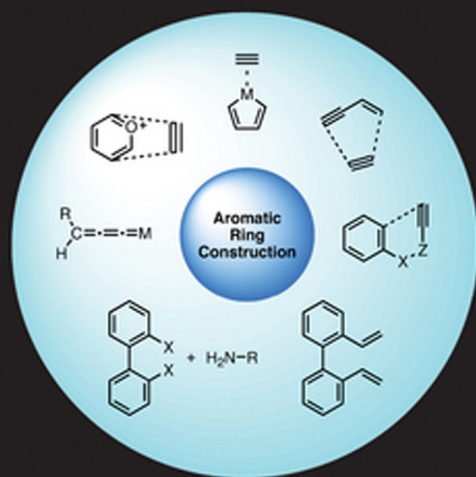


# Transition- Metal-Mediated Aromatic Ring Construction



Edited By  
**KEN TANAKA**

**WILEY**



# **TRANSITION-METAL-MEDIATED AROMATIC RING CONSTRUCTION**



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**Edited by**

**KEN TANAKA**

Tokyo University of Agriculture and Technology  
Tokyo, Japan

**WILEY**

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Published by John Wiley & Sons, Inc., Hoboken, New Jersey.  
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***Library of Congress Cataloging-in-Publication Data:***

Transition-metal-mediated aromatic ring construction / edited by Ken Tanaka, Tokyo University of Agriculture and Technology, Tokyo, Japan.

pages cm

Includes bibliographical references and index.

ISBN 978-1-118-14892-1 (hardback)

1. Aromatic compounds—Synthesis.
2. Transition metal catalysts. I. Tanaka, Ken, 1967–  
QD331.T73 2013  
547'.6—dc23

2012049882

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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# PREFACE

Because complex aromatic compounds have been utilized in various functional organic materials (e.g., liquid crystals, organic light-emitting devices), functional reagents (e.g., ligands, catalysts), and biologically active compounds (e.g., medicines, pesticides), the development of new reactions for the synthesis of aromatic compounds is a hot research field in modern organic synthesis. A conventional synthetic route to aromatic compounds is that of substitution reactions of aromatic nucleus, but this approach is not satisfactory in some cases. Recent significant advances in the area of transition-metal-mediated aromatization reactions enable the efficient construction of substituted aromatic rings in practical as well as convenient ways. These aromatic ring construction reactions would open promising new routes to complex aromatic compounds. Consequently, these reactions have been the subject of intense research in recent years, as evidenced by the number of research papers and reviews that have appeared.

Although transition-metal-mediated substitution reactions of aromatic nucleus have been well described in a number of books, a book that focuses on the transition-metal-mediated construction of aromatic rings has not appeared to date. A book explaining the use of transition-metal-mediated aromatic ring construction reactions for the complex aromatic compounds targeted would, therefore be useful for both academic and industrial chemists. For these reasons, in this book we demonstrate comprehensively how to use transition-metal-mediated aromatic ring construction reactions for the synthesis of complex aromatic compounds.

I would like to thank the authors of the individual chapters, each of whom is as a world expert in their area of research into aromatic ring construction reactions, for their willingness to contribute. I would also like to thank the team at Wiley, especially Jonathan Rose, for his valuable assistance and encouragement during this project. Finally, I deeply appreciate students in my research group for their valuable assistances.

KEN TANAKA

*November 2012*



# **PART I**

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## **[2 + 2 + 2] AND RELATED CYCLOADDITION REACTIONS**



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# 1

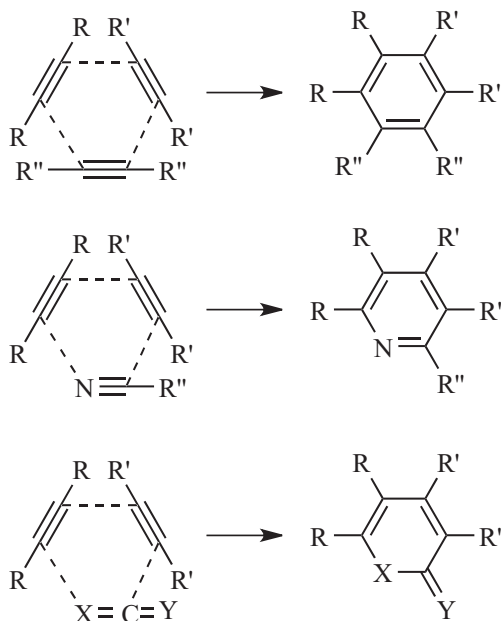
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## COBALT-MEDIATED [2 + 2 + 2] CYCLOADDITION

VINCENT GANDON

### 1.1 INTRODUCTION

An expedient way to envisage the synthesis of conjugated six-membered rings such as benzenes, pyridines, pyridones, and related heterocycles is by a [2 + 2 + 2] cycloaddition retrosynthetic approach. These conjugated systems can indeed be viewed as cycloadducts of three readily available unsaturated partners, such as alkynes, nitriles, isothiocyanates, carbon disulfide, isocyanates, and carbodiimides (Scheme 1.1, X = N, S; Y = N, O, S). Although the thermal version of this reaction is usually hardly feasible [1], it becomes straightforward in the presence of the appropriate catalyst. The first example of transition-metal-catalyzed [2 + 2 + 2] cycloaddition was reported by Reppe and Schweckendiek in 1948 [2]. A nickel complex was used as a precatalyst to cyclotrimerize alkynes into benzenes. Until the early 1970s, it was shown that many other metals could be employed, notably cobalt. Afterward, led by Vollhardt, who reported a considerable number of applications, this chemistry clearly proved to be priceless in organic synthesis. Since the topic has already been thoroughly reviewed [3], in this chapter we emphasize the latest development of the cobalt-catalyzed [2 + 2 + 2] cycloaddition reaction over the past 10 years.



## 1.2 SYNTHESIS OF BENZENES

### 1.2.1 New Catalytic Systems

The typical cobalt complexes used to form benzenes by [2 + 2 + 2] cycloadditions can be classified into three categories (Figure 1.1). The first concerns those containing cyclopentadienyl ligands ( $\text{CpCoL}_2$ ,  $\text{Cp}^*\text{CoL}_2$ , or other modified  $\text{Cp}'\text{CoL}_2$ ). The most common ones are  $\text{CpCo}(\text{CO})_2$ ,  $\text{CpCo}(\text{C}_2\text{H}_4)_2$ , and  $\text{CpCo}(\text{COD})$ , sometimes associated with a phosphine.  $\text{CpCoL}_2$  catalysts can be used in a variety of organic solvents, as well as supercritical  $\text{CO}_2$  or  $\text{H}_2\text{O}$  [3m]. The functionalization of the Cp (cyclopentadienyl) ring with a polar side chain allows the reaction to take place

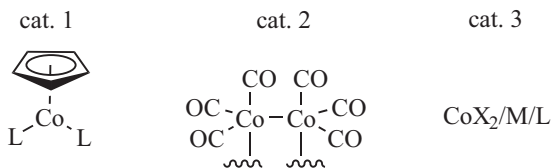


FIGURE 1.1

in aqueous solution [4]. As shown below, new complexes of type CpCo(alkene)(L) have recently been used as catalysts. The second category deals with such cobalt carbonyls as  $\text{Co}_2(\text{CO})_8$ ,  $\text{Co}_3(\text{H})(\text{CO})(\text{PMe}_3)_6$ , and  $\text{Co}_4(\text{CO})_{12}$ . A new versatile complex has also been developed. The third category contains cobalt halides of type  $\text{CoX}(\text{PR}_3)_3$  or  $\text{CoX}(\text{PR}_3)(\text{CO})_2$  ( $\text{X} = \text{Cl}, \text{Br}$ ;  $\text{R} = \text{Ph}, \text{Me}$ ), as well as  $\text{CoX}_2/\text{M}/\text{L}$  catalytic systems ( $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ;  $\text{M} = \text{Mn}, \text{Zn}, \text{NaBH}_4$ , etc.;  $\text{L} =$  phosphines, imines, etc.). These systems, based on Co(II) sources, have aroused great enthusiasm in the past 10 years.

**1.2.1.1 [CpCo] Complexes** Various problems associated with the synthesis of benzenes have been circumvented recently by using precatalysts **I** to **III**, displayed in Figure 1.2.

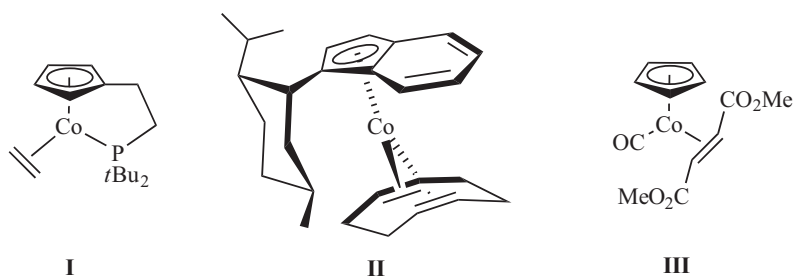
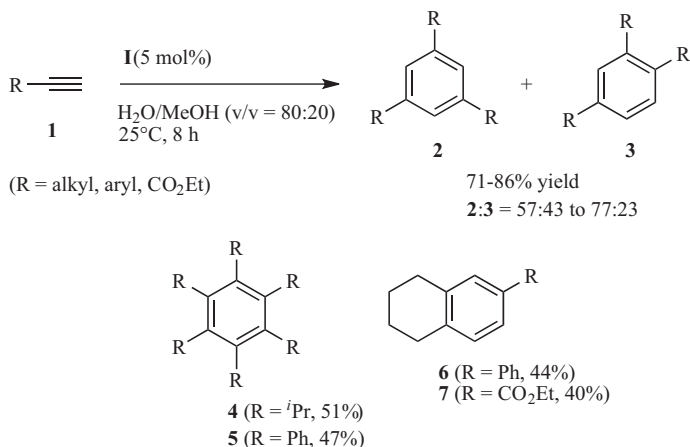


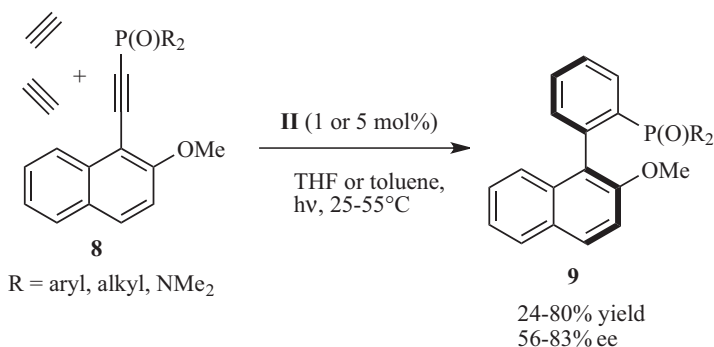
FIGURE 1.2

Yong and Butenschön succeeded in achieving alkyne cyclotrimerizations in an aqueous medium at room temperature using **I** [5]. While standard catalysts such as CpCo(COD) allow the formation of pyridines at room temperature in water [6], this feature has so far not been possible for benzenes, for which an elevated temperature is required [4]. Complex **I** was tested toward the cyclotrimerization of mono-substituted alkynes **1** and gave the expected regioisomeric mixture **2/3** in good yields and often good selectivities compared to reactions carried out in organic solvents (Scheme 1.2). The cyclotrimerization of the disubstituted alkynes 2,5-dimethyl-3-hexyne and diphenylacetylene to give **4** and **5**, respectively, was also reported, as well as bimolecular reactions between 1,7-octadiyne and phenylacetylene or ethyl propiolate to give **6** and **7**, respectively. Catalyst **I** could also be used to assemble pyridines (see Section 1.3.1.1).

The [2 + 2 + 2] cycloaddition reaction can give rise to chiral compounds, especially biaryls [3q]. Control of the enantioselectivity in such transformations is of prime importance, notably because biaryls can be used as ligands in asymmetric catalysis. This topic is covered in detail in Chapter 9. Nowadays, cobalt still looks like a poor relation in this field, which is largely dominated by rhodium. Nevertheless, a report from Heller et al. shows for the first time that phosphorus-bearing axially chiral biaryls **9** can be formed by enantioselective benzene formation using the neomenthyl-indenyl cobalt complex **II** as a catalyst (Scheme 1.3) [7]. Good yields



SCHEME 1.2



SCHEME 1.3

and ee values were obtained after the cycloaddition of 2 equiv of acetylene with alkynyl phosphine oxides **8**.

In many cases, standard catalysts such as CpCo(CO)<sub>2</sub> or CpCo(COD) necessitate heat and visible light irradiation to be active. Conversely, CpCo(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub> turns over at room or lower temperatures [8]. However, these catalysts are sensitive to oxygen and usually require thoroughly degassed solvents. Complex **III** is a new air- and moisture-stable catalyst for [2 + 2 + 2] cycloadditions [9]. Heat is still necessary, but not irradiation. The reaction can be carried out in hot toluene or in microwaved dimethylformamide (DMF). Crude solvents can be used as found in the laboratory without purification. The catalyst is still active after months of storage in simple vials. Whereas the first report focused on simple cycloadditions of alkynes **10** or triynes **14** (Scheme 1.4), complex **III** proved useful as well with more sophisticated systems (see Section 1.2.2).