

Preface

One of the current trends in development of both academic and industrial organic synthesis is orientation of chemists on using “chlorine-free” ecologically benign processes, based on direct methods of C–H functionalization of aromatic compounds, avoiding halogenated starting materials or intermediates.

The synthesis and structural modifications of aromatic systems have always been a subject of considerable interest to many chemists. Electrophilic aromatic substitution of hydrogen S_EAr and nucleophilic aromatic substitution of halogen and other good leaving anionic groups S_NAr^{ipso} , became the main synthetic methodologies and basic industrial processes of the last century. For many decades they have been exploited by chemists to obtain enormous number of derivatives of this important class of organic compounds.

A great variety of effective metal-catalyzed cross-coupling reactions (Heck, Stille, Suzuki-Miyaura, Sonogashira, Kumada, Negishi, Buchwald-Hartwig, Hijama, and others) have been advanced during the last three decades, however most of these catalytic methods are also based on using aryl halogenides, as starting materials. The situation is far from ideal from an atom economy point of view (for instance, bromination of aromatics – debromination), to say nothing of its poor correspondence to other principles of the green chemistry. Besides that, metal-catalyzed cross-coupling reactions often require the presence of palladium-containing catalysts and phosphorus-containing ligands, traces of which could not be admitted in pharmaceutical products. This is why the roundtable of leading global pharmaceutical companies, arranged by the American Chemical Society and Green Chemistry Institute, put the C–H activation of aromatics (including cross-coupling reactions, avoiding the preparation of haloaromatics) in the list of promising “aspirational” reactions (for detail see: [1]).

We believe that it is a high time to draw attention of both academic and industrial chemists to a relatively new synthetic methodology, which is based on the direct metal-free nucleophilic displacement of hydrogen in aromatic systems (S_N^H).

This volume of *Topics in Heterocyclic Chemistry* is composed of six chapters presented by an international set of authors, which responded to our proposal to

review the recently published data on the S_N^H reactions, proceeding without organometallic intermediates.

The chapter “Metal-Free C–H Functionalization of Aromatic Compounds Through the Action of Nucleophilic Reagents” by Valery Charushin and Oleg Chupakhin (Postovsky Institute of Organic Synthesis; Ural Federal University, Ekaterinburg, Russia) presents a general concept of the S_N^H reactions. It is supposed to demonstrate a common character of the S_N^H reactions, as a fundamental property of aromatic and hetero-aromatic compounds, and to show the practical value of metal-free C–H functionalization of aromatics.

The chapter “Nucleophilic Substitution of Hydrogen in Arenes and Heteroarenes” by Mieczysław Mąkosza and Krzysztof Wojciechowski (Institute of Organic Chemistry, The Polish Academy of Sciences, Warsaw, Poland) provides us with the comprehensive review on both oxidative and eliminative versions of the S_N^H reactions, including the so-called vicarious nucleophilic substitution, which appears to be a very essential part of the S_N^H methodology. Indeed, the presence of a vicarious (auxiliary) group facilitates elimination of hydrogen with pair of electrons from the intermediate σ^H -adducts.

The chapter “Direct Functionalization of C–H Fragments in Nitroarenes as a Synthetic Pathway to Condensed N-Heterocycles”, authored by Svyatoslav Shevelev and Alexey Starosotnikov (Zelinsky Institute of Organic Chemistry, Moscow, Russia), deals with the direct functionalization of C–H fragments in nitroarenes, followed by intramolecular cyclizations, as an effective synthetic pathway to condensed nitrogen heterocycles.

The chapter “C–H Functionalizations of Heteroaromatic N-Oxides”, prepared by Yoshinori Kondo (Tohoku University, Sendai, Japan), gives an excellent account of the recent advances in the field of nucleophilic C–H functionalization of heteroaromatic N-oxides, by using metal-free S_N^H processes, as attractive environmentally benign methods of organic synthesis.

The chapter “The S_N^H -Amination of Aromatic Compounds”, authored by Anna Gulevskaya and Alexander Pozharsky (Rostov-on-Don University, Russia), presents a comprehensive review on the direct S_N^H amination of electron-deficient heteroaromatic compounds. Recent advances in this area and many new aspects of the S_N^H amination are discussed, including new types of reagents, metal-free catalysts, solvents and the hydride ion acceptors. The review shows that the S_N^H amination is rather promising synthetic alternative to both classic and transition metal-catalyzed amino-dehalogenation reactions.

Finally, the chapter “Electrochemical C–H Functionalization of Arenes ” by I luminada Gallardo and Gonzalo Guirado (University of Barcelona, Spain) provide us with an excellent review showing a practical importance of electrochemical methods for the direct C–H functionalization of aromatic and heteroaromatic compounds – a very promising area that has been advanced significantly by these authors.

It is worth noting that three chapters of this volume have been written by the Russian chemists, and it seems to be a good opportunity to discuss the results

obtained by these research groups and to reflect properly a considerable body of the data on the S_N^H reactions published in the Russian chemical journals.

We believe that numerous examples and methods for the direct metal-free C–H functionalization of arenes and heteroarenes, presented by an international team of chemists in six chapters of this volume, are not only complementary to each other, but also create the whole picture of the S_N^H reactions, enabling one to estimate their current scope, synthetic potential and value as “chlorine-free” ecologically benign processes.

In conclusion, we would like to express our sincere gratitude to all authors for their valuable contributions. Also we are thankful to professor Bert Maes (University of Antwerp, Belgium), who encouraged us to prepare this volume, and Elizabeth Hawkins and Tanja Jaeger from Springer DE for their help and fruitful cooperation.

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Reference

1. Constable DJC et al (2007) *Green Chem* 9:41.

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Nucleophilic Displacement of Hydrogen

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