

1

Introduction

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1.1

Why Asymmetric Dearomatization Reactions?

Arenes and heteroarenes are widely distributed in nature, and some simple arenes are produced multimillion metric tons annually. They are recognized as fundamental synthetic materials in both academia and industry. The chemistry involving aromatic compounds is thus rich and of prime importance. Tremendous efforts have been devoted to various substitution reactions of aromatic compounds, and many name reactions such as Friedel–Crafts reaction and Sandmeyer reaction have become elementary contents of organic chemistry textbooks. These fully developed processes are undoubtedly essential tools for the total synthesis of natural products. Moreover, they provide chemists with the access to a huge library of aromatic compounds, which are extremely important in the discovery of pharmaceuticals, materials, and other functional molecules. In contrast, dearomatization reactions, another important branch of transformations of aromatic compounds, have been undervalued for a long time despite their potentials to convert simple molecules into complex structures. The specific feature of building quaternary carbon centers and interesting structures makes them straightforward protocols to construct spiro or bridged compounds. In spite of a long history of application in the total synthesis of natural products, only recently the systematic methodology exploration of dearomatization reactions has received huge interest. In this area, asymmetric dearomatization reactions are of particular importance due to the great demand of highly efficient strategies toward the construction of complex chiral molecules.

1.2

Discovery of Aromatic Compounds and Dearomatization Reactions

Although aromatic compounds exist widely in nature, it was only in 1825 that benzene was first isolated by Michael Faraday. Several years later, Eilhard Mitscherlich also obtained this substance and identified its molecular formula

as C_6H_6 . He gave it the name “benzin.” The highly unsaturated structure of benzene remained controversial for a long time, and various proposed structures were full of imagination. In 1865, Friedrich A. Kekulé postulated that benzene contains a six-membered ring of carbon atoms with alternating single and double bonds. Today, the famous Kekulé formula is still widely used. In 1931, by quantum mechanical calculations, Erich Hückel explained the unique stability of benzene different from other unsaturated hydrocarbons, namely, aromaticity. He differentiated the bonding electrons as π electrons and σ electrons, and the Hückel “ $4n + 2$ ” rule becomes a basis for estimation of aromatic compounds. Around the same time with or after the discovery of benzene, several other aromatic compounds have been discovered, and today, most of them have become extremely important industrial chemical starting materials (Figure 1.1).

Great demand on diverse arenes and heteroarenes has stimulated the related synthetic chemistry. Besides some very simple ones coming from petrochemicals (e.g., benzene, toluene, xylene, phenol), the vast majority of aromatic compounds need to be synthesized. Fundamental electrophilic aromatic substitution reactions including nitration, sulfonation, halogenation, Friedel–Crafts alkylation, and Friedel–Crafts acylation are frequently used synthetic tools, and the nucleophilic aromatic substitution reactions via diazonium ions also provide reliable routes to complicated aryl compounds. Moreover, recent development of transition-metal-catalyzed cross-coupling reactions between aryl halides (or equivalent) and organometallic compounds has enriched the transformations of aromatic compounds, and the direct use of aryl compounds through C–H functionalization is an alternative straightforward method. Meanwhile, the chemistry of heteroarene synthesis has also gained significant progress.

Compared with the chemistry to synthesize aromatic compounds, dearomatization reactions also have a long history. In 1885, the Buchner ring expansion of benzene with ethyl diazoacetate was reported to provide cycloheptatriene under thermal or photochemical conditions, and this methodology was further improved by the introduction of transition metal catalysts (Scheme 1.1) [1, 2]. The Birch reduction was first reported in 1944 to partially hydrogenate benzene to 1,4-cyclohexadiene (Scheme 1.2) [3]. The Reimer–Tiemann reaction discovered in 1876 was originally used for the *ortho*-formylation of phenols, and an interesting phenomenon was observed later that a dearomative by-product was generated when *para*-methyl phenol reacted with dichlorocarbene (Scheme 1.3) [4].

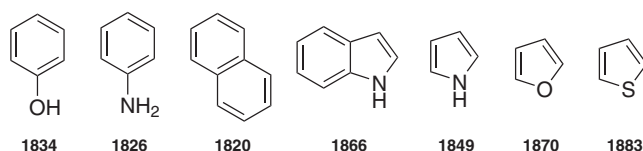
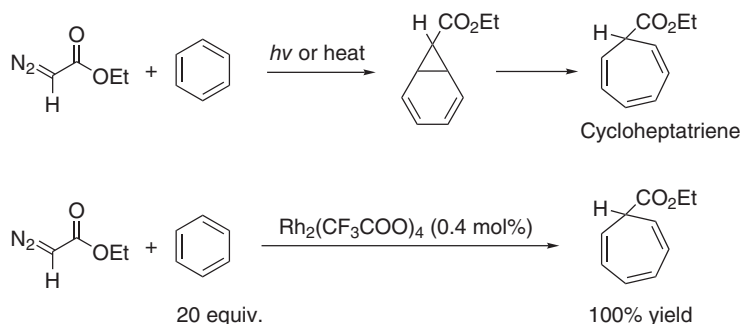
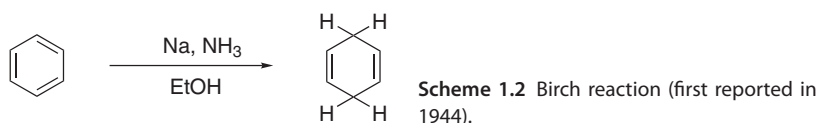


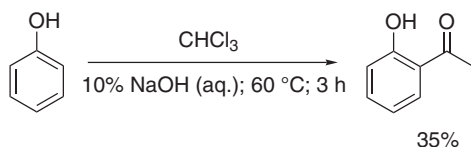
Figure 1.1 The representative arenes and heteroarenes and their discovery years.



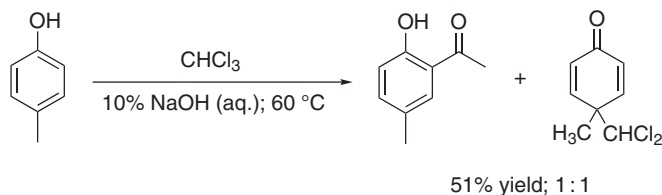
Scheme 1.1 Buchner ring expansion reaction (first reported in 1885).



Reimer–Tiemann reaction (first reported in 1876)



Dearomative by-product of Reimer–Tiemann reaction (reported in 1884)



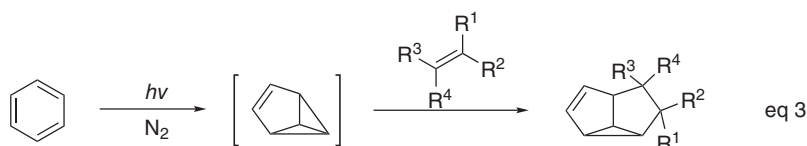
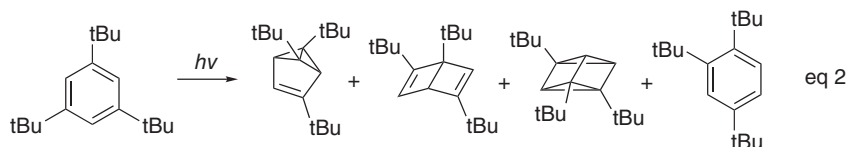
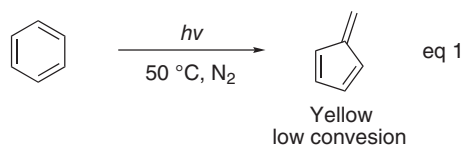
Scheme 1.3 Reimer–Tiemann reaction.

1.3

Development of Dearomatization Reactions

The history of dearomatization reactions can be dated back to the nineteenth century. Early studies on dearomatization reactions include photochemical processes, transition-metal-mediated processes, hydrogenation processes, enzyme-catalyzed processes, and so on.

In 1957, Blair and Bryce-Smith discovered that fulvene was generated by subjecting pure benzene under the irradiation conditions (Scheme 1.4, eq 1) [5].

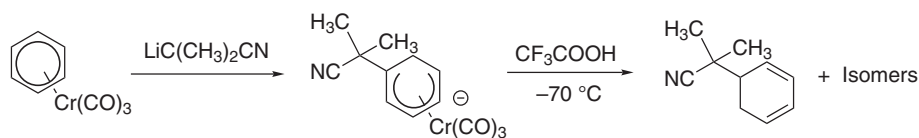
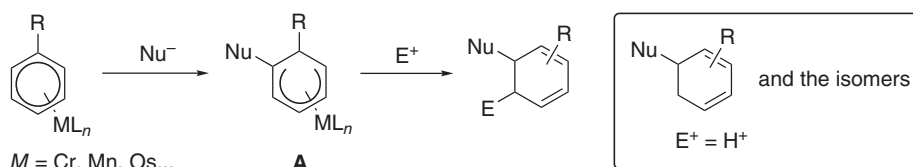


Scheme 1.4 Dearomatization reactions via photochemical process.

Although the conversion of this dearomatization reaction was low, it was believed to be the “first example of the direct isomerization of an aromatic to a nonaromatic hydrocarbon” [5]. Soon after, many related studies emerged, such as the irradiation of substituted benzenes (Scheme 1.4, eq 2) [6]. Meanwhile, the photochemical reaction between benzene and alkene was also investigated (Scheme 1.4, eq 3) [7]. However, this type of dearomatization reaction was not developed into an applicable level due to the multiple reaction pathways to deliver complicated mixtures of dearomatized products.

Early studies of transition metal–arene complexes in the 1950s were emphasized on their preparation, as exemplified by the synthesis of $C_6H_5Cr(CO)_3$ by Fischer in 1957 [8]. Activation of the aromatic ligands by transition metal centers toward nucleophiles was then discovered and explored [9]. Among the versatile transformations of the nucleophilic addition intermediates (Scheme 1.5, A), protonation and other electrophilic trapping generally deliver dearomatized products [10]. However, this type of dearomatization reaction is mediated by stoichiometric amount of transition metal complexes, and recent rapid growth is focused on transition-metal-catalyzed dearomatization processes. Chapters 4, 6, 7, and 9–11 elucidate the detailed development of transition-metal-catalyzed asymmetric dearomatization reactions.

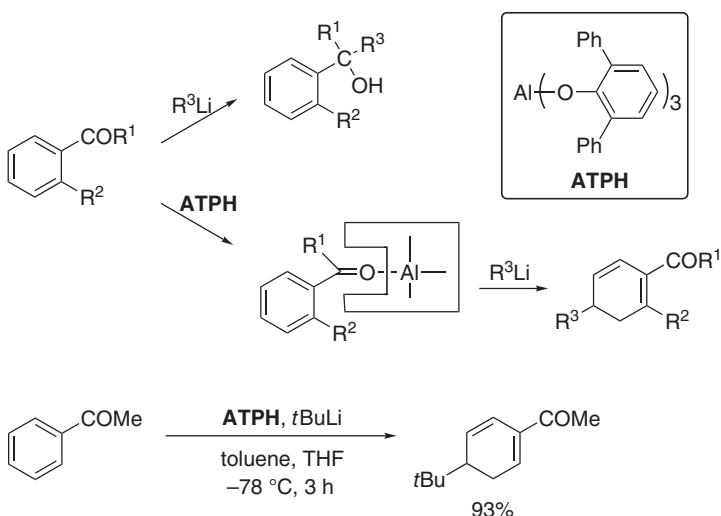
Dearomatization reactions of aromatic compounds by hydrogenation process (Scheme 1.2) and enzymatic process also have a long history. Chapters 3 and 4 introduce organocatalytic and transition-metal-catalyzed asymmetric dearomatization reactions by hydrogenation process, respectively. Chapter 12 is devoted



Scheme 1.5 Dearomatization through arene metal complexes.

to the development of enzymatic dearomatization reactions including the details on both history of discovery and current status.

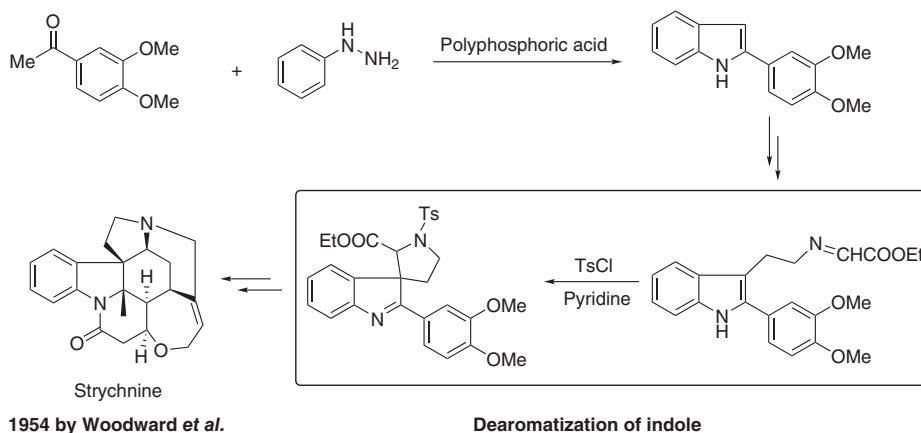
Meanwhile, some interesting approaches taking advantage of the steric effect provide alternative strategies for dearomatization. For instance, Yamamoto and coworkers designed the bulky Lewis acid ATPH that enabled the addition of *t*BuLi to phenyl methyl ketone occurring at the *para* position of the phenyl ring, delivering dearomatized product in excellent yield (Scheme 1.6) [11].



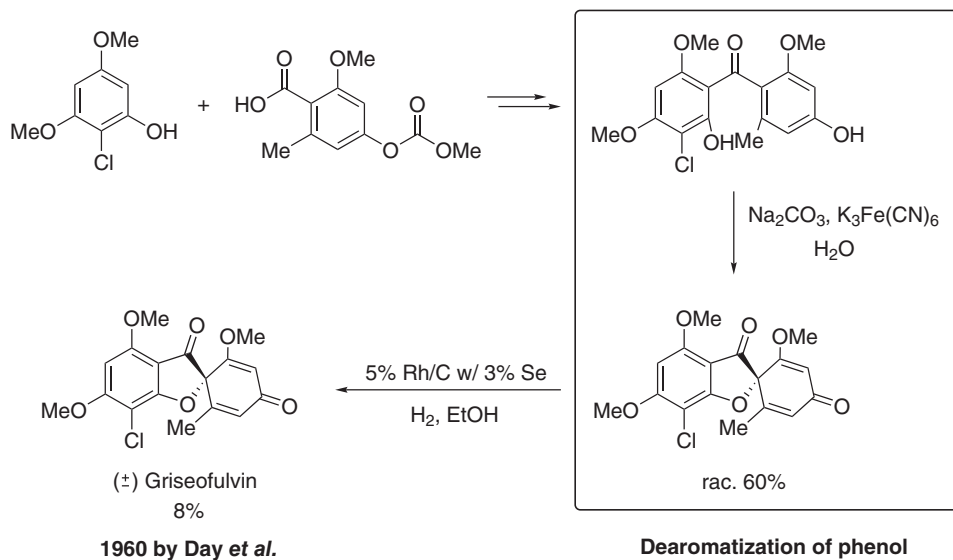
Scheme 1.6 Alternative strategy for dearomatization processes.

As attractive strategies, dearomatization reactions are frequently applied to the total synthesis of natural products, providing more efficient synthetic routes, in many cases biomimetic synthesis as a result of inspiration by nature. In 1954,

Woodward and coworkers first reported an elegant total synthesis of strychnine, in which the Pictet–Spengler-type dearomatization of indole core was employed as one key step to construct the complex polycyclic framework (Scheme 1.7) [12]. In 1960, Day and coworkers first completed the total synthesis of racemic griseofulvin, in which the dearomatization step was inspired by its biosynthetic pathway (Scheme 1.8) [13]. Numerous fabulous total syntheses were then reported with the application of dearomatization strategy, and Chapter 13 introduces this topic in detail.



Scheme 1.7 Dearomatization step in the total synthesis of strychnine .



Scheme 1.8 Dearomatization step in the total synthesis of griseofulvin.

Despite the wide utilization of dearomatization reactions in total synthesis of natural products, the systematic studies to develop practical dearomatization methodologies are still rare. Many of the known dearomatization methods are limited with scope and selectivity, and difficult to be practically used. For instance, the photochemical processes of arenes generally deliver a complicated mixture of dearomative products due to the poor selectivity (Scheme 1.4). The transition-metal-mediated processes require stoichiometric metal sources and the subsequent removal of metal is also needed to make it less appealing (Scheme 1.5). Various hydrogenation processes could only generate simple skeletons from the corresponding aromatic compounds, as the hydrogenation reaction generally forms C(X)–H bonds only (Scheme 1.2). For the enzyme-catalyzed processes, only specific substrates could be used. As said, the great potentials of dearomatization reactions, especially in an enantioselective manner, have been much more underdeveloped. On the other hand, dearomatization reactions are such powerful tools to provide various ring systems including heterocyclic skeletons directly from relatively simple planar aromatic rings. The advantage to build quaternary carbon centers makes them extremely straightforward routes to construct spiro or bridged compounds via intramolecular dearomatization reactions. Due to these features and great demand on chiral molecules, dearomatization reactions, particularly asymmetric ones, have received the renaissance recently.

1.4

Asymmetric Dearomatization Reactions

We have briefly introduced the history and early development of dearomatization reactions, and have shown their application in the total synthesis of natural products. Although quite a number of dearomatization protocols have been reported either in the methodology development or during the synthesis of functional molecules, the vast majority of them are limited within racemic studies. The enantioselective versions of dearomatization reactions are rather rare, especially those employing catalytic methods. The known asymmetric dearomatization reactions rely heavily on the chiral substrate–controlled strategy. The challenging of high energy barrier encountered during the process of dearomatization generally requires harsh reaction conditions, which pose formidable challenges in the control of regioselectivity and stereoselectivity. Delightfully, both asymmetric dearomatization reactions by chiral reagents and catalytic asymmetric dearomatization (CADA) reactions have received great attention and gained fruitful progress in the past few years. With the worldwide increased efforts in this field, we believe that every single type of asymmetric reaction would eventually become compatible with dearomatization process. In addition, more and more types of aromatic compounds can undergo the CADA reactions sooner or later.

There are many books focusing on the topic of aromatic compounds, but few of them describe dearomatization reactions. Given the dramatic progress in the field

of asymmetric dearomatization reactions, this book is aiming to provide readers very detailed information about recent developments of asymmetric dearomatization reactions, especially the CADA approaches.

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