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Electrochemical and Nucleophilic Dearomatization Strategies for the Synthesis of Spirocyclic and N-Heterocyclic Compounds

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Abstract

Dearomatization provides a powerful and direct strategy for rapidly building molecules with enhanced three-dimensional (3D) complexity from simple, inexpensive, and abundant planar substrates. The resulting non-aromatic products are often reactive intermediates that can be used in further synthetic transformations, thereby increasing the accessible chemical space. Consequently, these features have sparked significant interest in the field, leading to a surge in the development of novel dearomatization methodologies, especially over the last three decades. The introduction to this thesis focuses on two key strategies within this rapidly expanding field: oxidative dearomatization and the nucleophilic dearomatization of *N*-heteroaromatic compounds. The review details the foundational principles and synthetic merit of each approach, establishing the context for the original research presented. Furthermore, the introduction outlines the principles of organic electrochemistry, highlighting its historical development, theoretical concepts, and key experimental parameters as a sustainable and powerful tool for organic synthesis.

The second chapter of this thesis details the integration of organic electrochemistry with oxidative dearomatization to address the limitations of conventional oxidative procedures. This work describes a novel electrochemical protocol for the oxidative *ortho*-dearomatization of naphthols and phenols, leading to intramolecular C–O bond formation. Notably, the reaction scope was extended to include free arenols as starting materials, a deviation from existing electrochemical procedures that typically require protected aryl methyl ether substrates. Through careful optimization, a diverse array of spirolactones and spiroethers were synthesized in excellent yields. The method operates under simple constant-current conditions in an undivided cell without requiring an inert atmosphere. This inherently green and sustainable approach avoids the use of chemical catalysts or stoichiometric oxidants, such as hypervalent iodine reagents, and generates hydrogen as the sole byproduct.

The third chapter deals with the dearomatization of *N*-heteroaromatic substrates via nucleophilic addition. Specifically, it describes an intermolecular Morita–Baylis–Hillman (MBH) reaction employing *N*-benzylquinolinium salts as electrophiles. The reaction proceeds with high C4-selectivity, a reversal of the C2-regioselectivity observed in previous work. This switch was accomplished by changing the counterion in the quinolinium salt to PF_6^- and altering the reaction conditions, most notably by using DABCO as the catalyst. This methodology provides access to functional group-rich products featuring the important 1,4-dihydroquinoline scaffold, complementing earlier methods that produced the corresponding 1,2-dihydroquinoline

regioisomers. The reaction proved robust, with a substrate scope that was successfully extended to include acridinium salts.

Keywords: Dearomatization, Electrosynthesis, Oxidation, Spirolactonization, Spiroetherification, Naphthols, Phenols, Morita-Baylis-Hilman reaction, Regioselectivity, Quinolinium, Acridinium

Streszczenie

Tytuł w języku polskim: *Strategie elektrochemicznej i nukleofilowej dearomatyzacji do syntezy związków spirocyklicznych i N-heterocyklicznych*

Dearomatyzacja stanowi użyteczną i bezpośrednią strategię konstrukcji cząsteczek o zwiększonej, trójwymiarowej (3D) złożoności z prostych, niedrogich i łatwo dostępnych planarnych substratów. Generowane w jej wyniku produkty niearomatyczne są często reaktywnymi związkami, które można wykorzystać w dalszych przemianach syntetycznych, zwiększając w ten sposób dostępną przestrzeń chemiczną. Powyższe zalety wzbudziły duże zainteresowanie tym obszarem badań, prowadząc do gwałtownego rozwoju nowych metod dearomatyzacji, zwłaszcza w ciągu ostatnich trzech dekad. Wprowadzenie do niniejszej rozprawy skupia się na dwóch kluczowych strategiach w ramach tej szybko rozwijającej się dziedziny: utleniającej dearomatyzacji i nukleofilowej dearomatyzacji związków *N*-heteroaromatycznych. W przeglądzie literatury omówiono szczegółowo te dwa podejścia, w tym ich zalety syntetyczne, ustanawiając kontekst dla przedstawionych wyników badań oryginalnych. Ponadto we wprowadzeniu nakreślono podstawy elektrochemii organicznej, jako zrównoważonego i potężnego narzędzia syntezy organicznej. W szczególności omówiono jej rozwój historyczny, koncepcje teoretyczne i kluczowe parametry eksperymentalne.

W drugim rozdziale niniejszej pracy opisano zastosowanie elektrochemii organicznej do utleniającej dearomatyzacji, mające na celu wyeliminowanie szeregu ograniczeń charakteryzujących konwencjonalne procedury. Omówiono w nim nową metodę elektrochemicznej utleniającej *orto*-dearomatyzacji naftoli i fenoli, prowadzącą do wewnątrzcząsteczkowego tworzenia wiązania C–O. Warto zauważyć, że zakres stosowalności reakcji został rozszerzony o wolne arenole jako substraty, co stanowi istotny postęp w stosunku do wcześniejszych procedur elektrochemicznych, które zazwyczaj wymagają substratów zabezpieczonych w postaci eterów arylo-metylowych. Dzięki starannej optymalizacji warunków prowadzenia reakcji udało się zsyntetyzować z doskonałymi wydajnościami różnorodną gamę spirolaktonów i spiroeterów. Rekcja przebiega w prostych warunkach stałego natężenia prądu, w celi niepodzielonej, bez konieczności stosowania atmosfery ochronnej. To ekologiczne i zrównoważone podejście pozwala uniknąć stosowania katalizatorów chemicznych i stechiometrycznych utleniaczy, takich jak związki jodu hiperwalenycjnego, a jedynym produktem ubocznym jest wodór.

Trzeci rozdział dotyczy dearomatyzacji substratów *N*-heteroaromatycznych poprzez addycję nukleofilową. W szczególności opisuje on międzycząsteczkową reakcję Mority–Baylisa–

Hillmana (MBH) z wykorzystaniem soli *N*-benzylochinolinowych jako elektrofilii. Reakcja przebiega z wysoką selektywnością wobec pozycji C4 pierścienia chinolinowego, co stanowi odwrócenie regioselektywności wobec pozycji C2 obserwowanej poprzednio. Zmianę tę osiągnięto poprzez zamianę przeciwjonu w soli chinolinowej na PF_6^- oraz zmianę warunków prowadzenia reakcji, w szczególności poprzez zastosowanie DABCO jako katalizatora. Opracowana metoda umożliwia dostęp do produktów zawierających wiele grup funkcyjnych i syntetycznie ważny szkielet 1,4-dihydrochinoliny, co czyni ją komplementarną do wcześniejszych reakcji, generujących regioizomeryczne pochodne 1,2-dihydrochinoliny. Reakcja okazała się cechować dużą uniwersalnością, a zakres substratów został z powodzeniem rozszerzony o sole akrydynowe.

Słowa kluczowe: dearomatyzacja, elektrosynteza, utlenianie, spirolaktonizacja, spiroeteryfikacja, naftole, fenole, reakcja Mority-Baylisa-Hilmana, regioselektywność, sole chinolinowe, sole akrydynowe

List of Publications

This thesis is based on the following publications:

I. Electrochemical Dearomatizing Spirolactonization and Spiroetherification of Naphthols and Phenols
Sarvi Beigbaghlou, S.; Yafele, R. S.; Kalek, M. *Synthesis* **2023**, *55*, 4173-4180

II. C4-Regioselective Dearomatization of Quinolinium Salts via Morita-Baylis-Hillman Reaction
Yafele, R. S.; Bernard, R. S.; Pareek, A.; Kalek, M. *Eur. J. Org. Chem*., **2025**, *28*, e202500621

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Abbreviations

1,10-phen = 1,10-phenanthroline
3D = three-dimensional
Ac = acetyl group
Ar = aryl group
ATPH = aluminium tris(2,6-diphenylphenoxide)
aq.= aqueous
BDD = boron doped diamond
BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn = benzyl group
Boc = *tert*-butyloxycarbonyl group
Bpin = pinacolboryl group
Bu = butyl group
Cat = catalyst
Cbz = benzyloxycarbonyl
CCE = constant current electrolysis
COD = 1,5-cyclooctadiene
Cp* = pentamethylcyclopentadienyl ligand
CPME = cyclopentyl methyl ether
Cy = cyclohexyl group
DABCO = 1,4-diazabicyclo[2.2.2]octane
Dba = dibenzylideneacetone
DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene
DCC = *N,N'*-Dicyclohexylcarbodiimide
DCE = 1,2-dichloroethane
DCM = dichloromethane
DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFMS = difluoromethanesulfinate
DFT = density functional theory
DIBAL-H = diisobutylaluminium hydride
DMAP = 4-dimethylaminopyridine

DME = 1,2-dimethoxyethane
DMF = dimethylformamide
DMMS = dimethoxymethylsilane
DMSO = dimethylsulfoxide
DoE = design of experiment
dr = diastereomeric ratio
E^+ = electrophile
EDG = electron donating group
ee = enantiomeric excess
Et = ethyl group
eq. = equivalent
EWG = electron withdrawing group
FDA = Food and Drug Administration
Fc = ferrocene
FG = functional group
GF = graphite felt electrode
HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol
HOMO = highest occupied molecular orbital
HSAB = hard-soft acid-base
HTIB = hydroxy(tosyloxy)iodobenzene
***i*Pr** = isopropyl group
LDA = lithium diisopropylamide
LEDs = light-emitting diodes
L^n = ligand
LUMO = lowest unoccupied molecular orbital
M = any metal atom
MBH = Morita-Baylis-Hillman
***m*CBA** = *meta*-chlorobenzoic acid
***m*CPBA** = *meta*-chloroperoxybenzoic acid
Me = methyl group
Ms = methanesulfonyl group
MTAD = 4-methyl-1,2,4-triazoline-3,5-dione
MTBE = methyl *tert*-butyl ether
MW = microwave
NAD^+ = nicotinamide adenine dinucleotide
Na-DFMS = sodium difluoromethanesulfinate
NBS = *N*-bromosuccinimide

***n*Bu** = *n*-Butyl group
NCS = *N*-chlorosuccinimide
NDO = naphthalene dioxynease
NIS = *N*-iodosuccinimide
NMR = nuclear molecular resonance
Nu = nucleophile
NXS = *N*-halosuccinimide
PCA = principal component analysis
Ph = Phenyl group
Phth = Phthalimide group
PIDA = phenyliodine(III) diacetate
PIB = bis(pivalate)iodobenzene
PIFA = phenyliodine(III) bis(trifluoroacetate)
Piv = pivalic acid
Py = Pyridine
r*Aae*UPO = recombinant peroxygenase from *Agrocybe aegerita*
rt = room temperature
RVC = reticulated vitreous carbon
SDS = sodium dodecyl sulfate
SET = single electron transfer
SOMO = singly occupied molecular orbital
SP = sulfonated polystyrene
***t*Bu** = *tert*-butyl group
TBDMS = *tert*-butyldimethylsilyl group
TBDPS = *tert*-butyldiphenylsilyl group
Tc = thiophene-2-carboxylate
TEMPO = (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES = triethylsilyl group
Tf = triflyl group
TFA = trifluoroacetic acid
TFE = 2,2,2-trifluoroethanol
TFP = 3,3,3-trifluoropropanol
TFAA = trifluoroacetic anhydride
TFT = α,α,α-trifluorotoluene
THF = tetrahydrofuran
TLe = *tert*-Leucine amino acid
$^{5\text{-tips}3}$tpa = tris((5-(triisopropylsilyl)piridin-2-yl)methyl)amine

$^{(tips,NMe2)2}$pdp = 6,6'-([2,2'-bipyrrolidine]-1,1'-diylbis(methylene))bis(*N,N*-dimethyl-3-(triisopropylsilyl)pyridin-4-amine)

TIPS = triisopropylsilyl group

TMG = 1,1,3,3-tetramethylguanidine

TMS = trimethylsilyl group

Troc = 2,2,2-trichloroethoxycarbonyl

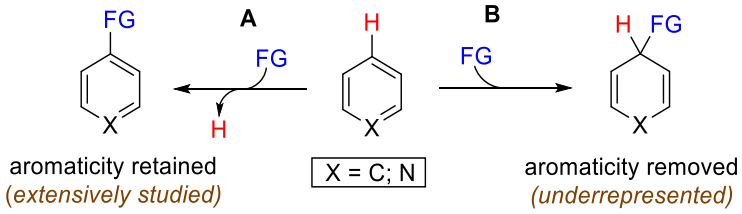
Ts = tosyl group

XPhos = dicyclohexyl[2′,4′,6′-tris(propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane

Chapter 1
Introduction

1.1. Brief Overview on the History and Development of Dearomatization

Aromatic compounds are ubiquitous in nature as evidenced by their presence in countless biomolecules and in some fossil fuels.[1–4] Many simple aromatic molecules, for example benzene, phenol, or pyridine, are mass produced annually.[5,6] As such, these compounds serve as a convenient and affordable raw material to chemists in both academia and industry.[1,7] Unsurprisingly, over the years the synthetic chemistry regarding their transformation has been exceedingly enriched. Such an enrichment can be predominantly attributed to the considerable advancements that have been made concerning protocols that are geared towards their functionalization. These protocols include aromatic substitution reactions that encompass name reactions such as the Friedel-Crafts reaction and the Sandmeyer reaction, which have been firmly established as useful tools in the synthesis of many libraries and natural products. The methodologies mentioned generally proceed well as the aromaticity of the ring system is retained (Scheme 1.1A).[5,7,8] Conversely, dearomatization, a process in which the substrate irreversibly losses its aromaticity after functionalization, was not as extensively represented for a long time (Scheme 1.1B). This is because permanently disrupting aromaticity is regarded as challenging on the account of the substrate's inherent resonance stabilization which renders it resistant to this manner of transformation. [6,9–11]



Scheme 1.1. General types of reactivity that aromatic compounds are classically known for: **A**) aromatic substitution and **B**) dearomatization reactions.

Nevertheless, the potential held by dearomatization processes to swiftly grant direct access to molecules with enhanced three-dimensional (3D) complexity from simple, abundant, and inexpensive planar substrates has not been overlooked.[1,12] Moreover, dearomatization products are typically reactive intermediates with which further synthesis can be performed on, thus, increasing the accessible chemical space.[9,13] Consequently, these striking features have aroused great interest in dearomatization, especially, in the synthesis of natural and bioactive compounds wherein more sophisticated molecular scaffolds are often desired. In addition, the push to develop novel methodologies to efficiently conduct dearomatization reactions was also considerably stimulated, and this growth in popularity and use for the technique has mainly transpired during the last three decades (Figure 1.1).[8]

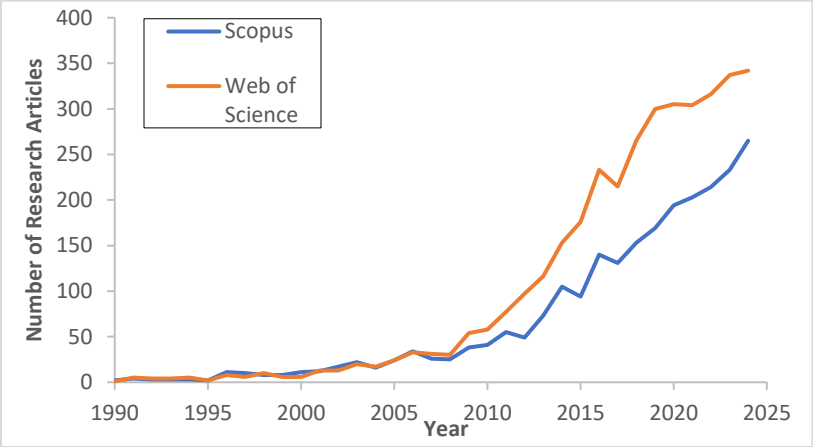
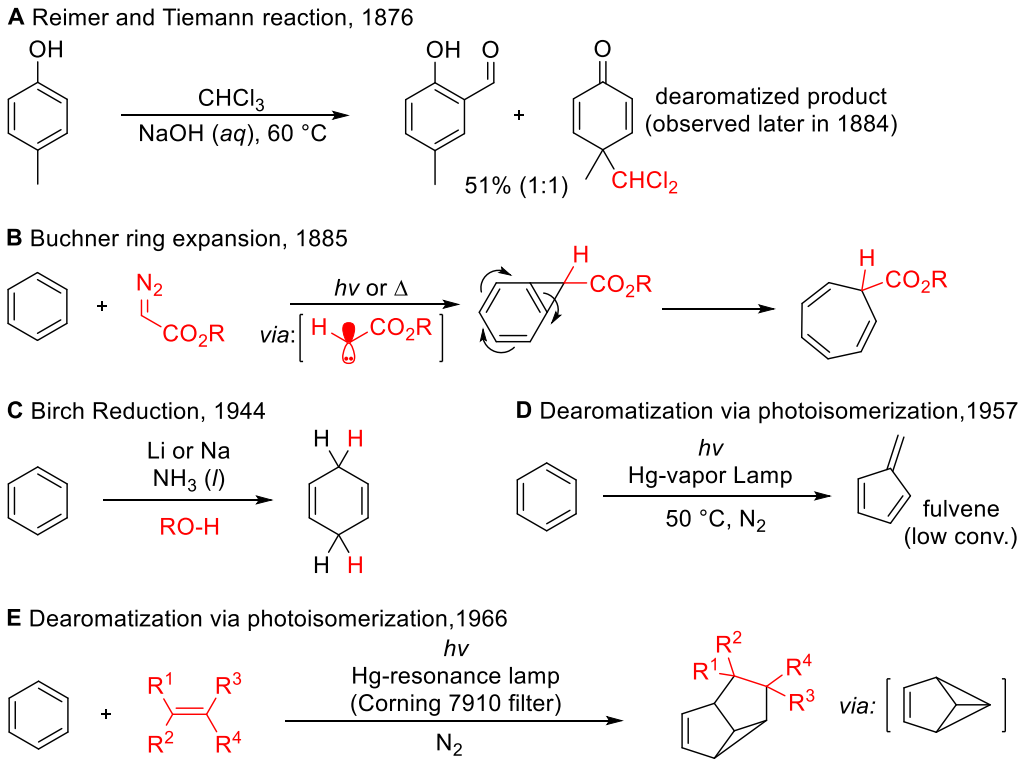


Figure 1.1. The growth in the number of research articles using the term ''dearomatization'' in the title, abstract, or as a keyword since the year 1990 according to scopus.com and webofscience.com.

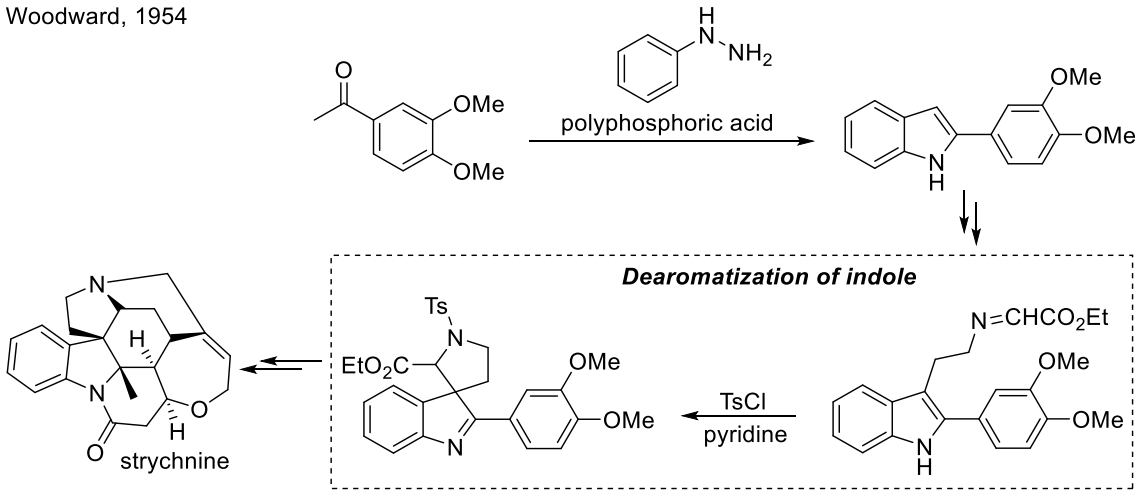
One of the earliest known dearomatization process was discovered by chance by Auwers when he carried out the Reimer-Tiemann reaction. This reaction had been originally discovered in 1876 to perform *ortho*-formylations on phenol until Auwers observed the dearomatized side product in 1884 (Scheme 1.2A).[14,15] The following year, another dearomatization reaction, now known as the Buchner ring expansion, was discovered by Buchner and Curtius. Herein, the benzene ring is expanded by coupling it with a carbene that is generated *in situ* from an alkyl diazoacetate to yield cycloheptatriene (Scheme 1.2B).[5,16] This reaction was initially carried out under high temperature or photochemical conditions but, in 1981, Teyssié and co-workers improved the protocol by employing rhodium(II) carboxylates as the catalytic promoters.[5,17] What is arguably the most famous among the classical dearomatization techniques, Birch reduction, was discovered in 1944 for the partial saturation of benzene to 1,4-cyclohexadiene. This technique often requires the use of an excess amount of the lithium or sodium metal, together with liquid ammonia at very low temperatures to produce solvated

electrons that drive the reaction (Scheme 1.2C).[18–20] The Birch reduction quickly became a vital tool, most famously in steroid synthesis, enabling the construction of the complex polycyclic frameworks central to hormones and other bioactive molecules. In 1957, Blair and Bryce-Smith made a report which outlined the treatment of benzene with irradiation from a mercury vapor lamp to produce fulvene. Regardless of the low conversion that was observed, their discovery was presumed to be "the first case of the direct isomerization of an aromatic hydrocarbon to a nonaromatic one" (Scheme 1.2D).[5,21] This discovery was quickly followed up by similar reports such as the photo-isomerization of substituted benzenes to generate prismane and benzvalene derivatives.[22] Moreover, studies on other photo-promoted dearomatization processes such as the cycloaddition reaction between benzene and alkenes were also set in motion (Scheme 1.2E).[23] Unfortunately, these early versions of photochemical dearomatizations were never development into useful methodologies because challenges with chemoselectivity could not be solved; more precisely, the reactions often resulted in a complex mixture of dearomatized products.

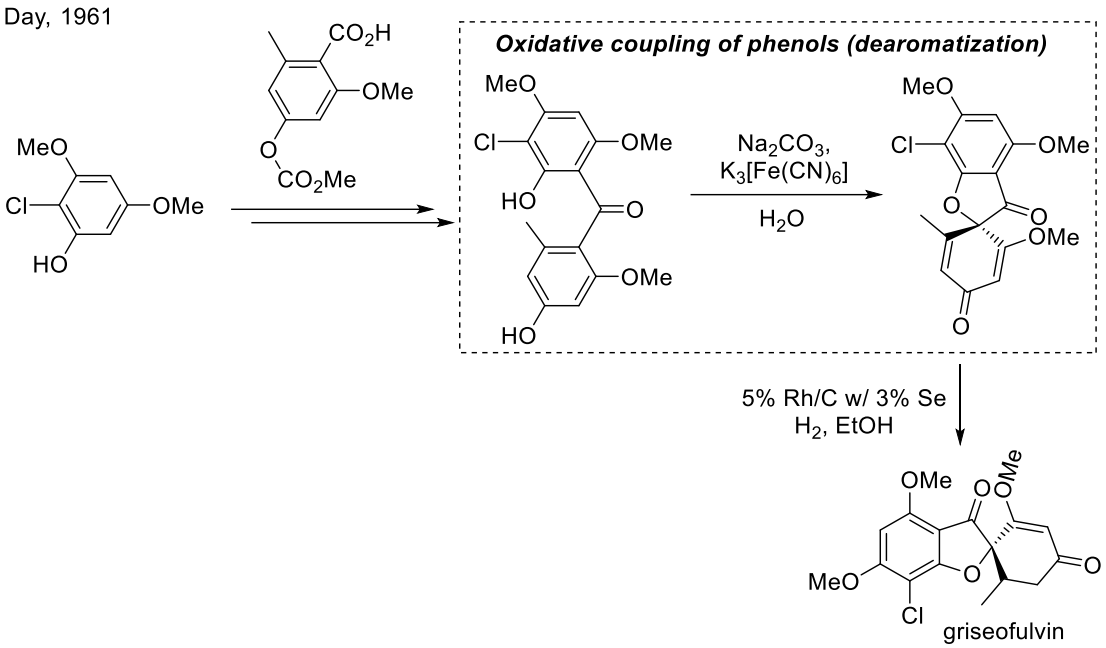


Scheme 1.2. The history of dearomatization reactions.

The prevalence of cyclic motifs as core features of natural products and other bioactive compounds was already well recognized by the 1950s.[24] This understanding justified the incorporation of dearomatization strategies into the total synthesis of such molecules. The approach was further supported by the fact that dearomatization significantly simplified the synthesis of these structurally complex targets. Put simply, acquiring, modifying, and subsequently dearomatizing aromatic precursors was often far easier than selectively functionalizing preformed alicyclic structures or constructing them *de novo*. [8,9,25,26] In this regard, in 1954, Woodward and co-workers reported on the total synthesis of the alkaloid strychnine. A crucial step of their synthesis involved the dearomatization of an indole core via a Pictet-Spengler type reaction which provided access to a critical section of the target molecule's polycyclic core.[27] (Scheme 1.3). This work highlighted dearomatization as a very capable synthetic tool that could be incorporated into more complex synthetic projects. In 1960, Day and co-workers provided another important account of the application of dearomatization in total synthesis. In this work, the synthesis of griseofulvin, an antifungal agent, was described. The key dearomatization step, wherein the oxidative intramolecular coupling of phenols was attained (Scheme 1.4), was inspired by the presumed natural biosynthetic pathway of the target compound.[28]

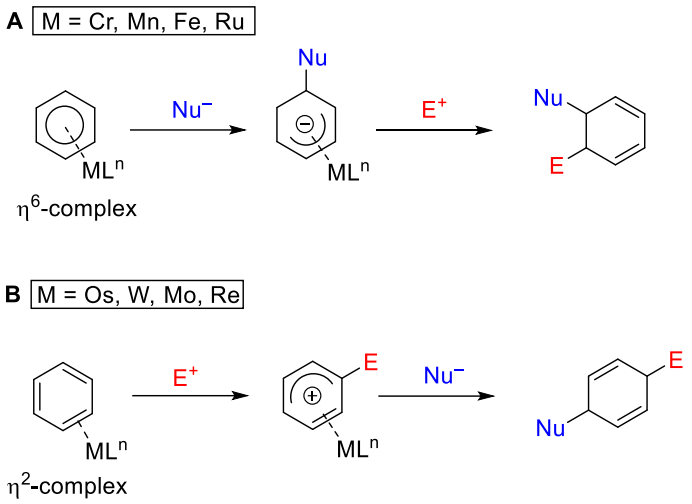


Scheme 1.3. Crucial dearomatization step in Woodward's synthesis of strychnine.



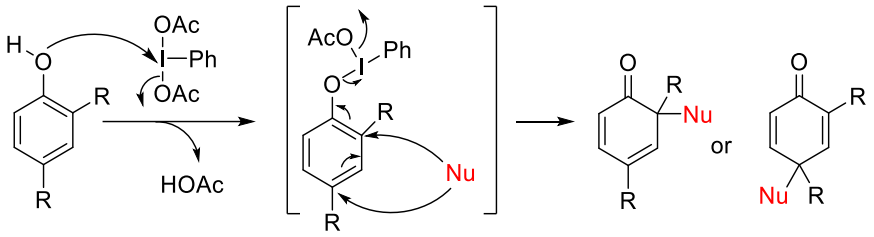
Scheme 1.4. Crucial dearomatization step in Day's synthesis of griseofulvin.

The success of Woodward and Day in incorporating dearomatization into their natural product syntheses further consolidated the merit of this transformation. Their work encouraged organic chemists to develop new dearomatization methodologies. Consequently, when transition metal-arene complexes emerged in the late 1950s,[29,30] it was quickly recognized that coordinating an aromatic ring to certain metal centers (e.g., Cr) activated it for nucleophilic attack. This newfound reactivity triggered the rapid discovery and exploration of various chemical transformations.[31–33] Some of these transformations involved electrophilic trapping of the electron-rich intermediates that were generated immediately after nucleophilic addition, thereby affording dearomatized products (Scheme 1.5A).[34–36] Alternatively, the η^2-coordination of arenes with metals like osmium increased their electron density and rendered them susceptible to dearomative reactions with electrophiles instead (Scheme 1.5B).[37,38] Unfortunately, achieving dearomatization in this manner required stoichiometric amounts of transition metal complexes, which naturally caused the eventual development of transition metal-catalyzed dearomatization processes.[39]



Scheme 1.**5.** Transition-metal mediated dearomatization.

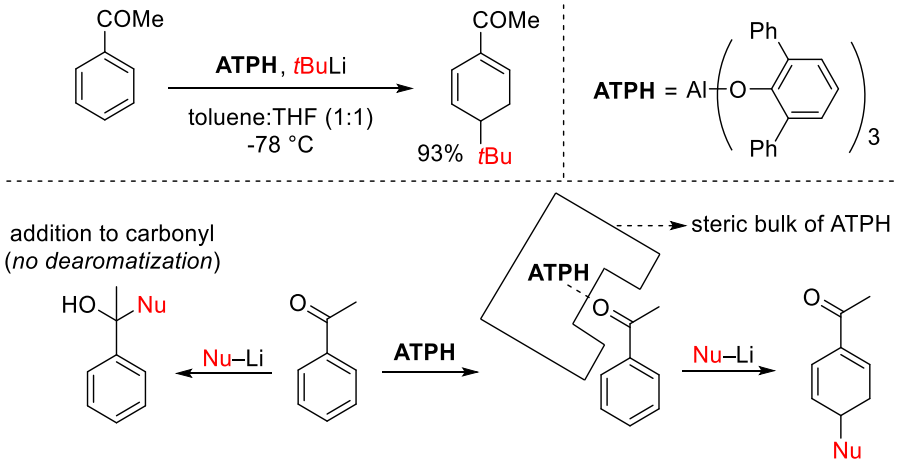
From the 1960s onwards, the development of dearomatization methodologies increasingly became more diverse. For example, hypervalent iodine(III) compounds had already gained traction as efficient oxidative dearomatization reagents of electron-rich phenols by the 1980s.[40,41] Phenolic substrates were oxidized with reagents like phenyliodine diacetate (PIDA) to generate highly reactive intermediates that were then captured by nucleophiles to provide cyclohexadienones, synthetically useful intermediates (Scheme 1.6).[42–45] Unlike the metal-derived oxidants or catalysts, e.g., the $K_3[Fe(CN)_6]$ that was used in Day's griseofulvin synthesis, hypervalent iodine reagents offered improved selectivity and could be utilized at milder reaction conditions. These reagents were also perceived as metal-free alternatives which added to their prominence in this field.[30,42,46]



Scheme 1.6. Dearomative oxidation of phenols with PIDA.

Other innovative approaches have exploited steric effects to enable dearomatization via nucleophilic addition, as exemplified by the work of Yamamoto and co-workers in 1995 (Scheme 1.7).[47] In this study, the use of a sterically demanding Lewis acid, aluminium tris(2,6-diphenylphenoxide) (ATPH), facilitated the dearomatization of an aromatic ketone substrate (e.g., acetophenone) which was realized via nucleophilic addition of a carbanion (e.g.,

organolithium reagents; *t*BuLi) at the *para*-position. From the 1990s to the present day, dearomatization has been effectively achieved through a diverse array of methodologies, including electrochemistry,[1] biocatalysis (e.g., with enzymes or microorganisms),[48,49] hydrogenation reactions,[50] and both nucleophilic[51] and electrophilic additions[52]. This broad applicability continues to solidify dearomatization as a powerful and versatile synthetic tool in organic chemistry.



Scheme 1.7. ATPH-enabled dearomatization via nucleophilic addition.

1.2. Oxidative Dearomatization of Carbocyclic Arenes

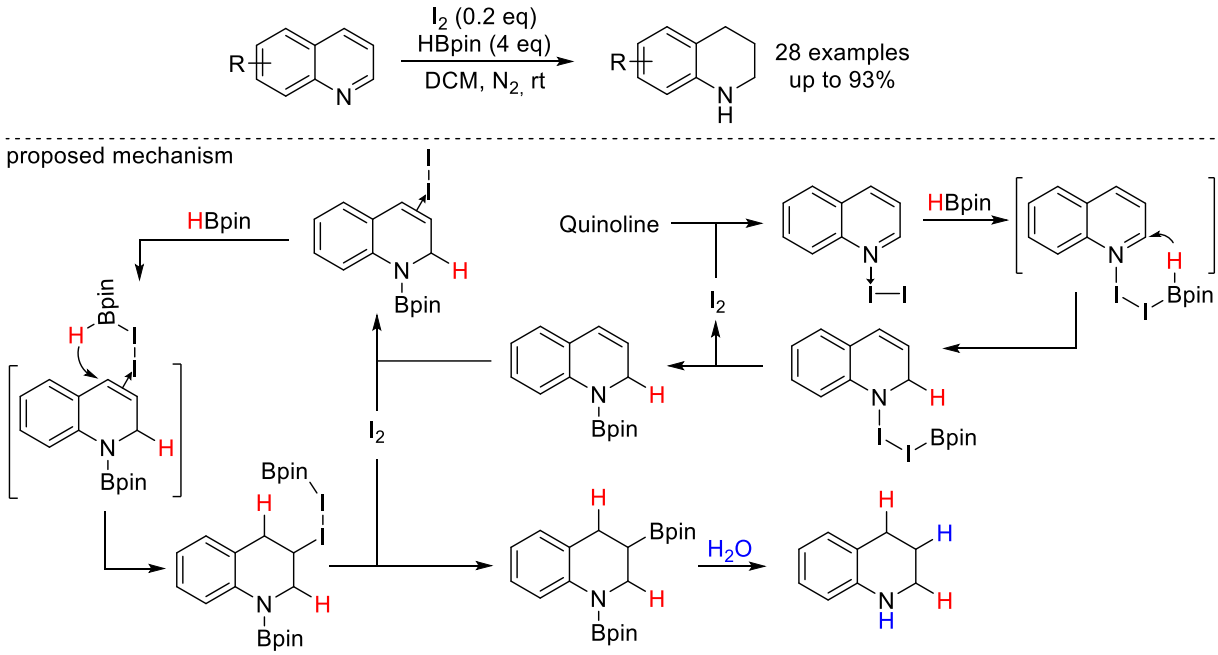
As outlined in the previous section, despite the inherent stability of aromatic systems, numerous dearomatization methods have been developed over the last two centuries. These methods can be classified into distinct categories based on how the process is initiated, with reductive and nucleophilic dearomatization being prominent examples. While each area of dearomatization warrants a detailed discussion, this section will be limited to oxidative dearomatization, due to its relevance to the subject of this thesis. In this approach, the loss of aromaticity is typically accompanied by the formation of one or more new C−O, C−N, or C−C bonds, which requires an irreversible oxidation event. The oxidation generates highly reactive intermediates, such as radical ions or arenium ions, *in situ*. These intermediates subsequently react with available nucleophiles or other suitable substrates, resulting in bond formation and yielding the final dearomatized product. The conversion of a high-energy oxidant into its more stable reduced form, combined with the new bond-formation, provide the thermodynamic

driving force required to overcome the aromatic stabilization, thereby enabling access to valuable products from aromatic precursors.[53]

1.2.1.Azaarene Dearomatization enabled by Lewis Acid Activation

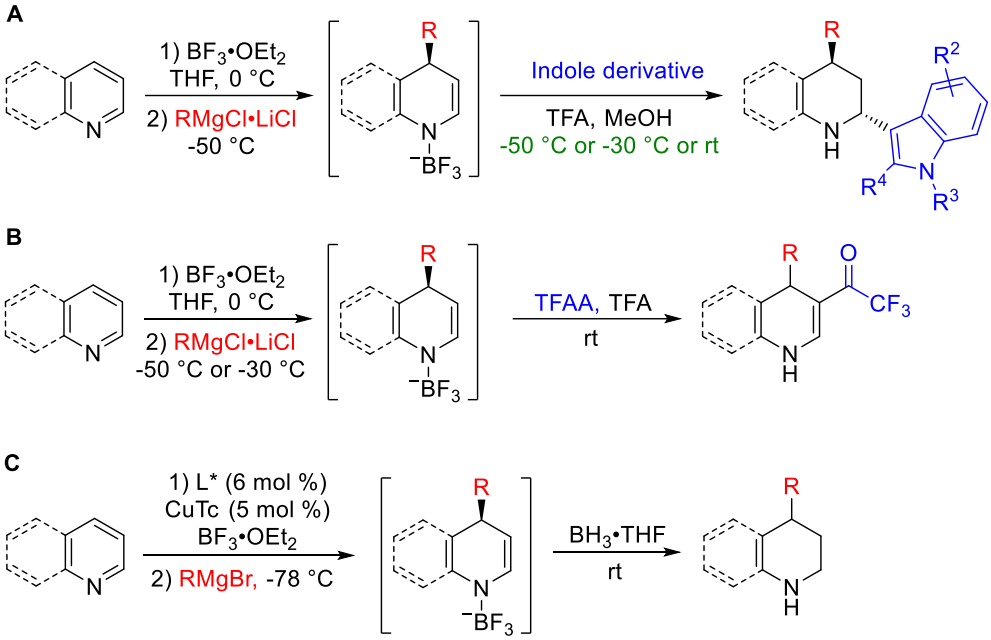
The use of Lewis acids as transient *N*-activators of azaarenes for their nucleophilic dearomatization has also been explored. For instance, in 2018, Chang, Yang, and co-workers employed molecular iodine (I_2) as a Lewis acid catalyst in their conversion of quinolines to 1,2,3,4-tetrahydroquinolines, using pinacolborane (H–Bpin) as the hydride source (Scheme 1.44).[142] The reported reaction conditions were mild, provided good yields, and exhibited broad functional group compatibility. This protocol also successfully reduced other azaarene substrates, including isoquinoline, acridine, 1,10-phenanthroline, and quinoxaline.

The authors proposed a plausible mechanism based on their NMR experiments and previously reported studies. Accordingly, the process begins with the activation of the quinoline substrate by I_2 via complexation at the nitrogen atom. This is followed by a hydride transfer from H–Bpin to the complex, which likely occurs via iodine-boron interactions and is accompanied by the trapping of the borenium ion released after B–H bond cleavage. Next, the borenium ion shifts from the iodine to the substrate's nitrogen atom, which regenerates the I_2 catalyst and produces a 1,2-dihydroquinoline intermediate. I_2 then coordinates to the intermediate's C=C bond, forming a new complex. A second sequence of hydride transfer and borenium transfer, analogous to the first, converts this complex into a 1,2,3,4-tetrahydroquinoline bearing two borane groups. Finally, hydrolysis of this complex yields the final product.



Scheme 1.44. Iodine catalyzed dearomatization of quinolines.

In 2019, Wang and co-workers employed boron trifluoride etherate ($BF_3 \cdot OEt_2$) as a Lewis acid mediator in a one-pot dearomative double nucleophilic addition to quinolines and pyridines.[143] In this protocol, the first step involved the addition of a Grignard reagent to a $BF_3 \cdot OEt_2$-activated azaarene, followed by a second nucleophilic addition of an indole derivative under acidic conditions, affording tetrahydro-products (Scheme 1.45A). Preliminary investigations using sodium borohydride, methanol, trimethylsilyl cyanide, and pyrrole as secondary nucleophiles further demonstrated the potential for a broader substrate scope. The same group later developed a related protocol, also relying on $BF_3 \cdot OEt_2$ for substrate activation. In this case, partial saturation of quinolines or pyridines was achieved through nucleophilic addition of a Grignard reagent. The resulting dihydro-intermediates were subsequently functionalized in one pot at the C3 position with a trifluoroacetyl group, yielding push–pull enone products (Scheme 1.45B).[144] In 2020, Harutyunyan and co-workers reported a similar strategy that combined $BF_3 \cdot OEt_2$ activation with a chiral copper catalyst and a Grignard reagent.[145] This synergistic system provided chiral tetrahydroquinoline products with excellent enantioselectivity, reaching an average *ee* of 98% across 25 examples (Scheme 1.45C).



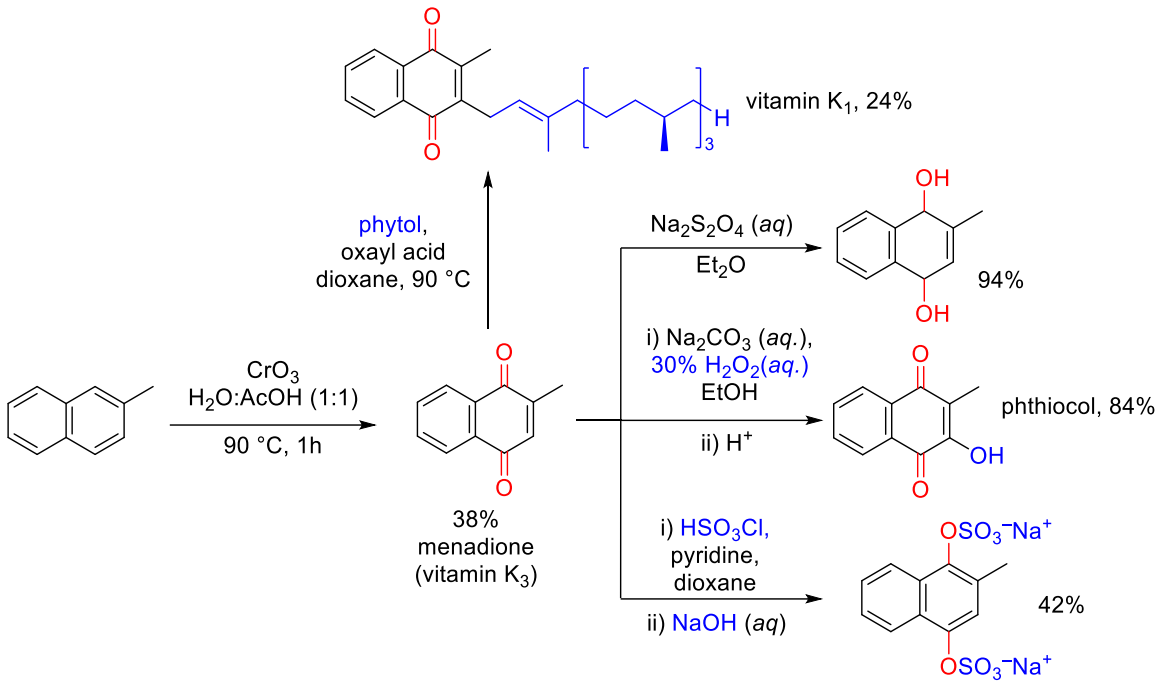
Scheme 1.45. $BF_3 \cdot OEt_2$ mediated dearomatization of quinolines.

1.2.2. Oxidative Dearomatization of Non-functionalized Hydrocarbons

Non-functionalized aromatic hydrocarbons, such as benzene, are difficult to dearomatize due to their substantial resonance energy. Consequently, their dearomatization often requires either the application of harsh conditions or the initial weakening of their aromaticity by extending the π-system, as seen in polycyclic derivatives like naphthalene and anthracene. Nevertheless, oxidative dearomatization presents an effective method for this substrate class. Accordingly, many diverse examples have emerged in over the years, some of which will be discussed below.[54]

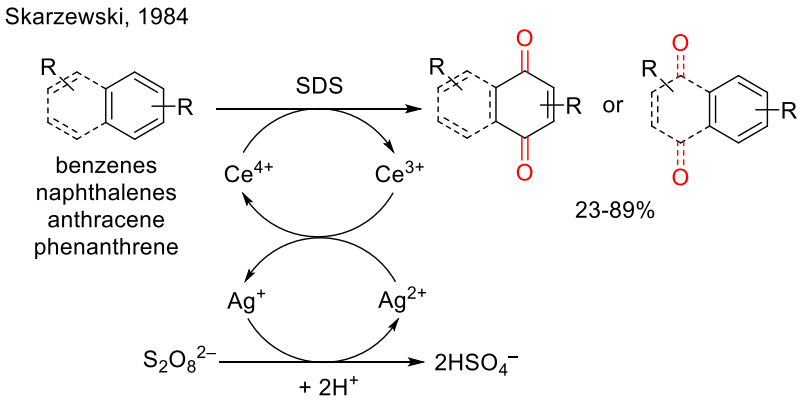
A practical procedure for the preparation of menadione (vitamin K_3) via the oxidative dearomatization of 2-methylnaphthalene was reported by Fieser in 1940.[55] The method employed chromium trioxide in an aqueous acetic acid medium. Menadione obtained from this process served as a key intermediate for the synthesis of phthiocol, vitamin K_1, and other menadione analogs (Scheme 1.8). An alternative version of the methodology was introduced by Palomo and co-workers in 1984, utilizing a crown ether (18-crown-6) solvent system.[56] This protocol efficiently oxidized various simple polycyclic aromatics, including naphthalenes, anthracenes, and phenanthrenes, into their corresponding quinones, with yields ranging from 50% to 98%. Additionally, a few activated benzenes (e.g., substituted phenols) were

successfully dearomatized under similar conditions, achieving more consistent yields in the range of 79% to 85%. However, the use of large quantities of chromium trioxide posed significant environmental and safety concerns, particularly due to the need for extensive wastewater treatment. As a result, by the 1980s, industrial-scale quinone synthesis via oxidative dearomatization largely shifted toward the use of hydrogen peroxide (H_2O_2)-based systems as more sustainable and environmentally benign alternatives.[57,58]



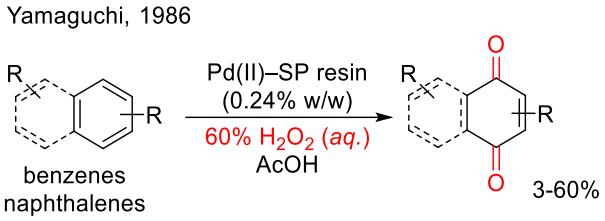
Scheme 1.8. Chromium(VI) oxide-mediated dearomative oxidation of 2-methyl naphthalene.

To address the environmental drawbacks of stoichiometric chromium-based oxidants, catalytic methodologies were developed to reduce the burden associated with wastewater treatment. In 1984, Skarżewski reported a catalytic oxidative dearomatization of anthracene, phenanthrene, naphthalene, and benzene derivatives using a Ce(III)/Ce(IV) redox cycle in a sodium dodecyl sulfate (SDS)-enriched aqueous medium.[59] The system employed ammonium peroxydisulfate ($(NH_4)_2S_2O_8$) as the terminal oxidant and silver nitrate ($AgNO_3$) as a co-catalyst (Scheme 1.9).



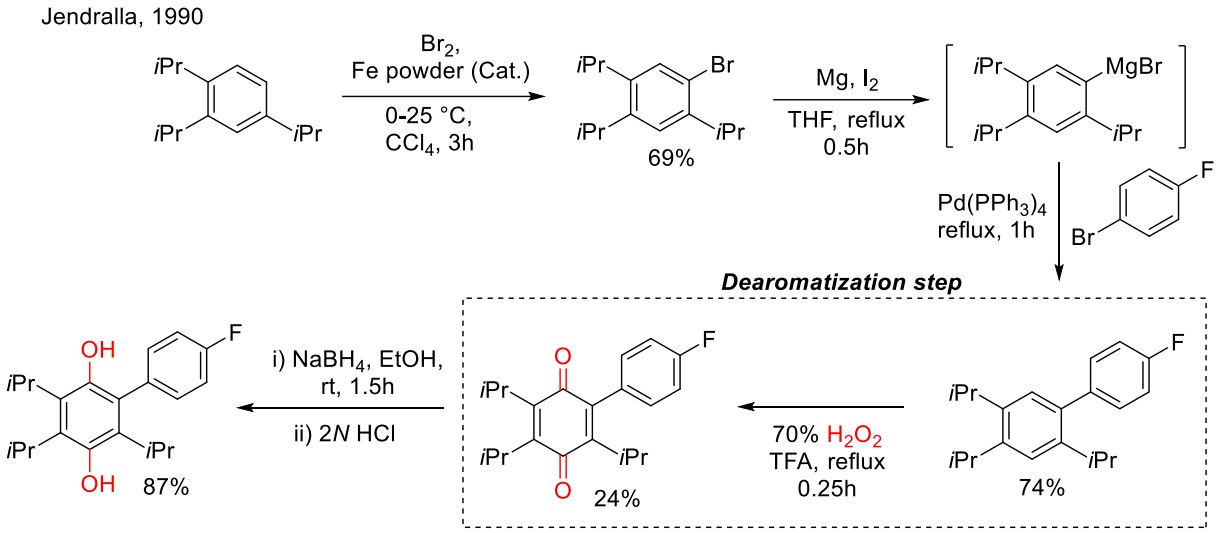
Scheme 1.9. Ce(III)/Ce(VI) catalyzed dearomatization of aromatic carbocycles.

In 1986, Yamaguchi and co-workers described the oxidative dearomatization of substituted benzenes and naphthalenes using palladium(II) acetate immobilized on a sulfonated polystyrene-type (SP) resin.[60] The reaction was carried out in acetic acid, with hydrogen peroxide serving as the terminal oxidant to regenerate the Pd(II) catalyst. This setup facilitated the easy recovery of the catalyst and enabled its reuse across multiple batches (Scheme 1.10).



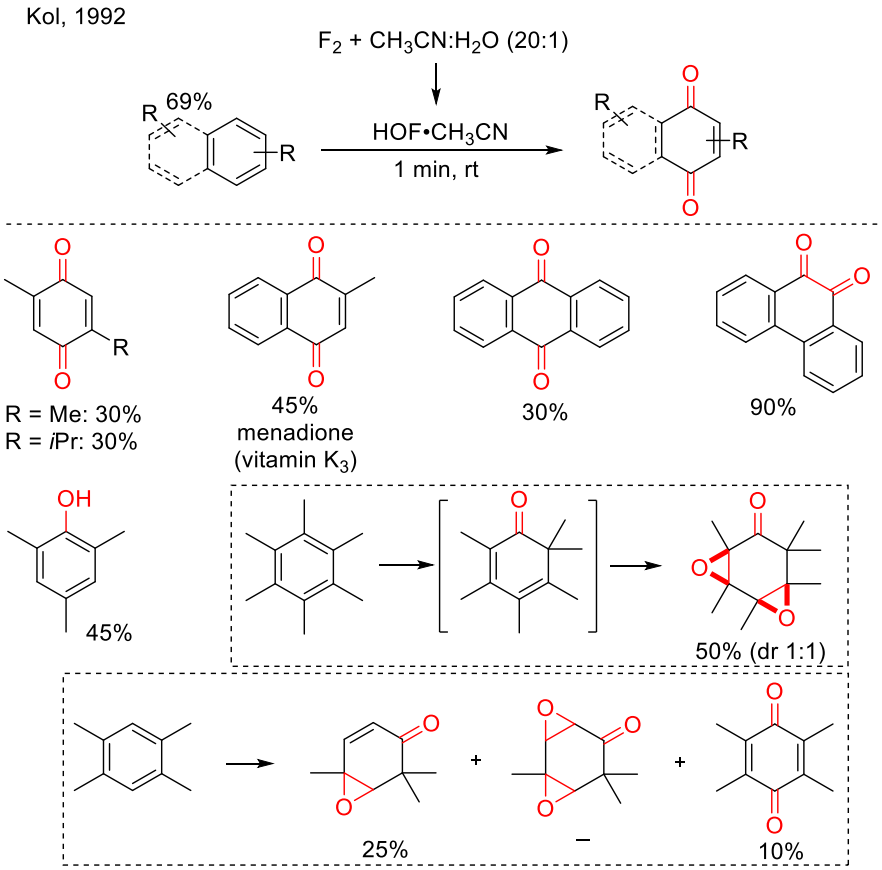
Scheme 1.10. The application of immobilized Palladium for the dearomatization of aromatic carbocycles.

A metal-free variant was reported in 1988 by Orita et al., who employed only hydrogen peroxide in acetic acid to oxidize methyl-substituted and methoxy-activated benzenes.[61] Although substrate conversion was generally high, the yields and selectivity of the desired quinone products were inferior to those obtained from metal-catalyzed methods. Moreover, when electron-withdrawing substituents were present, the reaction predominantly yielded phenols rather than quinones. A related peroxide-based method was described by Jendralla and Chen in 1990, in the context of biaryl synthesis via arylation.[62] In this case, trifluoroacetic acid (TFA) was employed in place of acetic acid, enabling oxidative transformations without the use of metals (Scheme 1.11).



Scheme 1.11. Metal-free dearomatization of aromatic carbocycles with H_2O_2.

In 1992, Kol and Rozen reported a metal-free protocol for the oxidative dearomatization of selected aromatic carbocycles to quinones (Scheme 1.12).[63] The oxidant employed was a mixture of hypofluorous acid with acetonitrile (HOF·CH_3CN), which is notable for being the only reagent known to possess a truly electrophilic oxygen atom. Owing to this unique property, the reagent enables highly efficient oxygen transfer reactions, even with relatively unreactive substrates, and under ambient conditions.[64] However, due to its high reactivity, the oxidation protocol was limited to a runtime of only one minute to avoid the formation of tars. Despite the briefness of the reaction, the method successfully afforded the desired quinones, albeit in low to moderate yields. Interestingly, oxidation of 1,3,5-trimethylbenzene resulted exclusively in the formation of the corresponding phenol. In the cases of hexamethylbenzene and 1,2,3,5-tetramethylbenzene, the reaction led to methyl group migration, and the oxidation products also exhibited epoxidation of the alkene moieties present in the resulting quinones. On one hand, the use of HOF·CH_3CN as an oxidant is appealing from a sustainability perspective, as its complete consumption leaves behind only acetonitrile. The stoichiometric amount of hydrogen fluoride (HF) generated during the reaction can be readily neutralized with a suitable base, rendering the overall process moderately "green." On the other hand, the preparation of HOF·CH_3CN requires elemental fluorine (F_2), a highly toxic and extremely reactive gas. Consequently, many chemists are hesitant to adopt this methodology in routine synthesis due to significant safety concerns associated with handling F_2.[64]

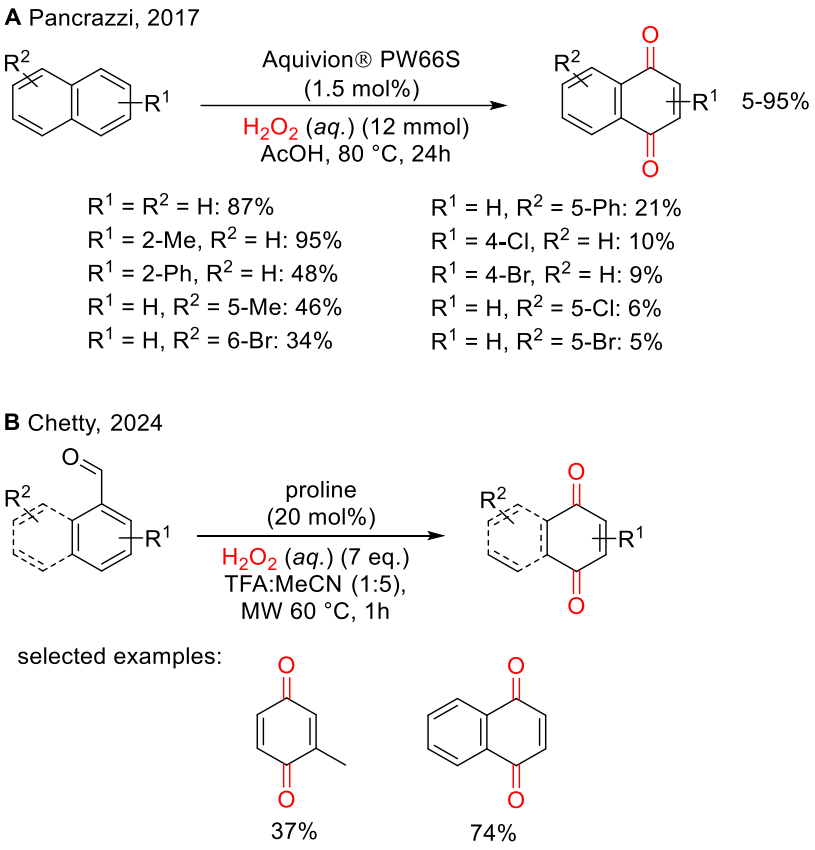


Scheme 1.12. HOF·CH_3CN as an effective oxidative agent in the dearomatization of aromatic carbocycles.

A more recent example of metal-free arene oxidation leading to quinone formation was reported in 2017 by Pancrazzi et al.[65] In this work, a polymeric perfluorinated sulfonic acid (Aquivion® PW66S) immobilized on silica was employed as a heterogeneous catalyst for the H_2O_2-mediated oxidation of aromatic substrates. As in Orita's 1988 study,[61] this methodology emphasized waste minimization: water was the sole by-product, and the solid-supported Aquivion catalyst enabled facile recovery and reuse. While the system was primarily effective with activated phenol substrates, it also showed good reactivity with substituted naphthalenes bearing methyl, phenyl, or halogen groups (Scheme 1.13A).

In 2024, Chetty and co-workers advanced H_2O_2-based oxidation systems by introducing a catalytic amount of proline under microwave irradiation in an acidic solvent.[66] The role of proline was proposed to involve activation of hydrogen peroxide through hydrogen-bond donation, thereby facilitating the oxidation process. The reaction proved highly efficient, with short reaction times ranging from 30 minutes to 1 hour. While most substrates were activated phenols and naphthols, a particularly noteworthy finding was the successful oxidative

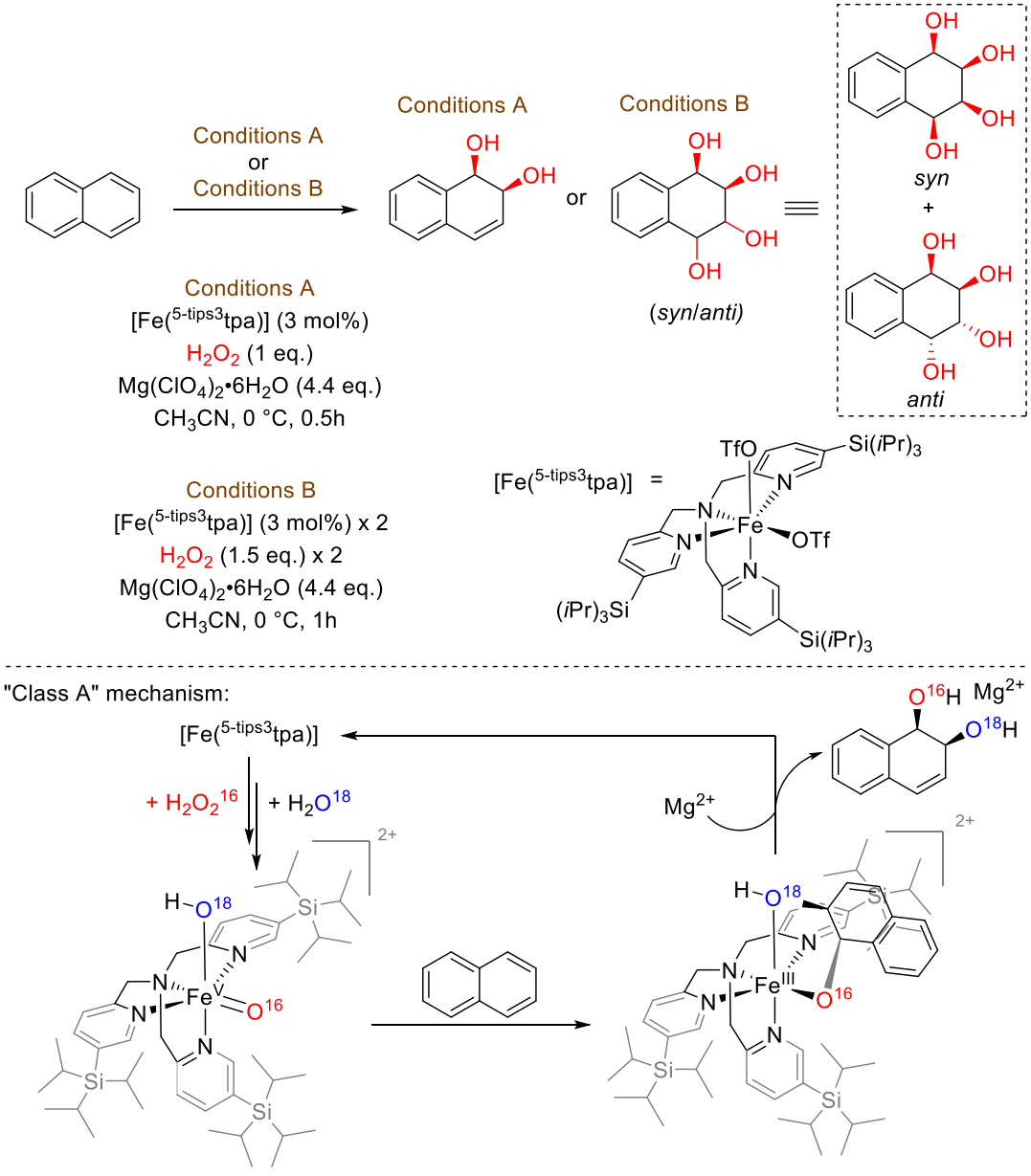
dearomatization of aromatic aldehyde, an uncommon and synthetically valuable transformation (Scheme 1.13B).



Scheme 1.13. Metal free dearomatization of aromatic carbocycles with H_2O_2 in presence of a catalytic amount of (**A**) Aquivion PW66S or (**B**) proline.

Recently, Afailal and co-workers reported an iron-catalyzed dearomative *syn*-dihydroxylation of naphthalene and its derivatives.[67] The reaction was conducted in the presence of a Lewis acid, using hydrogen peroxide (H_2O_2) was used as the terminal oxidant. The catalyst, [Fe($^{5-tips3}$tpa)], was designed to emulate the reactivity of the bacterial enzyme naphthalene dioxygenase (NDO). The methodology proved to be effective for a broad range of substrates, achieving moderate to good yields with naphthalenes bearing either electron-donating or electron-withdrawing substituents (Scheme 1.14). Notably, oxidation preferentially occurred on the unsubstituted aromatic ring. The initial dihydroxylation generated an olefinic intermediate that was susceptible to a second dihydroxylation. Consequently, the researchers developed conditions to enable selective access to either mono-dihydroxylated diols or fully bis-dihydroxylated tetraols.

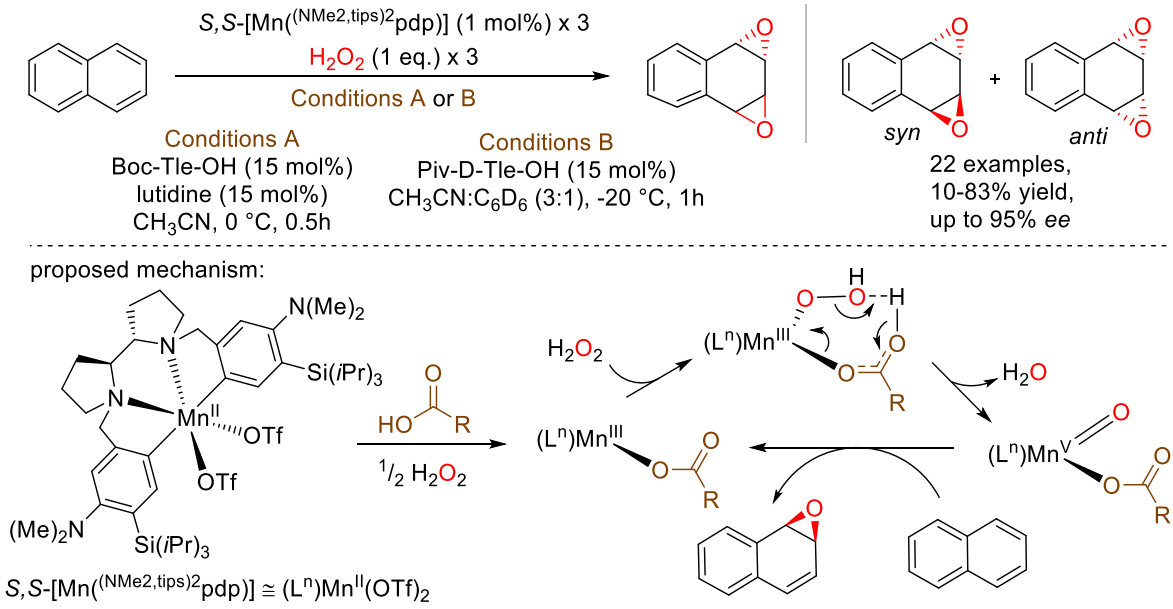
Mechanistic studies using isotopically labeled oxygen revealed that the transformation proceeded via a highly electrophilic $[L^{N4}Fe^{V}(O)(OH)]^{2+}$ intermediate. This finding supports a "Class A" mechanism that was previously established in alkene dihydroxylation with the same iron catalyst.[68] The generation of this high-valent iron-oxo species is key to overcoming the aromatic stability of the naphthalene ring and enabling dearomatization.



Scheme 1.14. Iron catalyzed dearomative di- and tetrahydroxylation of aromatic carbocycles.

Afailal and co-workers followed this up with a report on the enantioselective dearomative epoxidation of naphthalenes and its derivatives with a manganese-catalyst and aqueous hydrogen peroxide as the oxidant, in the presence of an *N*-protected amino acid additive

(Scheme 1.15).[69] This manganese-catalyst strongly resembled the iron-catalyst, [Fe($^{5-tips3}$tpa)], that was previously employed in the *syn*-hydroxylation described above. Furthermore, structurally comparable manganese catalysts bearing an aminopyridine tetradentate ligand have been applied in the enantioselective epoxidation of olefins and in the oxidation of aliphatic C–H bonds.[70,71,71–76] In this regard, the researchers rationalized that their Mn-catalyst would promote an oxidative pathway that would also be similar to the established reactivity of the related Mn-complexes in these previous reports. In particular, it was hypothesized that the crucial mechanistic step where dearomatization is accomplished also likely involved a strongly oxidising, highly electrophilic and high-valent manganese(V)-oxo species. This logic guided them in their development of two different conditions that rendered diepoxides from naphthalene substrates in moderate to good yields and excellent enantioselectivities of up to 95% *ee*. Similar to the *syn*-dihydroxylation with [Fe($^{5-tips3}$tpa)], an initial epoxidation event generated a reactive olefin that was subsequently epoxidized to produce the desired product. However, unlike the *syn*-dihydroxylation reaction, *anti*-diepoxidation was favored. Another benefit was that the established conditions required very low temperatures and completed within an hour, which probably inhibited the decomposition of the epoxide products which are notorious for being highly reactive.



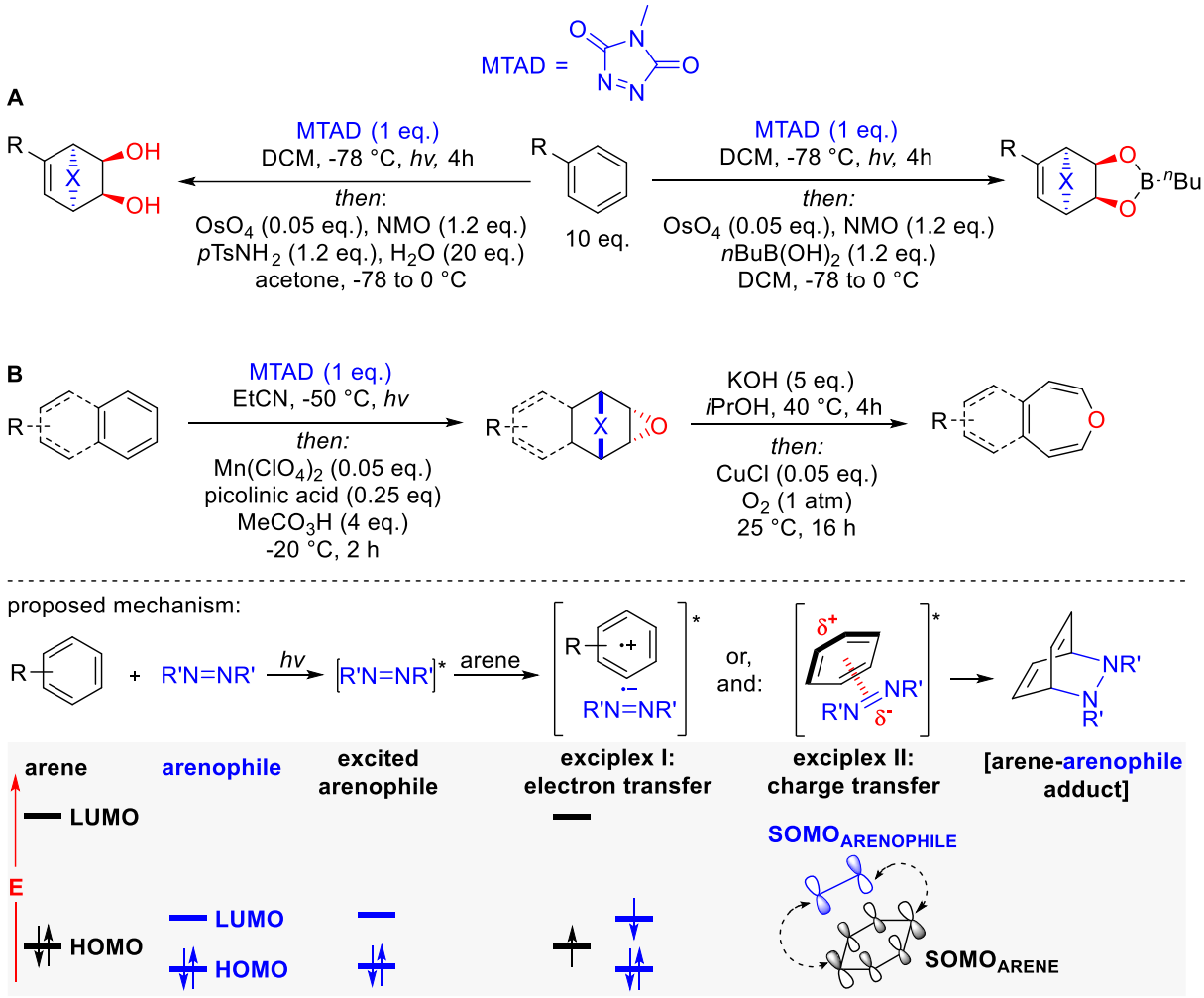
Scheme 1.15. Manganese catalyzed dearomative epoxidation of aromatic carbocycles.

As previously mentioned, the dearomatization of non-functionalized aromatic hydrocarbons often requires forceful conditions. Although effective, these harsh approaches can lead to issues

such as overreaction and decomposition. This problem arises because the powerful reagents used tend to react preferentially with the highly reactive dearomatized products over their less reactive parent arenes.[77]

A fruitful approach that avoids this issue is the use of photoactivable 2π-components known as 'arenophiles'. These compounds react with arenes in a *para*-cycloaddition, a process reminiscent of thermal cycloadditions. The resulting arene-arenophile cycloadduct can then be subjected to various functionalization techniques, including olefin-based reactions and transformations catalyzed by transition metals. These functionalizations can be followed by the cycloreversion or fragmentation of the arenophile group to yield the final dearomatized products.[10,77–79] This concept was demonstrated by Southgate and co-workers in 2016. In their work, they used the arenophile 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) in tandem with an osmium-catalyzed dihydroxylation to selectively transform aromatic hydrocarbons into their corresponding dearomatized dihydrodiols or boronate esters in a single pot (Scheme 1.16A).[77] Later, in 2020, the same group paired this MTAD-mediated dearomatization platform with manganese-catalyzed epoxidation to access arene oxides and oxepines (Scheme 1.16B).[80]

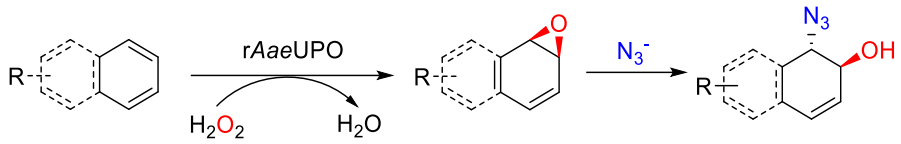
Although the mechanism is not yet fully understood, it is proposed to proceed through the formation and collapse of two distinct exciplexes (Scheme 1.16). Crucially, the provided light energy is sufficient to excite only the arenophile. This selectivity arises because its highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are lower in energy and have a smaller gap compared to those of the arene. Furthermore, this proposed pathway implies an important electronic prerequisite. Specifically, the energies of both the arenophile's HOMO and LUMO must lie within the energy range of the arene's HOMO.[10,77,78]



Scheme 1.16. Arenophile-mediated dearomative oxidation reactions. (**A**) Dearomative dihydroxylation. (**B**) Dearomative epoxidation.

Enzymatic oxidation also represents a powerful biocatalytic strategy for achieving dearomatization. These reactions predominantly feature epoxidation and *cis*-dihydroxylation, which are typically catalyzed by cytochrome-type monooxygenases/peroxygenases and bacterial dioxygenases, respectively.[81,82] A recent example of enzymatic epoxidation was demonstrated by Zhang and colleagues in 2019.[83] In their work, a recombinant peroxygenase from *Agrocybe aegerita* (r*Aae*UPO) was used to catalyze the dearomative epoxidation of naphthalene in a buffered hydrogen peroxide (H_2O_2) solution (Scheme 1.17). A recurring challenge in this transformation is the notorious instability of the resulting epoxide intermediates. To overcome this, the researchers introduced a novel approach by performing a sequential, one-pot nucleophilic ring-opening of the epoxide with an azide. This strategy

effectively trapped and isolated the otherwise transient dearomatized product. While epoxidation is effective, *cis*-dihydroxylation is a more frequently reported pathway for enzymatic dearomatization. A classic example was reported by Jenkins et al. in 1995, where they achieved the oxidative dearomatization of electron-poor benzoic acid by employing a benzoate dioxygenase.[84]

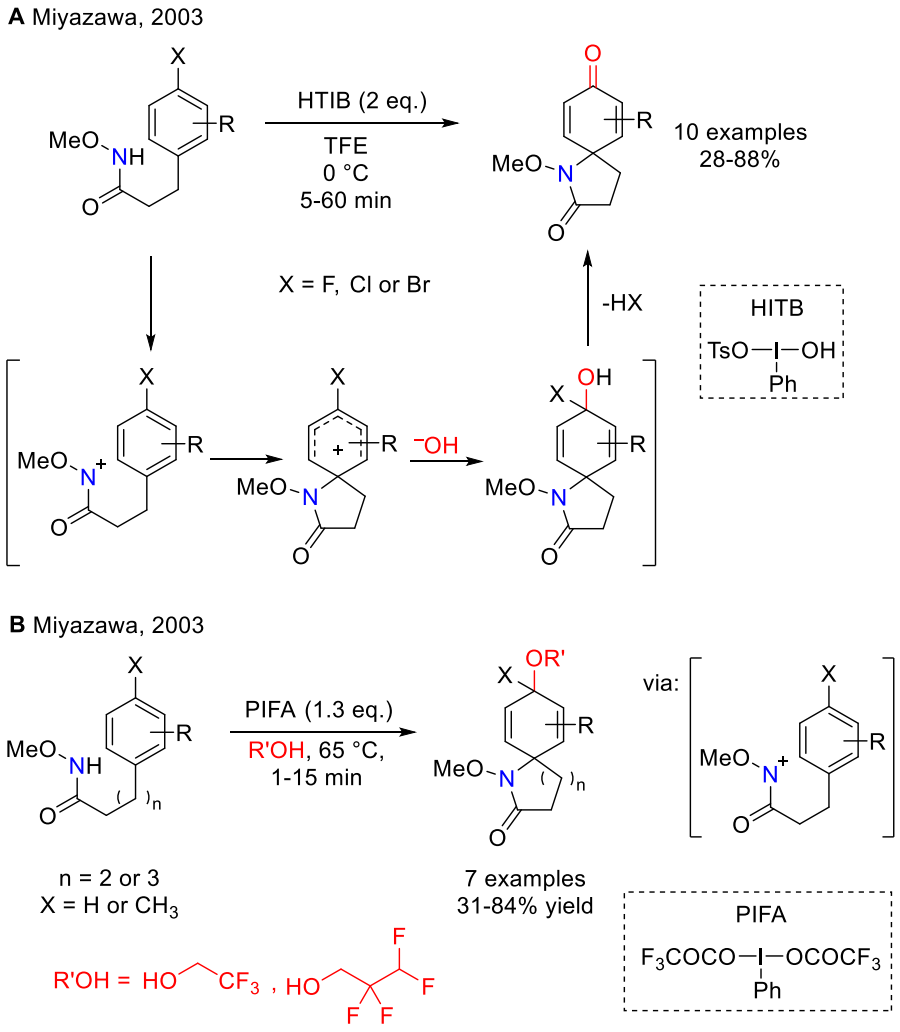


Scheme 1.17. Enzyme catalyzed dearomative epoxidation of naphthalene coupled with a ring-opening reaction.

1.2.3. Oxidative Dearomatization Leading to Cyclic Molecular Frameworks

1.2.3.1. *Nitrenium Ion Mediated Dearomatization*

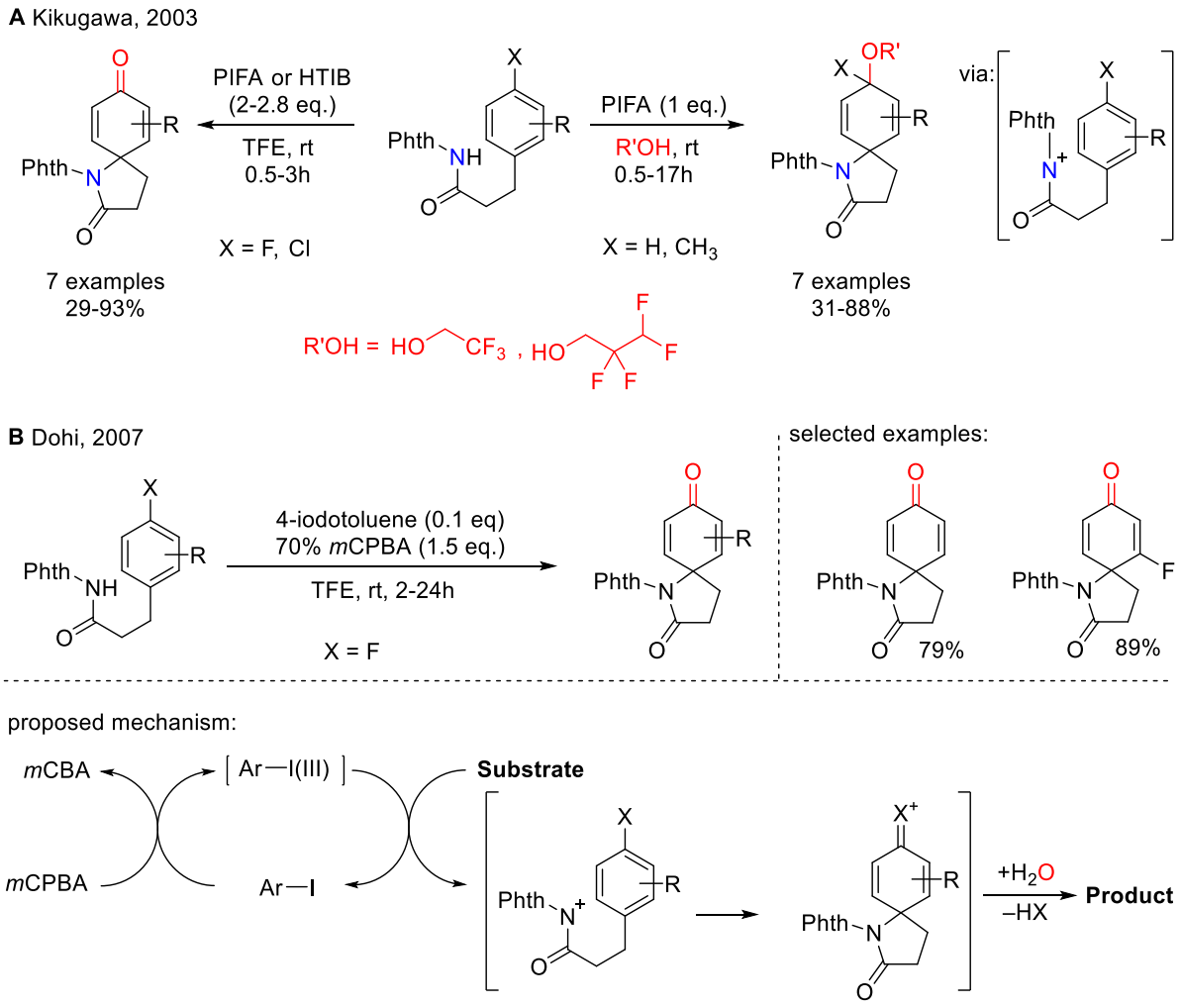
The oxidative dearomatization of non-activated arenes provides a powerful route to complex cyclic products like spirocycles. This strategy has been explored and refined by several research groups. In 2003, Miyazawa and co-workers reported the synthesis of the 1-azaspiro[4.5]decane framework through an oxidative spirocyclization of haloarenes (Scheme 1.18A).[85] The key step was an intramolecular *ipso*-attack by a tethered *N*-acylnitrenium ion. This electrophilic intermediate was generated by oxidizing the starting *N*-methoxyamide with the hypervalent iodine(III) reagent hydroxy(tosyloxy)iodobenzene (HTIB**)**, also known as Koser's reagent. The method successfully produced the desired spirocycles from at least ten haloarenes with yields of up to 88%. Later that year, the same group showed that phenyliodine(III) bis(trifluoroacetate) (PIFA) could also mediate the reaction (Scheme 1.18B).[86] While their substrate scope included anisole derivatives, seven non-activated arenes were also tested. Interestingly, these non-activated substrates yielded 2,5-cyclohexadiene products rather than the corresponding 2,5-cyclohexadienones.



Scheme 1.18. Early examples of the synthesis of spiro[4.5]dienones via nitrenium ion intermediates.

Also in 2003, Kikugawa's group expanded this methodology by replacing the *N*-methoxyamide with an *N*-acylaminophthalimide group, which they proposed would further stabilize the nitrenium ion intermediate (Scheme 1.19A).[87] Their work established conditions to selectively access either spirocyclohexadienone or spirocyclohexadiene products. Spirocyclohexadienones were obtained by treating C4-halogenated arenes with either PIFA or HTIB in 2,2,2-trifluoroethanol (TFE), whereas spirocyclohexadienes were formed from unsubstituted arenes (or arenes lacking a C4-substituent) using PIFA in a suitable nucleophilic solvent. A major development came in 2007 when Dohi *et al.* reported the first catalytic version of this spirocyclization.[88] Their method employed a catalytic amount of 4-iodotoluene with *meta*-chloroperoxybenzoic acid (*m*CPBA) as the terminal oxidant in TFE. Notably, two fluoro-

substituted, non-activated substrates were successfully transformed into the target spirocyclic hexadienone products in 79% and 89% yield, respectively (Scheme 1.19B).

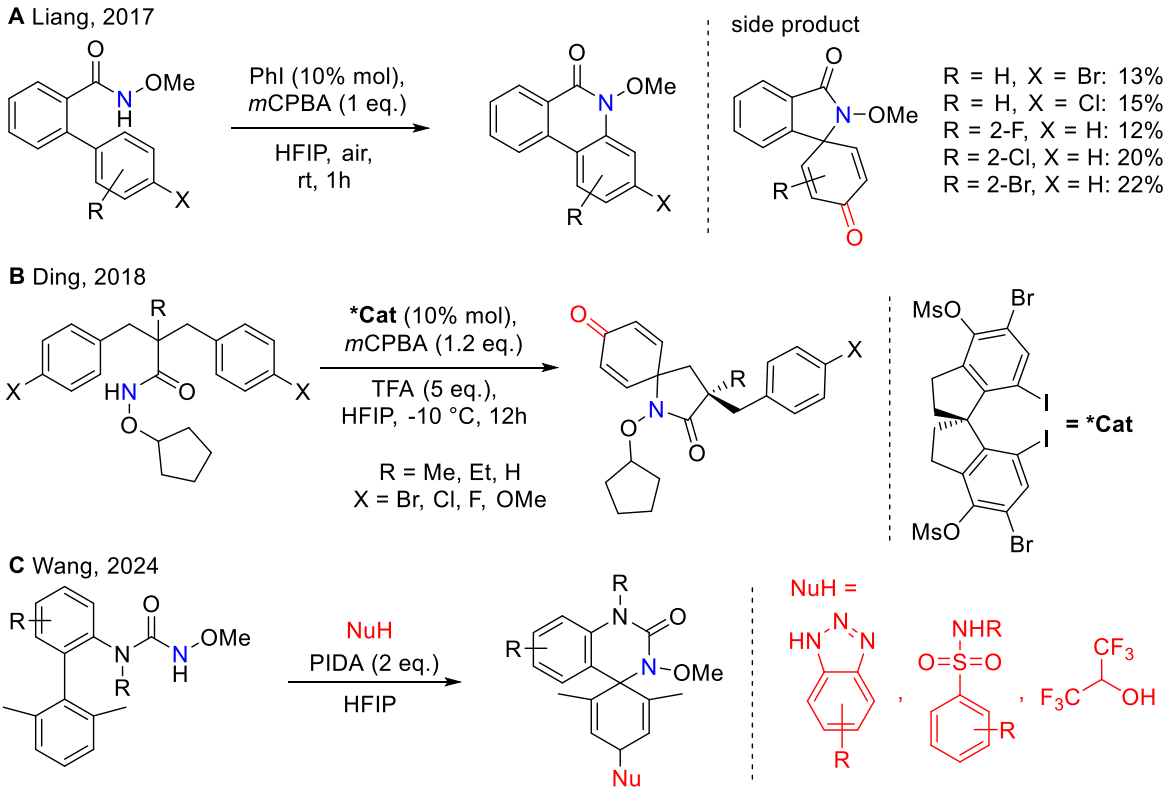


Scheme 1.19. Early examples of the synthesis of spiro[4.5]dienones via nitrenium ion intermediates.

A couple more dearomatization reactions proceeding through an *ipso*-attack of a nitrenium intermediate have been reported within the previous decade. In 2017, Liang et al. described a metal-free, hypervalent iodine(III)-catalyzed synthesis of phenanthridinones via oxidative C–H amidation (Scheme 1.20A).[89] While this was the main focus, several substrates also formed dearomatized side products in low yields (12-22%). With the exception of a *para*-fluoro substrate, this dearomatization only occurred with *ortho*- and *para*-halo-substituted arenes. Notably, *ortho*-bromo substrates yielded the dearomatized product almost quantitatively, with only trace amounts of the expected phenanthridinone detected.

In 2018, Ding and co-workers reported a similar process that also relied on catalytic hypervalent iodine(III) chemistry.[90] However, their method uniquely employed a chiral iodine catalyst. This enabled an enantioselective, oxidative C−N bond formation, where a symmetrical substrate undergoes dearomative spirolactonization to yield unsymmetrical products (Scheme 1.20B). The method demonstrated a small substrate scope (6 examples), accommodating halogenated arenes and an activated methoxy-substituted arene. This protocol afforded products in very good yields (78-85%) with high enantioselectivity (up to 89% enantiomeric excess).

More recently, Wang and colleagues demonstrated that a urea moiety can also act as a nitrenium ion precursor for such transformations (Scheme 1.20C).[91] They designed biphenylurea substrates that, upon oxidation with a hypervalent iodine(III) reagent, formed a nitrenium intermediate. This intermediate subsequently cyclized via an *ipso*-attack to generate dearomatized spirocyclic carbocation. The positively charged intermediate was then trapped by either an *N*- or *O*-centered nucleophile, achieving a C−N/C−N or C−N/C−O bond formation in a single step. This versatile strategy successfully provided access to a wide array of highly functionalized spirocyclic products (42 examples) in moderate to high yields (23-76%).



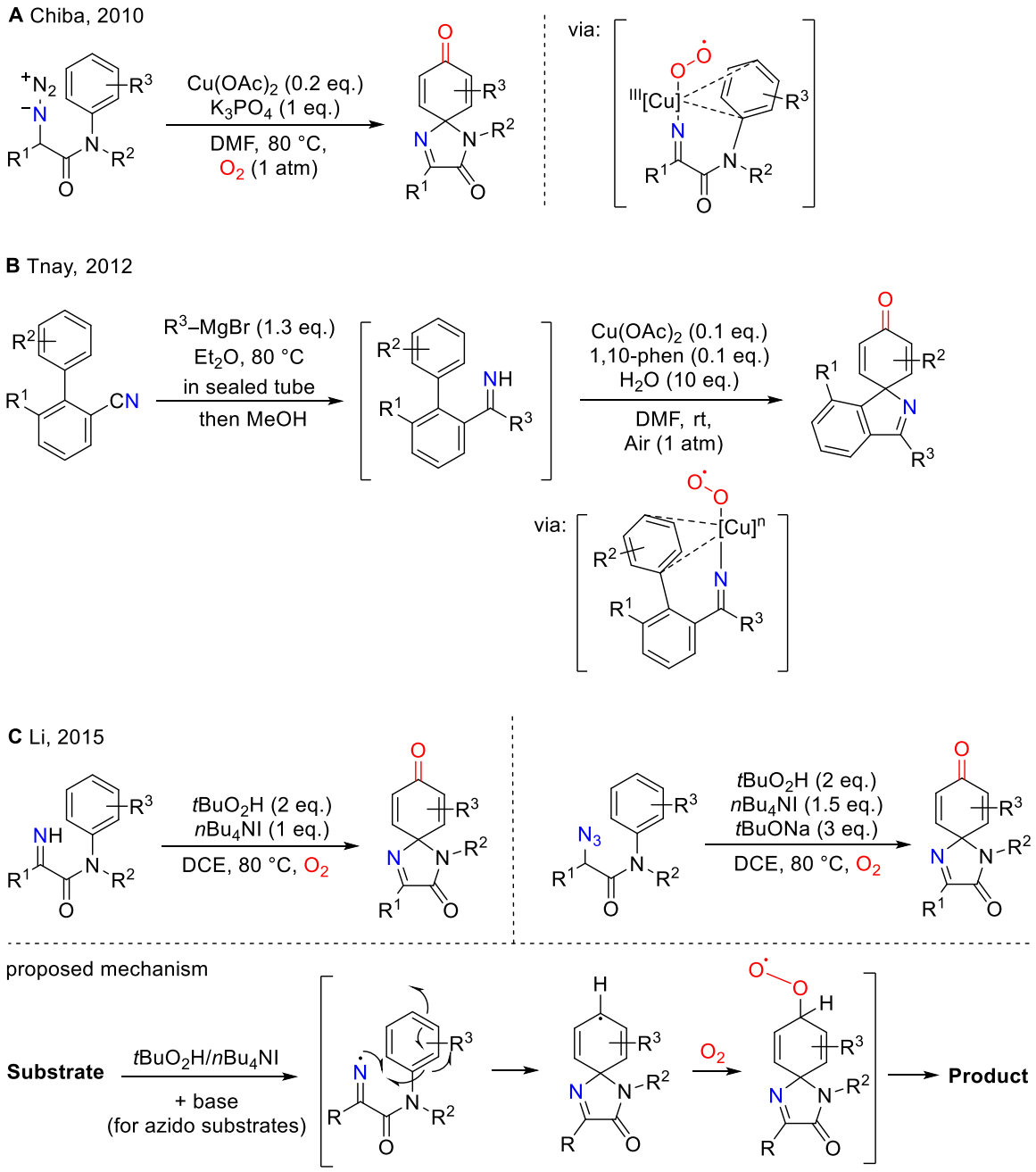
Scheme 1.20. Recent examples of the synthesis of spiro[4.5]dienones involving nitrenium ion intermediates.

1.2.3.2. *Imidyl and Amidyl Radical Mediated Dearomatization*

In 2010, Chiba and co-workers developed a copper(II)-catalyzed aerobic oxidative synthesis of azaspirocycles from α-azido-*N*-arylamide substrates (Scheme 1.21A).[92] The proposed mechanism begins with the formation of an iminyl-copper species from the azide precursor, accompanied by the extrusion of dinitrogen (N_2). This intermediate then undergoes an intramolecular *ipso*-attack onto the arene in a dearomative imino-cupration step. Subsequent C=O bond formation at the *para*-position releases the azaspirocyclic product and regenerates the Cu(II) catalyst. The reaction showed good functional group tolerance, providing 22 examples with product yields as high as 83%.

Building on this success, in 2012 the group adapted this chemistry for the spirocyclization of biaryl-*N*-H-imines, which were prepared by reacting biaryl-2-carbonitriles with a Grignard reagent (Scheme 1.21B).[93] Their rationale was informed by a previous phenanthridine synthesis where they had observed an intramolecular C–H amination pathway. They hypothesized that introducing a suitable *ortho*-substituent would restrict rotation around the biaryl axis, thereby controlling the substrate's helical conformation. This conformational constraint would favor the interaction of the iminyl-copper intermediate with the aromatic π-face (*ipso*-attack) over an interaction with a peripheral C–H bond, thus promoting the desired dearomative spirocyclization. Their hypothesis proved correct as the methodology afforded 29 different azaspirocycles in moderate to good yields (32-87%). Crucially, the cyclization of an enantiomerically pure substrate proceeded without any loss of stereochemical integrity, confirming that racemization via rotation around the biaryl axis did not occur under the reaction conditions.

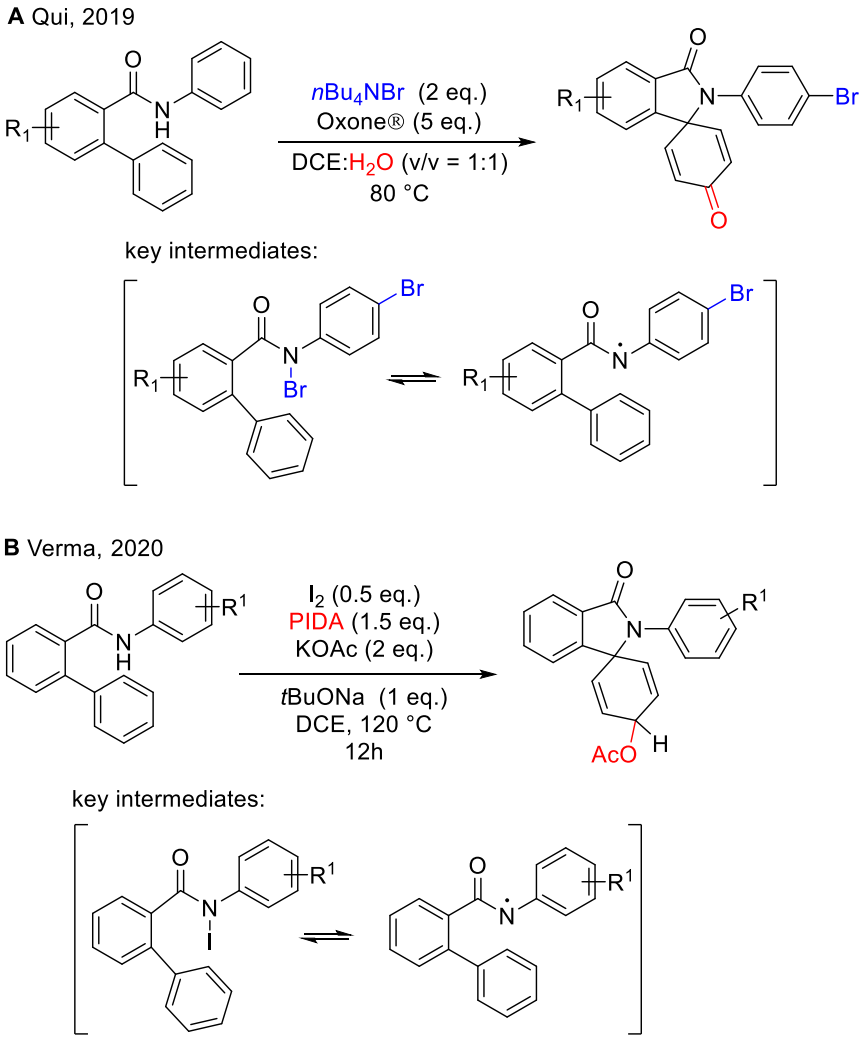
Later, in 2015, Li and co-workers demonstrated that this type of transformation could be achieved under metal-free conditions (Scheme 1.21C).[94] Using an oxidizing system of *tert*-butyl hydroperoxide (tBuO$_2$H) and tetrabutylammonium iodide (nBu$_4$I), they performed the spirocyclization on both α-imino-*N*-arylamides and α-azido-*N*-arylamides. The reaction proceeds through a mechanism analogous to the copper-catalyzed variants but relies on a key iminyl radical intermediate rather than an organometallic species.



Scheme 1.21. Examples of oxidative dearomative spirocyclizations involving imidyl radical intermediates.

In 2019, Qui and colleagues reported on a related metal-free, *5-exo-trig ipso*-cyclization of 2-arylbenzamide substrates using a similar oxidant/nBu$_4$NX system (Scheme 1.22A).[95] The reaction is initiated by an amidyl nitrogen-centered radical, which undergoes *ipso* cyclization. However, unlike previous reports, this transformation was accompanied by a halogenation reaction on one of the non-dearomatized arene provided that was bear any substituents on its

para position. Furthermore, mechanistic studies indicated that water (H_2O), not atmospheric oxygen, was the source for the newly installed carbonyl group. This method achieved the dearomatization of 22 non-activated arenes in good yields (45-80%). A year later, Verma and co-workers reported the serendipitous discovery of an iodine/PIDA system for constructing spiro-isoindolinones from 2-arylbenzamide substrates (Scheme 1.22B).[96] An amidyl nitrogen-centered radical was again presumed to be the key intermediate in the dearomative cyclization. Uniquely, this methodology also resulted in concurrent acetylation at the *para*-position of the dearomatized ring. It is also important to mention that one of the earliest oxidative preparations of spirolactams via amidyl radicals was achieved by using an excess amount of *N*-iodosuccinimide with alkoxybenzene derivatives as substrates.[97]



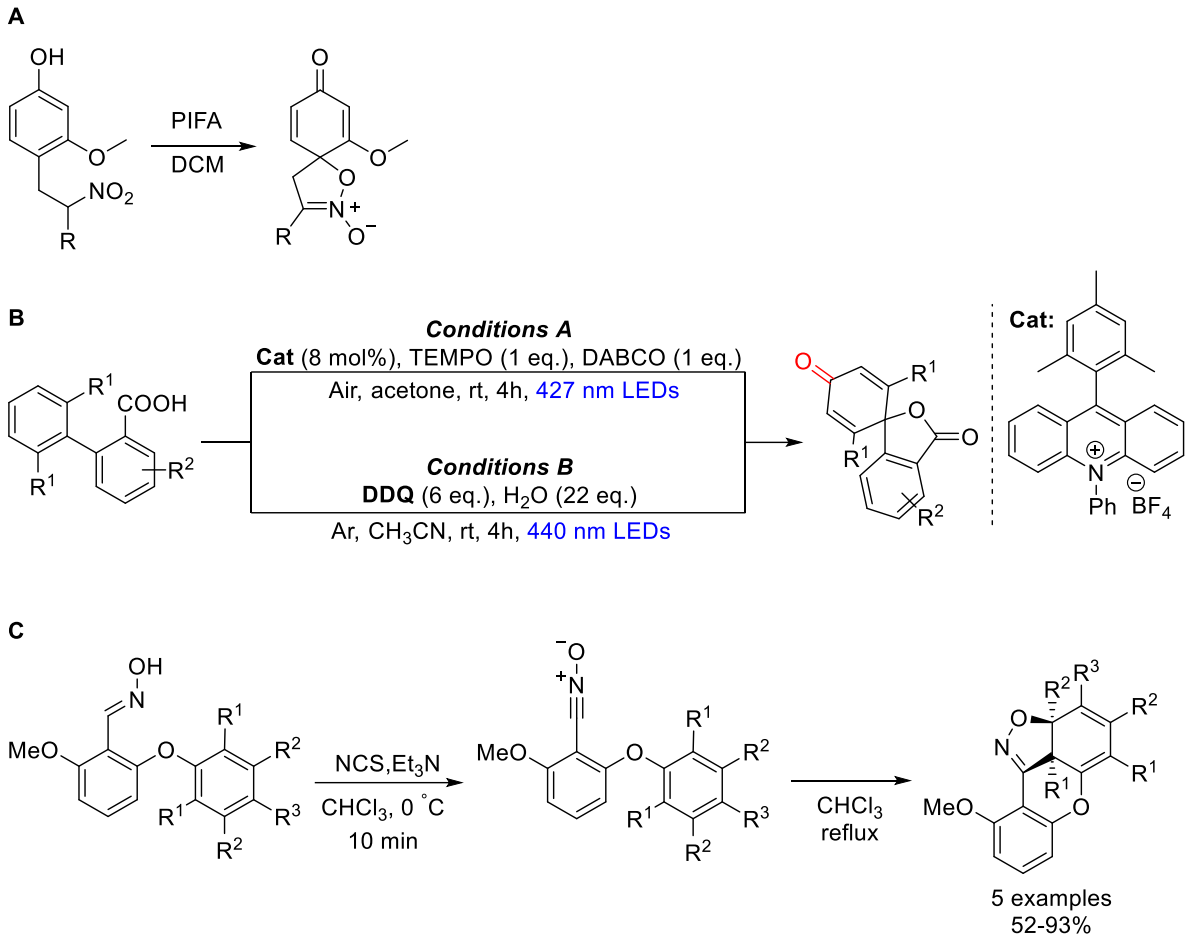
Scheme 1.22. Examples oxidative dearomative spirocyclization reactions involving amidyl radical intermediates.

1.2.3.3. *Dearomatization via Other Intermediates*

Beyond nitrogen-based species, spirocyclizations arising from *O*-centers have been achieved. For instance, the synthesis of several unique spironitronates was reported by Marsini et al., in 2007 (Scheme 1.23A).[98] This reaction likely goes through a phenoxonium intermediate that is followed by an *5-exo-trig* intramolecular nucleophilic attack by the oxygen atom from the tethered nitro group.

An *O*-centered radical, particularly the carboxyl radical, has also been employed in the preparation of spirocyclic compounds through the dearomatization of non-phenolic arene substrates. Historically, intramolecular reactions involving this radical strongly favored C–H functionalization over the desired dearomative *ipso*-attack.[99–101] A key breakthrough came from Gonzales and co-workers during their study of the dehydrogenative lactonization of 2-arylbenzoic acids to their corresponding benzo-3,4-coumarins.[100] They discovered that the preference for C–H functionalization could be nullified by simply blocking the substrate's *ortho*-positions, which effectively directs the carboxyl radical towards the *ipso*-cyclization pathway. This insight was further developed by Li and colleagues, who developed a photooxidative dearomatization of *ortho*-substituted, non-phenolic biaryls (Scheme 1.23B).[101] Their protocol, mediated by a carboxyl radical, utilizes either an acridinium or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as a photocatalyst. The method proceeded smoothly for 20 substrates, successfully accommodating extended aromatic systems like naphthalene and anthracene derivatives.

Non-spirocyclic intramolecular cycloadditions have also been initiated with *O*-centered intermediates. A representative example is Takata's intramolecular 1,3-dipolar cycloaddition of 2-phenoxybenzaldoximes (Scheme 1.23C). [102] In this process, the substrate's oxime functional group is oxidized by *N*-chlorosuccinimide (NCS) to form a labile nitrile *N*-oxide. This 1,3-dipolar intermediate then undergoes an intramolecular (3+2)-cycloaddition with the tethered benzene ring under reflux conditions, yielding a dearomatized isoxazoline product.

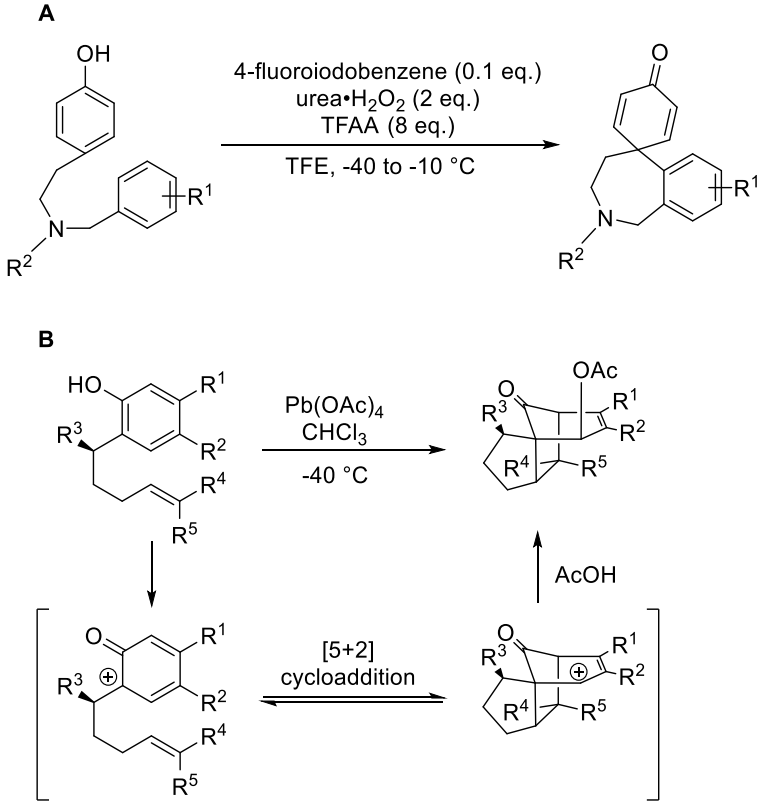


Scheme 1.23. Examples of oxidative cyclic dearomatization reactions involving *O*-centers. (**A**) An intramolecular dearomatization involving attack by a nitro group. (**B**) A photooxidative dearomatization reaction involving a carboxyl radical intermediate. (**C**) An intramolecular dearomatization proceeding through an *N*-nitrile oxide not resulting in a spirocycle.

Concerning reactions with carbon nucleophiles , an important development was reported by Dohi and coworkers in 2008. They established the first iodoarene-catalyzed dearomative C–C cyclization of phenols to synthesize precursors for galanthamine-type Amaryllidaceae alkaloids (Scheme 1.24A).[103] The proposed mechanism involves the oxidation of the phenol substrate by a hypervalent iodine(III) species to generate a phenoxenium ion. A subsequent intramolecular attack on the *ipso*-carbon by a tethered arene nucleophile forges the final spirocyclic framework.

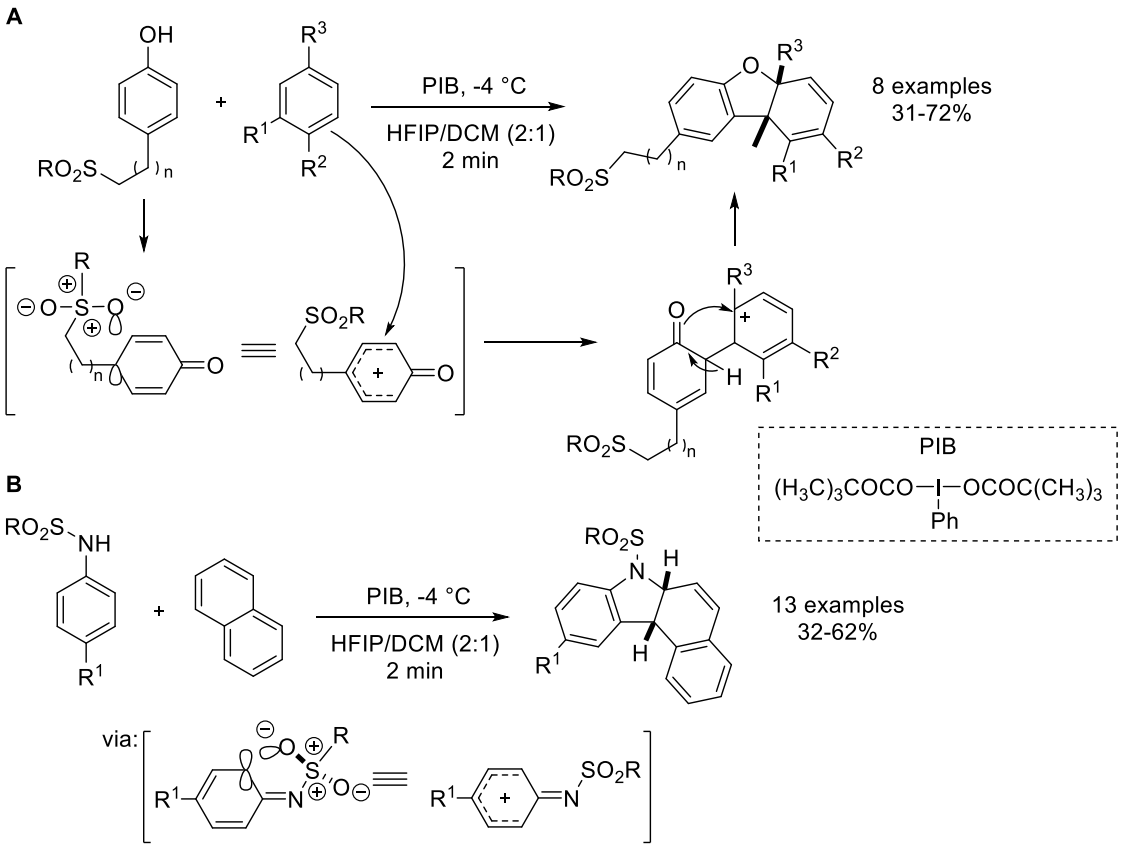
Later, in 2011, Green and Pettus developed a bio-inspired oxidative dearomatization of various *ortho*-(pent-4-enyl)-phenols using lead(IV) acetate, $Pb(OAc)_4$ (Scheme 1.24B). The transformation is initiated by the oxidation of the phenol to a phenoxonium intermediate. This reactive species then undergoes an intramolecular (5+2)-cycloaddition with the tethered olefin.

The cascade is terminated by the addition of acetic acid, affording a tricyclic adduct. These products served as valuable precursors for the synthesis of natural products such as α-cedrene, α-pipitzol, and *sec*-cedrenol.



Scheme 1.24. Examples of oxidative cyclic dearomatization reactions involving *C*-centers.

Intermolecular dearomative cycloadditions have also been developed, often relying on the oxidative *umpolung* of phenols or anilines. This strategy converts the electron-rich phenol into an electrophilic species that can be trapped by unactivated arenes in a (3+2)-cycloaddition. Canessi and co-workers demonstrated this principle in 2013, using various sulfonyl phenols and anilines as coupling partners for arenes like benzenes, naphthalene, anthracene and furan.[104] The oxidative activation was achieved by using bis(pivalate)iodobenzene (PIB) in a mixture of hexafluoroisopropanol (HFIP) and dichloromethane (DCM) at -4 °C (Scheme 1.25). The authors proposed that the combination of the highly polar, non-nucleophilic solvent (HFIP) and the lone pairs on the oxygens of the electron-withdrawing sulfonyl group was crucial for stabilizing the electrophilic intermediate, preventing polymerization and allowing it to be trapped by the arene nucleophile. This approach proved highly effective, affording products for 23 substrates in just two minutes with generally good yields (31-72%).

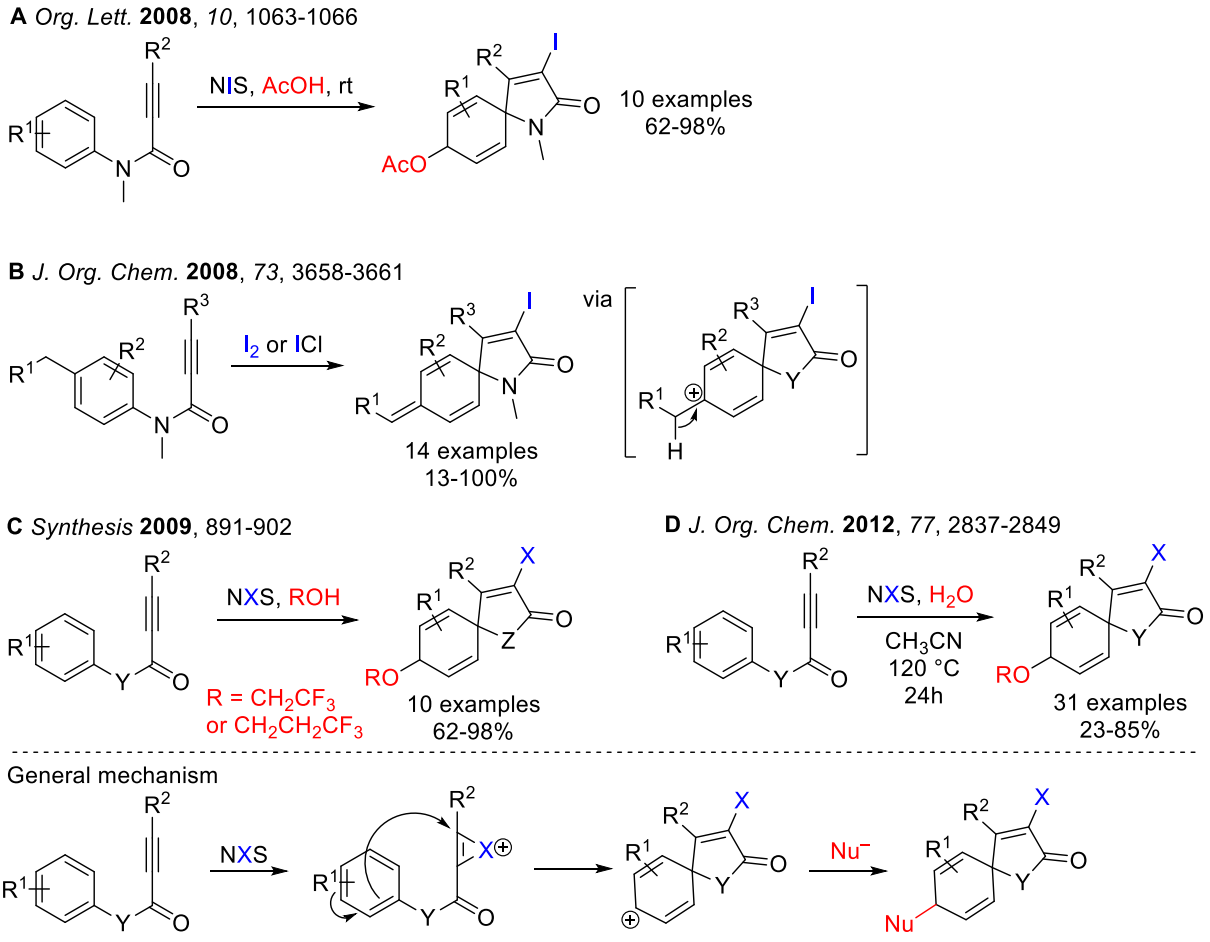


Scheme 1.25. Examples of intermolecular dearomatization reactions with phenoxonium and nitrenium intermediates.

1.2.3.4. *Dearomatization via the ipso-Annulation of Arylalkynes (spiro[4,5]trienyl and Spiro[5,5] trienyl products)*

Arylalkynes are prominent substrates in dearomatization reactions, often leading to functionalized spiro[4,5]trienyl or spiro[5,5]trienyl products. The work of Li and co-workers has been particularly significant in this area. In 2008, Li et al. reported one of the first examples of selectively synthesizing spiro[4,5]trienyl acetates from the oxidative dearomatization of *para*-unactivated *N*-arylpropiolamides (Scheme 1.26A).[105] The proposed mechanism begins with the formation of an iodonium intermediate between the substrate's alkyne moiety and the *N*-iodosuccinimide (NIS) reagent. This intermediate undergoes an intramolecular *ipso*-cyclization to generate a dearomatized, iodofunctionalized spirocyclic carbocation, which is then trapped by acetic acid (AcOH) to yield the product. That same year, they developed a selective synthesis of 8-methyleneazaspiro[4,5]trienes from *para*-methyl-substituted *N*-arylpropiolamides using either iodine (I_2) or iodine monochloride (ICl) as the oxidizing reagent (Scheme 1.26B) .[106] Unlike the acetate synthesis, the spirocyclic carbocation intermediate in this reaction undergoes a β-hydride elimination rather than a nucleophilic attack. This

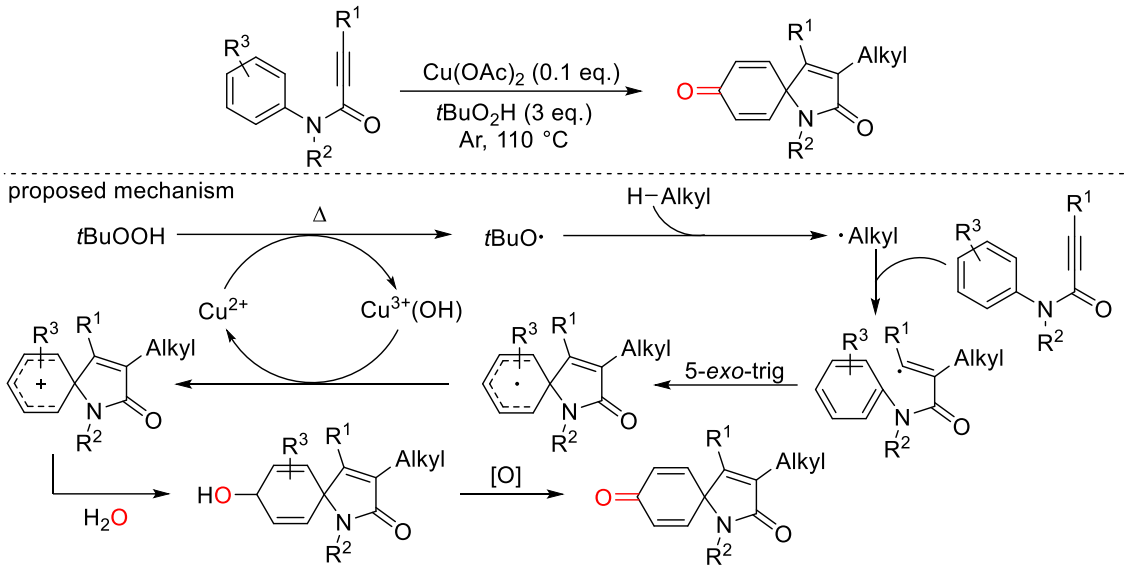
development was significant as the product contained both iodo and methylene groups, providing reactive sites for further functionalization. The following year, they made a report that was analogous to the spiro[4,5]trienyl acetate synthesis which explored the use of different nucleophiles, such as TFE or 3,3,3-trifluoropropanol (TFP), and other *N*-halosuccinimide (NXS) reagents (Scheme 1.26C).[107] Later, in 2012, Li's group developed an *ipso*-halocyclization protocol that transformed *para*-unsubstituted arylalkynes into spiro[4,5]trienones. The reaction, conducted with *N*-bromosuccinimide (NBS) or NIS in the presence of water, again proceeded through a halofunctionalized spirocyclic carbocation. This intermediate was subsequently trapped by water (H_2O) to furnish the desired spirocyclic product (Scheme 1.26D).[108]



Scheme 1.26. Hypervalent iodine mediated dearomative synthesis of azaspiro[4,5]trienones via electrophilic *ipso*-cyclization, selected reports from Li's group (2008 - 2012).

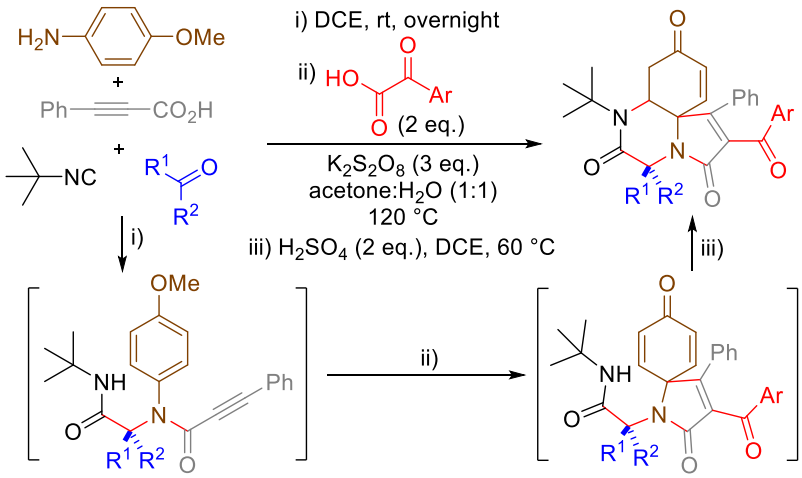
Building on this foundation, researchers have explored other electrophilic triggers beyond halogenation. Exploring alternatives to halogen-based protocols, Li's group reported a synthesis of 3-nitro azaspiro[4,5]trienones in 2015.[109] The reaction uses a TEMPO/O_2 system as the oxidant and *tert*-butyl nitrite (*t*BuONO) as the nitro source in the presence of water. The proposed pathway is analogous to the halogen-mediated reactions, proceeding through a 3-nitro-functionalized spirocyclic carbocation that is trapped by water. Similarly, in 2015, Wen and co-workers reported a spirocyclization accompanied by sulfonation rather than halogenation. Using an oxidative system of iodine pentoxide (I_2O_5) and *tert*-butyl hydroperoxide (*t*BuO_2H) with sulfonylhydrazides as sulfonating agents, they developed a versatile and efficient method with a wide substrate scope (27 examples) and good yields (up to 89%).[110] In 2016, Zhou and co-workers demonstrated that *para*-fluoro substituted arylalkynes could be used to access spiro[4,5]trienones using an oxidative combination of PIFA and boron trifluoride etherate ($BF_3{\cdot}OEt_2$).

Metal catalysis, typically with earth-abundant metals like copper or iron, provides another powerful route to 3-functionalized spiro[4.5]trienones. Li et al., has described a Cu-catalyzed synthesis of 3-alkyl spiro[4.5]trienones from *N*-arylpropiolamides and unactivated alkanes using a $Cu(OAc)_2$/*t*BuO_2H system (Scheme 1.27).[111] Zhang and co-coworkers developed a Cu-catalyzed synthesis of 3-silyl azaspiro[4.5]trienones from *N*-arylpropiolamides and hydrosilanes using a CuI/*t*BuO_2H system.[112] An iron-catalyzed dearomatization of biaryl ynones with benzyl alcohols to access 3-acylated spiro[5.5]trienones using an $Fe(OAc)_3$ /*t*BuO_2H system was reported by Shi and company.[113] Using Li's report as a representative example, the mechanism is initiated by the Cu(II)-mediated homolysis of *t*BuO_2H, generating a *tert*-butoxy radical and a high-valent Cu(III)-hydroxide species. The *tert*-butoxy radical abstracts a hydrogen atom from the alkane, and the resulting alkyl radical adds to the substrate's alkyne moiety to produce a vinyl radical. This intermediate undergoes a *5-exo-trig* dearomative radical *ipso*-cyclization to give a spirocyclic radical, which is then oxidized by the Cu(III) species to a carbocation. Trapping of this carbocation by water, followed by a final oxidation event, furnishes the spiro[4.5]trienone product (Scheme 1.27).



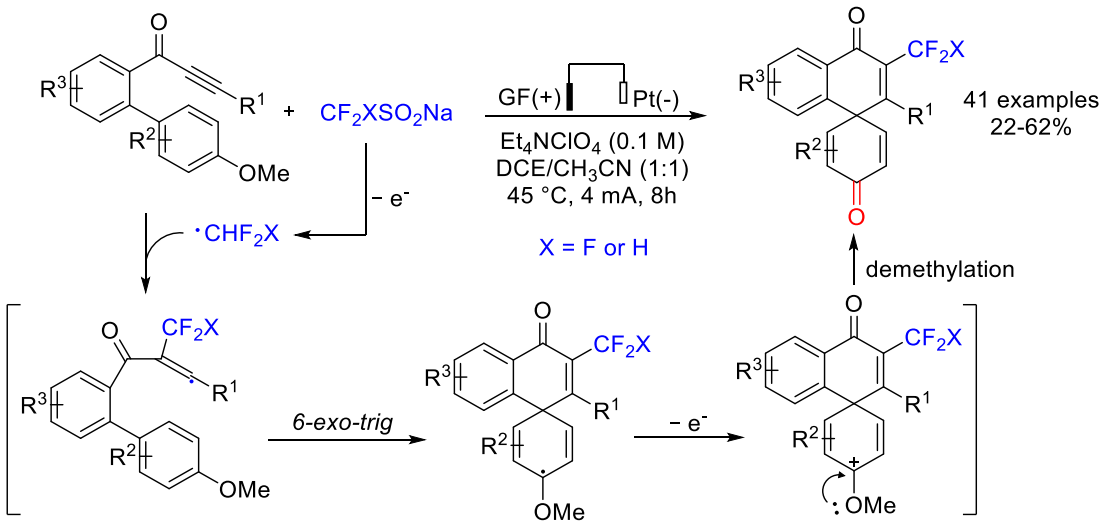
Scheme 1.27. Cu-catalyzed dearomative synthesis of azaspiro[4,5]trienones via radical *ipso*-cyclization.

Metal-free, multicomponent variations have also been developed. Notably, Nair and co-workers devised a five-component synthesis of acylated tricyclic azaspirotrienones (Scheme 1.28). The sequence begins with a four-component Ugi reaction to furnish an *N*-arylpropiolamide intermediate. This is then coupled with phenylglyoxylic acid in a dearomative *ipso*-cyclization. Finally, an intramolecular aza-Michael addition completes the synthesis of the tricyclic product. An intermolecular example was reported by Dong and co-workers, who developed a photocatalytic process where 2-benzyl-2-bromomalonate is regioselectively cyclized with various alkynes to provide spiro[4,5]decane frameworks.[114]



Scheme 1.28. One-pot multicomponent dearomative synthesis of tricyclic azaspiro[4,5]trienones.

More recently, electrooxidative methods have been developed by Ackermann et al. (2021) and Chen et al. (2023).[115,116] Ackermann's report is distinct in that it yielded spiro[5,5]trienones containing an all-carbon quaternary center (Scheme 1.29). The dearomative ipso-cyclization was coupled with trifluoromethylation (CF_3) or difluoromethylation (CF_2H) using Langlois' reagent or sodium difluoromethanesulfinate (Na-DFMS), respectively. The reaction was performed at a constant current of 4 mA in an undivided cell, affording products for 41 substrates in moderate yields (22-62%). Mechanistic studies indicated that anodic oxidation generates a CF_2X radical, which adds to the alkyne. The resulting vinyl radical undergoes *ipso*-cyclization, followed by further oxidation and demethylation to furnish the final product. Chen's 2023 electrochemical protocol extended the substrate scope to include the synthesis of dearomatized tricyclic frameworks from quinoline-based propiolamides, further highlighting the potential of these metal-free, electrochemical strategies.

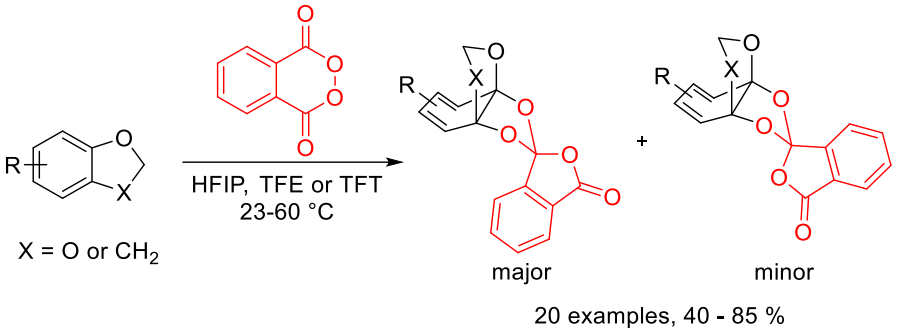


Scheme 1.29. Electrooxidative dearomatization of arylalkynes for the synthesis of CF_3 functionalized spiro[5.5]trienones.

1.2.4. Oxidative Dearomatization of Arenols

The oxidative dearomatization of aromatic compounds is significantly aided by the presence of electron-donating groups (EDGs). Hydroxy (-OH), alkoxy (-OR), and amino (-NH_2/-NHR/-NR_2) groups increase the electron density of the ring, making it far more susceptible to oxidation than non-functionalized hydrocarbon arenes. This increased reactivity allows for the use of much milder oxidizing conditions to effect the dearomatization. For instance, in a report by Eliassen *et al.*, an activated substrate was successfully dearomatized using phthaloyl peroxide, a relatively gentle oxidant (Scheme 1.30).[117] This contrasts sharply with methods

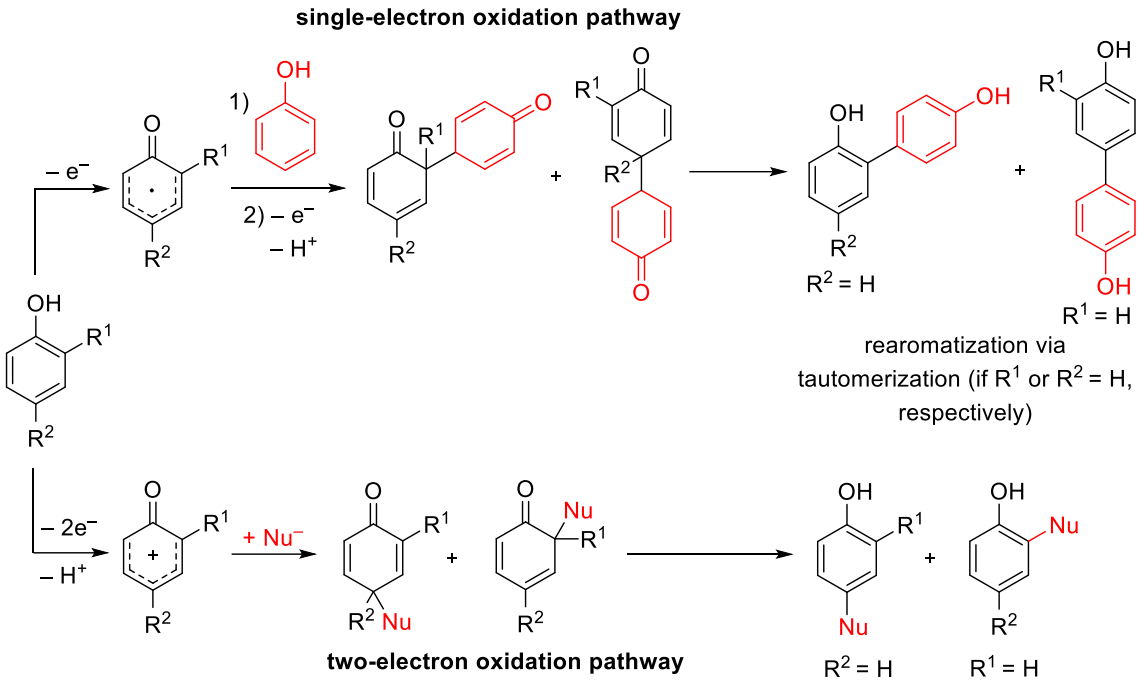
that require stronger reagents like hydrogen peroxide (H_2O_2) for less activated systems. Consequently, a plethora of synthetic methods have been developed that specifically target these electron-rich substrates, including phenol, anisole, and aniline derivatives.



Scheme 1.30. Dearomatization of an electron-rich arene using phthaloyl peroxide.

The oxidative dearomatization of electron-rich arenes can proceed through two distinct mechanistic pathways, depending on the nature of the employed oxidant. The first one begins with a single-electron transfer (SET) from the electron-rich arene to the oxidant. This generates a radical intermediate. This species typically undergoes a bond-forming reaction first, followed by a second oxidation step (Scheme 1.31). Alternatively, the reaction can proceed via a formal two-electron oxidation. This pathway bypasses the radical intermediate, directly generating a cationic species from the starting arene. This electrophilic intermediate is then captured by a nucleophile to complete the dearomatization (Scheme 1.31).[43,53,118]

An important attribute of both pathways is the regioselectivity of the bond-forming events. Due to the major resonance structures of intermediate species (radical or cation), these reactions occur exclusively at either the *ortho* or *para* position of the arene relative to the electron donating group. In order for the dearomatized product to be stable, the site of bond formation must be substituted (i.e., resulting in the formation of a fully-substituted carbon center). Otherwise, the incipient cyclohexadienone adduct will easily and irreversibly rearrange to the more stable aromatic tautomer (Scheme 1.31).[43]

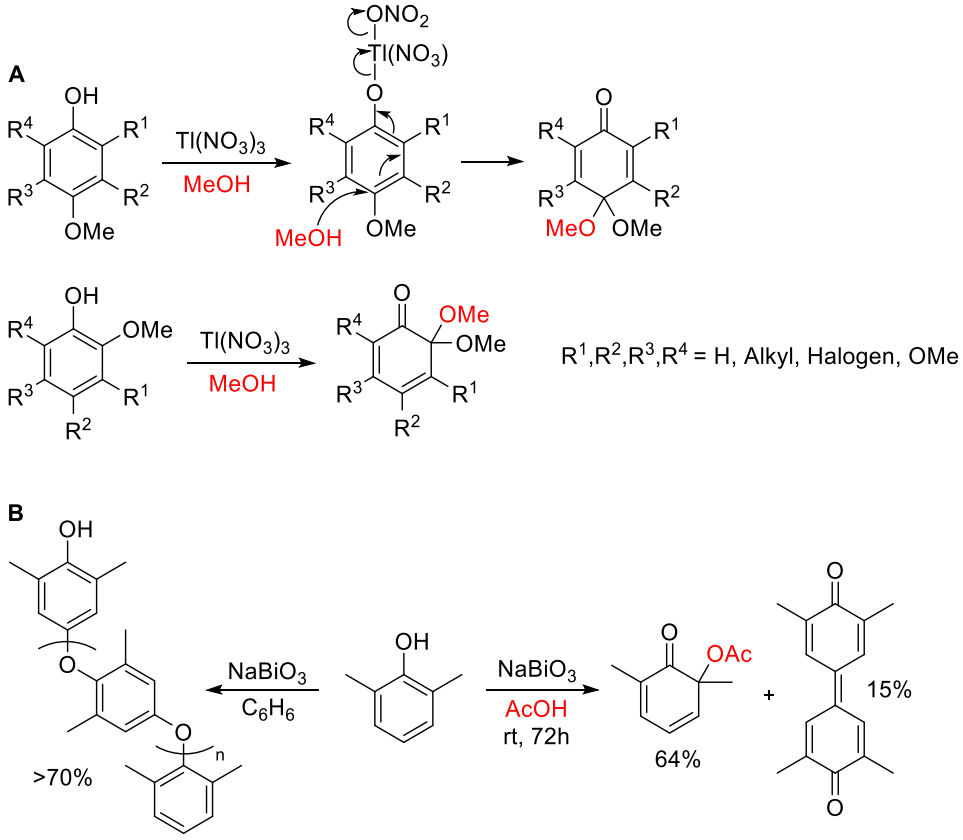


Scheme 1.31. The two reaction pathways of oxidative dearomatization of phenols and related electron rich arenes.

The two-electron oxidation pathway is a powerful strategy in organic synthesis because it inverts the natural electronic character of electron-rich arenes. This reactivity reversal, known as 'aromatic ring umpolung', transforms a nucleophilic substrate, such as a phenol, into a potent electrophile.[43] Certain heavy metal reagents are particularly effective at promoting this transformation. In 1976, McKillop *et al*., published a landmark investigation into the oxidation of phenols using thallium(III) nitrate ($Tl(NO_3)_3$) (Scheme 1.32A). Their contribution was significant due to its comprehensive scope; they examined a diverse array of phenolic substrates, moving well beyond the structurally simple molecules that had typified most prior studies.[119]

In addition to thallium(III), bismuth(V) salts like sodium bismuthate ($NaBiO_3$) have also been used as two-electron oxidants for phenol dearomatization. However, the outcome of these reactions is highly dependent on the solvent system. In acidic media, a two-electron oxidation is predominant, affording dearomatized quinol acetate products (Scheme 1.32B). In a neutral aromatic solvent, a SET event typically occurs, leading to oxidative polymerization and the formation of polyphenylene oxides. This solvent-dependent switch was clearly demonstrated by Kon and McNeils in 1976 (Scheme 1.32B). When they oxidized 2,6-xylenol with $NaBiO_3$ in neutral benzene, the SET pathway dominated, yielding the corresponding polymer in high yields (~70%). However, upon introducing acetic acid, the reaction mechanism shifted. In a

strongly acidic solution (e.g., glacial acetic acid), the SET pathway was completely suppressed, and the two-electron oxidation product, an *ortho*-quinol acetate, was isolated as the major product (64%), with no polymer detected.[120]

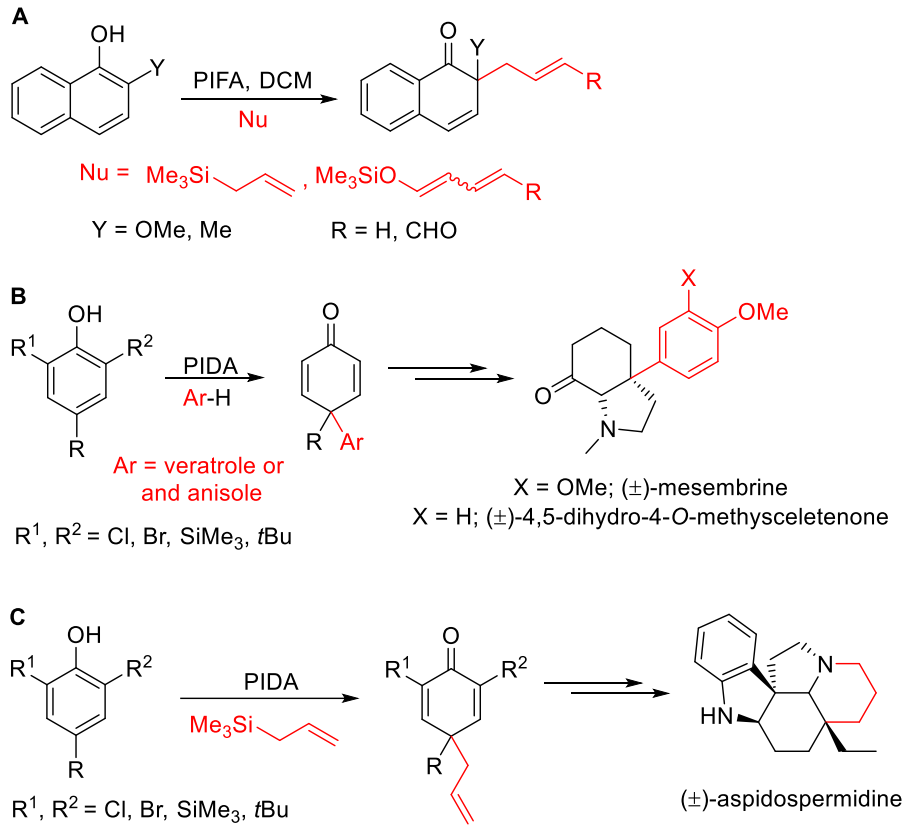


Scheme 1.32. Oxidation of phenols with thalium(III) nitrate and sodium bismuthate.

Due to the high toxicity of heavy metal reagents, particularly those containing thallium(III) and lead(IV), the field of oxidative dearomatization has largely embraced safer alternatives. Therefore, hypervalent iodine reagents have emerged as the preferred oxidants as they are less toxic, cost-effective, and readily available. In particular, λ³-iodanes like PIDA and PIFA have become routine reagents in this field. They are widely used to convert phenols and other electron-rich arenes into their corresponding cyclohexadienones via the formation of C–C, C–O, or C–N bonds. The following sections will focus on key examples of *intermolecular* dearomatization reactions using these reagents.

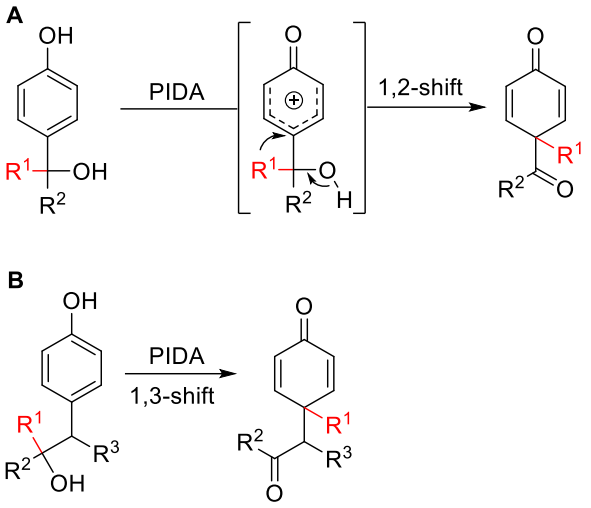
In 1999, Quideau and coworkers reported a pioneering example of an intermolecular dearomative C–C bond formation (Scheme 1.33A) by exploiting the 'aromatic ring umpolung'

concept. They developed a PIFA-mediated coupling between 2-substituted naphthols and carbon nucleophiles originating from allylsilanes or silyl enol ethers. This method provided access to naphthoid *ortho*-quinol products in good yields, a significant achievement for a reaction type that was previously rare and inefficient.[121] Nearly a decade later, Canesi's group also took advantage of 'aromatic ring umpolung' by investigating the reactivity of polysubstituted phenols as electrophiles (Scheme 1.33B). They developed a PIDA-mediated oxidative Friedel-Crafts process, wherein phenols were coupled with nucleophilic arenes like furan, veratrole, benzodioxolone, and various anisoles. This strategy provided a convenient entry to complex products containing a dienone, a quaternary carbon, and an aromatic ring. The utility of the method was also showcased in the synthesis of natural products from the *Amaryllidaceae* alkaloid family.[122] Later that same year, Canesi's group further highlighted the synthetic prowess of hypervalent iodine reagents in their total synthesis of (±)-aspidospermidine (Scheme 1.33C). The key step was a PIDA-mediated oxidative Hosomi-Sakurai reaction between a polysubstituted phenol and allyltrimethylsilane. This transformation, akin to Quideau's earlier work, leveraged umpolung chemistry to furnish a crucial dienone intermediate, which was then elaborated to complete the synthesis of the complex natural product.[123]



Scheme 1.33. λ³-Iodane-mediated phenol dearomatization with carbon–carbon bond formation.

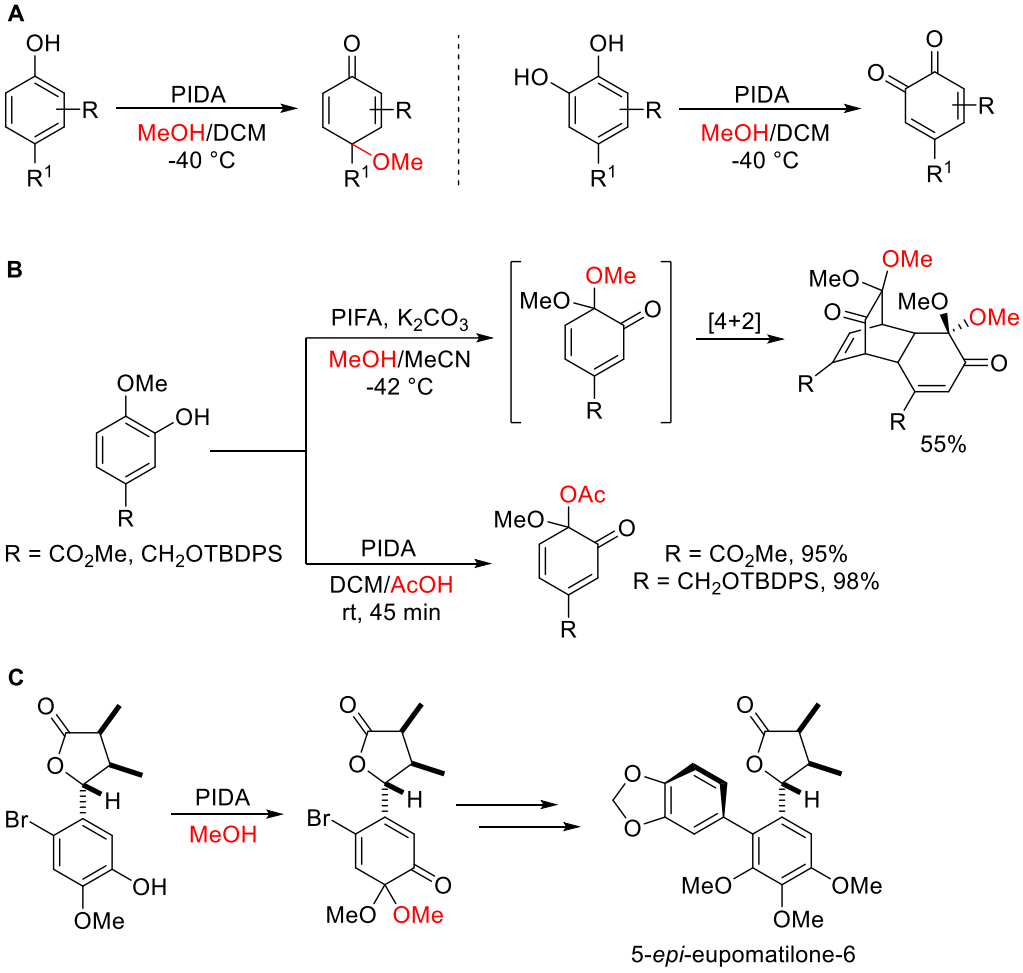
Although neither cyclic nor intermolecular in nature, oxidative 1,2- and 1,3-alkyl shifts that effect phenolic dearomatization accompanied by the simultaneous formation of a new C–C bond and a carbonyl functionality are also noteworthy. A representative example was reported in 2012 by Canesi and co-workers, in which various benzylic alcohol systems were oxidized with PIDA in HFIP (Scheme 1.34).[124]



Scheme 1.34. λ³-Iodane-mediated phenol dearomatization via 1,2- and 1,3-alkyl shift processes.

Intermolecular C–O bond formation represents another major class of oxidative dearomatization reactions. The work of Pelter and Elgendy in 1993 provides a suitable example. They demonstrated that treating various phenols with PIDA in methanol resulted in different products based on the substrate's structure (Scheme 1.35A). Biphenols and dihydroxybenzenes (e.g., hydroquinone) were oxidized to their corresponding *ortho*- or *para*-quinones. Whereas, simple alkyl- or alkoxy-substituted phenols underwent oxidative addition at the *para* position to afford 4,4-disubstituted cyclohexa-2,5-dienones. These transformations were generally efficient, with yields ranging from 65-100%.[44] Achieving *ortho*-selectivity in these reactions presented a unique challenge for certain phenols, as explored by Quideau et al. Their initial attempt to perform an *ortho*-methoxylation using PIFA yielded a highly reactive 6,6-dimethoxycyclohexa-2,4-dienone. This product immediately dimerized via a Diels-Alder reaction, preventing its isolation (Scheme 1.35B). The problem was solved by switching from methoxylation to acetoxylation. Using PIDA as the oxidant furnished a stable *ortho*-quinol acetate, which did not dimerize and could be isolated in yields of up to 95% (Scheme 1.35B).[45,125,126] The synthetic utility of this methodology is evident in its application in natural product synthesis. For example, Hong and McIntosh employed a dearomative C–O bond

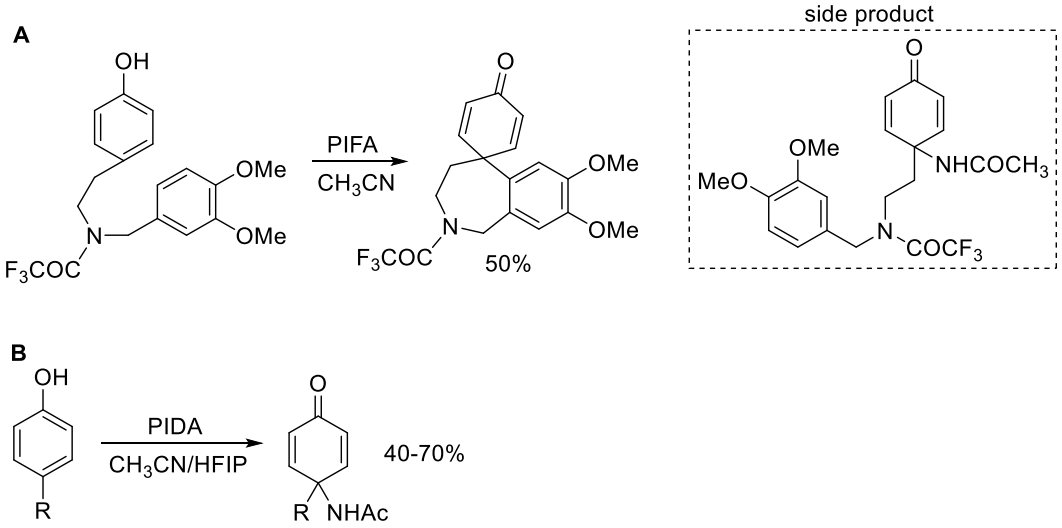
formation as a key step in their synthesis of 5-*epi*-eupomatilone-6, a lignan isolated from the Australian shrub *Eupomatia bennettii*. This crucial step involves the oxidation of a complex phenolic substrate with PIDA in methanol, which efficiently produced the desired *o*-quinone monoketal intermediate in 91% yield (Scheme 1.35C).[127] Additionally, Runcie and Taylor performed a similar oxidation of 4-bromoguaiacol with PIDA in the presence of methanol to access an important bromocyclohexadienone intermediate in excellent yield for their synthesis of scyphostatin analogues.[128]



Scheme 1.35. λ^3-Iodane-mediated phenol dearomatization with carbon–oxygen bond formation.

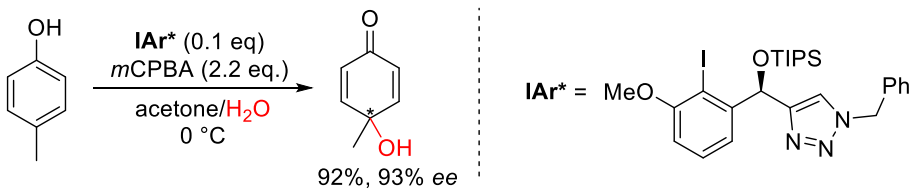
Regarding C–N bond formation, during their development of an intramolecular oxidative coupling in 1996, Kita and coworkers, observed the formation of an unexpected amidation side product when using acetonitrile as the solvent (Scheme 1.36A).[126] This competing side reaction was proposed to occur via a Ritter-type reaction, where an acetonitrile molecule attacks the electrophilic phenoxenium ion intermediate. Canesi and coworkers later developed this side reaction into a deliberate and systematic method for intermolecular C–N bond formation. [129]

In their 2004 study, they treated various phenols with PIDA in a solvent mixture of HFIP and acetonitrile (Scheme 1.36B). This approach successfully afforded 4-aza-substituted dienones in practical yields of 40-70%. The methodology also showed flexibility, working effectively with another nitrile, namely, propionitrile.



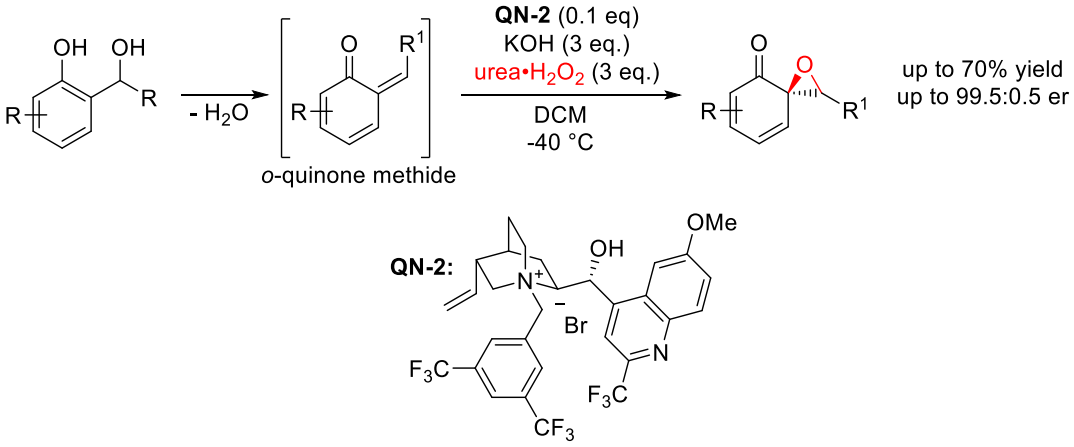
Scheme 1.36. λ^3-Iodane-mediated phenol dearomatization with carbon–nitrogen bond formation.

A remarkable development in this field was the report of a catalytic and asymmetric dearomatization of a 4-substituted phenol by Abazid and Nachtsheim. Their method efficiently converted this phenol into a chiral *para*-quinol (93% *ee*) using water as the nucleophile (Scheme 1.37).[130] What is central to their approach is the use of a chiral iodoarene as a catalyst. This chiral iodoarene is oxidised *in situ* by a terminal oxidant to generate the active chiral hypervalent species, which is regenerated after each catalytic cycle. This effectively eliminates wasteful approaches that would otherwise employ stochiometric chiral hypervalent iodine reagents. The report by Stunkel and Gilmore in 2023 describes another catalytic and highly enantioselective process, in which the dearomative fluorination of a wide range of phenols (20 examples) was achieved via chiral I(I)/I(III) catalysis.[131]



Scheme 1.37. Enantioselective hypervalent iodine-catalyzed phenol dearomatization.

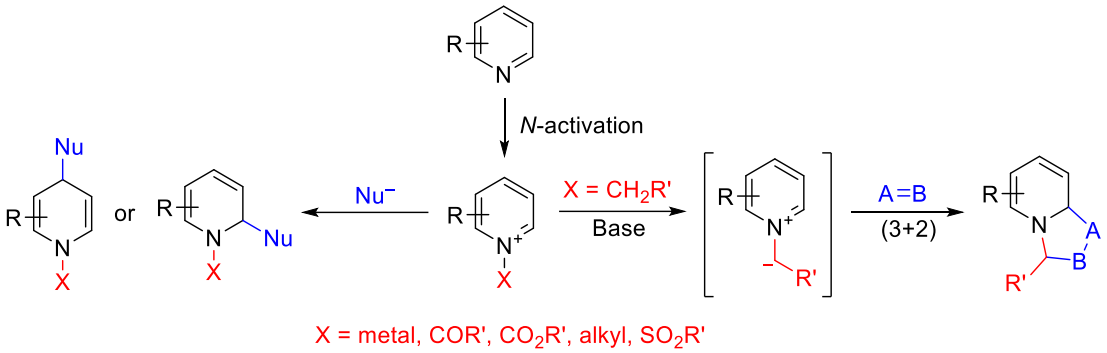
In addition to the above examples, McLaughlin and co-workers reported an oxidative dearomatization of phenolic substrates proceeding via a transient quinone methide (Scheme 1.38), in contrast to the classical one- and two-electron oxidation pathways that typically dominate this field.[132] In this study, the enantioselective oxidative dearomatization of 2-(hydroxymethyl)phenols was achieved through their corresponding bis(dichloroacetates). Using H_2O_2 as a mild oxidant in combination with a newly developed cinchona alkaloid-derived phase-transfer catalyst, the reaction furnished enantioenriched *o*-spiroepoxydienones-a transformation that the Alder-Becker oxidation could not accomplish.



Schemes 1.38. Oxidative phenol dearomatization proceeding via a quinone methide.

1.3. Dearomatization of Heteroaromatic Compounds via Nucleophilic Addition

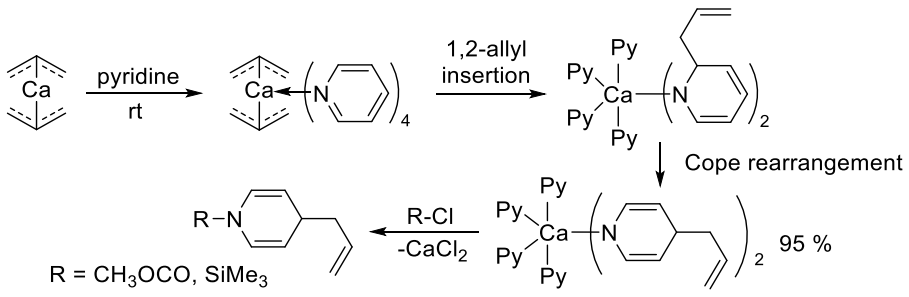
Aromatic heterocycles such as quinolines, pyridines, and acridines, collectively known as azaarenes, possess lower resonance energy than benzene, yet their direct dearomatization remains challenging. Disrupting their aromaticity requires reduction or nucleophilic addition, wherein the azaarene acts as the electrophile. However, since these heterocycles are generally insufficiently electrophilic on their own, prior activation of the azaarene core is required. This activation is usually accomplished by functionalizing the ring's nitrogen atom, which enhances the molecule's electrophilicity. Since the nitrogen's lone pair does not participate in the ring's aromaticity, it is free to coordinate or react with electrophiles (Scheme 1.39). Consequently, this *N*-functionalization facilitates subsequent dearomatization by either reduction or nucleophilic addition.[133–137]



Scheme 1.39. General scheme of the dearomatization an azaarene enabled by *N*-activation.

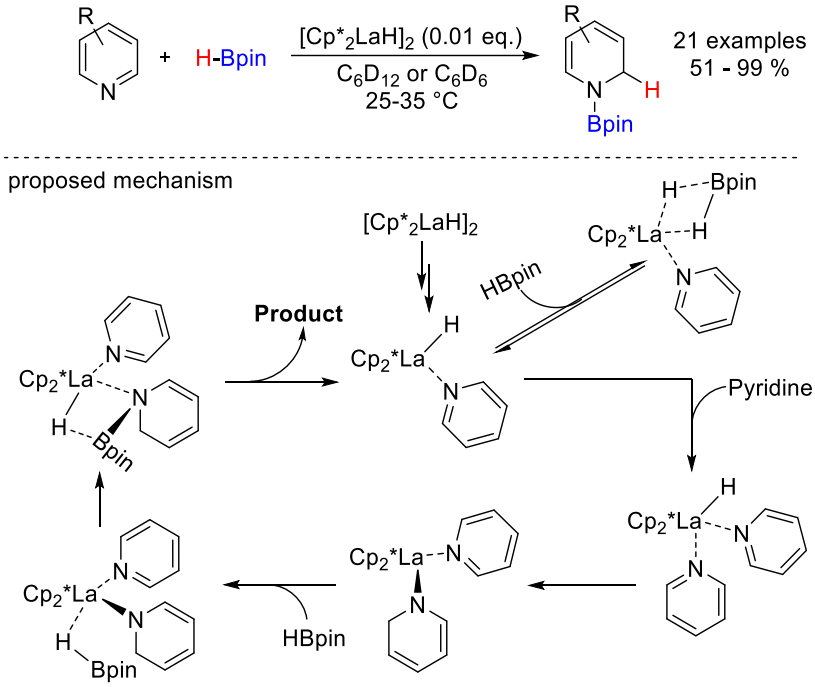
1.3.1.Azaarene Dearomatization enabled by Transient *N*-Metal Activation

While the formation of azaarenium salts is the most common activation strategy, transient activation through the formation of an *N*-metal coordination bond has also been utilized. For example, in 2010, Okuda, Maron, and co-workers showed that pyridine could be regioselectively dearomatized to a 1,4-dihydropyridine derivative (Scheme 1.40).[138] This was achieved via an insertion reaction into the polar calcium-allyl bond of bis(allyl)calcium. The reaction yielded a stable coordination complex comprising a central calcium atom surrounded by four pyridine and two 4-allyl-1,4-dihydropyridine ligands. Mechanistic studies, supported by NMR spectroscopy and Density Functional Theory (DFT) calculations, suggested a pathway involving the initial coordination of pyridine to bis(allyl)calcium. This furnished an activated species that underwent a swift 1,2-insertion, followed by a 1,3-shift (Cope rearrangement), to give the final calcium complex. Subsequent treatment of this complex with either methyl chloroformate or trimethylsilyl chloride released the desired *N*-substituted 4-allyl-1,4-dihydropyridines alongside $CaCl_2$.



Scheme 1.40. Dearomatization of pyridine with an organocalcium reagent.

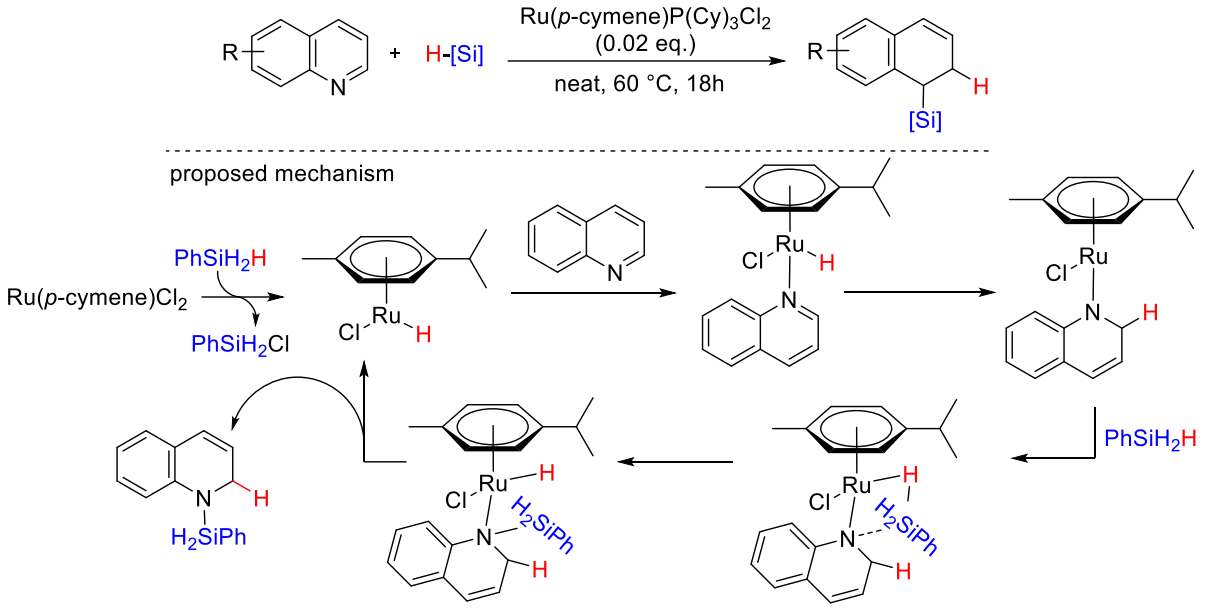
Additionally, many examples of dearomative hydroboration and hydrosilylation of pyridines exist that rely on a similar activation principle.[139] For instance, in 2014, Marks, Delferro, et al. used a dimeric lanthanocene hydride complex, $[(Cp*)_2LaH]_2$, to catalyze the 1,2-hydroboration of pyridine with pinacolborane under mild conditions (Scheme 1.41). The proposed mechanism, supported by both experimental and computational data, begins with the dimeric complex reacting with pyridine. This interaction rapidly converts the dimer into a monomeric pyridine adduct, $(Cp*)_2LaH(Py)$. This adduct then coordinates a second pyridine molecule, which subsequently undergoes 1,2-insertion into the lanthanum-hydride bond. Following this insertion, pinacolborane coordinates to the complex and undergoes a rapid σ-bond metathesis between the La–N and H–B bonds. This final step releases the hydroborated product and regenerates the monomeric adduct, completing the catalytic cycle.



Scheme 1.41. Lanthanum-catalyzed 1,2-hydroboration of pyridines.

In 2021, Gunanathan, Suresh, and co-workers employed the ruthenium precatalyst [Ru(p-cymene)P(Cy)$_3$Cl$_2$] in the 1,2-hydrosilylation of quinoline with phenylsilane and diethylsilane, affording *N*-silyl-1,2-dihydroquinoline products (Scheme 1.42).[140] The method was straightforward, mild, and required no additional reagents beyond the catalyst and substrates. It proved effective across a wide range of azaarenes, including pyridines, isoquinolines, pyrazines, quinoxalines, benzimidazole, and acridine, often delivering products in good to excellent yields. Based on control experiments and DFT calculations, the authors proposed a mechanism analogous to the 1,2-hydroboration previously reported with lanthanide complexes.

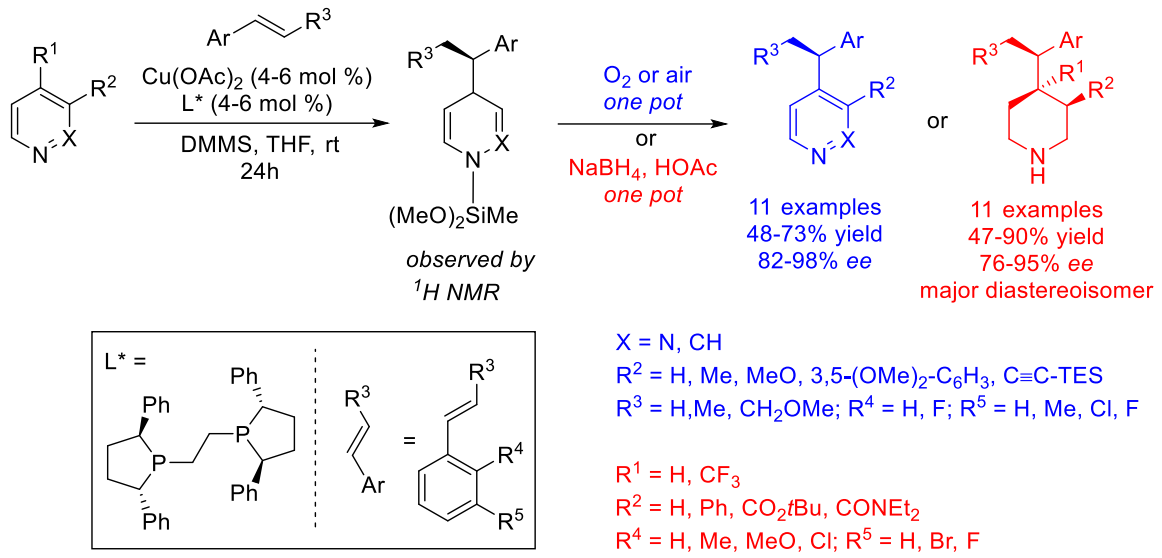
The process begins with dissociation of a PCy_3 ligand from the Ru precatalyst. Subsequent reaction with the silane generates the active ruthenium hydride species along with dissociated chlorophenylsilane. Coordination of the azaarene substrate to the metal center then occurs, followed by 1,2-insertion of the *N*-heteroaromatic into the Ru–H bond. Finally, coordination of an additional silane enables a σ-bond metathesis between the Ru–N and H–Si bonds, releasing the *N*-silyl-1,2-dihydroquinoline product and regenerating the catalytically active ruthenium hydride for the next cycle.



Scheme 1.42. Ruthenium-catalyzed 1,2-hydrosilylation of pyridines.

Given that hydride addition to azaareniums through transient *N*-metal activation has been demonstrated in many reports, analogous reactions involving the addition of carbon nucleophiles have also been developed. Buchwald and co-workers reported one such transformation in which a chiral copper catalyst promoted the regioselective dearomatization of pyridines (and pyridazines) via C4 addition of styrenes in the presence of excess dimethoxymethylsilane (DMMS).[141] This process afforded unstable *N*-silyl-1,4-dihydropyridines, which could be detected either by NMR analysis or indirectly through reduction or oxidation to the corresponding piperidines or substituted pyridines, respectively (Scheme 1.42). The method exhibited broad compatibility, accommodating styrenes with ortho- or *meta*-substituents, styrenes bearing internal alkenes, as well as pyridines substituted at the C3- or C4-positions. Moreover, upon reduction to piperidines, the products consistently

displayed high enantiomeric excess and, in the cases involving substituted pyridine substrates, acceptable levels of diastereoselectivity.



Scheme 1.43. Copper-catalyzed 1,4-addition of olefins to pyridines.

1.3.2. Dearomatization of Azaarenium Salts

The pre-activation of azaarene substrates through the formation of azaarenium salts can be achieved by treatment with an appropriate electrophile. Cations of the *N*-acyl, *N*-oxide, *N*-sulfonyl, *N*-alkyl, and related types have been generated in this way and successfully applied in nucleophilic dearomatization reactions. These cations typically feature electrophilic sites at the C2 (or C6) and C4 positions. In addition, the substituent attached to the nitrogen atom can introduce an extra reactive site, such as the carbonyl group in *N*-acyl salts.[133,146]

Nucleophiles can attack either of these electrophilic centers to afford dearomatized 1,2- or 1,4-adducts, which themselves bear nucleophilic character at the C3 or C5 positions. Upon subsequent treatment with an electrophile, these adducts regenerate electrophilicity at either the C2 or C4 positions, depending on the type of azaarene used.[147] This reactivity, arising directly from the dearomatization of azaarenium salts, opens valuable synthetic opportunities for accessing diverse and complex *N*-heterocyclic architectures. Consequently, the nucleophilic dearomatization of azaarenium salts has been extensively investigated with a broad range of nucleophiles, several of which will be discussed in this section.

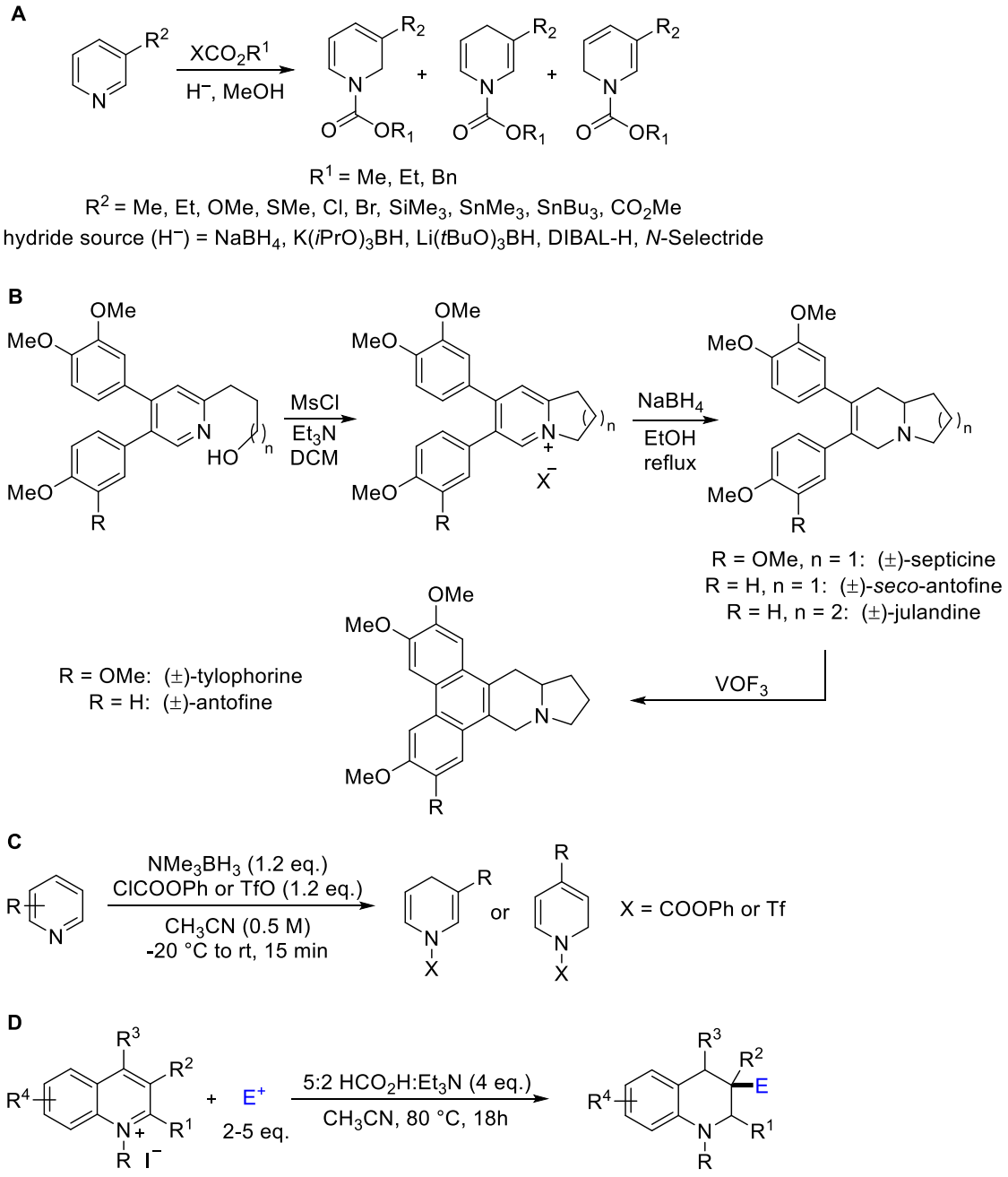
1.3.2.1. *Nucleophilic Addition of Hydrides*

The most straightforward method for introducing a hydride nucleophile into an azaarenium cation is through borohydride reagents such as $NaBH_4$. This approach was first reported in 1972 by Fowler in the synthesis of 1,2- and 1,4-dihydropyridines from an *in situ*-generated carbomethoxypyridinium salt.[148] In 1986, Fowler's reduction had become more widely adopted and was employed by Sundberg, Hamilton, and Trindle in their preparation of *N*-heterocyclic dienes for use in subsequent Diels–Alder reactions. In their study, 3-substituted pyridines were reduced to mixtures of 1,2-, 1,4-, and 1,6-dihydropyridine products using various borohydrides, including $NaBH_4$, K(*i*PrO)$_3$BH, Li(*t*BuO)$_3$AlH, diisobutylaluminium hydride (DIBAL-H), and *N*-Selectride (Scheme 1.46A).[149] In 1996, Ciufolini and Roschangar utilized this reduction as a key step in the synthesis of phenanthroizidine alkaloids and their *seco*-relatives (Scheme 1.46B). More recently, Pratap and Maji reported the stepwise synthesis of C3-nitro-substituted tetrahydroquinolines, in which dearomatization with $NaBH_4$ served as the critical initial step.[150]

In addition, Barton and co-workers demonstrated that sodium hydrogen telluride (NaHTe) could serve as an alternative to borohydride reagents for this dearomatization process. In their report, treatment of 1,3-dimethylpyridinium iodide and 1-methyl-3-acetylpyridinium iodide with NaHTe under basic conditions (pH 10-11) afforded mixtures of 1,2-, 1,4-, and 1,6-dihydropyridine products, with ratios of 4:1:2 for the alkylpyridinium and 2:1:2 for the acylpyridinium substrate, respectively.[151] More recently, in 2021, Glorius and colleagues showed that ammonia–borane (NH_3BH_3) could also be used in place of $NaBH_4$ for the reduction of *in situ*–generated *N*-acyl and *N*-sulfonyl pyridinium salts (Scheme 1.46C). Unlike Fowler's original conditions, the use of NH_3BH_3 proved to be more selective, often affording a single dihydropyridine product. This method also displayed broader substrate compatibility, extending beyond pyridines and quinolines to other *N*-heteroaromatic systems.[152]

In 2022, Donohoe employed a formic acid-triethylamine complex to achieve a related hydride addition on quinolinium and isoquinolinium substrates, generating transient *in situ* 1,4-dihydroquinolines and 1,2-dihydroisoquinolines, respectively. This dearomatization was coupled to a Stork-type enamine alkylation, affording C3-functionalized tetrahydroquinoline products (Scheme 1.46D).[153] A year later, Kuram, Kant, and Yadav built on this concept by combining hydride-driven dearomatization with a subsequent functionalization reaction. As in Donohoe's work, the formic acid–triethylamine complex was used as the hydride source;

however, functionalization was achieved using tosyl azides rather than enones, leading instead to C2-functionalized products.[154]



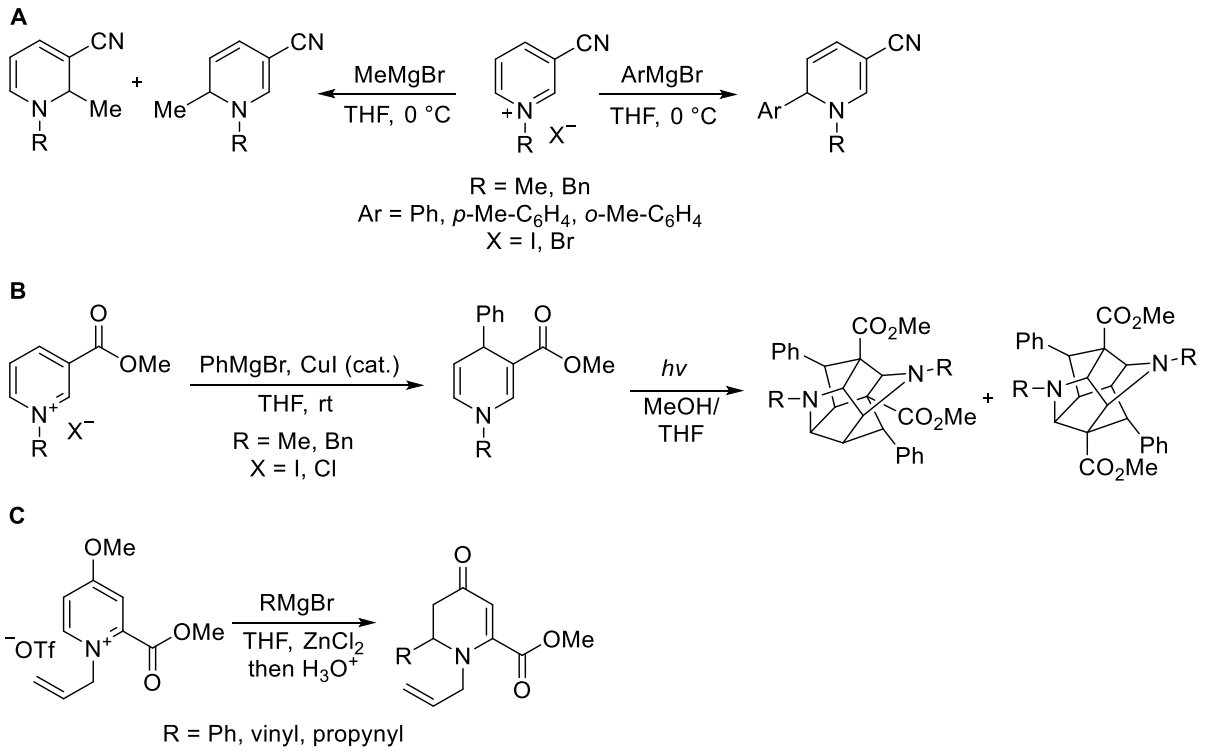
Scheme 1.46. Examples of reduction of pyridinium and quinolinium salts initiated by hydride addition.

1.3.2.2. *Nucleophilic Addition of Organometallic Reagents*

The addition of organometallic reagents to *N*-functionalized heteroaromatic salts has emerged as an efficient approach for preparing dearomatized products. Among them, Grignard reagents are widely employed as powerful carbon nucleophiles in these processes and typically favor addition at the C2 position, affording 1,2-dihydropyridine adducts. Significant progress in this area was already evident in the 1970s. For instance, in 1971 Lyle and co-workers reported the reaction of 1-alkyl-3-cyanopyridinium halides with alkyl or aryl Grignard reagents (Scheme 1.47A).[155] When methylmagnesium bromide was added to an *N*-methyl-3-cyanopyridinium salt, mixtures of 1,2- and 1,6-dihydropyridines were obtained. By contrast, the reaction of various aryl Grignard reagents with either *N*-methyl- or *N*-benzyl-3-cyanopyridinium salts furnished exclusively the 1,6-dihydropyridine products. In 1977, the same group extended this strategy to *N*-acyl pyridinium salts, which in this case delivered the 1,2-dihydropyridine product in 56% yield.[156]

In 1982, Comins and Abdullah further explored the reactivity of Grignard reagents with *N*-acyl pyridinium salts, obtaining both 1,2- and 1,4-dihydropyridine intermediates en route to substituted pyridines. Recognizing the lack of regioselectivity, they observed that the inclusion of a catalytic amount of copper(I) iodide strongly biased the reaction outcome, delivering exclusively the C4 addition products. Hilgeroth and Baumeister later applied this method in 2000 to access 4-aryl-1,4-dihydropyridines, which they elaborated into functionalized 6,12-diazatetrakishomocubanes for the first time (Scheme 1.47B).[157]

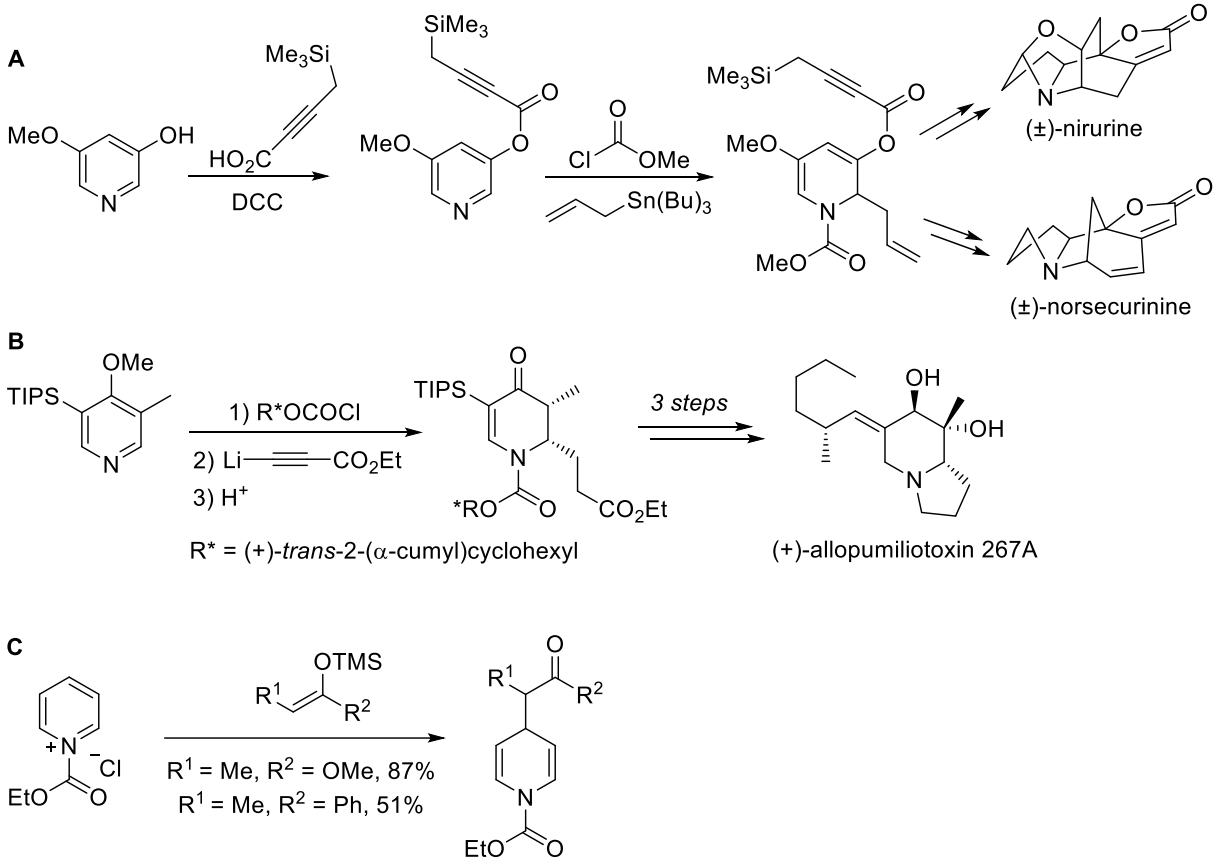
More recently, in 2009, Donohoe and co-workers reported the regioselective addition of diverse Grignard reagents to 4-methoxy-2-(methoxycarbonyl)-*N*-methylpyridinium salts. Treatment with alkyl Grignard reagents predominantly afforded 1,2-addition products, whereas alkenyl and alkynyl Grignard reagents gave the corresponding 1,6-addition products. When the *N*-substituent was varied to an allyl group, addition of aryl and vinyl Grignard reagents produced a 1:1 mixture of 1,2- and 1,6-dihydropyridine products. The authors rationalized these results by proposing that harder nucleophiles favored attack at C2, while softer nucleophiles preferred addition at C6. To validate this hypothesis, they pre-treated the Grignard reagent with zinc chloride, generating an organozinc species *in situ*. Under these conditions, exclusive C6 addition was observed, consistent with their mechanistic rationale (Scheme 1.47C).



Scheme 1.47. Examples of nucleophilic addition of Grignard reagents to pyridinium salts.

Other classes of organometallic reagents have also been employed as nucleophiles in the dearomatization of azaarenium salts, including organotin and organocadmium species. In fact, in the same study where Lyle and co-workers (1971) examined the addition of Grignard reagents to pyridinium salts, they also investigated organocadmium reagents.[155] Both methyl- and phenylcadmium reagents afforded outcomes comparable to the Grignard additions, giving mixtures of C2 and C6 products. Notably, these reagents displayed chemoselectivity, as no reaction occurred at the carbonyl group of the C3 ester substituent. Yamaguchi and co-workers reported the regioselective 1,2-addition of allylic stannanes, such as allyltributylstannane, to 3-substituted *N*-acyl pyridinium, quinolinium, and isoquinolinium salts.[158] This selective dearomatization method was later adopted by Magnus in his bioinspired syntheses of (±)-nirurine (Scheme 1.48A) and (±)-norsecurinine from 3-hydroxy-5-methoxypyridine (Scheme 1.48A).[159,160] Nucleophilic addition with organolithium reagents has also been explored. In 1986, Meyers and Oppenlaender described the C4 selective addition of an organolithium reagent to an acyl-activated pyridine. In this case, the pyridine substrate carried a chiral oxazoline auxiliary, which enforced diastereoselective addition.[161] Comins and co-workers further expanded on organolithium chemistry by reacting 4-methoxy-5-methyl-3-triisopropylsilylpyridine with an alkynyllithium in the presence of (+)-*trans*-2-(α-cumyl)cyclohexanol chloroformate as the activating agent. After acidic workup, the reaction

furnished a C2 alkynylated dihydropyridone, which was subsequently elaborated to (+)-allopumiliotoxin 267A (Scheme 1.48B).[162] Finally, Akiba and co-workers demonstrated that silyl enol ethers derived from ketones, as well as silyl ketene acetals, undergo C4 addition to *in situ* generated 1-ethoxycarbonylpyridinium salts (Scheme 1.48C)[163]

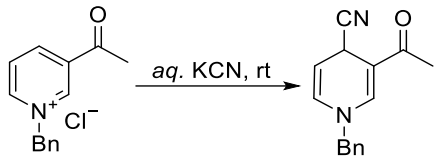


Scheme 1.48. Examples of other organometallic reagents to pyridinium salts.

1.3.2.3. *Nucleophilic Addition of Other Nucleophiles*

Nucleophilic addition of cyanide nucleophiles to *N*-acyl heteroaromatic salts was first reported in 1905 by Reissert. In this account, quinoline was treated with aqueous potassium cyanide (KCN) in the presence of benzoyl chloride, affording 1-benzoyl-2-cyano-1,2-dihydroquinoline.[164] Appropriately, such reactions are now referred to as Reissert reactions or Reissert-type reactions. In 1941, Grosheintz and Fischer expanded on this transformation by varying the acyl substituents attached to the nitrogen atom of the quinolinium substrate.[165] Since then, the reaction has been successfully extended to other heteroaromatic systems, most

notably pyridines, quinolines, and isoquinolines. A general trend observed in cyanide addition to pyridinium salts bearing an electron-withdrawing group at C3 is exclusive C4 addition, which affords stable products. Anderson and Berkelhammer's reaction of 3-acetyl-*N*-benzylpyridinium with KCN, which yielded only the 1,4-dihydropyridine product, exemplifies this selectivity (Scheme 1.49).[166] A related case was reported by Foster and Fyfe, who examined the NMR spectra of several pyridinium salts treated with cyanide in DMSO and likewise observed exclusive C4 addition.[167]

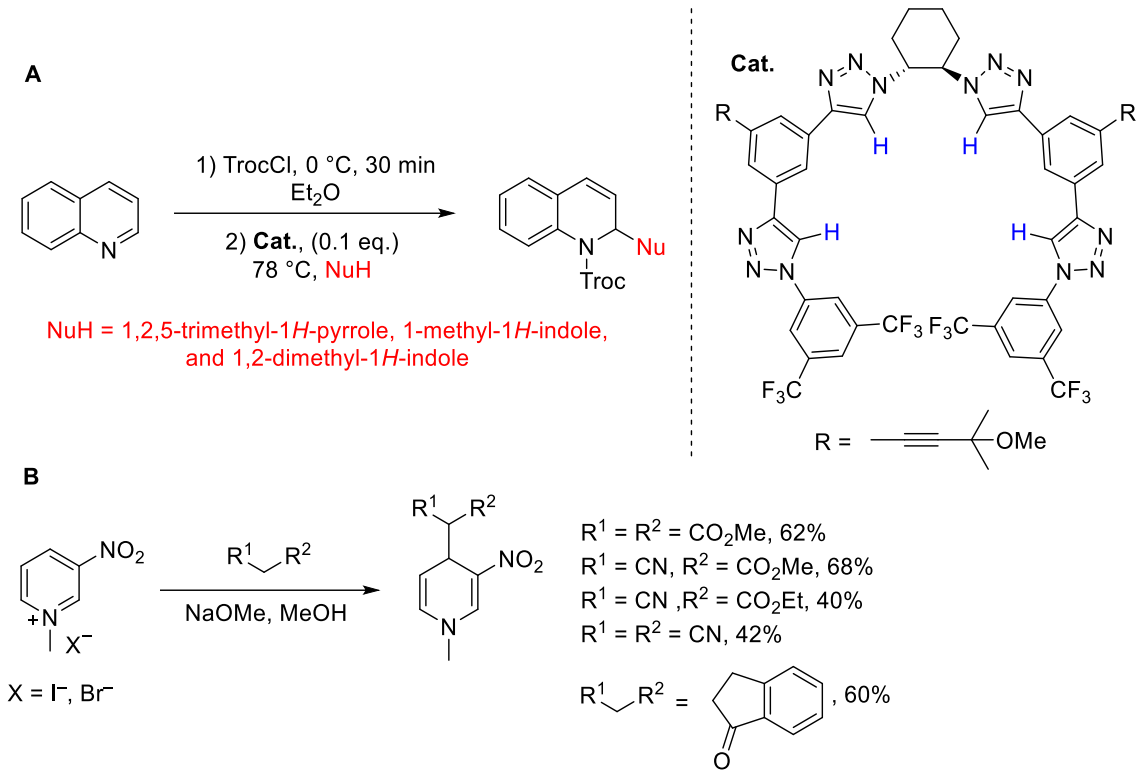


Scheme 1.49. Representative example of a Reissert reaction.

Electron-rich aromatic systems such as indoles and pyrroles have also been employed as nucleophiles in the dearomatization of azaarenium salts. Duong, Schifferer, and Mancheño demonstrated this in their 2019 report, wherein 1,2,5-trimethyl-1*H*-pyrrole, 1-methyl-1*H*-indole, and 1,2-dimethyl-1*H*-indole were added to quinoline in the presence of a chiral tetrakis(triazole) anion-binding catalyst and trichloroethyl chloroformate (Troc–Cl) as the activator (Scheme 1.50A).[168]

1.3.2.4. *Addition of Carbon Nucleophiles via Aromatics, Enolates, and Enamines*

Other carbon nucleophiles include *in situ* base-generated enolates from malonic esters and other appropriate carbonyls or nitriles. Pioneering work emerged from the Kröhnke group in the 1950s, which included the C4 addition of acetone to *N*-(2,6-dichloro)benzylpyridinium.[169] Severin, Lerche, and Bätz subjected 1-methyl-3-nitropyridin-1-ium to enolates derived from malonates, nitriles, and a 1-indanone, all of which resulted in the formation of their corresponding 1,4-dihydropyridines with yields ranging from 40% to 60% (Scheme 1.50B).[170]

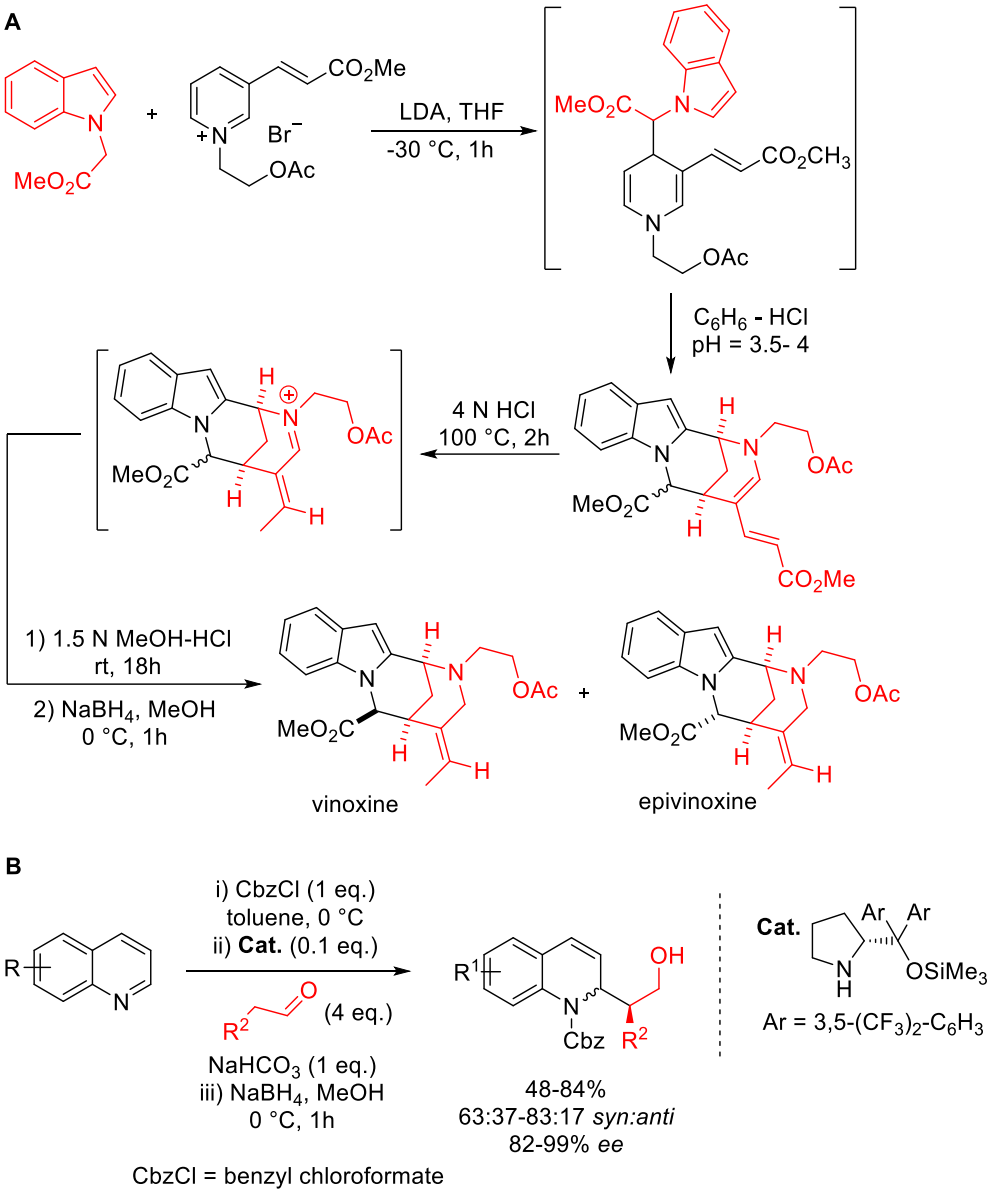


Scheme 1.50. Addition of indole and enolate based nucleophiles to azaarenium salts.

Furthermore, pyridiniums bearing an electron-poor substituent at C3 produce enamines upon C4 addition of an enolate, which can undergo a cascade cyclization process to yield 1,2,3,4-tetrahydropyridines. In this process, the enamine is first captured by a proton to generate a 3,4-dihydropyridinium ion that can react with a second nucleophile in either an inter- or intramolecular fashion. This process is referred to as the "Wenkert procedure," and the report by Bennasar and co-workers is an instance in which this was demonstrated. In their report, the nucleophilic addition of indole acetic ester enolates to *N*-alkylpyridinium salts was performed, followed by subsequent reactions in accordance with the "Wenkert procedure" to form vinoxine and epivinoxine (Scheme 1.51A).[171,172] This process was also extended to quinolinium salts possessing an electron-donating group at C2, as was reported by Moghaddam and co-workers, who formed heterotetracyclic benzoxazocines via the addition of 1,3-dicarbonyls.[173]

The addition of enamine nucleophiles has also been reported, as in a publication by Beifuss where a C2 selective addition of enamines was performed on 4-silyloxyquinolinium triflates, giving high yields.[174] Cozzi and Gualandi reported the stereoselective addition of aldehydes to acylpyridiniums in the presence of a catalytic amount of a chiral secondary amine (Scheme

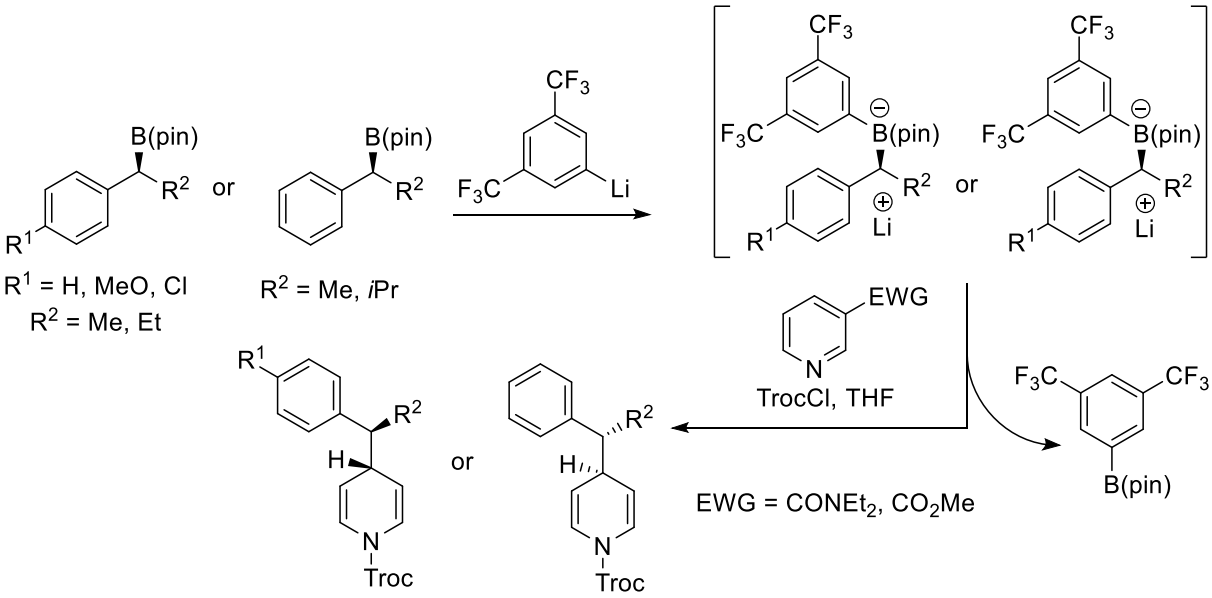
1.51B).[175] Long before this, Jørgensen and co-workers reported an intramolecular variation of this concept with *N*-alkylated isoquinolinium substrates. In Jørgensen's case, the 1,2-dihydroisoquinoline product required further modifications—in particular, the introduction of a trifluoroacetyl group at the 4-position (β-position)—to stabilize them.[176]



Scheme 1.51. (**A**) Preparation of vinoxine and epivinoxine via "Wenkert procedure" and (**B**) Utilization of enamine chemistry for the dearomatization of quinolines.

The Aggarwal group developed configurationally stable chiral lithiated boronic esters and examined their reactivity with *N*-acylpyridinium salts bearing electron-withdrawing groups at C3.[177] (Scheme 1.52) The reactions proceeded efficiently with high diastereoselectivity, which

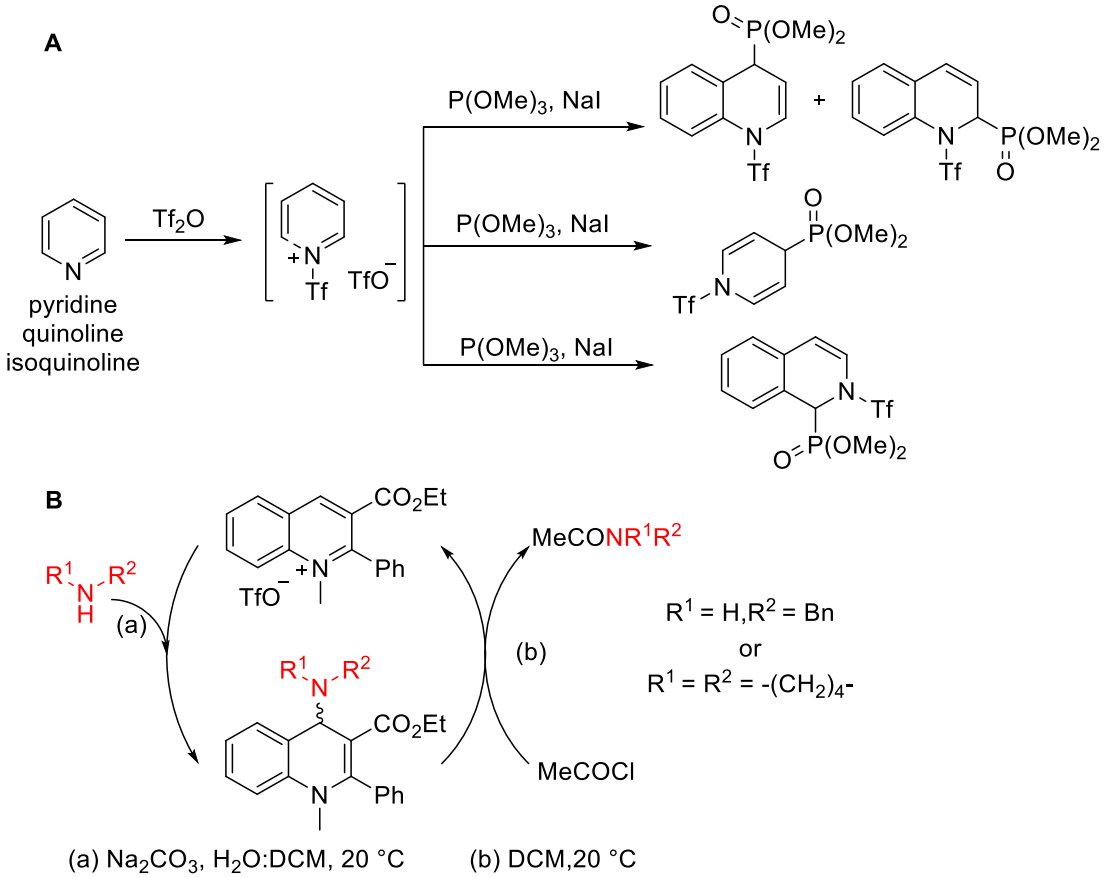
the authors attributed to favorable cation–π interactions between the pyridinium ion and the electron-rich boron-ate complex, combined with minimized steric interactions. Takemoto and co-workers further advanced the field with the asymmetric dearomatization of quinolines using vinylboronic acids as nucleophiles. This transformation, catalyzed by a chiral thiourea, gave 1,2-adducts in 28-78% yield and with excellent enantioselectivity (82-97% *ee*). Here, both the activation of the pyridinium substrate and the boronic acid, as well as stereocontrol, were facilitated by the thiourea catalyst.[178] In 2020, Karimov and co-workers employed boronic acids in a Rhodium-catalyzed dearomatization of pyridinium salts. The catalytic system, consisting of $Rh(COD)_2BF_4$ and BINAP, displayed broad functional group tolerance and efficiently accommodated diverse boronic acid substrates.[179]



Scheme 1.52. Example of nucleophilic addition of a chiral Aggarwal's reagent.

Beyond carbon-based nucleophiles, procedures involving phosphorus-, nitrogen-, and oxygen-centered nucleophiles have also been developed. In 1999, Anders and colleagues described the addition of trimethyl phosphite to in situ-generated *N*-(trifluoromethylsulfonyl) pyridinium, quinolinium, isoquinolinium, and acridinium triflates (Scheme 1.53A). Levacher and co-workers achieved C4 dearomatization of a biomimetic NAD^+-quinolinium derivative using amine nucleophiles, yielding 1,4-dihydroquinolines that served as amide-transfer reagents when treated with acetyl chloride under neutral conditions, thereby regenerating the quinolinium salt (Scheme 1.53B). Finally, as part of a mechanistic study on pyridinium-

catalyzed glycosylations, Berkessel and colleagues observed C2 addition of benzyl alcohol to a pyridinium ion, generating a 1,2-dihydropyridinium intermediate. Similar additions were also reported with methanol, benzylamine, and benzyl mercaptan.



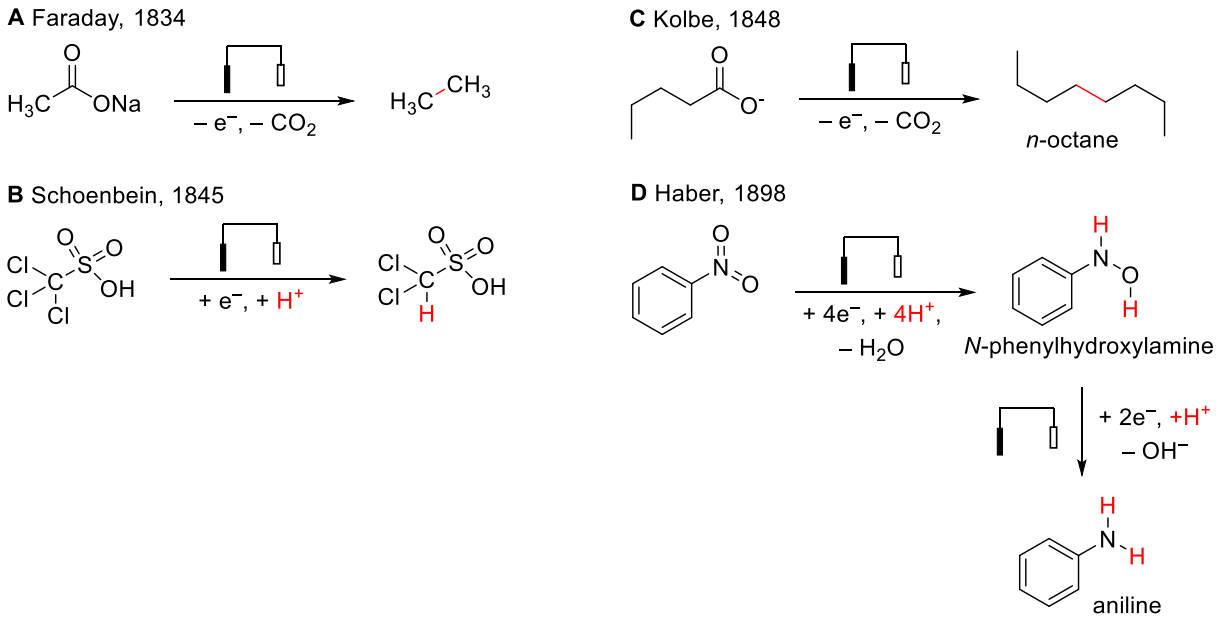
Scheme 1.53. Examples of heteroatom nucleophile additions to azaarenium salt.

The above examples illustrate the remarkable range of nucleophiles that can participate in the dearomatization of azaarenium salts. From the earliest cyanide additions to modern enantioselective transformations, the choice of nucleophile and activation strategy has proven decisive in steering regio- and stereoselectivity. The resulting methodologies have not only broadened the synthetic utility of these reactions but also established them as powerful tools for constructing complex heterocyclic frameworks with high precision.

1.4. Organic Electrochemistry

1.4.1. History and Development of Electroorganic Chemistry

Prior to the 1970s and 80s, the only standards for a reaction that a synthetic organic chemist of that time would primarily focus on in order to develop a potentially useful process was the selectivity and the yield. They were not restricted by other reaction parameters that delt with reagent or solvent toxicity and waste treatment, which were also not taken as significant issues. These attitudes led to misguided practices concerning industrial scale chemical production, use, and disposal, which inevitably resulted in notable negative environmental and health impacts.[180,181] Naturally, this eventually evoked a counter in the form of sustainable development goals and the 12 principles of green chemistry. In this context, reducing waste generation and keeping clear of hazardous reagents while maintaining an optimal atom economy became a benchmark in the method development of organic transformations. Furthermore, in addition to cost reduction, the circular economy is progressively treating these sustainability and green objectives as a "permit to operate".[180–183] As such, the development of synthetic protocols that inherently adhere to these goals is increasingly becoming more important. Fortunately, electrochemistry can serve as a suitable approach for the development of such environmentally benign synthetic methodologies.



Scheme 1.54. Examples of the earliest electroorganic reactions.

The assimilation of the principles of electrochemistry into an organic process is known as electroorganic synthesis. Herein, electricity is directly employed as a reagent to initiate and propel the redox processes. In this way, the technique meets the requirements that qualify it as "green" since electrons are used in place of stoichiometric amounts of traditional and hazardous redox reagents, which essentially prevents waste production while increasing safety.[184–187] The origin of this discipline is understood to have begun in 1800 when the first version of a modern electric battery, the voltaic pile, was invented by Alessandro Volta.[188] This discovery was quickly followed up by a report on the electrolysis of water, alcohols and aliphatic oils which was made by Vasily V. Petrov in 1803. [189] Thereafter, Michael Faraday made the most significant contributions that ultimately kindled the recognition of electrochemistry as a viable technique for organic synthesis. These contributions even included the terminology that is regularly used in electrochemical protocols such as anode, cathode and electrolysis. His first major addition to the field began with his discovery of the foundational Faraday's laws in 1833. Furthermore, Faraday's insightful observation on the behavior of ions in solutions as a result of an electrochemical potential led to the eventual utilization of ionic salts as electrolytes in organic systems.[190] In 1834, he discovered that the electrolysis of an aqueous acetate solution led to the presumed formation of ethane and carbon dioxide (Scheme 1.54A).[191] This report is regarded as the first preparative electroorganic synthesis. A more practical equivalent of this synthesis known as Kolbe electrolysis was then developed in 1848 (Scheme 1.54C).[192] In this revered process, the dimerization of alkyl radicals that have been accessed via the electrochemical oxidative cleavage of alkyl carboxylic acids is observed. Two years prior to this, the first electrochemical reduction, namely, the dehalogenation of trichloromethanesulfonic acid, was discovered by Schoenbein (Scheme 1.54B).[190,193] These early undertakings served as important displays of the synthetic potential of electrochemistry which was enough to influence many bold chemists into embracing it and incorporating it into their organic experiments. Acceptance of this new methodology was maintained over the remainder of the 1800s and was carried over in the early part of the 20th century. This was typified by further findings such as the discovery of the electrochemical reduction of nitrobenzene to aniline and *N*-phenylhydroxylamine by Haber in 1898 (Scheme 1.54D).[194,195] In this experiment, Haber made a sharp observation that would later play major role in the evolution of this technique. He became aware of the fact that maintaining the same current density resulted in the gradual decrease in potential which, in turn, directly affected the reaction's selectivity. Less negative potentials favored the formation of *N*-phenylhydroxylamine while aniline formation was preferred at more negative potentials. In this regard, he rationalized that keeping a steady reduction potential at the working electrode was essential, but achieving this feat was not convenient at the time.[195] Running experiments at constant potential only became more practical after Hickling invented the potentiostat in 1942.

Haber's findings showcased that electrode potential was a crucial parameter in electrochemical processes which initiated the events that eventually led to the invention of this instrument. The potentiostat was a vital development since interest in electroorganic synthesis had been depreciating for nearly three decades prior to its introduction. This decline in interest was likely due to the lack of selectivity that was predominant in a number of previous publications. Hence, attaining an instrument that allowed for convenient control over the reaction's potential was very beneficial in addressing some of these selectivity issues.

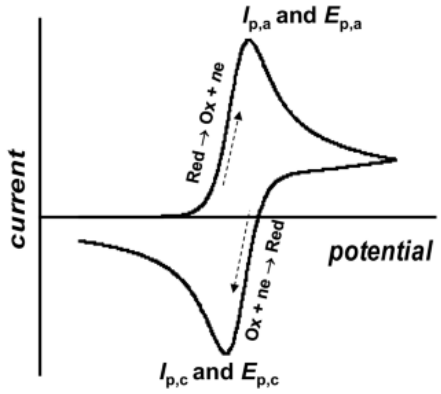
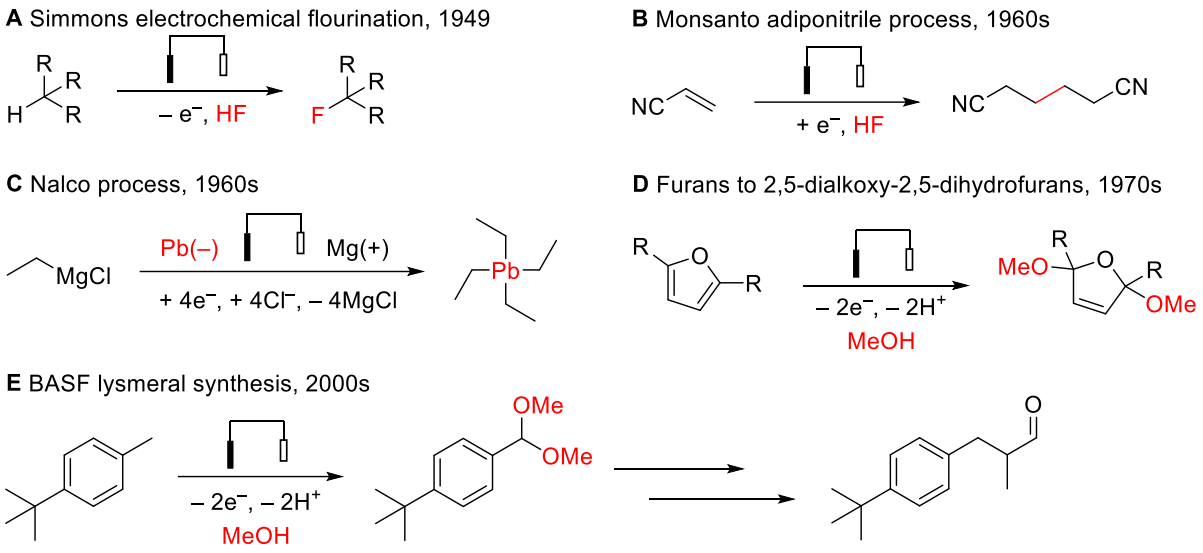


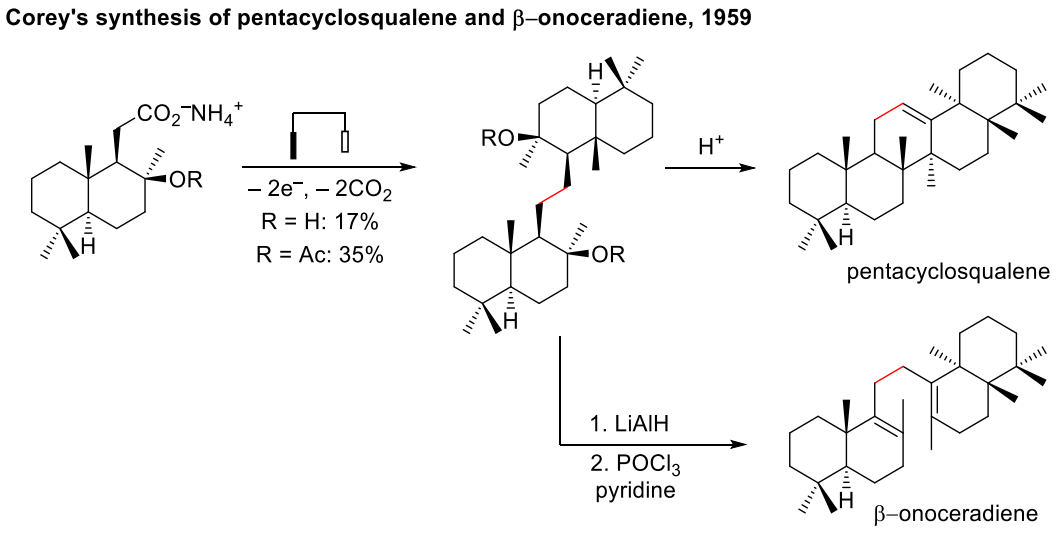
Figure 1.2. A typical cyclic voltammogram belonging to an analyte that can undergo reversible oxidation and reduction reactions; $\boldsymbol{I}_{\mathbf{p,a}}$ and $\boldsymbol{I}_{\mathbf{p,c}}$ represent the anodic and cathodic currents, respectively, while $\boldsymbol{E}_{\mathbf{p,a}}$ and $\boldsymbol{E}_{\mathbf{p,c}}$ depicts the corresponding electrode potentials (vs a reference) of a maximal reaction rate.[196]

Another plausible reason that could justify the weakening of electrosynthesis during this period was the lack of knowledge on the key kinetic and mechanistic aspects of these reactions. This major barrier was overcome when polarography and cyclic voltammetry (Figure 1.2) emerged in 1922 and 1948 respectively.[197,198] With these electroanalytical methods in hand, it became possible to accurately measure the individual electrochemical potentials of any functional groups within a given molecule. Gaining the tools to be able to determine this electrochemical redox property with good precision made it possible to suitably "fine-tune" the potentiostatic electrolysis of any substrate that had been analyzed beforehand.[190] Additionally, the thermodynamic and kinetic information gained from these electroanalytical techniques was not only restricted to the heterogenous events occurring at the electrode interface but also extended to the succeeding chemical reactions.[199] This remarkable progress in the theory of electrode kinetics together with the relevant technological advancements resulted in the development of long-standing industrial scale electrochemical processes. Some well-known examples of this significant development include the Simmons electrochemical fluorination,

the Monsanto adiponitrile process, the Nalco process, the production of 2,5-dialkoxy-2,5-dihydrofurans from furan and BASF lysmeral synthesis (Scheme 1.55).[200–204] This was also a demonstration of the intrinsic scalability of electroorganic synthesis. An additional merit of electroorganic chemistry that was demonstrated during this period was its use in natural product synthesis, particularly, in the total synthesis of pentacyclosqualene and onoceradiene (Scheme 1.56).[205]



Scheme 1.55. Industrial scale electroorganic reactions.



Scheme 1.56. One of the earliest examples of the utilization of an electrochemical reaction in natural product synthesis.

Having a clearer insight of electrode kinetics increased recognition of the importance of the electrodes. Further inquiries indicated that difficulties with electrode deactivation (passivation) and the occasional requirement to apply an overpotential (high kinetic barriers) were directly linked to the heterogenous electron transfer events that occurred at the interface.[190,206–210] These were the complications that inspired the strategy of indirect electrolysis (Figure 1.3), an approach where a redox-active species is used to mediate the electron transfer between the substrate and the electrode. Indirect electrolysis was introduced as early as 1900 and a representative example is the chromium mediated oxidation of naphthalene or anthracene to their corresponding quinones.[211] Redox mediators were exclusively inorganic until many reports from the 1960s onwards uncovered triarylamines and other organic molecules as effective mediators as well.[212–214] Steckhan efforts to formalize the fundamental principles of indirect electrolysis in the 1980s also facilitated the growth of this concept.[209,210]

Aside from electrode passivation during direct electrolysis with undivided setups, another issue that emerged for situations involving high energy electro-generated intermediates was their premature quenching at the counter electrode. The employment of a divided cell was implemented to counter this issue. In divided setups, a partially permeable membrane is used as a boundary between the anodic and cathode sections.[215] Early applications of this membrane electrolysis were pioneered by Maigrot and Stabates in 1889.[216] A number of problems still arose in membrane divided cells when non-aqueous solvents were utilized.[203] In this case, particularly for cathodic reduction reactions, an undivided system using a sacrificial anode served as a suitable work around. Sacrificial anodes stave off any unwanted oxidation processes since their oxidative dissolution is favored.[190,203]

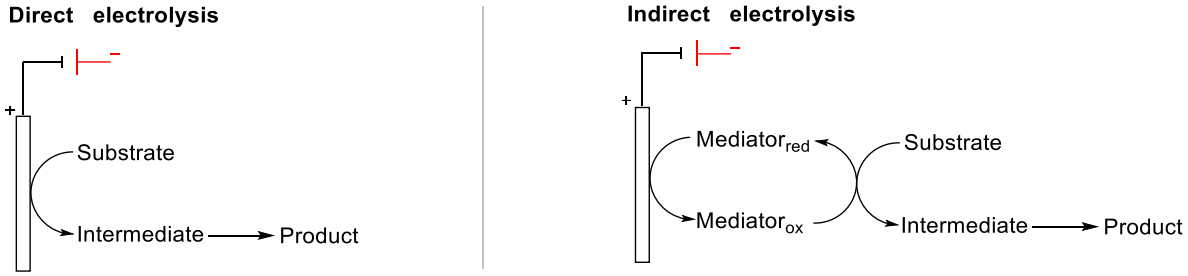


Figure 1.3. Electron transfer in organic electrochemistry.

Another pivotal electroorganic development was the Shono oxidation, in 1975. It is a methodology that grants access to α-functionalized alkyl amides, and the fact that it remained one of most researched and most used transformations up to now is a testament of its

resourcefulness.[217] Within the same year, Miller and co-workers invented a chiral electrode where the working electrode was chemically modified by covalently attaching (*S*)-phenylglycine to its surface.[218] This development presented a novel possibly to perform asymmetric reactions with an electroorganic setup. Yoshida brought in the idea of employing electro-auxiliaries in 1986.[219] Here, the substrates were selectively modified with either silicon or sulfur containing functional groups in order to lower their electrochemical potential, hence, enabling control over regio- and chemoselectivity. Yoshida also introduced the concept of the "cation pool" in 1999. The context of this concept is related to the nucleophilic capturing of anodically generated cationic intermediates. Because nucleophiles can also undergo electro-oxidation their presence in electrochemical systems can impede the desired oxidation processes. In this regard, Yoshida conducted anodic oxidation under cryogenic conditions without including any nucleophiles in the reaction mixture. This facilitated the build-up of reactive cationic intermediates (a cation pool) that could be coupled to a variety of nucleophiles in downstream functionalizations.[220,221] 1999 was also a crucial year for paired electrolysis which was successfully implemented on an industrial scale by BASF for the simultaneous preparation of phthalide and *t*-butylbenzaldehyde dimethylacetal. Paired electrolysis maximizes both atom economy and energy efficient since both electrodes contribute towards product formation.[222] Several research groups have been instrumental in using the classical electroorganic strategies outlined above to establish new reactivities. For instance, research led by Moeller[223–227] has illustrated that two nucleophilic groups could be coupled via anodic oxidation. These new methodologies are important additions to the retrosynthetic toolbox as they offer a wide range of convenient umpolung disconnections. This synthetic utility is appropriately represented in Moeller's synthesis of alliacol A.[228] A report of the total synthesis of dixiamycin B by Baran and co-workers was crucial in highlighting the enabling reactivity that is provided by electroorganic synthesis.[229] Their publication detailed how they were finally able to attain the desired reactivity via electrochemistry when rigorous attempts with chemical oxidants had appeared to be futile. After such an impressive showing of the synthetic potential of electrochemistry, Baran embraced the technique and later advocated for the development of standardized instrumentation. This was quickly followed by unveiling of the Electrasyn 2.0 in 2017 which IKA® developed by cooperating with Baran's lab.[230] Other efforts from Baran include some outstanding reviews that are designed to serve as informative guidelines, to help improve the general perception of electrosynthesis and to ease entry into this research.[190,230–234] Similar detailed reviews have also been published by Waldvogel and his other works include coupling electrochemistry with laboratory software to achieve automated optimization that is facilitated by a statistical tool such as Design of Experiment (DoE).[184,185,204,235–240] In addition, Waldvogel and co-workers have also paired Density Functional Theory (DFT) computations with Principal Component Analysis (PCA) to help in

the selection of a suitable supporting electrolyte for some selected reduction reactions.[241,242] Although all of the accounts described above are not exhaustive, they are sufficient representations of the monumental occasions that championed electroorganic synthesis. They helped in sustaining this area of study during the various periods where it experienced significant declines in research interest.

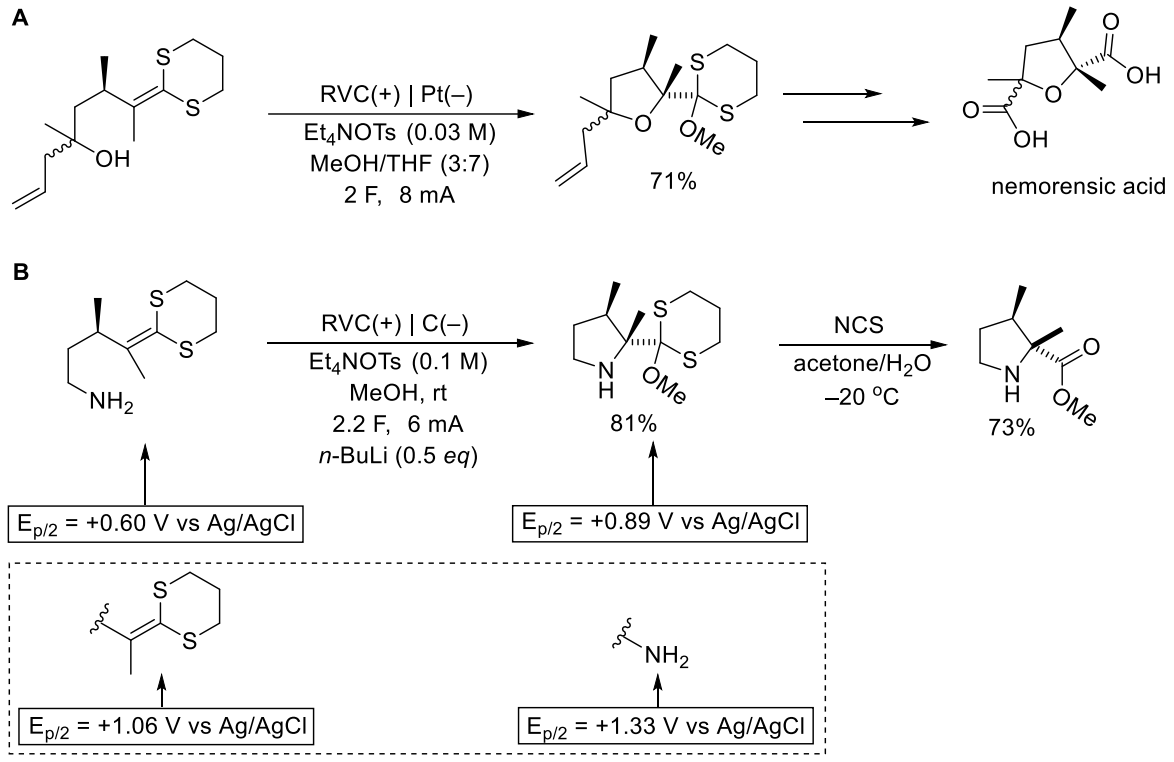
1.4.2. The Electrochemical Setup and Parameters

1.4.2.1. *Modes of Operation*

The two main modes of cell operation that are primarily used to conduct electroorganic synthetic reactions are the galvanostatic and potentiostatic modes. Under galvanostatic conditions, the current is kept constant, conversely, it is the potential of the working electrode that is kept constant under potentiostatic conditions. When utilizing the potentiostatic mode, the potential observed at the working electrode is maintained relative to the reference electrode. This mode provides maximum selectivity since the potential that is used is selected in accordance with the redox potential of the substrate of interest. During the course of a potentiostatic reaction, a gradual decrease in the flow of current is experienced as the substrate molecules are being consumed. As such, the reaction will essentially terminate itself when the substrate molecules are depleted. Due to this, the retardation of substrate conversion occurs as the reaction progresses. As a result, it is difficult to push them to completion which is a major drawback of this mode.[235,243]

For the galvanostatic mode, the potential observed at the working electrode changes. As soon as the reaction is initiated, the potential at the working electrode will adjust itself to match that of any substrate in the solution with the lowest redox potential. The electrode potential will then stabilize at that point until that substrate is consumed. When the concentration of this substrate goes below a certain point, especially near the electrodes, the flow of electric current becomes more difficult. In order to stop any decrease in current and maintain it, the potential at the working electrode will automatically readjust until it matches itself to that of another species with the next lowest redox potential. This other species could potentially be the product, the solvent or even some component of the supporting electrolyte, hence, selectivity can be lost at the later stages of the reaction which is a major drawback of this mode. Fortunately, this negative effect is minimized by keeping the current low. In this way, the potential will not adjust again until at least 90% of the desired (initial) substrate is consumed. Additionally, unlike the

potentiostatic cell, the set up for a galvanostatic cell is simpler and does not require a reference electrode.[235,243]

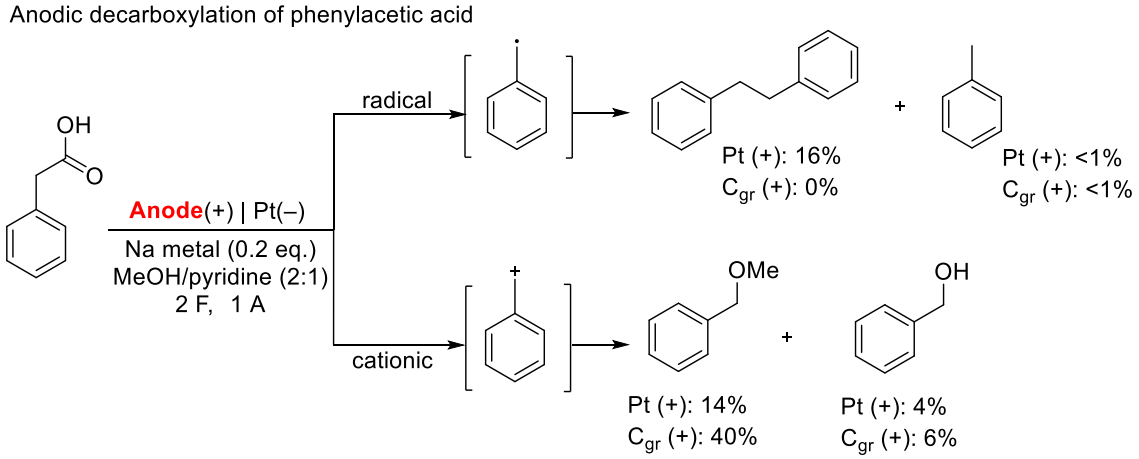


Scheme 1.57. Reactions originating from the anodic oxidation of a dithioketene acetal under constant current conditions.

Owing to the beneficial features of the constant current mode mentioned above, the versatility of this mode also received a positive evaluation when weighed up against conventional chemical methods. In his review, Moeller[243] pointed out that the unique attribute of a galvanostatic cell to auto-adjust its working potential in accordance with the substrate indicates that the same electrochemical setup and reaction conditions can be applied to virtually any substrate. This was nicely demonstrated with the two examples that are outlined in Scheme 1.57. In these examples, the oxidative cyclization in both cases was initiated by the oxidation of the dithioketene acetal moiety. In the first example (Scheme 1.57A), the preparation of a tetrahydrofuran derivative that is used as an intermediate in the synthesis of nemorensic acid was achieved.[244] Here, electrode potential changed and stabilised at +1.06 V vs Ag/AgCl, the approximated oxidation potential of the substrate's dithioketene acetal functional group. Access to a proline product was achieved in the second case (Scheme 1.57B), again, the same principle where the working potential automatically changes to that of the substrate applies.[245] In this case, the substrate potential was lower (+0.60 V vs Ag/AgCl) owing to the rapid

cyclization reaction that depletes the cationic intermediates near electrode surface. At this lower potential, the overoxidation of the cyclized product is circumvented. On the other hand, it is not possible to elect a single chemical oxidant that can successfully work for both substrates even though both transformations arise from the oxidation of the same functional group. A chemical oxidant that would be ideal for the second case (Scheme 1.57B) is not going to be powerful enough to even initiate the reaction depicted in Scheme 1.57A. Similarly, a chemical oxidant that is suitable for the first case (Scheme 1.57A) would be too aggressive for the second case (Scheme 1.57B) and will not result in the selective formation of the proline product. Clearly, this dilemma disappears when constant current electrolysis is employed due to its capacity to self-regulate the potential of the working electrode.

1.4.2.2. *Other Important Technical and Experimental Considerations*



Scheme 1.58. Effect of the anode material on reaction outcome.

Electrodes are another technical aspect that deserve consideration since the outcome of the electrochemical reaction, with respect to yield and selectivity, can be strongly associated to the electrode material.[246] A suitable demonstration of this effect is shown in Scheme 1.58 where the use of platinum and carbon-based electrodes as anodes in an identical oxidative reaction is compared.[247] In this example, the products that are observed either originated from a 1-electron oxidation (radical pathway) or a 2-electron oxidation (cationic pathway). It is plain that the radical pathway is preferred when the anode is platinum while the cationic pathway is favored when the anode is carbon-based. This is because platinum anodes are not as effective as carbon anodes at performing 2-electron oxidations.[248] This contrast in the oxidative ability of the electrodes is proposed to stem from the higher adsorption probability that the radicals have for

carbon due to the presence of paramagnetic centers in the material. The adsorbed radicals are more likely to be further oxidized to carbocations that are then electrostatically repelled by the anode and are ready to react with any nucleophile. Conversely, the radicals generated at the platinum's interface are mostly desorbed, thus, they are more likely to engage in radical reactions.[249]

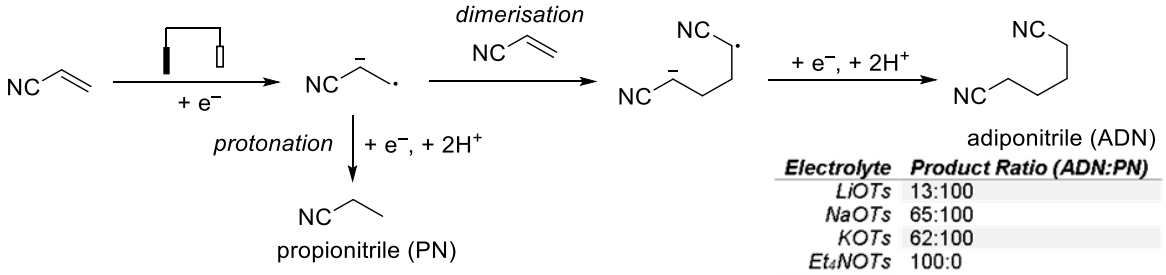
Other qualities of the electrode that are paramount to the outcome of the reaction include electrode arrangement and the surface area.[235,250] Electrode arrangement governs the electric field distribution within the electrolysis cell and in doing so affects selectivity and current density. A homogenous electric field is preferred and the electrode layouts that result in one are the concentric or coplanar arrangements. The backsides of the electrodes are insignificant in relation to the effected synthesis. Typically, a direct correlation exists between the current density that is bordered by both electrodes and the density of the field lines in the electric field. Thus, when there is a smaller electric field, then a lower voltage is generated which leads to the eventual creation of areas without electro-conversion. Additionally, an inconsistent distribution of the voltage across the electrode surfaces is linked to instabilities in the current density. Electrodes with irregular surfaces supply higher currents at the peaks, which also accounts for electrochemical hotspots. The selectivity of electro-conversion is degraded if the electric field is not homogenous, as such, an angular arrangement of the electrodes should also be avoided. The manner in which the electric field distributed when the electrodes are angular is not beneficial since it decreases the effective electrode surface area that is available for substrate conversion.[235,251]

Regarding the electrode surface area, it is involved in the regulation of the reaction's current density. Hence, if maintaining a low current density during the reaction is crucial then the employment of large surface area electrode would be beneficial. This is because the current density is considered as the electrochemical equivalent of the "concentration of the oxidant" that is used. As an example, the oxidative cyclization portrayed in Scheme 1.57A & B went through a highly reactive radical cation intermediate that can readily dimerize. In this regard, a high surface area RVC anode was used in order to sustain a low current density, thus, the concentration of radical intermediates was kept low effectively subduing dimerization and promoting cyclization.[243]

Further requirements for an electrode material also encompass inertness, adequate electrical conductivity, robustness towards corrosion, convenient mechanical manipulation, non-toxicity, and affordability.[246,250,252]

The last variable that is crucial to the electrochemical setup is the supporting electrolyte. It facilitates the passage of current, thus, enabling electrical conductivity in the reaction medium.[242] The minimum criteria for the selection of a supporting electrolyte is sufficient conductivity and solubility.[250] During the electrochemical reaction, cationic intermediates are generated by the anode while the cathode produces anionic intermediates. However, it becomes more difficult to introduce more ionic intermediates as more charge accumulates at each electrode. This where the supporting electrolyte comes into play as it supplies the counterions for the ionic intermediates that are being generated.[243] Common supporting electrolytes are composed of an organic cation, typically a tetraakylammonium (NR_4^+), that is paired with an inorganic anion such as hexafluorophosphate (PF_6^-), tetrafluoroborate (BF_4^-), perchlorate (ClO_4^-) and so on. The anion component of the electrolyte may also be organic such as acetate (OAc^-), triflate (OTf^-) and tosylate (OTs^-). Other typical supporting electrolytes may be entirely inorganic, such as lithium perchlorate ($LiClO_4$).[253–255]

The ions of the supporting electrolyte have also been shown to directly influence the outcome of the reaction, particularly its selectivity and rate.[256] To rationalize this effect, it is essential to consider the immediate environment at each electrode when an electrochemical process begins. Upon initiation, the anions of the supporting electrolyte accumulate at the positively charged anode, forming a compact layer. This is followed by a secondary layer of cations from the electrolyte. A similar ionic arrangement occurs at the cathode, with the roles of ions reversed. Together, these structured layers constitute what is known as the electrochemical double layer, which defines the local environment at the electrode surface. Electron transfer at either electrode, as well as any rapid chemical reactions that follow, takes place predominantly within this double layer. Consequently, the chemical composition and properties of the double layer can have a significant influence on the reaction pathway.[204,243,246,257]



Electrolyte	Product Ratio (ADN:PN)
LiOTs	13:100
NaOTs	65:100
KOTs	62:100
Et₄NOTs	100:0

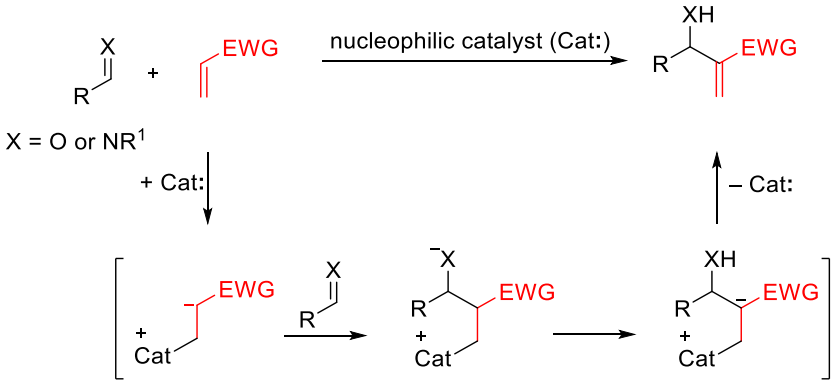
Scheme 1.59. The effect of the choice of the supporting electrolyte on the product selectivity in the cathodic reduction of acrylonitrile.

The adiponitrile process is a notable example where the nature of the electrical double layer significantly influences the reaction outcome. In this reaction, acrylonitrile molecules are first reduced at the cathode to form radical anions, which then dimerize to produce adiponitrile (Scheme 1.59).[200] Adiponitrile is obtained as the major product, with only trace amounts of other plausible by-products. This was particularly interesting, as the reaction was conducted in water, where the protonation of the intermediate radical anions to form propionitrile would typically be more favorable than dimerization. This interesting result can be primarily attributed to the use of tetraethylammonium tosylate as the supporting electrolyte. This electrolyte generates a relatively hydrophobic double layer at the cathode surface, effectively excluding the more polar water molecules from the interfacial region. As a result, a reaction pathway favoring dimerization was preferred.[243,258–260]

1.5. The Morita–Baylis–Hillman (MBH) Reaction

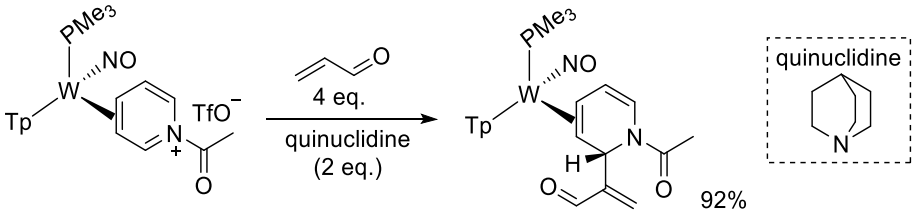
As one of the most convenient approaches for selectively constructing a new carbon-carbon bond, the Morita-Baylis-Hillman (MBH) reaction is held in high regard. As the name suggests, the MBH reaction was discovered by Morita in 1968, who reported the tricyclohexylphosphine-catalyzed coupling of acrylonitrile or methyl acrylate with various aldehydes to afford vinyl products, commonly referred to as Morita-Baylis-Hillman adducts, in yields of at least 70%.[261] In 1972, Baylis and Hillman followed up with a patent detailing a modification of this methodology wherein the phosphine catalyst was replaced with an amine catalyst.[262] Since then, many groups have recognized the synthetic potential of this protocol, expanding the research area through major reviews and systematic studies of the substrate scope.[263–265]

Consequently, it is now a well-established process that exhibits good atom economy, often requires mild conditions, and does not typically involve any metal additives. An additional advantage is that readily available and simple starting materials are converted into versatile products that can be further elaborated, thus magnifying their molecular complexity.[264] At its core, the MBH reaction is an umpolung strategy involving the nucleophilic addition of electron-poor alkenes (such as enones) to electrophilic carbonyls or imines under the influence of a phosphine or amine organocatalyst (Scheme 1.60).[266,267] Other activated alkenes successfully employed as nucleophiles include acrylonitrile, vinyl sulfones, vinyl sulfonates, vinyl phosphonates, nitroalkenes, and even allenes.[263,268,269] Conversely, the electrophilic scope is largely restricted to carbonyls and imines, although other electrophiles such as Michael acceptors, allyl and alkyl halides, or epoxides have been explored to a much lesser extent.[263,268,270] However, from a dearomatization perspective, only the use of *N*-activated heteroaromatic salts as electrophilic partners is of particular interest.



Scheme 1.60. General representation of a classic MBH reaction.

In this context, Harman and co-workers reported one of the earliest examples of a dearomative nucleophilic addition to a pyridinium molecule under MBH conditions.[271] In their study, an η^2-pyridinium complex of tungsten was used as the substrate. In this state, the pyridinium's π-system is localized, enabling it to couple with mild carbon nucleophiles in a regio- and stereoselective manner. Thus, treating the acetylpyridinium tungsten complex with acrolein in the presence of either quinuclidine, DABCO, or PPh_3 gave the corresponding C2-substituted dihydropyridine complex (Scheme 1.61).



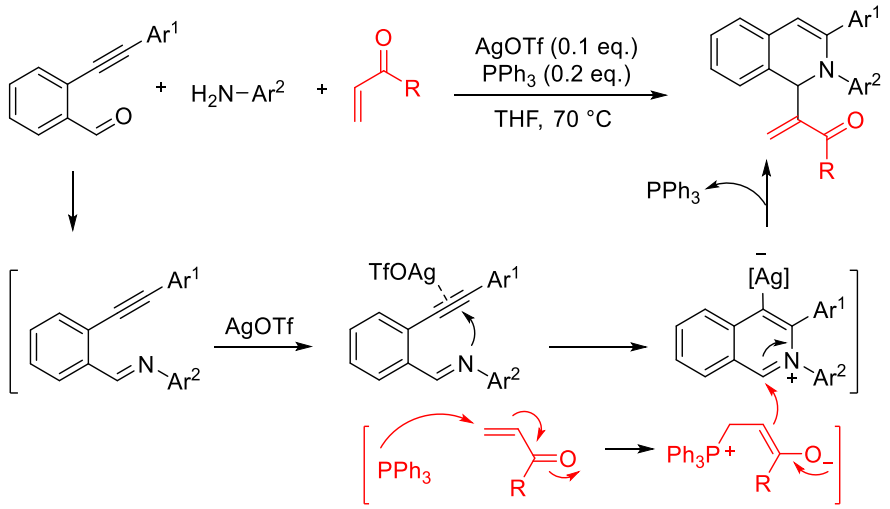
Scheme 1.61. Harman's aza-Morita-Baylis-Hillman reaction.

A year later, Ye and Wu reported the multicomponent synthesis of dihydroisoquinolines from 2-alkynyl benzaldehydes, anilines, and alkyl vinyl ketones, using silver triflate and triphenylphosphine as co-catalysts.[272] This synthesis leveraged Morita-Baylis-Hillman chemistry, where an *in situ*-generated isoquinolinium species is attacked by a phosphine-generated enolate nucleophile derived from the vinyl ketone (Scheme 1.62).

According to the proposed mechanism, the 2-alkynyl benzaldehyde and the aniline first form an imine. The alkyne moiety of this imine then coordinates to the silver triflate, activating it for attack by the imine nitrogen. A subsequent 6-*endo*-cyclization takes place to generate the key

isoquinolinium intermediate. Concurrently, the triphenylphosphine catalyst attacks the alkyl vinyl ketone to afford a zwitterionic enolate. This enolate then acts as the nucleophile, attacking the isoquinolinium intermediate to form the desired 1,2-dihydroisoquinoline product and regenerate the phosphine catalyst. Although many dihydroisoquinoline products (16 examples) were efficiently accessed with Ye and Wu's protocol, this methodology was confined to using only alkyl vinyl ketones as the alkene coupling partners.

In 2017, Basavaiah and Thamizharasi reported a significant improvement to this reaction.[273] They expanded the protocol to tolerate a variety of other activated alkenes, namely, alkyl acrylates (CO_2Me, CO_2Et, CO_2tBu, and CO_2Ph) and acrylonitrile. Their improved method also used DABCO as the organocatalyst instead of triphenylphosphine.



Scheme 1.62. Silver triflate and triphenylphosphine co-catalyzed three-component MBH reaction.

These examples demonstrate the successful adaptation of the Morita-Baylis-Hillman reaction for the dearomative functionalization of azaarenes. By employing *in situ*-generated pyridinium or isoquinolinium salts as non-traditional electrophiles, these methodologies effectively merge the principles of organocatalysis with modern dearomatization strategies.

1.6. Rationale and Objectives of the Thesis

The first chapter illustrates the development of dearomatization, from early discoveries to its standing as an indispensable tool in modern organic synthesis. The significant progress in this field is highlighted by the diverse and expansive range of available methodologies, including the oxidative and nucleophilic strategies that were discussed. Despite these advancements, key opportunities for further innovation remain, which form the motivation for the research presented in this thesis.

Many examples of oxidative dearomatizations reactions that were covered exposed a reliance on stoichiometric equivalents of the oxidant. This includes hypervalent iodine reagents like PIDA, peroxides like *tert*-butyl hydroperoxide (*t*BuO_2H), *N*-halosuccinamide (NXS), toxic reagents like lead(IV) acetate ($Pb(OAc)_4$), and so on. Although catalytic workarounds for these reactions have been developed, these methods still rely on stoichiometric amounts chemical terminal oxidants such as *m*CPBA, H_2O_2, O_2 etc. In contrast, the overview of organic electrochemistry clearly shows its potential as an intrinsically green substitute that does away with any stoichiometric redox reagents. The recent commercial availability of standardized electrochemical setups further enhances the convenience and accessibility of this technique for modern synthesis. In this regard, we selected the *ortho*-intramolecular dearomatization of phenols leading to spirooxacycles, a well-established transformation mediated by hypervalent iodine reagents, and sought to develop a straightforward electrochemical protocol for this reaction that would also enable a systematic study of its substrate scope and mechanism.

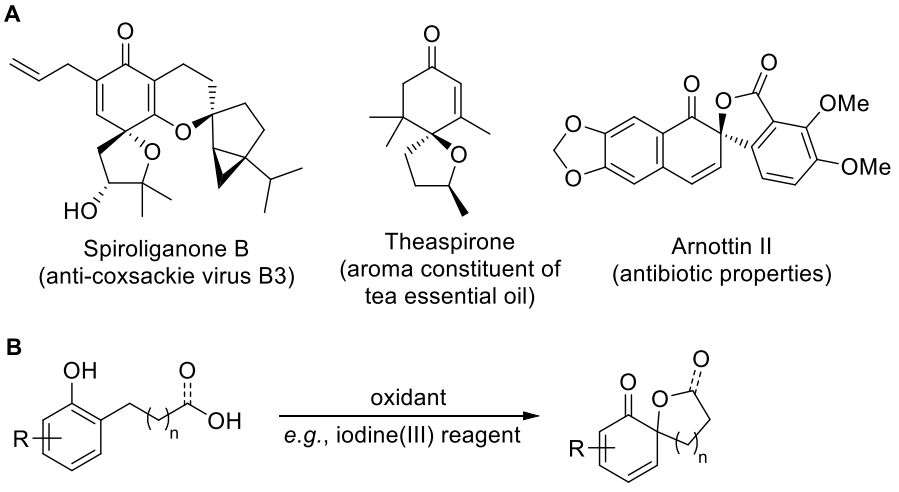
Most of the established examples covering nucleophilic addition to pre-activated azaarenium salts focus on controlling regioselectivity and stereoselectivity. A recurring theme in the progression of this chemistry is that this control is often achieved through the strategic choice of the *N*-activation method, the nature of the nucleophile, and the increasing use of catalytic and asymmetric systems. Within this context, the Morita-Baylis-Hillman (MBH) reaction represents a comparatively recent and less-explored approach. Although it has progressed significantly since Harman's initial proof-of-concept with a metal-complexed pyridinium substrate, it is not as established as other dearomative methods. In this regard, we sought to expand the application of the MBH reaction in dearomatization. Our objective is to broaden its substrate scope, showcase its synthetic utility, and investigate the factors governing the selectivity of these dearomative nucleophilic additions.

Chapter 2

Electrochemical Dearomative Spirolactonization and Spiroetherification of Naphthols and Phenols

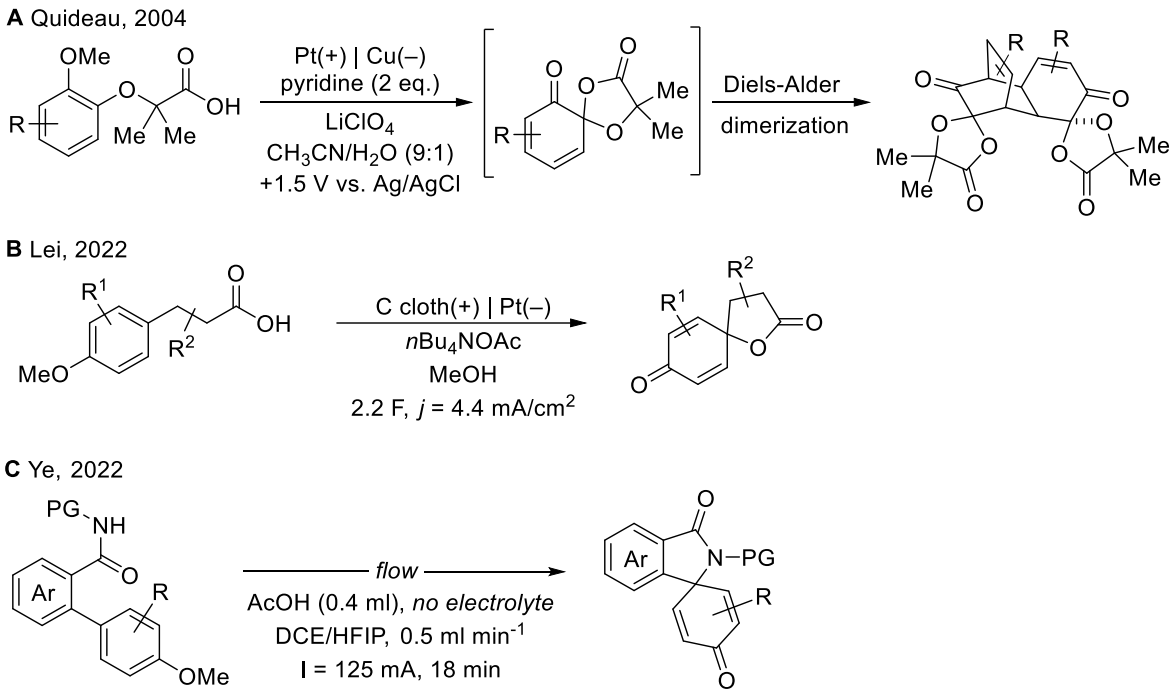
2.1. Background

Spirooxacyclic moieties are prevalent in numerous natural products and compounds of biological and medicinal relevance, including alkaloids and antibiotics (Scheme 2.1A).[274–277] A very powerful synthetic strategy that is routinely employed to construct spirooxacyclic compounds relies on the oxidative dearomatization of phenols that proceeds through the intramolecular addition of a tethered oxygen nucleophile (Scheme 2.1B).[9,45,278–283] Hypervalent iodine reagents have been most commonly used to promote such dearomatization reactions,[43] but other oxidants have been employed for that purpose as well.[284–289] In particular, over the last decade, significant progress has been made in the area of enantioselective intramolecular spirolactonization and spiroetherification of phenols using catalysis with chiral iodoarenes.[290–300]

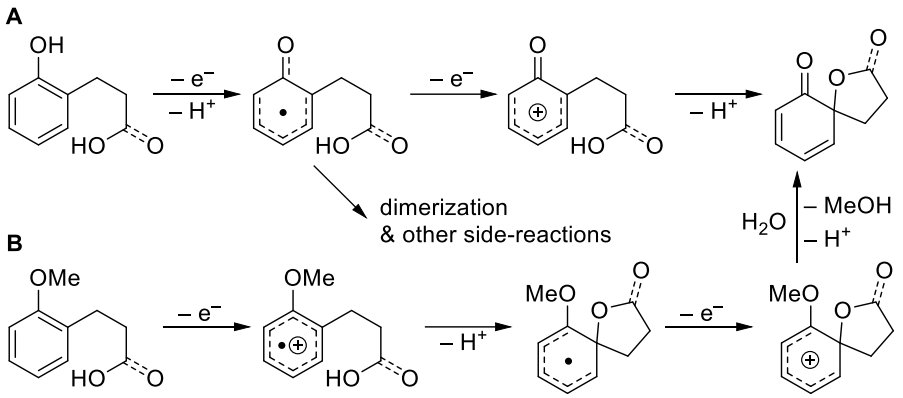


Scheme 2.1. (**A**) Examples of bioactive natural products containing a spirolactone or spiroether moiety and (**B**) the oxidative dearomatization of phenols with the intramolecular addition of tethered oxygen nucleophiles.

Due to the emergence of easily accessible standardized instrumentation, electrochemistry has in recent years become a handy and valuable synthetic tool for conducting organic redox transformations.[187,190,231,252,301–304] One of its major advantages is sustainability that stems from the exchange of stoichiometric amounts of often toxic, expensive, and high energy redox reagents, additionally accompanied by similarly problematic waste streams, with electrical stimuli that both move the electrons and provide the driving force for the reaction. However, despite phenols being common substrates in electrochemical transformations,[53,118,235,305–308] the anodic oxidative dearomatization of phenols leading to spirooxacyclic compounds has not been systematically investigated. Reports of isolated examples of such processes are scarce and exclusively confined to *para*-dearomatizations.[309–318] Instead, an analogous approach employing aryl methyl ethers rather than phenols has been pursued by Quideau (Scheme 2.2A) and, more recently, Lei (Scheme 2.2B) and Ye (Scheme 2.2C).[317,319–321] This is because, upon the initial single-electron oxidation, phenols are converted into phenoxyl radicals, which are prone to dimerization and other side processes (Scheme 2.3A).[118,235,305,306] These undesired pathways mitigate the efficiency of the spirooxacyclization by competing with the second oxidation step that is required to generate a phenoxenium ion, priming the ring for the addition of the oxygen nucleophile. Conversely, the SET oxidation of aryl methyl ethers affords the corresponding radical cations (Scheme 2.3B), which are readily quenched by the nucleophile, preventing the formation of side products. [317,319,320]

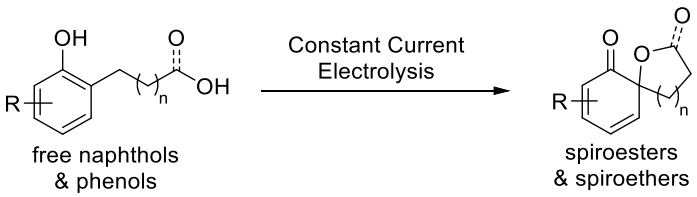


Scheme 2.2. Existing procedures for the synthesis of spirolactones via electrochemical oxidative dearomatizations of aryl methyl ethers.



Scheme 2.3. Comparison of mechanistic pathways for the anodic oxidation of (**A**) free phenols and (**B**) aryl methyl ethers with a tethered oxygen nucleophile (the two protons and two electrons removed in each of the pathways are combined at the cathode to generate H_2).

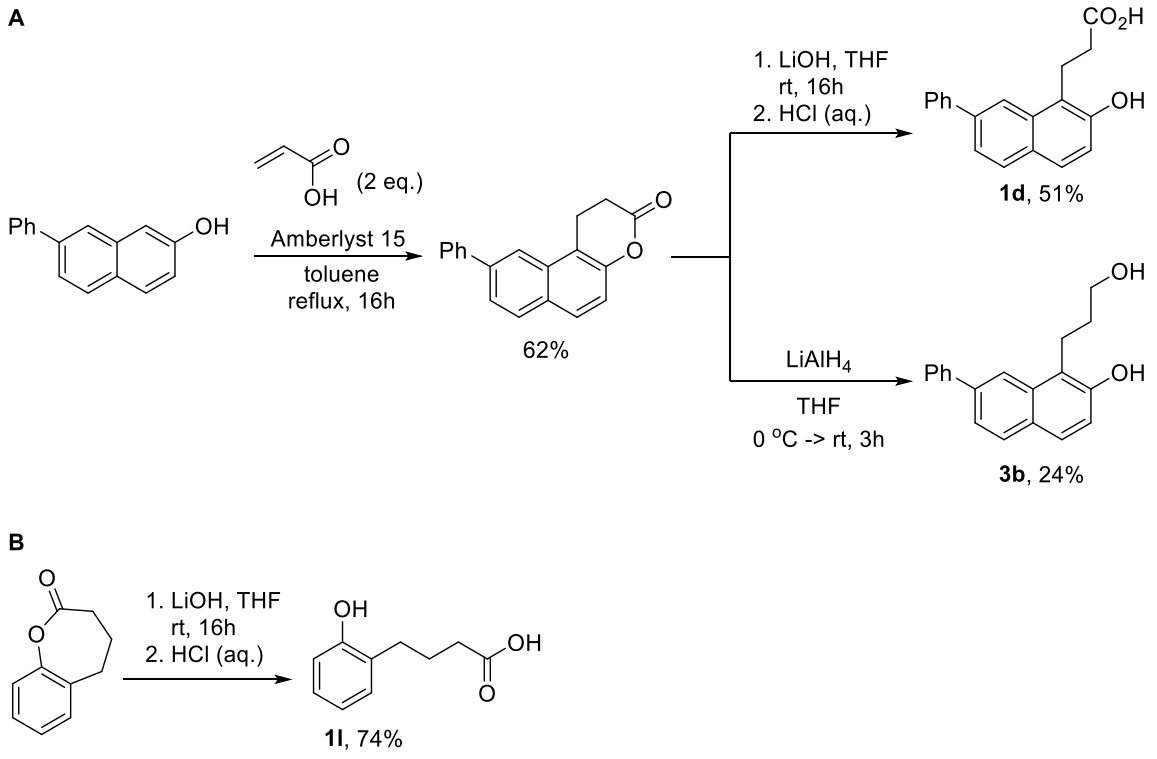
Although considerably more challenging, the preparation of spirooxacycles under electrochemical conditions directly from free phenols would benefit from much greater availability of the starting materials and a shorter, thus more economical and greener, synthetic sequence. Specifically, introducing a methyl group onto a phenol to merely facilitate the electrochemical dearomatization constitutes an additional synthetic step, utilizing extra reagents and resources necessary for carrying out the reaction as well as the isolation and purification of the methyl ether intermediate. Therefore, we set out to develop the direct electrochemical oxidative dearomatization of free phenols toward the formation of spirolactones and spiroethers (Scheme 2.4). Given the existence of scarce precedents,[309–311] we assumed that, since electrochemistry offers many possibilities to control the course of the reaction and its outcome by the choice of the respective electrolytic parameters, we would be able to find conditions under which the SET oxidation of the phenoxyl radical prevails over the alternative undesired side processes. We focused especially on *ortho*-dearomatizations, which have never been realized before via the electrochemically promoted oxidation of free phenols.[322]



Scheme 2.4. The intended direct electrochemical dearomative oxidation of free phenols leading to spirolactones and spiroethers.

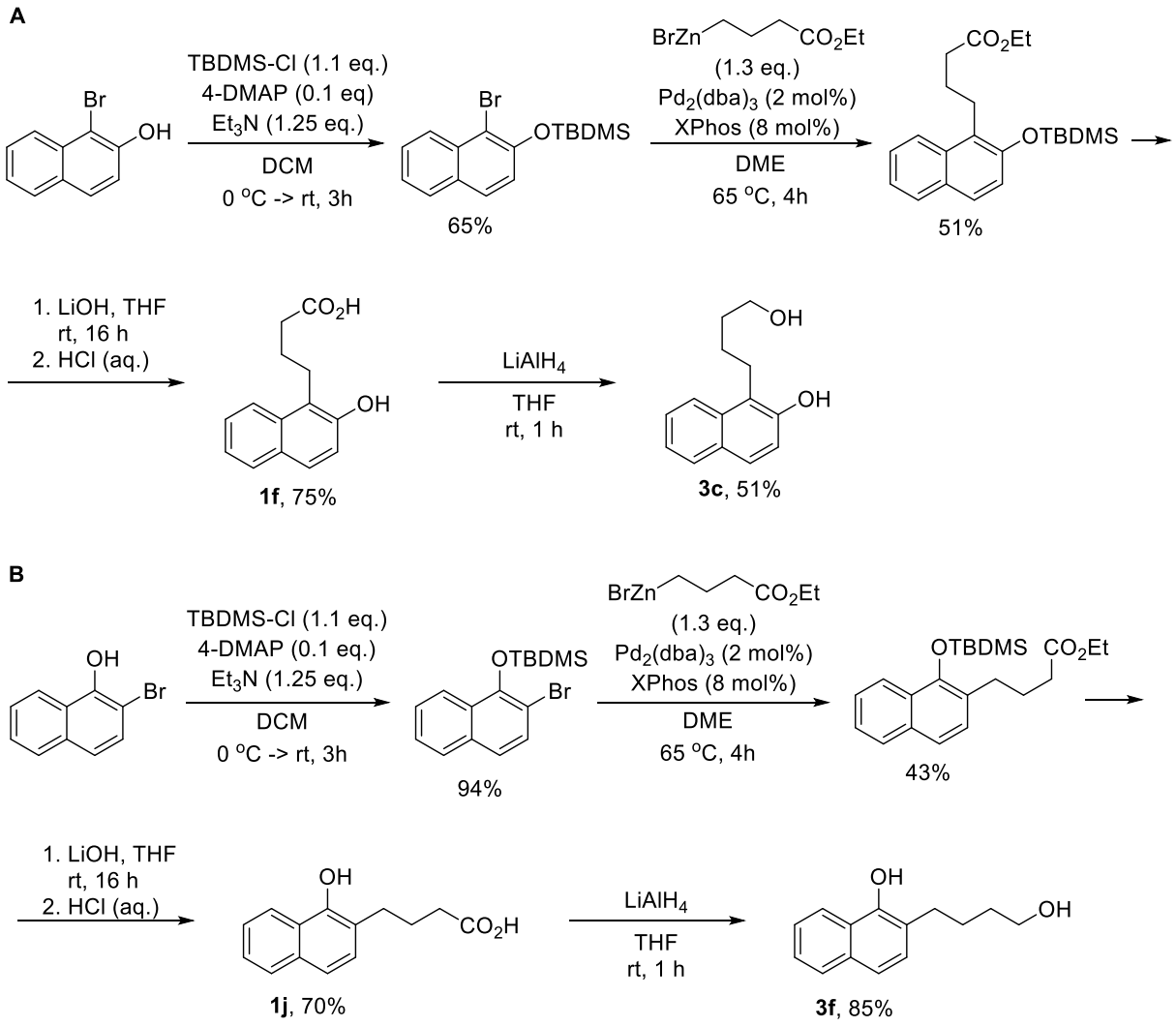
2.2. Preparation of Starting Materials

Since substrates **1d**, **1f**, **1j**, **1l**, **3b**, **3c**, **3f** are reported here for the first time, their synthesis is described. The synthesis of substrates **1d** and **3b** commenced with an Amberlyst 15-promoted condensation reaction between 7-phenylnaphthalen-2-ol and acrylic acid, which was carried out in toluene under reflux conditions. The resulting product was then either hydrolyzed under basic conditions to yield **1d** or reduced with $LiAlH_4$ to afford **3b** (Scheme 2.5A).[323,324] Similarly, a compound resembling the intermediate condensation product observed during the synthesis of **1d** and **3b** was hydrolyzed to yield **1l** (Scheme 2.5B).



Scheme 2.5. Synthetic routes to substrates **1d**, **3b**, and **1l**.

The synthetic route to substrates **1f** and **3c** commenced with the silylation of 1-bromo-2-naphthol using *tert*-butyldimethylsilyl chloride (TBDMS-Cl). The resulting TBDMS-protected naphthol was then subjected to Negishi coupling to introduce an ethyl butanoate tether.[325] Subsequently, a single hydrolysis step simultaneously cleaved both the ester and the TBDMS groups to yield **1f**. The reduction of **1f** with $LiAlH_4$ then afforded the other target substrate, **3c** (Scheme 2.6A). This same route, starting with 2-bromo-1-naphthol, was employed to synthesize **1j** and **3f** (Scheme 2.6B).



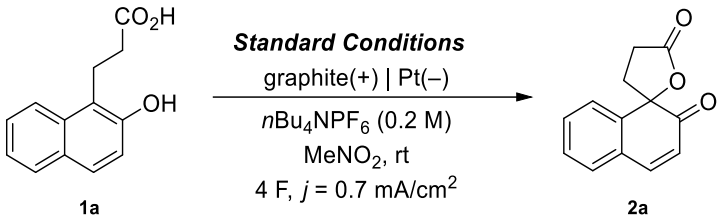
Scheme 2.6. Synthetic pathway to substrates **1f**,**1j**, **3c** and **3f.**

2.3. Optimization of Reaction Conditions

We began with our investigations by optimizing the reaction conditions for the electrochemical spirolactonization of a model 2-naphthol-derived carboxylic acid **1a** (Table 2.1). Indeed, for this generic substrate, we were able to identify a set of parameters that secures a nearly quantitative formation of the desired product **2a** (entry 1). This consists of a constant current electrolysis (CCE) of the solution of the substrate in nitromethane in an undivided cell, using a graphite anode and a platinum cathode at a current density of 0.7 mA/cm$_2$, with 4 F of total charge passed. *n*Bu$_4$NPF$_6$ is employed as a supporting electrolyte, and the electrolysis is carried out at room temperature under air. The impact of different parameters on the efficacy

of the electrochemical spirolactonization of **2a** is shown in Table 2.1. To this end, replacing $MeNO_2$ with CH_3CN as the reaction solvent results in the yield of spirolactone **2a** being reduced to 78% (entry 2). The application of other solvents, such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), 2,2,2-trifluoroethanol (TFE), and dichloromethane, was found to be detrimental for the reaction (entries 3-5). When the electrolysis was carried out using $LiClO_4$, instead of nBu$_4$NPF$_6$, as the supporting electrolyte, the yield was decreased to 75% (entry 6). Lowering the concentration of nBu$_4$NPF$_6$ from 0.2 M (5 eq. relative to the substrate) to 0.12 M (3 eq.) leads to a diminished efficiency of the spirolactonization (entry 7), and only a trace amount of **2a** is obtained in the absence of the supporting electrolyte (entry 8). Regarding the materials of the electrodes, utilizing glassy carbon in place of graphite as the anode results in a very low yield of the product, while replacing the platinum cathode with a graphite one decreases the yield to 71% (entries 9 and 10, respectively). To effect a quantitative spirolactonization, as much as 4 F of charge needs to be passed through the electrodes, since lowering this value to 3 F already affects the yield considerably (entry 11). The reaction affords the product in an unchanged yield under an inert atmosphere (entry 12), demonstrating that oxygen is not involved in the reaction. Finally, no product was observed in the absence of the electric stimuli (entry 13).

Table 2.1. Effect of reaction parameters on the electrochemical spirolactonization of 2-naphthol-derived carboxylic acid **1a**.



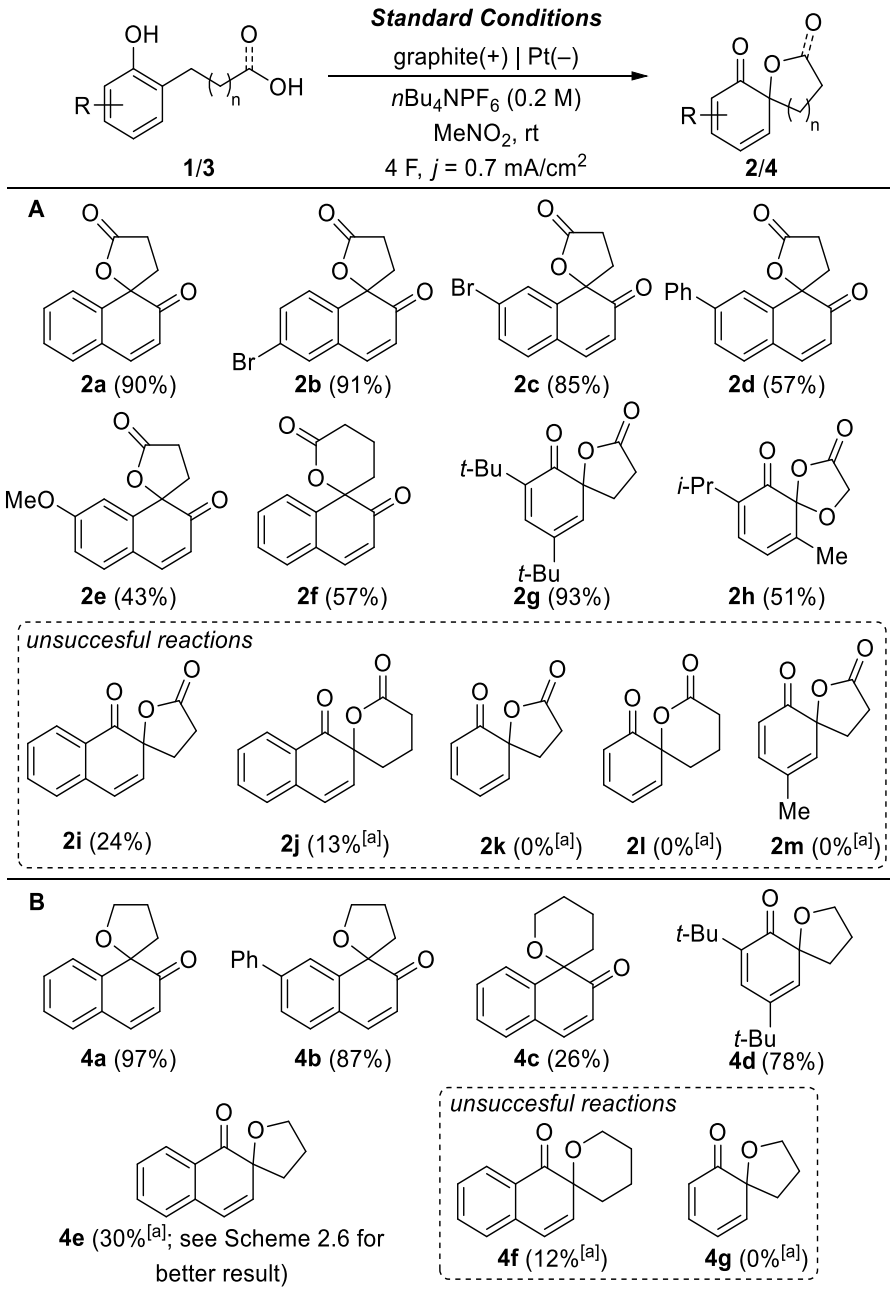
1a 2a

Entry	Variation from the Standard Conditions	Yield (%)[a]
1	none	96
2	CH_3CN, instead of $MeNO_2$	78
3	HFIP, instead of $MeNO_2$	30
4	TFE, instead of $MeNO_2$	9
5	CH_2Cl_2, instead of $MeNO_2$	3
6	$LiClO_4$, instead of nBu$_4$NPF$_6$	75
7	0.12 M nBu$_4$NPF$_6$, instead of 0.2 M	85
8	no nBu$_4$NPF$_6$	trace
9	glassy carbon(+), instead of graphite(+)	10
10	graphite(–), instead of Pt(–)	71
11	3 F, instead of 4 F	58
12	under N_2 atmosphere	94
13	no electric current	0

HFIP = 1,1,1,3,3,3-hexafluoroisopropanol; TFE = 2,2,2-trifluoromethanol. [a] Determined by ^{1}H NMR spectroscopy.

2.4. Scope and Limitations

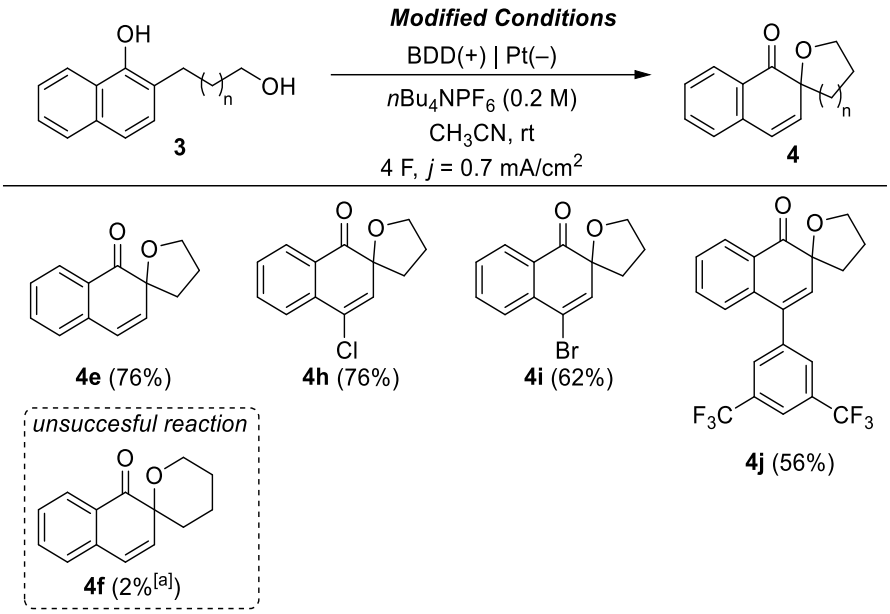
With the optimized conditions established, we proceeded to investigate the substrate scope of the electrochemical spirooxacylization of phenols (Scheme 2.7A). First, we explored the spirolactonization of 2-naphthol derivatives **1** with a propionic acid moiety tethered at position 1, affording the corresponding five-membered oxacyclic esters. Thus, the preparative electrolysis of the model substrate **1a** provided spirolactone **2a** in 90% isolated yield. The synthesis of analogous dearomatized spirolactones with a bromine substituent at either position 6 or 7 of the naphthalene ring also proceeded uneventfully, affording the respective products **2b** and **2c** in excellent yields (91% and 85%, respectively). A slightly reduced reaction efficiency was observed for the 2-naphthol substrates containing a phenyl and a methoxy substituent at position 7 (**2d** and **2e**). Interestingly, we were also able to successfully obtain a dearomatized product **2f** possessing a six-membered lactone, which has never been synthesized before, even with a chemical oxidant. The desired spirooxacyclic product was also afforded from suitably substituted phenols. In particular, an excellent 93% yield was attained for the phenol with alkyl substituents in positions 4 and 6 (**2g**), while the phenol containing a 3,6-substitution pattern underwent the spirolactonization in 51% yield (**2h**). Next, we tested substrates derived from 1-naphthol, which, unfortunately, were found to undergo the reaction with a considerably lower efficiency. Products **2i** and **2j** containing five- and six-membered lactone rings were generated in only 24% and 13% yield, respectively. Finally, we established that the phenols furnishing easily dimerizing radicals do not provide the corresponding lactones at all (**2k**-**m**), making the direct two-electron oxidation with a chemical oxidant the only viable option in these cases.[326]



Scheme 2.7. Scope of the electrochemical oxidative (**A**) spirolactonization and (**B**) spiroetherification of phenols under the standard conditions (isolated yields shown). [a] NMR yield.

Next, we moved to examine the anodic *ortho*-dearomatization of phenols **3** with tethered alcohols, leading to spiroethers (Scheme 2.7B). In this regard, both unsubstituted and 7-phenyl-substituted 2-naphthol-derived alcohols underwent a facile electrochemical dearomatization, providing the corresponding five-membered cyclic ethers in high yields (**4a** and **4b**, respectively). On the other hand, the six-membered tetrahydropyran counterpart was not generated efficiently (**4c**). Similarly to the case of the spirolactonization described above, the corresponding product was generated in a good yield from the phenol containing large alkyl substituents, hindering the dimerization of the radical intermediate (**4d**). Concerning the alcohol derivatives of 1-naphthol, they were also found not to be suitable substrates for the reaction under the standard conditions (**4e**,**f**; however, see below). Finally, the electrochemical spiroetherification involving an alcohol moiety tethered to unsubstituted phenol did not lead to the desired product (**4g**).

The somewhat disappointing results obtained for the 1-naphthol derivatives prompted us to attempt to reoptimize the reaction conditions specifically for this class of substrates. Thus, we established that a slight modification of the electrochemical parameters can, indeed, considerably improve the efficacy of the spiroetherification of 1-naphthol-derived compounds (the efforts to enhance the corresponding spirolactonization were not successful). Specifically, the material of the anode was changed to boron-doped diamond (BDD) and nitromethane was replaced by acetonitrile as the solvent (Scheme 2.8). Under these conditions, the dearomative spiroetherification of 1-naphthol-derived alcohols proceeded much better, providing the desired products in good yields (**4e**,**h-j**), with the exception of the six-membered spiroether **4f**. We speculate that for the particular case of 1-naphthol substrates with tethered hydroxyl group, the combination of BDD anode and CH_3CN solvent facilitates the oxidation of the phenoxyl radical to the phenoxenium cation, thereby enhancing the formation of the desired spiroether product. This may be due to the peculiar characteristics of BDD[327,328] coupled with the solvating properties of CH_3CN toward the phenoxyl radical itself, as well as affecting its intramolecular interactions with the OH group.



Scheme 2.8. Scope of the electrochemical oxidative spiroetherification of substrates derived from 1-naphthol under the modified conditions (isolated yields shown). [a] NMR yield

2.5. Plausible Mechanism

The cyclic voltammograms for the four generic substrates **1a**, **1i**, **3a**, and **3e** (Figure 2.1) confirm the general mechanistic picture depicted in Scheme 2.3A. Namely, all these compounds display oxidation peaks with similar onset potentials in the range of 0.75-0.90 V relative to Fc/Fc^{+}. Thus, their divergent reactivities do not originate from the different susceptibility to undergo anodic oxidation. The irreversible oxidation peaks (except for **1i**, for which a partial reversibility is observed), corresponding to the formation of the respective phenoxyl radicals, demonstrate that the radicals are short-living species. Therefore, the relative rates of their further oxidation vs. dimerization/polymerization determine the efficiency of the spirooxacyclization.

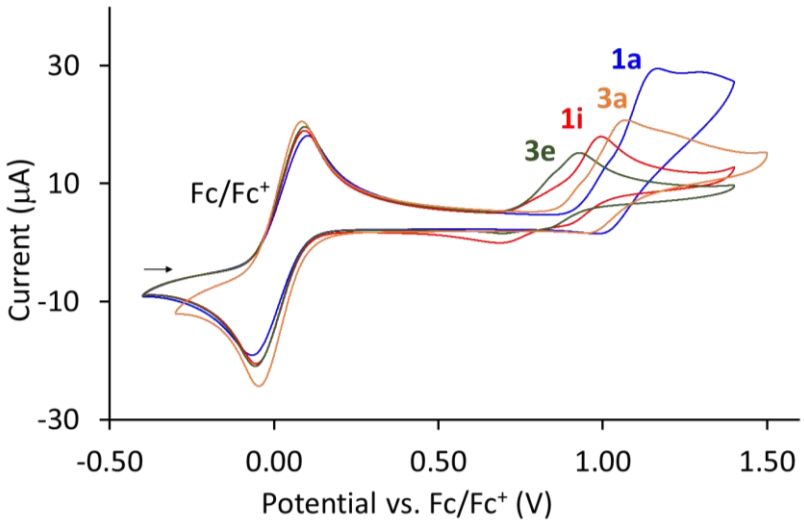


Figure 2.1. Cyclic voltammograms of substrates **1a**, **1i**, **3a**, and **3e** in HFIP using a glassy carbon working electrode. [Analyte], [Fc] = 2 mM, [nBu$_4$NPF$_6$] = 0.10 M, scan rate = 0.1 V·s^{-1}, counter electrode: Pt wire, pseudo-reference electrode Ag wire.

2.6. Conclusions

In conclusion, we developed an electrochemical oxidative *ortho*-spirolactonization and *ortho*-spiroetherification of free phenols. The method constitutes a chemical-oxidant-free entry to important molecular scaffolds, generating hydrogen as the sole side product. The reaction displays a broad scope, encompassing both naphthol and phenol derivatives, with the exception of ones furnishing easily self-coupling radicals. It provides moderate to high yields and proceeds under simple constant current conditions in an undivided cell.

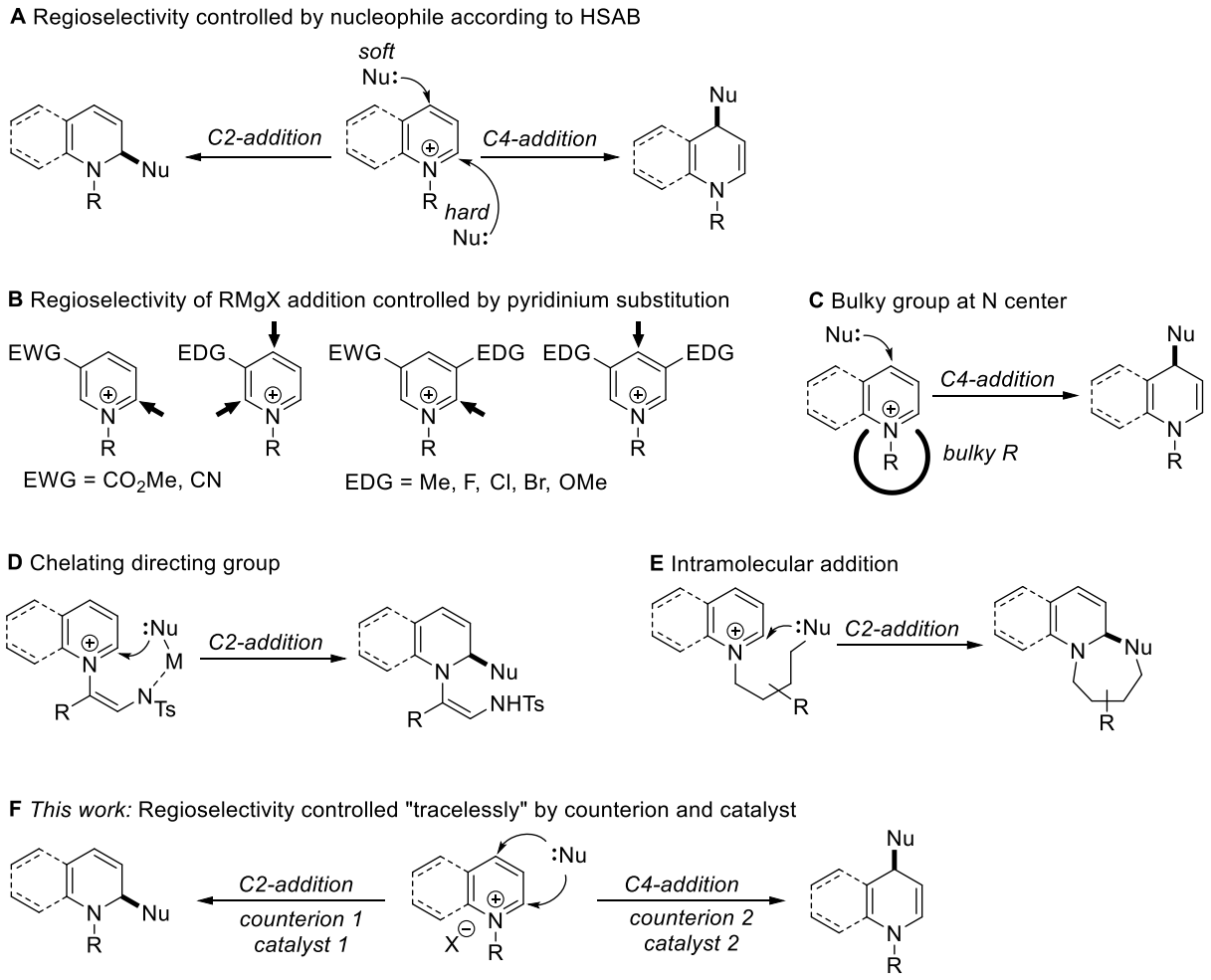
Chapter 3
C4-Regioselective Dearomatization of Quinolinium Salts via Morita-Baylis-Hillman Reaction

3.1. Background

The prevalence and significance of *N*-heterocycles as bioactive molecules in the pharmaceutical and agrochemical industries is well recognized. This is clearly illustrated by the fact that 59% of all small molecule drugs that had ever been approved by the Food and Drug Administration (FDA) until 2014 contain an *N*-heterocyclic moiety.[329,330] In fact, this predominance of the *N*-heterocyclic moiety increased to 82% for all FDA-approved small molecules that were released within the previous decade.[331] Moreover, an in-depth analysis of the composition of an extensive range of drug candidates and natural products revealed that there was a noticeable correlation between the number of saturated sp^3 carbon atoms, including stereogenic ones, in a molecule and its clinical success.[332,333] In this context, developing methodologies that are geared toward the synthesis of functionalized and partially saturated *N*-heterocyclic systems plays a key role in pharmaceutical research and development.[334] Due to the wide availability of substituted pyridines and related *N*-heteroaromatic families, such as quinolines and acridines, the dearomatization of these compounds is regarded as one of the most practical approaches of introducing the desired structural motif of partially saturated *N*-heterocycles.[133,137,335–338]

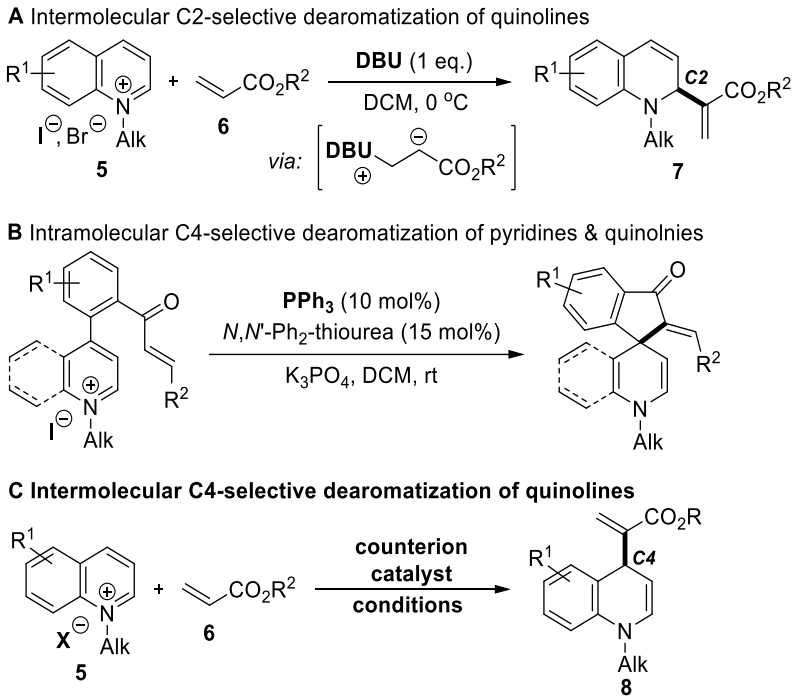
The dearomatization of the pyridine scaffold is typically performed via a nucleophilic addition to its activated azaarenium form, wherein the nucleophile may attack either the C2 or C4 position of the ring. Therefore, a key feature of any method for the dearomatization of pyridinium and quinolinium moieties is its regioselectivity. Achieving a regioselective addition has often proven to be challenging.[339–343] The great majority of reported reactions rely on the intrinsic preferences of the reactants to dictate the position of the nucleophilic addition. In particular, the hard and soft acid and base (HSAB) theory has been invoked to rationalize the regioselectivity, predicting that hard nucleophiles (e.g., organometallic reagents of main-group

metals) preferentially add to the C2 position, whereas soft nucleophiles (e.g., malonates and related species) favor the C4 position (Scheme 3.1A).[136,344] Regarding the impact of the *N*-heteroaromatic substrate, Knight and coworkers have carried out a systematic study on the dearomative addition of Grignard reagents to *N*-alkyl pyridinium salts, which enabled predictions of regioselectivity based on the arrangement and type of substituents present on the pyridinium ring (Scheme 3.1B).[345] However, the principles above are not absolute, as many other factors such as π–π stacking, hydrogen bonding, and ion–ion interactions may affect the regioselectivity.[346] In several cases, the desired structural arrangement of a complex *N*-heterocyclic product has been achieved through the dearomatization of an azaarenium ring by sequentially adding the nucleophiles in the proper order, thereby selectively blocking the available reactive sites.[347–351]



Scheme 3.1. Strategies for controlling the regioselectivity during the dearomative nucleophilic addition to pyridinium and quinolinium moieties.

Because it is not always possible to obtain the desired regioisomer by relying solely on the preferences of the pyridinium/quinolinium substrate, several strategies have been developed to overrule this intrinsic regioselectivity during the nucleophilic addition. A common approach involves the installation of a bulky group at the nitrogen center, thereby hindering access to C2 and directing the nucleophilic attack to the C4 position (Scheme 3.1C).[177,339,342] In the case of organometallic nucleophiles, chelating groups have been employed to guide the approaching reagent toward the desired position (Scheme 3.1D).[352,353] Other reported strategies rely on tethering the nucleophile to the pyridinium scaffold, so that the intramolecular addition can take place only at one of the reactive sites (Scheme 3.1E).[354,355] All of these approaches require a specific modification of substrate structure, which may be undesirable from the perspective of the target molecule, for instance, necessitating additional synthetic steps to remove the directing group. A more advantageous option would be to control the regioselectivity of addition in a "traceless" fashion, an approach with very few examples, which are typically limited to noncatalytic processes, and are not particularly efficient.[356,357] Herein, we report a method for switching the regioselectivity during the dearomatization of quinolinium salts just by the application of a different counterion in the starting azaarenium salt and the alteration of reaction conditions, including the catalyst (Scheme 3.1F).



Scheme 3.2. Existing (**A**-**B**) and the novel (**C**) dearomatization of quinolinium salts under Morita-Baylis-Hillman conditions. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Recently, we have developed the dearomatization of *N*-alkylquinolinium salts through Morita–Baylis–Hillman reaction (MBH), leading to dihydroquinolines that are functionalized with an acrylate group (Scheme 3.2A).[358] The reaction employs 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the dual role of a catalyst and a base, and it displays high selectivity toward the C2 position. Our work was followed by the report by Ramasastry et al., who have applied electron-poor alkenes tethered to the quinolinium ring, thereby forcing an intramolecular MBH reaction at the C4 site (Scheme 3.2B).[355] In our continued desire to broaden the utility of MBH chemistry in the dearomatization of quinolinium salts, we have now turned our focus on achieving an intermolecular C4-regioselective variant (Scheme 3.2C). Our interest in the C4-selective dearomatization stems from the high synthetic usefulness of the enamine-containing 1,4-dihydroquinoline scaffold, which is a key intermediate in various protocols, wherein it acts as a nucleophile, a coupling partner, or a mediator.[359–362] It is also a valuable motif in medicinal chemistry, as 1,4-dihydroquinoline derivatives possess a wide range of biological activities, including P-glycoprotein inhibition in cancer cells, as well as cardioprotective, antimalarial, and antibacterial activity (Figure 3.1).[363–367] Furthermore, the 1,4-dihydroquinoline moiety is present in registered pharmaceuticals, such as Elvitegravir, Levofloxacin, and Ciprofloxacin (Figure 3.1).[368,369] Finally, 1,4-dihydroquinolines have also been utilized as fluorescent probes to detect and track biochemical processes involving reactive oxygen species in living cells (Figure 3.1).[370] In this context, developing a C4-selective dearomatization of quinolinium salts with an MBH nucleophile will provide facile access to functional group-rich building blocks, featuring multiple centers of orthogonal reactivity, thus allowing for further functionalization and synthetic elaboration into important biologically relevant molecules.

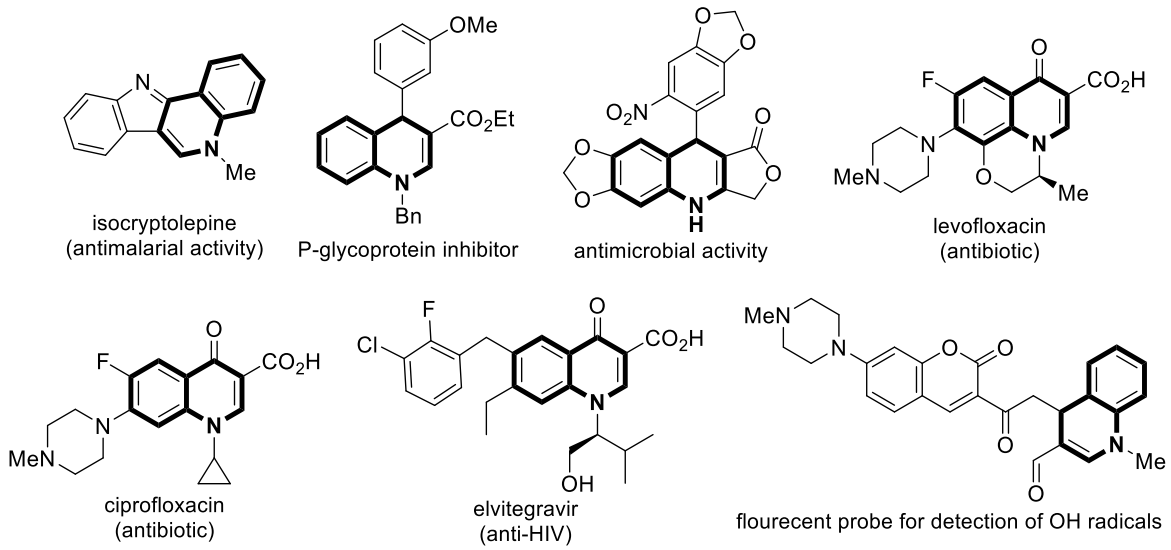
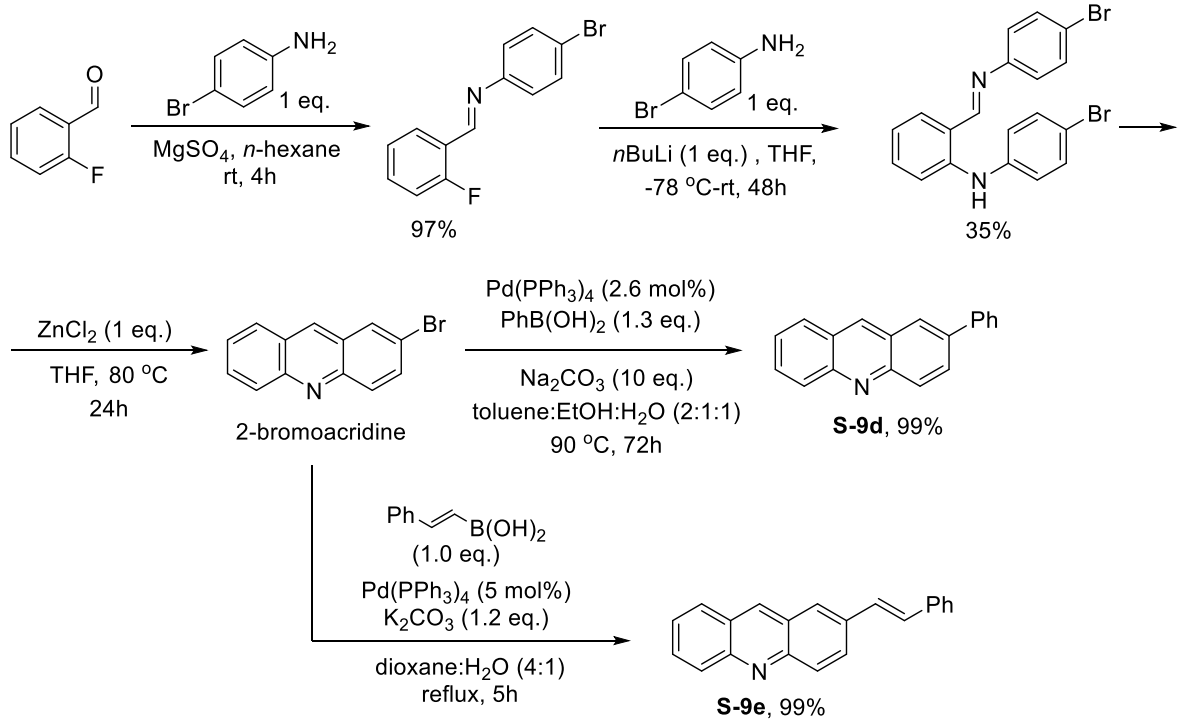


Figure 3.1. Examples of biologically relevant compounds containing a 1,4-dihydroquinoline scaffold.

3.2. Preparation of Starting Materials

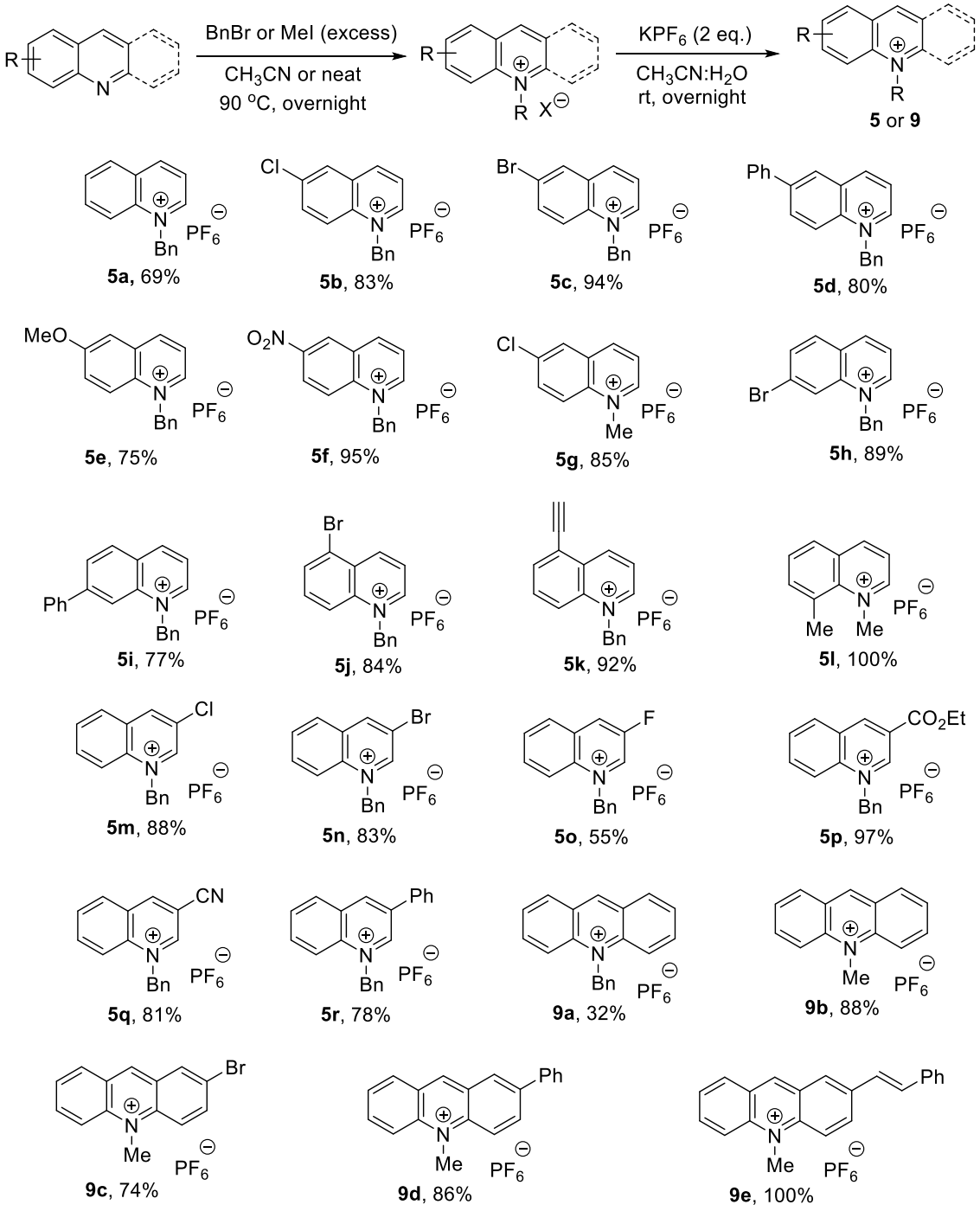
As the required 2-substituted acridinium substrates were not commercially available, their acridine precursors had to be synthesized. First, 2-bromoacridine was prepared from an *ortho*-arylaminophenyl Schiff base via a $ZnCl_2$-promoted cyclization reaction (Scheme 3.3). Subsequently, the other 2-substituted acridines, specifically 2-phenylacridine (**S1**) and (*E*)-2-styrylacridine (**S2**), were prepared through the Suzuki-Miyaura coupling of 2-bromoacridine with phenylboronic acid and (*E*)-styrylboronic acid, respectively.[371,372]



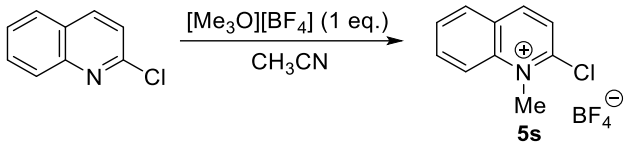
Scheme 3.3. Synthesis of the acridine precursors.

The preparation of the substrates was a straightforward S_N2 reaction between the corresponding quinoline or acridine and the alky halide either in acetonitrile or under neat conditions, in accordance with existing protocols in literature.[154,358] Thereafter, an appropriate anion exchange reaction was performed in the presence of KPF_6 to afford the final hexafluorophosphate salts in very good yields ranging as shown in Scheme 3.4. These substrates were then fully characterized using proton (^1H) and carbon (^{13}C) NMR as well as FT-IR spectroscopy and high resolution and mass spectrometry. Starting material **5s** was prepared

by treating 2-chloroquinoline with a strong methylating agent, trimethyloxoniumtetrafluoroborate (Scheme 3.5).[373]



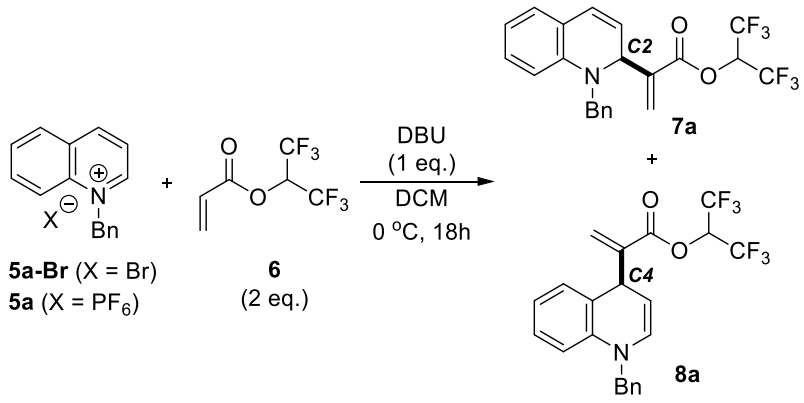
Scheme 3.4. Preparation of **5a-r** and **9a-f**.



Scheme 3.5. Preparation of **5s**.

3.3. Optimization of Reaction Conditions

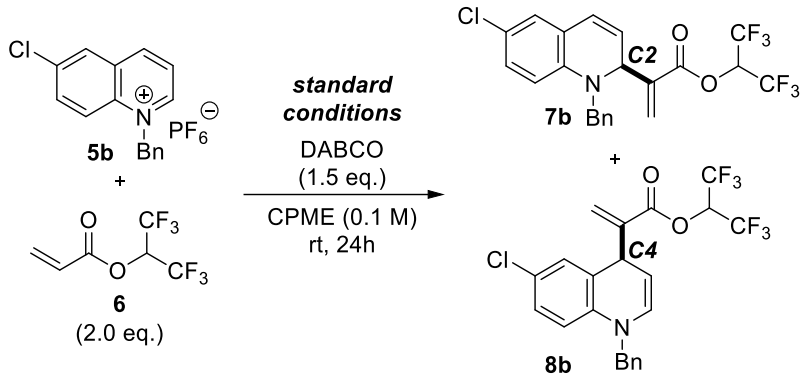
While reinvestigating the previously reported C2-selective dearomatization of *N*-alkylquinolinium salts under MBH conditions,[358] we observed that, for some substrates, the regioselectivity was strongly affected by the counterion present in the salt. Notably, the incorporation of the PF_6^- anion somewhat favored the formation of the corresponding C4-functionalized product (Scheme 3.6). Building on this observation, we established an alternative set of reaction parameters that provided this isomer of the product with high selectivity. Specifically, using 1-benzyl-6-chloroquinolinium hexafluorophosphate **5b** and 1,1,1,3,3,3-hexafluoroisopropyl (HFIP) acrylate **6** as model substrates, the highest yield and desired C4 regioselectivity were achieved in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in cyclopentyl methyl ether (CPME) as a solvent (Table 3.1, entry 1). Similar to the C2-selective process, the applied amine served a dual role as both catalyst and stoichiometric base, and was therefore used in 1.5 equivalents.



Scheme 3.6. The previously developed C2-selective dearomatization of *N*-benzylquinolinium salts through MBH reaction employing Br salt and the discovered effect of PF_6 counterion on the regioselectivity.

As outlined in Table 3.1, various other conditions were surveyed to study the impact of each reaction variable on both yield and regioselectivity. Looking at the effect of the counterion in detail, replacing PF_6^- with TfO^- had little impact on the outcome (entry 2). Conversely, the Br^- and BF_4^- salts provided reduced yields and decreased regioselectivities (entries 3,4), while the presence of the I^- anion was detrimental to the yield (entry 5). Efficient progression of the reaction required tuning of the acrylate's electronic properties, with the HFIP ester proving optimal, while all the other tested esters gave significantly lower yields or regioselectivities (entries 6–8). Among the examined catalysts, in addition to DABCO, DMAP also favored C4 functionalization, albeit with a somewhat lower yield (entry 9). In contrast, DBU and TMG gave mixtures of regioisomers in low overall yields (entries 10,11). Regarding the reaction media, dichloromethane performed comparably to CPME (entry 12), whereas toluene and alternative ethereal solvents were somewhat less effective with respect to the yields and regioselectivities (entries 13–16). Reducing the amount of the acrylate from 2 to 1.5 equivalents resulted in a minor drop in regioselectivity (entry 17); however, this was recovered by conducting the reaction at 0 °C for 48 h (entry 18). Notably, for certain substrates, room temperature remained preferable due to improved reactivity (see Scheme 3.4). To summarize, efficient formation of the C4-isomer of the product was accomplished by fine-tuning both the counterion in the azaarenium substrate and the reaction conditions. The most pronounced impact on regioselectivity reversal arose from replacing Br^- with PF_6^- and switching the catalyst from DBU to DABCO.

Table 3.1. Effect of reaction parameters on reaction efficiency and selectivity (NMR yields)

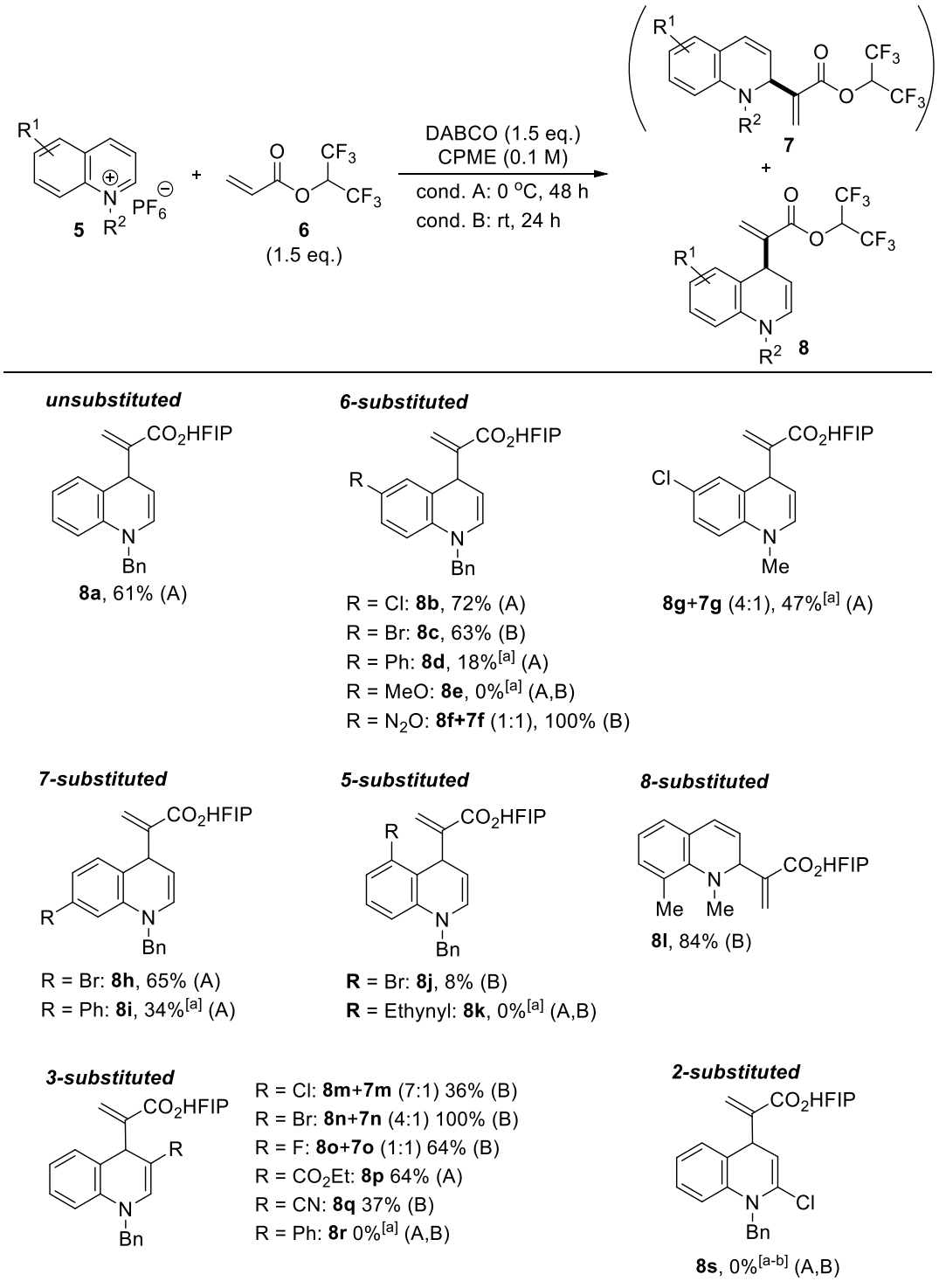


Entry	Variation from the standard conditions	Yield **7b** (%)[a]	Yield **8b** (%)[a]
1	none	3	91
2	TfO^-, instead of PF_6^-	4	86
3	Br^-, instead of PF_6^-	18	62
4	BF_4^-, instead of PF_6^-	11	78
5	I^-, instead of PF_6^-	5	41
6	CH_2CF_3, instead of HFIP	<3	26
7	Ph, instead of HFIP	47	34
8	Me, instead of HFIP	<3	<3
9	DMAP, instead of DABCO	4	80
10	DBU, instead of DABCO	16	24
11	TMG, instead of DABCO	14	11
12	DCM, instead of CPME	<3	89
13	toluene, instead of CPME	5	69
14	THF, instead of CPME	4	88
15	MTBE, instead of CPME	8	87
16	Et_2O, instead of CPME	7	86
17	1.5 eq. of **6**; instead of 2.0 eq.	6	92
18	1.5 eq. of **6**, 0° C and 48h; instead of 2.0 eq., rt and 24h	3	92

[a] Determined by ^1H NMR spectroscopy; CPME = cyclopentyl methyl ether; DABCO = 1,4-diazabicyclo[2.2.2]octane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP = 4-(dimethylamino)pyridine; HFIP = 1,1,1,3,3,3-hexafluoropropan-2-yl; MTBE = *tert*-butyl methyl ether; TMG = 1,1,3,3-tetramethylguanidine.

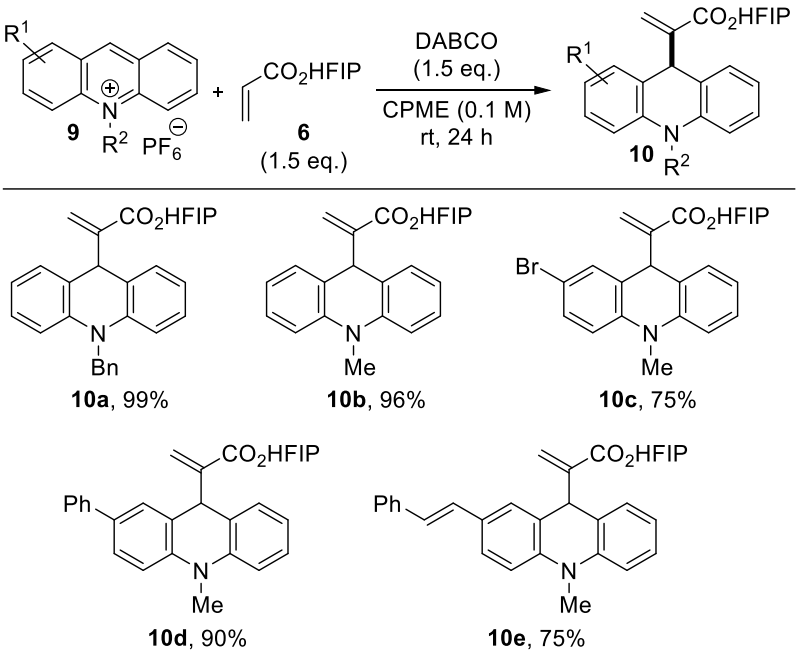
3.4. Scope and Limitations

Having established the optimal conditions, we moved on to systematically examine the substrate scope and limitations of this C4-selective dearomatization of *N*-alkylquinolinium salts through the MBH reaction (Scheme 3.7). With a few exceptions, very high C4-selectivity was observed for the majority of examined quinolinium substrates. Thus, the dearomatized product that was derived from the unsubstituted quinoline was obtained in 61% isolated yield (**8a**). Among the reactants containing a substituent at position 6, halogenated derivatives provided comparable yields (72% and 63% for **8b** and **8c**, respectively). In contrast, the presence of a phenyl or, in particular, a methoxy group at this position hindered the reaction (**8d** and **8e**), likely due to the decreased electrophilicity of the substrate, a trend that was also observed in the C2-selective variant. A highly activated quinolinium salt bearing a nitro substituent was dearomatized in a quantitative yield, but with no selectivity (**8f** + **7f**). Substitution at the nitrogen atom also played a key role, as replacing the *N*-benzyl group with a methyl group led to lower reactivity and diminished regioselectivity (**8g** + **7g**). This result demonstrated that a larger *N*-benzyl substituent assists the C4-selective addition to the pyridinium ring, but does not obstruct the previously developed C2-selective pathway (Scheme 3.7).[357] The substituents at position 7 of the quinoline moiety displayed analogous effects to those that were at position 6, namely, the bromine-containing product was isolated in 65% yield (**8h**), whereas the one with a phenyl substituent did not form efficiently (**7i**). Any substituent at position 5 was detrimental for the reaction (**8j** and **8k**), presumably creating too much steric hindrance that impeded nucleophilic attack. Because the *N*-benzylation of 8-methylquinoline had proven to be unfeasible, we prepared and used the corresponding *N*-methylquinolinium salt. Surprisingly, this substrate underwent dearomatization exclusively via the C2-selective route (**7l**). We speculated that this was due to the combined effects of the small *N*-substituent (*cf.* **8g** + **7g**) and the electron-donating properties of the 8-methyl group, which further deactivated the C4 position. Regarding the substitution in the pyridinium ring, interestingly, having halogens at position 3 led to diminished regioselectivity in the following order: Cl > Br > F (**8m** + **7m**, **8n** + **7n,** and **8o** + **7o**, respectively). In comparison, the presence of a carboxylic ester (**8p**) and a cyano group (**8q**) in this position led to a C4 selective addition, albeit in moderate yields. Finally, a quinolinium salt containing a phenyl group at position 3 did not react under the developed conditions (**8r**). Similarly, the blocking of position 2 prevented product formation (**8s**).



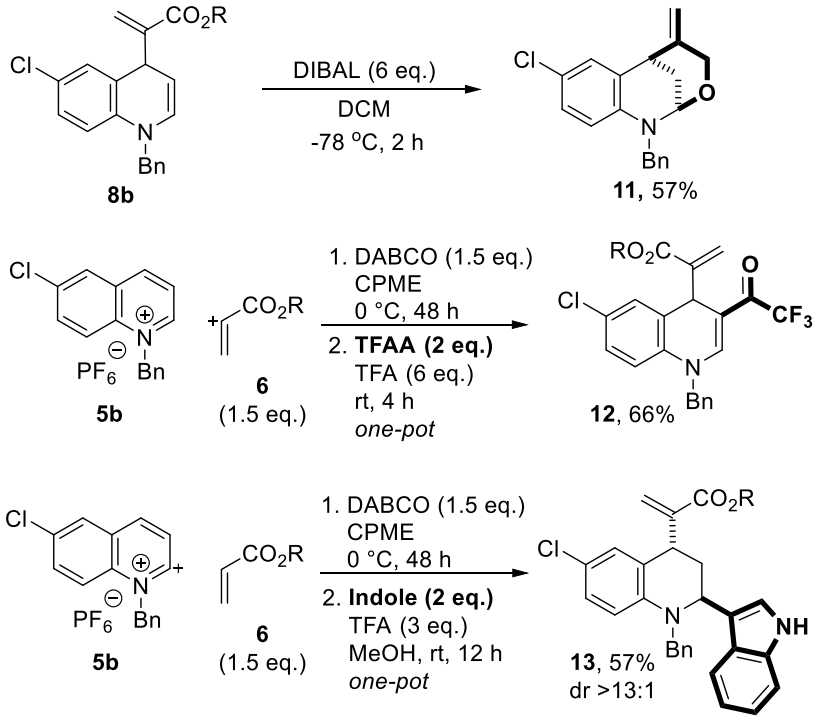
Scheme 3.7. Scope and limitations of the dearomatization of *N*-alkylquinolinium salts through MBH reaction under the developed C4-selective conditions (isolated yields; unless stated otherwise, the regioselectivity was >95:5). [a]NMR yield; [b]BF_4 salt was used.

To further extend the utility of the developed MBH protocol, the dearomatization of several *N*-alkylacridinium salts **9** was carried out (Scheme 3.8). In the case of these azaarenium substates, the reaction was generally uneventful and good yields were obtained for the majority of the examined compounds (**10a**–**10e**). This includes acridine derivatives with both benzyl and methyl substituents at the nitrogen atom. Contrary to the quinolinium family of substrates (Scheme 3.4), the phenyl substituent in the acridinium moiety was well-tolerated (**10d**).



Scheme 3.8. Dearomatization of *N*-alkylacridinium salts through MBH reaction (isolated yields).

We performed a few postsynthetic transformations of product **8b** to illustrate its potential as a useful organic synthon and to highlight the synthetic utility of the developed procedure (Scheme 3.9). First, the reduction of **8b** with DIBAL-H afforded a bicyclic hemiaminal ether **11** in a moderate yield of 57% as a single diastereomer. Hemiaminal ethers are important synthetic intermediates[374] and, in particular, the bridged ones are a common motif in medicinal chemistry.[375] Next, two one-pot reactions were conducted, each utilizing a different reactivity offered by the 1,4-dihydroquinoline moiety. Specifically, treatment of the completed reaction mixture with trifluoroacetic anhydride (TFAA) and trifluoroacetic acid (TFA) led to the formation of a synthetically useful "push–pull" enamine **12**.[144] In the second transformation, a one-pot nucleophilic addition of indole under acidic conditions was successfully performed, leading to product **13** with high diastereoselectivity.[347]

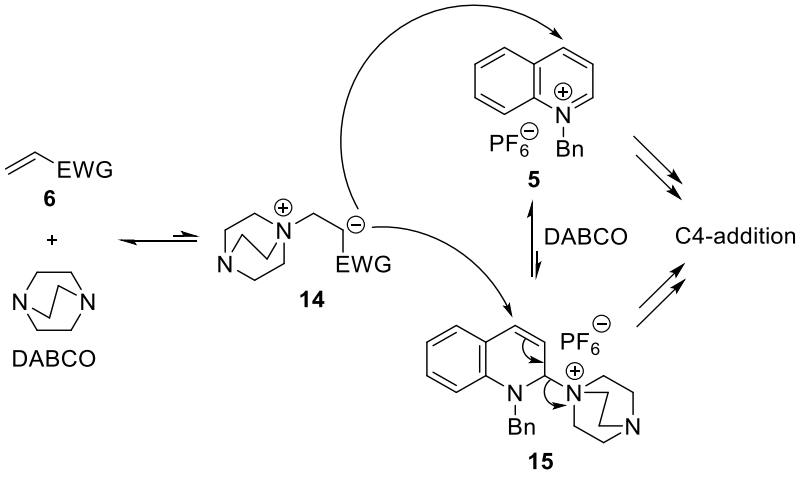


Scheme 3.9. Examples of transformations of product **8b** (R = 1,1,1,3,3,3-hexafluoropropan-2-yl).

3.5. Plausible Mechanism

Regarding the origin of the observed regioselectivity during the dearomatization of the quinolinium salts, there exist two alternative putative explanations (Scheme 3.10). In the first one, the zwitterionic intermediate **14**, which is formed from acrylate **6** and DABCO in accordance to the generally accepted mechanism for the MBH reaction,[376] simply favors the addition to the C4-position of the pyridinium ring in substrate **5** (contrary to the analogous intermediate derived from DBU, which would favor the C2-addition, instead). This preference may in part stem from, or be reinforced by, the presence of PF_6^- ion. The second possible option to account for the C4-selectivity follows a mechanistic rationale put forward by Bernardi and coworkers in their report on a related dearomatization of electron-poor pyridinium salts.[377] This pathway assumes the formation of adduct **15** between DABCO and quinolinium salt **5**. Because of the intrinsically higher reactivity of the C2 site, the tertiary amine would preferentially attack at this position, blocking it, and directing any other nucleophiles toward C4. This effect may be further reinforced by the poor solubility of hexafluorophosphate salt **5** compared to the better solubility of adduct **15**. Accordingly, adduct **15** would practically

be the sole electrophilic species available in solution to react with the MBH zwitterion **A** via an S_N2' substitution.[378]



Scheme 3.10. Putative mechanistic possibilities accounting for the C4-regioselectivity of the reaction.

In an effort to distinguish between these two possibilities, we attempted to detect species **15** by NMR spectroscopy and mass spectrometry, however, neither of these techniques showed the formation of **15** in any appreciable amount in the solution containing the mixture of **5b** and DABCO. This is corroborated by the computation of the free energy of **15** by density functional theory (DFT) calculations, which was found to be higher by ≈ 6 kcal mol^{-1} relative to the energy of the parent compounds, thus, **15** is indeed predicted to be an unstable, transient species.[379] Nevertheless, the results above do not allow for the rejection of the involvement of adduct **15** in the mechanism and its role in controlling the regioselectivity (in fact, similarly, intermediate **14** could also not be detected in the mixture of acrylate **6** and DABCO, despite its obvious involvement in the mechanism). Therefore, more profound experimental and computational investigations are necessary to elucidate the details of the mechanism and gain insight into the origins of regioselectivity for both the C2- and C4-selecive versions of the reaction. These studies are currently underway.

3.6. Conclusions

In conclusion, we have developed a C4-selective intermolecular dearomatization of quinolinium salts through the MBH reaction, complementing the previously reported C2-selective protocol. Notably, the regioselective addition to the C4 position was attained "tracelessly" without the inclusion of any regio-directing substituents on either of the substrates and it relies solely on the alteration of the counterion in the azaarenium salt and the change in

reaction parameters. In particular, the key to reversing the selectivity was the replacement of halide counterion in the quinolinium substrate with hexafluorophosphate and the application of DABCO instead DBU as a catalyst. Presented methodology constitutes a direct entry to a highly functionalized 1,4-dihydroquinoline scaffold, providing facile access to a diverse range of important *N*-heterocyclic compounds, including acridine derivatives.

Concluding Remarks

This thesis explores electrochemistry and nucleophilic addition as effective strategies for the dearomatization of phenolic and *N*-heteroaromatic compounds, respectively.

The first project (Chapter 2) further elevated organic electrochemistry as a sustainable and green methodology. In this work, the use of stoichiometric oxidants or catalysts was avoided, with molecular hydrogen generated as the only byproduct. Deviating from the norm of using aryl ether substrates in related electrochemical transformations, the scope was also extended to free phenols and naphthols. Thus, a method for the electrochemical oxidative *ortho*-spirolactonization and *ortho*-spiroetherification of free arenols under simple constant current conditions was developed.

The second project (Chapter 3) focused on the nucleophilic addition of an activated alkene to quinolinium and acridinium salts under Morita-Baylis-Hillman conditions. To the best of our knowledge, prior to my work, there were only about five examples where Morita-Baylis-Hillman chemistry was leveraged to achieve the dearomatization of pyridinium, isoquinolinium, or quinolinium salts. Moreover, one of these examples came from our research group. My work expanded the utility of MBH chemistry in this manner by drawing attention to the factors influencing regioselectivity, revealing the counterion and the nucleophilic catalyst as major contributors. In addition, the scope of this methodology was expanded via the inclusion of acridinium substrates. Hence, a general and direct route to synthetically valuable 1,4-dihydroquinolines was developed.

I anticipate that the work presented in this thesis will add to the established foundational work and promote further inquiry into this research area.

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Appendix A (Publications)

The experimental procedures, characterization data, and NMR spectra for all synthesized compounds can be found in the supplementary information of the associated publications.

ERRATA

Doctoral thesis: Electrochemical and Nucleophilic Dearomatization Strategies for the Synthesis of Spirocyclic and *N*-Heterocyclic Compounds. (**Author**: Robert Yafele)

After printing the thesis, a few editing errors have been identified and are corrected here.

Section Relocation and Renumbering:

Relocation of Section 1.2.1: The entire section titled "1.2.1 Azaarene Dearomatization enabled by Lewis Acid Activation", which spans from page 8 to 10 under subchapter 1.2, should be relocated to appear as "1.3.2. Azaarene Dearomatization enabled by Lewis Acid Activation" under subchapter 1.3.

Correction of Subsequent Subchapter Headings:

Consequential Renumbering: As a result of the section relocation described above, the subsequent Headings must be renumbered as follows:

Original Heading Number	New Corrected Heading Number
1.2.2.	1.2.1.
1.2.3.	1.2.2.
1.2.3.1.	1.2.2.1.
1.2.3.2.	1.2.2.2.
1.2.3.3.	1.2.2.3.
1.2.3.4.	1.2.2.4.
1.2.4.	1.2.3.
1.3.2.	1.3.3.
1.3.2.1.	1.3.3.1.
1.3.2.2.	1.3.3.2.
1.3.2.3.	1.3.3.3.
1.3.2.4.	1.3.3.4.