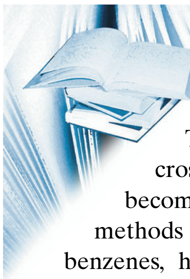

Modern Nucleophilic Aromatic Substitution

The great success of Pd-catalyzed cross-couplings of arenes, which has become one of the most important methods for the synthesis of substituted benzenes, has attracted much attention in recent years. In contrast, progress in the classical fields of arene chemistry, such as electrophilic and nucleophilic aromatic substitutions, has received much less attention. Most textbooks restrict the treatment of nucleophilic aromatic substitutions to discussions of addition-elimination mechanisms via Meisenheimer-analogous intermediates and to elimination-addition sequences via arynes. Thus, many chemists are not aware of important developments in this field during the past few decades, such as the tremendous synthetic potential of Makosza's "vicarious nucleophilic substitutions of hydrogen", or the fact that S_NAr processes do not always proceed via intermediate σ-adducts but can also proceed in a concerted fashion. Terrier's monograph gives an excellent overview of recent developments in this area, and provides a thorough and comprehensive description of our present understanding of the corresponding mechanisms and synthetic applications. This book is not an update of Terrier's 1991 monograph, just adding hundreds of new examples of nucleophilic aromatic substitutions. Instead, it is an authoritative analysis of the present status of the field, presented by one of the best physical organic chemists of our time, who has been active for many years in investigating this subject.

Chapter 1 provides a comprehensive overview of the mechanisms of nucleophilic substitutions of acceptor-substituted benzenes, pyridines, and related six- and five-membered heteroarenes. It describes how detailed information about the mechanisms has been obtained from kinetic measurements, NMR spectroscopic investigations of the intermediate σ-adducts, and quantum-chemical calculations. Detailed tables, with literature references, show the influence of the structure of the arene, leaving group, nucleophile, and solvent on the rates of formation of the σ-adducts and the subsequent re-aromatization.

Chapter 2 reports on the structural characteristics of stable σ-adducts, mostly obtained by X-ray crystallography and NMR spectroscopy. The section on the thermodynamics and kinetics of σ-adduct formation is a treasure trove for the physical organic chemist who is interested in rate–equilibrium relationships. The reactivities of a group of strongly electron-deficient heteroaromatic compounds, nitro-2,1,3-benzoxadiazols (nitrobenzofurazans), and their 1-oxides (nitrobenzofuroxans), which are described in Chapter 3, focus on the author's own research. Some of these compounds are called superelectrophiles, because they have a high affinity towards water and behave as moderate to strong acids in aqueous solution, with pK_a values between 7 and 0. However, I have to admit that I am biased when commenting on this chapter, because it is a marvellous demonstration of the ordering principle of our reactivity scales. While the nitro group is well known to be a strong activator for nucleophilic displacements of leaving groups in *ortho* and *para* positions, Chapter 4 describes how the nitro group has also been employed as a good nucleofuge in many synthetic transformations. As the synthetic aspects of nucleophilic aromatic substitutions have already been extensively reviewed, Chapter 4 emphasizes the results reported since 1990. The great potential of intramolecular S_NAr reactions in heterocycle synthesis is illustrated in Chapter 5. Replacement of hydrogen, the most important variant of electrophilic aromatic substitutions, where hydrogen is removed as a proton, is less facile in nucleophilic aromatic substitutions. However, Chapter 6 shows that nucleophilic substitutions of hydrogen can be achieved by oxidative removal of hydride from the intermediate σ-adducts or by Makosza's "vicarious nucleophilic substitutions". The latter method employs carbanions with leaving groups (e.g., Cl^-) in the α position that can be eliminated with the hydrogen at the sp^3 carbon of the σ-adduct. Less common S_NAr substitution pathways are briefly summarized in Chapter 7.

In line with Seebach's often quoted 1990 statement that discoveries of fundamentally new reactions with Main Group elements are unlikely, Terrier's monograph does not report reactions showing unprecedented reactivity. However, it beautifully shows how much new chemistry can still be created by intelligently combining known principles of organic reactivity. For that reason, this book can be recommended not only for synthetic chemists interested in nucleophilic aromatic substitutions but to everyone who considers employing the principles of physical organic chemistry for the design of organic syntheses.

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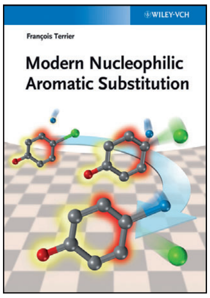

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