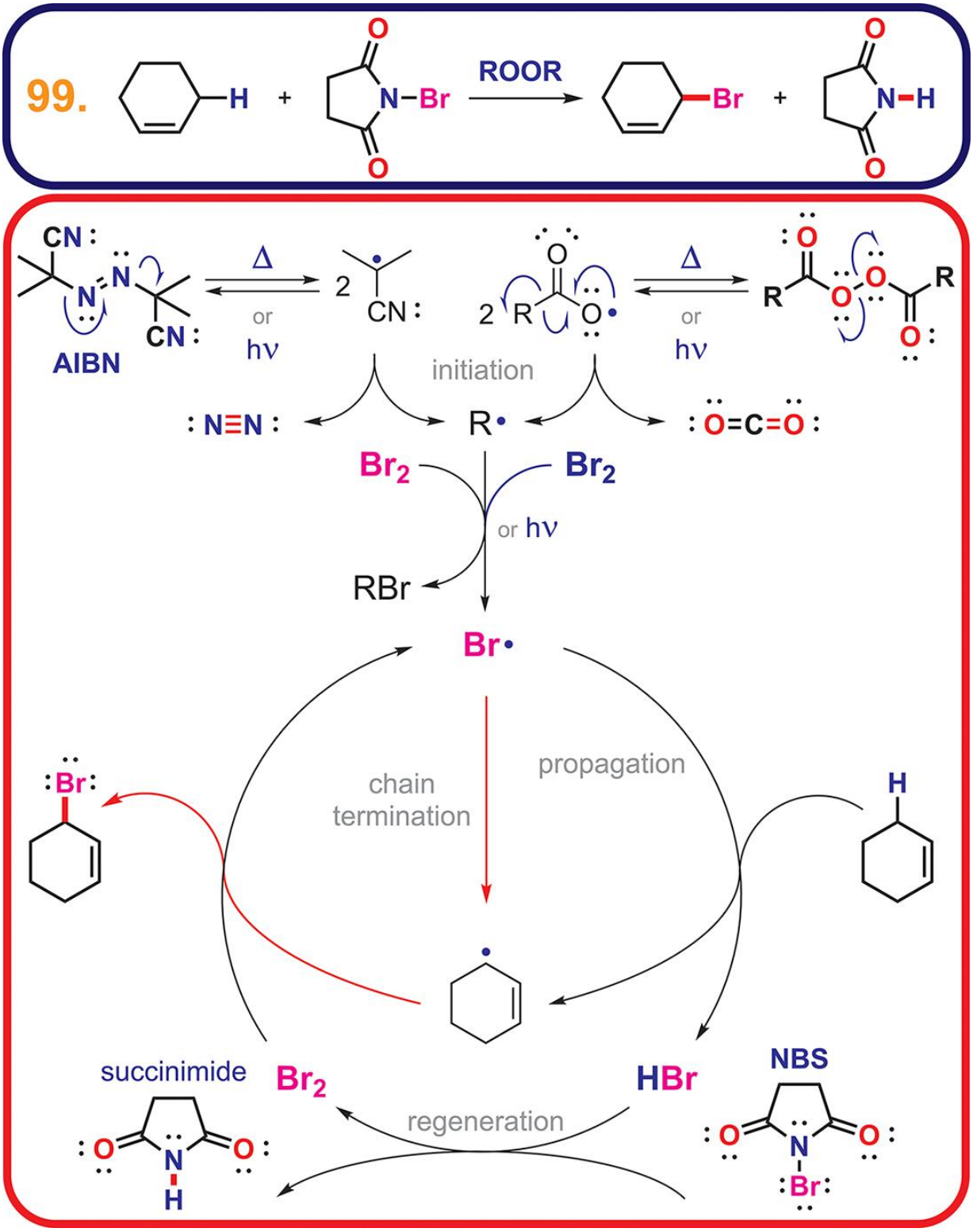


Fig. 99.1: The ***Wohl–Ziegler*** *reaction* mechanism.[358]

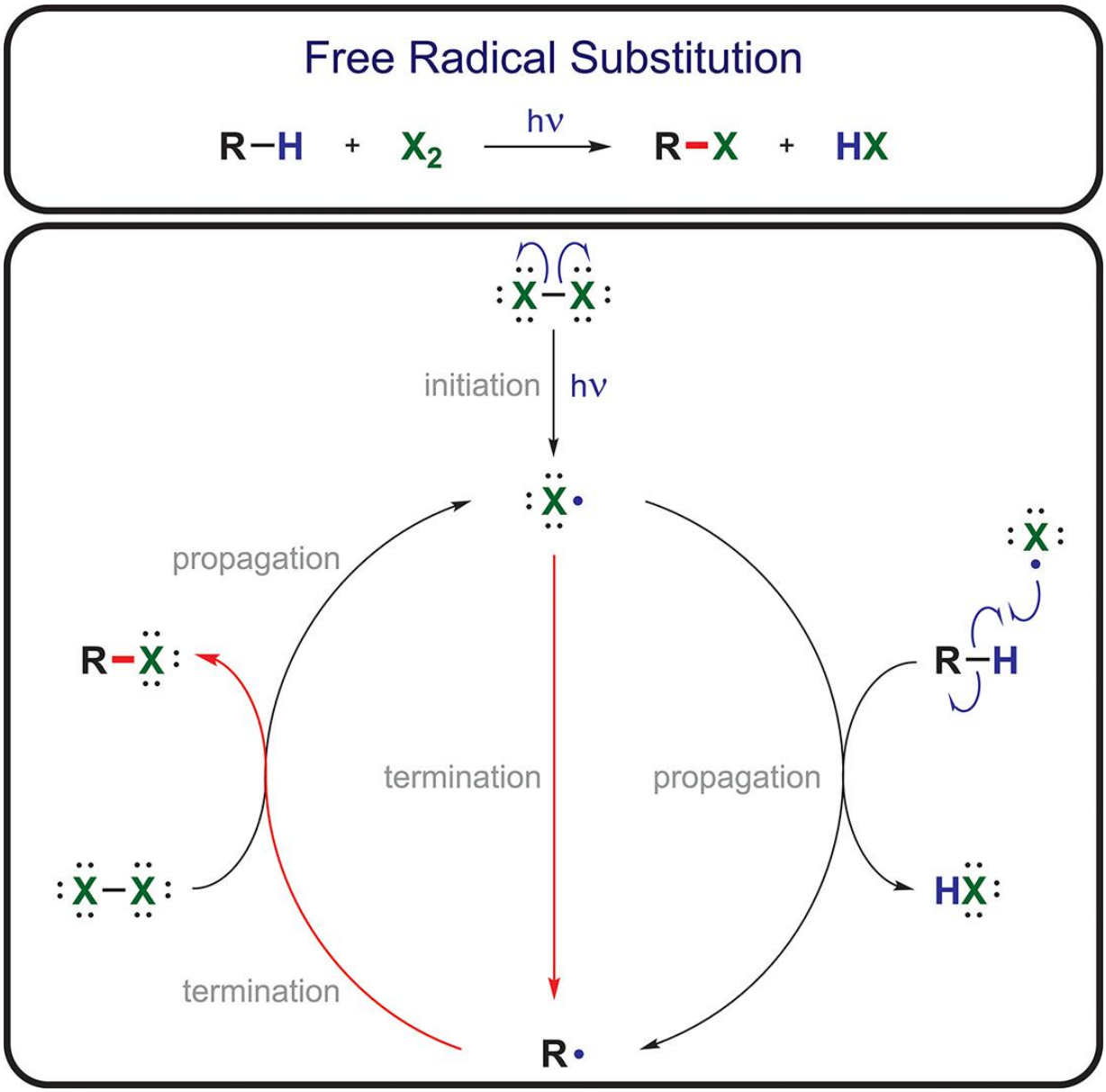


Fig. 99.2: The *free radical substitution* mechanism.[359]

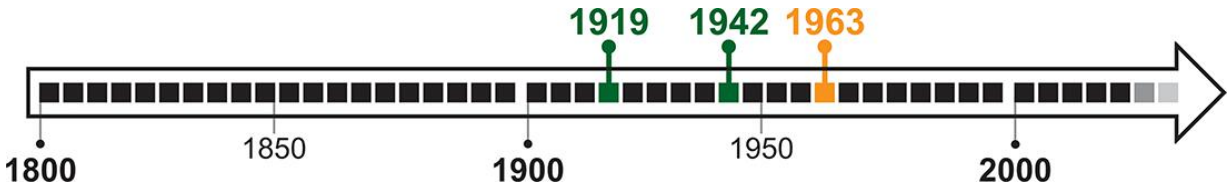


Fig. 99.3: The discovery of the ***Wohl–Ziegler*** *reaction*.[360]

100 Wolff–Kishner Reduction

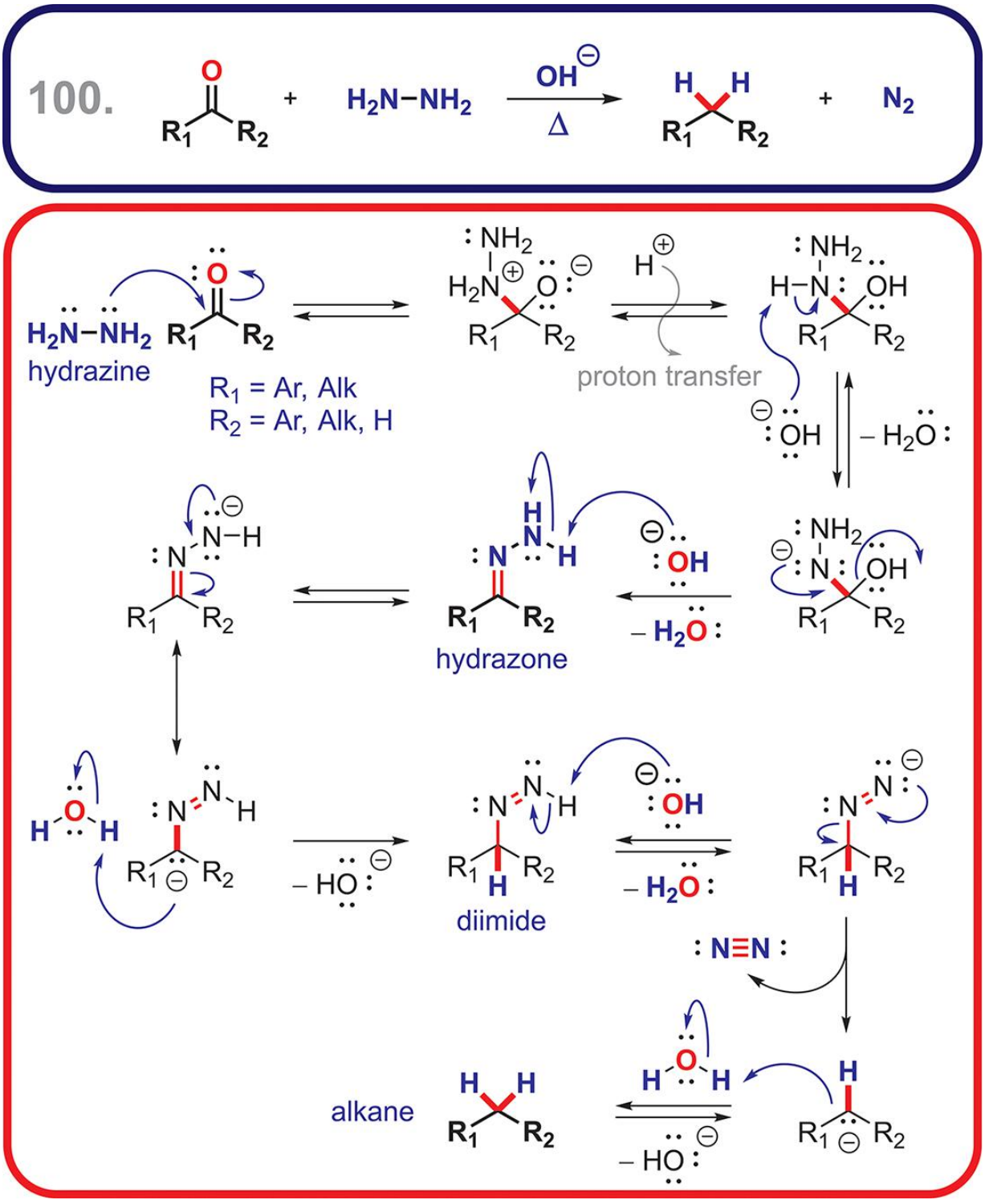


Fig. 100.1: The ***Wolff–Kishner*** *reduction* mechanism.[361]

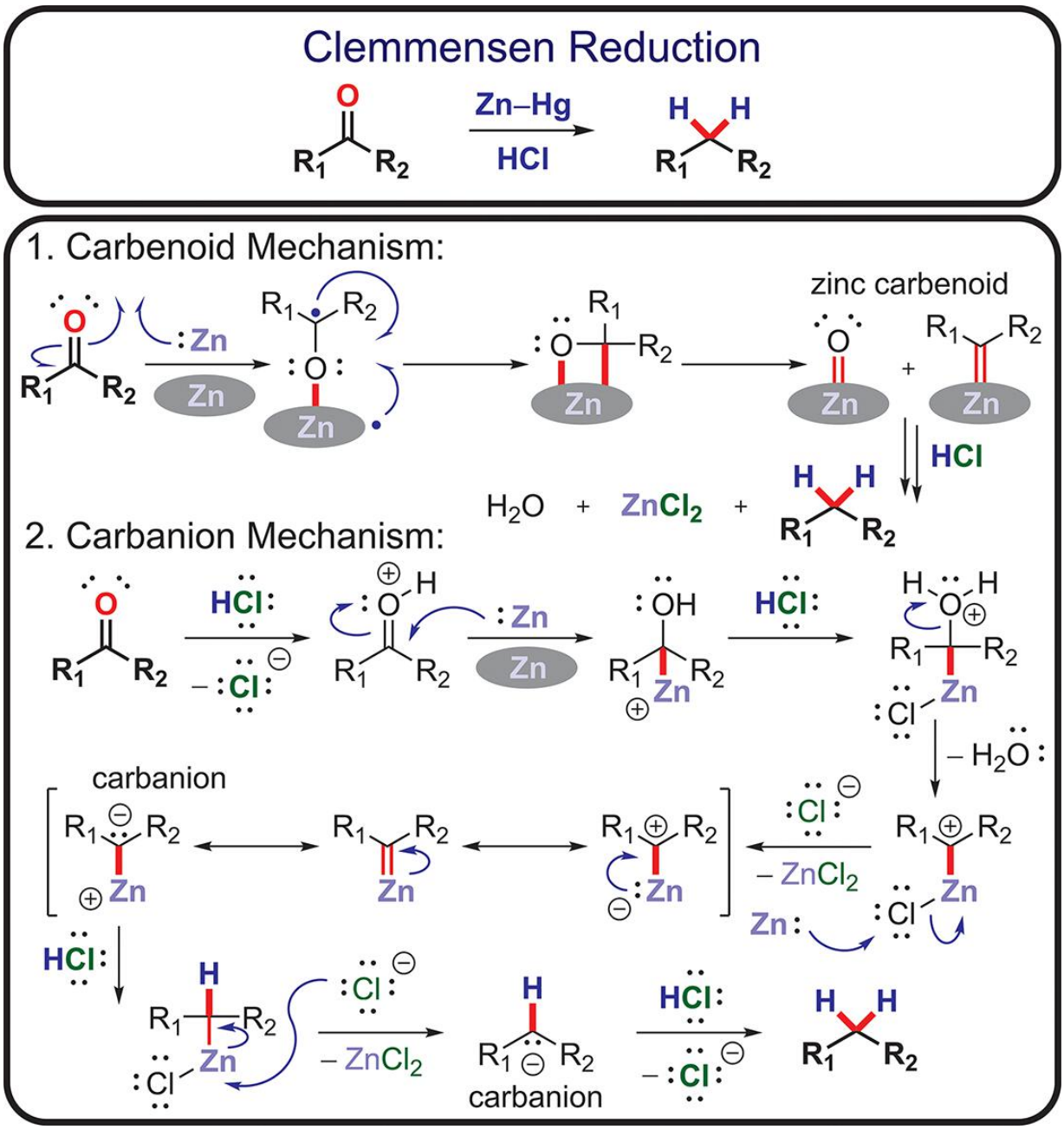


Fig. 100.2: The ***Clemmensen*** *reduction* mechanism.[362]

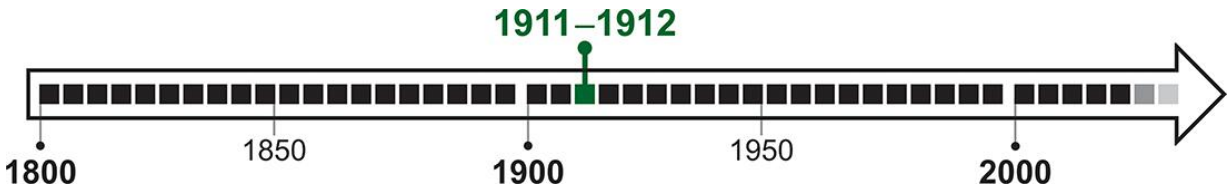


Fig. 100.3: The discovery of the ***Wolff–Kishner*** *reduction*.[363]

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.

The images and infographic summaries ("*MechanoGraphics*") in this book were prepared by the author. Any reference to trademarks or service marks is based on common usage or reference in the discipline or practice, and each such mark is the property of its respective owner and use here does not mean and is not intended to suggest an endorsement. All the "*MechanoGraphic*" schemes are based on common knowledge in the discipline and are supported either by original references, where they were first mentioned, or by other articles and reviews in the literature (where necessary). The reader should be sure to conduct primary research and utilize their own professional judgment, including consultation with peers and more experienced scientists, before planning any studies or research as the illustrations alone are not sufficient as a sole reference.

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

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Notes

1 Symbol **Ad_E2** 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 reactants. In the bromination of cyclohexene, it is the ***electrophile*** (**E** or **Br_2**) and ***alkene*** (**C=C**): *rate* = *k*[**E**]$^{\mathbf{1}}$[**C=C**]$^{\mathbf{1}}$.

2 Symbol **Ad_E3** 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**]$^{\mathbf{1}}$[**HCl**]$^{\mathbf{1}}$[**C=C**]$^{\mathbf{1}}$ **=** *k*[**HCl**]$^{\mathbf{2}}$[**C=C**]$^{\mathbf{1}}$. 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).

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

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* = $k[\mathbf{Nu}]^1[\mathbf{RL}]^1$.

5 Symbol $\mathbf{S_EAr}$ or $\mathbf{S_E(Ar)}$ 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* = $k[\mathbf{E}]^1[\mathbf{ArH}]^1$. To emphasize that it is a bimolecular mechanism, sometimes $\mathbf{S_E2Ar}$ or $\mathbf{S_E2(Ar)}$ notation is used (the use of simple $\mathbf{S_E2}$ symbol can be confusing, since it can also apply to an **A**liphatic **E**lectrophilic **S**ubstitution).

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*.

7 An example of an aromatic electrophilic substitution: bromination of anisole (a substrate with an ERG).

8 An example of an aromatic electrophilic substitution: nitration of (trifluoromethyl)benzene (a substrate with an EWG).

9 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* = $k[\mathbf{Nu}]^1[\mathbf{ArX}]^1$. To emphasize that it is a bimolecular mechanism, sometimes $\mathbf{S_N2Ar}$ notation is used.

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

11 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.

12 Symbol **$S_{RN}1$** 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.

13 The substitution of a diazonium group by iodide is an example of the **SET** (**S**ingle **E**lectron **T**ransfer) mechanism. Please note that 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).

14 This figure summarizes the Lewis (electron) dot structures of various SET processes: ***cation*** → ***radical*** → ***anion*** or ***cation radical*** → ***diradical*** or ***lone pair*** → ***anion radical***, and provides several common examples. Please note that 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).

15 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].

16 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): $\mathbf{(E1cB)_R} = \mathbf{(E1cB)_{rev}}$. 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**): $rate \approx k[\mathbf{B}]^{\mathbf{1}}[\mathbf{RL}]^{\mathbf{1}}/[\mathbf{BH}]$. (Scenario B) Step 1 is slow and irreversible (**I** or **irr**) (rate-determining) and step 2 is fast: $\mathbf{(E1cB)_I} = \mathbf{(E1cB)_{irr}}$. 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**): $rate = k[\mathbf{B}]^{\mathbf{1}}[\mathbf{RL}]^{\mathbf{1}}$. (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**): $rate \approx k[\mathbf{RL}]^{\mathbf{1}}$.

17 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**]$^{\mathbf{1}}$[**RL**]$^{\mathbf{1}}$.

18 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**]$^{\mathbf{1}}$.

19 Symbol **E$_{\mathbf{i}}$** 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*[**S**]$^{\mathbf{1}}$.

20 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.

21 Only the key *β-elimination* examples are covered in this book.

22 The reaction is also called the *acyloin* ***ester*** *condensation*. Please note that an *acyloin* is an α-hydroxy ketone.

23 Several reactions are mechanistically related to the *acyloin condensation*: the ***Bouveault–Blanc*** *reduction* of esters [→1a,

→7a].

24 Several reactions are mechanistically related to the *acyloin condensation*: the ***Bouveault–Blanc*** *reduction* of ketones [→1a, →7a].

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

26 Several reactions are mechanistically related to the *acyloin condensation*: 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)*.

27 The reaction is also called the *alkyne isomerization reaction* or the *alkyne–allene rearrangement*.

28 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.

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

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

31 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].

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

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

34 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].

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

36 The *ketene* (prop-1-en-1-one) formed during the ***Arndt–Eistert*** *synthesis* is trapped by methanol.

37 The ***Wolff*** *rearrangement* (α-diazoketone) is part of the ***Arndt–Eistert*** *synthesis* mechanism [→10a].

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

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

40 The reaction was likely first described around 1899 [→11b]. In **1905**, Johann Friedrich Wilhelm Adolf von Baeyer received the Nobel Prize in Chemistry [→11c].

41 The order of group migration is essential for the *asymmetrical* ketones. Please note that this preference for migration is a general empirical trend and not an absolute rule [→1].

42 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].

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

44 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.

45 The *decarboxylation* reaction was likely first described between 1980 and 1985 [→12a, →12b], and the *deoxygenation* reaction was likely first described between 1975 and 1980 [→12c, →12d]. In **1969**, Derek H. R. Barton (jointly with Odd Hassel) received the Nobel Prize in Chemistry [→12e].

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

47 Many variations of the ***Baylis–Hillman*** *reaction* exist, depending on the nature of EWG (the *Michael* acceptor) and

carbonyl compound (the electrophile). Please note that for X = NR, it is called the *aza-**Baylis–Hillman** reaction*.

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

49 The ***Beckmann*** *rearrangement* is seldom called the ***Beckmann*** *oxime–amide rearrangement*.

50 The reaction was likely first described around 1886 [→14a].

51 This is an example of the ***Beckmann*** *rearrangement* mechanism of cyclohexanone oxime to azepan-2-one (also known as **caprolactam**) [→14b]. 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).

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

53 The reaction was likely first described around 1832 and the mechanism was proposed in 1903 [→15c, →15d].

54 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).

55 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).

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

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

58 The ***Bergman*** *cyclization* is also known as the ***Bergman*** *reaction (isomerization or cycloaromatization)*.

59 The ***Myers–Saito*** *cyclization* or *cycloaromatization* of enyne-allenes is related to the ***Bergman*** *cyclization* and the ***Schmittel*** *cyclization* (not shown) [→17c].

60 The reaction was likely first described around 1972 [→17a, →17b].

61 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).

62 The *alkyne trans-reduction (alkyne metal reduction)* mechanism is much like the ***Birch*** *reduction*. Please note that 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.

63 The reaction was likely first described around 1944 [→18c].

64 The ***Bischler–Napieralski*** *cyclization (reaction)* is a classic example of **aromatic electrophilic substitution** (the ***arenium ion*** mechanism or $\mathbf{S_EAr}$, Chapter 3).

65 Several named reactions are related to the ***Bischler–Napieralski*** *cyclization*: the ***Friedel–Crafts*** *acylation* and *alkylation* (covered in Chapter 39), and the ***Pomeranz–Fritsch*** *reaction*, which is an alternative way to make *isoquinolines* [→19a, →19b].

66 The reaction was likely first described around 1893 [→19c].

67 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.

68 There are numerous examples of 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].

69 The reaction was likely first 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].

70 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*.

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

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

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

74 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].

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

76 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].

77 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].

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

79 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.

80 An example of the ***Chichibabin*** *amination* of quinoline to yield 2-aminoquinoline [→24c].

81 The reaction was likely first described around 1914 [→24a, →24b].

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

83 The ***Dieckmann*** *condensation* is the *intramolecular* ***Claisen*** *condensation* and their mechanisms are almost identical. The ***Dieckmann*** *condensation* is ideal for the formation of five-, six-, and seven-membered rings [→25a].

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

85 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)*.

86 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].

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

88 The ***Cope*** *elimination* or the ***Cope*** *reaction* is an example of the *five-membered* **internal** or **intramolecular β-elimination** reaction (**E_i**), mentioned in Chapter 6.

89 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).

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

91 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*).

92 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), and the *azo-**Cope** rearrangement* [→28a].

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

94 The ***Cope*** *rearrangement* of (3*R*,4*R*)-3,4-dimethylhexa-1,5-diene to (2*E*,6*E*)-octa-2,6-diene.

95 The ***Cope*** *rearrangement* of (2*E*,4*R*,5*R*,6*E*)-4,5-dimethylocta-2,6-diene to (2*E*,4*S*,5*S*,6*E*)-4,5-dimethylocta-2,6-diene.

96 The ***Cope*** *rearrangement* of (2*Z*,4*R*,5*R*,6*E*)-4,5-dimethylocta-2,6-diene to (2*E*,4*R*,5*S*,6*E*)-4,5-dimethylocta-2,6-diene.

97 The ***Cope*** *rearrangement* of (2*Z*,4*R*,5*S*,6*E*)-4,5-dimethylocta-2,6-diene to (2*Z*,4*S*,5*R*,6*E*)-4,5-dimethylocta-2,6-diene.

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

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

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

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

102 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 reactions*. Please note that 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].

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

104 The reaction was likely first described around 2002 [→30d, →30e] and the mechanism, in its current form, proposed around 2013 [→30f]. In **2022**, Carolyn R. Bertozzi, Morten Meldal, and K. Barry Sharpless received the Nobel Prize in Chemistry for the development of click chemistry and bioorthogonal chemistry [30g, 30h].

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

106 The reaction was likely first described around 1890 [→31a, →31b].

107 The ***Schmidt*** *reaction* is also a rearrangement.

108 The reaction was likely first described between 1923 and 1924 [→31c, →31d].

109 The ***Hofmann*** *rearrangement* is also known as the ***Hofmann*** *reaction*. It is completely different from the ***Hofmann*** *elimination* (see Chapter 49).

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

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

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

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

114 The reaction was likely first described around 1904 [→32c].

115 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).

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

117 2-Iodoxybenzoic acid (**IBX**) is a precursor for the preparation of the ***Dess–Martin*** *periodinane* (**DMP**). IBX can also be used as an oxidant.

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

119 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].

120 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 (the slow step) depends on the concentration of one reactant, the *diazonium salt* (**ArN_2^+**): $rate = k[\mathbf{ArN_2^+}]^1$. 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*. It is also different from the *benzyne* mechanism (the *elimination–addition* mechanism, Chapter 16).

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

122 The ***Diels–Alder*** *cycloaddition reaction* or the **[4 + 2]**-*cycloaddition reaction* is a pericyclic reaction with a concerted mechanism. Note that 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 with the *1,3-dipolar cycloaddition* (Chapter 30).

123 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 **$[4_\pi + 2_\pi]$** = ***Diels–Alder*** *cycloaddition*.

124 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].

125 The ***Diels–Alder*** *cycloaddition reaction* using buta-1,3-diene (diene) and either *fumaronitrile* or *maleonitrile*. Please note the difference in the reaction outcome.

126 The ***Diels–Alder*** *cycloaddition reaction* using either (2*Z*,4*E*)-hexa-2,4-diene or (2*E*,4*E*)-hexa-2,4-diene and ethene (dienophile). Please note the difference in the reaction outcome.

127 The ***Diels–Alder*** *cycloaddition reaction* using (2*Z*,4*E*)-hexa-2,4-diene and either *fumaronitrile* or *maleonitrile*. Please note the difference in the reaction outcome.

128 The ***Diels–Alder*** *cycloaddition reaction* using (2*E*,4*E*)-hexa-2,4-diene and either *fumaronitrile* or *maleonitrile*. Please note the difference in the reaction outcome.

129 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].

130 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 $\mathbf{^3(\pi, \pi^*)}$ [→2b].

131 The reaction was likely first described between 1966 and 1967 [→36].

132 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).

133 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).

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

135 An example of the ***Favorskii*** *rearrangement* of 2-chlorocyclohexan-1-one yielding ring-contracted ethyl cyclopentanecarboxylate.

136 The tandem ***Favorskii*** *rearrangement* plays the key role in the synthesis of cubane-1,4-dicarboxylic acid and other cubane derivatives [→37e, →37f].

137 The ***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)*.

138 The key mechanistic step in the ***Fischer*** *indole synthesis* is related to the ***Cope*** *rearrangement*, the *aza-**Cope***, and/or *aza-**Claisen*** *rearrangement* (Chapter 28). Other related reactions include the ***benzidine*** *rearrangement* (its mechanism is not well-understood) [1, 38a].

139 The reaction was likely first described around 1883 [38b, 38c]. In **1902**, Emil Fischer received the Nobel Prize in Chemistry [38d].

140 The ***Friedel–Crafts*** *acylation* mechanism is an example of the **aromatic electrophilic substitution** (the *arenium ion* mechanism or $\mathbf{S_EAr}$, covered in Chapter 3). The linear *acyl halides* react via *acylium cation* and form *aryl ketones* with *linear* alkyl chains.

141 The reaction was likely first described around 1877 [→39a].

142 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.

143 The reaction was likely first described around 1877 [→39b].

144 An example of the ***Friedel–Crafts*** *acylation* of anisole yielding 1-(4-methoxyphenyl)propan-1-one.

145 An example of the ***Friedel–Crafts*** *alkylation* of benzene yielding *tert*-butylbenzene.

146 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*.

147 The ***Delépine*** *reaction* mechanism (*urotropine* acts as the nitrogen nucleophile). There are other synthetic transformations yielding *primary amines*: the ***Mitsunobu*** *reaction* (Chapter 61) or other $\mathbf{S_N2}$ reactions using various **N** (nitrogen) nucleophiles [→40b].

148 The reaction was likely first described around 1887 [→40c].

149 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].

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

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

152 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.

153 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].

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

155 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).

156 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].

157 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].

158 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.

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

160 An example of the ***Grob*** *fragmentation* of (1*R*,3*S*)-3-chloro-1-methylcyclohexan-1-ol yielding hept-6-en-2-one.

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

162 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).

163 The *haloform reaction* can be carried out with most halogens: (Cl) the *chloroform reaction*, (Br) the *bromoform reaction*, and (I) the *iodoform reaction*, also known as the *iodoform test* or the ***Lieben*** *iodoform test* (it is used as an indication of the presence of methyl ketones) [→45].

164 The reaction was likely first described between 1822 and 1870 [→45].

165 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.

166 The *oxidative addition* step can be represented in several ways, including a catalyst with: 1. a ***not*** *(less) hindered monodentate ligand*; 2. a *large hindered monodentate ligand*; and 3. a *hindered chelating (bidentate) ligand*. For simplicity, $\mathbf{L_mPd}$ or $\mathbf{L_nPd}$ representation will be used henceforth [→2a].

167 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].

168 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).

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

170 The rearrangement mechanism of bicyclo[2.2.2]octane system to bicyclo[3.2.1]octane system [→47d].

171 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.

172 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].

173 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 o*rganosilanols*).

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

175 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 the **β-elimination** (Chapter 6).

176 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 А. М. Зайцев) [→49a].

177 Several reactions are related to the ***Hofmann*** *elimination*: the ***Cope*** *elimination* (**E_i** mechanism, Chapter 27), the fragmentation of quaternary ammonium salts (**E2** mechanism), and others [→1, →49b].

178 The reaction was likely first described around 1851 [→49c, →49d].

179 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).

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

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

182 The ***Peterson*** *olefination* reaction relies on the use of *organosilanes*. The outcome of the ***Peterson*** *elimination* step differs depending on the basic or acidic conditions [→50b].

183 The ***Corey–Chaykovsky*** *reaction* (also known as the ***Johnson–Corey–Chaykovsky*** *reaction*) [→32a, →32b] is related to both the ***Darzens*** *condensation* (Chapter 32) and the ***Wittig*** *reaction* (Chapter 98).

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

185 There are numerous examples of chromium oxidizing reagents, derived from chromium oxide(VI): *pyridinium chlorochromate* (PCC) [→51b, →51c] is one of the most important.

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

187 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].

188 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 that 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).

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

190 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* = *organomagnesium compound*). For teaching purposes, a simplified and general mechanism is shown. Note that the (1) *concerted oxidative addition* step to a low-coordinate ($14e^-$) **Pd**-complex is more complicated [→2a].

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

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

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

194 The ***Upjohn*** *dihydroxylation* (covered in Chapter 93) is related to the ***Ley–Griffith*** *oxidation*. Please note that the reaction outcome is different depending on the stereochemistry of the starting alkene.

195 The reaction was likely first described around 1987 [→54b].

196 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.

197 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.

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

199 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.*

200 The ***Mannich*** *reaction* can be also catalyzed in (b) *basic* media (via a *hemiaminal* intermediate).

201 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].

202 The reaction was likely first described around 1912 [→56b].

203 The ***Kabachnik–Fields*** *reaction* is a 3-CR yielding peptidomimetic compounds [→56c, →56d].

204 The ***Petasis*** *reaction* (also known as the ***Petasis*** *boronic acid–**Mannich** reaction*) is a 3-CR reaction. Its mechanism is not fully understood [→62b].

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

206 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.

207 The reaction was likely first described around 1974 [→57c].

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

209 The ***Oppenauer*** *oxidation* is a reversed process of the ***MPV*** *reduction* (see Chapter 69).

210 The reaction was likely first described around 1925 by Meerwein and Verley [→58a, →58b], and then in 1926 by Ponndorf [→58c].

211 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.

212 There are variations of this reaction; for example, the *retro-**Michael** addition* and the ***Robinson*** *annulation* (covered in Chapter 83).

213 The reaction was likely first described around 1887 [→59b].

214 The mechanism of the ***Stetter*** *reaction* [→59a] is related to both the ***Michael*** *addition* and the *benzoin condensation* (Chapter 15). In case of *aromatic* aldehydes, it is catalyzed by **cyanide ions**.

215 The mechanism of the ***Stetter*** *reaction* [→59a] is related to both the ***Michael*** *addition* and the *benzoin condensation* (Chapter 15). In case of *aliphatic* aldehydes, it is catalyzed by **thiazolium salts**.

216 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).

217 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].

218 The reaction was likely first described between 1968 and 1971 [→60d, →60e].

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

220 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 so on [→61b, →61c].

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

222 In this example of ester formation via the ***Mitsunobu*** *reaction* mechanism, please notice the *inversion* of the stereochemistry in the final product. Compare with the ***Fischer*** *esterification* (→Fig. 61.5) [→61f].

223 In the case of the ***Fischer*** *esterification* mechanism [→61f], please notice the *retention* of the configuration of the chiral center in the final product. Compare with the ***Mitsunobu*** *reaction* (→Fig. 61.4).

224 The ***Miyaura*** *borylation* is a type of **Pd**-*catalyzed cross-coupling* reaction (C–B bond formation using *aryl halides* and *bis(pinacolato)diboron* or **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.

225 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), and ***Liebeskind–Srogl*** *cross-coupling* (covered in Chapter 55). The ***Petasis*** *reaction* is a mechanistically different three-component reaction, but it uses boronic acids as well [→62b].

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

227 The revised ***Mukaiyama*** *RedOx hydration* mechanism was recently proposed by **Nojima** [→63a].

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

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

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

231 The ***Woodward–Hoffmann*** *rules* (the pericyclic selection rules) [→64a, →64b] for the *electrocyclization reactions*. Please note that 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].

232 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*.

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

234 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.

235 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, →65a]. Please note that the reaction was likely first reported by Konovalov [→65b].

236 The reaction was likely first described around 1894 [→65c, →65d].

237 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 that the (1) *concerted oxidative addition* step to a low-coordinate (14e$^-$) **Pd**-complex is more complicated [→2a].

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

239 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].

240 The ***Norrish type I*** *reaction* is a photochemical decomposition (**α-cleavage**) of *aldehydes* and *ketones*. The products are formed after initial *fragmentation* and subsequent *disproportionation* or *(re)combination* of radical species. Upon *direct irradiation* of aromatic ketones (benzophenone), the reaction usually occurs from the *triplet* excited state $\mathbf{T_1 = {}^3(n, \pi^*)}$ [→2b].

241 The ***Norrish type II*** *reaction* is a photochemical intramolecular **γ-H abstraction**. The products are 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].

242 The **type I** and **II** reactions were likely first described between 1932 and 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].

243 The ***Ru****-catalyzed olefin (alkene) metathesis* mechanism starts with the *stable catalyst (16e⁻) initiation cycle (**α**)*: theoretically it can go either via a dissociative pathway (14e⁻), or

an associative pathway (18e⁻), and an interchange pathway is not shown here [→68a].

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

245 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].

246 The most common catalysts used in the ***Ru**-catalyzed olefin metathesis* are ***Grubbs'** catalysts* (first and second generation) [→68e, →68f] and ***Hoveyda–Grubbs'** catalysts* (first and second generation) [→68g].

247 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); and 8. ROM (ring-opening metathesis).

248 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*.

249 The ***MPV** reduction* is a reversed process of the ***Oppenauer** oxidation.* It is also covered in Chapter 58.

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

251 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*.

252 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*.

253 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*.

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

255 An example of the *ozonolysis* reaction mechanism of (1*R*,4*S*)-7,7-dimethyl-2-methylenebicyclo[2.2.1]heptane (also known as (−)-α-fenchene).

256 An example of an anomalous (interrupted) *ozonolysis* reaction mechanism of (1*S*,4*S*)-7,7-dimethyl-2-methylenebicyclo[2.2.1]heptan-1-ol yielding two unexpected products [→70h].

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

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

259 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).

260 Thiophenes (2-aminothiophenes) can be prepared via the ***Gewald*** *condensation* (see Chapter 41).

261 The reaction was likely first described around 1884 [→71b, →71c].

262 The ***Paternò–Büchi*** *reaction* is a photochemical **[$2_\pi + 2_\pi$]** 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].

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

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

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

266 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*.

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

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

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

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

271 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 [→74]). The most common additives (catalysts) used in the *peptide synthesis* are HOBt [→74i] and HOAt, among others.

272 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].

273 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 $\mathbf{S_EAr}$, which was covered in Chapter 3).

274 The cyclization ($\mathbf{S_EAr}$) step is allowed according to *Baldwin's rules*: **6-endo-trig** [→75a].

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

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

277 An example of the ***Bischler–Napieralski*** *cyclization* of *N*-phenethylacetamide yielding 1-methyl-3,4-dihydroisoquinoline.

278 The ***Pomeranz–Fritsch*** *reaction* [→19a, →19b] yielding 1-methylisoquinoline.

279 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***.

280 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].

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

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

283 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.

284 The reaction was likely first described around 1927 [→77c].

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

286 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].

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

288 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.

289 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].

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

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

292 The reaction was likely first described around 1909 [→80a].

293 The ***Polonovski*** *reaction* mechanism (Chapter 77) is related to the ***Pummerer*** *rearrangement*. Here an *amine oxide* plays a similar role as a *sulfoxide* (in the ***Pummerer*** *rearrangement*) [→80b, →80c].

294 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].

295 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*.

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

297 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).

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

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

300 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).

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

302 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].

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

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

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

306 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.

307 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) acetylide*s) [→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).

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

309 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].

310 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].

311 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]. In **2022**, Carolyn R. Bertozzi, Morten Meldal, and K. Barry Sharpless

received the Nobel Prize in Chemistry for the development of click chemistry and bioorthogonal chemistry [→30g, →30h].

312 Types of the ***Staudinger*** *ligation*: *non-traceless* and *traceless* ***Staudinger*** *ligation* [→86d, →86e, →86h].

313 Types of the ***Staudinger*** *ligation*: *non-traceless* and *traceless* ***Staudinger*** *ligation* [→86d, →86e, →86h].

314 The ***Steglich*** *esterification* is an *ester coupling reaction* (compare to the *peptide (amide) coupling* mechanism in Chapter 74 or the ***Fischer*** *esterification*, Fig. 61.5). The mechanism involves the use of *carbodiimide* coupling reagents (DCC) and DMAP catalyst [→87a].

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

316 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.

317 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.

318 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*).

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

320 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].

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

322 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].

323 [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) or **Pd(dppf)Cl_2** is one of the most common **Pd** catalysts [→89e, →89g].

324 Tetrakis(triphenylphosphine)palladium(0) or **Pd(PPh_3)$_4$** is one of the most common **Pd** catalysts [→89f, →89g].

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

326 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) and the ***Jones*** *oxidation* (Chapter 51).

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

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

329 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), and the ***Pauson–Khand*** *reaction* (Chapter 73).

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

331 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 *organocopper* intermediates (Cu(I) or Cu(II)) is postulated: mechanism I (**a**).

332 The reaction was likely first described around 1901 [→92a, →92b].

333 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**).

334 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).

335 The mechanism varies and depends on the type of substrates, ligands, and other factors. Here is an example of the ***Ullmann*** *biaryl ether* coupling catalyzed by Cu(I) with a neutral bidentate ligand (often *N*,*N*-bidentate ligand) [→92f, →92g].

336 The mechanism varies and depends on the type of substrates, ligands, and other factors. Here is an example of the ***Ullmann*** *biaryl amine* coupling catalyzed by Cu(I) with a neutral bidentate ligand (often *N*,*N*-bidentate ligand) [→92f, →92g].

337 The ***Upjohn*** *dihydroxylation* (**a**) yields racemic products (*cis-1,2-glycols* = *cis*-1,2-diols) [→93a].

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

339 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].

340 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].

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

342 A few named reactions are related to the ***Vilsmeier–Haack*** *reaction*: the ***Friedel–Crafts*** *formylation* using *dichloro(methoxy)methane* (covered in Chapter 39) and the ***Reimer–Tiemann*** *reaction* using *chloroform* (limited to the *ortho*-formylation of *phenols*) [→94a].

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

344 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].

345 Mechanism (**b**) is proposed by Bäckvall: ***Bäckvall's*** *anti-addition* (outer-sphere) [→95a, →95b].

346 The reaction was likely first described around 1959 [→95c].

347 The ***Wagner–Meerwein*** *rearrangement* is a rearrangement of newly 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).

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

349 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].

350 An **adamantane** (tricyclo[3.3.1.1^{3,7}]decane) can be prepared from various saturated polycyclic compounds via a sequence of isomerizations catalyzed by Lewis acids [→96d, →96e]. There are many possible pathways [→96f]. The key step in each pathway is the ***Wagner–Meerwein*** *rearrangement* (here, WM = 1,2-alkyl shift) and 1,2-H shift or 1,n-H shift (here, multiple sequential 1,2-H shifts) [→96g].

351 An **adamantane** (tricyclo[3.3.1.1^{3,7}]decane) can be prepared via a sequence of the ***Wagner–Meerwein*** *rearrangements* (WM) and 1,2-H shifts or 1,n-H shifts [→96f, →96g].

352 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].

353 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].

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

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

356 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* [$PO(OR)_2R$], often made via the ***Arbuzov*** *reaction* (Chapter 9).

357 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].

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

359 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].

360 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].

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

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

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