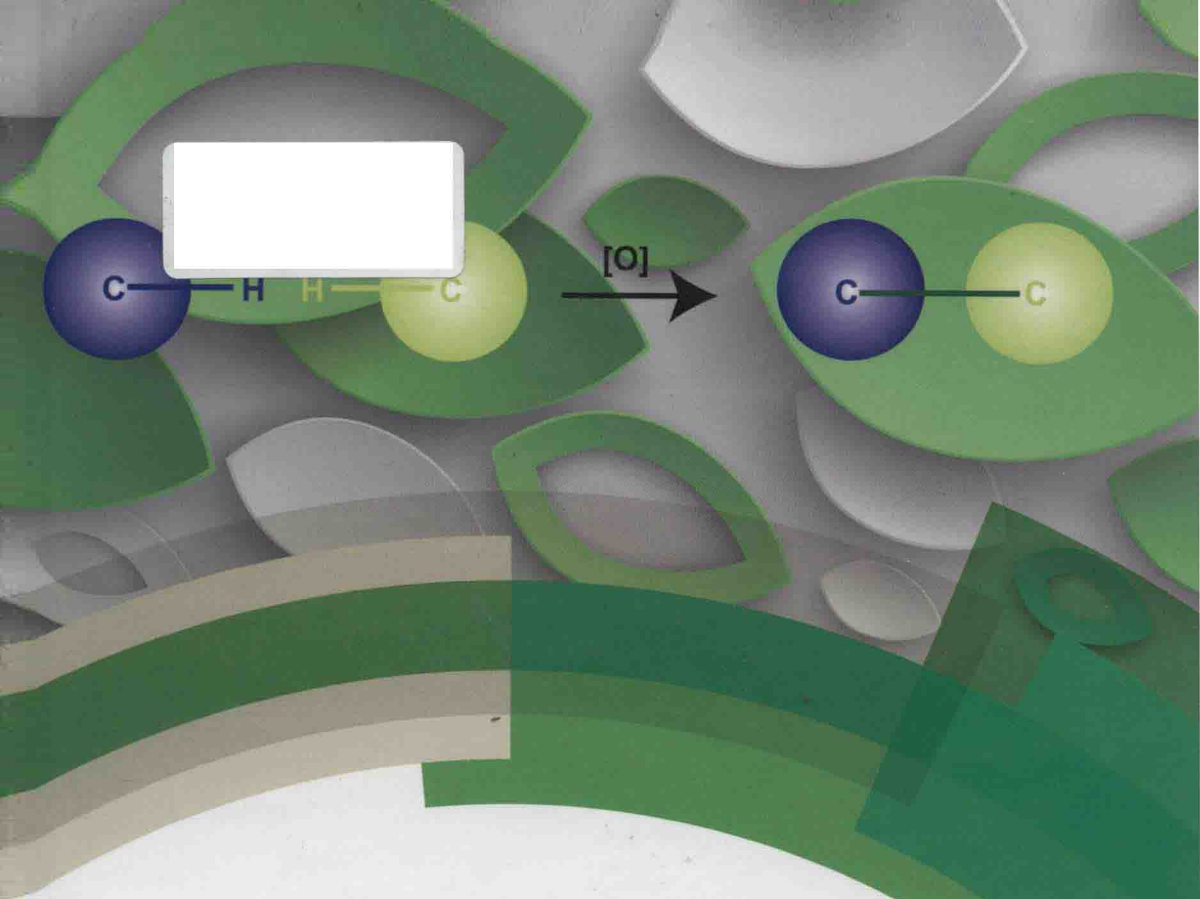

RSC Green Chemistry

From C-H to C-C Bonds

Cross-Dehydrogenative-Coupling

Edited by Chao-Jun Li

ROYAL SOCIETY
OF CHEMISTRY

From C–H to C–C Bonds
Cross-Dehydrogenative-Coupling

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RSC Green Chemistry

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Preface

The ability to achieve any goals in our society is largely dependent upon, and limited by, the state-of-the-art tools available. While the speed and ease of the construction of large objects, such as buildings, are rapidly enhanced by the creation of various heavy machines, established fundamental chemical reactions, in combination with our creative and intelligent designing skills, ultimately determine the synthesis of chemical products.

The development of novel chemical reactivities and reaction conditions that can improve resource efficiency, energy efficiency, product selectivity, operational simplicity, as well as environmental health and safety, represents both an ideology and an aspiration for generations of synthetic chemists, more so than ever at this time. Ever since the synthesis of urea by Friedrich Wöhler in 1828, organic chemistry has become increasingly important in modern society. The invention of organic reactions over the past two centuries has allowed us to create synthetic organic compounds and materials that have now touched essentially every corner of our life: from cosmetics to fashion, from pharmaceuticals to agrochemicals, from transportation to the interior of skyscrapers, and from electronics to genetic modification. However, the archetypical requirements of standard classical chemical transformations are the functional groups, which provide the platform for chemical conversions that have led to the synthesis of millions of both naturally existing and non-naturally existing molecules in just less than two centuries, only a blinking moment in human history. In spite of the great successes, there are still various shortcomings: the pre-functionalized starting materials need to be synthesized in separate steps, and the amount of waste associated with solvent usage, purification and isolation maneuvers, as well as the required manpower to perform a synthesis increases exponentially with the number of synthetic steps. With recent concerns regarding the adverse effects of chemical production processes, as well as the

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emphasis on green chemistry and chemical sustainability, various frontiers of synthetic chemistry have been explored. Among them, the concept of the cross-dehydrogenative-coupling (CDC) reaction was formulated in 2003. The direct generation of a C–C bond from two different C–H bonds constitutes an ideal that has game-changing potential in synthetic design. The subject has become a very rapidly expanding field. This edited book will cover some of the key developments in this area.

Chao-Jun Li
Montreal, Canada

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CHAPTER 1

The Evolution of the Concept of Cross-Dehydrogenative-Coupling Reactions

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1.1 Introduction

Among the countless reactions developed throughout the history of organic chemistry, carbon–carbon bond formation reactions are very special, as such reactions create the framework for organic molecules to build on and for functional groups to be attached to. Thus, the development of methods for forming C–C bonds plays a central role in the design and synthesis of organic matter: molecules and materials.[1] Historically, nucleophilic additions, substitutions, and Friedel–Crafts type reactions formed the pillars of methods to connect two simpler molecules *via* the formation of a C–C bond in acyclic structures.[2] The development of pericyclic reactions[3] laid the foundation for synthesizing cyclic structures. Over the past four decades, transition metal catalyses *via* cross-coupling and metathesis have overcome some limitations of the classical reactions, *e.g.*, nucleophilic substitutions involving sp^2 carbon centers, and have greatly increased the efficiency of C–C bond formations, especially those involving arenes and alkenes, in modern

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organic chemistry.[4] Their importance is attested by the awarding of Nobel Prizes in both 2005 and 2010.[5]

However, in spite of the great success of both classical C–C bond formation methods and the modern extraordinary achievements of transition metal catalysis, state-of-the-art C–C bond formation reactions must use pre-functionalized starting materials, which require extra steps (sometimes multiple steps) to synthesize. In many cases, during the core C–C bond formation processes, the pre-formed functional groups are simultaneously 'lost'. The necessity of these repetitive pre-functionalization and defunctionalization steps plus the associated isolations and purifications, ultimately diminishes the overall material efficiency in the synthesis of complex organic molecules and increases chemical waste. The reduction in efficiency is aggravated with an increase in the complexity of molecules, as exemplified by the E-factor of Sheldon.[6] To reduce the number of steps involved and increase the efficiency in synthetic chemistry, we must explore new frontiers of chemical reactions, in which various chemical bonds in widely available natural resources, petroleum, natural gas, biomass, N_2, CO_2, O_2, water, and others can be selectively transformed directly without affecting other bonds and without the need for excessive pre-activations. As part of this effort, the transition metal catalyzed C–H bond activation and subsequent C–C bond formations have, thus, attracted much interest in recent years.[7] Outstanding achievements have been made in this area and many complex compounds can be made much more rapidly. However, these reactions still require at least one functionalized partner in order to generate the desired C–C bond formation products.

Historically, the copper-mediated oxidative homodimerization of alkynes (the Eglinton reaction), an first reported over a century ago, represents the earliest success of directly generating a C–C bond from two C–H bonds.[8] The reaction requires a stoichiometric quantity of $Cu(OAc)_2$ as both mediator and oxidant. The Glaser–Hay coupling modified such oxidative homodimerization of alkynes by using a catalytic Cu(I) catalyst with oxygen as the terminal oxidant.[9] On the other hand, the oxidative homodimerization of electron-rich arenes has also become highly successful in generating arene dimers and polymers for a wide range of applications: from fine chemicals and pharmaceuticals to electronic materials.[10] Both types of reaction, however, are limited to homodimerizations and are beyond the present book.

In synthetic chemistry, what is very challenging and highly desirable is the selective formation of two different C–H bonds from two completely different compounds (or two chemically different sites within a molecule). As C–H bonds are generally relatively inert, compared to all other bonds in organic molecules, such cross-oxidative couplings involving only C–H bonds in the presence of, and without affecting other more reactive bonds, would be unthinkable within classical chemical knowledge.

Prior to the concept of cross-dehydrogenative-coupling (CDC), Moritani and Fujiwara developed the oxidative formation of Heck-type reaction products directly from arenes and alkenes, instead of aryl halides and